Cardiology
An Illustrated Textbook

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VOLUME 1

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Foreword



It is a privilege to write this foreword for this comprehensive *Cardiology—An Illustrated Textbook*. Because of the excessive morbidity and mortality from cardiovascular disease, the subject is extensively discussed in the world's literature and existing textbooks. A fair question from the reader is: why do we need another textbook of cardiology? That question can be answered in different ways.

First of all, our knowledge of and ability to treat all kinds of cardiovascular diseases have expanded exponentially in the past few decades. I recall when I was a cardiology fellow at the Peter Bent Brigham Hospital, Boston (USA), and watched my first Vineberg procedure as an attempt to revascularize the heart. It was a brutal punishing treatment for the myocardium, and was a great disincentive to the cardiologist to refer such patients to the cardiac surgeon. Now, when we approach coronary artery disease, we have so many options available to us; including angioplasty, stents, "keyhole" surgery and potent pharmacologic ways to alter the lipid profile. Rapid advances in noninvasive imaging and electrophysiology remind us how quickly our knowledge base is changing.

Second, it is always useful to know and compare the different approaches to cardiovascular disease at world-class institutions. The Contributors and Editors of this textbook are primarily based at the University of Iowa and the University of California, San Francisco, USA, two well-known centers for research and treatment of cardiovascular disease. Many other institutions are also represented. This unique blending of knowledge and expertise also reflects the fact that the principal editor, Dr Kanu Chatterjee, has spent most of his career at University of California, San Francisco (UCSF) and the University of Iowa, USA. It was my privilege to be associated with him as a colleague at UCSF, and to appreciate his broad knowledge of cardiology. His receipt of "best teacher" awards from the Department of Medicine attest to his ability to transmit that knowledge to students, housestaff, fellows and faculties.

Third, we are part of the fast- food generation. We are bombarded by so much information that we frequently are more attentive to our electronic devices than we are to the real people around us. We love photographs and graphs which can tell a whole story at a glance. I think that the reader will be pleased with the quality of the illustrations in the textbook, and find it easy-to-learn from them. I suppose that a few people (perhaps cardiology fellows and those studying for the cardiovascular boards) will sit down and read the textbook from cover to cover. More likely, however, it will serve as a reference text, wherein the reader can go to a specific chapter, and benefit from a concise and informative discussion of the particular problem at hand.

Fourth, every textbook of Cardiology has its strengths and weaknesses, and its distinctive sections. I believe that the reader will be pleased to review the Section on Evolving Concepts. Subjects such as the genomics of cardiovascular disease, gene therapy and angiogenesis, and stem cell therapy, to mention but a few chapters, will be of interest to all those concerned with cardiovascular disease.

Overall, the comprehensive textbook will continue the tradition of excellent textbooks of cardiology. It will be of great interest not only to the cardiologist but also to all those interested in cardiovascular disease including internists and other specialists. I am pleased to recommend the book most highly.

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Preface

Cardiology—An Illustrated Textbook is a revived but really a new textbook in cardiology. "Cardiology" was initially published as a loose-leaf referenced textbook. In 1993, it was published as a hard copy illustrated and referenced textbook. Since its publication, almost two decades ago, there have been enormous advances in every aspect of cardiology. Substantial progress has occurred in the understanding of coronary circulation, the molecular mechanisms of myocyte function and in the assessment of regional and global ventricular functions in physiologic and pathologic conditions. In this textbook, these advances have been emphasized.

The advances in cardiovascular pharmacology have also been considerable. The advantages and disadvantages of diuretic therapy, vasodilators, neurohormone modulators, positive inotropic agents, antilipid, antithrombotic and antiplatelet agents have been discussed. The clinical pharmacology of these agents in the management of various cardiovascular disorders has been emphasized. In the textbook, these advances are the subject of entirely new chapters.

We have witnessed the development of newer diagnostic techniques and the refinement of older diagnostic methods for detection of cardiovascular pathology. Molecular imaging and three-dimensional echocardiography and intravascular ultrasound imaging have been introduced. Advances have occurred in nuclear, cardiovascular computerized tomographic and magnetic resonance imaging. In the textbook, the advances in these diagnostic techniques and their clinical applications in the practice of cardiology have been extensively discussed. The role of rest and stress and electrocardiography and echocardiography has been emphasized.

During last two decades, we have witnessed enormous advances in the understanding of the genesis of atrial and ventricular arrhythmias, in the techniques of electrophysiologic and the pharmacologic and nonpharmacologic treatment of arrhythmias. The function and dysfunction of ion channels and the diagnosis and management of supraventricular and ventricular arrhythmias have been presented in details.

There have been revolutionary changes in the understanding of the pathophysiologic mechanisms and management of acute coronary syndromes. The new therapeutic modalities for the management of chronic coronary artery diseases have been discovered and devoted to discuss.

The diagnosis and management of valvular heart disease and heart failure are discussed in detail as well as chemotherapy and radiation-induced cardiovascular disorders. The progress in vascular biology, in genetics and pharmacogenomics in cardiology has also been considerable. In recent years, awareness of the cost of health care, errors in the practice of cardiology and gender and geographic differences in the incidence, diagnosis and management of cardiovascular disorders has risen. In the textbook, we have addressed these important and controversial topics.

We have also added modified guidelines for the management of angina, arrhythmias, heart failure, valvular heart diseases and perioperative cardiac evaluations.

All the chapters in the textbook have been written by the nationally and internationally recognized experts in their respective fields. The editors are very appreciative of and grateful to the contributors.

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Kanu Chatterjee
Mark Anderson
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Richard E Kerber

Volume 1

Section 1
BASIC CARDIOLOGY

1. Cardiac Anatomy 3
Melvin D Cheitlin, Philip C Ursell

Pericardium and Heart in the Mediastinum 3
Cardiac Surface Anatomy 6
Internal Structure of the Heart 8
Right Atrium 8
Tricuspid Valve 10
Right Ventricle 11
Pulmonic Valve 12
Pulmonary Arteries 13
Left Atrium 13
Mitral Valve 13
Left Ventricle 14
Aortic Valve 15
Conduction System 16
Coronary Arteries 18
Intramural Vessels 19
Coronary Veins 19
Cardiac Lymphatics 21
Cardiac Innervation 21

2. Cardiac Function in Physiology and Pathology 23
Joel S Karliner, Jeffrey Zimmet

Beta-adrenergic Receptor-mediated Signaling 23
Calcium Regulation 24
Links Between B-adrenergic Signaling and Calcium Regulation 24
Mitochondria 24
Cardiac Hypertrophy 26
α_1-adrenergic Receptors and Hypertrophy 26
Congestive Heart Failure 27
Micro-RNAs 28
Ischemia/Reperfusion Injury 28
Mechanisms of Cardioprotection 28
Aging 30

3. Coronary Circulation in Physiology and Pathology 34
Kanu Chatterjee

Coronary Vascular Anatomy 34
Regulation of Coronary Blood Flow 34
Coronary Vascular Resistance 35
Modulation of Coronary Blood Flow 36
Coronary Collateral Circulation 39
Coronary Circulation in Pathologic States 40

Section 2
CARDIOVASCULAR PHARMACOLOGY

4. Diuretics 53
Michael E Ernst

Normal Renal Solute Handling 53
History and Classification of the Diuretic Compounds 53
Clinical Pharmacology of the Diuretic Compounds 55
Adaptive Responses to Diuretic Administration 56
Individual Diuretic Classes 57
Clinical Use of Diuretics in Cardiovascular Diseases 62
Adverse Effects of Diuretics 67

5. Vasodilators and Neurohormone Modulators 71
Gary S Francis, Suma Konety

Vasodilator Drugs and Low Blood Pressure 72
Arteriolar Vasodilators 72
Renin-angiotensin-aldosterone System (RAAS) Blockers 74
Mineralocorticoid (Aldosterone) Receptor Blockers 78
Phosphodiesterase Type 5 Inhibitors 81
Intravenous Vasodilators 82
Oral B-adrenergic Blocking Drugs 83

6. Positive Inotropic Drugs 89
Carl V Leier, Garrie J Haas, Philip F Binkley

Intravenously Administered, Short-term Positive Inotropic Therapy 89

7. Antilipid Agents 104
Jennifer G Robinson

Appropriate Uses 104
Statins 105
Add-on to Statin Therapy 110
Bile Acid Sequestrants 111
Ezetimibe 111
Niacin 112
Triglyceride-lowering Therapy 113
Fibrates 113
Omega-3 Fatty Acids 114
Drugs in Development 114

8. Antithrombotic and Antiplatelet Agents 116
Louis P Kohl, Ethan Weiss

Clotting—A Primer 116
Antithrombotic Agents 119
Ave-5206 121
Vitamin K Antagonists (VKA) 121
Ati-5923 122
Direct Factor Xa Inhibitors 122
Direct Thrombin Inhibitors 124
Antiplatelet Agents 127

Section 3
DIAGNOSIS

9. History 143
Kanu Chatterjee

The History 143

10. Physical Examination 151
Kanu Chatterjee

General Appearance 151
Measurement of Arterial Pressure 153
Auscultation 160

11. Plain Film Imaging of Adult Cardiovascular Disease 174
Brad H Thompson, Edwin JR van Beek

Chest Film Technique 174
Overview of Cardiomediastinal Anatomy 175
Cardiac Anatomy on Chest Radiographs 176
Cardiac Chamber Enlargement 177
Radiographic Manifestations of Congestive Heart Failure 179

Cardiac Calcifications 182
Acquired Valvular Heart Disease 183
Pericardial Disorders 187

12. Electrocardiogram 189
Donald Brown

Basis of Electrocardiography 189
Component Parts of the Electrocardiogram 191
Lead Systems Used to Record the Electrocardiogram 191
Common Electrode Misplacements 192
Other Lead Systems 194
Identification of Atrial Activity 194
Characterization of QRS Complex 201
ST-T Wave Abnormalities 206
The "U" Wave 206
The QT Interval 207

13. ECG Exercise Testing 209
Abhimanyu (Manu) Uberoi, Victor F Froelicher

Before the Test 209
Methodology of Exercise Testing 211
During the Test 213
After the Test 220
Screening 221

14. The Left Ventricle 228
Rakesh K Mishra, Nelson B Schiller

Systolic Function 228
Contrast-enhanced Echocardiography 236
Other Echo-derived Indices of LV Systolic Function 237
Strain-derived Indices 237
Recognizing the Etiology of Cardiac Dysfunction 237
Dilated Cardiomyopathy 238
Hypertrophic Cardiomyopathy 238
Restrictive Cardiomyopathy 239
Left Ventricular Noncompaction 240
Visual Qualitative Indicators of Systolic Dysfunction 240
Diastolic Function 242

15. Ventricular Function—Assessment and Clinical Application 252
Kanu Chatterjee, Wassef Karrowni, William Parmley

Determinants of Left Ventricular Performance 252
Left Ventricular Pump Function 255
Heart Rate 258
Diastolic Function 259
Right Ventricular Function 260

16. Transthoracic Echocardiography 265
Byron F Vandenberg, Richard E Kerber

Chamber Quantitation 265
Doppler ECHO 269
Diastolic Function 270
Pulmonary Hypertension 272
Pericardial Disease 273
Valvular Heart Disease 274
Infective Endocarditis 285
Intracardiac Masses 285
Contrast Echocardiography 286
Cardiac Resynchronization Therapy 289

17. Stress Echocardiography 291
Ellen El Gordon, Richard E Kerber

Using Stress Echocardiography in Clinical Decisions 291
The Future of Stress Echo 305

18. Transesophageal Echocardiography 309
Seyed M Hashemi, Paul Lindower, Richard E Kerber

History 309
Guidelines 309
Performance 309
Safety 310
Views 310
Major Clinical Applications 310
Structural Valve Assessment 313
Acute Aortic Dissection 316
Procedural Adjunct or Intraoperative TEE 316

19. Real Time Three-dimensional Echocardiography 319
Manjula V Burri, Richard E Kerber

Technique 320
Clinical Applications 324
Future Directions 339
Limitations 342

20. Intravascular Coronary Ultrasound and Beyond 349
Teruyoshi Kume, Yasuhiro Honda, Peter J Fitzgerald

Intravascular Ultrasound 349
Optical Coherence Tomography 364
Angioscopy 370
Spectroscopy 374

21. Cardiovascular Nuclear Medicine—Nuclear Cardiology 381
Elias H Botvinick

Pathophysiologic Considerations 382
Myocardial Perfusion Imaging 385
Risk Assessment of General and Specific Patient Populations 393
Positron Emission Tomography Perfusion and Metabolism 394
Imaging Myocardial Viability 395
Imaging Perfusion 397
Quantitation of Regional Coronary Flow and Flow Reserve 397
Blood Pool Imaging—Equilibrium Radionuclide Angiography and First Pass Radionuclide Angiography 398
First Pass Curve Analysis 398
Equilibrium Gated Imaging—ERNA 399
The Value of Functional Imaging 401
Phase Analysis 401
Imaging Myocardial Sympathetic Innervation 401
Radiation Concerns 402

22. Cardiac Computed Tomography 408
Isidore C Okere, Gardar Sigurdsson

Technical Aspects 408
Coronary Artery Disease 414
Myocardium and Chambers 417

Pulmonary Veins 418
Cardiac Veins 419
Valvular Disease 420
Pericardium 421
Masses 422
Incidental Findings 423
Future 423

23. Cardiovascular Magnetic Resonance 431
Robert M Weiss

Diagnosis of Epicardial Coronary Artery Stenosis 432
Assessment of Global and Regional Left Ventricular Function at Rest and during Inotropic Stress 432
Myocardial Perfusion Imaging 433
Cardiovascular Magnetic Resonance Coronary Angiography 433
Unrecognized Myocardial Infarction 433
Dilated Cardiomyopathy 434
Hypertrophic Cardiomyopathy 437
Restrictive Cardiomyopathy 439
Cardiovascular Magnetic Resonance-guided Therapy 440
Valvular Heart Disease 440
Diseases with Right Ventricular Predominance 442
Miscellaneous Conditions 445

24. Molecular Imaging of Vascular Disease 450
Eric A Osborn, Jagat Narula, Farouc A Jaffer

Molecular Imaging Fundamentals 450
Molecular Imaging Modalities 452
Molecular Imaging of Vascular Disease Processes 453

25. Cardiac Hemodynamics and Coronary Physiology 470
Amardeep K Singh, Andrew Boyle, Yerem Yeghiazarians

Cardiac Catheterization—The Basics 470
Catheterization Computations 472
Cardiac Cycle Pressure Waveforms 473
Hemodynamics in Valvular Heart Disease 474
Hemodynamics in Cardiomyopathy 479
Hemodynamics in Pericardial Disease 481
Coronary Hemodynamics 482

26. Cardiac Biopsy 485
Vijay U Rao, Teresa De Marco

History and Devices 485
Techniques 485
Safety and Complications 487
Analysis of EMB Tissue 487
Indications 488
Disease States 491
Cardiac Transplantation 497

27. Swan-Ganz Catheters: Clinical Applications 503
Dipti Gupta, Wassef Karrowni, Kanu Chatterjee

Historical Perspective and Evolution of Catheter Designs 503
Placement of Balloon Flotation Catheters 503
Normal Pressures and Waveforms 504
Abnormal Pressures and Waveforms 506
Clinical Applications 507
Indications for Pulmonary Artery Catheterization 512
Complications 512

28. Coronary Angiography and Catheter-based Coronary Intervention 517
Elaine M Demetroulis, Mohan Brar

Indications for Coronary Angiography 517
Contraindications for Coronary Angiography 518
Patient Preparation 518
Sites and Techniques of Vascular Access 519
Catheters for Coronary Angiography 520
Catheters for Bypass Grafts 522
Arterial Nomenclature and Extent of Disease 523
Angiographic Projections 524
Normal Coronary Anatomy 524
Congenital Anomalies of the Coronary Circulation 528
General Principles for Coronary and/or Graft Cannulation 531
The Fluoroscopic Imaging System 535
Characteristics of Contrast Media 535
Contrast-induced Renal Failure 536
Access Site Hemostasis 536
Complications of Cardiac Catheterization 537
Lesion Quantification 539
Degenerated Saphenous Vein Grafts 540
Lesion Calcification 540
Physiologic Assessment of Angiographically Indeterminate Coronary Lesions 541
Clinical Use of Translesional Physiologic Measurements 541
Non-atherosclerotic Coronary Artery Disease and Transplant Vasculopathy 542
Potential Errors on Interpretation of the Coronary Angiogram 543
Percutaneous Coronary Intervention 544
Pharmacotherapy for PCI 545
Parenteral Anticoagulant Therapy 548
Equipment for Coronary Interventions 549
Percutaneous Transluminal Coronary Angioplasty 550
Coronary Stents 550
Types of Stents 551
Stent Deployment 551
Adjunctive Coronary Interventional Devices 551
Embolic Protection Devices for Venous Bypass Graft PCI 552
Clinical Outcomes 553
Procedural Success and Complications Related to Coronary Intervention 555
Complications Specific to PCI 555

Section 4
ELECTROPHYSIOLOGY

29. Arrhythmia Mechanisms 565
Mark Anderson

Arrhythmia Initiation 565

30. Antiarrhythmic Drugs 578
Rakesh Gopinathannair, Brian Olshansky

Arrhythmia Mechanisms and Antiarrhythmic Drugs 579
Indications for Antiarrhythmic Drug Therapy 579
Proarrhythmia 579
Classification Scheme 579
Vaughan-Williams Classification 579
Miscellaneous Drugs 594
Newer Drugs 594
Emerging Antiarrhythmic Drugs 595

Antiarrhythmic Drug Selection in Atrial Fibrillation 595
Out-patient versus in-hospital Initiation for Antiarrhythmic Drug Therapy 595
Antiarrhythmic Drugs in Pregnancy and Lactation 596
Comparing Antiarrhythmic Drugs to Implantable Cardioverter Defibrillators in Patients at Risk of Arrhythmic Death 596
Antiarrhythmic Drug-device Interactions 597

31. Electrophysiology Studies 601
Indrajit Choudhuri, Masood Akhtar
Cardiac Electrophysiology Study: Philosophy, Requirements and Basic Techniques 601
Fundamentals of the Cardiac Electrophysiology Study 605
Programmed Electrical Stimulation and Associated Electrophysiology 609
Cardiac Electrophysiology Study for Evaluation of Drug Therapy 624
Electrophysiology Study to Guide Ablative Therapy 624
Complications 625

32. Syncope 627
Vijay Ramu, Fred Kusumoto, Nora Goldschlager
Epidemiology 628
Diagnostic Tests 629
Approach to the Evaluation of Syncope 638
Specific Patient Groups 639
Syncope and Driving 642

33. Atrial Fibrillation 647
Vasanth Vedantham, Jeffrey E Olgin
Definition and Classification 647
Epidemiology 647
Etiology and Pathogenesis 649
Diagnosis 652
Management 653

34. Supraventricular Tachycardia 665
Renee M Sullivan, Wei Wei Li, Brian Olshansky
Classification 665
Diagnosis 674
Treatments 678

35. Clinical Spectrum of Ventricular Tachycardia 686
Masood Akhtar
Monomorphic Ventricular Tachycardia 687
Polymorphic Ventricular Tachycardia 692

36. Bradycardia and Heart Block 698
Arthur C Kendig, James B Martins
Conduction System Anatomy and Development 698
Bradycardia Syndromes/Diseases 698
Clinical Presentation 700
Measurement/Diagnosis 700
Sinus Node Disease 700
AV Node Disease 700
Hemiblock 701
Bundle Branch Block 702
Treatment 702

37. Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy 705
Richard NW Hauer, Frank I Marcus, Moniek GJP Cox
Molecular and Genetic Background 706
Epidemiology 708
Clinical Presentation 708
Clinical Diagnosis 709
Non-classical ARVD/C Subtypes 713
Differential Diagnosis 713
Molecular Genetic Analysis 714
Prognosis and Therapy 714

38. Long QT, Short QT and Brugada Syndromes 718
Seyed M Hashemi, Peter J Mohler
LQT Syndrome 718
SQT Syndrome 722
Brugada Syndrome 724

39. Surgical and Catheter Ablation of Cardiac Arrhythmias 728
Yanfei Yang, David Singh, Nitish Badhwar, Melvin Scheinman
Supraventricular Tachycardia 728
Atrioventricular Nodal Re-entrant Tachycardia 729
Wolff-Parkinson-White Syndrome and Atrioventricular Re-entrant Tachycardia 730
Focal Atrial Tachycardia 731
Atrial Flutter 734
Ablation of Ventricular Tachycardia in Patients with Structural Cardiac Disease 736
Idiopathic Ventricular Tachycardia 744

40. Cardiac Resynchronization Therapy 758
David Singh, Nitish Badhwar
CRT: Rational for Use 758
CRT in Practice 759
Summary of CRT Benefit 761
Prediction of Response to CRT Therapy 762
Role of Dyssynchrony Imaging 764
Dyssynchrony Summary 767
LV Lead Placement 767
CRT Complications 767
Emerging CRT Indications 768

41. Ambulatory Electrocardiographic Monitoring 777
Renee M Sullivan, Brian Olshansky, James B Martins, Alexander Mazur
Holter Monitoring 777
Event Recorders 780
Mobile Cardiac Outpatient Telemetry 782
Implantable Loop Recorders 783
Key Considerations in Selecting A Monitoring Modality 783

42. Cardiac Arrest and Resuscitation 788
Christine Miyake, Richard E Kerber
Overview or Background 788
Basic Life Support 792
Advanced Cardiac Life Support 795
Cessation of Resuscitation 799
Post-resuscitation Care 800

43. Risk Stratification for Sudden Cardiac Death 804
Dwayne N Campbell, James B Martins
Healthy Athletes 804
Brugada Syndrome 805
Long QT Interval Syndrome 805
Early Repolarization 805
Short QT Syndrome 805

Catecholamine Polymorphic Ventricular Tachycardia 805
Wolff-Parkinson-White Syndrome 805
Arrhythmogenic Right Ventricular Cardiomyopathy 806
Hypertrophic Cardiomyopathy 806
Marfan Syndrome 806
Noncompaction 806
Congenital Heart Disease 806
Non-ischemic Cardiomyopathy 807
Coronary Artery Disease 807

44. Cardiocerebral Resuscitation for Primary Cardiac Arrest 811
Jooby John, Gordon A Ewy

Etiology and Pathophysiology of Cardiac Arrest 812
Drug Therapy in Cardiac Resuscitation 821
Cardiac Resuscitation Centers 822
Ending Resuscitative Efforts 823

Section 5
CORONARY HEART DISEASES

45. Coronary Heart Disease: Risk Factors 829
Bilal Aijaz, Vera Bittner

CHD Screening and Prevention 830
Clustering and Multiplicative Effects of Risk Factors 830
CHD Risk Estimation 830
Measures to Evaluate Risk Prediction Models 832
Traditional CHD Risk Factors 833
Emerging Risk Factors 838
Sub-clinical Atherosclerosis 839
Translating Risk Factor Screening into Event Reduction 840

46. Changing Focus in Global Burden of Cardiovascular Diseases 844
Rajeev Gupta, Prakash C Deedwania

CVD in High Income Countries 844
Low and Middle Income Countries 845
Risk Factors 849
Global Response for Combating CVD 850

47. Evaluation of Chest Pain 854
Kirsten E Fleischmann, Raveen Pal

Scope 854
History 854
Differential Diagnosis 854
Patient's Description 855
Angina 855
Past Medical History 856
Physical Examination 856
Investigations 858
Estimation of Risk 859
Diagnostic Testing 859

48. Acute Coronary Syndrome I (Unstable Angina and Non-ST-Segment Elevation Myocardial Infarction): Diagnosis and Early Treatment 871
Saket Girotra, Theresa M Brennan

Pathophysiology 871
Clinical Features 873
Risk Stratification—Putting it All Together to Determine the Optimal Treatment Strategy 875
Early Medical Therapy 877
Early Invasive or Initial Conservative Strategy 884
Revascularization 885

49. Acute Coronary Syndrome II (ST-Elevation Myocardial Infarction and Post Myocardial Infarction): Complications and Care 892
Theresa M Brennan, Patricia Lounsbury, Saket Girotra

Pathophysiology 893
Clinical Presentation 894
Reperfusion 902
Early Medical Therapy 906
Post Myocardial Infarction Care 909
Complications 912
Special Considerations 914
Continued Medical Therapy for Patients with A Myocardial Infarction 916
Discharge 919

50. Management of Patients with Chronic Coronary Artery Disease and Stable Angina 927
Prakash C Deedwania, Enrique V Carbajal

Current Therapeutic Approaches for Stable Angina 927
Antianginal Drug Therapy 928
Newer Antianginal Drugs 929
Combination Therapy 930
Other Drugs in Patients with Stable Angina and Chronic CAD 930
Role of Myocardial Revascularization 931
Comparison of Revascularization with Pharmacological Antianginal Therapy 931
Medical Therapy versus Percutaneous Revascularization or Strategies Comparing Invasive versus Optimal Medical Therapy 933

51. Variant Angina 938
Reza Ardehali, John Speer Schroeder

Incidence and Predisposing Risk Factors 938
Pathophysiology 939
Clinical Presentation 939
Diagnosis 940
Differential Diagnosis 942
Management 943
Natural History and Prognosis 946

52. Cardiogenic Shock in Acute Coronary Syndromes 949
Sanjay K Shah, Eugen Ivan, Andrew D Michaels

Incidence 949
Mortality 949
Predictors of Cardiogenic Shock 950
Pathophysiology 950
Pathology 951
Other Cardiac Causes of Cardiogenic Shock 951
Diagnostic Evaluation 954
Medical Management 954
Mechanical Support 954
Revascularization 957

53. Acute Right Ventricular Infarction 960
James A Goldstein

Patterns of Coronary Compromise Resulting in RVI 960

Right Ventricular Mechanics and Oxygen Supply-demand 961
Effects of Ischemia on RV Systolic and Diastolic Function 961
Determinants of RV Performance in Severe RVI 961
Natural History of Ischemic RV Dysfunction 962
Effects of Reperfusion on Ischemic RV Dysfunction 963
Rhythm Disorders and Reflexes Associated with RVI 964
Mechanical Complications Associated with RVI 964
Clinical Presentations and Evaluation 964
Noninvasive and Hemodynamic Evaluation 965
Differential Diagnosis of RVI 965
Therapy 965

54. Surgical Therapy in Chronic Coronary Artery Disease 969
Joss Fernandez, Samad Hashimi, Karam Karam, Jose Torres, Robert Saeid Farivar
Technique of Surgical Therapy for Chronic Coronary Artery Disease 969
Indications for Surgical Coronary Revascularization Advantages of CABG Over Medical Treatment 970
Comparing CABG to PTCA 971
The Changing CABG Population 971
When CABG may be Indicated 971
When CABG is not Indicated 972
Risk Factors for in-hospital Mortality Following CABG 972
Outcomes of Surgery 975
Major Clinical Trials in Chronic Coronary Artery Disease 976

Volume 2

Section 6
VALVULAR HEART DISEASES

55. Aortic Valve Disease 985
Blase A Carabello
Aortic Stenosis 985
Aortic Regurgitation 992

56. Mitral Valve Disease 1000
Satyavan Sharma, Bharat V Dalvi
Normal Mitral Valve Morphology and Function 1000
Global Burden of Rheumatic Heart Disease 1000
Mitral Stenosis 1001
Mitral Regurgitation 1007

57. Tricuspid Valve Disease: Evaluation and Management 1018
Pravin M Shah
Embryology 1018
Valve Anatomy 1019
Normal Tricuspid Valve Function 1019
Tricuspid Valve Dysfunction 1019
Clinical Presentation 1021
Laboratory Diagnosis 1021
Treatment 1023

58. Congenital Pulmonic Stenosis 1028
Jullien Hoffman
Valvar Pulmonic Stenosis 1028
Isolated Infundibular Stenosis 1034
Supravalvar Stenosis 1035

59. Catheter-based Treatment of Valvular Heart Disease 1040
Hjalti Gudmundsson, Philip A Horwitz
Catheter-based Treatment of Mitral Valve Disease 1040
Catheter-based Treatment of Pulmonary Valve Disease 1044
Percutaneous Tricuspid Balloon Valvuloplasty 1045
Catheter-based Therapies for Aortic Stenosis 1045
Summary/Future Directions 1048

60. Infective Endocarditis 1052
Ehrin J Armstrong, Ann Bolger, Henry F Chambers
Epidemiology 1052
Pathogenesis 1054
Microbiology 1057
Patient Presentation and Diagnosis 1059
Management 1062

61. Prosthetic Heart Valves 1072
Byron F Vandenberg
Risk of Valve Replacement 1072
Types of Prosthetic Valves 1073
Selecting the Optimal Prosthesis 1079
Prosthesis-patient Mismatch 1081
Long-term Management 1084
Long-term Complications 1090

62. Antithrombotic Therapy in Valvular Heart Disease 1098
Michael H Crawford
General Considerations 1098
Prophylactic Antithrombic Therapy 1099
Native Valvular Heart Disease 1100
Rheumatic Valvular Heart Disease 1100
Mitral Valve Prolapse 1100
Calcified or Degenerative Valvular Disease 1100
Prosthetic Valves 1100
Bioprosthetic Valves 1101
Valvuloplasty and Valve Repair 1101
Management Issues 1101

Guidelines for Valvular Heart Diseases 1104

Section 7
VASCULAR DISEASES

63. Evaluation and Management of the Patient with Essential Hypertension **1129**
Edward D Frohlich

Evaluation of the Patient with Hypertension 1129
Antihypertensive Therapy 1133
Hemodynamic Concepts 1135
Clinical Pharmacologic Concepts 1136
Treatment Algorithms Advocated Over the Years 1142

64. Peripheral Vascular and Cerebrovascular Disease **1145**
Babak Haddadian, Suhail Allaqaband, Tanvir Bajwa

Peripheral Arterial Disease 1145
Carotid Artery Disease 1155
Renal Artery Stenosis 1157
Subclavian Artery Stenosis 1159
Vertebrobasilar Artery Stenosis 1160
Mesenteric Ischemia 1160

65. Aortic Dissection **1166**
Ariane Neyou

Predisposing Factors 1166
Classification 1168
Clinical Manifestations 1169
Diagnosis 1170
Treatment 1171

66. Endovascular Treatment of Aortic Aneurysm and Dissection **1175**
AM Timothy, DM Chuter

History of Endovascular Aortic Repair 1176
Stent Graft Design: The Lessons of Experience 1176
Anatomic Substrate for Endovascular Aneurysm Repair 1177
Current Stent Graft Designs for Abdominal Aortic Aneurysm (AAA) 1177
Adjunctive Devices and Techniques 1178
Endoleak 1179
Late-occurring Complications of Endovascular Aneurysm Repair 1179
Follow-up Imaging 1180
Branched and Fenestrated Stent Grafts 1180
Current Thoracic Aortic Stent Graft Designs 1181
Endovascular Repair of Thoracic Aortic Aneurysms 1181
Thoracic Aortic Dissection 1181
Acute Type B Dissection 1182
Chronic Type B Dissection 1183
Complications of Thoracic Endovascular Aortic Repair 1184
Intramural Hematoma 1185
Penetrating Aortic Ulcer 1185

67. Autonomic Dysfunction and the Cardiovascular System **1187**
Milena A Gebska, Christopher J Benson

Autonomic Regulation of the Cardiovascular System 1187
Autonomic Testing 1190
Primary Chronic Autonomic Failure 1193
Secondary and Congenital Autonomic Failure 1194
Chronic Orthostatic Intolerance 1195
Syndromes Associated with Episodic Autonomic Failure 1197
Autonomic Perturbations Associated with Cardiovascular Conditions 1198

Section 8
HEART FAILURE

68. Heart Failure: Epidemiology **1207**
Kanu Chatterjee

Epidemiology 1207
Prevalence 1207
Incidence 1209
Secular Trends 1211

69. Heart Failure: Diagnosis **1213**
Kanu Chatterjee

Analysis of Symptoms 1213
Physical Examination 1214
Electrocardiogram 1215
Chest Radiograph 1218
Echocardiography 1218
Radionuclide Ventriculography 1219
Cardiac Magnetic Resonance 1220
Cardiac Tomography 1220
Routine Laboratory Tests 1221
Biomarkers 1221
Exercise Tests 1223
Six-minute Walk Test 1224
Coronary Arteriography 1224
Myocardial Ischemia 1224
Endomyocardial Biopsy 1224
Genetics Studies 1225

70. Systolic Heart Failure (Heart Failure with Reduced Ejection Fraction) **1228**
Kanu Chatterjee

Historical Perspective 1228
Ventricular Remodeling 1229
Functional Derangements and Hemodynamic Consequences 1235
Initial Treatment of Systolic Heart Failure 1235
Symptomatic Systolic Heart Failure 1237
Follow-up Evaluation 1245

71. Diastolic Heart Failure (Heart Failure with Preserved Ejection Fraction) **1251**
Kanu Chatterjee

Definition 1251
Epidemiology 1251
Pathophysiology 1252
Clinical Presentation 1255
Diagnosis 1256
Prognosis 1256
Treatment Strategies 1258
Future Directions 1261

72. Anemia in Patient with Chronic Heart Failure (Prevalence, Mechanism, Significance and Treatment) **1264**
James Prempeh, Barry M Massie

Overview of the Problem 1264

Prevalence of Anemia in Heart Failure Patients 1264
Mechanisms Underlying Anemia in Heart Failure Patients 1264
Prognostic Significance of Anemia in Heart Failure Patients 1265
Should Anemia be Treated in Heart Failure Patients? 1265
Safety Concerns Related to ESPS in A Variety of Anemic Patients 1266
Treatment of Anemia in Heart Failure Patients 1266

73. Hyponatremia and Congestive Heart Failure 1272
Anne Mani, David J Whellan

Mechanisms Causing Hyponatremia and Heart Failure 1274
Treatment of Hyponatremia 1276
Role of Diuretic Therapy in Hyponatremia 1276
Role of Vasopressin Receptor Antagonists in Hyponatremia 1277
Tolvaptan 1277
Lixivaptan 1278
Conivaptan 1279

74. Cardiorenal Syndrome: The Interplay between Cardiac and Renal Function in Patients with Congestive Heart Failure 1281
Nestor Mercado, J Thomas Heywood

Epidemiology of Chronic Kidney Disease in Patients with Heart Failure 1281
Prognosis of Worsening Renal Function 1282
Definition of the Cardiorenal Syndrome 1283
Pathophysiology of the Cardiorenal Syndrome 1286
Role of Decreased Cardiac Output 1286
Role of Elevated Central Venous Pressure 1287
Role of Evidence-based Therapies in Patients with Heart Failure and the Cardiorenal Syndrome 1288
Role of Ultrafiltration on Diuretic Resistance and the Cardiorenal Syndrome 1292
Treatment of the Cardiorenal Syndrome: An Approach to the Individual Patient 1292

75. Acute Heart Failure Syndromes 1298
Peter S Pang, Michel Komajda, Mihai Gheorghiade

Definition 1298
Epidemiology 1298
Patient's Characteristics 1298
Classification 1299
Pathophysiology 1300
Acute Heart Failure Syndromes Management 1301
Clinical Trials in Acute Heart Failure Syndromes 1306

76. Cardiopulmonary Exercise Testing and Training in Heart Failure 1312
Ileana L Piña

Normal Response to Exercise 1312
Exercise Response in Heart Failure 1313
Cardiopulmonary Exercise Testing 1314
Indications for CPX Testing in Heart Failure 1316
Exercise Training in Heart Failure 1318

77. Hibernating Myocardium 1323
Kanu Chatterjee

Historical Perspective 1323
Definition 1323
Pathophysiology 1324
Hibernation and Stunning: Clinical Prevalence 1325
Detection of Hibernating Myocardium 1325
Revascularization of Hibernating Myocardium and Changes in Ventricular Function 1328
Revascularization of Hibernating Myocardium and Changes in Prognosis 1328

78. Advanced Cardiac Therapies for End Stage Heart Failure: Cardiac Transplantation and Mechanical Circulatory Support 1334
Ashrith Guha, Frances Johnson

Identifying Candidates for Advanced Cardiac Therapies 1335
Heart Transplantation 1338
Mechanical Circulatory Support 1343

79. Palliative Medicine and End of Life Care in Heart Failure 1352
KellyAnn Light-McGroary

Epidemiology of Heart Failure 1352
Economic Impact of Heart Failure 1352
History of Palliative Care/Definitions 1353
Feasibility of the Use of Palliative Care in Heart Failure 1354
Issues of Prognostication 1355
Communication and Patient's Understanding of their Disease 1355
Suffering in End Stage Heart Failure 1357
Symptom Management in Heart Failure 1357
Management of Implantable Cardiac Devices 1360

Guidelines for Heart Failure 1366

Section 9
MYOCARDIAL AND PERICARDIAL DISEASES

80. Hypertrophic Cardiomyopathy 1377
M Fuad Jan, A Jamil Tajik

Definition 1377
Epidemiology and Genetic Considerations 1377
Pathology 1379
Pathophysiology 1381
Clinical Presentation 1387
Diagnosis 1390
Natural History 1400
Management 1402
Additional Points of Interest 1412

81. Dilated Cardiomyopathy 1424
Jalal K Ghali

Definition 1424
Epidemiology 1425
Pathology 1425
Etiology 1425
Prognosis 1430
Predictors of Mortality 1430

82. Restrictive and Obliterative Cardiomyopathies 1439
G Vijayaraghavan, S Sivasankaran

Restrictive Cardiomyopathies 1440

Tropical Endomyocardial Fibrosis (Davie's Disease) 1442
Right Ventricular Endomyocardial Fibrosis 1444
Left Ventricular Endomyocardial Fibrosis 1446
Loeffler's Endocarditis 1449
Hemochromatosis 1450
Idiopathic Restrictive Cardiomyopathy 1451
Other Forms of Cardiomyopathies 1452

83. Amyloid Heart Disease 1454
Eveline Oestreicher Stock, Dana McGlothlin

History of Amyloid 1454
Amyloidogenesis 1455
Overview of Cardiac Amyloidosis 1456
Classification of Amyloidosis 1456
Cardiac Amyloidosis 1456
Clinical Features of Cardiac Amyloidosis 1459
Treatment of Amyloid Cardiomyopathy 1464

84. Peripartum Cardiomyopathy 1473
Uri Elkayam, Nudrat Khatri, Mohamad Barakat

Definition 1473
Incidence 1473
Etiology 1473
Risk Factors 1473
Clinical Presentation 1473
Prognosis 1474
Treatment 1475
Labor and Delivery 1475

85. Chemotherapy-induced Cardiomyopathy 1479
Wassef Karrowni, Kanu Chatterjee

Classification of Chemotherapy-induced Cardiotoxicity 1479
Risk Factors 1480
Pathophysiology of Anthracycline-induced Cardiomyopathy 1480
Mechanism of Chemotherapy-induced Cardiac Dysfunction 1482
Diagnosis 1483
Monitoring 1484
Management 1484
Treatment 1486

86. Pericardial Diseases 1489
Masud H Khandaker, Rick A Nishimura

Acute Pericarditis 1489
Chronic Relapsing Pericarditis 1491
Pericardial Effusion and Pericardial Tamponade 1493
Constrictive Pericarditis 1496

87. Radiation-induced Heart Disease 1505
Wassef Karrowni, Kanu Chatterjee

Radiation-induced Pericardial Disease 1505
Radiation-induced Myocardial Disease 1506
Radiation-induced Coronary Artery Disease 1507
Radiation-induced Valvular Heart Disease 1508
Conduction System Disease 1509
Carotid and Other Vascular Disease 1509
Prevention 1509

88. Chagas Disease 1513
Diane C Kraft, Richard E Kerber

Life Cycle 1513
Transmission 1513
Epidemiology 1513
Clinical Manifestations 1513
Echocardiography 1516
Cardiac Magnetic Resonance Imaging 1516
Treatment 1516
Prevention 1517
Chagas Disease in the United States 1517

Section 10
PULMONARY VASCULAR DISEASE AND ADULT CONGENITAL HEART DISEASE

89. Pulmonary Arterial Hypertension 1521
Dana McGlothlin, David MaJure

Definitions and Classifications 1521
Pathophysiology and Epidemiology of Pulmonary Arterial Hypertension 1524
Diagnostic Evaluation 1528
Survival and Prognostic Factors of Pulmonary Arterial Hypertension 1535
Therapeutic Options for the Treatment of Pulmonary Arterial Hypertension 1536
Treatment Algorithm and Evaluating Response to Therapy 1541
Therapy of Decompensated Right Heart Failure in Pulmonary Arterial Hypertension 1542

90. Congenital Heart Disease in the Adult Patient 1550
Deepa Upadhyaya, Elyse Foster

Acyanotic Heart Disease 1551
Congenital Valvar Aortic Stenosis 1551
Supravalvar Aortic Stenosis and Subvalvar Aortic Stenosis 1554
Coarctation of the Aorta 1554
Right Ventricular Outflow Tract Obstruction 1557
Valvar Pulmonic Stenosis 1557
Subvalvar and Supravalvar Pulmonic Stenosis 1559
Atrial Septal Defects 1559
Ventricular Septal Defects 1562
Patent Ductus Arteriosus 1566
Other Acyanotic Lesions 1568
Ebstein's Anomaly 1568
Cyanotic Congenital Heart Disease 1570
Palliative Shunts 1571
Endocarditis 1572
Pregnancy and Contraception 1572
Tetralogy of Fallot 1572
Truncus Arteriosus 1577
D-transposition of the Great Arteries 1578
Congenitally Corrected Transposition of the Great Arteries 1582
Total Anomalous Pulmonary Venous Return 1583
Double-outlet Right Ventricle 1584
Tricuspid Atresia/Univentricular Heart 1586
Double-inlet Left Ventricle 1587
Hypoplastic Left Heart 1588
Eisenmenger's Syndrome 1589

Section 11
SECONDARY DISORDERS OF THE HEART

91. Alcohol and Arrhythmia 1595
Mary Gray

Direct Effects of Ethanol Exposure on Heart Cells and Tissues 1595

Ethanol Ingestion and the Normal Cardiac Conduction System 1595
Binge Drinking and Transient Clinical Arrhythmias—Holiday Heart 1596
Alcohol Consumption, Chronic Atrial Fibrillation and Atrial Flutter 1596
Alcohol Consumption and Sudden Cardiac Death 1597
Summary and Clinical Guidelines 1598

92. Insulin-resistance and Cardiomyopathy 1600
Dipanjan Banerjee, Ronald Witteles, Michael B Fowler
Epidemiology 1600
Diastolic Heart Failure and Insulin-resistance 1601
Pathophysiology 1602
Myocardial Energy Metabolism 1602
Metabolic Effects of Insulin Resistance—Energy Metabolism 1603
Other Metabolic Effects of Insulin-resistance 1604
Detection of Metabolic Effects of Insulin-resistance 1604
Structural Effects of Insulin-resistance 1605

93. Cardiac Complications of Substance Abuse 1613
Hugh H West
Magnitude of the Problem 1614
Substances of Abuse 1615
Marijuana, Tetrahydriocannabinol, Hashish 1624
Club Drugs: MDMA, GHB, Ketamine, Rohypnol 1625
Hallucinogenic Drugs 1627
Body Image Drugs 1627
Inhalants 1628
Narcotics 1629
Prescription and Over the Counter Drugs 1630
Alcohol and Tobacco 1631

94. HIV/AIDS and Cardiovascular Disease 1636
Jennifer E Ho, Priscilla Y Hsue
HIV and Coronary Heart Disease 1636
Surrogate Measures of Atherosclerosis 1641
Other Cardiovascular Conditions 1641

95. Systemic Autoimmune Diseases and the Heart 1648
Tamara Nelson, Jonathan L Halperin, Scott A Vogelgesang
Rheumatoid Arthritis 1648
Spondyloarthropathies 1651
Polymyositis-dermatomyositis 1653
Mixed Connective Tissue Disease 1654
Systemic Lupus Erythematosus 1654
Antiphospholipid Antibody Syndrome 1656
Coronary Arteritis 1656
Polyarteritis Nodosa 1656
Kawasaki Disease 1657
Churg-Strauss Vasculitis 1657
Wegener's Granulomatosis 1658
Giant Cell Arteritis 1658
Takayasu's Arteritis 1658

96. Cardiac Neoplastic Disease 1663
Elena Ladich, Naima Carter-Monroe, Renu Virmani
Clinical Symptoms 1663
Imaging Techniques 1665
Benign Cardiac Neoplasms 1667
Malignant Tumors 1675
Other Sarcomas 1681

97. Neurogenic and Stress Cardiomyopathy 1689
Hoang Nguyen, Ahsan Chaudhary, Kunal Mehtani, Stefanie Kaiser, Jonathan Zaroff
Neurogenic Cardiomyopathy 1689
Stress Cardiomyopathy 1693

98. Kidney and the Heart 1697
Mony Fraer
Definition 1697
Epidemiology 1697
Pathophysiology 1698
Cardiovascular Risk Factors in Chronic Kidney Disease 1698
Spectrum of Cardiovascular Disease in Chronic Kidney Disease 1700
Diagnostic Tests 1703
Principles of Treatment of Cardiovascular Disease 1704
Kidney Transplant Recipients 1704

99. Endocrine Heart Disease 1713
Aarthi Arasu, Umesh Masharani
Diabetes Mellitus 1713
Thyroid Disease 1716
Pituitary Disorders 1718
Adrenal Disorders 1720
Parathyroid Disorders 1722
Carcinoid Syndrome 1723

100. Cardiovascular Trauma as Seen by the Cardiologist 1729
Arthur Hill, Melvin D Cheitlin
History 1729
Classification and Physics of Traumatic Injury to the Cardiovascular System 1730
Classifying the Pathology of Cardiac Trauma 1731
Management of the Acutely Injured Patient with Thoracoabdominal Injury 1731
Intracardiac Injuries From Both Penetrating Wounds and Blunt Cardiac Injury 1737

101. Venous Thromboembolism and Cor Pulmonale 1750
Jorge Velazco, Christopher Spradley, Bernardo Menajovsky, Alejandro C Arroliga
Venous Thromboembolism 1750
Cor Pulmonale 1763

Section 12
RELEVANT ISSUES IN CLINICAL CARDIOLOGY

102. Noncardiac Surgery in Cardiac Patients 1773
Gabriel Gregoratos, Ameya Kulkarni
Preoperative Cardiac Risk Assessment 1773
Preoperative Diagnostic Testing 1778
Preoperative Risk Mitigation Strategies 1780
Intraoperative Management 1786
Management of Patients with Implanted Electronic Devices 1787

Postoperative Management 1788
Appendix 1789

103. Gender and Cardiovascular Disease **1798**
Susan Zhao, Rita Redberg

Prevalence of IHD in Women 1798
Identification and Management of IHD Risk Factors in Women 1799
Assessment of Symptoms and Myocardial Ischemia in Women 1802
Management of IHD in Women 1806
Heart Failure in Women 1809
Sex and Cardiac Arrhythmias 1812
Call for More Sex-specific Research 1813

104. Overview of the Athlete's Heart **1818**
Aaron L Baggish, Paul D Thompson

Historical Perspective 1818
Exercise Physiology and the Athlete's Heart: Overview 1818
Exercise-induced Cardiac Remodeling 1819
Issues Relevant to the Cardiovascular Care of Athletes 1821

105. Cardiovascular Aging **1829**
John A Dodson, Mathew S Maurer

Age-related Changes 1830
Clinical Syndromes 1834
Special Issues 1839

Section 13
PREVENTIVE STRATEGIES FOR CORONARY ARTERY DISEASES

106. Pathophysiology of Atherothrombosis **1847**
PK Shah

Sites of Predilection for Atherosclerosis 1847

107. Dyslipidemia **1856**
Mary Malloy, John Kane

Lipid Transport and Lipoprotein Metabolism 1856
Diagnosis of the Dyslipidemias 1859
Hyperlipoproteinemia 1859
Hypoalphalipoproteinemia 1863
Other Management Considerations 1863

108. Smoking and Air Pollution **1873**
Joaquin Barnoya, Ernesto Viteri, Stanton A Glantz

Epidemiology of Smoking and Exposure to Second-hand Smoke 1874
Active Smoking and Cardiovascular Disease 1874
Second-hand Smoke and Cardiovascular Disease 1875
Low-tar ("Light") Cigarettes 1876
Pathophysiology of Tobacco Smoke and Cardiovascular Disease 1876
Smoking Cessation 1879
Smoke-free Environments and Their Effect on Heart Attack Admissions 1883
Similar Effects and Mechanisms of Particulate Air Pollution 1883
Cardiologists as Tobacco Control Advocates 1884

109. Exercise and Rehabilitation **1890**
Lisa Bauer, Patrick McBride

Exercise: Definitions 1890
Exercise: Recommendations 1891
Responses to Exercise 1891
Benefits of Exercise 1891
Exercise Capacity 1891
Inflammation and Endothelial Function 1891
Safety Considerations 1892
Cardiac Rehabilitation Definition and Goals 1892
Cardiac Rehabilitation Phases 1892
Cardiac Rehabilitation Core Components 1893
Clinical Population Considerations 1895
Referral 1895
Reimbursement Issues 1895

Section 14
PREVENTIVE STRATEGIES FOR OTHER CARDIOVASCULAR DISEASES

110. Prevention of Heart Failure **1899**
Clay A Cauthen, WH Wilson Tang

Introduction 1899
Staging of Heart Failure 1899
Future Perspectives 1905

111. Stroke: Prevention and Treatment **1908**
Harold P Adams

Introduction 1908
Definitions 1908
Stroke as a Symptom 1909
Prevention 1916
General Acute Treatment 1919
Treatment of Acute Ischemic Stroke 1920
Treatment of Acute Hemorrhagic Stroke 1922
General in-hospital Care 1923
Rehabilitation 1924

112. Rheumatic Fever **1927**
V Jacob Jose

Pathogenesis 1927
Epidemiology 1928
Diagnosis of Rheumatic Fever 1928
Clinical Features 1929
Treatment 1931
Residual Heart Disease 1933
Management of Chorea 1933

Section 15
EVOLVING CONCEPTS

113. The Genomics of Cardiovascular Disease **1937**
Samir B Damani, Eric J Topol

A Genomic Primer 1937
Intermediate Phenotypes 1940
Coronary Artery Disease 1941
Arrhythmias 1942
Cardiovascular Pharmacogenomics 1943

SNP Profiling Studies 1946
Future Directions 1947

114. Cardiovascular Pharmacogenetics 1951
Deepak Voora, Victor J Dzau, Geoffrey S Ginsburg

Principles of Pharmacogenetics 1951
hMG-CoA Reductase Inhibitors 1953
Thienopyridines 1956
Aspirin 1958
Warfarin 1958
Diuretics 1960
Beta-blockers 1960
Antiarrhythmic Drugs 1962
Future Directions 1963

115. Preventing Errors in Cardiovascular Medicine 1969
Robert M Wachter

Modern Approach to Patient Safety 1969
How to Improve Patient Safety? 1970
Communication and Culture 1971
Learning from Mistakes 1972
Creating a Safe Workforce 1973
Preventing Diagnostic Errors 1973
What Can Patients do to Keep Themselves Safe? 1973
Changing Policy Context for Patient Safety 1973

116. Economics in Cardiovascular Medicine 1976
Paul A Heidenreich

Cost of Cardiovascular Care 1976
Trends in Health Expenditures (US versus Non-US) 1976
CV Contribution to the Rising Cost of Care 1977
Variation in Resource Use 1977
Resource Scarcity and Value 1977
Basic Concepts of Health Economics 1978
Benchmarks for Cost-effectiveness 1979
Evaluating Uncertainty 1979
Perspective 1980
Efficiency 1980
Government's Use of Cost-effectiveness 1980
Cost-effectiveness of Individual Treatments and Strategies 1981
Cost-effectiveness of Quality Improvement Interventions 1982
Future Estimates of the Cost of Heart Disease 1983

117. Stem Cell Therapy in Cardiology 1986
Franca S Angeli, Yerem Yeghiazarians

Stem Cell 1986
Skeletal Myoblast 1989
Adipose Tissue Derived Stem Cells 1989
Cardiac Stem Cells 1989
Fetal and Umbilical Cord Blood Cells 1989
Induced Pluripotent Stem Cells 1991
Stem Cell Clinical Trials 1991
Conclusion and Future Directions 1997

118. Gene Therapy and Angiogenesis 2003
Matthew L Springer

Gene Therapy Overview 2003
Basic Concepts of Angiogenesis 2007
Angiogenic Protein Therapy 2011
Angiogenic Gene Therapy 2011
Gene Therapy for Chronic Heart Failure 2014

119. Sleep and the Heart 2020
Tomas Konecny, Virend Somers

Physiologic Sleep 2020
Effects of Non-rapid Eye Movement Sleep on Cardiovascular Physiology 2020
Effects of Rapid Eye Movement Sleep on Cardiovascular Physiology 2020
Arousal 2021
Arrhythmias and Sleep 2021
Sleep Disordered Breathing 2022
Diagnosis of Sleep Apnea 2026
Treatment of Obstructive Sleep Apnea 2027
Central Sleep Apnea 2028

120. Integrative Cardiology: The Use of Complementary Therapies and Beyond 2031
Kevin Barrows

Non-conventional Therapies and Cardiology 2031
What Is Integrative Medicine? 2031
What Is Integrative Cardiology? 2032
Lifestyle Heart Trial 2032
What Other Integrative Medicine Therapies are Effective for Cardiovascular Conditions? 2032
Dyslipidemia 2032
Hypertension 2037
Coronary Artery Disease 2040
Heart Failure 2044
Botanical Medicines with Adverse Cardiovascular Effects 2047

Section 1

BASIC CARDIOLOGY

Chapter 1

Cardiac Anatomy

Melvin D Cheitlin, Philip C Ursell

Chapter Outline

- Pericardium and Heart in the Mediastinum
- Cardiac Surface Anatomy
- Internal Structure of the Heart
- Right Atrium
- Tricuspid Valve
- Right Ventricle
- Pulmonic Valve
- Pulmonary Arteries
- Left Atrium
- Mitral Valve
- Left Ventricle
- Aortic Valve
- Conduction System
- Coronary Arteries
- Intramural Vessels
- Coronary Veins
- Cardiac Lymphatics
- Cardiac Innervation

INTRODUCTION

Knowledge of the intimate anatomy of the heart was mostly of academic interest, known mainly to anatomists and pathologists, until nearly the middle of the 20th century. From the late 19th century, the heart could be imaged by the chest X-ray as a shadow projection on a 2-dimensional plane from several angles. Only the outline of the heart projected against the more radiolucent lungs is discernable by this method, and estimates of chamber enlargement can be made if the increased dimensions are prominent enough. For surgeons operating inside the heart, however, this 2-dimensional representation was not good enough.

With the advent of cardiac catheterization and angiocardiography in clinical practice in the mid-20th century, knowledge of internal cardiac anatomy became essential both to the cardiac surgeons and to the cardiologists. From the 1970s the utility of echocardiography as a diagnostic tool necessitated a detailed understanding of the 3-dimensional anatomy of the heart by all cardiologists and even physicians in many other fields. Shortly thereafter development of computed tomography and magnetic resonance imaging enabled 3-dimensional reconstruction of the heart, one layer at a time, so that the detailed internal anatomic structures could be visualized with a precision approaching that seen by anatomic dissection.

Knowledge of the intimate relationships of the internal structure of the heart permits the clinician to explain pathologic complications that occur during cardiac disease. For instance, the proximity of the aortic annulus to the conduction system (atrioventricular or His bundle passing through the right fibrous trigone) explains the common complication of various degrees of heart block in the patient with infective endocarditis and ring abscess. Similarly, calcification of the valvular annuli commonly associated with advanced age can lead to conduction system disorders, and aortic valve surgery for calcific aortic stenosis can be complicated by heart block and bundle branch block. Further, the proximity of structures to the sinuses of Valsalva can explain the development of fistulous communications following rupture of a sinus of Valsalva aneurysm or outflow tract fistulas after penetrating injury to the heart.

Instead of describing every aspect of cardiac anatomy in exhaustive detail as is done in many anatomy textbooks, this chapter describes the features of cardiac anatomy that are of particular importance to the clinician. It focuses on details that aid in understanding the cardiac anatomy visualized in the various diagnostic imaging techniques, in devising cardiac interventional procedures and in explaining the complications seen in patients with cardiac disease. Unless otherwise noted, the dimensions listed apply to normal adult human hearts of average size.

PERICARDIUM AND HEART IN THE MEDIASTINUM

The most anterior structure in the anterior mediastinum is the thymus gland remnant, anterior to the ascending aorta. Deep to the thymus is the pericardial sac containing the heart. Even when enclosed by the sac, the position and shape of the heart is discernible in the opened thorax. The heart essentially is a conical structure composed of layers of myocardium enclosing the atrial and ventricular chambers. The atrial and ventricular walls are anchored to the fibrous atrioventricular valve annuli. The aorta and main pulmonary artery arise from their respective fibrous valve rings, and these four fibrous rings together are termed the fibrous skeleton of the heart.

Located in the central chest, the heart within the pericardial sac resides in the middle mediastinum, with two-thirds of its volume to the left and one-third to the right of center (Fig. 1). The parietal pleura lie completely adjacent to the right and left lateral pericardium, so that only a small retrosternal portion of heart anteriorly on the left is uncovered by pleura. The two phrenic nerves pass through the middle mediastinum on the right and left surfaces of the pericardial sac, slightly posteriorly. The position of the phrenic nerves limits the extent of pericardiectomy done for constrictive pericarditis. Injury to the phrenic nerves can also occur during open-heart surgery, causing diaphragmatic paralysis and great difficulty in ventilating the patient postoperatively. The esophagus passes posterior to the heart, close to the left atrium. Superior and posterior to the left atrium is the bifurcation of the trachea. In the early days of catheterization, the left mainstem bronchus lying on the left atrium provided bronchoscopic access to the left atrium via needle puncture through the bronchus.

The myocardial wall consists of three layers: (1) the epicardium; (2) the myocardium and (3) the endocardium. The epicardium is comprised of a fatty connective tissue layer subjacent to the visceral pericardium. The myocardium comprises the bulk of the heart wall consisting of interdigitating layers of myocardial cells with accompanying vasculature and lymphatics. The endocardium consists of a thin layer of fibrocellular connective tissue with a single layer of endothelial cells lining the chambers of the heart. Developmentally, the growing heart in the embryo invaginates the pericardial sac, so that the mature heart becomes suspended only by the reflections of pericardium around the great vessels. These attachments of pericardial reflections form the dorsal mesocardium, one site at the sinoatrial surface around the venous inlets into the atria and the other at the great arteries as they exit the ventricles to form an arterial or conotruncal mesocardium. The autonomic nerves to the heart enter through these mesocardial attachments.

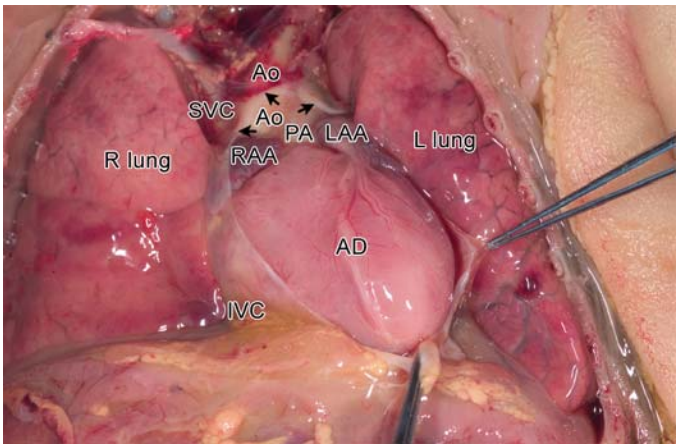


FIGURE 1: Pericardial sac and the cardiac silhouette. In the open thorax of a newborn infant, the parietal pericardium is reflected to expose the epicardial surface, showing the majority of the heart located to the left of the midline. The pericardial reflection over the great arteries (arrows) shows that portions of these vessels lie within the pericardial sac. Although the atrial appendages are the only portion of atriums visible, the anterior aspect of the ventricular surfaces are shown with the anterior descending branch of the left coronary artery as the landmark delimiting the interventricular septum. The connections of the superior vena cava (SVC) and inferior vena cava (IVC) with the right atrium are aligned vertically. (Abbreviations: AD: Anterior descending coronary artery; Ao: Ascending aorta; L: Left; LAA: Left atrial appendage; PA: Main pulmonary artery; R: Right; RAA: Right atrial appendage)

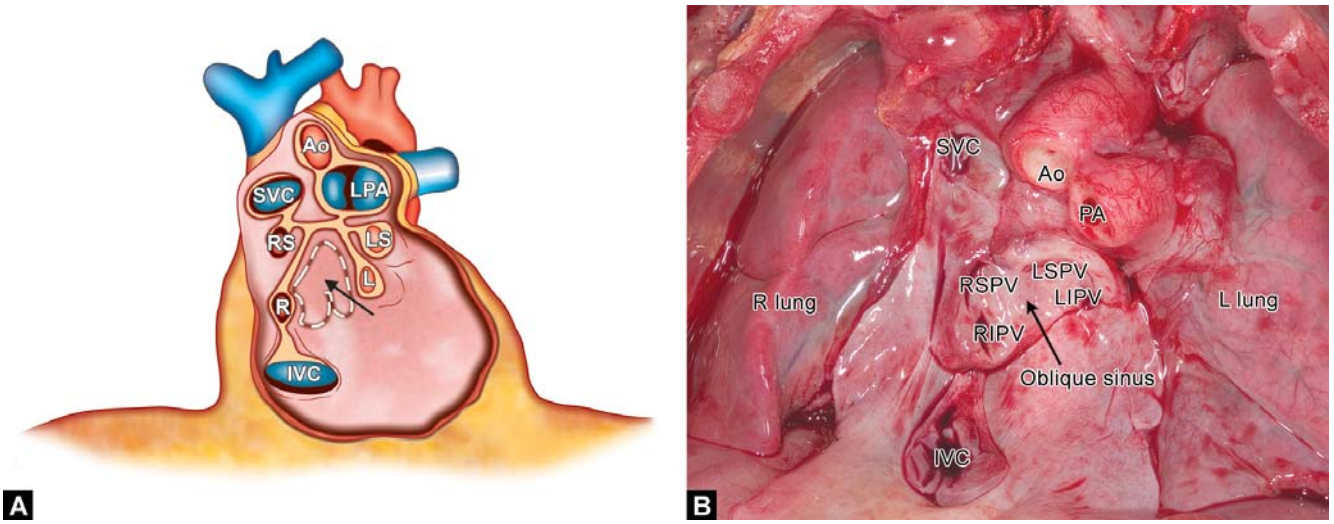
Although the parietal pericardium is fixed in position by attachments to the sternum anteriorly and diaphragm inferiorly, the heart suspended at the pericardial reflections is somewhat moveable within the pericardial space; the pericardial surfaces are lubricated by a small amount of serous fluid to reduce friction during systole and diastole. Other functions of the pericardium are: (1) to isolate the heart from mediastinal and pulmonary infection and (2) to stabilize the heart in the mediastinum with changes in body position or more violent trauma. The reflections of the pericardium on the great vessels are such that two-thirds of the ascending aorta and the main pulmonary artery are intrapericardial (Fig. 1). The pericardial reflections at the great veins place half of the superior vena cava and only a short segment of inferior vena cava within the pericardial sac.

Many pericardial recesses are formed as a result of the pericardial reflections around the great vessels (Figs 2A and B). One such recess is formed on the inferoposterior surface of the heart by the continuous reflection from the inferior vena cava to each of the right pulmonary veins and leftward to the left pulmonary veins. This semicircle of pericardial reflection encloses a small recess within the posteroinferior pericardial sac known as the oblique sinus. A larger recess within the pericardial sac is that potential space between the great arteries superiorly and the atria inferiorly, the transverse sinus (Fig. 3).

The clinical importance of these pericardial reflections is apparent in the high mortality rate seen in rupture of the ascending aorta (type A aortic dissection). Since the ascending aorta is mostly intrapericardial (Fig. 1), aortic rupture results in hemorrhage into the pericardial space. The normal pericardium is fibrous and relatively noncompliant, and sudden increases in intrapericardial volume may rapidly produce cardiac tamponade. Type B aortic dissection involves the descending aorta distal to the take-off of the left subclavian artery, so rupture and hemorrhage are contained by the posterior mediastinal structures and the pleura which almost completely surrounds the aorta. This type of dissection is less likely to be rapidly fatal.

The pericardial blood supply derives from the internal mammary arteries, which pass posterior to the rib cage 0.5 cm lateral to the right and left sternal borders. On reaching the diaphragm, the internal mammary arteries divide into the musculophrenic and the superior epigastric branches. Other blood supply to the pericardium is supplied by the intercostals, subclavian and posterior mediastinal arteries. In the pericardial reflections at the root of the great arteries are small connections between the epicardial coronary arteries and the internal mammary arteries; before the development of coronary bypass surgery, these connections were the basis for a fanciful idea of ligating the internal mammary arteries in patients with coronary artery disease to divert blood to the coronary arteries, a procedure that was proved ineffective.

The thoracic cage is supplied by blood from the intercostal arteries arising from the descending aorta and from the internal mammary arteries anteriorly. The veins of the thoracic cage follow the arterial distribution. The ten lower intercostal veins on the right enter the azygous vein that passes superiorly and anteriorly to connect with the superior vena cava (Fig. 4A).



FIGURES 2A AND B: Pericardial reflections and the oblique sinus. The neonatal heart has been removed from the thorax to show the pericardial reflections around the great veins and the pulmonary veins posteriorly. A reflection of pericardium extends between the vertically aligned superior vena cava (SVC) and the inferior vena cava (IVC). The oblique sinus (arrow) is a potential space resembling a cul-de-sac formed by the continuous reflection of the pericardium from the IVC around each of the pulmonary veins. (Abbreviations: Ao: Ascending aorta; L: Left; LIPV: Left inferior pulmonary vein; LSPV: Left superior pulmonary vein; PA: Main pulmonary artery; R: Right; RIPV: Right inferior pulmonary vein; RSPV: Right superior pulmonary vein)

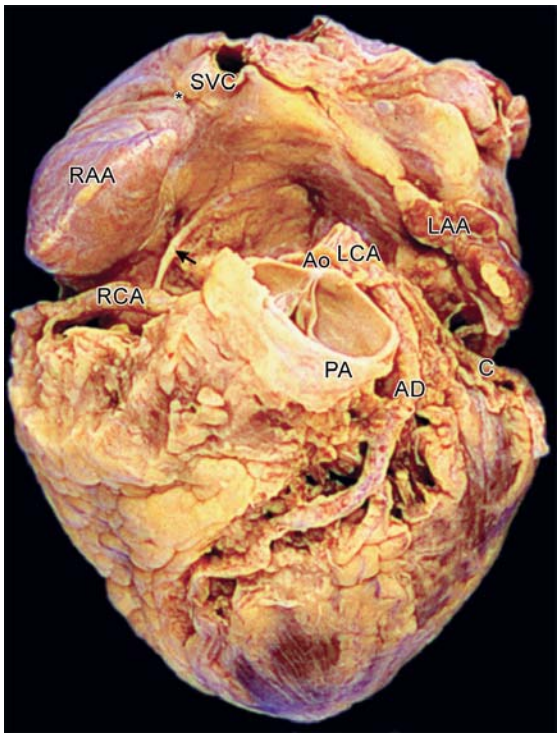


FIGURE 3: Epicardial anatomy: extramural coronary arteries and the transverse sinus. In this view of the isolated heart, the atria have been reflected posteriorly to exaggerate the transverse sinus between the atria and the great arteries. After epicardial fat has been dissected from the interventricular and atrioventricular sulci, the extramural coronary arteries can be identified as they course over the surface of the heart. Barely visible behind the pulmonary artery (PA), the aortic aorta (Ao) gives rise to the right coronary artery (RCA) and the left coronary artery (LCA). The relatively short left coronary artery divides into the circumflex (C) branch within the left atrioventricular sulcus and the anterior descending (AD) branch within the anterior interventricular sulcus. The sulcus terminalis marks the position of the sinoatrial node (*). In the transverse sinus an early atrial branch (arrow) of the right coronary artery provides a branch to the sinoatrial node. (Abbreviations: AD: Anterior descending coronary artery; LAA: Left atrial appendage; SVC: Superior vena cava; RAA: Right atrial appendage)

The two upper intercostal veins on the right enter the azygos or the right innominate vein. On the left side, the lower intercostal veins lead into the hemiazygos vein or the accessory hemiazygos vein (Fig. 4B). The hemiazygos vein crosses the midline behind the descending aorta at about the level of the eighth thoracic vertebral body and enters the right-sided azygos vein. With congestive heart failure and associated venous dilatation, the azygos vein can be seen as a round structure on the postero-anterior chest X-ray as it joins the superior vena cava.

The relationship of the great veins in the superior mediastinum is clinically important. The innominate (brachiocephalic) veins are formed by the confluence of the subclavian veins (passing over the first rib and posterior and inferior to the clavicles) and the internal jugular veins just behind the sternoclavicular joints. The left innominate vein passes anterior to the aortic arch, crossing the midline and joining the right innominate vein to form the superior vena cava. Deep to the venous structures are the great arteries arising from the aortic arch. The first branch from the aorta is the innominate or brachiocephalic artery, dividing behind the right sternoclavicular joint into the right subclavian artery (deep to the subclavian vein) and the right common carotid artery. The second great artery from the aortic arch is the left common carotid artery, and the third major branch is the left subclavian artery.

From the description of the thoracic great veins and arteries, it is apparent that the venous structures are superficial to the arteries and that both the left innominate vein and the aortic arch cross the midline. The position of the left innominate vein deep to the sternum explains the potential for injury to this vessel during a thoracotomy through a midline incision, especially during a repeat thoracotomy where adhesions are likely. Also, the relationship between the left innominate vein and the aortic arch explains the possibility of an aortoinnominate vein fistula after penetrating trauma. The relationship of the great veins to the clavicle and sternoclavicular joints makes these easily palpable bony structures

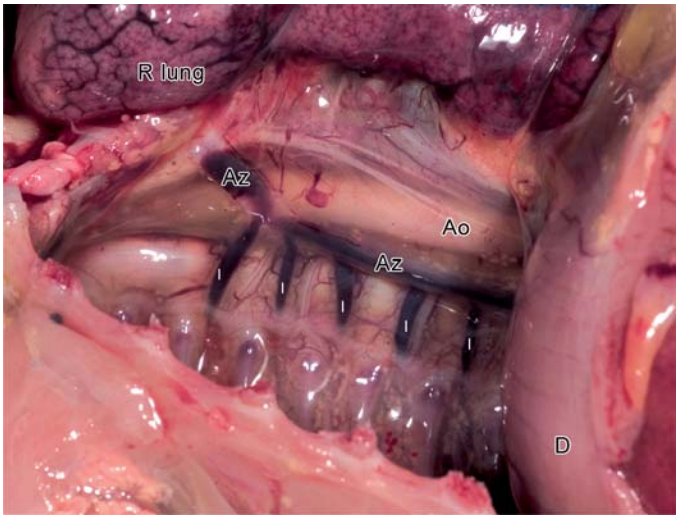


FIGURE 4A: Thoracic veins. With the right lung reflected out of the thorax (patient's head out of field at left), a lateral view of the posterior mediastinum shows intercostal veins (I) connecting with the azygos vein (Az) abutting the spine. More superiorly, the azygos vein will connect with the superior vena cava. (Abbreviations: Ao: Descending thoracic aorta; D: Right diaphragm; R: Right)

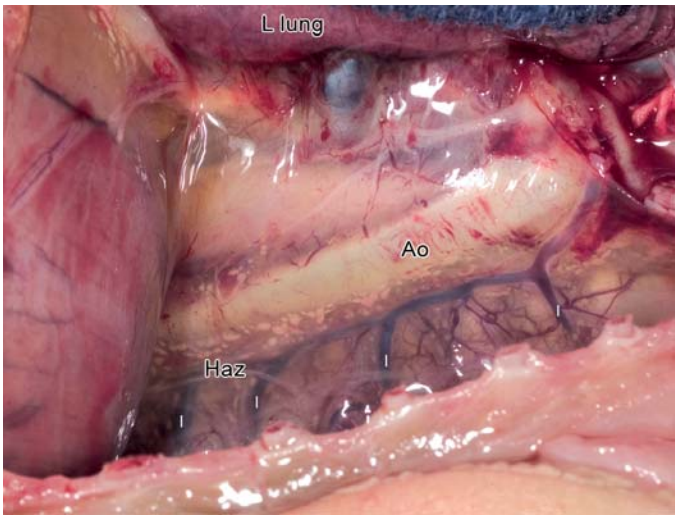


FIGURE 4B: With the left lung reflected out of the thorax (patient's head at right), a lateral view of the posterior mediastinum shows the highest intercostal veins (I) that will connect with the left innominate (brachiocephalic) vein superiorly. The lower intercostal veins connect with the hemiazygos vein (Haz) that will drain into the azygos vein

valuable landmarks for the percutaneous placement of central venous catheters into the internal jugular and subclavian veins.

CARDIAC SURFACE ANATOMY

With the pericardium opened and the heart exposed anteriorly, the right atrium forms the right lateral border with the superior vena cava superiorly and the thoracic segment of the inferior vena cava as it enters the right atrium inferiorly (Fig. 2). Further superiorly the ascending aorta forms the right border and on the left, the knob of the aortic arch; below the aortic arch and to the left, the main pulmonary artery is seen as it courses leftward and posteriorly. Just below the bulge of the main pulmonary artery on the cardiac silhouette is the left atrial appendage, and below that the muscular left ventricle forms the left cardiac border including the apex near the diaphragm. The right atrial appendage is not a border-forming structure, because it protrudes medially as a superior triangular structure anterior to and hiding the root of the ascending aorta. In fact from an anterior view, the great arteries are embraced on either side by the right and left atrial appendages, the right abutting the aorta as mentioned and the left next to the main pulmonary artery (Figs 1 and 5). On a posterior-anterior chest X-ray, the cardiac silhouette is formed by the same structures, and distortion of the image can indicate individual chamber or vessel enlargement.

Similarly, the epicardial surface provides clues as to the internal anatomy of the heart. A straight line between the two vena cavae indicates the inlet portion of the right atrium (sinus venarum) (Figs 1 and 2). The inferolateral border of the right atrium is marked on the cardiac surface by the right atrioventricular sulcus. Although not a border-forming structure the right atrial appendage overhangs the right atrioventricular groove in which the right coronary artery runs, the vessel usually being buried in epicardial fat. The position of the heart in the chest is such that the right atrioventricular groove is almost vertical, and this groove marks the position of the tricuspid annulus. The right ventricle is an anterior structure that in the frontal plane roughly projects as a triangle with the inlet as one side and the outlet as another side; its most superior angle marks the right ventricular outflow tract leading to the main pulmonary artery anteriorly. About 1 cm medial of the left cardiac border lies the interventricular sulcus marking the interventricular septum and thus the anterior portions of the right and left ventricles. In this groove lies the anterior descending coronary artery, again covered by fat (Fig. 5).

Observing the heart in the frontal plane, the superior parallel vascular structures from right to left are the superior vena cava, the ascending aorta and the main pulmonary artery (Fig. 5). The main pulmonary artery is 4–5 cm in length and bifurcates into the right pulmonary artery that passes transversely posterior to the ascending aorta (Fig. 6) and the left pulmonary artery which passes posteriorly and inferiorly. Posterior to the right atrial-superior vena caval junction, the right pulmonary artery divides into a superior and an inferior branch at the hilum of the right lung. At the right lung hilum, the superior branch of the right pulmonary artery courses under or side by side with the bronchus to the right upper lobe; this airway-vessel relationship is termed eparterial. In line with the main pulmonary artery, the left pulmonary artery arches leftward and posteriorly toward the hilum of the left lung. Just distal to the bifurcation of the main pulmonary artery, the ligamentum arteriosum connects the superior surface of the left pulmonary artery to the proximal descending aorta (Fig. 5). At the left lung hilum, the left pulmonary artery courses *over* the bronchus (hyparterial relationship).

The ascending aorta arises from the aortic fibrous annulus and passes superiorly. The root of the aorta refers to the aortic origin where the three semilunar leaflets of the closed aortic valve define three cup-like spaces bounded by the aortic walls

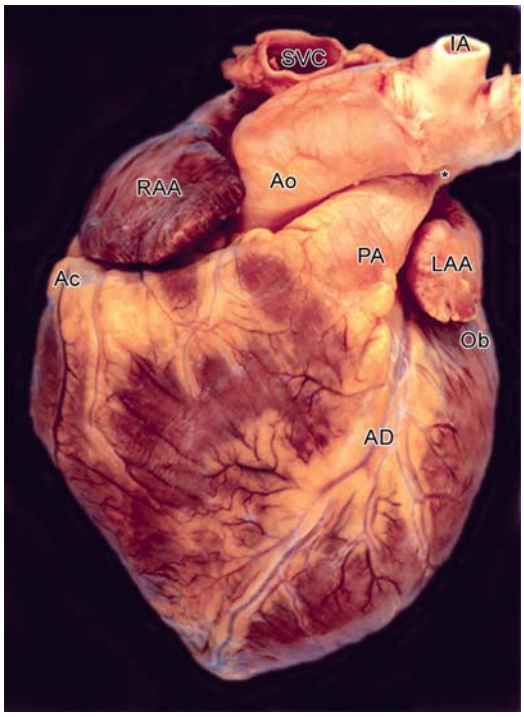


FIGURE 5: Epicardial anatomy: anterosuperior surface of the heart. The anterosuperior surface of the heart shows the great arteries crossed at their roots. The right atrial appendage abuts the ascending aorta, and the left atrial appendage is adjacent to the pulmonary artery. (Abbreviations: *: Ligamentum arteriosum; Ac: Acute margin of heart; AD: Anterior descending coronary artery; Ao: Ascending aorta; IA: Innominate (or brachiocephalic) artery; LAA: Left atrial appendage; PA: Main pulmonary artery; Ob: Obtuse margin of heart; RAA: Right atrial appendage; SVC: Superior vena cava)

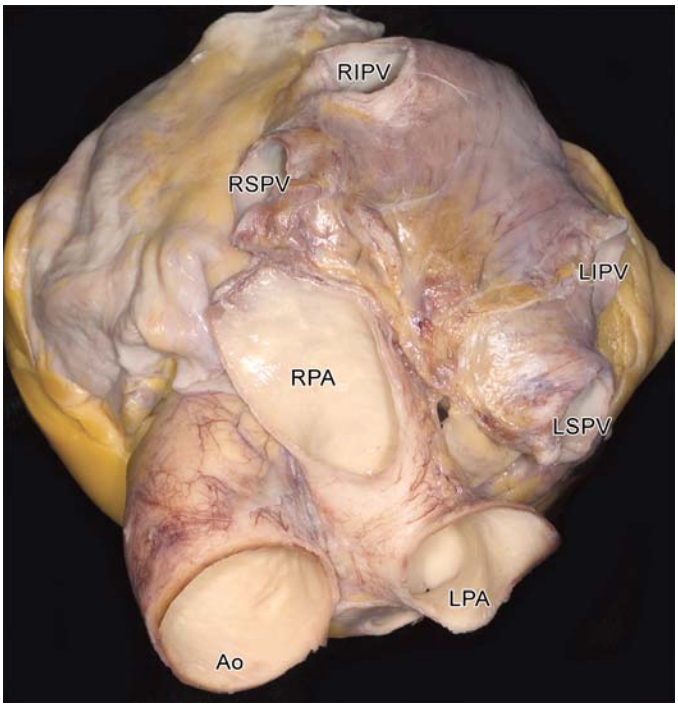


FIGURE 6: Relationship between the right pulmonary artery and the left atrium. The superior aspect of the heart shows the right pulmonary artery (RPA) between the ascending aorta (Ao) and the left atrium with the pulmonary vein connections. (Abbreviations: LIPV: Left inferior pulmonary vein; LSPV: Left superior pulmonary vein; RIPV: Right inferior pulmonary vein; RSPV: Right superior pulmonary vein; LPA: Left pulmonary artery)

(sinuses of Valsalva). The first arteries arising from the aorta are the right and left coronary arteries, their ostia usually being located in the sinuses. As the aorta passes superiorly, leftward and posteriorly forming the aortic arch it gives rise to the innominate (or brachiocephalic) (Fig. 5), left common carotid and left subclavian arteries. The aortic arch passes over the left mainstem bronchus, thus marking this arch as "left-sided". In a small percentage of patients the aortic arch passes over the right mainstem bronchus ("right-sided" aortic arch). After the left subclavian artery arises, the descending aorta assumes a left paravertebral position and courses caudally in the posterior mediastinum to the left of the spine (Fig. 4 lower panel). Twelve paired intercostal arteries arise from the descending aorta, and a variably placed anterior spinal artery and several bronchial arteries arise from the anterior descending aorta.

In the frontal view of the heart, the acute angle defined by the atrioventricular groove anteriorly and the right edge of the right ventricle is the basis for references to the "acute margin" of the heart (Fig. 5). On the left side of the heart the corresponding heart border is the "obtuse margin" of the heart.

Viewed from the right lateral aspect as in a chest X-ray, the anterior heart border is formed by the right ventricle and the posterior border by the right atrium inferiorly and the left atrium superiorly (Fig. 5). The right ventricular outflow tract and the initial part of the main pulmonary artery form the superior portion of the anterior aspect of the right ventricle. Above the pulmonary artery is the ascending aorta. From the left lateral aspect, the right ventricle is anterior and the posterior border is formed by the left atrium superiorly and the left ventricle inferiorly. Thus, orienting the heart in space, the right ventricle is rightward and anterior and the left ventricle is leftward and posterior. The atria are posterior and superior to the ventricles, with the right atrium anterior and rightward and the left atrium posterior and leftward.

From the posterior aspect, the aortic arch rises superior to the root of the left lung. The main pulmonary artery bifurcates into the right and left pulmonary artery branches above the left atrium. The left atrium receives four pulmonary veins, the right and left superior and inferior pulmonary veins (Figs 6 and 7). The right pulmonary veins pass posteriorly into the left atrium between the superior vena cava above and the inferior vena cava below. This close relationship explains the developmental error of the right superior pulmonary vein draining into the superior vena cava or the right atrium instead of the left atrium (anomalous pulmonary venous connection).

From the posterior aspect to the right of the connection of the pulmonary veins with the left atrium is a long-axis depression known as Sondergaard's groove, a shallow epicardial indentation marking the position of the interatrial septum internally (Fig. 7). In accessing the mitral valve, surgeons use Sondergaard's groove as a landmark to enter the left atrium from the posterior or right thoracotomy approach by making an incision just to the left of the groove. To the right of Sondergaard's groove there is another indentation, the sulcus terminalis denoting the site of the specialized muscle of the sinoatrial node. Marking the outlet portions of the atria is the posterior atrioventricular groove. In the right side of this groove the right coronary artery passes posteroinferiorly to the crux of the heart and then turns to course within the posterior

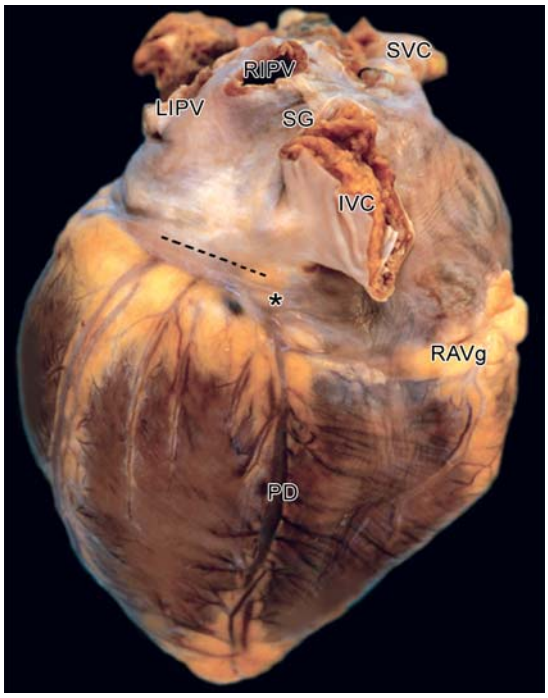


FIGURE 7: Epicardial anatomy: inferior (diaphragmatic) surface of the heart. The inferior (diaphragmatic) surface of the heart shows the posterior descending coronary artery (PD) as the landmark for the interventricular septum. The right pulmonary veins are just leftward of an imaginary line drawn from the caval veins. Between the right pulmonary veins and this line is Sondergaard's groove (SG) marking the interatrial septum. (Abbreviations: *: Crux of heart;- - - - - -: Position of coronary sinus within left atrial wall; IVC: Inferior vena cava; LIPV: Left inferior pulmonary vein; RAVg: Fat-filled right atrioventricular groove; RIPV: Right inferior pulmonary vein; SVC: Superior vena cava)

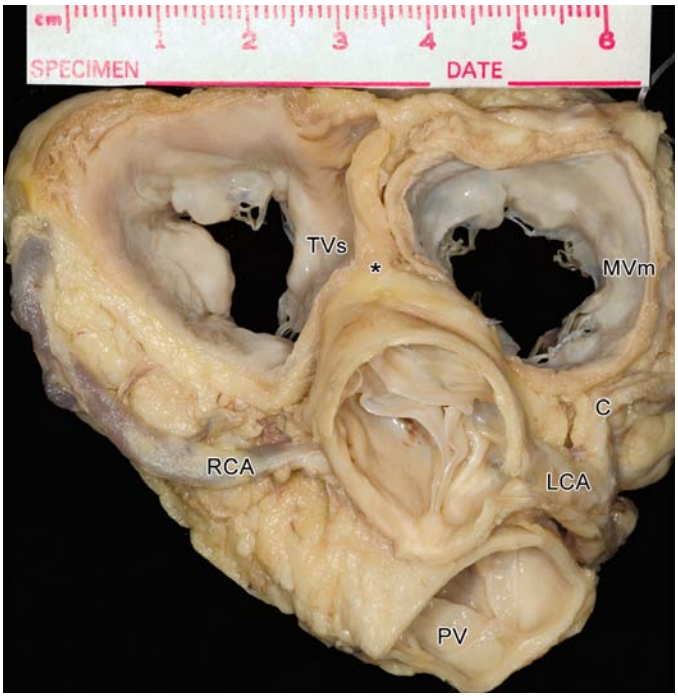


FIGURE 8: Relationship of the atrioventricular and arterial valves. Viewed from the superior aspect, the base of the heart with most of the atria cut away shows the aortic valve wedged between the two atrioventricular valves. Deep to the dissection plane illustrated, the three valves come together at the right fibrous trigone or central fibrous body (*), while the pulmonary valve (PV) is separate from the fibrous skeleton of the heart. (Abbreviations: C: Circumflex coronary artery within left atrioventricular groove; LCA: Left coronary artery; MVm: Mural leaflet of mitral valve; RCA: Right coronary artery within right atrioventricular groove; TVs: Septal leaflet of tricuspid valve)

interventricular groove toward the apex as the posterior descending coronary artery. The crux of the heart is the point at which Sondergaard's groove, the right and left atrioventricular grooves and the posterior interventricular groove all intersect (Fig. 7). In other words, the crux (represented by a shallow dimple) is the point on the inferior surface at which all four chambers of the heart meet. The coronary sinus runs in the left side of the atrioventricular groove along the diaphragmatic surface. This conduit passes rightward and empties into the right atrium through the coronary sinus orifice.

INTERNAL STRUCTURE OF THE HEART

The heart can be said to have a fibrous "skeleton" on which the muscles of the atria and the ventricles are anchored. The "skeleton" consists of fibrous connective tissue that forms the valvular annuli and electrically isolates the atrial and ventricular muscles except in one small area. The only normal muscular connection between atrial and ventricular myocardium is via the atrioventricular (His) bundle, a tiny cord-like isthmus of specialized myocardial cells with conduction properties that propagates the electrical impulse from the atrioventricular node to the right and left bundle branches. The fibrous "skeleton" consists of the mitral, tricuspid and aortic annuli in a close triangular arrangement (Fig. 8); the separate pulmonic annulus is anterior and leftward of the aortic annulus. The small fibrous junction between the mitral, tricuspid and aortic annuli is called the right fibrous trigone (central fibrous body), and the small fibrous junction between the mitral and aortic annuli on the left behind the left atrial appendage is called the left fibrous trigone. Thus, the atrioventricular bundle penetrates the right fibrous trigone in coursing toward the left side of the interventricular septum.

RIGHT ATRIUM

The right atrium is anterior and rightward of the left atrium, the two chambers being separated by the interatrial septum. Embryologically the atria become partitioned by the sequential ingrowth of two muscular septa. During development the septum primum grows from the roof of the atrium toward the atrioventricular region. Closure of the septum primum is completed by tissue contributions from the endocardial cushions. Prior to closure, a second opening in the midportion of the septum primum appears, the foramen ovale, allowing blood to continue to flow from the right atrium to the left atrium. To the right of the septum primum, a second partition, the septum secundum, grows down as a superior and posterior crescent. The septum secundum finally grows to overlap the foramen ovale in such a way that greater left atrial pressure can close the opening. The fossa ovalis, a crater-like depression in the atrial septum as seen from the right atrial aspect, is the site at which the two septa overlap. Thus, normally, with the first breaths by the newborn infant, the left atrial pressure comes to

exceed the right atrial pressure during all phases of the cardiac cycle, and the flap against the foramen ovale is closed, allowing no shunting between the atria. In most individuals the foramen ovale becomes permanently sealed during infancy. In approximately 20% of individuals, however, the two septae never completely fuse, allowing a slit-like potential communication at the foramen ovale throughout life, usually at the anterior margin of the fossa ovalis. Under some circumstances, for instance after release of a Valsalva maneuver, the right atrial pressure transiently exceeds that of the left and a right-to-left shunt occurs. This is the basis for a potential paradoxical embolism in patients with a patent foramen ovale but an otherwise normal heart. Other circumstances in which a patent foramen ovale can result in a right-to-left shunt include tricuspid regurgitation or right ventricular diastolic dysfunction with right ventricular hypertrophy or failure where right atrial pressure is abnormally elevated.

When formed abnormally the atrial septal partition can be the site of at least three distinctive malformations. The commonest defect, the secundum atrial septal defect, results from a failure of the septum primum to cover the foramen ovale. Less common is the ostium primum defect, a result of failure of the endocardial cushions to fuse with the inferior edge of the septum primum. A rare third defect, the sinus venosus atrial septal defect, results from a failure of the embryonic sinus venosus to be incorporated into the embryonic right atrium; the defect is usually located at the posterosuperior or, less commonly, at the posteroinferior aspect of the atrial septum. This defect often is associated with anomalous pulmonary venous connection to the superior vena cava or the right atrium.

In the adult heart, the fossa ovalis is about the size of a dime (Fig. 9). Surrounding the membranous tissue in the base of the crater, there is a ridge of atrial muscle superiorly and posteriorly called the limbus of the fossa ovalis, an important landmark in performing a trans-septal left-sided cardiac catheterization (Figs 10 and 11). In this procedure, a Brockenbrough needle with a curve at its end sheathed within a catheter is placed into the superior vena cava and rotated so that the needle is pointed posteromedially; it then is slowly pulled back until it

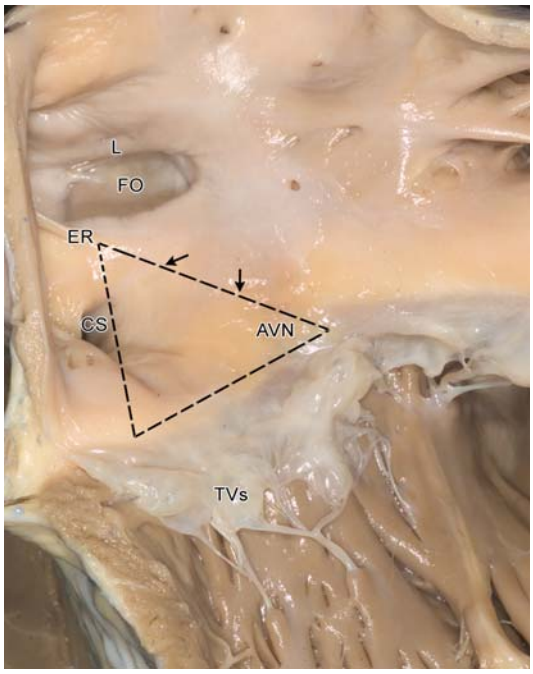


FIGURE 10: Right atrium and landmarks for the atrioventricular node. A close-up view of the right atrial septum and vestibule of the tricuspid valve discloses the Eustachian ridge (ER, or sinus septum) separating the fossa ovalis (FO) and coronary sinus. The tendon of Todaro courses along the crest of the ridge subendocardially (arrows). The triangle of Koch (dashed lines) is the landmark for the atrioventricular node (AVN) and bundle: at the angle formed by the tendon of Todaro and the annulus of the septal leaflet of the tricuspid valve, the atrioventricular bundle penetrates the central fibrous body on its way to the left side of the septum. (Abbreviations: CS: Coronary sinus os; L: Limbus of fossa ovalis; TVs: Septal leaflet of tricuspid valve)

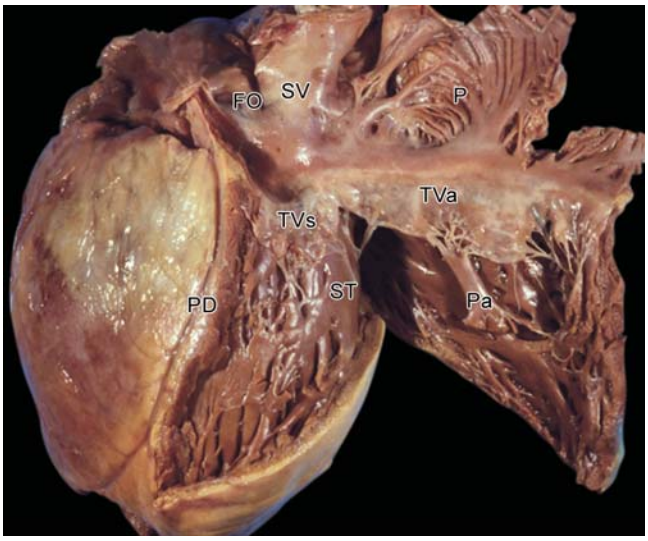


FIGURE 9: Right atrium and right ventricular inlet. The opened right atrium (including right atrial appendage) and right ventricular inlet demonstrates the pectinate muscles (P) of the "rough" part of the right atrium and the smooth endocardial surface of the sinus venarum portion (SV). Within the ventricle, the free wall thickness is less than 0.4 cm. (Abbreviations: FO: Fossa ovalis; Pa: Anterior papillary muscle; PD: Posterior descending coronary artery; ST: Septomarginal trabeculum; TVa: Anterior leaflet of tricuspid valve; TVs: Septal leaflet of tricuspid valve)

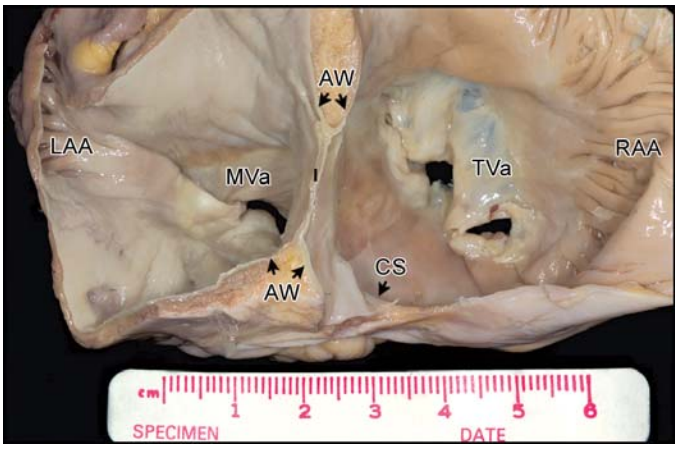


FIGURE 11: Interatrial septum. Viewed from the superior aspect, a cut through the fossa ovalis demonstrates the primary atrial septum (I) essentially as a membrane, while the adjacent tissue is comprised of the infolded atrial walls (AW). Thus, the blade septostomy should be performed in the fossa ovalis without deviation into the limbus. (Abbreviations: CS: Coronary sinus os; LAA: Opened left atrial appendage; MVa: Anterior leaflet of mitral valve; RAA: Opened right atrial appendage; TVa: Anterior leaflet of tricuspid valve)

passes across the limbus and springs into the fossa ovalis, causing a sharp movement of the needle which can be both seen under fluoroscopy and felt. At that point the needle is in the fossa ovalis and can be safely advanced through the septum into the left atrium. Deviation outside of this dime-sized oval may result in complications; because the limbus marks the boundary of the true atrial septum and the infolded atrial walls (Fig. 11), puncturing the limbus results in the blade coursing outside of the atrial wall into epicardial tissue (where there are vessels and nerves) before entering the left atrium.

The inner surface of the right atrium has a smooth part and a "rough" part (Fig. 9). The smooth part of the right atrium is that part of the wall between the vena cavae. In contrast, the free wall of the right atrium including the atrial appendage has numerous muscle ridges known as pectinate muscles. The relatively large number of pectinate muscles and the fact that they extend beyond the appendage is one feature that distinguishes the right atrium from the left atrium. This "rough" part of the chamber represents the contribution of the embryonic atrium. Very thin walls, much less than a millimeter thick, separate the fine muscle ridges. If a catheter is pressed against the lateral wall of the right atrium and under fluoroscopy does not appear to be almost pressing against the lung, then the wall is abnormally thick; usually this means a thickened pericardium as seen in constrictive pericarditis, or a pericardial effusion. Another consequence of the thin atrial wall is the danger of cardiac perforation when maneuvering within the right atrium with a stiff catheter.

After passing through the diaphragm the inferior vena cava connects with the right atrium. In some hearts the right atrium has a thin, crescentic membrane coursing anteromedially from the inferior vena cava within the cavity; this structure is known as the valve of the inferior vena cava or the Eustachian valve, a vestige of an embryologic venous valve that guarded the inferior vena cava orifice. On occasion a more substantial, cobweb-like remnant of the Eustachian valve called a Chiari network can extend into the lumen of the right atrium, and in some cases this structure can be discerned echocardiographically as moving erratically in the cavity of the right atrium. The orifice of the inferior vena cava is rightward and inferior to the fossa ovalis (Fig. 12). In the fetus, oxygenated umbilical vein blood from the inferior vena cava is directed at the foramen ovale, creating a shunt of oxygenated blood to the left heart and head and neck, bypassing the developing lung. The proximity and orientation of the inferior vena caval orifice to the fossa ovalis facilitates a catheter from the inferior vena cava passing through an atrial secundum defect.

The superior vena cava connection with the right atrium superiorly is aligned with the atrial connection of the inferior vena cava, but is slightly anterior in position. On the inner surface of the right atrium at the junction between the superior vena cava and the right atrium laterally, the crista terminalis is a robust ridge of muscle that corresponds to the sulcus terminalis seen on the epicardial surface (Fig. 12). As the crista terminalis courses inferiorly, it flattens and becomes indistinct near the inferior vena cava. Between the crista terminalis and the interatrial septum posteriorly, the right atrial wall is smooth (without pectinate muscles) and is called the sinus venarum cavarum (Fig. 12). This smooth part of the right atrium is derived

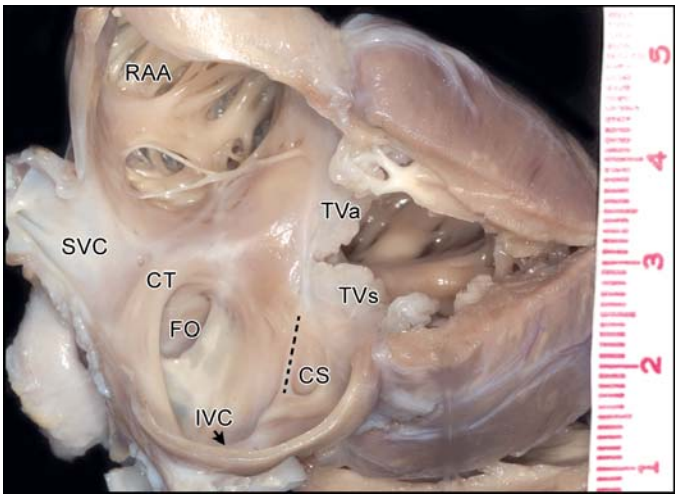


FIGURE 12: Sinus venarum ("smooth" part of the right atrium). En face the opened right atrium of a newborn's heart demonstrates the adjacent relationship between the inferior vena cava (IVC) and fossa ovalis (FO) where the fetal interatrial shunt occurs. (Abbreviations: - - - - - -: Subendocardial position of tendon of Todaro on the Eustachian ridge; CS: Coronary sinus os; CT: Crista terminalis; RAA: Right atrial appendage; SVC: Superior vena cava; TVa: Anterior leaflet of tricuspid valve; TVs: Septal leaflet of tricuspid valve)

from the right horn of the embryonic sinus venosus. Immediately anterior to the inferior vena caval orifice and between the fossa ovalis and the tricuspid annulus is the orifice of the coronary sinus. It is "guarded" by another vestigial valvular structure, the valve of the coronary sinus or thebesian valve. Coursing from the inferior vena cava in an anteromedial direction, a subendocardial fibrous ligament termed the tendon of Todaro passes to the right fibrous trigone (Figs 10 and 12). Opening into the right atrial cavity are a variable number of small orifices from the thebesian veins, especially on the anterior and lateral walls. Occasionally with contrast injection into the right atrium, contrast can be seen entering these vessels retrograde.

The floor of the right atrium (vestibule of the tricuspid valve) is comprised of a circumferential wall of atrial muscle that funnels blood toward the outlet. Situated on the floor of the right atrium, the right atrioventricular orifice is directed anteriorly and leftward and is guarded by the tricuspid valve.

TRICUSPID VALVE

From the right atrioventricular annulus the tricuspid valve leaflets hang into the cavity of the right ventricle (Fig. 9). The leaflet attachment is continuous around the right atrioventricular ring; however, the hinge line varies from segment to segment. Medially, the hinge of the tricuspid valve crosses the middle of the membranous portion of the interventricular septum (Fig. 13). The fibromembranous tissue comprising the leaflets can be divided roughly into three leaflets, the largest being the anterior leaflet and the smallest the posterior, with the septal leaflet being intermediate in size (Fig. 9). The notched or undulating leaflet edges or free margins are attached to the papillary muscles by fibrous cords called chordae tendineae that branch once or twice before their leaflet attachments at variable distances from the edge. The chordae are thinnest at the leaflet edge and thicker in attaching on the

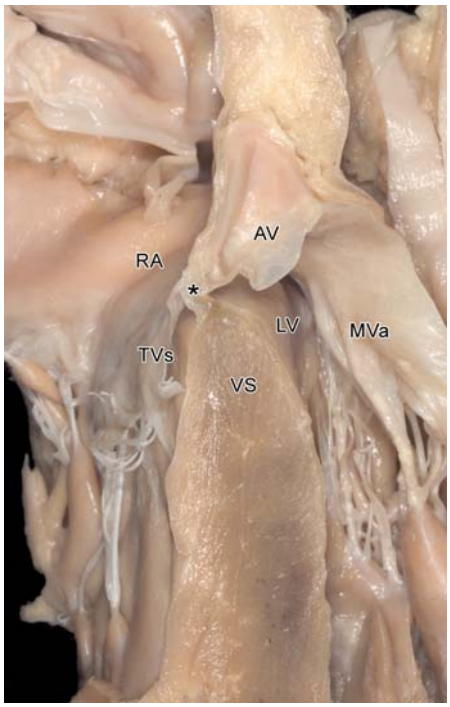


FIGURE 13: In this simulated four-chamber view, the attachment of the septal leaflet of the tricuspid valve (TVs) to the membranous portion of the interventricular septum (*) can be the basis for a left ventricular (LV)-to-right atrial (RA) shunt in patients with a malformation in this region. (Abbreviations: AV: Aortic valve; MVa: Anterior leaflet of mitral valve; VS: Ventricular septum)

ventricular aspect of the leaflets. Each leaflet receives chordae from more than one papillary muscle.

The smooth atrial surface of each leaflet is the surface that coapts (or fits together) during systole. The anterior leaflet is situated subjacent to the sternocostal area where it is tethered by chordae primarily from the anterior papillary muscle, with a limited contribution of chordae from a small papillary muscle near the outlet septum (papillary muscle of the conus or muscle of Lancisi) (Fig. 14). The septal leaflet has chordae that insert directly into the interventricular septum. The posterior leaflet is positioned inferiorly and is tethered by chordae from a variable number of very small papillary muscles along the right ventricular inlet inferiorly. There can be supernumerary leaflets at the intervalvular spaces. Of clinical significance is the attachment of the tricuspid valve at the commissure between the anterior and septal leaflets, across the membranous septum (Fig. 13). Due to this attachment, it is possible to have a perimembranous septal defect with a left ventricle-to-right atrial shunt.

RIGHT VENTRICLE

The right atrioventricular orifice is inferior and faces anteriorly and slightly leftward into the inflow portion of the right ventricle. The free wall of the normal right ventricle is thin (up to 0.4 mm) and lined by muscle columns called trabeculae carneae that make up two-thirds of the wall's thickness with a narrow layer of compact muscle subjacent to the epicardium (Fig. 9). The right ventricle may be thought of as roughly triangular, with one side the right atrioventricular orifice, the second side the diaphragmatic aspect and the third side the

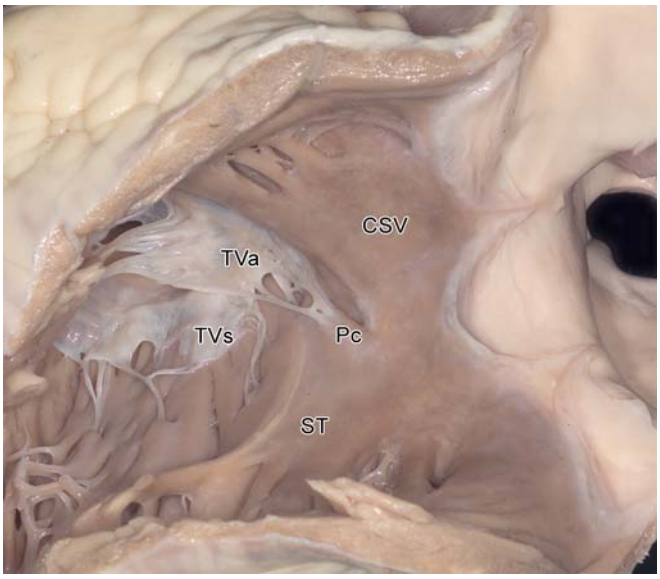


FIGURE 14: Right ventricular outlet (infundibulum). The transition between the inlet and outlet portions of the right ventricle is marked by the papillary muscle of the conus (muscle of Lancisi) (Pc). In the right ventricular outflow tract, the crista supraventricularis (CSV) separates the pulmonary valve from the other three valves. (Abbreviations: ST: Septomarginal trabeculum; TVa: Anterior leaflet of tricuspid valve; TVs: Septal leaflet of tricuspid valve)

one adjacent to the interventricular septum (Fig. 15). The superior extent of the triangle leads to the right ventricular outflow tract. Seen echocardiographically, the robust interventricular septum bulges into the cavity of the right ventricle, because the pressure during ventricular systole is so much higher in the left as compared with the right ventricle. The short-axis cross section of the right ventricle is therefore crescentic, and the right ventricle can be considered as "wrapping around" the more round left ventricle (Fig. 16). Separating the inflow and the outflow tracts of the right ventricle is a muscle ridge called the crista supraventricularis (Figs 14 and 15); this structure forms an arch with one arm

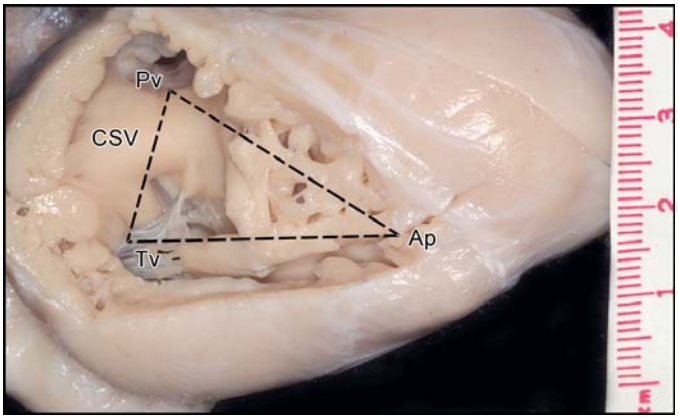


FIGURE 15: Cut away view of right ventricular cavity. In this infant's heart, a frontal view of the right ventricle with the free wall removed discloses a triangular cavity with the inlet inferiorly and the outlet superiorly. The inlet and outlet dimensions intersect at the apex (Ap). The third side of the triangle is an imaginary line through the crista supraventricularis (CSV). (Abbreviations: Pv: Pulmonary valve; Tv: Tricuspid valve)

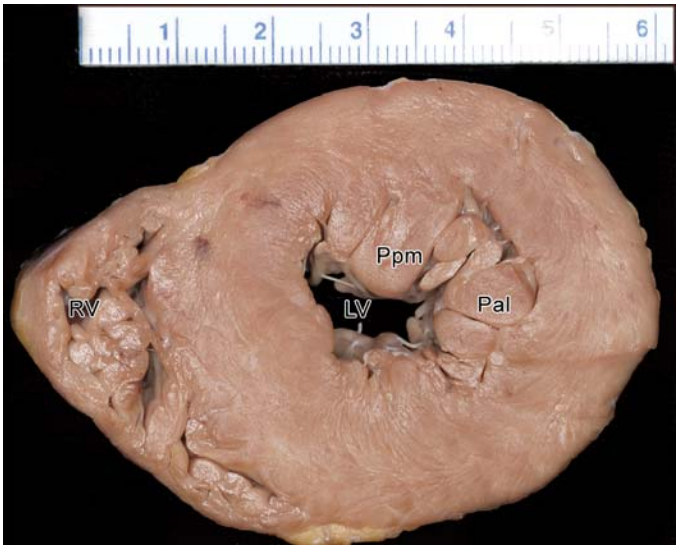


FIGURE 16: Venticles in short axis. A slice of heart in the short axis demonstrates the crescentic shape of the right ventricle adjacent to the more spherical left ventricle. At this level the prominence of the trabeculae carneae in the right ventricle can be appreciated. The increased wall thickness of the left ventricle and septum reflects myocardial hypertrophy. (Abbreviations: LV: Left ventricle; Pal: Anterolateral papillary muscle; Ppm: Posteromedial papillary muscle; RV: Right ventricle)

on the interventricular septum (the septal band) and the other on the free wall of the right ventricle (the parietal band). Anatomically distinctive of the right ventricle, the crista supraventricularis is derived from the inferior margin of the embryologic conus arteriosus. Also characteristic of the right ventricle is the trabeculated septal surface (Fig. 9), unlike the left ventricular septal surface that is smooth. One of the more prominent trabeculums, the septomarginal trabeculum, courses in the long axis along the anterior septum (Figs 9 and 14). At its apical end, a short muscular trabecular bridge called the moderator band courses between the distal septum and the free right ventricular wall. Visible by echocardiography the moderator band carries right bundle branches of the conduction system. The papillary muscles of the right ventricle are somewhat variable in configuration. An anterior papillary muscle arises on the free wall of the right ventricle (Fig. 9). Also distinctive the papillary muscle of the conus (muscle of Lancisi) arises from the superior end of the septomarginal trabeculum and can be considered the start of the right ventricular outflow tract (Fig. 14).

In summary the right ventricle is distinctive anatomically because of a number of features:

- Its roughly triangular shape enabling it to "wrap around" the left ventricle.
- The coarse trabeculation of the ventricular septal surface.
- The septal leaflet of the tricuspid valve with chordae tendinae tethering it to the septal surface.
- The configuration of the septomarginal trabeculum and moderator band.
- The papillary muscle of the conus (muscle of Lancisi).
- The separation of inflow and outflow tracts by the crista supraventricularis that separates the pulmonary valve from the other three valves.

Many of these features can be visualized by echocardiography, computed tomography and magnetic resonance imaging. In patients with congenital heart disease, recognizing features that characterize a ventricle as being an anatomic right or left ventricle often is key to understanding the congenital anomaly.

PULMONIC VALVE

Situated superior-most in the right ventricular triangle and separating the right ventricle from the main pulmonary artery is the pulmonic valve that faces posteriorly and superiorly. This semilunar valve has three leaflets, right and left anterior leaflets and a single posterior leaflet, named according to their orientation to the main axis of the body when the heart is *in situ* (Figs 17 and 18). The valve leaflets are thin and translucent, with a fibrous thickening at the midpoint of the free margin, the nodulus Arantius. Radiating from the nodule over each leaflet are fibrous thickenings. Along the leaflet edge, these crescentic thickenings are called lunulae. Of similar configuration as the aortic leaflets, the pulmonic valve leaflets are thinner due to the lower forces sustained by the pulmonic

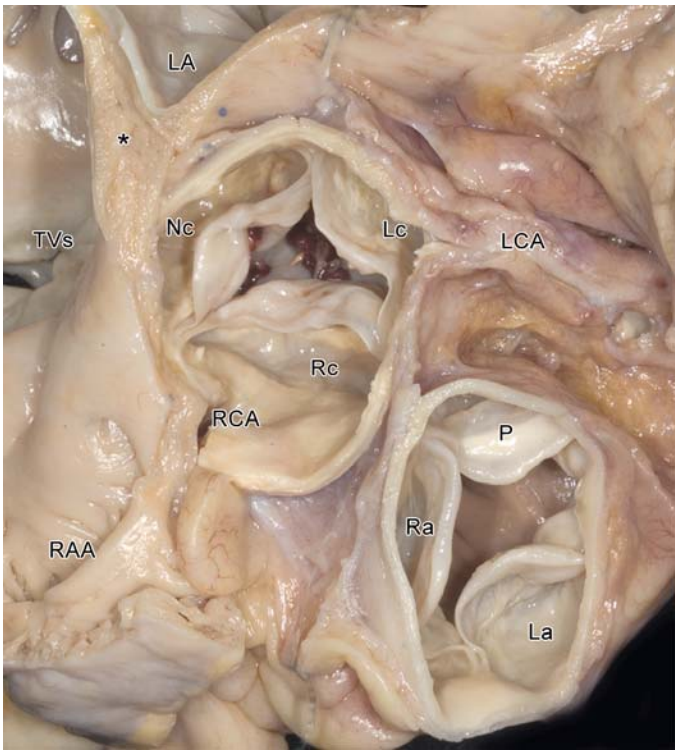


FIGURE 17: Relationship between aortic and pulmonary valves. Because of the crista supraventricularis and right ventricular conus, the pulmonary valve is a little more superior to the aortic valve. A close-up view of the two semilunar valves shows the right coronary (Rc), left coronary (Lc) and noncoronary (Nc) leaflets of the aortic valve. The noncoronary leaflet of the aortic valve is closest to the atrial septum. The adjacent leaflets of the pulmonary valve are designated differently. (Abbreviations: *: Fused medial walls of the left and right atria near interatrial septum; La: Left anterior leaflet of pulmonary valve; LA: Left atrium; LCA: Left coronary artery; P: Posterior leaflet of pulmonary valve; Ra: Right anterior leaflet of pulmonary valve; RAA: Right atrial appendage; RCA: Right coronary artery os; TVs: Septal leaflet of tricuspid valve)

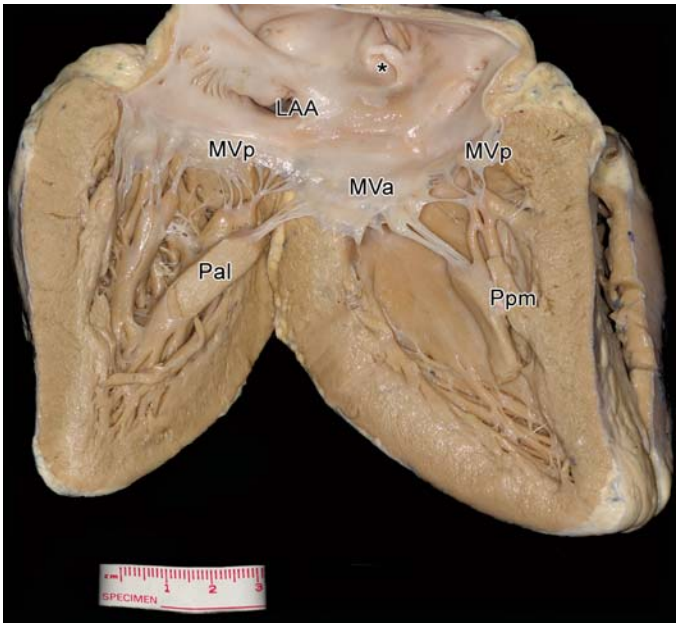


FIGURE 18: Left atrium and left ventricular inlet. The opened left atrium is notable for the pulmonary vein connections, left aspect of the interatrial septum (*) and the relatively narrow orifice that communicates with the left atrial appendage. Pectinate muscles are limited to the left atrial appendage, with only few visible around the orifice. The mitral orifice is guarded by a two-leaflet valve. The septal or aortic leaflet subtends roughly one-third of the annular circumference and has a greater height than the shallower posterior or mural leaflet that subtends two-thirds of the circumference. (Abbreviations: LAA: Orifice of left atrial appendage; MVa: Anterior leaflet of mitral valve; MVp: Posterior (or mural) leaflet of mitral valve; Pal: Anterolateral papillary muscle; Ppm: Posteromedial papillary muscle)

valve as compared with the aortic valve during diastole. In systole the leaflets flex at their wall attachments to form a rounded triangular orifice, about 3 cm^2 in diameter. In diastole the leaflets close by coapting along their ventricular surface.

PULMONARY ARTERIES

The main pulmonary artery arises above the pulmonic valve annulus and passes leftward first superiorly and then posteriorly around the medial (left-facing) aspect of the ascending aorta. Normally the artery is approximately 3 cm in diameter and 4–5 cm long (Fig. 5). When the valve is closed, the pulmonic valve leaflets define three cup-like sinuses at which the pulmonary artery wall bulges slightly outward. Beyond the level of the left atrium the pulmonary artery divides into the right and left pulmonary arterial branches. The right pulmonary arterial branch passes rightward behind the ascending aorta just above the left atrium, and the left pulmonary arterial branch, essentially a continuation of the main pulmonary artery, passes over the left mainstem bronchus. This leftward superior orientation of the left pulmonary artery is fixed by the attachment of the ligamentum arteriosum (Fig. 5). Distal to the ligament, the left pulmonary artery courses sharply inferiorly. From the superior and anterior surface of the left pulmonary artery, there are four branches to the upper lobe of the left lung. The remainder of the left pulmonary artery passes inferiorly into the left lower pulmonary lobe. Coursing rightward and slightly posterior behind the ascending aorta, the right pulmonary artery lies anterior to the right mainstem bronchus and posterior to the superior vena cava and the right superior pulmonary vein. At the hilum of the right lung the pulmonary artery divides into two major branches, the superior or ascending branch supplying the upper lobe of the right lung, and the descending or interlobular branch supplying the middle and lower lobes of the right lung.

The branches of the pulmonary artery generally follow the branches of the bronchial system and supply similar pulmonary segments. The relationship of the various pulmonary artery branches to the bronchi at the lung hilums is important, since their positions can be visualized on chest X-ray and can identify the "anatomical" left and right lungs, critical in some cardiovascular malformations. As noted above, the right pulmonary artery passes anteriorly and inferiorly to the right mainstem bronchus, therefore the right bronchus is "eparterial" at the right hilum. On the left, the left upper lobe bronchus is inferior to the left pulmonary artery, making this the "hyparterial" bronchus.

LEFT ATRIUM

The left atrium is posterior and leftward of the right atrium and posterior to the aortic root. The right pulmonary artery is directly superior to the left atrium. The left atrial appendage lies to the left and anterior to the main pulmonary artery (Figs 1 and 5). The left atrial inner wall is smooth with the exception of the tubular left atrial appendage that has some pectinate muscles; however, the narrow orifice of the atrial appendage hides these ridges (Fig. 18). Viewed en face, the endocardium of the left atrium is thicker and more opaque than that of the right atrium. The four pulmonary veins, two right and two left, superior and inferior veins, connect with the left atrium posteriorly. The two right pulmonary vein ostia are near the left side of the atrial septum, and the left pulmonary vein ostia are posterior on the lateral wall of the left atrium. The left side of the atrial septum is smooth, but there is a flap of membranous tissue that corresponds to the fossa ovalis where the septum primum fused to the septum secundum (Fig. 18). At the atrial outlet, the vestibule of the mitral valve consists of a circumferential wall of muscle that funnels blood toward the valve orifice.

MITRAL VALVE

The mitral valve, so-called because of its fancied resemblance to a Bishop's miter, guards the entrance to the left ventricle. Hanging from the annulus, the leaflet tissue includes the anterior (or aortic) leaflet and the posterior (or mural) leaflet. The leaflets are anchored to the left ventricular wall by chordae tendineae that originate from papillary muscles. In addition, the mural leaflet has some chordae that come directly from the left ventricular wall. Due to the junction between the aortic and mitral annuli (left fibrous trigone), the anterior leaflet of the mitral valve contacts the noncoronary and left coronary portions of the aortic annulus (Figs 19 and 20). Thus, there is fibrous continuity between the mitral and aortic valves, unlike the right ventricular outlet where the tricuspid and pulmonary valves are separated by the crista supraventricularis. The part of the anterior leaflet from its aortic ring attachment to its point of flexion is known as the intervalvular membrane. In a superior view onto

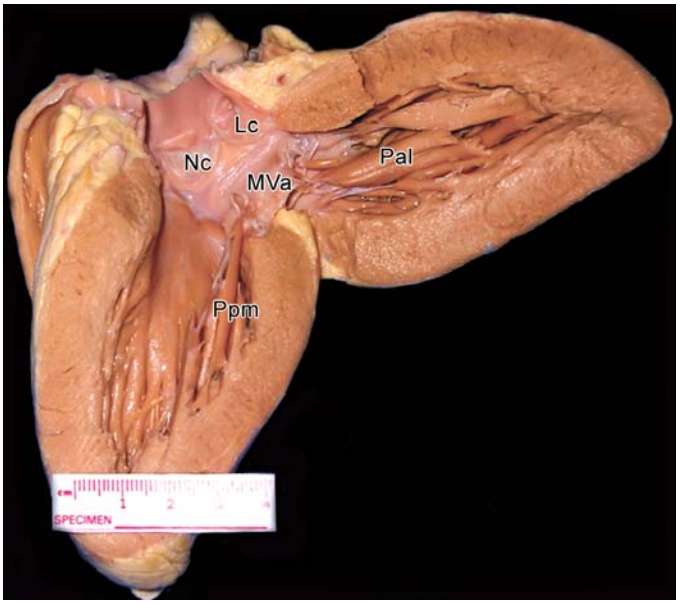


FIGURE 19: Left ventricular outlet. In this view of the left ventricular outlet, the free wall of the left ventricle has been retracted to show the smooth septal surface near the base of the heart. The noncoronary (Nc) and left coronary (Lc) leaflets of the aortic valve are visible. In contrast to the outlet of the right ventricle, there is no muscle between the mitral valve and the aortic valve; thus, there is fibrous continuity between the mitral and aortic valves. (Abbreviations: MVa: Anterior leaflet of mitral valve; Pal: Anterolateral papillary muscle; Ppm: Posteromedial papillary muscle)

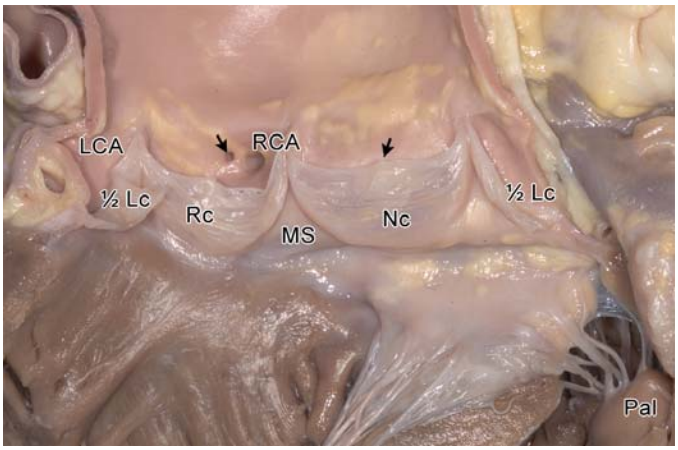


FIGURE 20: Aortic valve. In a close-up view of the aortic valve (with the left coronary leaflet (Lc) cut in half), the membranous portion of the interventricular septum (MS) is present between the noncoronary (Nc) and right coronary (RC) leaflets. In addition to the ostia leading to the main coronary arteries, a separate tiny ostium (short arrow) leading to the conal branch of the right coronary artery is identified as a normal variant. Facilitating valve closure, a tiny midline fibrous nodule on the free margin of each semilunar leaflet is known as the nodule of Arantius. Fibrous thickenings termed lunulae are barely visible in the noncoronary and right coronary leaflets, and two small fenestrations may be identified near the free margin of the right coronary leaflet. (Abbreviations: LCA: Left coronary artery os; Pal: Posterolateral papillary muscle; RCA: Right coronary artery os)

the isolated left ventricle, the "orifice" of the left ventricle, known as the left ventricular OS, contains the nonmuscular fibrous mitral valve to the left and posterior and the aortic valve to the right and anterior. With the anterior leaflet of the mitral valve hanging into the left ventricle, the chamber of the left ventricle is divided into the inflow tract posteriorly and the outflow tract anteriorly.

The mitral leaflets are somewhat scalloped (Fig. 18). At the commissures fan-like arrangements of chordae can be identified on the ventricular aspect. The two major commissures separating the anterior and posterior leaflets are the anterolateral and posteromedial commissures. The posterior leaflet is seen to have two other minor commissures subdividing the leaflet into anterolateral, medial and posteromedial scallops. The clinical significance of this minor anatomical point is that each of these scallops can prolapse back into the left atrium during systole, forming a distinct angiographic and echocardiographic picture. In the majority of cases mitral regurgitation caused by mitral valve prolapse is amenable to mitral valve repair rather than replacement.

The chordae originating from the papillary muscles attach to the free margins of the leaflets and also onto the ventricular surface of the leaflet beyond the free edge. This architecture subdivides the septal leaflet into a rough crescentic area adjacent to the free edge (1 cm wide at the center of the leaflet, narrowing as it approaches the commissures) and a smooth portion that extends medially and superiorly; in the anterior leaflet, the smooth portion becomes the intervalvular membrane that attaches to the noncoronary and left coronary portion of the aortic annulus. The posterior leaflet hangs from that portion of the mitral annulus that is adjacent to the position of the coronary sinus.

Closure of the mitral valve during systole is accomplished by coapting the atrial surfaces of the two leaflets. The overlap of the closed leaflets is important to the proper seal of the valve. The chordae tendineae keep the mitral leaflets from prolapsing into the left atrium. The chordae originate from the anterolateral and posteromedial papillary muscles and distribute to both leaflets. In contrast to the tricuspid valve, there are no mitral valve chordae that attach to the ventricular septum in the normal heart. The mitral valve apparatus includes three groups of chordae:

1. First-order chordae arise as fibroelastic cords from the tips of the papillary muscles and insert into the free margin of the valve. These chordae can divide two or three times before their leaflet attachment.
2. Second-order chordae at or near the tips of the papillary muscles arise as strong tendinous cords and attach to the ventricular surface or rough area of the anterior leaflet.
3. Third-order chordae originate from the left ventricular wall near the atrioventricular ring and attach to the ventricular surface of the posterior leaflet only.

LEFT VENTRICLE

The left ventricle has an oblong, truncated shape with an open end (prolate ellipsoid), the left ventricular OS, which contains the mitral valve posteriorly and the aortic valve anteriorly. The ventricle tapers from the OS to the apex (Figs 5, 7 and 19). Viewing the heart from its anterior aspect, the left ventricular wall forms the gently curving obtuse margin of the heart (Fig. 5). The ventricular wall extends anteriorly to the interventricular sulcus, and the right anterior wall of the left ventricle is formed by the interventricular septum. As evident in the short

axis, the wall of the left ventricle is thicker than that of the right ventricle (Fig. 16), normally about 1 cm thick, and is divided into an outer two-thirds zone of compact muscle and an inner one-third trabeculated zone. The trabeculae carneae of the left ventricular inner surface are thinner and more delicate than those of the right ventricle; at the apex they can have the configuration of a rope hammock. Remodeled overtime by high left ventricular systolic pressures, these muscle ridges may become flattened, but in hypertrophied hearts they can be quite robust. Without many trabeculae carneae superiorly, the left ventricular aspect of the septum in the outflow tract appears smooth as compared with the septum of the right ventricle (Fig. 19).

In diastole, the half-football-shaped left ventricle approximates an ellipsoid of revolution. The two papillary muscles project into the left ventricular cavity from their anterolateral and posteromedial positions (Figs 18 and 19). Although the number and positions of the papillary muscles are constant, there are a variable number of papillary muscle heads, usually two or three, with the posteromedial one more variable than the anterolateral.

The ventricles viewed in short axis show the left ventricle to be circular (Fig. 16). Recall that the anterior wall being the interventricular septum bulges toward the right, making the cross section of the right ventricular cavity crescentic. The outflow tract of the left ventricle shows the smooth surface of the muscular septum superiorly. Just proximal to the aortic valve the interventricular septum includes the membranous portion that abuts the aortic annulus (Fig. 20). The opposing margin of the left ventricular outflow tract is the anterior leaflet of the mitral valve, especially at its junction with the annulus. From the left ventricular outflow tract, the membranous septum appears as a small rhomboid membrane present between the lines of attachment of the right and noncoronary leaflets at the aortic annulus. Viewing the opaque membrane en face, it is difficult to appreciate the proximity of the septal leaflet of the tricuspid valve on the right ventricular aspect (Fig. 13). In fact, on the right side the septal leaflet and anterior leaflet of the tricuspid valve attach to the middle of the membranous septum. Therefore, part of the membranous septum on the right is above the attachment of the tricuspid valve and is called the atrioventricular portion of the membranous septum. Congenital defects in this area of the septum can result in a left ventricle-to-right atrial shunt. Defects in other areas of the membranous septum produce a purely interventricular shunt.

As in the right ventricle, the anatomic left ventricle is characterized by a number of distinctive anatomic features:

- The shape is oblong, shaped like a prolate ellipsoid.
- The interventricular septal surface is smooth.
- There is fibrous continuity between the mitral and the aortic valves. Thus, the inflow and outflow tracts of the left ventricle are separated only by the anterior leaflet of the mitral valve.
- The apical trabeculae are thin and cobweb like.
- The left atrioventricular valve, the mitral valve, is bicuspid and its chordae insert only into papillary muscles, not the ventricular septum.

The clinical importance of these differences is that many can be recognized by echocardiography and other imaging techniques. These anatomic details are keys to discerning congenital malformations.

The orientation of the muscle bundles of the left ventricle is critical to understanding the mechanics of left ventricular contraction. Fiber orientation is a complex topic, however, beyond the scope of this anatomy chapter. In simple terms, the compact outer two-thirds of the left ventricular free wall are comprised of syncytial layers of myocardial cells supported loosely by a continuous matrix of fibrous tissue. The great majority of the muscular septum is compact, with myofiber contributions from both ventricles. In general the muscle layers of the left ventricle are oriented orthogonally, each layer spiraling toward the cardiac apex. This arrangement is responsible for the pump function of the ventricles—the longitudinal shortening that pulls the base of the left ventricle toward the apex and the circumferential shortening that rapidly reduces the left ventricular volume and ejects the stroke volume during systole. At the same time the orthogonal spiral arrangement of myofibers generates a twisting motion of the left ventricle during systole. Thus, the muscle bundles are arranged such that they form superficial and deep layers as well as circumferential bands that with ventricular contraction shorten both the minor as well as the major (longitudinal) axis of the left ventricle. These motions allow for the estimation of stress in different layers of the left ventricle by speckle-tracking Doppler echocardiography and magnetic resonance imaging.

AORTIC VALVE

The aortic valve guards the outlet from the left ventricle. The valve is semilunar with three leaflets suspended from the aortic annulus (Figs 8, 17 and 20). The leaflets are named for their positions *in situ* relative to the body axis—right (or anterior) coronary leaflet and left (or left posterior) coronary leaflet and noncoronary (or right posterior) leaflet. During diastole the aortic walls in the root of the aorta expand well-beyond the limits of the aortic annulus, increasing the volumes of the three sinuses of Valsalva and visible angiographically. The coronary arteries usually arise from the aortic wall that surrounds these sinuses. Like the pulmonary valve leaflets, the aortic leaflets have noduli Arantius at the midportion of the free margin and crescentic lunulae (Fig. 20).

The anatomic relationships of the sinuses of Valsalva are of clinical importance. The right coronary's sinus bulges into the posterior aspect of the right ventricular outflow tract (Fig. 8). The left coronary's sinus abuts the outlet septum anteriorly and faces the transverse sinus posteriorly, as well as the right pulmonary artery as it passes posterior to the ascending aorta. The noncoronary sinus is adjacent to the medial wall of the right atrium and the interatrial septum. Injury or aneurysmal formation and rupture in each of these sinuses can result in fistulous communication into these respective cardiac chambers or even into the pericardial space.

In diastole, the three aortic leaflets close by apposition of their ventricular surfaces. Along the edges near the commissures, the leaflets commonly contain holes or fenestrations (Fig. 20). Normally these do not cause valvular regurgitation, because they are above the line of closure. Nonetheless, these fenestrations as well as incomplete aortic leaflet coaptation are

considered the cause for the small aortic regurgitation jets seen in about 5% of normal hearts by Doppler echocardiography. In systole, the opening of the aortic valve forms a rounded triangular orifice with flexion at the wall attachments of the leaflets. If this flexion area becomes calcified (as is often seen in advanced age), various degrees of aortic valve stenosis occur.

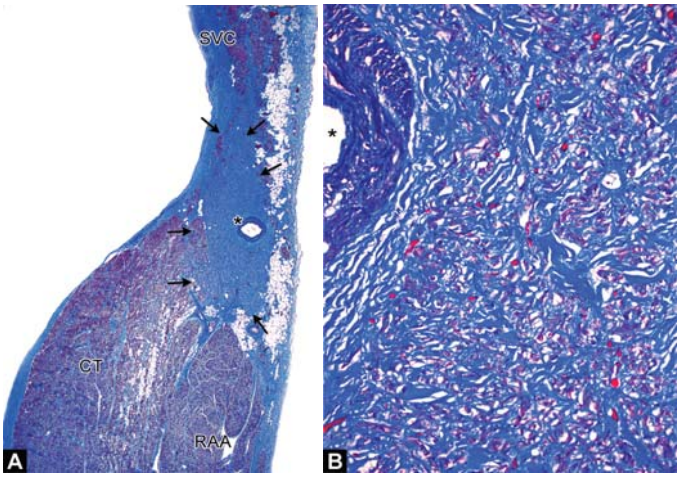
The fibrous aortic annulus or ring forms the junction between the outflow tract (or subaortic sinus) of the left ventricle and the aorta. The transition from cardiac muscle to the smooth muscle of the aortic media occurs at this junction. The actual attachments of the aortic leaflets at the aortic annulus form crescents, the highest points being the attachments at the commissures. Thus, the composition of the heart muscle-smooth muscle interface in the wall varies according to the level.

CONDUCTION SYSTEM

Although the work of the heart is dependent on myocardial contractility, the mechanism that initiates and provides order to the phasic contraction and relaxation of the cardiac muscle is dependent on the other two fundamental properties of cardiac muscle, automaticity and conductivity. The conduction system—including nodes, bundle branches and Purkinje fibers—consists of modified myocardial cells that are positioned to either facilitate or slow impulse conduction. Both the sinoatrial node and the atrioventricular node are comprised of specialized myocardial cells with highly developed automaticity, and the myocardial cells of the His bundle, bundle branches and Purkinje fibers have the specialized property of rapid conductivity.

None of the collections of specialized muscle in the heart is discernible grossly. All were discovered through tedious dissection and microscopy. The major portion of the adult sinoatrial node, a 3 by 10 mm body of pacemaker nodal cells, normally initiates the depolarization that causes the atrial muscle to contract. The node is situated in subepicardial tissue superolaterally near the junction between the superior vena cava and the right atrial appendage; in other words, the specialized muscle lies within the sulcus terminalis (Figs 3 and 5). The sinoatrial node, also called the SA node, is derived from the right horn of the embryonic sinus venosus.[1] The SA node receives its blood supply from the sinoatrial nodal artery (Fig. 3). This small artery is located in a relatively constant position centrally within the specialized muscle (Figs 21A and B—histology of SAN). Although the SA node is often considered as a discrete sausage-shaped mass, an attenuated extension of specialized muscle trails inferiorly along the sulcus terminalis.[2] The electrical impulse initiated in the specialized muscle spreads over the working atrial muscle in organized fashion along preferential pathways; however, there are no histologically recognizable anatomic tracts between the SA node and the atrioventricular or AV node.[3] Thus, the preferential conduction likely occurs along bundles of working muscle in particular orientation. For example, along the anterior aspect of the transverse sinus, a fascicle of atrial muscle serving as a pathway carrying the impulse from the right atrium to the left atrium is called Bachmann's bundle.

After the impulse spreads through the atrium, it reaches the atrioventricular node (AV node) (Figs 10 and 22). From the



FIGURES 21A AND B: Histology of sinoatrial node. At low magnification (A), the sinoatrial node (outlined by arrows) is seen on the epicardial aspect between the superior vena cava (SVC) and the right atrial appendage (RAA). Relatively constant in position, the artery to the SA node indicated by the stars courses within the specialized muscle. At high magnification (B), the specialized muscle fibers (red in this trichrome stain) are coursing in haphazard array, separated by collagen (blue). (Abbreviations: CT: Crista terminalis; RAA: Right atrial appendage)

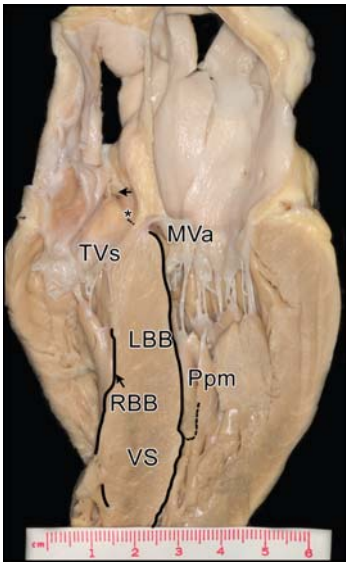
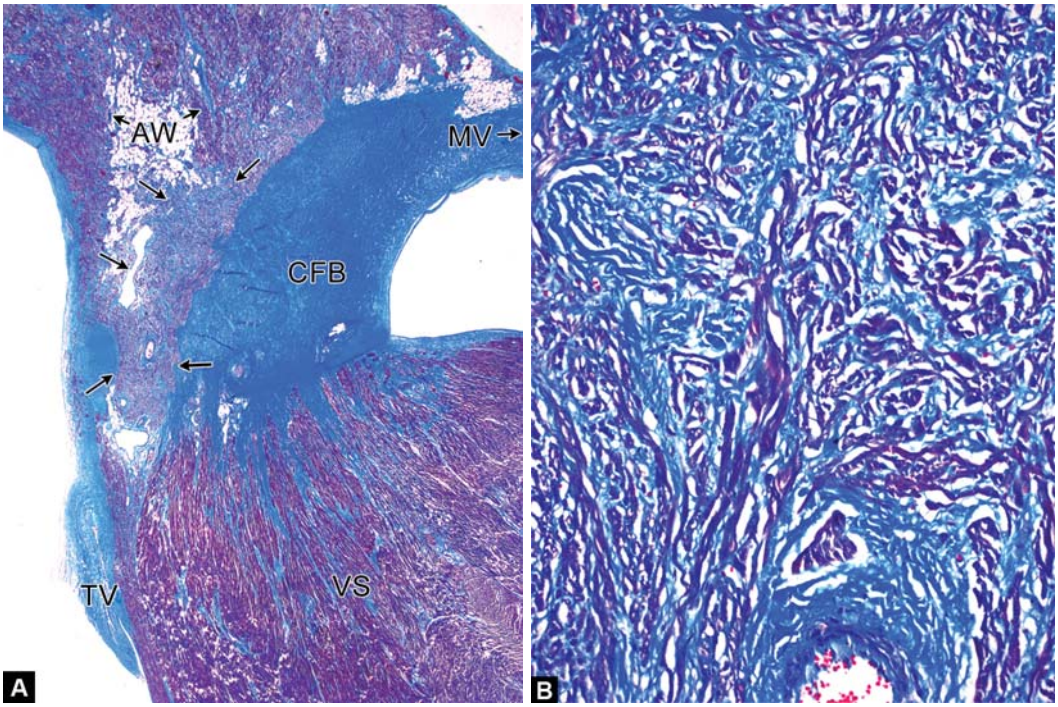


FIGURE 22: Position of atrioventricular node and course of atrioventricular bundle. In a simulated four-chamber view with the inferior side of Koch's triangle represented by the coronary sinus os (arrow), the more anterior atrioventricular node (*) abuts the central fibrous body and connects with the atrioventricular bundle (- - - - -). The bundle courses anteriorly along the inferoposterior margin of the membranous portion of the interventricular septum (not shown) and projects left and right bundle branches (LBB and RBB) subendocardially on either side of the muscular septum. (Abbreviations: MVa: Anterior leaflet of mitral valve; Ppm: Posteromedial papillay muscle; TVs: Septal leaflet of tricuspid valve; VS: Ventricular septum)

endocardial aspect within the right atrium, the landmarks for the AV node form Koch's triangle bounded by the tendon of Todaro superiorly, the annulus of the septal leaflet of the tricuspid valve apically and an imaginary line in the long axis through the coronary sinus ostium inferiorly (Fig. 10). The AV node is comprised of a small bean-shaped mass of specialized myocardial cells that abuts the right fibrous trigone between the right and left atria (Figs 23A and B). In 90% of hearts, the



FIGURES 23A AND B: At low magnification (A), the atrioventricular node is seen abutting the central fibrous body (CFB). Somewhat variable in its course, the artery to the AV node is present within the specialized muscle. At high magnification (B), the narrow-caliber specialized muscle fibers (red in this trichrome stain), similar to the SA node, appear haphazard in orientation and are separated by collagen (blue). (Abbreviations: AW: Atrial wall; MV: Mitral valve; TV: Tricuspid valve; VS: Ventriculum septum)

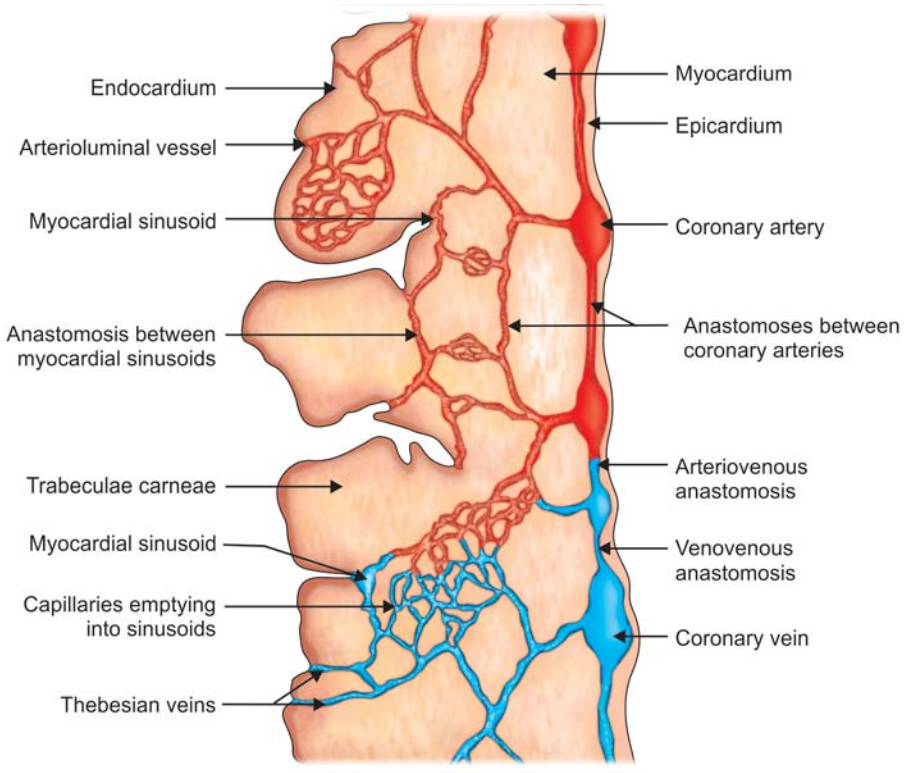


FIGURE 24: Relationship of the intramural vascular channels of the left ventricular wall (*Source:* Modified from Barry A, Patten BM. Structure of the human heart. In: Gould SE (Ed). Pathology of the Heart. Springfield, IL: Charles C. Thomas; 1968)

AV nodal artery originates from the right coronary artery near the crux of the heart. In the other 10% of hearts, the artery arises from the left circumflex coronary artery.

Slowing conduction, the AV node conveys the impulse to the His (or atrioventricular) bundle that is approximately 10–20 mm in length and 1–3 mm in diameter (Fig. 24). From the apex of Koch's triangle (angle formed by the junction between the tendon of Todaro and the annulus of the septal leaflet of the tricuspid valve, Fig. 10), the His bundle courses anteriorly within the right fibrous trigone and passes down to

the crest of the muscular interventricular septum, posterior and inferior to the membranous septum. Within the His bundle is an artery arising from either branches of the left anterior descending coronary artery or posterior ventricular branches of the right or left circumflex coronary artery. At the crest of the muscular interventricular septum, the His bundle divides into the right and left bundle branches.

The left bundle branches spread out in a subendocardial fan-like distribution posteroinferior to the membranous portion of the interventricular septum. Although the subendocardial left bundle fibers are not so discrete anatomically, they function as anterior and posterior fascicles (or divisions), with possibly an intermediate fascicle. The anterior fascicles fan out toward the apex, forming a subendocardial plexus that branches at the anterolateral papillary muscle. The posterior fascicles reach the area of the posteromedial papillary muscle and spread out as Purkinje fibers to the rest of the left ventricular muscle. The Purkinje fibers spread from the subendocardium intramurally to the subepicardium.

From the His bundle the right bundle branch continues 10–20 mm as a discrete 1–3 mm diameter structure deeply buried in the muscle of the interventricular septum; it resurfaces near the papillary muscle of the conus (muscle of Lancisi) superiorly on the septomarginal trabeculum. The subendocardial right bundle branch becomes more compact in passing down this robust trabeculum toward the apex. The right bundle can pass over the moderator band to the right ventricular free wall or, more frequently, passes over one of the trabeculae carneae to reach the ventricular wall near the anterior papillary muscle of the right ventricle. When it reaches the free wall, it branches into a finely distributed, subendocardial anastomosing plexus. A small branch bends sharply back along the upper interventricular septum to the conus. The blood supply to the right bundle branch is principally from the septal branches of the left anterior descending coronary artery.

In some hearts there are accessory muscle bundles that span the fibrous atrioventricular rings, connecting atrial to ventricular muscle directly and thus bypassing the AV node. Called bundles of Kent,[4] these muscle bridges offer low-resistance pathways for the impulse to travel from atrium to ventricle, and they form the anatomic basis for the Wolff-Parkinson-White syndrome or accelerated atrioventricular conduction. Kent bundles can be situated anywhere along the atrioventricular annuli. In 1931, Mahaim[5] described "paraspecific" septal fibers leaving the left side of the His bundle at the membranous septum and reaching the upper left septal muscle, and James[6] described fibers that bypass the AV node and join the His bundle. These muscle fiber bridges that bypass the AV node form the anatomic basis for the described elecrocardiographic abnormalities.

CORONARY ARTERIES

The main coronary arteries arise from funnel-like openings in the aortic wall at the right coronary leaflet and the left coronary leaflet, most often in the midline of the sinuses (Figs 17 and 20). There is usually a single ostium for each main coronary artery, left and right; however, occasionally there will be a separate small ostium near the right coronary ostium for the conus branch of the right coronary artery. Another common variant is a separate ostium for the left anterior descending and the left circumflex coronary artery. Thus, at coronary arteriography, the perceived absence of a left anterior descending or a left circumflex coronary may be due to the selective catheterization of one of the two ostia.

Arising from the left posterior aortic sinus of Valsalva, the left main coronary artery is a muscular artery that passes anterior and somewhat leftward, posterior to the right ventricular outflow tract and anterior to the left atrium (Fig. 8). The left main coronary artery is short (usually less than 1 cm) and bifurcates into the left anterior descending and left circumflex coronary arteries. The coronary arteries are enveloped by loose connective tissue and epicardial fat. The left anterior descending coronary lies in the anterior interventricular sulcus, extending down the anterior surface of the heart inferiorly to the apex and frequently around the apex to the distal part of the inferior cardiac surface (Figs 3 and 5). The anterior descending coronary artery gives off a number of branches including a first and often a second diagonal branch that supply the anterior left ventricular free wall, one or more large septal perforator branches and a number of septal branches that supply the anterior two-thirds of the muscular interventricular septum. On the cardiac surface there are small ventricular branches that supply the medial aspect of the right ventricular free wall.

Frequently there is a prominent coronary artery (the intermedius coronary artery) arising from the bifurcation of the left main coronary. This artery supplies the anterolateral portion of the left ventricle.

Coursing in the left atrioventricular sulcus, the circumflex coronary artery gives off superiorly 1–3 anterior branches, one lateral and one posterior branch to the left atrial wall. The circumflex artery continues in the atrioventricular groove around the left lateral aspect of the heart. Several branches called obtuse marginal arteries supply the anterolateral wall of the left ventricle. Deep to the coronary sinus, the circumflex coronary artery continues posteroinferiorly to the crux of the heart. In about 15% of hearts, the circumflex coronary artery crosses the crux on the diaphragmatic surface and turns toward the apex to become the posterior descending coronary artery supplying the inferior wall of the left ventricle and also portions of the inferior right ventricle adjacent to the posterior interventricular sulcus. With this coronary artery arrangement the heart is said to have a left-dominant circulation. In about 25% of hearts, the superior vena caval ostial artery that gives rise to the sinoatrial nodal artery is a branch of the circumflex coronary artery, but in 70% of hearts the sinoatrial artery arises from the proximal portion of the right coronary artery. In the remaining 5% of hearts, the blood supply to the sinoatrial node has a dual source from both right and left circumflex coronary arteries.

The right coronary artery originates from the anterior or right coronary sinus of Valsalva and passes rightward under the right atrial appendage in the right atrioventricular sulcus (Figs 3, 8 and 17). The first branch is the right ventricular conal artery that passes anteriorly to the right ventricular outflow tract. In about 20% of hearts, the conal artery arises from a separate orifice in the right coronary sinus (Fig. 20). This clinically important vessel becomes the major source of collateral circulation to the left anterior descending coronary system when that vessel is occluded. At catheterization of patients with

obstructed left anterior descending arteries, the conal branch should be visualized to see if the distal anterior descending is patent beyond the obstruction. Another early branch from the right coronary artery is the artery to the superior vena caval orifice that gives rise to the sinoatrial nodal artery (Fig. 3). The right coronary artery gives branches superiorly to the right atrial wall and one to three branches inferiorly to the free wall of the right ventricle. At the acute margin of the heart, the acute marginal artery is a large vessel supplying the anterior wall of the right ventricle. The right coronary artery continues inferiorly in the right atrioventricular sulcus, passing under the inferior vena cava at its connection with the right atrium. The right coronary artery continues posteriorly to the crux of the heart and makes an anterior loop into the posterior atrial septum. In 90% of hearts, a branch—the AV nodal artery—passes in the inferior interatrial septum superiorly to supply the AV node. After giving off the AV nodal artery, the right coronary artery turns toward the apex to course in the posterior interventricular sulcus as the posterior descending coronary artery that supplies the posteroinferior surface of the left ventricle, parts of the posterior right ventricle adjacent to the posterior interventricular sulcus and, by small septal perforators, the posterior one-third of the interventricular septum (Figs 7 and 9). When the posterior descending coronary artery is a continuation of the right coronary artery as occurs in 75% of hearts, the heart is said to have a right-dominant circulation. In some hearts, the posterior descending coronary artery wraps around the apex and supplies the distal portion of the anterior left ventricular wall. The terminal distribution of the left circumflex and the right coronary arteries posteriorly are reciprocally related, and the blood supply to the posterior wall of the left ventricle depends on whether there is a right dominant or a left dominant circulation. In 5% of hearts, the right coronary artery is a congenitally small vessel, supplying only branches to the right ventricle, with the entire left ventricle supplied by the left coronary artery.

INTRAMURAL VESSELS

The extramural coronary arteries that lie on the epicardial surface give off branches that penetrate the walls of all four cardiac chambers. These intramural resistance vessels do not develop atherosclerosis. A complex meshwork of anastomosing vessels arises from these perforating arteries, eventually supplying capillary vessels that form a network around the myocardial muscle fibers. The pattern of this branching varies, some extending down to the subendocardial areas where they spread out, others arising at right angles from the perforating arteries in a comb-like pattern at all levels of the ventricular wall (Fig. 24). There is controversy as to whether there are anastomosing connections between the perforating arteries in the subendocardial region or whether they are end-arteries. Most likely, there are both patterns present. The endocardium, especially in the papillary muscles, are supplied either through the distal portion of the epicardial coronary arteries or from the left ventricular cavity through luminal channels. In fact arterioluminal channels between the arteriolar arteries and the left ventricular cavity via intertrabecular spaces have been described.[7]

There have been many reports of direct connections of arteriolar vessels emptying into ventricular and atrial cavities, the names of these vessels depending on the connections and the histology of the small vessels involved. Other vessels or channels called sinusoids are thin walled and capillary like, but with lumens of variable size and shape; some of these vessels connect directly to the ventricular chambers and some to venous structures that then empty into the ventricles. These have been called venoluminal channels. The ostia of these various vessels can be seen on careful inspection of the endocardium of the right and left ventricles, and collectively they are called thebesian veins or, more appropriately, thebesian vessels. They are more numerous or at least visible in the atria than in the ventricles.

Postmortem radiographic and dissection studies have documented subarteriolar collateral connections from about 100 μm to over 200 μm between the coronary arterial systems. These collateral vessels are most numerous near the apex and through the muscular interventricular septum, but they may also be identified in the interatrial septum, at the crux of the heart, between the sinoatrial nodal artery and other atrial arteries, as well as over the anterior surface of the right ventricle. In the human with nonobstructed coronary arteries, there are only rarely epicardial collateral vessels. When atherosclerosis results in progressive obstruction to the epicardial coronary arteries, the intramural potential collateral vessels enlarge and become clinically important. There are also extracoronary anastomotic connections between the coronary arteries and the systemic arteries, primarily at the base of the great vessels and around the ostia of the pulmonary veins and vena cavae. The systemic arteries involved are primarily the pericardial vessels derived from the internal mammary and intercostal arteries, usually at the pericardial reflections. In general, these systemic-to-coronary artery collaterals are clinically unimportant, even in obstructive coronary artery disease.

CORONARY VEINS

The cardiac veins generally follow the epicardial distribution of the coronary arteries. They lie embedded in epicardial fat and are superficial to the coronary arteries. They receive blood from the myocardial capillaries and carry it back to the right atrium. Most of the venous return to the right atrium is via the coronary sinus (Figs 25 and 26).

The great cardiac vein accompanies the anterior descending coronary artery in the anterior interventricular sulcus. It drains toward the base of the heart and then follows the left circumflex coronary artery posteriorly in the left atrioventricular sulcus, joining the coronary sinus just beneath the left inferior pulmonary vein. The great cardiac vein has valves at its connection with the coronary sinus. Throughout its course it receives veins from the anterior muscular interventricular septum, the anterior and lateral walls of the right and left ventricles, and the left atrium. Coursing on the diaphragmatic surface of the left ventricle, the posterior cardiac vein of the left ventricle accompanies the circumflex coronary artery to connect with the coronary sinus at its distal end.

The middle cardiac vein lies in the posterior interventricular sulcus overlying the posterior descending coronary artery; it receives tributaries from the posterior muscular interventricular septum and posterior ventricular walls and empties into the

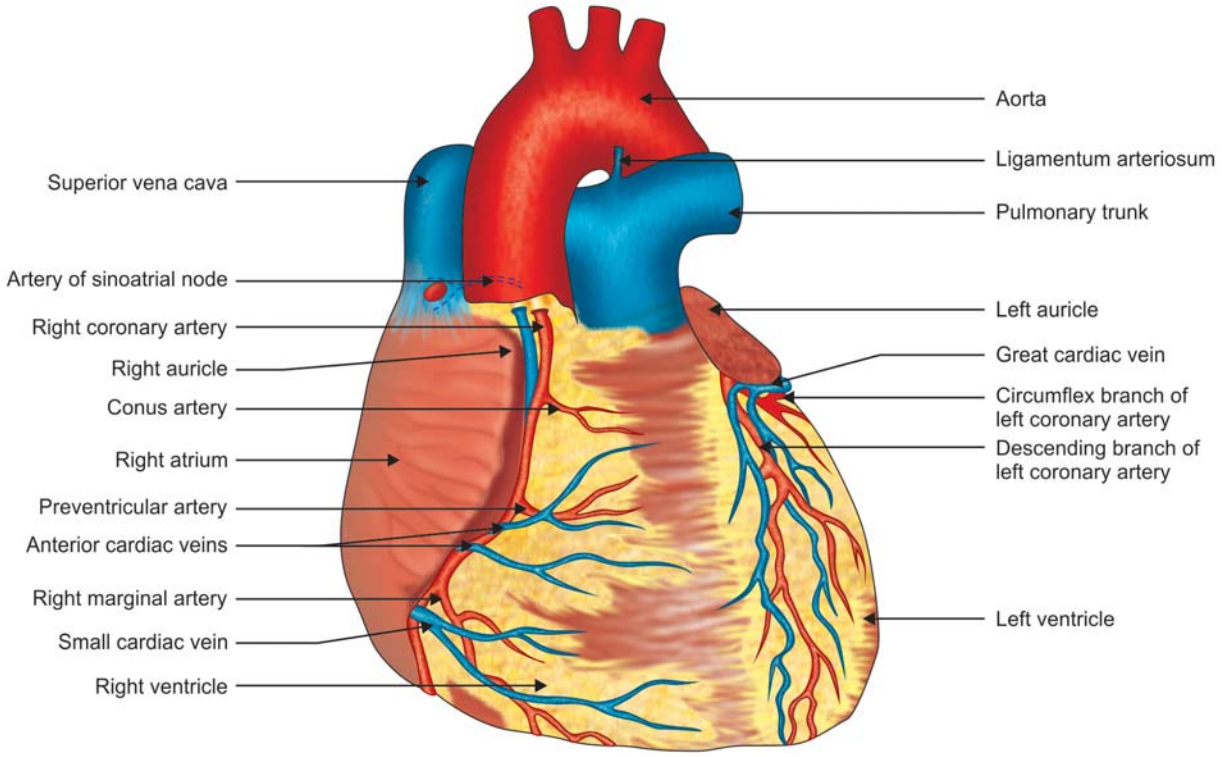


FIGURE 25: Ventral surface of the heart showing coronary arteries and veins (*Source:* Modified from Barry A, Patten BM. Structure of the human heart. In: Gould SE (Ed). Pathology of the Heart. Springfield, IL: Charles C. Thomas; 1968)

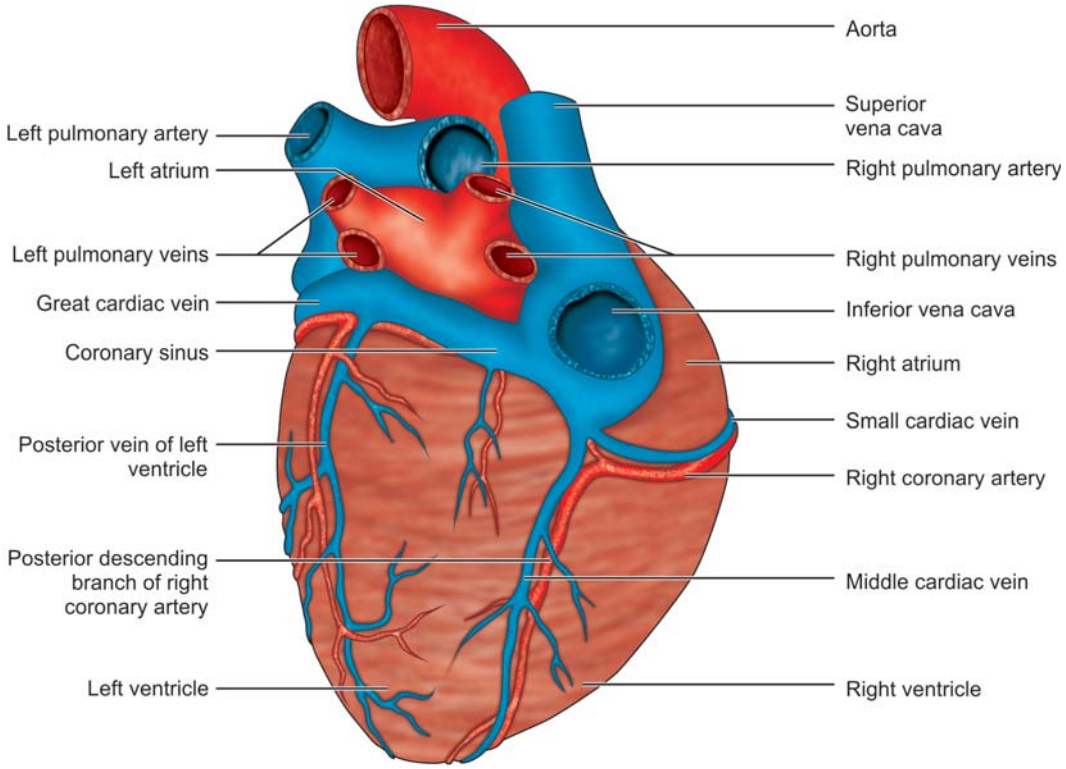


FIGURE 26: Dorsocaudal surface of the heart showing coronary arteries and veins (*Source:* Modified from Barry A, Patten BM. Structure of the human heart. In: Gould SE (Ed). Pathology of the Heart. Springfield, IL: Charles C. Thomas; 1968)

coronary sinus close to the coronary sinus ostium. The small cardiac vein on the surface of the right ventricle accompanies the acute marginal artery and drains the anterolateral wall of the right ventricle. It follows the course of the right coronary artery in the right atrioventricular sulcus, receives tributaries from the right atrium and empties into the coronary sinus near its ostium at the right atrium. On the anterior aspect of the right ventricle there are 3–12 anterior cardiac veins that empty through the ventricular wall in the conal region, into the small cardiac vein, or directly into the right atrium through separate orifices.

The coronary sinus is the continuation of the great cardiac vein; it is 3–5 mm in diameter and 2–5 cm in length. It courses in the left atrioventricular sulcus inferiorly, receiving veins from the left atrial and ventricular walls. A small vein draining from the roof of the posterior left atrium between the left and right pulmonary veins, called the oblique vein of the left atrium or vein of Marshall, is the remnant of the embryologic left common cardinal vein. When this cardinal vein remains patent, it is called a persistent left superior vena cava and connects the left innominate vein with the coronary sinus. This is clinically important in that catheters passed through the left median basilic vein enter the right atrium through the coronary sinus and are difficult to maneuver into the right ventricle and out the pulmonary artery.

CARDIAC LYMPHATICS

In the subendocardial connective tissue of all four cardiac chambers there is a plexus of valved lymphatic vessels. These channels drain through a web of anastomosing lymphatic vessels that envelop the myocardial fibers. The lymphatics course through the interstitial connective tissue, draining toward the epicardium where they form an epicardial lymphatic plexus. These vessels join on the epicardium to form several large lymphatic vessels that follow the course of the epicardial coronary arteries and veins. The major lymphatic trunks drain into the atrioventricular sulcus and form a single large trunk that passes over the top of the left main coronary artery and under the arch of the main pulmonary artery. This trunk courses to the left of the aortic root where it exits the pericardial sac to join the left mediastinal lymphatic plexus, draining into the mediastinal lymph nodes and finally into the thoracic duct.

CARDIAC INNERVATION

Both sympathetic and parasympathetic afferent and efferent nerves innervate the heart. The preganglionic neurons of the sympathetic chain are located in the upper five or six thoracic levels of the spinal cord and synapse with second-order neurons in the cervical sympathetic ganglia. The postganglionic sympathetic axons terminate in the heart and on the adventitia of the great vessels. The parasympathetic preganglionic neurons are located in the dorsal efferent nucleus of the medulla; these axons project as branches of the vagus nerve to the heart and great vessels where they synapse with second-order neurons in epicardial ganglia and adventitia of the great vessels (Fig. 27).

Both sympathetic and parasympathetic fibers enter the heart for the most part by common autonomic nerve trunks from the mediastinum by way of the dorsal mesocardia. The autonomic nerves are interdigitated within two neuroplexuses, divided for convenience into a superficial cardiac plexus on the anterior

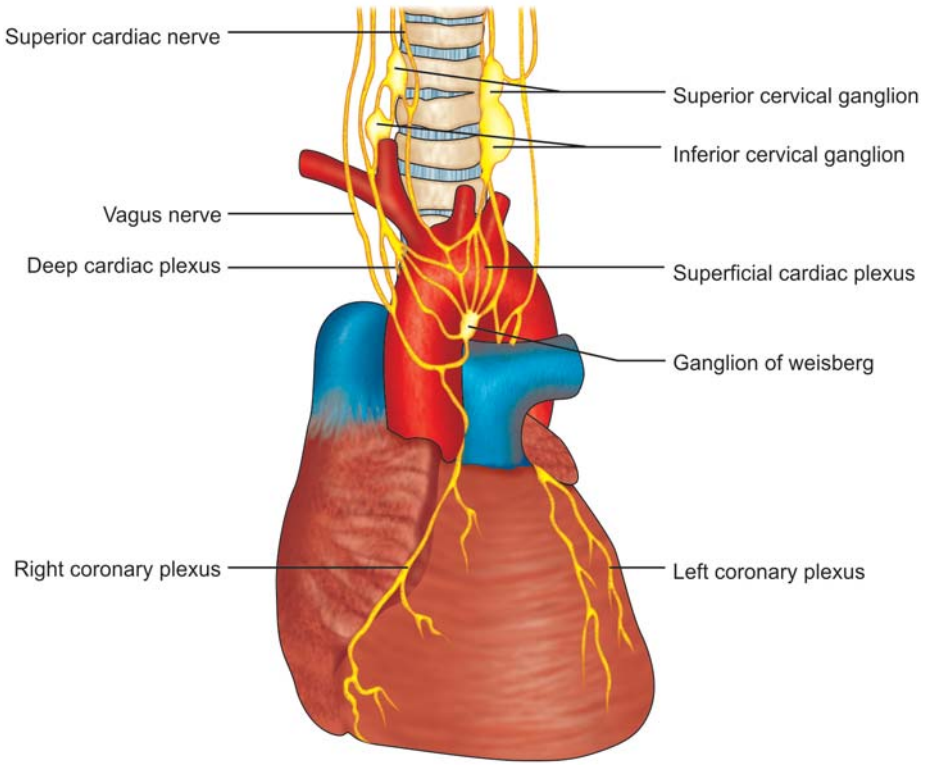


FIGURE 27: Autonomic nerve supply to the heart (*Source:* Modified from Tandler J. In: Anson BJ (Ed). Lehrbuch der Systematischen Anatomie. Berlin: Springer-Verlag; 1926)

ascending aorta, the aortic arch and the pulmonary trunk, as well as a deep cardiac plexus located above the bifurcation of the trachea on the right between the trachea and the right side of the aortic arch.

Since the left fourth and sixth embryonic aortic arches develop into the left aortic arch and the ductus arteriosus, cardiac branches of the left vagus nerve and left-sided sympathetic nerves distribute primarily to the aortic arch and pulmonary trunk, forming the arterial and conotruncal plexi. Embryologically the venous side favors the right-sided structures, since the right superior vena cava is retained, and the sinus venosus shifts to the right from midline and is incorporated into the right atrium. Therefore, the venous part of the heart is associated with cardiac nerves from the right cardiac sinoatrial plexus.

The sympathetic nerves arise from the superior and middle cervical ganglia, giving off the superior and middle cardiac nerves respectively. The inferior cardiac nerve originates from the fusion of the inferior cervical ganglion and the first thoracic ganglion, called the stellate ganglion. Each vagus nerve contributes to the cardiac plexuses by way of the superior and inferior cervical nerves, as well as a thoracic cardiac branch arising from the recurrent laryngeal nerve. The superficial cardiac plexus receives its contributions from the inferior cervical cardiac branch of the left vagus and the left superior cardiac nerves of the sympathetic nervous system. The ganglion of Wrisberg is associated with this plexus and lies between the aortic arch and the pulmonary trunk to the right of the ligamentum arteriosum.

The deep cervical plexus receives contributions from three right-sided sympathetic cardiac nerves, three cardiac branches of the right vagus nerve, three superior cervical and thoracic cardiac branches of the left vagus nerve, the middle and upper cardiac nerves from the sympathetic trunk, and direct branches from the five or six thoracic sympathetic ganglia.

From these autonomic nervous system plexi, the sympathetic and vagal nerves distribute to the walls of the great vessels, including the SA and AV nodes and the bundle of His. Sympathetic nerves and some parasympathetic nerves accompany the coronary arteries and innervate the ventricles. In the same nerves and through the same pathways, both afferent sympathetic and parasympathetic fibers pass back to the central nervous system.

CONCLUSION

Cardiac anatomy is complex and a thorough understanding requires detailed knowledge on a number of levels from gross relationships to histology and ultrastructure. The field has evolved over centuries, and information continues to accrue, stimulated in large part by clinical advances. This chapter provides an overview of cardiac anatomy that is relevant to general cardiology practice. This anatomical information forms the basis for an understanding of not only radiographic studies but also cardiac pathophysiology and the approach to therapeutic interventions. For various subspecialty works, more detailed information is available in the published literature.

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Chapter 2

Cardiac Function in Physiology and Pathology

Joel S Karliner, Jeffrey Zimmet

Chapter Outline

- Beta-adrenergic Receptor-mediated Signaling
- Calcium Regulation
- Links Between β-adrenergic Signaling and Calcium Regulation
- Mitochondria
- Cardiac Hypertrophy
- α_1-adrenergic Receptors and Hypertrophy
- Congestive Heart Failure
- Micro-RNAs
- Ischemia/Reperfusion Injury
- Mechanisms of Cardioprotection
- Aging

INTRODUCTION

Synchronous cardiac contraction and relaxation require the coordination of numerous complex systems both within and without the cardiac myocyte. The human heart has evolved to integrate these pathways to provide efficient energy production and utilization in order to maintain blood supply to other vital organs as well as to the heart itself. Disruption of these pathways can be both cause and effect of cardiac injury and failure. Among the two most prominent pathways that require moment to moment coordination and integration are the beta-adrenergic signaling pathway and calcium handling. Both are central to cardiac contraction and relaxation, are abnormal in pathophysiologic states, and are targets for therapeutic intervention.

BETA-ADRENERGIC RECEPTOR-MEDIATED SIGNALING

Located on the cell surface, β-adrenoceptors are prototypical G-protein coupled receptors. They are liganded by the naturally occurring catecholamines, norepinephrine and epinephrine. Norepinephrine is released from synaptic vesicles of sympathetic nerves that innervate the heart and is principally responsible for cardiac chronotropy and contractility. Signaling results from the downstream activation of cyclic adenosine monophosphate (cAMP), initiated by liganding of the receptor by the catecholamine. Through a series of complex interactions, cAMP activates the contractile apparatus and also influences the conductance of ion channels that govern heart rate.

Numerous studies have established that the β-adrenergic receptor is highly regulated. After the receptor binds to a stimulatory guanine nucleotide regulatory protein (Gs), adenylyl cyclase is activated to hydrolyze ATP and produce cAMP. The G-protein-receptor complex can be uncoupled from its downstream signaling effectors by a molecule called G-protein receptor kinase-2 (GRK-2, aka β-arrestin) in a process termed desensitization. The receptor then can recycle to the cell surface. These uncoupling proteins also target receptors to clathrin-coated pits resulting in receptor downregulation and eventual proteolysis. It has recently been shown that GRKs by themselves can activate parallel signaling pathways such as stretch-associated angiotensin-II activation.[1]

In the mid-20th century it was observed that catecholamines were elevated in patients with chronic congestive heart failure (CHF) and that this abnormality could be a cause of cardiac dysfunction in such individuals. This hypothesis led to the idea that blocking β-adrenoceptors might be a useful strategy in heart failure. Although it took many years to prove this hypothesis, β-blocker therapy is now routine in heart failure patients. Along the way, much was learned about β-receptors.

There are two principal types of β-receptors: β_1 and β_2. Early studies by Bristow and his colleagues in tissue obtained from advanced heart failure patients revealed that β_1 receptor density was reduced, while β_2 receptor density actually increased and switched its coupling to a guanine nucleotide inhibitory protein (Gi).[2] In heart failure the increase in β_2 receptor density is thought to be a compensatory response which is aimed at retaining adrenergic drive but which instead may result in further cardiotoxicity.

What adverse mechanisms are mediated by β-receptors in heart failure? Polymorphisms in the β_1- and α_{2C}-adrenergic receptors may play a role in some patients.[3,4] Another recently described mechanism in a rodent model may provide at least a partial answer.[5] β_1 and β_2 receptors are normally distributed differently in cardiomyocyte T-tubules, such that β_2-mediated signaling is spatially restricted compared to β_1 signaling. In heart failure, where β_1 signaling induces cell remodeling and programmed cell death, this spatial restriction is lost, such that β_1 and β_2 signaling resemble each other.

CALCIUM REGULATION

Another area of basic pathophysiology that has drawn much attention is the relation between β-adrenergic receptor signaling and calcium regulation. Calcium was first found to exert an influence on the heart in the second decade of the 20th century. Subsequently it has become clear that calcium is a universal second messenger and in the heart exerts effects on contractility, mitochondrial function, transcriptional regulation and action potential generation. Calcium control is tightly linked to β-adrenoceptor signaling via intracellular mechanisms that take up and release ionic calcium.

The sarcoplasmic reticulum (SR), equivalent to the endoplasmic reticulum in other cells, lies just beneath the sarcolemma, which consists of the cell surface and invaginated T tubules. Each junction between the sarcolemma and the SR, where L-type calcium channels and ryanodine receptors are clustered, constitutes a local calcium signaling complex or couplon.[6] Type 2 ryanodine receptors, named after their affinity to the plant alkaloid ryanodine, are located in close proximity in the SR, and govern calcium storage and release from the SR via chemical coupling. When calcium enters the cell via sarcolemmal L-type calcium channels, adjacent ryanodine receptors are activated. This leads to SR calcium release and a marked increase in intracellular calcium concentration. This process has been termed calcium-induced calcium release and results in enhanced cardiac muscle contraction. Calcium is then removed via an SR calcium ATPase (SERCA-2), which in turn is under the control of an adjacent protein called phospholamban, which tonically inhibits SERCA. This inhibition decreases the rate of muscle relaxation and contractility. In humans, SERCA accounts for 70% of cytoplasmic calcium removal. Most of the remaining cytoplasmic calcium is removed via the sodium-potassium exchanger. Inhibition of this exchanger resulting in increased cytosolic calcium is the basis of the action of digitalis glycosides, which for almost two centuries was the only effective heart failure treatment available.

When phospholamban is phosphorylated by protein kinase A (PKA) or by calcium/calmodulin kinase II (CamKII), both of which are activated by sympathetic stimulation, its ability to inhibit SERCA is lost. Thus, activators of PKA and CamKII, such as β-adrenergic agonists, enhance the rate of cardiac myocyte relaxation. In addition, since SERCA is more active, the next action potential will cause increased calcium release, resulting in augmented contraction. It has been found that SERCA protein and activity are diminished in heart failure, and replenishing this protein using gene therapy is a current therapeutic goal. Animal experiments have been successful, and a human clinical trial is under way.

LINKS BETWEEN β-ADRENERGIC SIGNALING AND CALCIUM REGULATION

As noted above, β-adrenergic blockade has emerged as successful conventional therapy for heart failure. Why this should be so has elicited considerable interest. In a canine model of myocardial infarction, upregulation of previously downregulated β-receptors in response to β-blockade has been reported.[7] One concept has elicited considerable interest as well as controversy. This involves the consequences of altered ryanodine receptor function and SR calcium loss. Studies have described increased ryanodine receptor open probability in isolated preparations and increased calcium loss from SR vesicles isolated from failing hearts. These findings point to a possible common mechanism underlying alterations of systolic and diastolic function seen in heart failure. The underlying hypothesis is that hyperphosphorylation of the L-type calcium channel, the ryanodine receptor and the SERCA/phospholamban complex by PKA and CamKII may lead to chronic calcium loss. Calcium channel hyperphosphorylation can also result in increased calcium current that predisposes to arrhythmias. Excess phosphorylation in the SR complex can result in depletion of SR calcium stores, causing impaired cytosolic calcium transients resulting in systolic and diastolic dysfunction. Thus, inhibition of excess β-adrenergic drive would be expected to reduce these responses and improve cardiac function, which indeed appears to be the case as documented by randomized, controlled clinical trials. As CamKII is upregulated both in hypertrophy and in heart failure, small molecule inhibitors of CamKII are being developed but to date remain at the preclinical stage.

Calcium is also involved in myofilament function via a calcium-dependent ATPase. It is required for ATP generation by mitochondria, which is the source of the ATP hydrolyzed by SERCA, sodium/potassium ATPase, as well as by myofilament ATPase. Thus, augmented or reduced mitochondrial generation of ATP under normal and pathological circumstances is dependent on calcium availability, and the relation between calcium flux and ATP generation is critical for fundamental processes such as contraction, relaxation and electrical activity.

The localization of mitochondria near calcium release sites on the SR places these organelles in position to accumulate calcium, thereby regulating the level of calcium in the cytosol. Conversely, mitochondria can prevent SR calcium depletion by recycling this ion to the SR. Mitochondrial calcium uptake is also necessary for dehydrogenase activation in the mitochondrial matrix which regulates the $NADH/NAD^+$ ratio. The role of calcium in oxidative phosphorylation and the production of ATP in the mitochondria are exquisitely balanced with the energy required for myocyte crossbridge cycling that is fueled by the hydrolysis of MgATP and regulated by calcium.[8,9] Thus, dysregulation of mitochondrial calcium can contribute to cell demise under pathophysiological conditions.

MITOCHONDRIA

Cardiac myocytes are richly endowed with mitochondria which, as noted, supply ATP which in turn provides energy to drive contraction of the heart. Mitochondria have two membranes: an outer membrane permeable to molecules of 10 kilodaltons or less and an inner membrane permeable only to oxygen, carbon dioxide and water. The inner membrane, which is layered and invaginated, forms cristae, thereby markedly increases its surface area. This membrane is home to the complexes of the electron transport chain (ETC), the ATP synthase complex, and transport proteins (Fig. 1). The space between the two membranes (intermembrane space) has an important role in the mitochondrion's

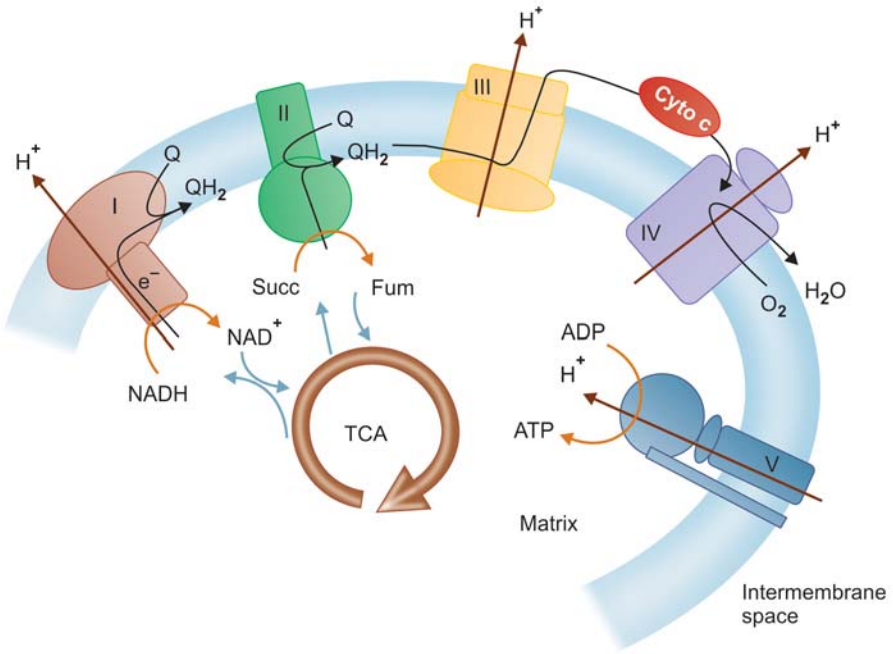


FIGURE 1: Electron transport chain and generation of ATP within the mitochondria. The Krebs (TCA) cycle takes place within the mitochondrial matrix. The cycle results in complete oxidation of the carbon atoms of the acetyl groups from acetyl-CoA. The net result of one turn of the cycle is the production of three molecules of NADH, 1 GTP and 1 $FADH_2$, and release of two molecules of CO_2. NADH generated from the cycle is oxidized by complex I (NADH:ubiquinone oxidoreductase), resulting in regeneration of NAD^+ needed as a cofactor for various steps of the cycle. Membrane-bound Complexes I, III and IV of the respiratory chain generate the proton gradient used by complex V (ATP synthase) to generate ATP. Complex II (succinate:ubiquinone oxidoreductase) is the only membrane-bound component of the TCA cycle. (Abbreviations: NAD^+: Nicotine adenine dinucleotide; NADH: Reduced nicotine adenine dinucleotide; Succ: Succinate; Fum: Fumarate; Q: Ubiquinone oxidoreductase; QH_2: Reduced ubiquinone oxidoreductase; e^-: Electrons; Cyto c: Cytochrome C; ATP: Adenosine triphosphate; ADP: Adenosine diphosphate)

raison d'etre which is the process of oxidative phosphorylation resulting in the generation of ATP. The inner membrane surrounds another compartment called the matrix which contains the enzymes responsible for citric acid (Krebs) cycle reactions. The folded cristae provide both a large surface area and intimate contact with the matrix, so that matrix components can rapidly diffuse to inner membrane complexes.

It should be noted that the only Krebs cycle reaction that occurs in the inner membrane itself is the oxidation of succinate to fumarate catalyzed by succinate dehydrogenase. This succinate dehydrogenase complex, which is composed of the enzyme, succinate and the energy carrier flavin adenine dinucleotide (FAD), is also called complex II of the ETC. This system accepts energy from carriers in the matrix and stores it in a form that can be used to phosphorylate ADP. Two carriers donate free energy to the ETC. These are nicotine adenine dinucleotide (NAD) and FAD. Reduced NAD carries energy to complex I (NADH-coenzyme Q reductase), while as noted above FAD is part of complex II.

NADH binds to a prosthetic group on complex I called flavin mononucleotide (FMN) and is reoxidized to NAD, which acts as an energy shuttle via recycling. FMN receives the resulting hydrogen from NADH and two electrons; it also garners a proton from the matrix and passes the electrons to iron-sulfur clusters that are part of the complex and forces two protons into the intermembrane space. Electrons pass to a carrier located in the membrane (Coenzyme Q) and are passed to complex III, which is associated with a further hydrogen translocation event. The next step in the pathway is cytochrome C and then further on to complex IV (cytochrome oxidase), where more protons are translocated. It is at this site that oxygen binds along with protons. Using the remaining pair of electrons and free energy, oxygen is reduced to water. This last step is diatomic, requiring two electron pairs and two cytochorme oxidase complexes. Thus, oxygen serves as an electron acceptor so that electron transport can operate continuously. From succinate, there is a similar pathway, but protons are not translocated at complex II.

What is the purpose of this complicated schema? It is to drive the activity of ATP synthase (complex V) which is dependent on the proton (chemiosmotic) gradient created by the ETC between the matrix and the intermembrane space. ATP forms spontaneously in the presence of ATP synthase, but the chemiosmotic gradient is necessary to cause the release of bound ATP, so that the cycle can continue and ATP can be continuously generated. When there is a threat that the gradient will be dissipated by the need for more ATP, electron transport is increased so that the gradient is maintained. As oxygen is the ultimate electron acceptor, the process of ATP generation is termed oxidative phosphorylation. All of the above reactions are summarized schematically in Figure 1. Much of mitochondrial pathophysiology revolves around the inability to maintain the chemiosmotic gradient and the consequences of this failure.

For mitochondria to maintain this proton-mediated pH gradient and the resulting membrane potential ($\Delta\psi_m$) necessary to drive oxidative phosphorylation, the inner mitochondrial membrane must remain impermeable to all, but a few ions and metabolites for which specific transport mechanisms have evolved. It has been hypothesized that water and restricted metabolites can pass through the inner membrane via a "pore", also called the permeability transition pore. The physical characterization of this permeability barrier remains controversial. Nevertheless, persistent opening of this barrier under oxidative stress causes collapse of the proton gradient and $\Delta\psi_m$ across the inner mitochondrial membrane, resulting in uncoupling of oxidative phosphorylation and initiation of a series of biochemical changes which lead to cell death.

As a normal byproduct of the electron transfer activity described above, mitochondria generate reactive oxygen species (ROS). The primary sources are complexes I and III. Thus,

somewhere between 0.2–2% of molecular oxygen consumed by mitochondria is converted to superoxide. Excess superoxide is toxic to the mitochondria, so its generation is kept in check by antioxidant enzymes located in the mitochondria, including manganese superoxide dismutase (MnSOD), catalase and glutathione peroxidase. MnSOD dismutes superoxide to hydrogen peroxide, which is converted to water by catalase and glutathione peroxidase. During oxidative stress these cardioprotective enzymes are overwhelmed and excess ROS are generated.

CARDIAC HYPERTROPHY

Physiologic cardiac muscle hypertrophy is a normal response to repetitive exercise. When hypertrophy occurs in disease states it is termed pathologic. Hypertrophy may be concentric, due to pressure overload (hypertension, aortic stenosis), or eccentric due to volume overload (mitral or aortic insufficiency, dilated cardiomyopathy). In some instances the cause is genetic and numerous mutations in cardiac muscle proteins, especially in the β-myosin heavy chain gene, have been found in humans. These are often familial, but how these mutations lead to hypertrophy remain largely mysterious.

Regardless of how hypertrophy is initiated, certain characteristic responses have been identified. These include reactivation of a fetal gene program, especially of β-myosin heavy chain and natriuretic peptides. The re-expression of β-myosin heavy chain is especially prominent in rodent models of hypertrophy, where the α-isoform predominates. However, in humans 90% of the myosin heavy chain pool consists of the β-isoform. Thus the isoform switch in humans is of problematic importance. Natriuretic peptide hormones are expressed in the atria and ventricles. The increase in these peptides, which in experimental settings inhibit the hypertrophic response via activation of cyclic guanosine monophosphate (cGMP), also serve as markers for heart failure. One postulated mechanism for the mechanism of cGMP is via cGMP-dependent protein kinase which inhibits L-type calcium channels, thus reducing calcium transient amplitude. This could result in inhibition of calcineurin-mediated activation of nuclear factor of activated T cells (NFAT), a nuclear transcription factor that is obligatory for hypertrophy. However, the counter-regulatory effect of natriuretic peptides is insufficient to inhibit the progression of hypertrophy in humans.

As the result of extensive experimental studies, especially employing genetically altered mice, numerous other pathways have been implicated in the pathogenesis of cardiac muscle hypertrophy.[10,11] Among these mediators of hypertrophy are pathways stimulated by norepinephrine, angiotensin II, the IL-6 family of cytokines, MAP kinases, Janus kinases (JAKs) and Cam kinases. One well-established mechanism of hypertrophy in rodent models is via the heterotrimeric G-protein Gq. Activation of Gq by norepinephrine, angiotensin II or endothelin results in PKC and inositol trisphosphate-mediated calcium release due to activation of phospholipase Cβ. As noted above, calcium release activates the protein phosphatase calcineurin and its target NFAT, which in cooperation with the cardiac-restricted zinc finger transcription factor GATA4 is a critical nuclear mediator of pathologic hypertrophy. It should be noted that the calcineurin-NFAT pathway can be activated by CamKII and inhibited by FOXO-3, a member of the Forkhead/winged helix family of transcription factors, which contain a conserved DNA binding domain called the Forkhead box (Fox). Norepinephrine and angiotensin II also activate α_1-adrenergic and angiotensin receptors, respectively. These are linked to Gq and subsequently to activation of extracellular signal-regulated kinases (ERKs). The latter then activate the protein kinase mammalian target of rapamycin (mTOR) which regulates protein translation and ultimately, hypertrophy. Another pathway that negatively regulates hypertrophy is mediated by glycogen synthase kinase-3β (GSK-3β).[12]

A number of other regulators of cardiac hypertrophy have also been experimentally determined. Among these are microRNAs, such as miR199a,[13] PKCβ[14] and histone acetylation/deacetylation. It has been found that class II histone deacetylases (HDACs) associate with the MEF2 transcription factor, among others, to maintain normal cardiac size and function. Stress signals result in the phosphorylation of class II HDACs and their export from the nucleus to the cytoplasm resulting in activation of genes involved in cardiac growth.[15] Thus, HDAC knockout mice develop massive cardiac hypertrophy in response to stress stimuli.[12] Sirtuins are histone deacetylases that have been implicated in aging, resistance to oxidative stress and blockade of hypertrophy in the heart.[16-18] Another process that may contribute to hypertrophy is autophagy, which is a complex process of cellular degradation that is initiated in response to nutrient limitation, cellular stress, ROS or accumulation of protein aggregates of damaged organelles.[19]

Cardiac fibroblasts are the most numerous cell types in the heart and contribute to the regulation of cardiac hypertrophy via paracrine mechanisms. Prominent among the factors involved in this molecular crosstalk that result in cardiomyocyte hypertrophy are TGFβ1, fibroblast growth factor 2 and members of the IL-6 cytokine family.[20] Agonists that stimulate fibroblasts to release these mediators are angiotensin II and norepinephrine. All of these interactions become more prominent during stress conditions such as pressure overload and left ventricular remodeling. A recently discovered member of the IL-1 family, interleukin-33, represents a novel paracrine signaling system that is antihypertrophic and antifibrotic.[20]

α_1-ADRENERGIC RECEPTORS AND HYPERTROPHY

Evidence from rodent studies has indicated that stimulation of α_1-adrenergic receptors causes cardiac myocyte hypertrophy and augments cardiac contractility. Such stimulation is also cardioprotective. In contrast to β-adrenergic receptors, which are downregulated by chronic agonist exposure, α-adrenergic receptors do not downregulate. Recent studies in humans have confirmed that α-adrenergic receptors, predominately the α_{1A} and α_{1B} subtypes, are present in human myocardium. In failing hearts, these receptors were not downregulated, similar to findings in rodent models of heart failure.[21] In right ventricular trabeculae from normal mouse hearts α-adrenergic stimulation produced a negative inotropic response, but this response was reversed in trabeculae from failing hearts. These findings were attributed in part to increased myofilament calcium sensitivity caused by a more abundant smooth muscle isoform of myosin

light chain kinase.[22] In contrast, α_1-mediated inotropic responses did not differ between normal and failing left ventricles. Both smooth muscle myosin light chain kinase mRNA protein levels were increased in right ventricles from failing human hearts. The risk of treating heart failure with an α-adrenergic antagonist was evident in a landmark primary prevention hypertension trial in which the α_1-adrenergic antagonist doxazosin was stopped early due to lack of any benefit for the primary outcome (fatal coronary heart disease or nonfatal myocardial infarction combined) and a signal suggesting potential harm in one of the secondary outcomes (heart failure).[23] It should be noted that the cardiovascular risk of using α-adrenergic blockers in patients with prostate enlargement has never been evaluated in a randomized, controlled clinical trial.

As noted above, myocardial hypertrophy is a well-described response to pressure-overload states. Of these conditions, the most prevalent is systemic arterial hypertension. Patients with hypertension who develop left ventricular hypertrophy have an increased risk of developing cardiovascular complications, including heart failure, atrial fibrillation and sudden cardiac death. Effective treatment of hypertension has long been known to result in regression of left ventricular hypertrophy. Early trials in humans demonstrated that antihypertensive therapy resulted in a decrease in left ventricular mass, and that patients who did show such a decrease also had improvements in measures of diastolic filling.[24] While multiple classes of medications have been studied, and for the most part all seem to be effective, there is evidence of a differential effect on left ventricular mass. Meta-analyses of randomized trials of the effects of antihypertensive agents on left ventricular mass showed that the reduction in hypertrophy was greatest with angiotensin II receptor antagonists (13% of patients showing a reduction in left ventricular mass index), followed closely by calcium channel blockers (11% of patients) and ACE inhibitors (10% of patients); beta-blockers seemed to be consistently less effective in this regard (6% of patients).[25,26]

CONGESTIVE HEART FAILURE

As noted above patients with persistent and progressive volume or pressure overload exhibit left ventricular hypertrophy and are at risk for congestive heart failure (CHF). Other patients suffer a myocardial infarction and develop compensatory left ventricular hypertrophy and dilatation which leads to CHF. Heart failure is the result of macrostructural changes collectively called remodeling. Other patients with cardiomyopathy due to various causes (e.g. hypertension, alcohol, myocarditis, diabetes, peripartum, amyloid) also develop CHF. For patients with valvular heart disease, effective treatment consists in valve replacement. For many patients with coronary heart disease revascularization is effective, but a minority of these individuals exhibit progressive CHF. Regardless of the cause, CHF which progresses to class IV and is refractory to medical therapy is one indication for cardiac transplantation. Due to the relative paucity of available hearts, many patients are placed on a waiting list. In the meantime, an increasing number are being treated with devices that augment their cardiac output, so-called left ventricular assist devices (LVADs). The use of LVADs has provided a platform to examine changes in myocardial structure and function brought about by chronic left ventricular unloading. Biopsy material and larger portions of hearts removed at the time of transplantation have been studied. In a few instances, the LVAD evolved to "destination therapy", i.e. was removed because of persistent recovery, but such instances are rare. In most cases, LVADs have been installed as a "bridge" to transplant.

The mechanism by which left ventricular hypertrophy and/or dilatation evolves into CHF is not clear. By looking through the large end of the LVAD "telescope" it is possible to study "reverse remodeling" and compare changes associated with CHF before treatment and the structural, molecular and biochemical alterations produced by this therapy.[27] Such studies in humans have revealed that LVAD treatment reduces cardiac pressure and volume overload. This leads to diminished wall tension and lessened myocardial oxygen demand thereby reducing the ischemic burden in patients with coronary artery obstruction. Hypertrophy regresses as evidenced by reduced echocardiographic left ventricular wall thickness.

The effect of LVAD support on improving distorted ventricular geometry has been well-described, and many LVAD-supported hearts show improvement in LV chamber dilatation and LV mass. Analysis of cardiac myocytes obtained at the time of cardiac transplantation has demonstrated that long-term LVAD support results in reductions in myocyte volume, length, width and cell length-to-thickness ratio, compared with unsupported hearts.[28] These observations suggest that favorable effects of the LVAD on the failing heart result at least in part from regression of hypertrophy at the cellular level. In patients with nonischemic cardiomyopathy, LVADs have shown promise in reversing clinical heart failure, allowing for later explantation of the device as described above.[29] Cardiac myocytes taken from LVAD-supported hearts at the time of transplant have subsequently been compared with those from hearts that recovered sufficiently to allow LVAD explantation.[30] Both groups showed a decrease in myocyte size, but only the recovery group showed improvements in indices of SR calcium handling. Thus, although LVAD support seems to consistently lead to regression of cellular hypertrophy, this is not necessarily associated with clinical recovery.

However, changes in fibrosis have not been consistently reported as a result of LVAD treatment. Similarly, changes in matrix metalloproteinases (MMPs), especially MMP-9, have been variable, while reductions in tissue inhibitors of metalloproteinases (TIMP-1 and TIMP-3) have been observed. Regardless of these variable alterations, total collagen content remains unchanged. Other ventricular properties that do not regress to normal during LVAD support include increased tissue angiotensin levels, myocardial stiffening and fetal gene expression.[31,32]

As noted above, heart failure causes β_1-adrenoceptor downregulation without a change in β_2-receptor density. However, the latter are functionally uncoupled. Chronic LVAD unloading reverses these changes and restores a normal inotropic response to the nonselective β-adrenergic receptor agonist isoproterenol. LVAD treatment also increases the gene expression and protein level of SERCA-2, restores the force-frequency relation of isolated trabeculae and normalizes the magnitude

and time course of the intracellular calcium transient. LVAD support returns natriuretic peptides and their signaling to normal. It also augments antiapoptotic signaling pathways and negatively regulates NF-κB which is responsible for activation of several factors contributing to the pathogenesis of CHF, such as interleukin-6, TNFα and Bcl-x_L.[27]

Additional understanding of the mechanism of evolution of CHF has been provided by experiments involving G-protein receptor kinase (β-arrestin) mentioned above. It is well-recognized that β_1-adrenergic receptors signal through a G-protein-mediated pathway that can be harmful under-conditions of chronic catecholamine stimulation as occurs in CHF.[33] Recent data indicate that β_1-receptors can also activate epidermal growth factor receptors in a β-arrestin dependent process called transactivation, which confers cardioprotection in response to a chronic increase in catecholamines.[34] Additionally it has been found that GRK-2 is upregulated in rats with chronic CHF due to myocardial infarction leading to enhanced catecholamine release via desensitization/down-regulation of the chromaffin cell α_2-adrenergic receptors that normally inhibit catecholamine secretion.[35] Experiments using gene-targeting of adrenal GRK-2 decreased circulating catecholamines and led to improved cardiac function and β-adrenergic reserve in postmyocardial infarction heart failure in a mouse model.[36] In rats with postinfarction heart failure, exercise training lowered GRK-2 and reduced sympathetic overdrive.[37] Thus, GRK-2 is a potential therapeutic target for the treatment of chronic CHF.

MICRO-RNAs

Micro-RNAs (miRs) are small, noncoding RNAs. They are short ribonucleic acid molecules, on average only 22 nucleotides in length and function as post-transcriptional regulators that bind to complementary sequences in the three prime untranslated regions of target messenger RNA transcripts, usually resulting in gene silencing. The human genome encodes over 1,000 miRNAs, which may target more than half of mammalian genes. Each miRNA may repress hundreds of mRNAs. Specific miRs have been implicated in the regulation of cardiac hypertrophy and ischemia/reperfusion injury.[38] Both antagonists of miRs, called antagomiRs, and miR mimetics, called agomiRs, have been synthesized to inhibit and enhance miR actions, respectively. The biology of miRs is an exciting new area which is likely to have important therapeutic implications.

ISCHEMIA/REPERFUSION INJURY

As coronary blood flow is abruptly decreased, cardiac myocytes are subjected to progressive oxygen deprivation. This results in disruption of the mitochondrial membrane gradient ($\Delta\psi_m$) described above, which is required to maintain oxidative phosphorylation, and eventually results in cessation of this process. Absent generation of sufficient ATP, the contractile elements are no longer able to function. Further injury occurs as a result of the decline in pH associated with increased lactate levels. As hydrogen ion concentration increases, the sodium/hydrogen antiporter is activated in an attempt to restore pH levels. This results in an increase in sodium levels and dysfunction of the sodium/calcium exchanger that results in increased intracellular calcium, causing calcium overload. As a result degradative enzymes, such as calpain, are activated. Simultaneous with these events, ROS generation from complexes I and III of the ETC increases and the mitochondrial transition barrier opens leading to release of cytochrome C. The latter associates with other proteins including caspase-9 to form a macromolelcular complex called the apoptosome, which in turn activates the effector, caspase-3. Caspases inactivate crucial cellular targets including essential subunits in complex 1. A major defense against ROS-induced damage, glutathione, is oxidized. This coincides with cleavage of BID, a proapoptotic protein, which transduces signals from the cytosol to the mitochondria, leading to caspase activation.

During ischemia/reperfusion injury, several other proapoptotic factors that have nuclear effects are also released from mitochondria, including Smac/Diablo and apoptosis inducing factor (AIF), among others. Release of AIF into the cytosol is followed by rapid translocation to the nucleus where it facilitates chromatin condensation and DNA fragmentation. Excessive oxidative stress also results in the activation of poly (ADP-ribose) polymerase 1 (PARP-1). Protein poly (ADP-ribosylation) is crucial for genomic integrity and cell survival and is catalyzed by PARP-1, which is a nuclear enzyme that functions as a DNA damage sensor and signaling molecule. PARP-1 binds to DNA strand breaks and participates in DNA repair processes. It utilizes NAD^+ to form poly (ADP-ribose) (PAR) polymers on specific acceptor proteins. Under conditions of moderate oxidative stress, PARP-1 activation facilitates DNA repair. However, excessive PARP-1 activation depletes the intracellular pool of its substrate NAD^+, thereby impairing glycolysis, decoupling the Krebs cycle and mitochondrial electron transport (Fig. 1), and eventually causing ATP depletion and consequent cell dysfunction and death by necrosis.

MECHANISMS OF CARDIOPROTECTION

Concurrent with an understanding of the mechanisms of cell death, both necrotic and apoptotic, described above, there has been an intensive effort to determine how the heart can be protected from injury. It would be desirable to have available approaches that can protect vulnerable tissue before damage occurs due to oxidative stress, such as frequently happens during cardiac or vascular surgery. Such protection before, during or immediately after catheter interventions would also be welcome. One approach that has proved successful is periprocedural β-blockade, which reduces myocardial oxygen demand by lowering heart rate and blood pressure. Another approach, still largely experimental, but beginning to have clinical application, is the concept of myocardial conditioning. Just as the well-trained athlete has learned to "warm-up" before a foot race or other strenuous activity, the heart (and other organs) can be "preconditioned". This phenomenon was first described by Murry et al. in 1986.[39] In a canine model, it was found that several brief periods of ischemia/reperfusion preceding a much more prolonged bout of ischemia/reperfusion could substantially reduce myocardial injury. This intervention was termed ischemic preconditioning. Its effect lasts for 1–3 hours. A delayed effect of preconditioning, occurring 24–72 hours following acute

ischemic preconditioning, called the second window of protection, has been recognized.[40] Subsequently, in 2003, an identical beneficial effect occurred when the conditioning stimulus was applied at the onset of reperfusion and has been called postconditioning.[41]

The mechanisms of these responses have been extensively studied and a variety of pathways have been elucidated, presumably many or all of them having evolved as redundant responses to cellular injury. A number of endogenous mediators that transduce signals via G-protein coupled receptors have been found to produce cardioprotection, including adenosine, bradykinin, opioids[42] and sphingosine 1-phosphate.[43] One such pathway activated by these endogenous mediators is called the reperfusion injury salvage kinase (RISK) pathway[44] and involves phosphorylation and activation of prosurvival kinases such as Erk 1/2, PI-3 kinase/Akt and GSK-3β (Fig. 2). Another separate but complementary pathway has been called the survivor activating factor enhancement (SAFE) pathway[45] (Fig. 2). This mechanism is activated by liganding of cytokine receptors on the cell surface thereby conveying signals to the nucleus via the JAK-STAT pathway, a process that rapidly results in activation of various cardioprotective effectors such as manganese superoxide dismutase, iNOS and COX-2.[46] The activation of both these enzymes, the former resulting in the production of NO, has been implicated as mechanisms of the second window of protection described above.

A recently described third pathway is activation of the enzyme sphingosine kinase which phosphorylates endogenous sphingosine to produce the second messenger sphingosine 1-phosphate (S1P). S1P is exported from the cell and ligands cognate cell surface receptors in an autocrine or paracrine manner to couple with the guanine nucleotide inhibitory protein (Gi) to initiate cardioprotection via PI3-K/Akt, Erk1/2 and GSK-3β as described above.[43,47] The sphingolipid pathway is also illustrated in Figure 2.

The importance of the sphingosine kinase/S1P axis in cardioprotection is further supported by measurements of S1P and sphingosine kinase activity in preconditioned hearts[48] and by abolition of the cardioprotective effect of ischemic preconditioning in sphingosine kinase isoform 1 knockout hearts.[49] Of note is that sphingosine, which has previously thought to be deleterious to the heart, is cardioprotective in low concentrations and utilizes cyclic nucleotide-dependent pathways that are independent of G-protein coupled receptors[50] (Fig. 2). Recent evidence indicates that endogenous cardioprotectants such as adenosine and S1P are released from cells via pannexin-I/P_2X_7 purinergic receptor channels[51] (Fig. 2). Volatile anesthetics are also preconditioning agents that activate sphingosine kinase and result in release of cytoprotective S1P.[52]

As summarized in Figure 2, all of the molecular prosurvival pathways described above converge on mitochondria. An alternative or parallel mechanism advanced by Garlid et al.[53] is that occupied receptors for the agonists described above migrate to caveolae, where signaling enzymes are scaffolded into signalosomes that bud off the plasma membrane and then continue their migration to mitochondria. Regardless of the mechanism involved, an initial mitochondrial event in this prosurvival cascade is opening of mitochondrial inner membrane K_{ATP} channels, although not all subscribe to this hypothesis.[54]

Nevertheless, the following events occur after ischemic or pharmacologic preconditioning are: increased mitochondrial potassium uptake, matrix alkalinization, volume increase, ROS production, especially by complex I and mitochondrial permeability transition inhibition. The latter occurs via ROS-mediated activation of PKCε that resides in mitochondria and/or has been translocated to these organelles.[53] Thus, increased low-level ROS generation activated by either ischemic and/or pharmacologic preconditioning enhances myocardial cell survival. For each intervention, or their combination, there is a ROS threshold beyond which the conditioning stimulus is ineffective and excess ROS release results in cell necrosis. In this connection, it has been suggested that another response to preconditioning in ischemia/reperfusion is upregulation of autophagy.[19] Under these conditions acutely enhanced autophagy would result in removal of unstable mitochondria thereby lowering cellular ROS production and reducing the likelihood of mPTP opening. Thus, Sirt 1, which upregulates autophagy through deacetylation of several autophagy proteins, has been linked to cardioprotection.[19]

Of special note is the translocation of PKCε to the mitochondria. Previous work had proposed a number of cytoprotective mechanisms resulting from this translocation, including inhibition of mitochondrial permability transition, opening of K_{ATP} channels, and phosphorylation of cytochrome oxidase subunit IV. Recently, a new mitochondrial substrate for PKCε, aldehyde dehydrogenase 2, has been described.[55] The function of this enzyme is to detoxify toxic aldehydes that are produced by lipid peroxidation during ischemia/reperfusion, such as the reactive 4-hydroxy-2-nonenal and its adducts. There is a strong inverse correlation between aldehyde dehydrogenase 2 and infarct size. A small molecule activator of aldehyde dehydrogenase 2 had a similar effect[55] (Fig. 3) and also conferred cardioprotection in PKCε knockout mice.[56]

Of interest, it has recently been reported in mouse cardiac myocytes that connexin 43 residing in or transported to mitochondria is a cytoprotective mediator of signal transduction by stimulating mitochondrial K_{ATP} channel opening.[57] Another recently described protector of mitochondrial integrity downstream of JAK/STAT and Akt signaling is Pim kinase-1.[58] The prosurvival Pim kinases are a family of three vertebrate protein serine/threonine kinases (Pim-1, -2 and -3) belonging to the CaMK (calmodulin-dependent protein kinase-related) group. Pim-1 translocates to mitochondria in response to ischemia/reperfusion injury and enhances expression of antiapoptoic Bcl-x_L and Bcl-2. It also preserves $\Delta\psi_m$ during oxidative stress, attenuates mitochondrial swelling in response to calcium overload and reduces cytochrome C release in response to a proapoptotic challenge.[58]

All of the interventions described above substantially, but not completely, prevent many of the harmful effects of oxidative stress, such as mitochondrial permeability transition, cytochrome C release, calcium overload and depression of oxidative phosphorylation. To achieve maximal cardioprotection, a combination of these approaches requires rigorous testing in animal models and ultimately in patients.

Postconditioning shares many if not all of the mechanisms attributed to preconditioning and holds promise to be an effective clinical strategy. Experimentally, using a "cocktail" approach,

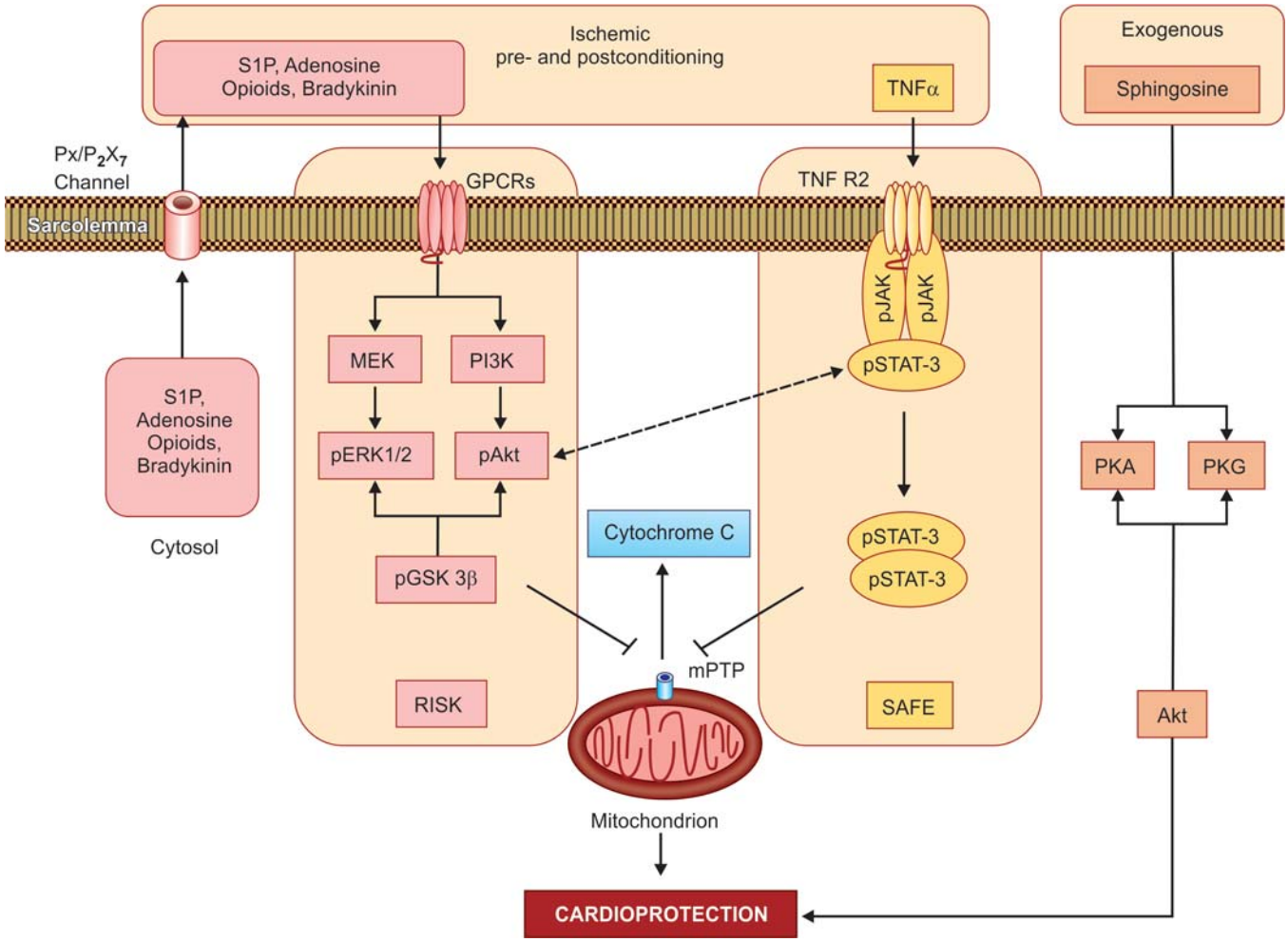


FIGURE 2: Pathways leading to cardioprotection following ischemic pre- and postconditioning. Pre- and postconditioning lead to intracellular generation of agonists such as S1P, adenosine, opioids and bradykinin which are exported across the sarcolemma via pannexin/P_2X_7 channels. Once these molecules have gained access to the outer surface of the sarcolemma they activate G-protein coupled receptors in an autocrine or paracrine fashion to generate the signals shown. Similarly, low concentrations of TNFα can be generated intracellularly and released or given exogenously to activate the pathway shown. Low dose exogenous sphingosine also has cardioprotective effects. See text for details. (Abbreviations: Px/P_2X_7: Pannexin/purinergic$_2X_7$ channels; S1P: Sphingosine 1-phosphate; GPCRs: G-protein coupled receptors; TNFα: Tumor necrosis factor alpha; TNF R2: Tumor necrosis factor receptor 2; MEK: Mitogen-activated protein kinase 1; pERK: Phosphorylated extracellular signal-related kinase; PI3K: Phosphoinositide 3-kinase; pAkt: Phosphorylated serine-threonine kinase also known as protein kinase B; pGSK 3β: Phosphorylated glycogen synthase kinase 3-beta; mPTP: Mitochondrial transition "pore"; pJAK: Phosphorylated Janus kinase; pSTAT: Phosphorylated signal transducer and activator of transcription; PKA: Protein kinase A; PKG: Protein kinase G; RISK: Reperfusion injury salvage kinase pathway; SAFE: Survivor activating factor enhancement pathway)

the combination of ischemic postconditioning, and infusion of both sphingosine and sphingosine 1-phosphate, salvaged rat myocardium subjected to as much as 90 min of global ischemia.[59] Postconditioning can be applied acutely in patients undergoing percutaneous coronary interventions. In over 400 patients in 8 studies, favorable results using a variety of short-term outcome measures have been reported.[42] The use of pharmacologic therapy for postconditioning has had mixed results, but the combination approach described above, which mimics the endogenous release of multiple effectors, has never been reported in humans.

AGING

Cardiac aging has been examined largely in rodent models. These studies reveal impairment of most of the mechanisms regulating cardiac myocyte function which is described above. Beta-adrenergic responses are diminished, including chronotropic and contractile responses. Coupling of β-adrenoceptors to the guanine nucleotide regulatory protein Gs is reduced and less cAMP is generated for a given stimulus. Decreased chronotropic responses to exercise are another feature of aged myocardium. With advancing age, SERCA-2 protein is reduced in rats, but not in mice. As noted above SERCA function is impaired in CHF in humans. During aging, the calcium sequestering properties of myocyte SERCA-2 protein are reduced, perhaps in part because of defective PKA-dependent phosphorylation of phospholamban. Calcium release (ryanodine) channels are also dysfunctional, possibly because of decreased phosphorylation by PKA and CaMK. This results in increased SR calcium leak that may contribute to both systolic and diastolic dysfunction with age. It is of considerable interest that

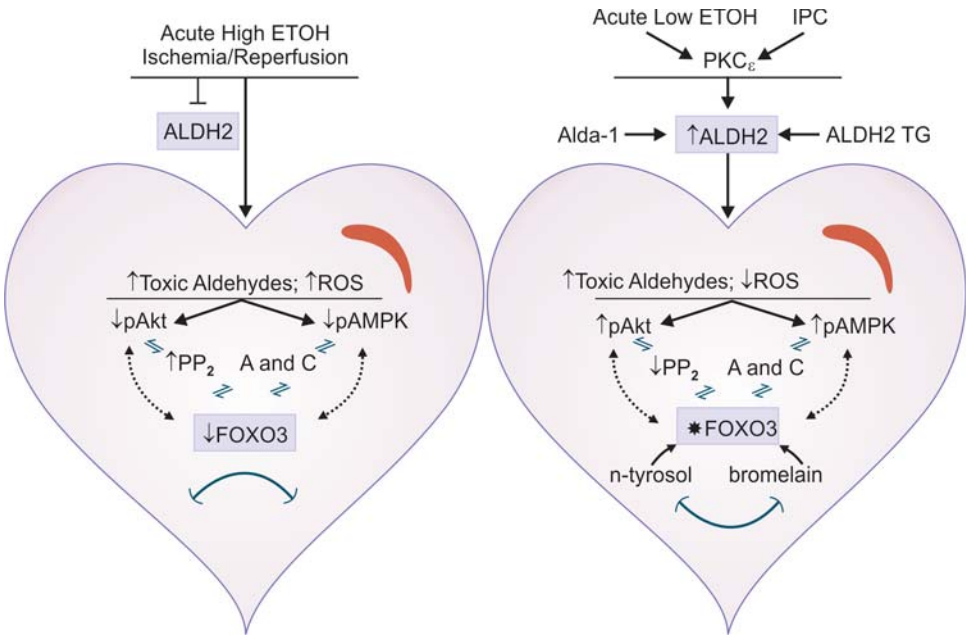


FIGURE 3: New roles for PKCε and aldehyde dehydrogenase in cardioprotection.

Depicted in the left panel is the "sad" heart, which is acutely depressed by ischemia/reperfusion injury. Toxic aldehydes and reactive oxygen species are produced that among other effects; reduce prosurvival signals such as those transduced by Akt, AMP-activated protein kinase and FOX3. In the "happy" heart on the right, these adverse responses can be prevented by overexpression of aldehyde dehydrogenase 2 or by a small molecule activator of this enzyme. During ischemic precondidtioning PKCε is translocated to the mitochondria (or PKCε resident in the mitochondria is activated) and stimulates the activity of aldehyde dehydrogenase 2 in the mitochondria, which results in detoxification of toxic aldehydes. (Abbreviations: Alda-1: Small molecule activator of aldehyde dehydrogenase 2; ALDH2: Aldehyde dehydrogenase 2; FOX3: Forkhead transcription factor of the O subtype; IPC: Ischemic; pAkt: Phosphorylated prosurvival serine-threonine kinase also known as protein kinase B; pAMPK: Phosphorylated adenosine monophosphate kinase; PKCε: Protein kinase C epsilon; PP_2 A and C: Protein phosphatase A and C; ROS: Reactive oxygen species; TG: Transgenic)

in male nonfailing aged human hearts there is extensive myocyte loss and hypertrophy of the surviving myocytes.[60] In contrast, this is not the case in females. In rats, the activity of telomerase, which correlates with cell replication, was decreased in aging male myocytes, but increased in females.[61]

In mitochondria prepared from old rat hearts the majority of genes whose expression is altered are those coding for proteins involved in oxidative phosphorylation, substrate metabolism and the tricarboxylic acid cycle, and most of these are downregulated.[62] This results in reduced mitochondrial functional capacity as manifested by diminished complex I and V activities leading to diminished ATP synthesis. There is also a substantial loss of cardioprotection with aging as indicated by the inability of aged rat myocardium to undergo successful ischemic pre and postconditioning as well as pharmacologic preconditioning with a variety of agents.[63] Of note is that sphingosine protects both old and young hearts from ischemia/reperfusion injury and in hearts from 27-month-old rats sphingosine is superior to S1P and ischemic pre and post-conditioning.[64] As noted above, there has been considerable interest in sirtuins as regulators of aging, and the heart is no exception.[16]

Human studies are sparse. One of two studies in isolated right atrial appendages showed a negative response to IPC and two other studies in humans with variable outcome measurements could not document any effect of IPC in older patients (>65 years of age compared with younger patients). These results are consistent with diminished mitochondrial functional capacity. Experimentally, this loss of cardioprotection with aging can be reversed by caloric restriction and exercise in rodents, and in one retrospective analysis by exercise in humans.[65]

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Chapter 3

Coronary Circulation in Physiology and Pathology

Kanu Chatterjee

Chapter Outline

- Coronary Vascular Anatomy
- Regulation of Coronary Blood Flow
  - Myocardial Oxygen Demand
  - Myocardial Oxygen Supply
- Coronary Vascular Resistance
  - Viscous Resistance
  - Compressive Resistance
  - Autoregulatory Resistance
  - Myogenic Resistance
- Modulation of Coronary Blood Flow
  - Flow Mediated Regulation
  - Metabolic Factors
  - Neurogenic Modulation
  - Hormonal Modulation
- Coronary Collateral Circulation
- Coronary Circulation in Pathologic States
  - Hypertension
  - Valvular Heart Disease
  - Hypertrophic Cardiomyopathy
  - Metabolic Disorders
  - Ischemic Heart Disease
  - Systolic Heart Failure

INTRODUCTION

Coronary circulation in physiologic and pathologic states is related to coronary vascular anatomy and factors that modulate coronary blood flow. Coronary blood flow changes in response to various coronary vascular intrinsic and extrinsic stimuli. The modulating and regulating mechanisms of coronary circulation, however, differ in different pathologic conditions.

CORONARY VASCULAR ANATOMY

The coronary vascular system consists of coronary arteries and veins. The epicardial coronary arteries are muscular arteries and serve as conduit vessels. The epicardial coronary arteries give rise to intramural branches that also contain smooth muscle cells. There are two types of branches that arise from these penetrating intramural arteries. The first type rapidly branches into an arterial network which provides blood flow to the outer two-thirds, approximately 60–70%, of the left ventricular myocardium; the second type courses to the endocardium and forms an arcade of anastomotic channels called the subendocardial plexus.[1] The endocardium and subendocardium, which constitute approximately 20–30% of the inner walls of the left ventricle, receive blood flow from the anastomotic arterial system. The intramyocardial arteries and the arterioles constitute the resistance vessels of the coronary circulation.

The arteriovenous and venovenous anastomotic channels form the cardiac venous system. The epicardial and myocardial veins usually run parallel to and accompany the coronary arteries. The larger veins form coronary sinus which drains into the right atrium. A substantial increase in right atrial pressure is associated with a similar increase in coronary sinus and intramyocardial venous pressures which impedes myocardial venous drainage and may impair myocardial perfusion.

REGULATION OF CORONARY BLOOD FLOW

MYOCARDIAL OXYGEN DEMAND

Coronary blood flow and myocardial oxygen supply is primarily determined by myocardial oxygen demand. The major determinants of myocardial oxygen demand are summarized in Table 1. The major determinants of myocardial oxygen demand and oxygen consumption (MVO_2) are heart rate, contractility and wall stress.[2] The faster is the heart rate, the higher is the myocardial oxygen requirement. Increase in oxygen demand is not only due to increased frequency of contraction but also to increased contractility resulting from positive force-frequency relation. In the failing myocardium, however, the contractility decreases with increasing heart rate due to inverse force

TABLE 1

The major determinants of myocardial oxygen demand

The major determinants of myocardial oxygen demand:
• Heart rate • Contractility • Wall stress • Ventricular pressure • Ventricular volumes • Ventricular wall thickness

frequency relation. The slower heart rate is associated with improved left ventricular perfusion due to longer perfusion time. Myocardial oxygen consumption is directly proportional to changes in contractility. During dobutamine infusion or exercise, MVO_2 increases due to increase in contractility.[3] The myocardial oxygen demand and MVO_2 are also directly proportional to wall stress. The wall stress is directly related to ventricular volume and systolic blood pressure, and is inversely related to wall thickness. The larger the ventricular volume, the higher the arterial pressure and thinner the ventricular wall, and higher is the wall stress which is associated with increased myocardial oxygen demand and MVO_2.

MYOCARDIAL OXYGEN SUPPLY

Myocardial oxygen supply is the product of coronary blood flow and myocardial oxygen extraction. Myocardial oxygen extraction is the difference in the coronary arterial—venous oxygen content. Even at basal metabolic demand, myocardial oxygen extraction is near maximum. Usually coronary sinus venous oxygen saturation at basal conditions is between 20% and 30%, corresponding to a partial arterial oxygen pressure (PaO_2) of about 20 mm Hg. Even at a very high and super-normal PaO_2, the dissolved arterial oxygen content increases only minimally. Thus, myocardial oxygen supply is primarily dependant on coronary blood flow. The factors that regulate coronary blood flow and myocardial oxygen supply and perfusion are summarized in Table 2. The perfusion pressure is the difference between aortic diastolic pressure and the coronary sinus venous pressure (right atrial pressure). However, it should be appreciated that left ventricular diastolic pressure and intramyocardial tissue pressure also offer resistance to forward coronary blood flow and myocardial perfusion. To maintain forward coronary blood flow, aortic diastolic pressure needs to be at least a few mm Hg higher than right atrial and left ventricular diastolic pressures. The transmyocardial pressure gradient is defined as the pressure difference between aortic diastolic pressure and left ventricular diastolic and coronary venous pressures. Myocardial perfusion is related to changes in transmyocardial perfusion pressure gradient. Transmyocardial pressure gradient may decrease either due to reduction in aortic diastolic pressure or due to an increase in left ventricular diastolic pressures. In many pathologic states, such as severe aortic stenosis, both hemodynamic abnormalities occur concurrently.

TABLE 2

The major determinants of coronary blood flow

- Perfusion pressure
- Epicardial coronary artery resistance
- Compressive resistance
- Basal viscous resistance
- Autoregulatory resistance
- Coronary arteriolar resistance
- Extravascular resistance
- Ventricular diastolic pressure
- Coronary sinus venous pressure

CORONARY VASCULAR RESISTANCE

Coronary vascular resistance consists of epicardial coronary artery resistance, intramyocardial coronary arterial resistance, coronary arteriolar resistance and resistance related to left ventricular diastolic and coronary venous pressures.

There are several functional components that influence resistance in the coronary vascular bed.

VISCOUS RESISTANCE

The basal viscous resistance is the resistance in the coronary vascular bed when the coronary vessels are fully dilated. Since coronary arteries are distensible, the viscous resistance varies with changes in the distending pressures.[4] It also varies with changes in coronary vascular cross-sectional area and changes in the caliber of the epicardial conduit arteries and blood viscosity. Normally, the basal viscous resistance is less in the inner portion than in the outer portion of the left ventricular wall. In contrast, the compressive component of the coronary vascular resistance, which involves intramyocardial coronary arteries and arterioles, is less in the inner portion than in the outer portion of the ventricular walls. This difference in the transmyocardial resistance contributes to maintaining the normal coronary blood flow distribution. The myocardial oxygen demand is greater in the subendocardium than in the outer layers of the ventricular wall. Normally, the differences in transmyocardial resistance contribute to maintaining adequate subendocardial blood flow. In the pathologic states, the alteration in the distribution of transmyocardial coronary blood flow can induce subendocardial ischemia.

COMPRESSIVE RESISTANCE

The compressive resistance results from compression of coronary arteries by myocardium. It varies during cardiac cycle and is higher during systole than in diastole. Compressive resistance decreases total coronary blood flow only slightly. Most myocardial blood flow occurs during diastole. Normally, the compressive resistance in diastole is of small magnitude; however, it increases with increase in ventricular diastolic pressure and in pericardial pressure.

AUTOREGULATORY RESISTANCE

Autoregulatory resistance is the principal mechanism by which coronary blood flow is maintained constant at a constant level of myocardial oxygen demand despite changes in perfusion pressure. Autoregulatory resistance is primarily determined by the caliber of the arterioles. The arteriolar resistance is inversely proportional to the fourth power of arteriolar radius. Thus, a slight change in the caliber of the arterioles is associated with a substantial change in autoregulatory resistance. The autoregulatory resistance is high at basal conditions but decreases when there is an increase in metabolic demand during exercise. During exercise, coronary blood flow may increase 4- to 6-fold. With intact autoregulation, coronary blood flow remains relatively unchanged with perfusion pressure ranging 60–120 mm Hg.

The normal resting coronary blood flow in humans is about 70–100 ml/min/100 gm of tissue. The normal weight of human

heart is approximately 300 gm and total coronary blood flow is about 250 ml/min. The endocardial and epicardial flows also have been estimated and are approximately 83 and 75 ml/min/100 gm.[1] The flow ratio of endocardium to epicardium usually ranges 1.06–1.16. With maximal coronary vasodilatation, this ratio is close to 1.0.[1] The autoregulatory coronary vascular resistance is modulated by metabolic, neurohormonal and myogenic factors.

MYOGENIC RESISTANCE

The myogenic mechanism involves spontaneous contraction or relaxation of the coronary vascular smooth muscles in response to changes in intraluminal pressure. There is a positive correlation between myogenic response and changes in intraluminal pressure.[5] The myogenic vascular constriction serves to protect distal vessels in response to a sudden increase in arterial pressure.[6] The myogenic resistance is substantial and tightly regulated in the coronary microcirculation, including arterioles.[7] The human coronary microcirculation also responds by vasoconstriction, with increasing intraluminal pressure.[6,8] Several mechanisms for regulation of myogenic resistance have been proposed.[6] It has been suggested that the cell membrane depolarization due to stretch-activated *cation* channels play a role.[6,9] The activation of protein kinase C (PKC) signaling pathways are also involved.[6,8] The activation of other protein kinases, such as mitogen-activated protein kinase (MAPK), have also been implicated.[6,10,11] In the animal studies the reactive oxygen species (ROS) appear to contribute to the regulation of myogenic resistance.[12] The elevated intramural pressure is associated with ROS production and contributes to myogenic microvascular constriction.

MODULATION OF CORONARY BLOOD FLOW

FLOW MEDIATED REGULATION

The flow-mediated vasodilatation (FMD) is an important mechanism of relaxation of the coronary vascular bed. A change in shear stress is associated with release of NO and other endothelium-derived relaxing factors which cause dilatation of the vascular smooth muscles. Human coronary conduit and resistance vessels dilate in response to shear stress. In absence of atherosclerotic coronary artery disease, the dilatation of the resistance vessels is not attenuated by indomethacin, an inhibitor of cyclooxygenase but significantly reduced by L-NAME, a nitric oxide (NO) synthase inhibitor, which suggests that NO release mediates coronary arteriolar dilatation.[12] In patients with coronary artery disease, however, the FMD is not affected by inhibition of synthesis of NO or of cyclooxygenase, suggesting that neither NO nor prostaglandins are involved in dilatation of the resistance vessels.[12] The FMD is inhibited, however, by blocking Ca^{+2} activated K^{+} channels, which suggests that endothelium-derived hyperpolarizing factors (EDHF) play an important role in inducing coronary arteriolar smooth muscle relaxation.[13] Endothelial-derived hydrogen peroxide, as an EDHF, contributes to dilatation of the human coronary resistance vessels in response to shear stress.[14] Hydrogen peroxide has been shown to reduce production of inhibitors of EDHF epoxyeicosatrienoic acids (EETs) in human coronary arterioles.[14,15] Bradykinins also produce endothelium-dependent coronary vasodilatation which is partly due to release of hydrogen peroxide and inhibition of EETs.[6]

METABOLIC FACTORS

The metabolic factors contribute substantially in autoregulation of coronary circulation. A number of metabolic factors, such as adenosine, oxygen and carbon dioxide tensions, pH, lactic acid, and potassium and phosphate concentrations, influence metabolic regulation of coronary circulation. Adenosine is an important metabolic mediator and causes coronary vasodilatation in response to increase in myocardial metabolic demand during exercise. Adenosine causes vasodilatation by activating adenosine receptors, and there are at least four subtypes: (1) A1; (2) A2A; (3) A2B and (4) A3. The regulation of coronary blood flow is primarily mediated by A2A adenosine receptor.[16] Adenosine decreases coronary vascular resistance which is associated with increased coronary blood flow. Adenosine dilates primarily resistance vessels (Fig. 1). The epicardial coronary artery cross-sectional area remains unchanged during adenosine infusion, whereas the average peak velocity measured by intracoronary Doppler ultrasound technique is increased and suggesting dilatation of the coronary resistance vessels. The magnitude of coronary vasodilatation in response to adenosine is not uniform in all vascular beds. In the presence of significant epicardial coronary artery stenosis, the vascular bed in the distribution of more severely stenosed epicardial coronary artery is already dilated. The magnitude of increase in coronary blood flow during a further increase in metabolic demand is less in this area than that in the area of distribution of normal or less severely stenosed epicardial coronary arteries. Thus, the perfusion of the different myocardial segments is not uniform, and forms the basis of stress perfusion imaging. The metabolic factors affect microarteries which are of 30–100 micrometers diameters.[16]

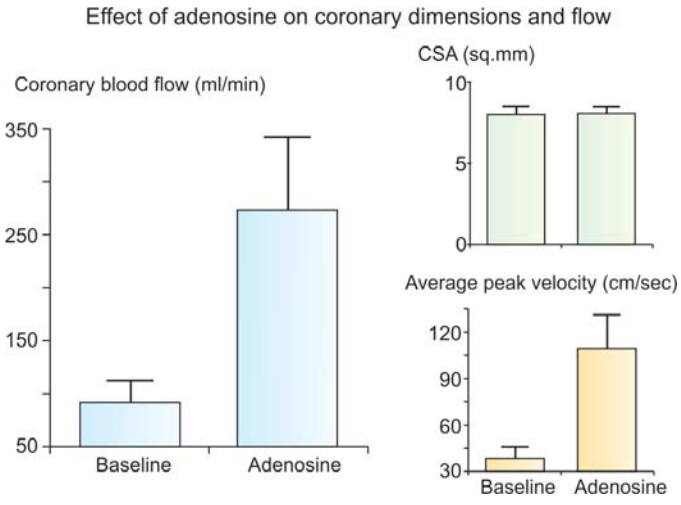


FIGURE 1: Effects of adenosine on coronary blood flow in dogs. Average peak velocity increased suggesting dilatation of the resistance vessels. There was very little change in coronary artery diameter suggesting that conduit artery resistance is relatively unaffected. Thus increased coronary blood flow is primarily due to reduction in arteriolar resistance

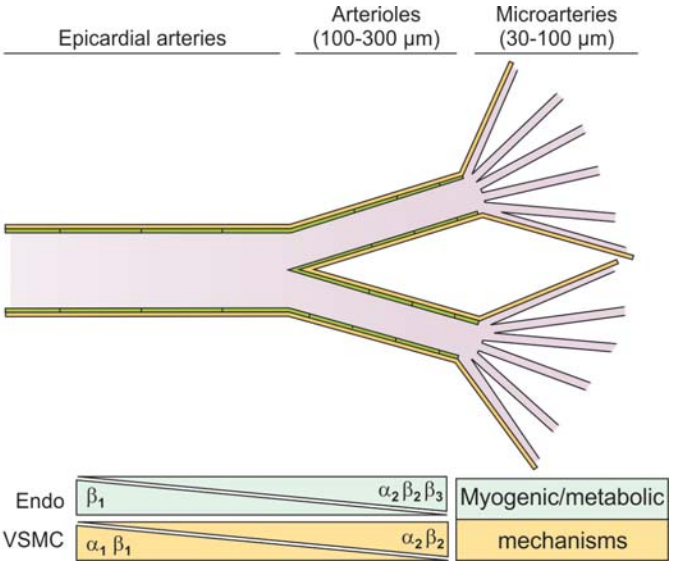


FIGURE 2: The schematic illustration of the coronary arterial system which consists of epicardial coronary arteries, arterioles (100–300 micrometers) and microarteries (30–100 micrometers). The adrenergic receptors are located primarily in the arterioles and the epicardial arteries. The metabolic and the myogenic factors affect the micro-arteries. (Abbreviation: VSMS: Vascular smooth muscle cells). (*Source:* Barbato E, Heart. 2009;95:603-8; Ref 16)

NEUROGENIC MODULATION

The neurogenic modulation of coronary vascular resistance is related to activation of vasoconstrictor alpha-adrenergic and vasodilator beta-adrenergic receptors. These adrenergic receptors are located primarily in the coronary arterioles which have diameters of 100–300 micrometers and also are present in the epicardial coronary arteries[17] (Fig. 2).

The adrenergic alpha-receptor subtypes—alpha-1 and alpha-2—are present in the vascular smooth muscle cells, and activation of these alpha receptors causes vasoconstriction. The distribution of the alpha-receptor subtypes is not uniform: alpha-1 receptors are present predominantly in the larger caliber arteries including epicardial coronary arteries, whereas the alpha-2 receptors density is higher in the arterioles. The alpha-2 receptors are also present in the vascular endothelium, and the activation of the endothelial alpha-2 receptors is associated with NO mediated vasodilatation.

The subtypes of beta-adrenergic receptors—beta-1, beta-2 and beta-3—are present in the vascular smooth muscle cells of the coronary vasculature and in the myocardium. The density of beta-2 receptors is highest in the arterioles and their stimulation is associated with coronary vasodilatation. The beta-1 receptors are present predominantly in the epicardial coronary arteries and their activation is associated with dilatation of the epicardial coronary arteries. The beta-3 receptors are present mostly in the endothelial cells of the arterioles, and activation of these receptors produce coronary vasodilatation via NO and hyperpolarization mechanisms. The beta-1 and beta-2 receptors are also present on endothelial cells but their functional significance remains unclear.

The coronary vasodilatation mediated by increased adrenergic activity stimulates cardiac metabolic activity. The phenomenon of coronary vasodilatation mediated by increased sympathetic and cardiac metabolic activity is called "feed forward sympathetic vasodilation".[18] The "feed forward coronary vasodilation" is partly mediated by activation of beta-1 and beta-2 adrenergic receptors.[19] The disturbances of this phenomenon may influence myocardial perfusion. In human studies, it has been reported that alpha-adrenergic receptors activation contributes to vasoconstrictor tone in the coronary vascular bed under basal conditions.[20] The beta-adrenergic receptors exert a minor vasodilatory effect at rest.

The activation of adrenergic activity during cold pressor test, mental stress or exercise causes vasodilatation of both the epicardial and coronary microvasculature in the presence of normal coronary arteries. Intravenous administration of dobutamine, a predominantly beta-adrenergic receptor agonist, causes dilatation of the epicardial coronary arteries and coronary arterioles. Coronary vasodilatation during dobutamine infusion is also meditated by increased metabolic demand. Nebivolol, which is a selective beta-1 receptor blocking agent with beta-3 receptor stimulating property, induces coronary vasodilatation and increases coronary flow reserve.[17] Thus, alpha-receptor blockade and stimulation of beta-1, beta-2 and beta-3 receptors are associated with coronary vasodilatation. In the presence of normal endothelial function, stimulation of cholinergic receptors causes coronary vasodilatation by releasing acetylcholine. Acetylcholine-mediated coronary vasodilatation is related to release of endothelium-dependant relaxing factors including NO (Figs 3 and 4). However, following inhibition of NO synthesis by LNAME, intracoronary infusion of acetylcholine is associated with a significant increase in the cross-sectional area of the epicardial coronary arteries. But the average peak velocity flow does not increase significantly suggesting that NO predominantly affects the conductance vessels and not the resistance vessels. Atherosclerotic coronary artery disease is associated with endothelial dysfunction, and acetylcholine causes paradoxical response.[21] It causes epicardial coronary artery constriction and increases coronary arteriolar resistance and decreases coronary blood flow.

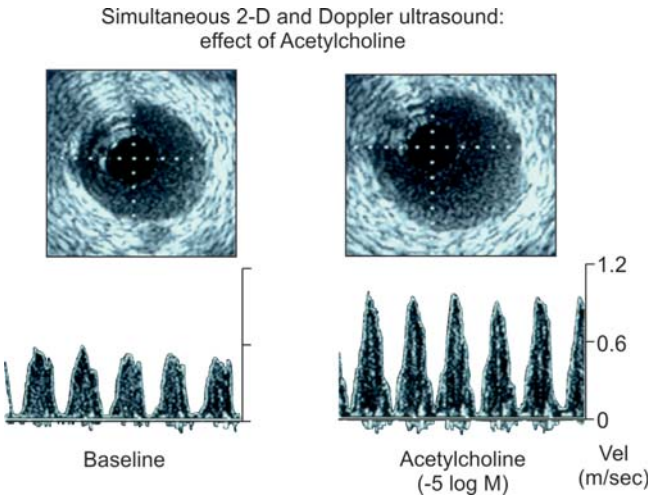


FIGURE 3: Effects of intracoronary infusion of acetylcholine in normal dogs. The intracoronary ultrasound imaging demonstrates an increase in coronary artery cross-sectional area indicating dilatation of the conduit vessels. There was also an increase in the average peak velocity (intracoronary Doppler technique) indicating dilatation of the resistance vessels in response to intracoronary infusion of acetylcholine

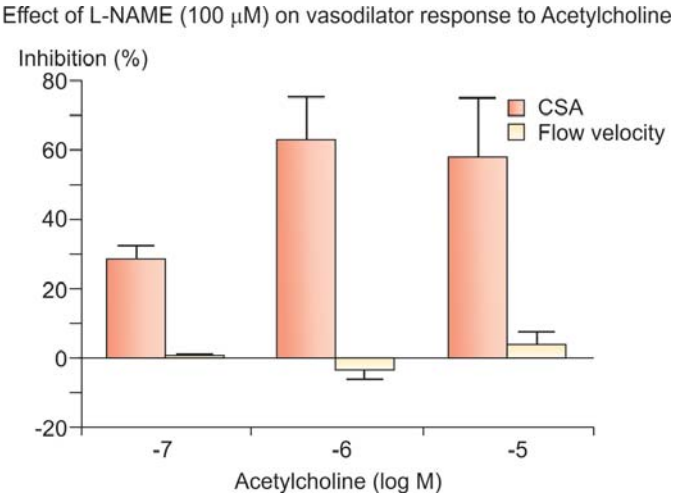


FIGURE 4: Effects of nitric oxide (NO) synthase inhibitor LNAME on coronary artery cross-sectional area (CSA) and average peak velocity. The magnitude of the increase in CSA was markedly attenuated after LNAME suggesting that NO pathway dilates the conductance vessels. The AVP was not substantially involved, indicating that the coronary resistance vessel dilatation is little affected by NO

In the presence of atherosclerotic coronary artery disease, coronary vasoconstriction also occurs in response to stimulation of alpha-adrenergic receptors. Coronary vasoconstriction during percutaneous coronary intervention has been observed, and it is reversed by the administration of alpha-adrenergic receptors antagonists.[22]

HORMONAL MODULATION

Hormonal modulation of coronary circulation in physiologic and pathologic states is related to activation of various neurohormonal systems. The renin-angiotensin-aldosterone system, catecholamines, endothelins, bradykinins, NO and natriuretic peptides influence coronary vascular tone. In the basal state, angiotensin appears to exert coronary vasoconstriction as angiotensin II receptor-1 (AT-1) blocking agent induces dilatation of the conduit and resistance vessels[23] (Fig. 5). The coronary vasodilatation induced by angiotensin receptor blockade is partly mediated by NO as LNAME, an NO synthase inhibitor which attenuates coronary vasodilatation (Fig. 6).[23] However, it is not abolished by inhibition of bradykinin or prostacyclin synthesis. Thus, it appears that the angiotensin system is involved in regulation of coronary vascular tone even at basal conditions. Intracoronary infusion of angiotensin-converting enzyme inhibitors that do not cause any systemic hemodynamic effects also cause coronary vasodilatation, which is markedly attenuated by bradykinin inhibition with administration of bradykinin-2 receptor antagonists[24] (Figs 7A to C). Thus, bradykinins also contribute in regulation of coronary vascular tone.[24]

In experimental studies, aldosterone appears to increase coronary vascular tone and decrease coronary blood flow.[25] In cardiac-specific, aldosterone synthase transgenic mice, the basal coronary blood flow decreased by more than 50% compared to that in the wild type mice. The decrease in coronary blood flow was attenuated in response to acetylcholine, bradykinin and sodium nitroprusside, suggesting that the decrease in basal coronary blood flow by aldosterone is mediated by both endothelium-dependent and endothelium-independent mechanisms.

Vasopressins are potent vasoconstrictors and vasoconstriction is caused by stimulation of vascular smooth muscles by activation of vasopressin-1 receptors. Vasopressins increase not only systemic vascular resistance but also coronary vascular resistance. In experimental animals, vasopressins cause coronary vasoconstriction and impair myocardial perfusion.[26]

Endothelins—primarily endothelin-1—are also potent coronary vasoconstrictors, increasing coronary vascular resistance and decreasing coronary blood flow.[27] Endothelins cause constriction of vascular smooth muscle cells primarily of the coronary resistance vessels. The endothelins exert their vasoconstrictive effects by activating specific receptors Endothelin-A and Endothelin-B. Endothelin-1 induces an

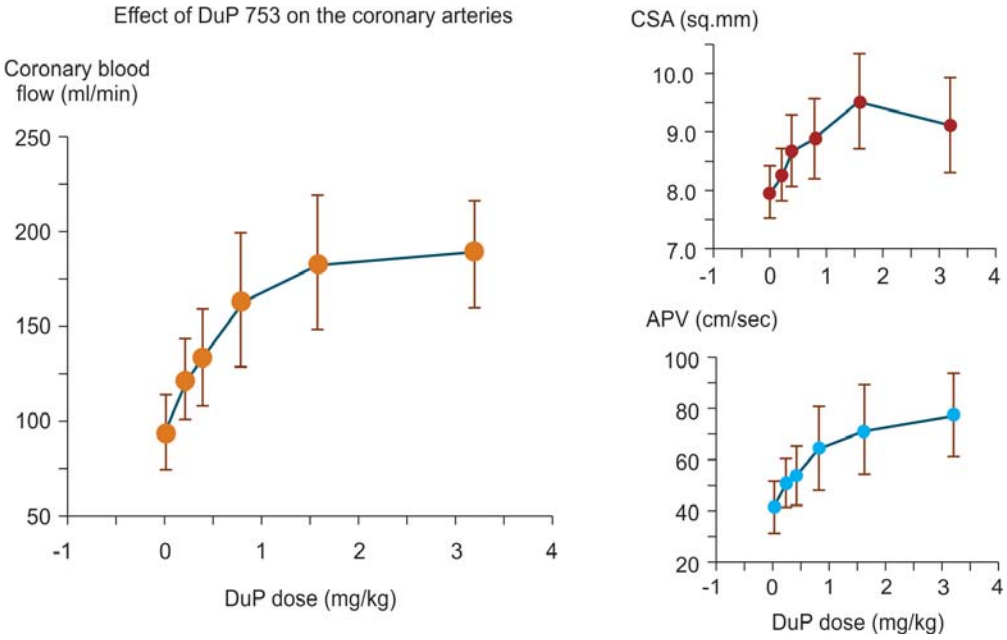


FIGURE 5: Effects of angiotensin receptor subtype-1 blocking agent DUP-753 (Losartan) on epicardial coronary artery cross-sectional area (CSA) and the average peak velocity (APV). There was dilatation of both conductance and resistance vessels and increase in coronary blood flow. (*Source:* Modified from Sudhir K, MacGregor JS, Gupta M, et al. Effect of selective angiotensin II receptor antagonism and angiotensin converting enzyme inhibition on the coronary vasculature in vivo: intravascular two-dimensional and Doppler ultrasound studies. Circulation. 1993;87(3):931-8)

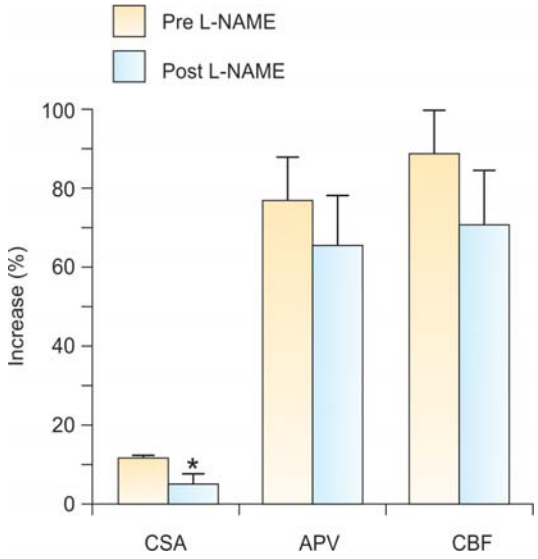


FIGURE 6: Effects of NO-synthase inhibitors on losartan induced dilatation of the conductance and resistance vessels. The magnitude of dilatation of the conductance vessels was attenuated by NO-synthase inhibition suggesting that NO pathway dilates the conductance vessels. There was no effect on resistance vessels. (Abbreviations: CSA: Cross-sectional area; APV: Average peak velocity; CBF: Coronary blood flow). (*Source:* Modified from Sudhir K, Chou T, Hutchison S, et al. Coronary vasodilation induced by angiotensin-converting enzyme inhibition in vivo: differential contribution of nitric oxide and bradykinin in conductance and resistance arteries. Circulation. 1996;93:1734-9)

exaggerated vasoconstrictor response in atherosclerotic coronary arteries.[27-31] Norepinephrine also increases coronary vascular resistance by activating alpha-adrenergic receptors of the coronary arteries.

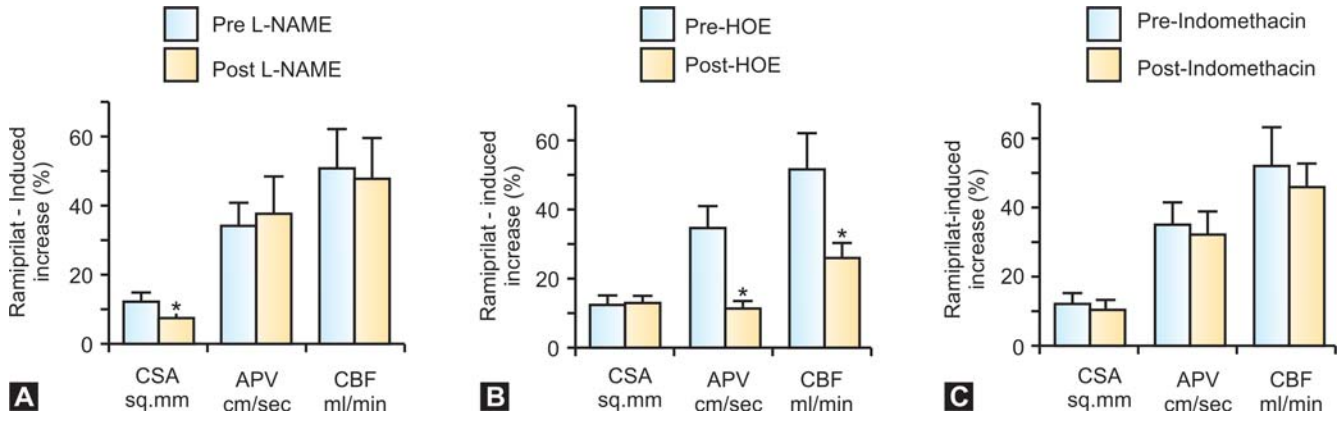
The B-type natriuretic peptide (BNP) causes relaxation of the coronary conduit and resistance vessels and increases coronary blood flow without any concomitant increase in myocardial oxygen demand[32,33] (Fig. 8). The exogenous administration of BNP is associated with both systemic arterial and venous dilatation. The coronary vascular relaxation by BNP is partially attenuated by indomethacin and NO synthase inhibitors suggesting that both prostaglandins and NO systems are involved. It remains unclear whether natriuretic peptides play a physiologic role in the regulation of coronary vascular tone.

The sex hormones estrogen and testosterone acutely cause coronary vasodilatation.[34-38] The mechanisms of coronary vasodilatation remain unclear. Activation of nuclear receptor mechanisms appears unlikely as vasodilatation occurs very quickly after their administration. The physiologic role of sex hormone-mediated coronary vasodilatation also remains unclear.

CORONARY COLLATERAL CIRCULATION

Coronary collateral vessels are anastomotic channels and serve as alternative sources of blood flow and myocardial perfusion in presence of obstructive coronary artery disease. Although anastomotic channels are normally present in the coronary circulation, collateral arteries that develop in obstructive coronary disease are larger muscular arteries have the anatomic composition similar to those of epicardial coronary arteries, and are present predominantly in the epicardium.[39] Like epicardial coronary arteries, collateral arteries are conductance arteries and connect the territory of one epicardial coronary artery to that of another.[40] The collateral vessels may also develop in the same epicardial coronary artery connecting the proximal to the distal segment across severely or totally occluded segments.

A number of factors have been identified which influence development of collateral vessels. The presence, severity and duration of ischemia have been documented as important stimuli.[41-43] More severe and longer duration of myocardial ischemia is more likely to cause development of significant coronary collateral vessels. The severity of the coronary artery stenosis, as assessed by the transstenotic pressure gradient, is another stimulus. A substantial pressure gradient is required to induce development of the collateral vessels. Slower induction of myocardial ischemia, as occurs when severe coronary artery occlusion develops gradually, is more likely to be associated with development of collateral vessels than when severe ischemia occurs suddenly following total occlusion of an epicardial coronary artery.[44]



FIGURES 7A TO C: Effects of angiotensin converting enzyme inhibitor on coronary circulation. It dilates both coronary conductance and resistance vessels. The conductance vessels dilatation is attenuated by NO-synthase inhibitor. Resistance vessels dilatation is attenuated by bradykinin inhibition suggesting that bradykinin is involved in angiotensin converting enzyme inhibitors mediated coronary vasodilatation. (Abbreviations: CSA: Cross-sectional area; APV: Average peak velocity; CBF: Coronary blood flow). (*Source:* Modified from Sudhir et al., Circulation, Ref. 22)

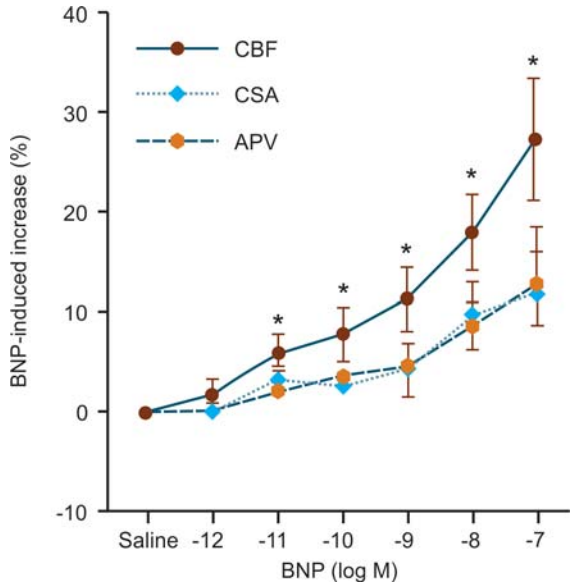


FIGURE 8: Effects of B-type natriuretic peptide on coronary circulation. There is a significant increase in coronary blood flow (CBF) due to dilatation of the conductance (CSA) and the resistance (AVP) vessels. (*Source:* Modified from Christian Zellner, Andrew A. Protter, Eitetsu Ko, et al. Coronary vasodilator effects of BNP: mechanisms of action in coronary conductance and resistance arteries. Am J Physiol- Heart and Circulatory Physiology. 1999:276)

Although the magnitude of collateral blood flow following epicardial coronary artery occlusion may be adequate in absence of increased myocardial oxygen demands, it is insufficient when oxygen demand is increased during exercise.[45] Coronary blood flow per gram of myocardium, dependent on collateral flow, is reduced compared to normally perfused myocardium.[46] One of the mechanisms of reduced flow is the reduced perfusion pressure of the collateral blood vessels. The pressure in the collateral arteries is similar to that in the arterial segment distal to the coronary artery stenosis. Coronary artery pressure distal to severe stenosis may be only 25–50% of aortic pressure.[47,48]

Neurohormonal regulation of collateral circulation may be contributing mechanisms to maintain adequate collateral blood flow. NO-mediated endothelium-dependent vasodilatation and its inhibition by NO synthase inhibitor in collateral blood vessels have been observed.[49,50] The release of vasoconstrictors thromboxane A2 and serotonin with platelet activation in the collateral vessels may decrease collateral blood flow particularly during increased oxygen demand at the time of exercise.[51]

The beta-adrenergic receptors have been identified in the collateral vessels and their activation causes dilatation of these vessels.[52] The beta blockade therapy is associated with impaired vasodilatation and reduced collateral blood flow during exercise.[53]

The precise mechanisms for the formation of collateral vessels remain unclear. The various growth factors, such as basic fibroblast growth factor (bFGF) and vascular endothelial growth factor (VEGF) known to promote vasculogenesis, have been implicated.[54,55]

The existence and regulation of coronary collateral circulation has several clinical significances. In patients with acute coronary syndromes pre-existence of collateral blood vessels have been shown to reduce infarct size after reperfusion.[56] The ventricular function is better in patients with collateral vessels than without collateral vessels.[57] The prognosis of patients with collaterals appears to be better in patients than without collaterals.[58] However, no controlled studies have been performed to assess the clinical significance of collateral vessels.

CORONARY CIRCULATION IN PATHOLOGIC STATES

HYPERTENSION

In patients with arterial hypertension but without coronary artery disease, coronary blood flow reserve is reduced.[59] When there is associated hypertrophy, there is microvasculature rarefaction which contributes to reduced coronary flow reserve. Coronary vascular resistance is elevated in hypertension due to impaired endothelium-dependent coronary vasodilatation.[59,60] There is impairment of vasodilatation of both coronary conductance and resistance vessels. Intracoronary infusion of both acetylcholine and substance P produced blunted vasodilatory response of conductance and resistance vessels in patients with hypertension compared to patients without hypertension.[61] Both acetylcholine and substance P produce endothelium-dependent vasodilatation but by different mechanisms. Acetylcholine and substance P activate different muscarinic receptors. Both acetylcholine and substance P-induced vasodilatation is blunted by NO synthase inhibitors, suggesting that the NO pathway is involved.[62] In hypertensive patients with subclinical renal damage, coronary flow reserve is impaired usually in patients with left ventricular hypertrophy.[63] Several potential anatomic and physiologic mechanisms have been proposed that include smooth muscle cell hypertrophy and impaired vasodilator reserve. In hypertension with hypertrophy, there is considerable medial hypertrophy of the coronary resistance vessels which is associated with impaired coronary blood flow reserve.[64] With long-term pharmacotherapy there may be regression of medial hypertrophy.[64] In hypertensive patients without coronary artery disease, coronary flow velocity reserve and aortic distensibility is reduced as measured by transesophageal echocardiography.[65]

Myocardial blood flow distribution is altered in hypertrophy. In absence of hypertrophy, the blood flow is higher in the endocardial layers. When there is concentric hypertrophy, for example, in response to pressure overload, the blood flow is higher in subepicardial and epicardial layers than in the endocardium.[66] The endothelium-dependent vasodilatation is impaired both in patients with concentric and eccentric left ventricular hypertrophy.[67,68] The endothelium-independent vasodilatation of the resistance vessels is impaired predominantly in patients with eccentric hypertrophy.[67]

In experimental animals with pressure-overloaded left ventricular hypertrophy, the subendocardial flow reserve is impaired at rest.[69] During induced stress, there is further reduction in subendocardial flow reserve which may cause diastolic dysfunction due to subendocardial ischemia.[69]

The changes in coronary microvascular function have been observed in patients with hypertension by positron emission

tomography (PET) studies.[70] At rest coronary flow response remains normal but it is blunted in response to increased metabolic demand.[70] The potential mechanisms of myocardial ischemia in hypertension are summarized in Table 3.

VALVULAR HEART DISEASE

In aortic valve stenosis, there is microvascular dysfunction which is associated with reduced subendocardial blood flow which can induce subendocardial ischemia and necrosis even in absence of epicardial coronary artery disease.[71] In patients with hemodynamically significant aortic stenosis without epicardial coronary artery disease, coronary sinus blood flow which approximates global coronary blood flow is increased both at rest and during isometric exercise.[72] However, normalized for left ventricular mass, coronary blood flow remains within normal limits. The ratio of the diastolic pressure time index and the systolic pressure time index (DPTI/SPTI), which reflects the myocardial oxygen supply/demand relation, is reduced, indicating that myocardial oxygen supply is inadequate for the oxygen demand.[72] In patients who had angina during isometric exercise, the DPTI/SPTI ratio decreased to a greater extent compared to those who did not experience angina suggesting that the myocardial oxygen supply and demand mismatch was higher in patients with angina.[72] In patients with severe aortic stenosis, coronary flow reserve is reduced due to decreased coronary blood flow as a result of reduced perfusion pressure and a concomitant increase in myocardial oxygen demand.[73] The decreased coronary flow reserve in aortic stenosis may reflect coronary microcirculatory dysfunction.[74] Reduced coronary flow reserve may be associated with myocardial ischemia, left ventricular dysfunction, and worse prognosis.[75]

Transthoracic Doppler and myocardial contrast echocardiography and myocardial biopsy during surgical interventions revealed that in patients with aortic stenosis, there was impaired coronary flow reserve, compared to the patients without aortic stenosis and in these patients, there was increased myocyte apoptosis.[76] Decreased coronary flow reserve is also associated with a long-term worse prognosis.[77] In severe aortic stenosis, transmyocardial perfusion pressure gradient is reduced as the aortic diastolic pressure is low and left ventricular diastolic pressure is increased. The coronary blood flow reserve is impaired in patients with significant aortic stenosis due to impaired coronary vasodilation which improves after aortic valve replacement.[78] It should be appreciated that coronary flow reserve may be impaired in patients with aortic sclerosis in absence of significant aortic valve stenosis and in absence of obvious epicardial coronary artery stenosis, suggesting that microvascular-endothelial dysfunction may be present during the early stages of the calcific aortic valve disease.[79]

In severe aortic regurgitation, a potential exists for myocardial ischemia due to increased myocardial oxygen demand and impaired myocardial perfusion.[71] In chronic severe aortic regurgitation, the left ventricular volume is increased. Although there is eccentric hypertrophy, the wall stress is increased due to disproportionate increase in left ventricular volume and dimensions. Thus, myocardial oxygen demand is increased. In severe chronic aortic regurgitation, aortic diastolic pressure, which is the myocardial perfusion pressure, is also low. If there is an increase in left ventricular diastolic pressure, the transmyocardial pressure gradient is reduced and subendocardial ischemia may occur. The slower heart rate can also be detrimental due to increased time for continuing regurgitation. In experimental volume overloaded model

TABLE 3

The potential mechanisms of myocardial ischemia in hypertension, valvular heart disease and hypertrophic cardiomyopathy

Hypertension:	
Changes in the determinants of myocardial oxygen demand	
Left ventricular systolic pressure	increased
Wall stress	decreased
Heart rate	unchanged
Contractility	unchanged or increased
Changes in the determinants of oxygen supply	
Perfusion pressure	normal or increased
Left ventricular diastolic pressure	normal or increased
Transmyocardial pressure gradient	unchanged or increased
Coronary vascular resistance	increased
Coronary vasodilatory reserve	impaired
Rarefaction of microvessels	
Redistribution of blood flow from endocardium to epicardium	
Valvular Heart Disease	
Aortic Stenosis:	
Changes in determinants of oxygen demand	
Left ventricular systolic pressure	increased
Wall stress	decreased
Heart rate	unchanged
Contractility	unchanged
Changes in the determinants of oxygen supply	
Perfusion pressure	normal or decreased
Left ventricular diastolic pressure	unchanged or increased
Transmyocardial pressure gradient	unchanged or decreased
Coronary vasodilatory reserve	impaired
Chronic aortic regurgitation	
Changes in determinants of oxygen demand	
Left ventricular systolic pressure	increased
Wall stress	increased
Heart rate	unchanged
Contractility	unchanged
Changes in determinants of oxygen supply	
Perfusion pressure	decreased
Left ventricular diastolic pressure	unchanged or increased
Transmyocardial pressure gradient	unchanged or decreased
Coronary vasodilatory reserve	impaired
Hypertrophic cardiomyopathy	
Changes in determinants of oxygen demand	
Left ventricular systolic pressure	normal or decreased
Wall stress	decreased
Heart rate	unchanged
Contractility	normal or decreased
Changes in determinants of oxygen supply	
Perfusion pressure	normal or decreased
Left ventricular diastolic pressure	unchanged or increased
Transmyocardial pressure gradient	unchanged or decreased
Coronary vasodilatory reserve	impaired

following creation of complete heart block, there is a little change in left ventricular coronary flow reserve after 6–7 weeks of creating complete heart block.[80] Thus, some increase in heart rate may be beneficial as it reduces total regurgitant volume. The potential mechanisms of myocardial ischemia in aortic valve disease are summarized in Table 3.

HYPERTROPHIC CARDIOMYOPATHY

Hypertrophic cardiomyopathy is a genetic disorder characterized by primary myocardial hypertrophy. The hypertrophy is usually asymmetric and left ventricular wall thickness is not uniform. A substantial abnormality of coronary circulation has been observed in patients with hypertrophic cardiomyopathy.[81-91]

The global myocardial oxygen demand is decreased in hypertrophic cardiomyopathy. Although the left ventricle is hypercontractile, left ventricular wall stress is reduced as left ventricular volume and systolic pressure in general are normal and its wall thickness is increased. However, regional and global coronary blood flow can be impaired particularly during stress.[83-86] Cardiac magnetic resonance studies have reported that in patients with hypertrophic cardiomyopathy, resting myocardial blood flow was similar to those of healthy controls.[88] However, hyperemic myocardial blood flow was lower in patients with hypertrophic cardiomyopathy compared to controls. The endocardial and epicardial blood flow ratio decreased in patients with hypertrophic cardiomyopathy during induced hyperemia. The reduction of subendocardial blood flow was greater with increasing wall thickness. In general, the magnitude of fibrosis was also greater with impaired hyperemic blood flow.[88]

The PET, with the use of 13N-ammonia to measure myocardial blood flow at rest and after dipyridamole, reported that the minimal coronary vascular resistance was higher in patients with hypertrophic cardiomyopathy. These findings suggest that there is impaired coronary vasodilatory reserve in hypertrophic cardiomyopathy.[87] Impaired coronary vasodilatation in the presence of normal epicardial coronary arteries may induce myocardial ischemia and reflects dysfunction of the microcirculation.[86] Reversible myocardial ischemia has also been documented during exercise by thallium 201 myocardial perfusion studies.[85] Abnormal myocardial lactate extraction during pacing has been observed in patients with hypertrophic cardiomyopathy which also indicates stress induced myocardial ischemia.[85] Impaired coronary flow reserve due to microvascular dysfunction not only contributes to myocardial ischemia but also to adverse ventricular remodeling, and worse long-term prognosis of patients with hypertrophic cardiomyopathy.[89]

Coronary flow reserve determined by intracoronary Doppler technique has reported an immediate improvement after alcohol septal ablation in patients with obstructive hypertrophic cardiomyopathy.[90] These findings suggest that hemodynamic causes such as severe left ventricular outflow gradient also contribute to coronary microvascular dysfunction.[90,91] The potential mechanisms for myocardial ischemia are summarized in Table 3.

METABOLIC DISORDERS

Anemia

In chronic anemia, there are changes both in the determinants of myocardial oxygen demand and oxygen supply. Due to reduced hemoglobin and decreased oxygen carrying capacity, there is a compensatory increase in coronary blood flow and increased oxygen extraction. There is an inverse relation between the hemoglobin level and coronary blood flow.[92] The coronary vascular resistance is also markedly decreased. Decreased viscosity is the predominant mechanism for the reduction of coronary vascular resistance.

Diabetes

Irrespective of the type of diabetes, coronary microvascular dysfunction has been observed.[93-95] In both type 1 and type 2 diabetes, endothelium-dependent and endothelium-independent coronary blood flow reserve is impaired. Thus, hyperglycemia appears to produce a direct adverse effect on coronary microvascular function.

ISCHEMIC HEART DISEASE

In acute coronary syndromes, there is a primary decrease in coronary blood flow without any significant changes in the determinants of myocardial oxygen demand. There is inadequate coronary vasodilatation related to impaired endothelial function. After percutaneous coronary intervention, there may be activation of alpha-adrenergic receptors inducing constriction of coronary vessels.

In patients with chronic stable angina, there are changes in both the determinants of myocardial oxygen demand and oxygen supply. However, the predominant changes in oxygen supply or in demand are related to the clinical subsets.

In patients with classic angina (Heberden's angina), there is an increase in heart rate, blood pressure and contractility during exercise or emotional stress that is associated with increased myocardial oxygen demand. There is also a decrease in coronary blood flow reserve due to endothelial dysfunction. Inadequate vasodilatation of the coronary conductance and resistance vessels result in a reduction in coronary blood flow. Thus, ischemic threshold is significantly lowered and ischemia occurs at a lower level of myocardial oxygen demand (Fig. 9).

In patients with vasospastic angina, the principal mechanism of myocardial ischemia is primary decrease of coronary blood flow due to "spasm" of the epicardial coronary arteries, and appears to be related to decreased NO.[96] The endothelium-dependent vasodilatation in response to acetylcholine is impaired at the site of vasospasm compared to that in normal segments.[97] But the magnitude of bradykinin-induced coronary vasodilatation of the epicardial coronary arteries at the spastic site is similar to that of a non-spastic site. Nitrate-induced vasodilatation was also similar in the spastic and non-spastic sites. These findings suggest that NO-mediated endothelium-dependent vasodilatation is impaired at the site of spasm of the epicardial coronary arteries but the bradykinin-mediated

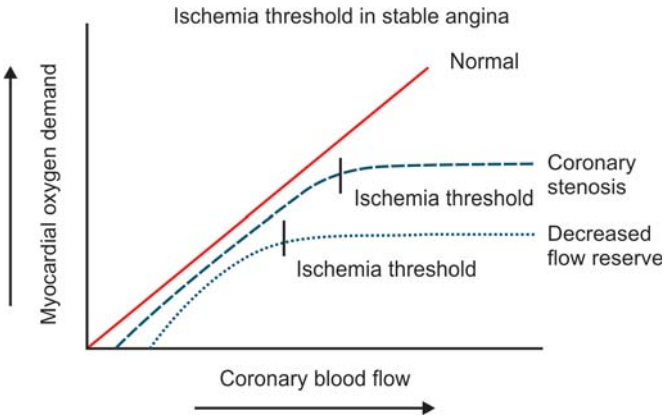


FIGURE 9: Effects of increased myocardial oxygen demand on coronary blood flow. With increasing myocardial oxygen demand there is demand-mediated increase in coronary blood flow. In presence of epicardial coronary artery stenosis when coronary blood flow cannot increase anymore and ischemia is precipitated (ischemia threshold). Due to associated endothelial dysfunction in presence of atherosclerosis coronary blood flow reserve is impaired and ischemia threshold occurs at a lower level of oxygen demand

endothelium-dependent vasodilatation is maintained. Intracoronary infusion of isosorbide dinitrate dilates the conductance vessels without a significant change in microvascular resistance in patients with vasospastic angina.[98]

Mixed angina is characterized by variable exercise level that precipitates angina. The changes in coronary blood flow with same degree of anatomic epicardial coronary artery stenosis may be related to endothelial dysfunction which decreases coronary blood flow due to increase in the microvascular resistance.

In linked angina, there is a disproportionate increase in coronary vascular resistance associated with a decrease in coronary blood flow. The increase in coronary microvascular resistance results from centrally mediated increase in sympathetic activity during visceral stimulation such as esophageal reflux. Increased coronary vascular resistance occurs in presence or absence of atherosclerotic coronary artery disease.

The cardiac "syndrome X" is characterized by exercise-induced angina with evidence of myocardial ischemia in absence of atherosclerotic obstructive coronary artery disease.[99] This clinical subset has been subsequently termed "microvascular angina".[100] Inappropriate increase in coronary microvascular resistance and a decrease in coronary flow reserve have been proposed as the potential mechanism. Both endothelium-dependent and endothelium-independent coronary vasodilatations are impaired.[99-103]

In response to vasoconstrictor stimuli during hyperventilation, mental stress and exposure to cold, an exaggerated response of coronary microcirculation may occur.[104-106] Abnormal cardiac adrenergic nerve function has also been observed in patients with cardiac syndrome X. A higher cardiac defect during 123-metaiodobenzylguanidine (MIBG) uptake has been observed in patients with syndrome X compared to healthy subjects.[106] The changes in coronary circulation in various subsets of angina are summarized in Table 4.

The effects of commonly used antianginal drugs on coronary circulation are summarized in Table 5. Beta-adrenergic receptors antagonists primarily decrease the determinants of myocardial oxygen demand. There is a substantial decrease in heart rate

TABLE 4

Changes in coronary circulation in clinical subsets of stable angina

Classic (Heberden's) angina	Demand and supply ischemia
Vasospastic (Prinzmetal's) angina	Supply ischemia
Mixed angina	Demand and supply ischemia
Linked angina	Supply ischemia
Cardiac syndrome X	Supply ischemia

and contractility and less changes in arterial blood pressure. Coronary vascular resistance may increase due to activation of alpha-adrenergic receptors in the coronary vessels. Myocardial perfusion may increase slightly due to an increase in diastolic perfusion time if there is a substantial decrease in heart rate.[107,108]

Nitrates decrease ventricular volumes due to dilatation of the systemic veins. There is also a decrease in arterial pressure. Thus, there is reduction in wall tension and myocardial oxygen demand. An increase in heart rate and contractility may occur from reflex activation of sympathetic system if there is a significant hypotension. These reflex increase in heart rate partly offset reduction in myocardial oxygen demand resulting from decreased wall tension.[108]

The non-dihydropyridine heart rate regulating calcium channel blockers decreases coronary blood flow due to decrease in myocardial oxygen demand. Contractility and heart rate decrease reduce myocardial oxygen consumption.[109] In contrast, dihydropyridine calcium channel blockers decrease myocardial oxygen demand by decreasing contractility and arterial pressure. However, there is also dilatation of the coronary conductance and resistance vessels.[110] The mechanism of decrease in myocardial ischemia by ranolazine has not been clearly determined. There is no change in heart

TABLE 5

The effects of commonly used antianginal drugs on coronary circulation

Beta adrenoreceptor blocking agents

- Decreased coronary blood flow and myocardial oxygen consumption predominantly due to decreased heart rate and contractility
- Increased coronary vascular resistance due to activation of alpha adrenergic receptors

Nitrates:

- Decreased myocardial oxygen consumption due to decreased ventricular volumes and pressure due to decreased venous return resulting from systemic venodilatation
- Dilatation of the conductance vessels

Calcium channel blocking agents

Dihydropyridines:

- Decreased myocardial oxygen demand due to decreased arterial pressure and contractility
- Dilatation of the conductance and resistance vessels

Heart rate regulating calcium channel blocking agents:

- Decreased coronary blood flow and myocardial oxygen consumption predominantly due to decreased heart rate, and contractility

Ranolazine:

- No direct effects on myocardial oxygen demand or coronary blood flow
- Inhibition of late sodium current resulting in a decreased calcium overload, improved diastolic tension and secondary increase in myocardial blood flow and perfusion

rate, arterial pressure or contractility. Thus, there is no change in myocardial oxygen demand. Ranolazine also does not increase coronary blood flow directly but it improves myocardial perfusion. In presence of myocardial ischemia, there is increased activation of late sodium current which stimulates the sodium/calcium exchange mechanism. Thus, there is myocardial cellular calcium over load which increases left ventricular diastolic tension and coronary vascular compressive resistance. Coronary blood flow and myocardial perfusion are reduced in endocardial and subendocardial layers. Ranolazine inhibits late sodium current and reverses ischemia-induced cellular calcium overload and improves myocardial blood flow and myocardial perfusion.[111]

SYSTOLIC HEART FAILURE

Abnormalities of coronary circulation are common in systolic heart failure. There are changes in myocardial oxygen demand and in coronary blood flow (Table 6).[112] The heart rate/systolic blood pressure product usually remains unchanged. The global contractile function is reduced. Left ventricular volume is markedly increased and the wall thickness is decreased or remains unchanged.[112] The net effect is increased myocardial oxygen demand and consumption (Fig. 10). Increased

TABLE 6

Changes in coronary circulation in systolic heart failure

Determinants of myocardial oxygen demand and consumption	
Heart rate x blood pressure	unchanged
Contractility	decreased
Wall stress	decreased (primarily due to increased volume)
Determinants of coronary blood flow	
Perfusion pressure	unchanged or decreased
End diastolic pressure (subendocardial compressive resistance)	increased
Transmyocardial perfusion pressure gradient	decreased
Coronary sinus venous pressure (resistive resistance)	increased
Microvascular resistance	increased
Coronary vasodilatory reserve	decreased

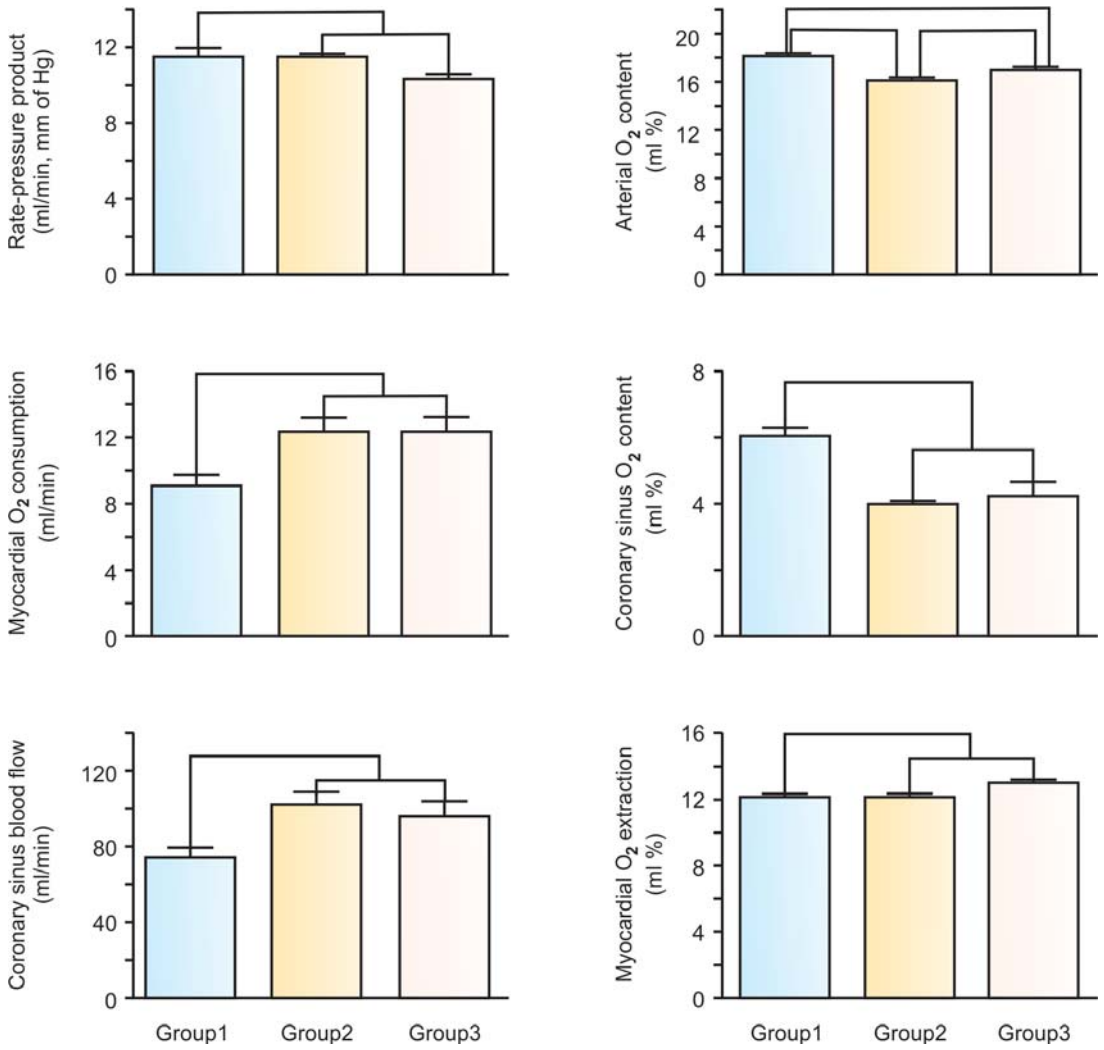


FIGURE 10: Changes in coronary circulation in patients with systolic heart failure. Rate-pressure product (rate x pressure) remains unchanged. Coronary sinus blood flow (CSBF) and myocardial oxygen consumption (MVO_2) were increased in both ischemic and non-ischemic dilated cardiomyopathy compared with patients without heart failure. (*Source:* Modified from Chatterjee, J Cardiac Fail, Ref. 112)

myocardial oxygen consumption is observed both in patients with ischemic and nonischemic dilated cardiomyopathy. The coronary sinus oxygen content decreases with increased myocardial oxygen consumption. The prognosis of patients with lower coronary sinus oxygen content is worse than that in patients with higher coronary sinus oxygen content (Fig. 11).

The coronary blood flow is increased parallel to the increase in myocardial oxygen demand. Coronary blood flow normalized for left ventricular mass, however, may remain normal or even decreased.[113] The perfusion pressure may remain unchanged or decrease depending on the severity of heart failure. Severe systolic heart failure is associated with a substantial increase in left ventricular diastolic pressure which increases endocardial and subendocardial compressive resistance and decrease subendocardial blood flow.[115]

Coronary blood flow reserve is impaired in patients with ischemic and nonischemic dilated cardiomyopathy. Both endothelium-dependent and endothelium-independent mechanisms of coronary vasodilatation are impaired.[112,114] Furthermore, increased release of cytokines and neurohormones enhance coronary vascular tone and decrease coronary blood flow reserve. Increased wall stress also contributes to impaired coronary blood flow reserve.[115]

There is a substantial activation of neurohormones in systolic heart failure. The enhanced adrenergic activity, renin-angiotensin-aldosterone system, vasopressin and endothelins exert adverse effects on coronary circulation (Table 7). Increased adrenergic activity is associated with increased coronary vascular resistance and decreased coronary blood flow. Angiotensins and endothelins also cause constriction of coronary resistance vessels, increase coronary vascular resistance and decrease coronary blood flow.

Vasopressin causes constriction of both conductance and resistance vessels by activating vasopressin 1A receptors which is associated with decreased coronary blood flow.

Myocardial metabolic function can be impaired in systolic heart failure. The serum levels of nonesterified free fatty acids are increased. Myocardial glucose and nonesterified fatty acid uptake and ATP concentrations are decreased. There is a shift from nonesterified fatty acid uptake to glucose uptake for myocardial substrate utilization which is associated with increased myocardial oxygen consumption.[112] During increased stress there is a marked increase in myocardial lactate release suggesting myocardial ischemia.[116]

Some compensatory mechanisms occur to maintain myocardial oxygen delivery when coronary blood flow becomes inadequate for myocardial oxygen demand. Myocardial oxygen extraction is increased. Blood levels of 2,3-diphosphoglycerate

TABLE 7

The effects of neurohormonal abnormalities on coronary circulation in heart failure

Activation of alpha-1 receptors—Coronary vasoconstriction
Increased coronary vascular resistance
Decreased coronary blood flow
Activation of alpha-2 receptors—NO-mediated coronary vasodilatation
• Myocardial beta-1 receptor—
Demand mediated increase in coronary blood flow
• Beta-2 receptors—
Primary coronary vasodilatation
Increased coronary blood flow
• Angiotensin—
Increased coronary vascular resistance
Decreased coronary blood flow
• Aldosterone—
Increased coronary vascular resistance
Decreased coronary flow reserve
• Vasopressin—
Coronary vasoconstriction
Decreased coronary blood flow
• Endothelins—
Coronary vasoconstriction
Increased coronary vascular resistance
Decreased coronary flow

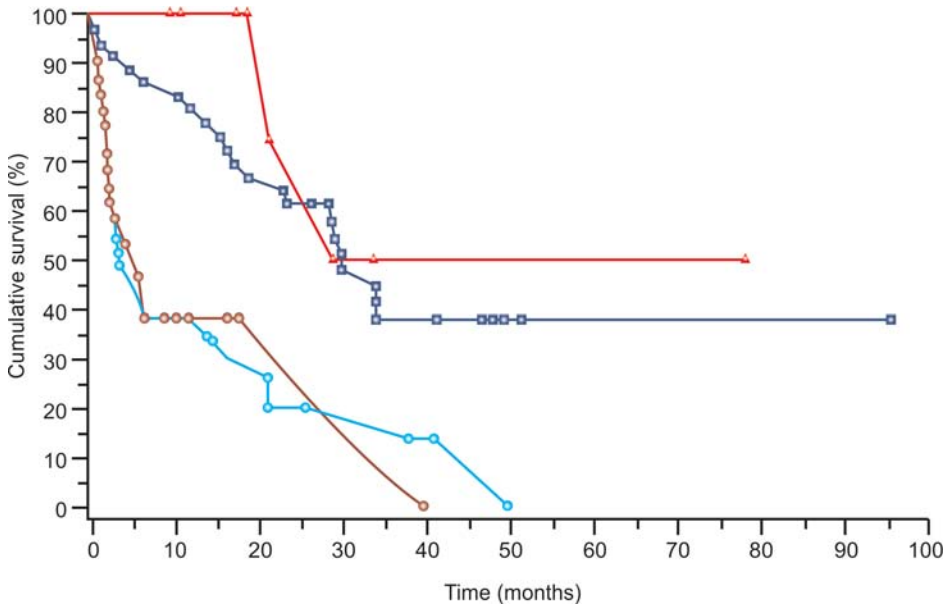


FIGURE 11: Survival curves for patients in group 1 (coronary artery disease) with high (squire) and low (triangle) coronary sinus oxygen content and in group 2 (idiopathic cardio myopathy) with high (diamond) and low (circle) coronary sinus oxygen content. In patients with low coronary sinus oxygen content (< 4.44 vol. percent) the survival was lower than in patients with high coronary sinus oxygen content (> 4.44 vol. percent) ($p < 0.001$). (*Source:* Modified from Chatterjee K. Coronary hemodynamics in heart failure and effects of therapeutic interventions. J Cardiac Fail. 2009;15:116-23)

(2,3-DPG) are increased. Oxygen tension for 50% oxygen saturation (P50) is increased, and there is a rightward shift of the oxygen dissociation curve which facilitates oxygen delivery and myocardial oxygen transport.[112]

The effects of commonly used therapies in systolic heart failure are summarized in Table 8.[112] Angiotensin inhibition with the use of converting enzyme inhibitors is associated with decrease in myocardial oxygen consumption and also a primary increase in coronary blood flow. In general, beta-adrenergic receptor antagonists decrease myocardial oxygen consumption. Some beta-adrenergic antagonists also decrease oxidative stress.

Aldosterone antagonists have the potential to decrease coronary vascular resistance by decreasing perivascular fibrosis. Hydralazine causes demand-related changes in coronary blood flow. There may also be an increase in coronary blood flow/demand ratio. Nitrates, in general, decrease myocardial oxygen demand and consumption. There is also dilatation of the conductance vessels.

Changes in coronary blood flow and myocardial oxygen consumption in response to angiotensin converting enzyme inhibitor captopril, alpha-adrenergic blocking agent prazosin and direct acting vasodilator hydrazaline are illustrated in Figures 12 and 13. Coronary blood flow and myocardial oxygen consumption decrease in response to captopril and prazosin. However, in response to prazosin, coronary blood flow may increase despite a decrease in myocardial oxygen demand suggesting a primary coronary vasodilatory effect of prazosin. In response to hydralazine, coronary blood flow and myocardial oxygen consumption changes in parallel to changes in myocardial oxygen demand. In experimental studies in dogs, intracoronary infusion of ramiprilat, an angiotensin converting

TABLE 8

Effects of commonly used therapies in systolic heart failure on coronary circulation

Angiotensin–converting enzyme inhibitors:	
	Decreased myocardial oxygen demand and consumption
	Improved myocardial efficiency
	Primary coronary vasodilatation
Beta-adrenergic antagonists	
Nebivolol	Decreased myocardial oxygen demand and consumption
	Improved coronary flow reserve
Metoprolol	Improved myocardial energetics
Carvedilol	Decreased oxidative stress
	Improved coronary hemodynamic
Aldosterone antagonists	Not adequately studied in patients
	Has potential to decrease coronary vascular resistance
Hydralazine	Demand mediated changes in coronary blood flow and consumption
	Increased myocardial flow/demand
Nitrates	Decreased myocardial oxygen demand and consumption
Exogenous B-type natriuretic peptides	Primary coronary vasodilatation
	No increase in myocardial oxygen consumption
Beta receptor agonist	Increased myocardial oxygen demand and consumption
	Demand mediated increase in coronary blood flow
Phosphodiesterase inhibitors	Primary coronary vasodilatation
	Decreased coronary vascular resistance
	Increased coronary blood flow
Levosimendan	Primary increase in coronary blood flow
	No increase in myocardial oxygen consumption
Chronic resynchronization	Increased coronary flow reserve
	Increased coronary blood flow

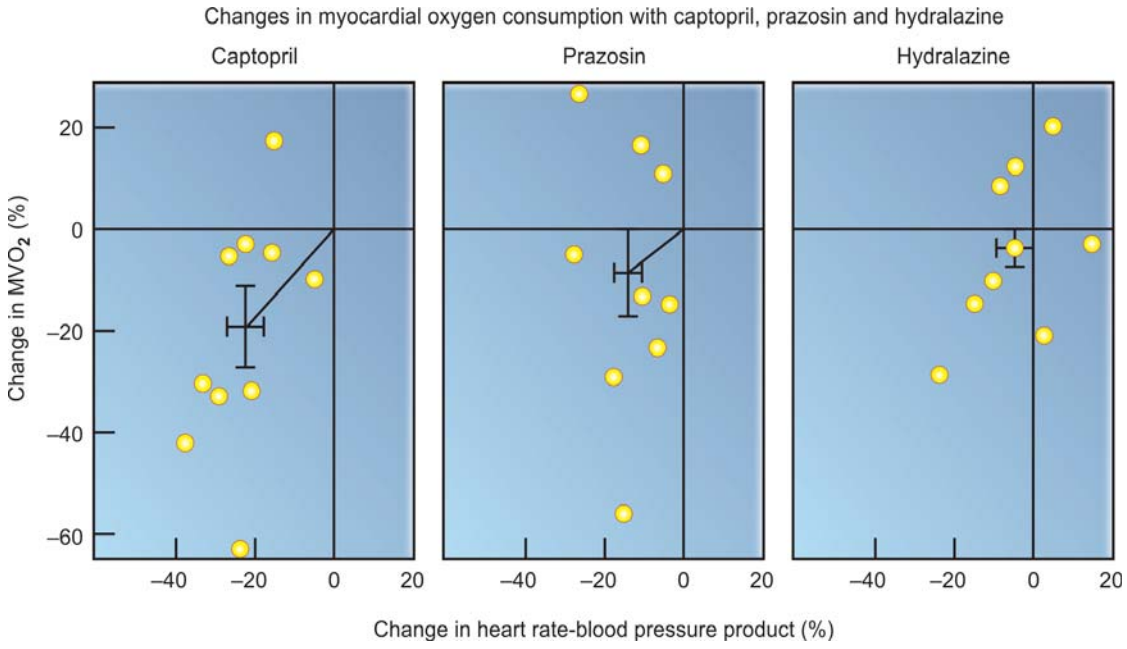


FIGURE 12: Effect of captopril, an angiotensin converting enzyme inhibitor, prazosin, an alpha-adrenergic blocking agent and hydralazine, a direct acting vasodilator on coronary hemodynamics in patients with systolic heart failure. With captopril and hydralazine changes in myocardial oxygen consumption (MVO_2) paralleled to the changes in heart rate blood pressure product indicating demand mediated changes in MVO_2. With prazosin, in some patients, there was an increase in MVO_2 despite a decrease in heart rate blood pressure product (myocardial oxygen demand)

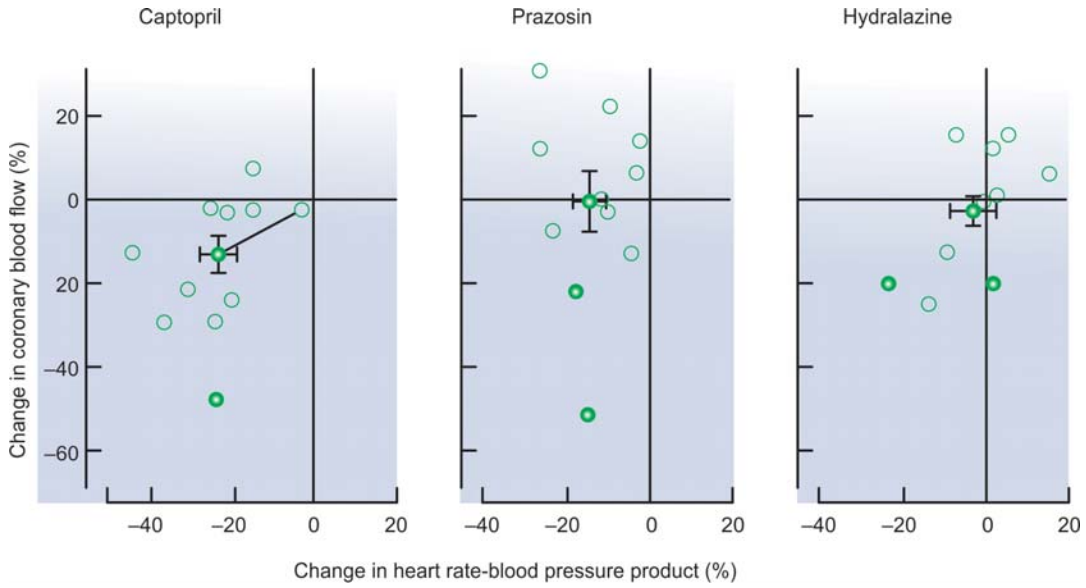


FIGURE 13: Effect of captopril, an angiotensin converting enzyme inhibitor, prazosin, an alpha-adrenergic blocking agent and hydralazine, a direct acting vasodilator on coronary blood flow in patients with systolic heart failure. In response to captopril and hydralazine changes in coronary blood flow paralleled to the changes in heart rate blood pressure product indicating changes in coronary blood flow were primarily demand mediated. In response to prazosin, there was an increase in coronary blood flow despite a decrease in heart rate blood pressure product indicating a direct coronary vasodilatory effect

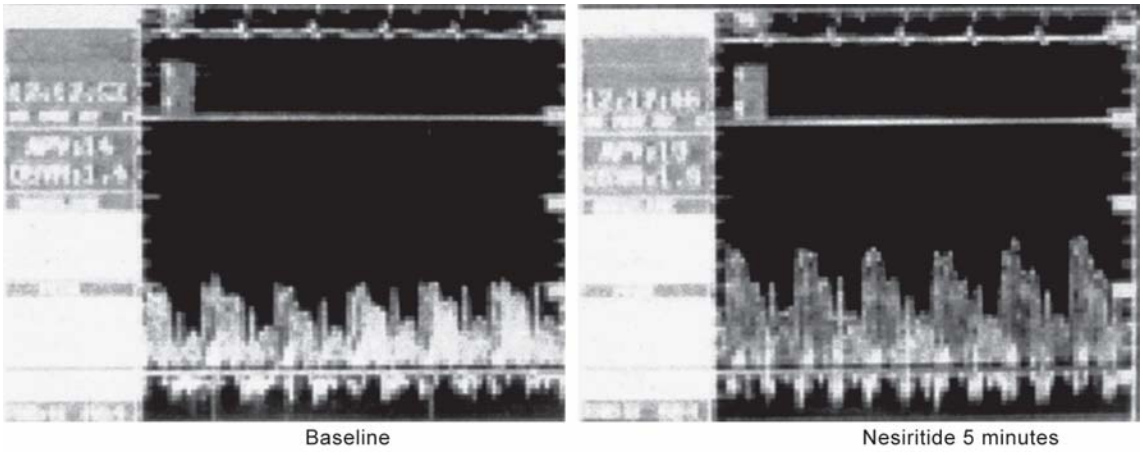


FIGURE 14: Effect of intravenous administration of nesiritide (exogenous BNP) on coronary hemodynamics. Intracoronary Doppler flow studies demonstrate an increase in coronary blood flow (*Source:* Michaeles AD et al. Circulation. 2003;107:2697-701)

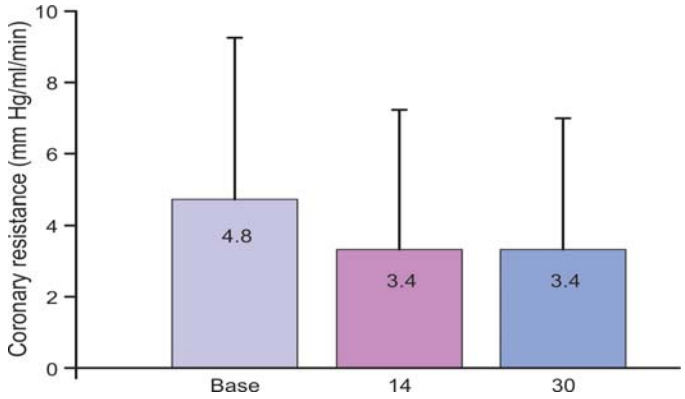


FIGURE 15: Effect of intravenous administration of nesiritide (exogenous BNP) on coronary vascular resistance which decreased indicating coronary vasodilatation (*Source:* Michaeles AD et al. Circulation. 2003;107:2697-701)

enzyme inhibitor is associated with increased coronary blood flow, average peak velocity and coronary artery cross sectional area. This coronary vasodilatory effect of ramiprilat is partially inhibited by nitric oxide synthase inhibitors and by bradykinin inhibitors but not by indomethacin. These findings suggest that coronary vasodilatation by angiotensin converting enzyme inhibitors is partly mediated by nitric oxide and bradykinins but not by prostacyclins.

Intravenous administration of exogenous BNP (B-type natriuretic peptide) is associated with a primary increase in coronary blood flow without an increase in myocardial oxygen consumption (Figs 14 to 16). Beta-receptors agonists increase myocardial oxygen demand and there is demand-related increase in coronary blood flow.

Phosphodiesterase inhibitors cause coronary vasodilatation and a primary increase in coronary blood flow without a significant increase in myocardial oxygen demand.

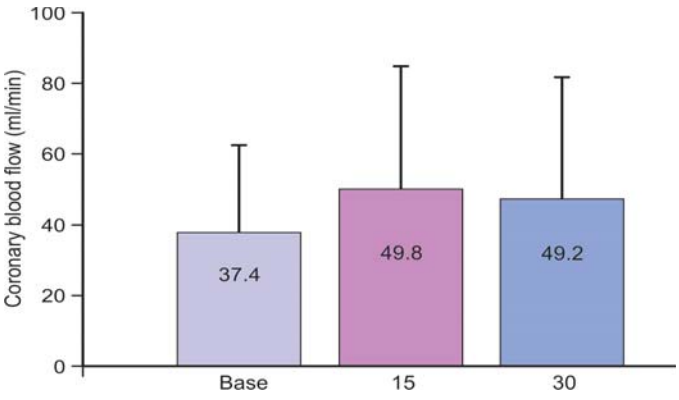


FIGURE 16: Effect of intravenous administration of nesiritide (exogenous BNP) on the epicardial coronary artery diameter which increased indicating dilatation of the coronary conductance vessels (*Source:* Michaeles AD et al. Circulation. 2003;107:2697-701)

The calcium sensitizing agent also causes a primary increase in coronary blood flow without an increase in myocardia oxygen consumption. Chronic resynchronization treatment, usually employed in patients with refractory heart failure, increases coronary flow reserve and coronary blood flow.

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Section 2

CARDIOVASCULAR PHARMACOLOGY

Chapter 4

Diuretics

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Chapter Outline

- Normal Renal Solute Handling
- History and Classification of the Diuretic Compounds
- Clinical Pharmacology of the Diuretic Compounds
  - General Pharmacokinetic and Pharmacodynamic Principles
- Adaptive Responses to Diuretic Administration
- Individual Diuretic Classes
  - Carbonic Anhydrase Inhibitors
  - Loop or High-ceiling Diuretics
  - Thiazide and the Thiazide-like Diuretics
  - Potassium-sparing Diuretics
- Clinical use of Diuretics in Cardiovascular Diseases
  - Diuretic Use in Hypertension
  - Diuretic Use in Edematous Disorders
- Adverse Effects of Diuretics

INTRODUCTION

The era of modern diuretic therapy in cardiovascular disease emerged in the late 1950s with the development of effective oral agents with improved tolerability. Until then, the only diuretics available had been intravenous or intramuscular mercurial derivatives, limited by difficulty in use and an unfavorable toxicity profile.

Today, the diuretic compounds are recognized as powerful tools that impair sodium reabsorption in the renal tubules. In doing so, they increase the fractional excretion of sodium, affect the rate of urine formation and alter long-term sodium balance. These are desirable therapeutic approaches for treating a variety of conditions involving abnormal fluid and electrolyte balance. After more than 50 years in clinical use, diuretics remain of considerable importance in the management of cardiovascular diseases. Diuretics have uses other than in hypertension and edematous disorders, such as in the treatment of hypercalcemia, diabetes insipidus, glaucoma and cerebral edema. This chapter will focus primarily on the pharmacology and clinical use of diuretics in the cardiovascular patient.

NORMAL RENAL SOLUTE HANDLING

Under conditions of normal physiology and sodium intake, nearly 100% of the sodium load is filtered through the glomerulus and progressively reabsorbed throughout different segments of the nephron, the basic urine-forming unit of the kidney. Each anatomic segment is highly specialized in function and the mechanism of action of each diuretic agent is best understood appreciating the relationship of both its site of action in the nephron and the normal physiology of the involved segment.

Reabsorption of sodium occurring throughout the nephron is controlled through the Na^+/K^+-ATPase pump located in the basolateral membrane of tubular epithelial cells. This pump is responsible for moving sodium from the cell into the interstitium and blood, and potassium from interstitium to cell, a process that maintains the cell interior in an electrically negative state in relation to the extracellular fluid.[1] The resulting electrochemical gradient drives sodium intracellularly across the apical membrane, a process accomplished through specific transport pathways of the luminal membrane which are unique between various segments of the nephron. As the sodium load passes through these segments, movement of sodium down the electrochemical gradient, from lumen to tubular cells and to interstitium, is coupled by movement of water and other solutes against or in parallel to their electrochemical gradient.[1]

In the absence of a specific pharmacologic intervention, up to 90% of the filtered load of sodium is reabsorbed in upstream segments of the nephron, primarily in the proximal tubule (65–70%) via a carbonic anhydrase pathway. An additional 20–30% is reabsorbed in the next segment, the loop of Henle, regulated by a $Na^+/K^+/2Cl^-$ exchange symporter. Reabsorption of the remaining filtered sodium reaching the distal segments, approximately 5%, is mediated through the Na^+/Cl^- exchange symporter.[2] The combined effects of these segments serve to tightly regulate the overall physiologic handling of sodium, achieving a remarkable consistently low sodium excretion despite fluctuations in the amounts ingested.

HISTORY AND CLASSIFICATION OF THE DIURETIC COMPOUNDS

A chance discovery in 1937 that the antibiotic, sulfanilamide, caused a mild diuresis accompanied by a metabolic acidosis,

presented an important finding which suggested that oral diuretic therapy might, in fact, be conceivable.[2] Shortly thereafter, the mechanism of sulfanilamide's diuretic and acidotic effects was determined to result from inhibition of carbonic anhydrase in the proximal tubule.[3] In hopes of developing an oral agent with improved diuretic efficacy, researchers quickly synthesized and screened numerous compounds for greater potency and specificity as inhibitors of carbonic anhydrase. In the process, chlorothiazide, both sulfonamide and a carbonic anhydrase inhibitor was discovered; however, unlike other carbonic anhydrase inhibitors, it unexpectedly increased chloride rather than bicarbonate excretion.[2] This key finding prompted the realization that sites other than the proximal tubule could also be pharmacologically targeted and eventually led to the development of the thiazides and other diuretic agents still in primary therapeutic use today.

Modern diuretic compounds are now viewed as a heterogeneous class of drugs that differ remarkably in several aspects, including their chemical derivation, mechanism and therapeutic efficacy. As the amount of sodium reabsorbed varies between the different segments of the nephron, the site of action, natriuretic and therapeutic efficacy, and ultimately the specific clinical indication of each class of diuretic is determined by the specific tubular ion transport systems with which they interfere.

The most common and clinically useful classification of diuretics is to group them into one of several categories on the basis of the primary site of their interference with sodium reabsorption (Fig. 1):

- Carbonic anhydrase inhibitors (e.g. acetazolamide), acting in the proximal tubule
- High-ceiling or "loop" diuretics (e.g. furosemide, bumetanide, torsemide), acting in thick ascending limb of the loop of Henle
- Thiazide and thiazide-like diuretics (e.g. hydrochlorothiazide, chlorthalidone, metolazone, indapamide) acting in the early portion of the distal convoluted tubule
- A fourth category, which are primarily utilized for their potassium-sparing capabilities, can further be subclassified into the sodium channel blockers (e.g. amiloride, triamterene) and the mineralocorticoid antagonists (e.g. spironolactone, eplerenone). These agents act in the late distal tubule and collecting duct.
- A final category of diuretics, the osmotic agents (e.g. mannitol), interfere with sodium reabsorption throughout all segments of the nephron by creating an osmotic force throughout the length of the renal tubule.

Distinguishing the diuretic compounds according to their primary site of action is important, as their therapeutic efficacy

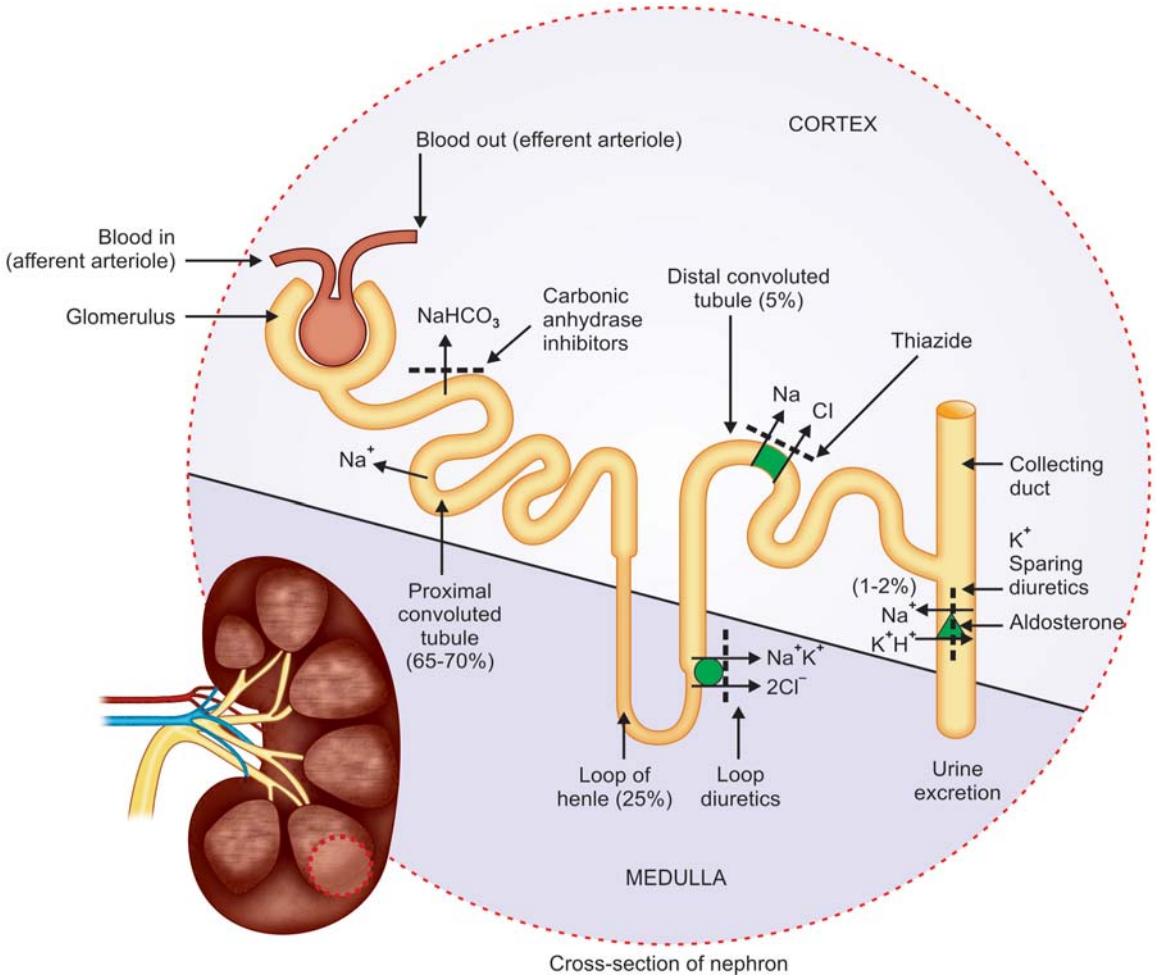


FIGURE 1: Diuretic sites of action in the nephron (Na^+: Sodium; Cl^-: Chloride; K: Potassium; $NaHCO_3$: Sodium bicarbonate; numbers in parentheses reflect the relative percentage of the sodium load reabsorbed in that segment)

TABLE 1

Characteristics of diuretics: classification, site and mechanism of action, clinical uses

Diuretic classification	*Major site of action*	*Enzyme/Channel inhibited*	*Maximum effect (% of filtered sodium load)*	*Clinical uses*
Carbonic anhydrase inhibitors	Proximal tubule	Carbonic anhydrase	3–5	Glaucoma, metabolic alkalosis, high altitude sickness
High-ceiling or Loops	Thick ascending limb of loop of Henle	$Na^+/K^+/2Cl^-$ symporter	20–25	Edematous disorders (congestive heart failure, cirrhosis, nephrotic syndrome), renal insufficiency, hypertension in kidney disease
Thiazide and Thiazide-like*	Early distal convoluted tubule	Na^+/Cl^- symporter	5–8	Hypertension, hypercalciuria, diabetes insipidus, pseudohypoaldosteronism type 2 (Gordon's syndrome)
Potassium-Sparing	Cortical collecting duct		2–3	
Pteridine derivatives		Epithelial sodium channel		Pseudoaldosteronism (Liddle syndrome), thiazide or loop diuretic-induced hypokalemia or hypomagnesemia
Aldosterone receptor antagonists		Aldosterone receptor		Primary and secondary aldosteronism, congestive heart failure, hyperandrogen states, thiazide or loop diuretic-induced hypokalemia or hypomagnesemia, resistant hypertension (independent of primary aldosteronism), Barrter syndrome
Osmotic agents	Multiple segments	Sugar acts as non-absorbable solute		Cerebral edema, intracranial hypertension

*The terms *thiazide* and *thiazide-like* are used to group thiazides based on the presence of a benzothiadiazine molecular structure. *Thiazide-like* diuretics lack the benzothiadiazine structure but share a similar mechanism of action.
(*Source:* Reference 4)

and primary clinical indications are not completely interchangeable (Table 1). Recognizing their sites of action also provides an avenue for additive effects that can be obtained when the different classes of diuretics are used in combination (i.e. "sequential nephron blockade") in certain types of patients.[4]

CLINICAL PHARMACOLOGY OF THE DIURETIC COMPOUNDS

GENERAL PHARMACOKINETIC AND PHARMACODYNAMIC PRINCIPLES

Some generalizations can be made about the pharmacology of the diuretics, despite heterogeneity by class and agent. At physiologic pH, diuretics are either organic anions (loops and thiazides) or cations (amiloride and triamterene). All diuretics, except mannitol, are highly protein bound, which limits filtration at the glomerulus and traps the diuretic in the vascular space; therefore, they must be actively secreted into the proximal tubule lumen to exert their effect. Active transport into the lumen occurs via an organic acid secretory pathway for the carbonic anhydrase inhibitors, loops and thiazides, and a parallel pathway for organic bases. Mannitol and spironolactone are exceptions; mannitol is freely filtered at the glomerulus and passes through the nephron, acting as a nonreabsorbable solute drawing water along with it, while spironolactone (although protein-bound) enters the renal tubules from plasma by competitively inhibiting the binding of aldosterone to the mineralocorticoid receptor at the basolateral surface.[4]

For the most part, diuretics have direct actions that are site-specific, acting on one or another of the tubular segments but not all of them. A few agents maintain a degree of secondary activity at another segment (e.g. some thiazides also inhibit carbonic anhydrase), but it is generally considered an irrelevant contribution to their overall therapeutic effect. This is because diuretic action at one site induces important adaptive changes in other segments of the kidney that attempt to preserve sodium, thereby minimizing the contribution of any secondary site of action to the overall natriuretic effect.

As diuretics are a heterogeneous class, discussion of their pharmacodynamics must occur in the context of distinguishing the features that constitute a clinically relevant response. In general, the desired response is to obtain some meaningful level of natriuresis, which can either correspond to a significant diuresis and reduction in extracellular volume as in the case of loop diuretics to relieve edematous states or a more prolonged low-level diuresis which reduces systemic vascular resistance and lowers blood pressure, as in the use of thiazides for hypertension. Regardless of the indication for use and desired effect, the pharmacodynamic characteristics of diuretics are influenced by a number of factors. Most importantly, a threshold

quantity of the drug must be achieved at the site of action before a clinically relevant response can be obtained.[5] When administered intravenously, bioavailability issues are not present; however, when given orally, diuretic response will be influenced by the rate and extent of absorption which can be highly variable among diuretic compounds and individual patients. The best index approximating diuretic drug delivery to the intraluminal site of action is its urinary excretion rate, as this corresponds to the observed natriuretic response.[5] This relationship exists for both loops and thiazides (although shallower for thiazides) and can be illustrated using a typical sigmoidal curve (Fig. 2) where the critical determinants are basal response, dose causing 50% response, upper asymptote (maximal response) and slope.

The plasma half-life of a diuretic governs both its expected duration of action and dosing frequency. Loop diuretics have very short half-lives and must be dosed multiple times per day, while thiazides and other distally acting diuretics have half-lives that are sufficient for them to be dosed once or twice daily. Empiric dosing of diuretics is generally based on expected population responses, but considering the pharmacodynamic relationship illustrated in Figure 2, diuretic dosing can be individualized to find the dose that delivers enough drug to the site of action to reach the steep portion of the dose-response curve as well as the lowest dose eliciting a maximal response. In normal subjects, there is a little need for such tailoring. One merely selects a typical starting dose and, if necessary, adjusts upward or downward based on the intended response. For thiazides (with a shallower dose/response curve) in the treatment of hypertension, this will be a limited range of 12.5–50 mg/day of hydrochlorothiazide or its equivalent. For loops, where more appreciable volume contraction and diuresis are desired, a starting intravenous dose of 40 mg of furosemide or its equivalent generally results in a maximal excretion of 200–250 mmol sodium in 3–4 liters of urine over 3–4 hours.[5]

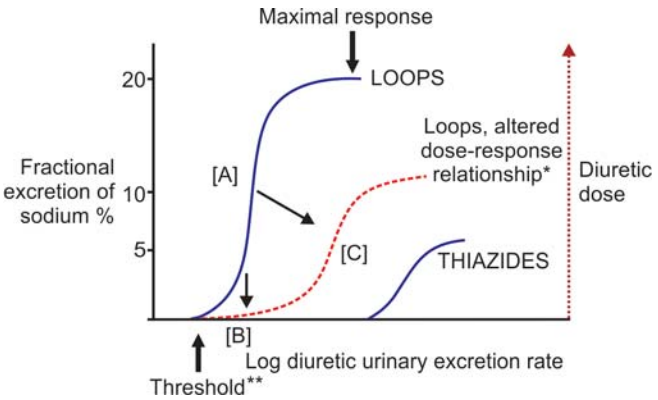


FIGURE 2: Pharmacodynamic illustration of the relationship between diuretic dose and response (adapted from reference 10)
* Nephrotic syndrome, congestive heart failure, cirrhosis
** Determinants of diuretic threshold and efficacy include: dose, bioavailability; tubular secretory capacity rate of absorption and time course of delivery. After identifying the threshold dose to achieve effect, a higher diuretic concentration [A] leads to significant natriuresis. When severe sodium retention occurs or sodium intake is reduced, the curve shifts to the right and the previous diuretic serum concentration achieved by the dose in [A] is no longer effective [B]. The dose of the diuretic must be increased to achieve clinically effective natriuresis [C]. Increasing the frequency of doses has no effect on sodium excretion as long as each dose is below the threshold

Under conditions of normal health, the maximal natriuretic response will be the same for all diuretic agents within a class, in any one patient. Once the diuretic threshold is met (as depicted in Figure 2), there is an optimal rate of delivery leading to maximal response, above which additional diuretic delivery does not result in greater diuresis. Several conditions may distort this diuretic dose-response relationship, such as congestive heart failure, cirrhosis and nephrotic syndrome, shifting the curve downward and to the right.[5] In such conditions, it becomes more important for the dose of the diuretic to be sequentially titrated in the individual to determine the dose that will deliver enough drug to the site of action to reach the steep portion of the curve and elicit the intended response. Such tailoring in these situations allows one to obtain a maximal response using the lowest effective dose, thereby minimizing unnecessary risks associated with more arbitrarily selected higher doses.

ADAPTIVE RESPONSES TO DIURETIC ADMINISTRATION

The "braking" phenomenon is a term, commonly used to refer to the short-term and long-term adaptive changes observed in the nephron as a result of diuretic administration. These changes are natural compensations intended to protect intravascular volume. Their net result is to stabilize volume losses that lead to the tolerance of the diuretic effect. Diuretic tolerance should be distinguished clinically from diuretic resistance states, the latter describing a phenomenon occurring in conjunction with pathophysiologic conditions such as renal failure, nephrotic syndrome, congestive heart failure and cirrhosis.[5] The mechanism of resistance in the setting of these comorbidities is more aptly explained by altered pharmacokinetics and pharmacodynamics rather than physiologic adaptations.

Two concepts are fundamental for understanding the adaptations to diuretic administration. First, because the various segments of the nephron are arranged in a series, a change in behavior of one segment, such as that induced by a diuretic, alters conditions for the downstream segments. For example, administration of a loop diuretic will cause more solute to be delivered to the distal segment. Chronic exposure to this higher solute load leads to structural hypertrophy of the distal segment, which enhances its overall resorptive capacity.[6] Secondly, diuretic-induced diminution of extracellular fluid stimulates hemodynamic, neural and endocrine mechanisms designed to conserve water and solutes. The sum of these conservative mechanisms results in increased reabsorption of salt and water at sites proximal and distal to the site of action of the administered diuretic, thereby limiting the overall amount of diuresis. A practical example of this can be seen in the normal subject, where administration of a diuretic results in an appreciable diuresis on the first day, less on the second day and essentially no effect on the third day.

Short-term tolerance to diuretics stems from a period of post-dose sodium retention, triggered by the initial reduction in extracellular fluid volume. Generally short plasma half-lives of most diuretics contribute to this mechanism.[7] Although the phenomenon is classically observed with the shorter-acting loop diuretics, it also applies to thiazides. Ordinarily, an initial diuretic-induced diuresis results in a net negative sodium

balance.[8] However, in the absence of continuous infusion, the diuretic effect dissipates before the next dose is administered. A period of rebound sodium retention follows when the drug concentration in plasma and tubular fluid declines below the diuretic threshold. Using furosemide as an example, the brisk natriuresis resulting in a negative sodium balance for six hours after the initial dose is followed by a compensatory 18-hour post-diuresis sodium retention period in which sodium excretion is reduced to a level lower than intake.[8] The degree of sodium retention may be of sufficient magnitude to nullify prior natriuresis, such that within a matter of days in nonedematous patients, weight loss is limited to 1–2 kg.[9] Dosing intervals for diuretics should generally exceed the duration of time when effective amounts of the drug are at the site of action, in order to avoid or limit this post-dose antinatriuresis period.

Short-term adaptations to diuretics are not explained solely by limitations imposed by their pharmacokinetic parameters or dosing strategies. Important contributors to the short-term adaptations also include activation of the renin-angiotensin-aldosterone (RAAS) and sympathetic nervous systems, suppression of atrial natriuretic peptide secretion and suppression of renal prostaglandin secretion.[10] The degree of post-dose sodium retention is significantly influenced by dietary sodium intake. Restriction of dietary sodium promotes overall negative sodium balance and enhances the therapeutic response to diuretics, while persistently high-dietary sodium offsets this effect by leading to net neutral salt balance.[11] Stated another way, the more sodium ingested, the more frequent is the need for the diuretic.[4]

Long-term diuretic tolerance is marked by a gradual return of sodium chloride balance to neutral. Many of the same mediators involved in post-diuretic sodium retention are also responsible for the chronic adaptations. Persistent volume removal triggers chronic activation of the RAAS-system and increases circulating angiotensin-II and aldosterone levels, both of which promote increased sodium reabsorption in the proximal and distal tubules. Interestingly, administration of α-adrenergic antagonists and RAAS-blockers do not appear to appreciably modify these processes.[12] This finding likely suggests the involvement of volume-independent mechanisms.[13,14] Such mechanisms include structural hypertrophy of distal nephron segments which enhances distal sodium reabsorption (occurring in response to long-term loop administration) as well as upregulation of sodium transporters downstream from the primary site of diuretic action.[6] For thiazides, micropuncture studies have shown that persistent volume contraction also leads to increased proximal solute reabsorption, limiting the overall delivery of sodium and chloride to the primary thiazide site at the distal tubule.[15]

INDIVIDUAL DIURETIC CLASSES

CARBONIC ANHYDRASE INHIBITORS

Carbonic anhydrase catalyzes the hydration of bicarbonate in the proximal tubule; thereby facilitating its reabsorption.[4] Normally sodium reabsorption accompanies bicarbonate in this process. Inhibitors of carbonic anhydrase (Table 1) interfere with this enzyme activity in the brush border and inside the epithelial cells of the proximal tubule, resulting in impaired sodium, bicarbonate and water reabsorption, as well as a brisk alkaline diuresis. As the majority of the filtered sodium load is reabsorbed in the proximal tubule, one would ordinarily expect a proximally acting agent to produce a substantial diuretic response. However, the net diuretic effect of carbonic anhydrase inhibitors is limited because sodium that is reabsorbed distal to the proximal tubule (mainly in the thick ascending limb of the loop of Henle) offsets these losses.

Additionally, the kidney compensates in several ways which serve to diminish the overall carbonic anhydrase-dependent component of sodium reabsorption. Sodium rejected proximally increases its delivery to the macula densa which activates the tubuloglomerular feedback mechanism, suppressing the glomerular filtration rate and amount of solutes filtered. Furthermore, the alkaline diuresis caused by the carbonic anhydrase inhibitor reduces bicarbonate levels in the serum, which results in overall less bicarbonate filtration.[1]

Acetazolamide (Table 2) demonstrates the most favorable diuretic features among several chemical derivatives of sulfanilamide that were synthesized while searching for more potent carbonic anhydrase inhibitors. Developed in 1945, it remains the prototype in the class, although it is now rarely used because of its nominal diuretic capabilities and the development of metabolic acidosis occurring with prolonged administration. Acetazolamide is completely absorbed orally, with a half-life of about 6–9 hours, reaching steady state after two days. It can be dosed twice daily. It is entirely renally excreted and should be used carefully, if at all, in those with compromised renal function.[4]

Acetazolamide's diuretic legacy is primarily one of historical significance in having helped elucidate the process of urinary acidification and diuresis in renal tubules rather than in any major clinical application in cardiovascular disease. Rarely, a case can be made for a minor role in heart failure patients which are refractory to loop diuretics, where proximal tubular reabsorption of sodium is increased and less sodium overall is delivered to the loop of Henle. The addition of acetazolamide can increase diuresis in some of these patients.[16]

Today, the primary uses of acetazolamide are not directly related to its diuretic action, but rather in the systemic metabolic acidosis induced as a byproduct. This can be helpful in remedying iatrogenic metabolic alkalosis occasionally caused by high doses of loop diuretics (typically in patients with cardiogenic pulmonary edema). Metabolic alkalosis can result in hypoventilation, a reflex designed to raise blood carbon dioxide concentrations to correct the systemic pH. In some patients, such as those with chronic obstructive pulmonary disease, this hypoventilation may compromise respiratory drive and lead to further hypoxemia.[4] Correcting alkalosis in these situations may improve oxygenation.[17]

Additionally, other clinical applications of acetazolamide involve carbonic anhydrase-dependent bicarbonate transport occurring outside the kidney. As carbonic anhydrase is involved in intraocular fluid formation, acetazolamide and its derivatives can be used to decrease intraocular pressure in patients with glaucoma. Acetazolamide has also proven effective in treatment and prophylaxis of acute mountain sickness. The exact mechanism is unknown, but is perhaps related to the iatrogenic metabolic acidosis induced by the drug.

TABLE 2

Approximate pharmacokinetic parameters of the commonly available diuretics

Diuretic class	*Oral bio-availability (%)*	*Vd (L/kg)*	*Protein binding (%)*	*Fate*	*$T_{1/2}$ (hr) (normal)*	*Duration of action (hr)* (normal)*	*Additional notes*
Carbonic Anhydrase Inhibitors							
Acetazolamide	100	0.2	70–90	R (100%)	6–9	8–12	Metabolic acidosis with prolonged use
Thiazide-type							
Chlorothiazide	15–30	1	70	R (100%)	1.5–2.5	6–12	Rarely used anymore
Hydrochlorothiazide	60–70	2.5	40	R (100%)	3–10	6–12	Increased absorption with food
Bendroflumethiazide	90	1–1.5	94	R (30%), M (70%)	2–5	18–24	Primarily used outside the US
Thiazide-like							
Chlorthalidone	65	3–13	99	R (65%)	50–60	24–72	Binds to carbonic anhydrase in erythrocytes
Metolazone	65	113 (total)	95	R (80%)	8–14	12–24	Retains efficacy in renal insufficiency
Indapamide	71–79	25 (total)	75	M (70%), R (5%)	14	24–36	Possible vasodilatory properties
High-ceiling or loops							
Furosemide	10–100	0.15	91–99	R (50%), 50% conjugated in kidneys	1.5	6	Slightly prolonged $T_{1/2}$ in renal insufficiency
Bumetanide	80–100	0.15	90–99	R (60%), M (40%)	1.5	3–6	Slightly prolonged $T_{1/2}$ in renal insufficiency
Torsemide	80–100	0.2	99	R (20%), M (80%)	3–4	8–12	Slightly prolonged $T_{1/2}$ in renal insufficiency
Ethacrynic acid	100	—	90	R (67%), M (33%)	1	4–8	Higher risk of ototoxicity; reserve for patients with documented allergy to other loops
Distal/Collecting duct							
Amiloride	15–25	350 (total)	0	R (50%), 50% fecal	17–26	24	$T_{1/2}$ = 100 hours in end stage renal disease
Triamterene	50	—	55–67	M (80%), R (10)	3	7–9	$T_{1/2}$ of active metabolite = 3 hours
Spironolactone	65	—	90	M (extent unknown)	1.5	16–24	$T_{1/2}$ of active metabolite = 15 hours
Eplerenone	69	43–90 (total)	50	M (extent unknown)	5	24	Less affinity for androgen receptors
Osmotic							
Mannitol	17–20	0.5	0	R (100%)	1	2–8	$T_{1/2}$ = 36 hours in end stage renal disease

* refers to natriuretic effect; — indicates insufficient data; R = renal excretion as intact drug; M = hepatically metabolized; V_d = volume of distribution; $T_{1/2}$ = elimination half-life
(*Source:* References 2 and 4)

LOOP OR HIGH-CEILING DIURETICS

Loop diuretics (Table 1), so named for their site of action in the thick ascending limb of the loop of Henle, were developed in the 1960s while searching for less toxic agents than the organic mercurials. Two agents, furosemide and ethacrynic acid, were developed independently around the same time.

Ethacrynic acid was synthesized following the strategy based on mercurial diuretics that assumed diuresis occurred as a result of inhibiting sulfhydryl groups in the kidney.[4] Screening of other compounds for diuretic activity identified a group of active sulfamoylanthranilic acids substituted on the amine group of the aromatic ring.[4] Among this group, furosemide was introduced first, followed later by bumetanide and torsemide. The identification and development of these compounds were heralded as major advances in diuretic therapy, as their sizeable effect proved useful in renal insufficiency and heart failure patients unresponsive to other agents. Loop diuretics are often referred to as "high-ceiling" agents due to the substantial diuresis they can cause; maximally effective doses can lead to excretion of 20–25% of filtered sodium, blocking nearly all of the reabsorption occurring in this segment.

Located within the apical membrane of epithelial cells of the thick ascending limb is the electroneutral $Na^+/K^+/2Cl^-$ cotransporter, which passively carries sodium, potassium and

chloride ions into the cell based on the electrochemical Na^+ gradient generated by the Na^+/K^+-ATPase pump of the basolateral membrane.[1] Some potassium is returned to the lumen via K^+-channels of the luminal membrane, such that the net effect of this pathway is Na^+Cl^- reabsorption and a voltage across the tubular wall oriented with the lumen positive in relation to the interstitium.[18] Mechanistically, loop diuretics bind to $Na^+/K^+/2Cl^-$ cotransporter at the chloride site, causing a diuresis of Na^+Cl^- and K^+Cl^-. In addition to prevent its reabsorption, potassium secretion from distal tubular sites is also promoted by loop diuretics by virtue of the increased delivery of sodium to these sites. The lumen positive charge at the thick ascending limb is also important for calcium and magnesium reabsorption; administration of a loop diuretic increases the fractional calcium excretion as well as a significant increase in magnesium excretion. The former may be useful in treating hypercalcemia.

The thick ascending limb is an important segment responsible for concentrating the urine. Since it is impermeable to water, solute removal from this area of the nephron generates the hypertonic medullary interstitium that serves as the osmotic force driving water reabsorption across the collecting duct, regulated under the influence of antidiuretic hormone. Loop diuretics prohibit solute removal at the thick ascending limb and decrease this osmotic force, thus impairing the ability of the kidney to generate concentrated urine.[1] In addition, solute removal at the thick ascending limb normally dilutes the tubular fluid, allowing free water generation during water deficits. By prohibiting solute removal, loop diuretics impair the kidney's ability to produce maximally diluted urine as well as prevent free water excretion during water loading.

Loop diuretic administration induces hemodynamic changes within the systemic and renal microcirculations. Within minutes, intravenous loop diuretics stimulate the RAAS at the macula densa, which can cause vasoconstriction, increased afterload and decreased renal blood flow.[19] This action is short lived, but can diminish the effectiveness of the diuretic briefly and may explain why certain patients fail to respond to bolus diuretic therapy, but experience effective diuresis with infusions. A second-phase response, characterized by an increase in renal release of vasodilating prostaglandins, such as prostacyclin, occurs within approximately 15 minutes of intravenous loop diuretic administration.[20] The accompanying venodilatation decreases cardiac preload and ventricular filling pressures, probably explaining the immediate symptomatic improvement often observed in patients with acute pulmonary edema even before diuresis has commenced.[4] A compensatory activation of the sympathetic nervous system can be triggered with increased afterload and decreased cardiac function as a result; however, the need to quickly induce diurese generally prevails over these concerns. The final stage of neurohormonal activation follows after prolonged volume removal and occurs with both intravenous and oral administration. This stage is characterized by chronic activation of the RAAS and increased circulating concentrations of angiotensin II and aldosterone, leading to the chronic adaptations to therapy as previously described in the earlier section.

The available loop diuretics include furosemide, bumetanide, torsemide and ethacrynic acid (Table 2). All are extensively bound to serum albumin (> 95%) and must gain access to the tubular lumen by active secretion through probenecid-sensitive organic anion transporters located in the proximal tubule. This process may be slowed by elevated levels of endogenous organic acids such as in chronic kidney disease as well as drugs that share the same transporter including salicylates and nonsteroidal anti-inflammatory drugs.

A number of important pharmacokinetic features must be considered when selecting among the available loop diuretics; among them are bioavailability, half-life and routes of metabolism. Furosemide is the most widely used of the class, but is subject to erratic within and between subject absorption, ranging from 10% to 100%.[21] In addition concomitant administration with food decreases the bioavailability. This wide degree of variability in absorption makes it difficult to reliably predict response, such that one must try different doses before the drug is judged to be ineffective.[4] The absorption of bumetanide and torsemide are more predictable, ranging from 80% to 100%.[22] For these agents, the dose is approximately the same when switching from intravenous to oral dosing. Assuming an average absorption of 50% for furosemide, the oral dose should be approximately twice the intravenous dose when switching routes.

The half-life of loop diuretics dictates their duration of action and frequency of dosing. Furosemide and bumetanide are rapidly acting, but have very short half-lives. Therapeutic response occurs within minutes after intravenous administration, while peak response is noted 30–90 minutes after oral dosing. With both routes of administration, response continues for approximately 2–3 hours, lasting up to 6 hours.[4] As their action is brief, loop diuretics are subjected to a significant post-dose rebound sodium retention. Furosemide and bumetanide must be given multiple times per day, which helps to ensure that adequate amounts of drug are maintained at the site of action, thereby minimizing the impact of the post-dose antinatriuresis period. Torsemide has somewhat a longer plasma half-life and duration of action, and can therefore be dosed less frequently.

Approximately 50% of a dose of furosemide is excreted unchanged in the urine and the remainder is conjugated to glucuronic acid in the kidney.[23] In contrast, bumetanide and torsemide are substantially metabolized (60% and 80%, respectively), primarily through hepatic routes.[24] In hepatic disease, the plasma half-life of bumetanide and torsemide are prolonged and their effects paradoxically enhanced.[25] Similarly, renal insufficiency will alter the pharmacokinetics of furosemide by prolonging both the plasma half-life and duration of action due to decreased urinary excretion and renal conjugation. Although bumetanide and torsemide are hepatically metabolized, their pharmacokinetic profiles in renal insufficiency will also change, but only as a function of decreased renal clearance of intact drug.[26] This is because renal disease impairs the delivery of all loop diuretics into the tubular lumen due to competition by endogenous organic acids that accumulate in renal disease. As a result, larger doses of all loops may be necessary in the presence of renal disease to effectively reach the site of action. Due to its greater ototoxic potential than other loops diuretics, ethacrynic acid should be reserved for use in patients with documented allergic reaction to other loops.[4]

Thiazide diuretics (Table 1) were serendipitously discovered while chemically modifying the sulfa nucleus of acetazolamide in an attempt to develop more potent inhibitors of carbonic anhydrase.[2] The finding that it produced increased chloride rather than bicarbonate accompanying sodium in the urine was an unanticipated consequence, but a major advancement that paved the way for further advances in diuretic therapy. Chlorothiazide, the prototype of the class, became available in 1957, effectively beginning the modern era of diuretic therapy and rendering obsolete the organometallic compounds previously available.

As a group, the thiazides are more properly designated as benzothiadiazines, because most of the compounds are analogs of 1,2,4-benzothiadiazine-1,1-dioxide. Although there is a significant variation in the substitutions and nature of the heterocyclic rings between the different thiazide congeners, all of them retain an unsubstituted sulfonamide group in common with the carbonic anhydrase inhibitors. As such, thiazides retain a wide range of potency with regard to carbonic anhydrase inhibition; however, their diuretic effect has clearly been dissociated from this activity.[2] This is because any solute rejected in the proximal tubule through carbonic anhydrase inhibition continues to downstream segments, where most is picked up by the large capacity thick ascending limb, thereby obviating any relevant clinical effect of action in the proximal tubule.[2]

Thiazide diuretics inhibit sodium reabsorption from the luminal side in the early segments of the distal tubule, by interfering with the electroneutral Na^+Cl^- symporter located in the apical membrane. The increased delivery of sodium to the collecting duct also increases the exchange with potassium, leading to potassium depletion. Magnesium excretion is also increased with thiazide administration. Adaptive mechanisms, as discussed earlier, result in increased proximal tubular solute reabsorption with chronic thiazide use. As the normal Na^+Cl^- reabsorption in the distal tubule contributes to tubular fluid dilution, thiazides impair the diluting capacity of the kidney, but preserve urinary concentrating mechanisms. The former characteristic can prove useful in paradoxically diminishing urinary output to half its pretreatment value in patients with diabetes insipidus.[4] In contrast to loop diuretics, thiazides actually enhance calcium reabsorption and can be used to treat nephrolithiasis due to hypercalciuria.

With few exceptions, the pharmacokinetic parameters of thiazides are not uniformly characterized (Table 2). Generally, all are orally absorbed, have volumes of distribution equal to or greater than equivalent body weight and are extensively bound to plasma proteins.[2] Thiazides must actively be secreted into the proximal tubule, as they are highly protein bound and subject to limited glomerular filtration. Thiazides compete with uric acid for secretion into the proximal tubule by the organic acid secretory system; this leads to reduced uric acid excretion and can precipitate gout in predisposed individuals.

Despite heterogeneity in their structure-activity relationships, which has given rise to designations of the analogs as either being thiazide-type or thiazide-like, the general designation of thiazide diuretic is inclusive of all diuretics sharing primary action in the distal tubule.[2] An exception is indapamide, which has less direct evidence for activity at the Na^+Cl^- symporter and has been suggested to possess vasodilatory effects.[27] All thiazides have demonstrated parallel dose-response curves and comparable maximal chloruretic effects. In general, their dose-response curve is much shallower than that of loops (Fig. 2), such that there is a little difference in efficacy between the lowest and maximally effective doses. Although the various analogs differ by potency in the dose required to produce their therapeutic effects, they do not differ in their optimal therapeutic or maximal responses and there is no direct evidence for superiority of effect of any particular thiazide when equipotent dosing is considered.

The average thiazide onset of action is approximately 2–3 hours, peaking at 3–6 hours, with progressively diminishing natriuretic effect occurring beyond 6 hours for most agents; chlorthalidone, as discussed later, is an exception.[2] There is a significant variation in the metabolism, bioavailability and plasma half-lives of the thiazides (Table 2). The latter two pharmacokinetic features are the most clinically relevant parameters as they influence the dose and frequency of administration. Chlorothiazide is relatively lipid insoluble and requires large doses to achieve concentrations, which are high enough for the drug to arrive at its site of action. Hydrochlorothiazide, the most widely used thiazide in the United States, has improved bioavailability with approximately 60–70% absorbed orally.[28] Coadministration of food slightly enhances absorption, most likely through interference with gastric emptying.

Several thiazides undergo hepatic metabolism (e.g. bendroflumethiazide, polythiazide, methyclothiazide, indapamide), while others are excreted nearly complete as intact drug in urine (e.g. chlorothiazide, hydrochlorothiazide). Chlorthalidone and metolazone are subjected to a mixed pathway of primarily renal (50–80%) with minor biliary excretion (10%).[28] Other than the 50% reduction in hydrochlorothiazide absorption, noted in patients with heart failure, almost no information exists regarding the influence of disease on the pharmacokinetics of thiazides.[28]

As the distal tubule only reabsorbs about 5% of the filtered sodium load, the overt diuretic efficacy of thiazides for volume removal in edematous disorders is limited. However, relative to the loop and other diuretics, an advantage of the thiazides is their long duration of action. This property is a major determinant allowing them to distinguish themselves primarily for their use as antihypertensive agents. Early studies assigned short elimination half-lives (1–3 hours), but most are now generally accepted to begin around 8–12 hours, approximating the threshold for effective once-daily dosing.[28] Chlorthalidone distinguishes itself from other thiazides as a true long-acting agent, possessing a significantly longer elimination half-life that averages 50–60 hours.[29] It has a larger volume of distribution than other thiazides with $\geq$ 99% of drug bound to erythrocyte carbonic anhydrase.[29] This strong binding affinity accounts for the lengthy half-life of chlorthalidone, with erythrocyte carbonic anhydrase functioning as a storage reservoir enabling a constant backflow of chlorthalidone into plasma to sustain a prolonged low level of diuresis and minimize the post-diuretic antinatriuresis period.[2] This property may have important clinical relevance in distinguishing chlorthalidone as a more effective

antihypertensive agent in the typical dosing range of thiazides utilized today.[30,31]

The duration of antihypertensive effect for thiazides exceeds that of their diuretic effect, mainly due to the important hemodynamic changes induced by the prolonged low-level diuresis. These hemodynamic effects can be separated into acute (1–2 weeks) and chronic (several months) periods (Fig. 3).[32] After commencing regular dosing of a thiazide, blood pressure-lowering is initially attributed to extracellular fluid contraction and reduction in plasma volume.[33] The accompanying decrease in venous return depresses cardiac preload and output, thereby reducing blood pressure. However, there is a clear dissociation between the degree of initial diuresis and antihypertensive effect, as the eventual chronic response to thiazides cannot be reliably predicted by the degree of initial fall in plasma volume.[34] Other significant changes occurring acutely include a transient rise in peripheral vascular resistance, likely the result of counter-regulatory activation of sympathetic nervous and RAAS systems. This transient rise in systemic resistance is not usually sufficient to negate the diuretic-induced blood pressure reduction and the counter-regulatory increases in sympathetic nervous and RAAS systems can be opposed by combining thiazides with RAAS-blocking agents such as angiotensin converting enzyme (ACE) inhibitors or angiotensin-II receptor blockers (ARBs).[2]

In the chronic phase of thiazide use, effects on plasma volume and cardiac output are insufficient to explain the antihypertensive response as these parameters return to near-normal levels.[35] The most likely explanation for the persistent blood pressure-lowering effects of thiazides is an overall reduction in total peripheral resistance. The exact mechanisms responsible for this change are unclear. Evidence for direct vasodilatory properties or a reverse autoregulation phenomenon is not definitive and factors such as structural membrane changes and altered ion gradients have been hypothesized, but not well studied. A more simple explanation may be that long-term thiazide administration induces a low level of prolonged diuresis, maintaining a nominal state of volume contraction which would promote downward shift in vascular resistance.[2]

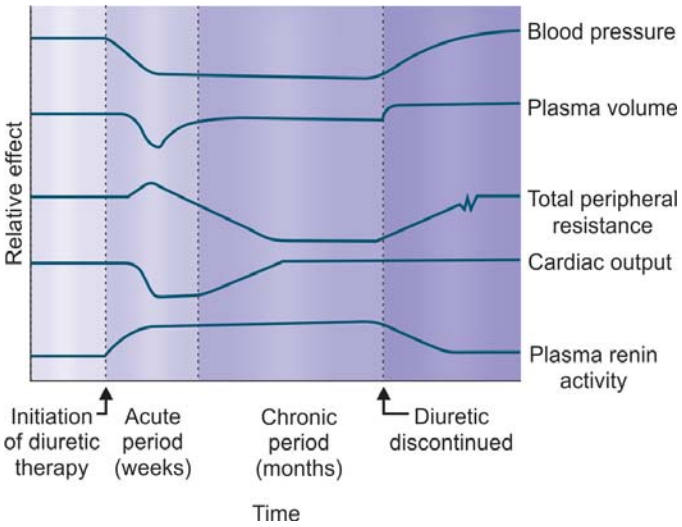


FIGURE 3: Time course of hemodynamic responses to thiazides (*Source:* Reference 32)

The residual effects of thiazides following their discontinuation are significant and persistent. Rapid volume expansion, weight gain and fall in renin levels occur, but blood pressure rises slowly and does not immediately return to pretreatment levels.[32] In fact, with adherence to lifestyle modifications (weight loss, reduction in sodium and alcohol), nearly 70% of patients remained free of antihypertensives for up to one year after being withdrawn from thiazide-based therapy in the "Hypertension Detection and Follow-up Program".[36]

POTASSIUM-SPARING DIURETICS

In the distal tubule and collecting ducts, sodium is reabsorbed through an aldosterone-sensitive sodium channel and by activation of an ATP-dependent sodium-potassium pump. With the help of both mechanisms, potassium and hydrogen are secreted into the lumen to preserve electroneutrality.[2] Potassium-sparing diuretics are divided into two distinct classes: (1) those acting as direct antagonists of cytoplasmic mineralocorticoid receptors and (2) those acting independent of mineralocorticoids. All potassium-sparing diuretics act primarily at the cortical part of the collecting duct and to a lesser extent in the final segment of the distal convoluted tubule and connecting tubule. As only a small amount of sodium is reabsorbed here, these agents are capable of limited natriuresis (excluding states of mineralocorticoid excess) in most patients. Their primary clinical utility resides in their potassium-sparing capabilities and to a lesser extent, their ability to correct magnesium deficiencies.

Spironolactone and eplerenone (Table 2) are competitive antagonists of aldosterone, the most potent of the naturally occurring mineralocorticoids and thereby interfere with the aldosterone mediated exchange of sodium for potassium and hydrogen. Spironolactone is well-absorbed orally and highly protein bound. The compound itself has a short half-life of only 1.5 hours, but it is extensively metabolized in the liver and its therapeutic action resides mainly in that of its several metabolites.[5] Among them, 7-α-thiomethylspirolactone and canrenone are the most well-characterized, with half-lives of about 15–20 hours, which are sufficiently long enough to permit once-daily dosing. As time must be allowed to accumulate active metabolites, spironolactone has a characteristically slow onset, up to 48 hours before becoming maximally effective.[4] Since spironolactone gains access to its site of action independent of glomerular filtration, it remains active in renal insufficiency. However, it must be used very carefully in this setting due to the propensity for hyperkalemia to occur.

Spironolactone has been available for use in hypertension for many years, while eplerenone is a newer agent demonstrating similar efficacy. Both drugs are rarely used alone, but rather in combination with other diuretics to avoid potassium deficiency. Their aldosterone-blocking capabilities also makes them a primary therapy in patients with essential hypertension due to mineralocorticoid excess such as in primary aldosteronism due to bilateral adrenal hyperplasia or in patients with aldosterone producing adrenal adenomas awaiting surgical resection, or those who are nonsurgical candidates. Additionally, patients with secondary hyperaldosteronism such as that

observed in hepatic cirrhosis and ascites, benefit from spironolactone. The major adverse effects of spironolactone are antiandrogenic and stem from the fact that it is a steroid that competitively inhibits testosterone and progesterone at the cellular level. In particular, gynecomastia can become a concern, especially with high doses. In the dose range of 12.5–50 mg/day, it is rarely a problem. Eplerenone appears to have more selectivity for aldosterone receptors and less affinity for androgen and progestin receptors than spironolactone.[2] Cost differences have traditionally favored spironolactone and it remains to be determined whether eplerenone's safety and efficacy constitute significant advancements over spironolactone.

The actions of amiloride and triamterene (Table 2) are quite different than spironolactone and eplerenone. Both are pteridine derivatives and exert their action by blocking epithelial sodium channels in the luminal membrane. In this manner, the electrical potential across the tubular epithelium falls, which reduces the driving force for secretion of potassium into the lumen.[4] About 50% of an oral dose of either agent is absorbed. Triamterene is the older of the two drugs in the class; both are rarely used strictly as antihypertensives because of their weak ability to lower blood pressure. Rather, they are most often used in fixed-dose combinations with a thiazide diuretic to offset the potassium and magnesium losses induced by thiazides.

Triamterene has a short half-life (3–6 hours) and duration of effect.[4] Ideally it should be dosed multiple times per day; however, because it is most commonly used in a fixed-dose combination with hydrochlorothiazide, it is rarely dosed more frequently than once-daily. Triamterene is converted to an active phase II sulfate-conjugated metabolite by the liver and the metabolite is then secreted into the proximal tubular fluid.[5] Both renal and liver disease significantly affect the disposition of triamterene; the former by impairing tubular secretion of the active metabolite and the latter by reducing formation of metabolite. Triamterene is a potential nephrotoxin associated with formation of crystals, nephrolithiasis, interstitial nephritis and acute renal failure. It must be used carefully when other potentially nephrotoxic drugs are coadministered.

Amiloride has a much longer half-life (17–26 hours) and can be dosed once or twice daily, achieving steady state in approximately two days.[4] It is preferred in patients with liver disease as there is no required metabolic activation. However, it is extensively renally cleared and accumulates rapidly when administered in patients with chronic kidney disease. In these situations, the dose and/or dosing frequency of amiloride should be reduced to avoid the potential for hyperkalemia.

OSMOTIC DIURETICS

The osmotic diuretic, mannitol (Table 2), is freely filtered through the glomerulus and poorly absorbed. As it is not reabsorbed in the nephron, mannitol does not interfere with specific tubular electrolyte transport systems. Rather it increases osmolality, as it remains in the tubule lumen and thus impairs the tubular water reabsorption normally driven by the osmotic gradient. As the medullary solute gradient is lost, the urinary concentrating ability of the kidney is greatly reduced and tubular fluid is diluted. The osmotic diuresis that prevails is similar to the glucose-mediated osmotic polyuria and diuresis observed in patients with uncontrolled diabetes.[4] Although some excretion of bicarbonate occurs in the proximal tubule, mannitol's effect is largely in promoting sodium and chloride wasting in the loop of Henle. The increased delivery of sodium to distal sites increases the exchange for potassium, such that potassium is also lost in the process. The onset of mannitol is quick, with a half-life of approximately one hour in patients with normal renal function.[37] The offset is equally fast and for this reason, it is best administered as a continuous infusion.

Mannitol is effective in reducing cerebral edema, first by osmotic fluid removal from the brain and then by osmotic diuresis, making it useful in neurosurgical procedures, head trauma and in other conditions of increased intracranial pressure.[1] Mannitol has been used as a preventive measure against acute renal failure in patients receiving cisplatin, radiocontrast exposure or other high-risk situations; however, there is no evidence that it is any more effective than insuring adequate volume status with parenteral fluids, a more appropriate strategy. In the same manner, mannitol has been investigated for use in oliguric acute renal failure to promote diuresis; again, limited data support this strategy and insuring adequate volume status is a more appropriate approach.[38] Furthermore, the half-life of mannitol is markedly prolonged in renal insufficiency (up to 36 hours). In this situation, mannitol remains in the vascular space and the osmotic effect can expand blood volume and is a concern for precipitating heart failure. Given its significant limitations, mannitol should be only rarely used as a diuretic.

CLINICAL USE OF DIURETICS IN CARDIOVASCULAR DISEASES

Aside from their chemical and mechanistic classifications, diuretics can be categorized functionally into one of three primary uses—treatment of essential hypertension, volume removal in edematous disorders, and correction of potassium and magnesium deficiencies. Thiazide diuretics appear to be the most effective diuretics over the long term in lowering blood pressure in patients with hypertension. Not only do they result in significant lowering of blood pressure as monotherapy, thiazides enhance the efficacy of nearly all other classes and they reduce hypertension-related morbidity and mortality.[2] Loop diuretics are the most powerful diuretics to evoke a substantial diuresis; therefore, they are agents of choice for symptomatic relief in patients with edematous disorders such as congestive heart failure, cirrhosis and nephrotic syndrome. In addition, they are used in preference to thiazides in patients with impaired renal function [glomerular filtration rate (GFR) < 40 ml/min/1.73 m^2], where thiazides are unlikely to be as effective. Finally, potassium-sparing agents are largely reserved for correcting potassium and magnesium deficiencies associated with thiazide diuretic administration and in other less common situations, including hyperaldosteronism and rare genetic conditions such as Liddle or Bartter syndromes.

While only one type of diuretic is generally used at a time, there are several conditions where diuretic tolerance is encountered. In these situations, combinations of two different

types of diuretics are often employed to improve response. Thus, to effectively utilize diuretics in the patient with cardiovascular disease, a clinician needs to first appreciate their unique interclass and intraclass characteristics and couple this with knowledge of the pathophysiology of the condition being treated. If both are considered in tandem, one can reliably predict the expected therapeutic response to diuretic administration.

DIURETIC USE IN HYPERTENSION

General Considerations

Thiazides have been a mainstay in the treatment of hypertension for many years and are preferred agents for chronic therapy in most hypertensive patients where a diuretic is indicated.[31] Thiazide administration typically results in a 10–15/5–10 mm Hg reduction in blood pressure compared to placebo.[2] Thiazide responders are often referred to as having low-renin or salt-sensitive hypertension, in deference to the large contribution volume and sodium play in the maintenance of their blood pressure. These patients typically include the elderly, blacks and high cardiac output states such as obesity. Although the aforementioned groups are often considered more likely to respond to thiazides, an advantage of thiazides is that they can be effectively combined with nearly any antihypertensive, producing a blood pressure-lowering effect that is additive of the two individual components in almost all cases.[2] Importantly, racial differences observed in the monotherapy response to RAAS-blocking agents, such as ACE inhibitors or ARBs (blacks often do not respond as well to monotherapy with these agents), are minimized. Combining thiazides with RAAS blocking agents also has the added practical advantage of minimizing potassium wasting and metabolic adverse effects caused by thiazides. Data from clinical trials indicate that most of the patients eventually require 2–3 antihypertensives to achieve their blood pressure goal. Given their ability to augment efficacy of nearly all other types of antihypertensives, thiazides are powerful tools which improve the capability of achieving blood pressure goals.[39] In patients considered to have resistant hypertension, lack of appropriate diuretic use has been identified as the primary drug-related cause.[40,41]

Thiazide dosing has evolved in parallel to our progressive understanding of their mechanism of action and dose-response relationships. When first introduced, thiazides were used in much higher doses than today, stemming from the belief that efficacy was directly linked to the amount of renal sodium excretion and reduction in plasma volume obtained; the larger the dose, the greater the assumed reduction in blood pressure.[31] However, the dose-response curve is much shallower than originally believed. Thiazides are now utilized in significantly lower doses and the term low-dose thiazide has become synonymous with 12.5–25 mg/day of hydrochlorothiazide or its equivalent.[2] Approximately 50% of patients will respond initially, even to these small doses. Increasing the dose of hydrochlorothiazide to 25 mg/day may add approximately 20% to the responders, while at 50 mg/day 80–90% of possible responders should experience measurable blood pressure decreases.[42]

Comparative Efficacy

The ability of thiazides to effectively lower blood pressure translates into reductions in cardiovascular events. Beginning with the completion of the landmark Veteran's Affairs Cooperative Group study in 1967 and continuing through the early 1990s, a series of randomized placebo-controlled trials involving more than 47,000 hypertensive patients convincingly demonstrated these effects. Most of these studies employed a stepped-care approach, beginning initially with a diuretic, followed by an adrenergic inhibitor (beta-blocker), then vasodilator. Combined meta-analyses and systematic review show that thiazide-based regimens reduce relative rates of heart failure by 41–49%, stroke by approximately 29–38%, coronary heart disease by 14–21% and overall mortality by 10–11% compared to placebo.[2] Effect sizes are homogeneous throughout major subgroups of patients, including by gender, age and presence of diabetes.[43-45] The results of these studies have collectively formed the basis for the recommendations contained in the first seven guideline reports of the Joint National Committee, all advocating thiazides as initial therapy for most patients.[39]

With the introduction in the 1980s and early 1990s of a host of "newer" antihypertensives (ACE inhibitors, ARBs, calcium channel blockers), comparative studies of their efficacy began with thiazide diuretic/beta-blocker regimens as the standard of comparison. Most of these studies were not sufficiently powered to identify small to moderate differences in risk reduction among the regimens, but rather to identify any large disparities. The Blood Pressure Lowering Treatment Trialists' collaboration was developed to maximize information obtained from these and future trials. Against active comparators, meta-analyses from this collaboration demonstrate lack of superiority of any antihypertensive class over thiazides, including within subgroups of age and gender.[44,45] Nevertheless, the 1980s and 1990s saw diminished use of diuretics as they were no longer patented and were subject to an active negative campaign of marketing which overemphasized their adverse metabolic and electrolyte effects, in contrast to those more neutral effects of the newer agents.[31]

In response to allegations that diuretics would be inferior to the newer agents, the largest randomized comparative study to date in hypertension was undertaken. The Antihypertensive and Lipid-lowering to prevent Heart Attack Trial (ALLHAT) has provided the most comprehensive information regarding the overall benefit of thiazides evaluated against other therapies.[46] The ALLHAT compared first-step treatment using chlorthalidone 12.5 mg daily to amlodipine, lisinopril or doxazosin in 42,418 high-risk participants aged 55 and older, including an oversampling of African Americans (35%). No differences were observed in the composite primary endpoint of fatal coronary heart disease or nonfatal myocardial infarction for all treatments; however, chlorthalidone was superior in several predefined secondary endpoints including heart failure (versus amlodipine, lisinopril, doxazosin) and stroke (versus lisinopril). Numerous analyses stratifying by race and metabolic status have consistently shown that none of the agents surpassed chlorthalidone in antihypertensive efficacy or event reduction.[47]

Class Effect Theory

The efficacy of thiazides, both in lowering blood pressure and in reducing cardiovascular disease events, has typically been considered a "class effect" despite absence of any substantial direct comparison studies within the class to validate this assumption.[2] Class effects can only be substantiated after determination of equipotent dosing; and when not directly compared in a cardiovascular event trial, assume that if both achieve similar blood pressure lowering, then both can achieve similar reduction in cardiovascular events. With regard to thiazides, this rationale is flawed because fundamental differences exist in their pharmacokinetics and pharmacodynamics. On the basis that it has reduced cardiovascular events in every study where used, some hypertension experts preferentially recommend chlorthalidone, while noting that other thiazide regimens have resulted in less consistent benefit in clinical trials.[2] The few trials of hydrochlorothiazide in which it has successfully lowered cardiovascular disease events have typically used higher doses (≥ 25–50 mg/day) than commonly used today.[30] This detail is widely underappreciated and the popular belief of thiazide interchangeability is reinforced by the exclusivity of fixed-dose combinations containing hydrochlorothiazide 12.5–25 mg doses. Interestingly, the only two comparative trials to actually use low-dose hydrochlorothiazide regimens found they were inferior to the comparator regimens in reducing cardiovascular disease events.[48,49]

The reason for the disparate findings is unclear, but may simply relate to differences in potency and blood pressure-lowering efficacy between the two drugs in low doses commonly employed. Despite the misperception of equipotency among hydrochlorothiazide and chlorthalidone at low doses, chlorthalidone is actually 1.5–2 times more potent than hydrochlorothiazide, based on doses required to achieve similar levels of blood pressure reduction.[50-52] Comparison using ambulatory blood pressure monitoring data suggests the antihypertensive efficacy of chlorthalidone (25 mg) may even exceed that of hydrochlorothiazide (50 mg).[51] These findings are attributed to the long-acting nature of chlorthalidone in maintaining its efficacy throughout the nighttime period, blunting "escape" in blood pressure occurring during the interval between daily dosages. It is possible that the exuberance for using low doses to minimize the adverse metabolic and electrolyte disturbances of thiazides may leave some patients without adequate volume contraction. Evidence for this can be found in a study of resistant hypertensives, where most demonstrated high systemic resistance despite already taking 3 or 4 antihypertensive medications including low-dose hydrochlorothiazide in more than 90% of patients.[53]

Whether a diuretic class effect exists with regard to cardiovascular protection is not easily resolved as there are no direct comparative outcome studies. In the absence of such data, clinicians should rely on the fact that cardiovascular events are lowered as a direct function of the degree of blood pressure lowering achieved. Since most patients require multiple agents to control blood pressure, a diuretic will likely be part of the regimen and it may be irrelevant which agent is selected as long as the desired level of blood pressure control can be achieved. As an example, a sustained-release indapamide regimen was reportedly associated with reductions of 39%, 64% and 21% in fatal stroke, heart failure and death in elderly patients over 80 years old.[54] Although tempting as it may be, relevant differences between thiazides, after accounting for equipotency, can only be viewed as speculative.

Special Considerations

An important clinical issue with thiazides is that they are generally considered less effective in renal insufficiency, particularly when GFR falls below 40 ml/min/1.73 m^2. This is a somewhat arbitrary cutoff, as research has not clearly answered the question of the exact level of GFR at which point the efficacy of each thiazide compound is abolished. Thus, in patients with chronic kidney disease, it is advisable to use a loop diuretic instead, keeping in mind that it may need to be dosed two or three times daily to maintain efficacy. Larger doses of thiazides have been shown to induce diuresis in patients with chronic kidney disease,[55,56] but the efficacy of thiazides in this setting has a specific ceiling, which is controlled by several factors including the reduced delivery of filtered solute and drug to the distal tubule site of action and the fact that the distal tubule is responsible for only a small amount of sodium reabsorption even under normal circumstances. Additionally, increasing the doses of thiazides is impractical given the risk of metabolic and electrolyte side effects. Metolazone, a thiazide-like quinazoline derivative, is an exception among thiazides as it retains efficacy in patients with renal insufficiency and other diuretic-resistance states. As it is limited by slow and erratic absorption, the more predictable bioavailability of other thiazides makes them better suited for chronic therapy of hypertension. Metolazone is generally reserved in combination with loop diuretics in volume-overloaded patients undergoing close monitoring of fluid and electrolyte balance. It is usually administered daily for a short period (3–5 days) with frequency of administration reduced to thrice weekly once euvolemia is achieved.[10]

In the absence of states of mineralocorticoid excess or certain rare genetic conditions, the primary role of potassium-sparing diuretics, such as triamterene or amiloride, in the treatment of hypertension is that of an ancillary to help offset the potassium and magnesium wasting induced by thiazides. Spironolactone is advantageous not only in that it can correct thiazide-induced potassium and magnesium wasting, but low doses of 12.5–50 mg daily show significant additive hypotensive effects in patients resistant to treatment regardless of ethnicity or baseline aldosterone level.[40,57] This finding likely reflects the importance of aldosterone's effect in supporting elevated blood pressure in hypertensive patients treated with RAAS-blocking agents. Amiloride, which is an epithelial sodium channel blocker, demonstrated greater efficacy than spironolactone in blacks resistant to treatment.[58] It is available as both a single agent and in combination with hydrochlorothiazide.

DIURETIC USE IN EDEMATOUS DISORDERS

General Considerations

Loop diuretics are the most potent diuretics available, making them agents of choice in patients with edematous disorders such

as renal insufficiency, hepatic cirrhosis, congestive heart failure and nephrotic syndrome. As previously stated, when GFR falls to less than 40 ml/min/1.73 m^2, other diuretics used as single agents are less likely to be effective owing to diminished delivery of drug to the site of action. Thus, loop diuretics are preferred for hypertension or volume control in patients with chronic kidney disease.

Several principles must be considered when using diuretics in the treatment of edematous disorders. First, while a cornerstone of therapy, diuretics themselves are not definitive therapy and the primary treatment of edema should be directed at correction of the underlying disorder whenever possible. As an ancillary strategy, sodium restriction should be promoted when edema accumulates, as this may be sufficient enough to correct the problem in patients with mild edema, in addition to enhancing the natriuretic efficacy of diuretics if administered.[59] Finally, it should be recognized that all patients with edema do not require treatment with diuretics. As an example, in the absence of pulmonary congestion and comprised respiratory function, peripheral edema itself is mainly a cosmetic issue and poses no immediate threat to the patient.

In most cases, the removal of excess extracellular fluid volume with diuretics should be gradual. This is necessary both to avoid precipitous electrolyte imbalances as well as reductions in effective blood volume that would be of sufficient magnitude to impair tissue perfusion. Thus, the rate of removal is critical. Initial losses in response to diuretic administration occur from the plasma volume. The rate at which vascular space is refilled by fluid mobilized from the interstitium is variable and this ultimately directs the maximal rate of diuresis that can be tolerated.[59] For generalized edema, interstitial fluid is rapidly mobilized and a diuresis of 1–2 l/day can be safely achieved.[59] Mobilization is much slower and diuresis must therefore be approached more gradually, for edema that is sequestered as ascites or in the pleural space.

As previously discussed, the pharmacodynamics of diuretics is altered in most edematous conditions; namely, such that maximal response is lower (Fig. 2). The mechanisms underlying this decreased responsiveness are uncertain, but may relate to increased proximal or distal reabsorption of sodium or an upregulation of the $Na^+/K^+/2Cl^-$ transporter.[4] From a clinical perspective, this means that administering larger single doses will not improve the diuretic response. As in normal patients, it is best to first start with small doses and then titrates upward according to response. This can be achieved practically by sequentially doubling the dose until response is observed or a ceiling dose is reached (Table 3). Escalating doses above these ceiling doses will result in no additional benefit, but an increase in side effects. If response is suboptimal, other strategies, such as continuous infusion or using combinations of diuretics as outlined below, may be tried.

Renal Insufficiency

In the absence of heart failure, cirrhosis or nephrotic syndrome, dysregulation of volume homeostasis is usually a late manifestation of renal insufficiency, often not developing until GFR falls to less than 10 ml/min.[59] As renal function declines, the ability to maintain sodium balance diminishes and the fraction of filtered sodium that must be excreted to maintain sodium balance rises progressively. In the setting of constant sodium intake, fractional excretion of sodium must increase fivefold when GFR falls to 20% of normal and tenfold when GFR is 10% of normal.[59] Normal kidneys are able to accommodate this over a wide range of sodium intake, but patients with renal insufficiency have limited ability to raise the fractional excretion of sodium above 50%.[59] Assuming sodium intake

TABLE 3

Ceiling doses and therapeutic regimens for loop diuretics in normal patients and in conditions with reduced diuretic response

Clinical scenario	*Furosemide IV*	*Furosemide PO*	*Bumetanide IV and PO*	*Torsemide IV and PO*
Continuous Infusion Rates (mg/hr)	40 mg loading dose		1 mg loading dose	20 mg loading dose
CrCl < 25	20, then 40		1, then 2	10, then 20
CrCl 25–75	10, then 20		0.5, then 1	5, then 10
CrCl > 75	10		0.5	5
Single-dose ceilings (mg)				
Renal insufficiency*				
Moderate (CrCl 20–50)	80–160	160	2–3	20–50
Severe (CrCl < 20)	160–200	400	8–10	50–100
Congestive heart failure** (preserved renal function)	40–80	80–160	1–2	20–40
Cirrhosis** (preserved renal function)	40	80	1	10–20
Nephrotic Syndrome** (preserved renal function)	80–120	240	2-3	40–60

*Mechanism of reduced effect is impaired delivery to the site of action. The therapeutic strategy is to use sufficiently high enough doses to attain effective amounts at the site of action, and increase frequency of administration of the effective dose.
**Mechanism of reduced effect is diminished nephron response (and binding of diuretic to urinary albumin in nephrotic syndrome). The therapeutic strategy is to increase the frequency of the effective dose.
(*Source:* References 5 and 10)

exceeds this reduced maximal excretion, extracellular fluid volume expands and edema develops.

Large doses of thiazides can induce a modest diuresis in patients with renal disease, but loop diuretics are preferred because they produce a more vigorous and reliable response. Renal clearance of loops falls in parallel with GFR because of decreased renal mass and accumulation of organic acids that compete for proximal secretion. Only 10–20% as much drug may be secreted into the tubular lumen in a patient with a creatinine clearance of 15 ml/min, compared to one with normal renal function.[5] That said, response to the diuretic expressed as fractional excretion of sodium is similar for patients with renal insufficiency to that of healthy patients; thus, residual nephrons seem to respond normally,[60] but the problem is in getting enough drug to the site of action to achieve the diuretic threshold.

As less diuretic reaches the urine in renal disease, there is a need to administer larger doses to attain adequate amounts at the site of action. Patients should be given increasing doses of a loop diuretic until an effective dose is identified (or a specific ceiling dose achieved). This is a key step in the process; otherwise, administering multiple small doses of a diuretic will be ineffective because adequate urinary concentrations will not be achieved. Once the effective dose is determined, it should be given as frequently as necessary to maintain response, which will be determined according to the duration of action of the drug in the particular patient as well as the extent of their ability to comply with sodium restrictions.[5] If intermittent doses are not sufficient, a continuous infusion may be tried. Before using a continuous infusion, a loading dose should be given first to reduce the time necessary to achieve a steady state therapeutic drug concentration. The rate of the continuous infusion is then determined based on renal function (Table 3).[5]

Patients with inadequate natriuresis despite the use of maximal doses of loop diuretics may benefit from the sequential nephron blockade brought about by using combinations of diuretic agents.[10] Addition of a distally acting diuretic, such as a thiazide, to the loop agent is the most common strategy. Several mechanisms contribute to the enhanced response with combination use in refractory states. First, the longer half-life of distally acting agents may decrease the effect of the post-dose sodium retention observed with the shorter-acting loops. Secondly, chronic administration of loop diuretics can induce hypertrophy of distal tubule cells, enhancing their reabsorption of sodium and blunting the response to loops.[10] As most thiazides retain minor effects on carbonic anhydrase in addition to their main site of action in the distal tubule, the addition of a thiazide can block reabsorption at these sites and usually increase the diuretic response.[61]

Of the thiazides, metolazone is frequently selected for use in combination with a loop because of its long half-life and preserved activity in renal insufficiency. Other thiazides can be used as well, but will require larger doses (e.g. hydrochlorothiazide 25–100 mg daily or equivalent) since they must reach the lumen of the nephron to be effective.[5] Rarely acetazolamide and collecting duct agents, such as spironolactone and amiloride, are used, but their response is less dramatic than that of a thiazide. Regardless of which agent is selected, combination diuretic therapy must be cautiously employed owing to the increased possibility of hyperkalemia or hypokalemia (depending on underlying renal function and which type of agent is added) as well as circulatory collapse resulting from too vigorous of a reduction in extracellular fluid volume.

Cirrhosis

Secondary hyperaldosteronism plays an important role in the pathogenesis of sodium retention in patients with cirrhotic edema. Spironolactone, a competitive inhibitor of aldosterone, is a mainstay of therapy in such patients. Not only it increases patient comfort, but it can also eliminate the need or reduce the interval between paracenteses, an advantage is that protein normally removed during paracenteses can also be spared. The usual dosing range of spironolactone is 50–400 mg/day, but doses above 200 mg/day are often not well tolerated due to painful gynecomastia.[5] An advantage of spironolactone is the once-daily dosing made possible by the sufficiently long half-lives of its active metabolites. As the onset of natriuresis may take 2–4 days, as a result dose adjustments should therefore not be more frequent than every 4–5 days.[59] Spironolactone itself is capable of only moderate diuresis; thus, edematous cirrhotic patients often require the addition of other diuretics, along with occasional paracentesis. Although either a thiazide or loop diuretic can be added, the presence of renal insufficiency usually necessitates the use of a loop diuretic.

The pharmacokinetics and pharmacodynamics of loop diuretics in cirrhotic patients are well characterized.[5] In the absence of concomitant renal insufficiency, the diuretic concentration in tubular fluid is normal.[62] However, for unknown reasons, cirrhosis shifts the dose-response curve downward and to the right (Fig. 2), such that tubular responsiveness remains diminished even in the presence of normal renal function. Since the decreased response does not result from inadequate delivery of drug to the site of action, larger doses will not increase the diuretic response; rather, more frequent doses alone or with a thiazide, may be effective.[5]

Cirrhotic patients with edema receiving diuretics are prone to complications such as intravascular volume depletion and pre-renal azotemia, in up to 20% of patients.[59] Once euvolemia is achieved, maximal diuresis should be limited to 500 ml/day. As in other conditions in which combinations of diuretics are used, close monitoring of electrolytes is necessary. Diuretic therapy should be reduced or discontinued if azotemia develops.[59]

Congestive Heart Failure

Patients with mild heart failure may not have appreciable edema and diuretic therapy is not an absolute necessity, particularly if patients can restrict sodium intake. If hypertension coexists, it is sensible to employ a thiazide diuretic, which may be sufficient to control mild edema, if present. However, most patients with congestive heart failure will eventually develop edema to the extent that requires the use of a loop diuretic.

Responsiveness to oral loop diuretics in patients with heart failure is dependent on several factors including gastrointestinal absorption and tubular secretion. The absolute bioavailability of the diuretic is unchanged, but the rate of absorption is slowed such that the peak response may not be observed for several

hours after the dose is administered.[5] The unpredictability of diuresis with furosemide in this situation may portend a worse outcome. Torsemide has a higher bioavailability than furosemide and evidence exists for less fatigue and readmittance for decompensated heart failure in patients receiving torsemide compared to furosemide, a finding potentially attributable to better bioavailability and more predictable response.[63]

As long as renal function remains preserved, delivery of diuretic into the tubular fluid remains normal in heart failure. However, renal responsiveness to loops as measured by the natriuretic response to maximally effective doses can be one-third to one-fourth than that of healthy individuals.[64] Larger doses will therefore not overcome this diminished response, unless renal insufficiency is present. Rather, the natriuretic response may be increased by giving moderate doses more frequently.[5] In this manner, intravenous therapy is often appropriate in patients with severe heart failure or acute pulmonary edema. In addition to avoiding troughs in drug concentration that can lead to intermittent periods of positive sodium balance, it also has the added advantage of bypassing the delayed gut absorption of the diuretic. A loading dose followed by a continuous infusion (Table 3) is preferred, as they seem to provide greater natriuresis with a lower incidence of toxicity than intermittent bolus injections.[65]

A thiazide diuretic can be added in combination to a loop diuretic in situations where the loop diuretic and sodium restriction are not adequate to control the edema.[10] The synergy provided by such combinations can result in profound diuresis and patients must be followed closely to prevent severe hypokalemia and volume depletion to the extent that could induce circulatory collapse.[5]

Distally acting, potassium-sparing agents may increase sodium excretion slightly in some patients. Potential responders can be identified by measuring urinary electrolytes. Low urinary sodium output in the presence of high urinary potassium concentrations indicate that sodium is being exchanged for potassium distally; the addition of a distally acting diuretic in this situation may enhance the natriuretic response.[5] More importantly, the empiric addition of spironolactone 25 mg/day to the standard regimen of an ACE-inhibitor and loop diuretic in patients with severe heart failure (ejection fraction < 35%) reduced death by 30% and hospitalizations by 35% in a pivotal trial.[66] These findings occurred independently of changes in body weight or urinary sodium excretion, suggesting that the blockade of aldosterone's effect on cardiac and vascular tissues is an important strategy in the management of these patients.

Nephrotic Syndrome

Diuretic resistance is often encountered in the nephrotic syndrome; a constellation of findings characterized by proteinuria, hypoalbuminemia and generalized edema. As serum albumin concentrations are low, there is an increase in the permeability of the glomerular basement membrane to plasma proteins.[59] The resulting decrease in plasma oncotic pressure alters Starling forces in the peripheral capillary beds, favoring fluid transudation into the interstitial compartment.[59] Since diuretics are primarily bound to albumin, hypoalbuminemia also causes more diffusion of diuretic into the extracellular fluid, leading to reduction in delivery to the secretory sites and ultimately, the diuretic site of action.[5] In severely hypoalbuminemic patients (< 2 g/dL), coadministration of albumin with the loop diuretic (30 mg furosemide mixed with 25 g albumin) may increase the diuretic response.[5] However, since tubular secretion of the diuretic is normal in the majority of patients with nephrotic syndrome (unless there is accompanying renal insufficiency), combined infusions are not necessary. Additionally, albumin administration can exacerbate hypertension and pulmonary congestion.

Despite adequate tubular secretion, diuretic response in the nephrotic syndrome is diminished. This is the result of increased binding of the diuretic to albumin in the tubular fluid, which reduces the amount of unbound, active drug available to exert its effect.[5] Nearly one-half to two-third of the diuretics reaching tubular fluid is bound to albumin when urinary albumin concentrations exceed 4 g/l.[5] As a result, the dose of diuretic must be increased twofold or threefold that is given to normal patients in order to deliver adequate amounts of unbound, active drug to the site of action. Additionally, the natriuretic response in nephrotic patients is further impaired by decreased cellular responsiveness in the loop of Henle and increased sodium retention in the distal tubule.[5] Doses of the loop diuretic must therefore be sufficient not only to overcome urinary binding, but they must also be administered more frequently. Metozalone or another thiazide diuretic may be combined with the loop diuretic as an additional strategy in nephrotic patients.[59]

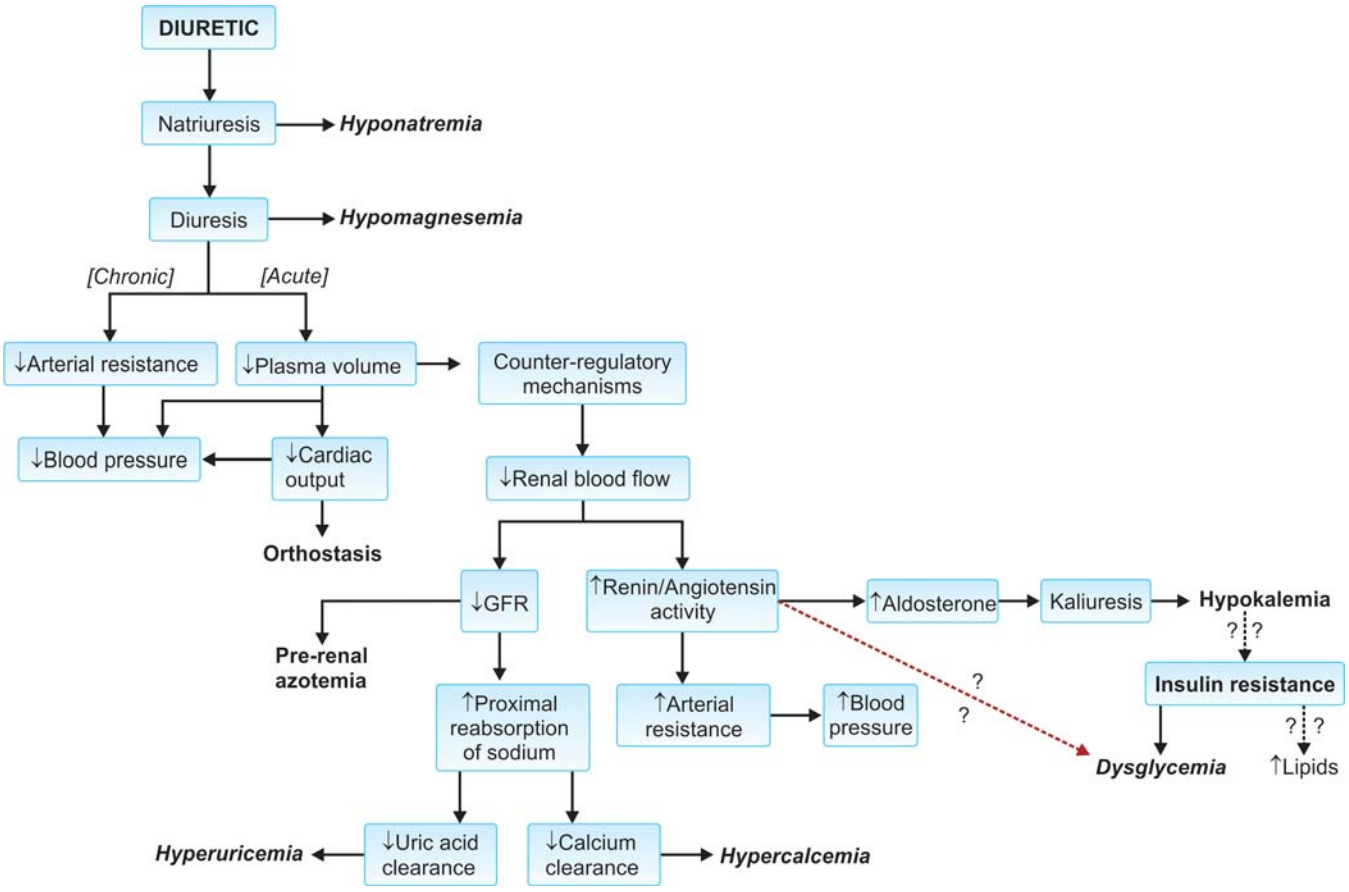
ADVERSE EFFECTS OF DIURETICS

A number of important and predictable adverse effects can occur with diuretics. Flow chart 1 illustrates some of the more commonly noted effects and the pathways by which they can occur. For the most part, adverse effects of diuretics are minimized by using lower doses as well as ensuring appropriate monitoring vigilance on the part of the clinician.

Both thiazide and loop diuretics increase potassium and magnesium excretion. On an average, potassium will fall by 0.3–0.4 mEq/l with typical dosing.[2] Among thiazides, chlorthalidone is commonly believed to cause more hypokalemia, but there is no compelling evidence of this finding when low doses are used.[52] The incidence of clinically relevant hypokalemia with thiazides is further reduced when they are combined with ACE-inhibitors or ARBs. Diuretic-induced hypokalemia can be managed by coadministering a potassium-sparing diuretic or oral potassium supplements. Potassium-sparing diuretics are generally more effective since they correct the underlying etiology and have the additional effect of reducing magnesium excretion.[2] The latter point is often unrecognized in its importance; magnesium deficiencies must be corrected first, otherwise potassium supplementation will be ineffective in normalizing potassium levels. Additionally, dietary sodium restriction can also help in minimizing the loss of potassium occurring with diuretics.[11]

Maintenance of potassium homeostasis is important, since epidemiologic evidence implicates hypokalemia in the pathogenesis of diuretic dysglycemia and new-onset diabetes.[67] It is important to recognize that new-onset diabetes will occur over time in many hypertensive patients regardless of type of

FLOW CHART 1: Proposed mechanisms leading to diuretic complications (in bold)



antihypertensive used. Data suggest long-term diuretic therapy over several years that may lead to an excess of 3–4% in diabetes cases as compared to other antihypertensives, but there is no evidence that it obviates their proven benefit in reducing CVD events.[2]

Hyponatremia is often caused by diuretics. Thiazides seem to have a greater propensity than loops, but its all diuretics are implicated.[68] Thiazide-induced hyponatremia usually manifests within the first two weeks of therapy, while loops can occur after a longer interval. Several risk factors predispose patients to diuretic-induced hyponatremia; these include older age, female gender, psychogenic polydipsia and concurrent antidepressant use (in particular, selective serotonin reuptake inhibitors).[68] In the presence of these conditions, hyponatremia can occur at any time. Most patients are asymptomatic, but careful monitoring of serum sodium should occur as well as counseling patients to avoid excessive free-water intake in order to minimize risks of its occurrence.

Diuretics can increase serum lipid levels, primarily total cholesterol and low-density lipoproteins, approximately 5–7% in the first year of therapy.[69] However, these increases are short lived and the high prevalence of statin background therapy in hypertensive patients generally makes this an inconsequential finding.

Few clinically relevant drug interactions occur with diuretics. As they compete with uric acid for secretion by the organic acid pathway, diuretics can increase serum uric acid and precipitate gout in some patients.[2] Nonsteroidal anti-inflammatory drugs can antagonize their therapeutic effects by causing sodium retention. Additionally, they can also increase the risk of hyperkalemia when combined with potassium-sparing agents, by decreasing secretion of renin and aldosterone. Likewise, the use of potassium-sparing diuretics with ACE-inhibitors or ARBs also entails an increased risk for hyperkalemia.

Other adverse effects of diuretics can include interstitial nephritis, ototoxicity (particularly with high-dose loop therapy), sun sensitivity, skin reactions and uropathy. Contrary to popular belief, diuretics do not need to be avoided in patients with a history of allergy to sulfonamide-based antibiotics.[70]

SUMMARY

For over 50 years, diuretic therapy has remained an important component of the management plan for a variety of cardiovascular-related disorders including hypertension and volume overload states such as congestive heart failure, cirrhosis, chronic kidney disease and the nephrotic syndrome. Few drugs in any class can boast of maintaining such prominence in therapy as when they were originally introduced.

Mutual attention paid to the diuretic site of action as well as an underlying knowledge of renal physiology and the pathophysiology of the disease provide a context in which to apply diuretic pharmacology in a manner that enables reliable prediction of their therapeutic and adverse effects. Tailoring therapy to the disease and the individual patient in this manner

insures that an effective diuresis can be achieved under a variety of circumstances.

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Chapter 5

Vasodilators and Neurohormone Modulators

Gary S Francis, Suma Konety

Chapter Outline

- Vasodilator Drugs and Low Blood Pressure
- Arterial versus Venous Effects of Vasodilator Drugs in Patients with Systolic Heart Failure
- Arteriolar Vasodilators
  - Hydralazine
  - Amlodipine
  - Oral Nitrates
- Renin-Angiotensin-Aldosterone System (RAAS) Blockers
  - Angiotensin Converting Enzyme Inhibitors (ACE inhibitors)
  - Angiotensin Receptor Blockers (ARBs)
- Mineralocorticoid (Aldosterone) Receptor Blockers
  - Aldosterone and Systolic Heart Failure
  - Spironolactone and Eplerenone in Chronic Heart Failure
- Phosphodiesterase Type 5 Inhibitors
  - Sildenafil and Tadalafil
- Intravenous Vasodilators
  - Nitroprusside
  - Metabolism and Toxicity of Nitroprusside
  - Nitroprusside and Severe Heart Failure
  - Intravenous Nitroglycerin
  - Limitations of Intravenous Nitroglycerin in the Treatment of Patients with Heart Failure
  - Nesiritide
- Oral β-adrenergic Blocking Drugs

INTRODUCTION

It has long been recognized that impedance to left ventricular (LV) outflow is a critical determinant of cardiac performance.[1–4] This is especially true of patients with impaired LV systolic performance such as in systolic heart failure (Fig. 1).[5] Ultimately, the failing heart loses its natural ability to respond to increased impedance to ejection (i.e. loss of homeometric autoregulation), although lowering systemic resistance by drugs can rescue myocardial systolic function to some extent.

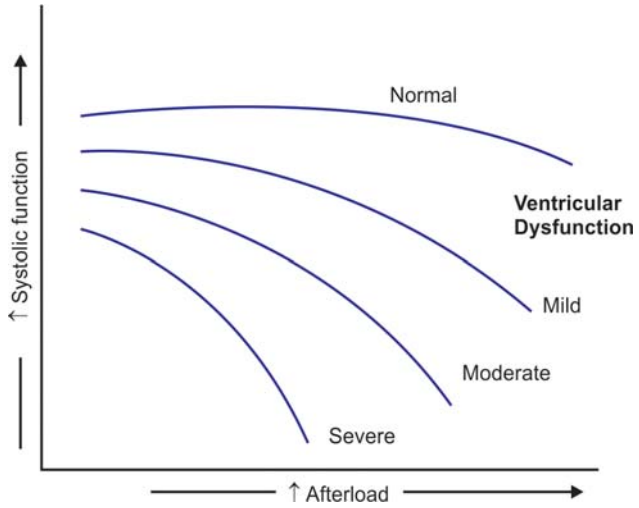


FIGURE 1: The relationship between various degrees of left ventricular dysfunction and afterload stress. (*Source:* Modified from Cohn JN, Franciosa JA. Vasodilator therapy of cardiac failure. N Engl J Med. 1977;297:27-31, 254-8, with permission)

Heightened resistance or impedance to LV ejection is often referred to as "afterload", but the term afterload originates from isolated muscle studies done in the mid-1970s and is not, strictly speaking, appropriately applied to the clinical setting. Afterload is defined as ventricular wall stress during shortening and cannot easily be measured in the intact circulation. Afterload is a product of LV cavity size (La Place relationship) and is inversely related to wall thickness or hypertrophy. In clinical practice, systemic vascular resistance (SVR) is frequently calculated [SVR = (mean arterial pressure – CVP) x 80/cardiac output] from right heart catheterization data, but this calculation is largely an estimate of small peripheral vessel caliber resistance. SVR is therefore only a part of the total impedance (Table 1) that the LV sees during ejection. Aortic impedance is also not typically measured as part of clinical care. Most bedside estimates of afterload are still derived by measuring SVR. The failing ventricles (both left and right) are exquisitely sensitive to afterloading conditions, and it is a logical extension of this concept that drugs that reduce aortic impedance will improve cardiac systolic performance, independent of any effect on myocardial contractility. Since aortic impedance is not routinely measured, SVR is used as a surrogate for impedance and tends to be equated with "afterload" by clinicians, but strictly

TABLE 1

Components of aortic impedance

- Large vessel distensibility
- Small vessel caliber (systemic vascular resistance)
- Small vessel compliance
- Blood viscosity
- Inertia

(*Source:* Tang WH, Young JB. Chronic heart failure management. In: EJ Topol (Ed). Textbook of Cardiovascular Medicine, 3rd edition. Philadelphia: Lippincott Williams and Wilkins; 2007. pp. 1373-405)

speaking, aortic impedance is a much more comprehensive concept than SVR.

VASODILATOR DRUGS AND LOW BLOOD PRESSURE

Patients with moderate-to-severe heart failure often have low blood pressure (BP) that is asymptomatic. Low brachial systolic pressure is sometimes perceived by physicians as a contraindication to the use of arteriolar dilator drugs such as nitrates, angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs) or carvedilol. However, vasodilator drugs can maintain or even increase systolic BP by increasing stroke volume in patients with systolic heart failure. Observations from large clinical trials have challenged the belief that vasodilators are deleterious in patients with low systolic BP.[6–8] Generally speaking, vasodilator drugs should be continued in patients with systolic heart failure and asymptomatic low systolic BP in the range of 90–110 mm Hg. Severe, symptomatic hypotension can sometimes occur in a volume deplete patient in response to an ACE inhibitor, e.g. following a robust diuresis. Such brisk falls in BP are now less common, as clinicians recognize that symptomatic hypotension is a well-described adverse event that can occur when ACE inhibitors or ARBs are used in the context of hypovolemia and an activated renin-angiotensin-aldosterone system (RAAS). Symptomatic reduction in systolic BP in response to vasodilators in a euvolemic or volume-overloaded patient with severe LV dysfunction is another matter. Such patients are said to be truly intolerant of vasodilators, and symptomatic hypotension in response to drug therapy is a very powerful sign of poor prognosis. Low BP without symptoms is far more common and can usually be ignored when using vasodilator drugs.

ARTERIAL VERSUS VENOUS EFFECTS OF VASODILATOR DRUGS IN PATIENTS WITH SYSTOLIC HEART FAILURE

Arteriolar dilating drugs, such as hydralazine or amlodipine, reduce aortic impedance and thereby increase the velocity of shortening during LV ejection. LV end-systolic volume is thus reduced and LV ejection fraction increases. With hydralazine, LV end-diastolic volume (i.e. preload) may not acutely be altered, so the stroke volume response can be markedly increased.[9] When vasodilator drugs, such as nitrates, are employed in patients with systolic heart failure, blood volume may acutely redistribute into the large capacitance veins and LV end-diastolic volume or preload may be reduced. The reduced LV end-diastolic volume may limit the increase in stroke volume to some extent.[10] With balanced arteriolar-venous vasodilator drugs, such as sodium nitroprusside, typically venous pressure falls (decongestion) and stroke volume still improves as a consequence of marked reduction in aortic impedance. Essentially, the hemodynamic effects of vasodilator drugs are dependent on the relative effects of the drug on resistance and capacitance vessels. In patients with severe regurgitant lesions, such as mitral or aortic regurgitation, vasodilator drugs reduce the regurgitant fraction and increase forward cardiac output, thus adding to their beneficial effects.

The reflex tachycardia observed in normal subjects in response to arteriolar dilating drugs is not seen in patients with advanced systolic heart failure.[11] This is likely due to the reduced cardiac norepinephrine spillover rate that occurs with unloading of the baroreceptors and low-pressure mechanoreceptors in response to systemic vasodilation in heart failure.[12] In fact, the magnitude of the blunted neurohumoral response to nitroprusside infusion in patients with systolic heart failure (i.e. lack of reflex tachycardia) may be a marker of the severity and prognosis of heart failure.[11]

In general, the beneficial response to vasodilator drug therapy is most obvious in patients with systolic heart failure and a dilated LV. Patients with normal LV cavity size may be more sensitive to changes in preload reduction, and hypotension can occur in response to reduced SVR if the heart is small or there is a relatively reduced preload.

ARTERIOLAR VASODILATORS

HYDRALAZINE

Hydralazine is an old drug, one of the first to be used to treat hypertension in the 1950s. Its mechanism of action is still not completely elucidated, but it appears to be a direct acting, potent arteriolar dilator that relaxes the smooth muscles of small resistance vessels. It has essentially no venodilating effects. Hydralazine primarily dilates the renal- and peripheral-resistant arterioles and has little effect on coronary or liver blood flow. It may also have antioxidant effects and can prevent tolerance to nitrates (Fig. 2).

It has been known for years that when hydralazine is used in non-systolic heart failure patients, e.g. in patients with systemic hypertension, large doses can produce reflex tachycardia, edema and even worsen angina. Reflex tachycardia in response to hydralazine is not typically observed in patients with more advanced systolic heart failure because of a blunted baroreceptor response.

Hydralazine can be given orally where it is rapidly absorbed from the gastrointestinal tract. However, the bioavailability is highly variable and depends on the rapidity that is acetylated by the liver, a genetically determined trait. In the United States, about half of the people are fast acetylators and half are slow acetylators. Acetylation activity is not routinely measured in patients. A lupus-like syndrome is more likely to occur in slow acetylators and this typically wanes when hydralazine is stopped. Fast acetylators may

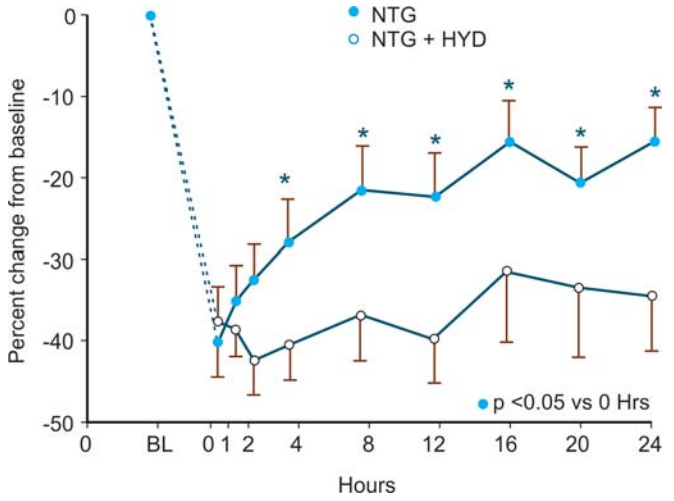


FIGURE 2: Nitroglycerin (NTG) alone is associated with the development of early tolerance, whereas the combination of NTG and hydralazine (HYD) 75 mg four times per day is associated with less NTG tolerance. (*: Statistically significant changes). (*Source:* Modified from Elkayam U. Nitrates in the treatment of congestive heart failure. Am J Cardiol. 1996;77:41C-51C, with permission).

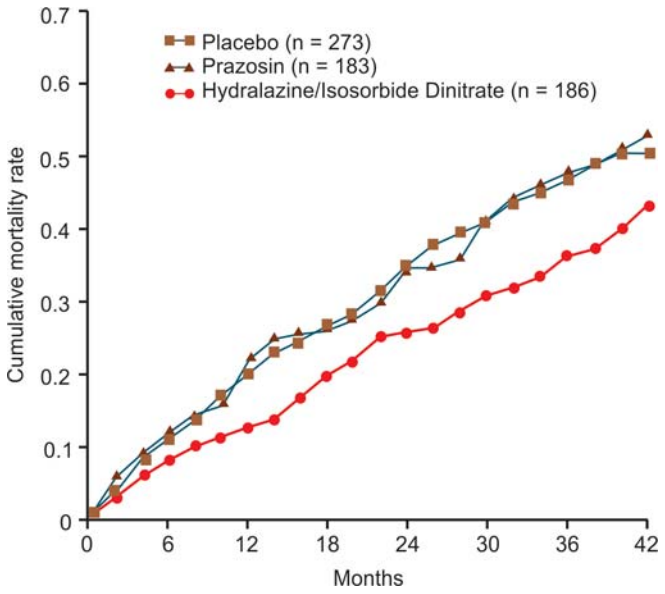


FIGURE 3: Mortality curves of patients with heart failure randomized to placebo, prazosin or isosorbide dinitrate/hydralazine in the first Vasodilator Heart Failure Trial (V-HeFT 1); p= 0.046 on the generalized Wilcoxan test, which gives more weight to the treatment differences in the early part of the mortality curves. (*Source:* Modified from Cohn JN, Archibald DG, Ziesche S, et al. Effect of vasodilator therapy on mortality in chronic congestive heart failure. Results of a Veterans Administration Cooperative Study. N Engl J Med. 1986;314:1547-52, with permission)

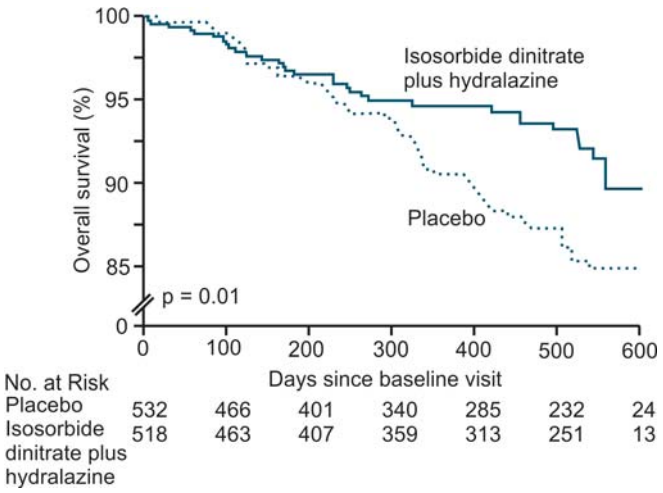


FIGURE 4: Mortality curves of African-American patients randomized to placebo or isosorbide dinitrate/hydralazine in addition to standard therapy for heart failure in the African-American Heart Failure Trial (A-HeFT). (*Source:* Modified from Taylor AL, Zliesche S, Yancy C, et al. Combination of isosorbide dinitrate and hydralazine in blacks with heart failure. N Engl J Med. 2004; 351:2049-57, with permission)

require higher doses of hydralazine. Chronic hydralazine use can cause vitamin B6 deficiency.

The hemodynamic response to chronic oral hydralazine therapy in patients with systolic heart failure is usually characterized by no change in heart rate, a fall in SVR and about a 50% increase in cardiac output.[13] Usually, BP does not change much. Patients with chronic mitral or aortic regurgitation demonstrate a reduction in the regurgitant jet by echo and auscultation, and forward stroke volume is markedly increased. There is no long-term improvement in exercise capacity despite a modest, persistent improvement in EF. The combination of hydralazine and isosorbide dinitrate ushered in the vasodilator era for the treatment of heart failure (Fig. 3).

Even today we do not know entirely how to dose hydralazine for individual patients with advanced heart failure. Because of the high success rate of other vasodilator drugs, such as ACE inhibitors and ARBs, hydralazine has been relegated to second-tier therapy. The one important exception is featured by the results of the African-American Heart Failure Trial (A-HeFT) (Fig. 4).[14] In this trial, the combination of hydralazine and isosorbide dinitrate in a combination of fixed-dose drug (BiDil®) added to standard therapy improved survival and other outcomes among black patients with systolic heart failure. One rationale for the trial was that isosorbide dinitrate might augment nitric oxide production, and therefore improve endothelial function. Hydralazine may also work as an antioxidant and can reduce nitrate tolerance.[15] The combination of hydralazine and isosorbide dinitrate today should be considered as an add-on therapy, superimposed on more conventional therapy, when patients are demonstrating signs and symptoms of worsening heart failure.

Typically, hydralazine is prescribed along with isosorbide dinitrate to improve cardiac output and reduce pulmonary capillary wedge pressure (PCWP). The initial hydralazine dose used in A-HeFT was 37.5 mg three times per day and gradually increased to 75 mg three times per day. Isosorbide dinitrate was titrated to a dose of 80 mg three times per day. Hydralazine and isosorbide dinitrate were combined in the drug BiDil®. Doses of hydralazine, as high as 1,200 mg/day, have been used to treat systolic heart failure, but onset of lupus syndrome is seen in 15–20% of patients receiving more than 400 mg/day. Fluid retention is also common when higher doses of hydralazine are used. There is likely a survival advantage associated with long-term hydralazine therapy when taken with isosorbide dinitrate to treat systolic heart failure.

Amlodipine is a dihydropyridine L-type calcium channel blocking agent that is widely used to treat hypertension and angina. It is a long-acting, potent, arteriolar dilating drug that is well tolerated. The typical starting dose is 2.5 or 5 mg/day and the target dose for many patients is 10 mg/day. Calcium channel drugs are vasodilators and have anti-ischemic effects, so it is logical that they would be investigated in patients with systolic heart failure. The most promising calcium channel blocker to emerge from these studies as potential heart failure therapy was amlodipine. The only drawback to amlodipine is the frequent development of pedal edema with the higher dose, but this is assumed to be due to benign vasodilation in the small arterioles and venules in the ankles, and not due to heart failure *per se*. Other non-dihydropyridine calcium channel blockers, such as verapamil and diltiazem, may either have negative inotropic properties, cause cardiac electrical conduction problems, or are simply not very powerful vasodilators. They do not play any role in the treatment of heart failure.

The effect of amlodipine on outcomes in patients with chronic systolic heart failure was evaluated in the two prospective randomized amlodipine survival evaluation (PRAISE) studies.[16,17] The earlier of the two studies demonstrated that all-cause mortality might be lower in a subset of patients with nonischemic dilated cardiomyopathy treated with amlodipine, although overall, the trial was neutral. A second PRAISE trial was then done solely in patients with nonischemic dilated cardiomyopathy. In PRAISE II, an overall neutral effect of amlodipine was once again observed. It seems clear that amlodipine is safe to use in patients with systolic heart failure when needed to control hypertension or angina. However, amlodipine is not effective as primary therapy for the treatment of systolic heart failure, despite its powerful vasodilating properties. Several other potent vasodilators have failed to improve mortality in patients with heart failure, including prazosin, flosequinan, nesiritide, and synthetic prostacyclin (epoprostenol) or Flolan. These observations suggest that vasodilation alone is not enough to provide a mortality benefit. Presumably it is not simple "vasodilation" that provides for the survival benefit, but there should be some neurohumoral modulation property or some other mechanisms beyond simple reduction in SVR.

ORAL NITRATES

Nitrates have been widely used to treat angina by physicians for well over 100 years. It is only in the past 25 years that they have been used to treat systolic heart failure. Their favorable effects on angina, systolic heart failure, mitral regurgitation and coronary spasm are now well known. The mechanism of action of nitrates is complex, but these molecules appear to undergo a metabolic biotransformation in vascular smooth muscle which leads to the formation of nitric oxide (NO) or a related S-nitrosothiol. These breakdown products of nitrates stimulate the enzyme guanylate cyclase, leading to the formulation of cyclic-guanosine monophosphate (c-GMP). c-GMP in turn reduces calcium influx, which leads to venous and arterial vasodilation.[18] It is also likely that the vascular endothelium responds to nitrates with the synthesis and release of prostacyclin,[19] thus improving endothelial function. Nitrates primarily cause venodilation, which typically increases capacitance and reduces preload, thus lowering end-diastolic volume, reducing cardiac wall tension and diminishing PCWP. Dyspnea is relieved. Larger doses lead to arteriolar dilation, further reducing afterload and improving forward flow. LV cavity size diminishes, reducing mitral regurgitation.[20] It is not surprising that oral nitrate therapy has emerged as an important treatment for systolic heart failure. Nitrates are among the few vasodilators that are able to increase exercise tolerance in patients with systolic heart failure.[21,22] However, nitrate tolerance occurs in many patients (Fig. 5), thus casting suspicion on long-term efficiency. This can be offset to some extent by hydralazine.[15]

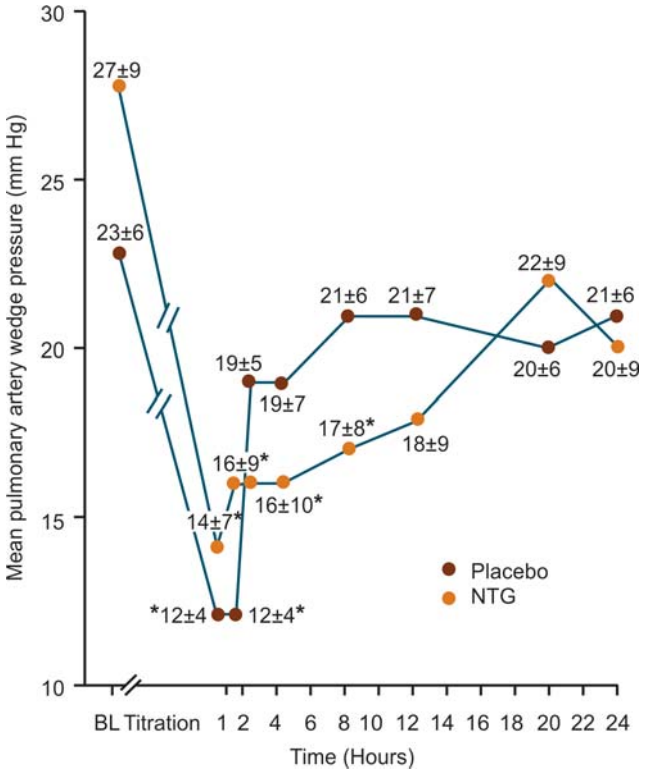
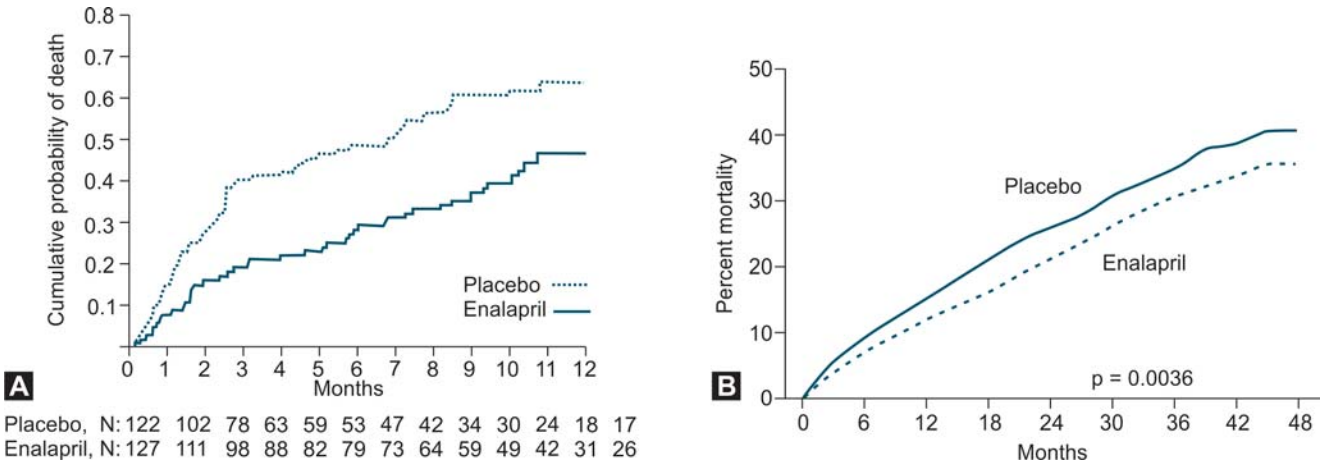


FIGURE 5: The data indicate that tolerance can develop to intravenous nitroglycerin (NTG) over 24 hours. There is a brisk initial response to IV NTG manifested by a fall in pulmonary capillary wedge pressure (PCWP) during titration; but during 24 hours of infusion, PCWP increases back toward control in both the NTG and the placebo arms of the study. (*Source:* Modified from Elkayam U, Kulick D, McIntosh N, et al. Incidence of early tolerance to hemodynamic effects of continuous infusion of NTG in patients with coronary artery disease and heart failure. Circulation. 1987;76:577-84, with permission)

RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM (RAAS) BLOCKERS

ANGIOTENSIN CONVERTING ENZYME INHIBITORS (ACE INHIBITORS)

ACE inhibitors were introduced into clinical practice in the 1980s for the treatment of hypertension and heart failure. This class of drug therapy has revolutionized therapy for these two conditions, and has been demonstrated to improve survival in patients with systolic heart failure (Figs 6A and B). The development of this class of drugs for the treatment of heart

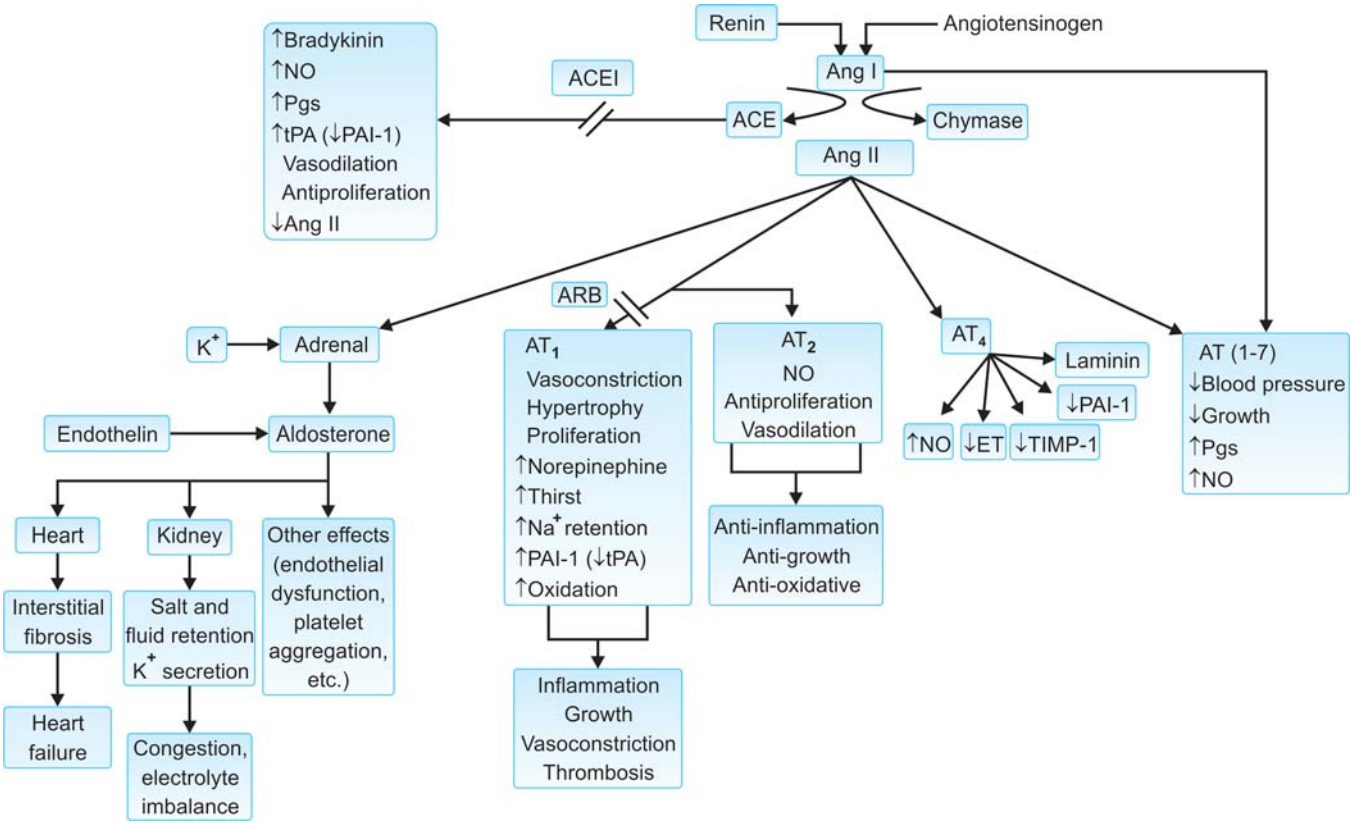


FIGURES 6A AND B: In the CONSENSUS Trial, the difference between treatments is even more striking, as the patients likely had more advanced heart failure. Kaplan-Meier survival curves (A) from The CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). (*Source:* Modified from N Engl J Med. 1987;316:1429-35, with permission). (B) From the SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. (*Source:* Modified from N Engl J Med. 1991;325:293-302, with permission)

failure was predicated on the observation that the RAAS is activated in chronic heart failure,[23] and contributes importantly to heightened afterload and to the LV remodeling process.

Angiotensinogen is produced in the liver and is converted in the blood by renin to form a small peptide, angiotensin I (Flow chart 1). Angiotensin I is then further cleaved to form angiotensin II, a very small peptide, but potent arteriole constrictor. Angiotensin II subserves a host of other biological activities primarily through the angiotensin II receptor, including promotion of volume retention, activation of and sensitization

FLOW CHART 1: The renin-angiotensin-aldosterone system



(Abbreviations: ACE: Angiotensin-converting-enzyme; ACEI: Angiotensin-converting-enzyme-inhibitor; ang I: Angiotensin I; ang II: Angiotensin II; AT: Angiotensin receptor; ET: Endothelin; NO: Nitric oxide; PAI: Plasminogen activator inhibitor; PGs: Prostaglandins; TIMP: Tissue inhibitor of metalloproteinase; tPA: Tissue plasminogen activator). (*Source:* Modified from Kalidindi SR, Tang WH, Francis GS. Drug insight: Aldosterone-receptor antagonists in heart failure—The journey continues. Nat Clin Pract Cardiovasc Med. 2007;4(7):368-78, with permission)

to the sympathetic nervous system (SNS), thirst, regulation of salt and water balance, modulation of potassium balance, cardiac myocyte and vascular smooth muscle growth, to name a few. Its actions are central to the development of acute and chronic systolic heart failure.

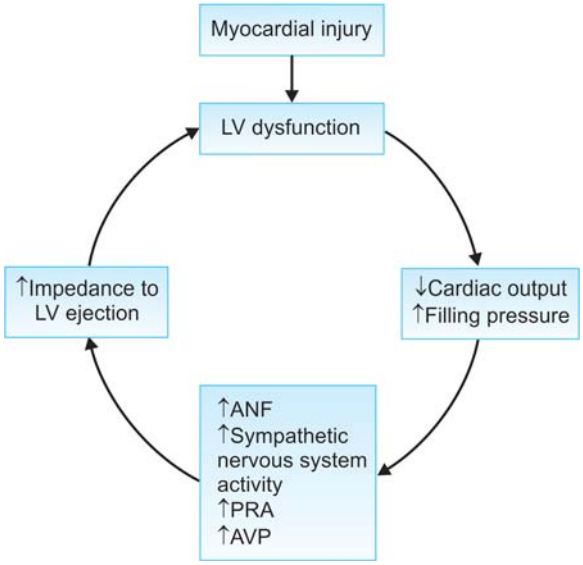
Early, overly simplistic thinking was that systolic heart failure was essentially a vasoconstricted state caused by excessive SNS activity and heightened levels of other vasoconstrictor neurohormones, including angiotensin II, arginine vasopressin (AVP) and endothelin. When it became apparent that ACE inhibitors could block the production of angiotensin II, ACE inhibitors became an attractive candidate for the treatment of patients with systolic heart failure. ACE inhibitors would be expected to reduce SVR, and in turn would increase cardiac output and forward flow. Although the initial clinical studies indeed supported this hypothesis,[24] it soon became clear that ACE inhibitors were doing much more than reducing SVR. Long-term clinical improvement was accompanied by reduced LV remodeling and improved patient survival when applied to post-myocardial infarction patients,[25] very similar to the seminal animal work of Pfeffer and his colleagues.[26] ACE inhibitors were no longer thought of as simple arteriolar dilators, but were neurohormone modulators that could very favorably alter the natural history of systolic heart failure and improve survival by inhibiting the progression of LV remodeling (Figs 6A and B).

We now recognize that neurohormonal activation plays a key role in the initiation and progression of heart failure. The RAAS is central to this neurohormonal cascade, as patients with systolic heart failure and high renin levels seemingly derive the most acute benefit from blocking the RAAS.[27] It is now well established that ACE inhibitors slow the progression of heart failure and improve survival in patients with a reduced ejection fraction and congestive heart failure.[28] Much of this improvement is believed to be due to "reverse remodeling". Even patients with a reduced ejection fraction, but few or no heart failure symptoms, derive clinical benefit from ACE inhibitor therapy.[29] The development of symptomatic heart failure is delayed in these patients. The activation of neurohormones (renin, norepinephrine and AVP) appears to occur early in the natural history of the syndrome, before symptoms occur.[30] This observation suggested that early introduction of neurohormonal blocking drugs before symptoms ensue may slow the progression of systolic heart failure or even delay its onset of signs and symptoms.[29] Indeed, today neurohumoral modulating drugs are recommended in patients who demonstrate impaired LV systolic function in the absence of symptoms. Many investigators observed that the RAAS was markedly activated during decompensated heart failure, but returns to normal once the patient clinically stabilizes, even though severe LV dysfunction may persist.[31] The concept that blocking the RAAS improved patients with systolic heart failure became widely recognized in the 1990s.

In the 1980s a number of hypotheses and concepts emerged that challenged the long-standing notion that systolic heart failure was fundamentally a mechanical problem. Katz introduced the idea that heart failure may be a disorder of abnormal gene expressional growth response to injury,[32] and many others believed that the myocardial remodeling was at least in part due to activation of neurohormonal systems,[33] which were also well known to be the cardiac growth factors when studied *in vitro*.[34] Alteration of loading conditions due to increased LV chamber size and increased wall stress also undoubtedly led to progressive LV remodeling.[34] Both mechanical and neurohormonal signals regulated the remodeling process, as did altered gene expression. It became clear that the all-important LV remodeling process was largely structural and not functional.[35] Additional data emerged indicating that excessive angiotensin II caused cardiac myocyte necrosis under experimental conditions.[36] Eventually a coherent story emerged suggesting that systolic heart failure was at least in part driven by excessive neurohormonal activation,[37,38] setting up a vicious cycle of worsening heart failure and death (Flow chart 2). Even though these neurohormonal systems are likely adaptive in an evolutionary sense,[39] and are not simple biomarkers or epiphenomena, they are known to directly contribute to LV remodeling[40–42] and even patient mortality.[43] The strong notion emerged that pharmacological inhibition of the RAAS (and the SNS) might reduce the progression of LV remodeling,[44–47] and therefore such drugs should improve patient survival.[28]

The ACE inhibitors were the first class of drugs to really test the neurohumoral hypothesis (Figs 6A and B). Needless to say, they have now become a standard of care for patients with hypertension, systolic heart failure, acute myocardial infarction and advanced cardiovascular disease. Their role in the treatment

FLOW CHART 2: Heart failure is a complex clinical syndrome characterized by extensive neuroendocrine activation. The release of neurohormones appears to be in response to reduced cardiac function and a perceived reduction in effective circulatory volume. It is as if neuroendocrine activity is attempting to protect the blood pressure and maintain circulatory homeostasis. Although this may be adaptive early on, chronic neuroendocrine activation leads to peripheral vasoconstriction, left ventricular remodeling and worsening left ventricular performance, and thus becomes an attractive therapeutic target. Drugs designed to block the exuberant neuroendocrine response, such as ACE inhibitors, have now becomes the cornerstone of treatment for heart failure



(Abbreviations: LV: Left ventricle; AVP: Arginine vasopressin; ANF: Atrial natriuretic factor; PRA: Plasma renin activity). (*Source:* Francis GS, Tang WH. In: JD Hosenpud, BH Greenberg (Eds). Congestive Heart Failure, 3rd edition. Philadelphia: Lippincott Williams and Wilkins; 2007. pp. 602-19)

of patients with systolic heart failure is now undoubted. The ACE inhibitor class of drugs reduces SVR, presumably by inhibiting angiotensin II arteriolar constriction reducing sympathetic tone. There is also marked venodilation with a fall in PCWP, presumably due to reduction in sympathetic activity to veins and desensitization of venous capacitance vessels to norepinephrine. Angiotensin II does not directly dilate veins, so there is no direct effect of ACE inhibitors on venous capacitance vessels. Venous capacitance vessels dilate in response to ACE inhibitors due to reduced sympathetic activity at the neuroeffector level. There is modest improvement in cardiac index with ACE inhibitors and the heart rate may be slightly slow. As previously mentioned, if the patient is acutely hyperreninemic from recent vigorous diuresis, there can be a substantial and prolonged fall in BP with even small doses of ACE inhibition. This is why many physicians prefer to use short-acting ACE inhibitors, such as captopril, in hospitalized patients with acute systolic heart failure, as patients are less likely to develop prolonged symptomatic hypotension. If symptomatic hypotension ensues, the patient should lie down and the feet should be elevated until these symptoms resolve and the BP improves. Usually a sense of well-being is established with the use of ACE inhibitors despite chronically low arterial pressures. Rarely, dysgeusia or loss of taste occurs, sometimes requiring withdrawal of the drug. Rash is uncommon with the smaller doses of ACE inhibitors used today. A dry, nonproductive cough occurs in some patients receiving ACE inhibitors, and the drug is discontinued in 5–10% of patients for this reason. The mechanism of cough is not entirely clear, but is believed to be due to the effects of bradykinin on sensory neurons in the proximal airways.

There is now a long list of ACE inhibitors to choose from (Table 2). They have somewhat dissimilar pharmacodynamics, pharmacokinetics and rates of elimination. In general, it is best to start with small doses of ACE inhibitors that have been tested in a large clinical trial and slowly titrate up over days to weeks to a target dose established as safe and effective by use in large clinical trials. It is expected that many patients with advanced systolic heart failure will have about a 20% increase in serum creatinine with ACE inhibitor use. This is usually not a reason to discontinue or lower the dose of the ACE inhibitor. However, this class of drug is contraindicated in patients with cardiogenic shock or acute renal failure, and can cause renal insufficiency when used in patients with renal artery stenosis. Occasionally, hyperkalemia can occur requiring alteration of the dose or temporary/permanent discontinuation of the ACE inhibitor. Careful, regular follow-up with a check on electrolytes, blood urea nitrogen (BUN) and serum creatinine is important in the care of these patients when making decisions about altering the dose of ACE inhibitors.

ANGIOTENSIN RECEPTOR BLOCKERS (ARBs)

Angiotensin receptors of the AT_1 subtype bind angiotensin II with a high structural specificity but limited binding capacity.[48] The remarkable success of ACE inhibitors in the treatment of hypertension, arterial disease, myocardial hypertrophy, heart failure and diabetic renal disease encouraged the development of alternative drugs to block the RAAS. It was eventually recognized that ACE inhibitor drugs blocked only one of several pathways that reduces angiotensin II activity, and that angiotensin II could "escape" from chronic ACE inhibition. ARBs do not demonstrate this "escape" phenomenon. ARBs do not cause cough. They can be used safely in patients who develop angioedema during treatment with an ACE inhibitor. Increased levels of angiotensin II peptides seen with the use of ARBs does not appear to have unexpected off-target effects despite activating AT_2 receptors. First-dose hypotension is not typically seen when ARBs are given to diuretic-treated patients, as often occurs with ACE inhibitors. This is probably because ARBs have a much slower onset of action. Orthostatic hypotension is rare. Rebound hypertension upon withdrawal of ARBs does not appear to be a problem. As with ACE inhibitors, acute renal failure may occur with ARBs if they are administered to patients with renal artery stenosis or cardiogenic shock. The incidence of renal dysfunction and hyperkalemia is comparable with ARBs and ACE inhibitors.[49] It is now reasonably clear that ACE inhibitors and ARBs should not be used together, as the likelihood of hyperkalemia, hypotension and worsening renal function is greater.[50]

Many randomized controlled trials of ARBs have been performed in patients with chronic systolic heart failure,[51,52] in patients with acute myocardial infarction complicated by heart failure or LV dysfunction[53] and in patients at high risk for vascular events.[54] Several important points have emerged from these large trials: (1) ARBs and ACE inhibitors appear to have very similar efficiency in these patient groups; (2) if the patient does not tolerate an ACE inhibitor, an ARB is a suitable substitution; (3) although generally more expensive, ARBs are better tolerated than ACE inhibitors and (4) the combination of an ACE inhibitor and an ARB (dual RAAS blocking effect) does not lead to more efficiency and is associated with more hypotension, worsening renal function and hyperkalemia.[55] Despite earlier favorable reports, ARBs do not appear to prevent recurrent atrial fibrillation.[56]

The dose of ARBs has generally been determined by pharmaceutical-generated data and subsequent verification of these doses in large clinical trials (Table 2). Extensive experience with RAAS blockers over the years has led to changes in dose recommendations. For example, a recent clinical trial demonstrated that losartan 150 mg daily reduced the rate of death or admission for heart failure to a greater extent than a dose of 50 mg per day.[57]

ACE inhibitors have been shown to attenuate LV enlargement and reduce mortality following myocardial infarction. We now have data to suggest that inhibition the RAAS with ARBs also results in favorable structural and functional changes. Treatment with the ACE inhibitor captopril, the ARB valsartan, or the combination of captopril plus valsartan resulted in similar changes in cardiac volume, ejection fraction and infarct segment length in a patient 20 months following acute myocardial infarction.[58] These observations suggest that ARBs have similar anti-remodeling properties as ACE inhibitors, and thus have added to their popularity for the treatment of hypertension and systolic heart failure. Unfortunately, their efficiency for the treatment of heart failure with preserved ejection fraction, as with ACE inhibitors, has not met with similar success.[59]

TABLE 2

Common drugs used in managing chronic heart failure in the United States

Drug	*Trade name*	*Heart failure indication*	*Post-myocardial infarction indication*	*Dosing*
Angiotensin-converting enzyme (ACE inhibitors)				
Benazepril	*Lotensin*	No	No	5-40 mg QD
Captopril	Capoten	Yes	No	6.25-150 mg TID
Enalapril	Vasotec	Yes	No	2.5-20 mg BID
Fosinopril	Monopril	Yes	No	10-80 mg QD
Lisinopril	Prinivil, Zestril	Yes	No	5-20 mg QD
Moexipril	*Univasc*	No	No	7.5-60 mg QD
Perindopril	*Aceon*	No	No	2-16 mg QD
Quinapril	Accupril	Yes	No	5-20 mg BID
Ramipril	Altace	Yes	Yes	2.5-20 mg QD
Trandolapril	*Mavik*	No	Yes	1-4 mg QD
Zofenopril	*Bifril*	NA	NA	7.5-60 mg QD
Angiotensin II receptor blockers (ARBs)				
Candesartan	Atacand	Yes	No	8-32 mg QD/BID
Eprosartan	*Teveten*	No	No	400-800 mg QD
Irbesartan	*Avapro*	No	No	150-300 QD
Losartan	*Cozaar*	No	No	50-100 mg QD/BID
Telmisartan	*Micardis*	No	No	40-80 QD
Olmesartan	*Benicar*	No	No	20-40 mg QD
Valsartan	Diovan	Yes	No	80-320 mg QD
β-Adrenergic receptor antagonists				
Carvedilol	Coreg	Yes	Yes	3.125-25 mg BID
Metoprolol succinate	Toprol XL	Yes	No	25-200 mg QD
Bisoprolol	*Zebeta*	No	No	1.25-10 mg QD
Nebivolol	*Nabilet*	No	No	1.25-10 mg QD
Aldosterone receptor antagonists				
Spironolactone	Aldactone	Yes	No	25-50 mg QD
Eplerenone	Inspra	No	Yes	25-50 mg QD
Others				
Amlodipine	*Norvasc*	No	No	2.5-10 mg QD
Hydralazone-isosorbid dinitrate	BiDil (37.5/20)	Yes	No	1-2 tablets TID
Digoxin	Digitek	Yes	No	0.125-0.25 mg QD

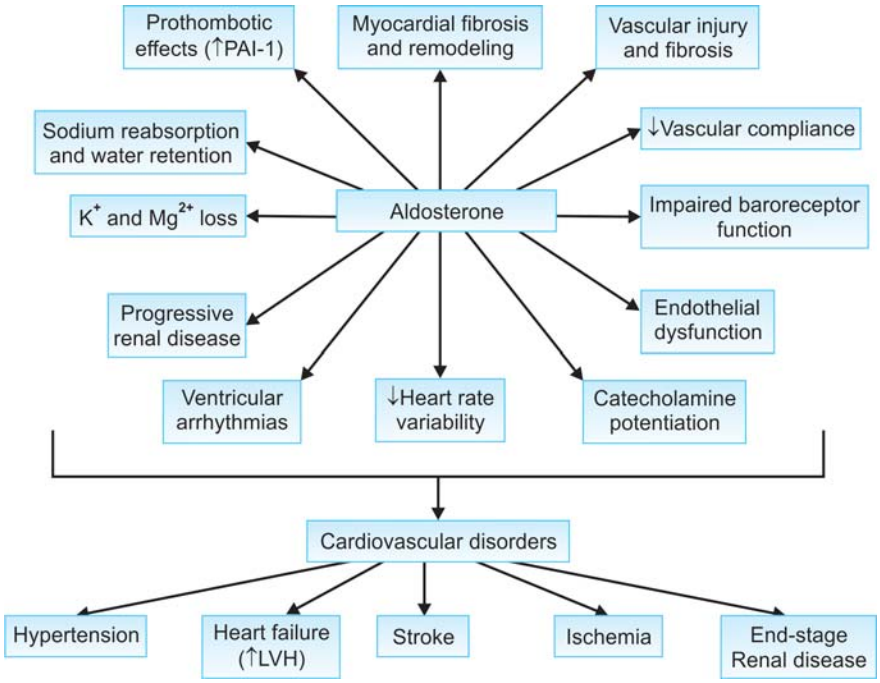
(Abbreviations: BID: Twice daily; QD: Once daily; TID: Three times daily. Italics indicate a drug that is currently not indicated by the US Food and Drug Administration for treating patients with heart failure). *Source:* Tang WH, Young JB. Chronic heart failure management. In: EJ Topol (Ed). Textbook of Cardiovascular Medicine, 3rd edition. Philadelphia: Lippincott Williams and Wilkins; 2007. pp. 1373-405)

MINERALOCORTICOID (ALDOSTERONE) RECEPTOR BLOCKERS

ALDOSTERONE AND SYSTOLIC HEART FAILURE

Aldosterone was structurally identified more than 50 years ago, and was soon after designated as mineralocorticoid due to its salt retaining properties. It also releases potassium from the kidney, gastrointestinal tract, sweat and salivary glands. It has long been known to play a pathophysiologic role in cardiovascular disease, including congestive heart failure (Flow chart 3).[60,61] In addition to its mineralocorticoid properties, which can cause hypokalemia and hypomagnesemia, aldosterone contributes in many ways to the development of heart failure.

FLOW CHART 3: Aldosterone is a mineralocorticoid that has a central role in a host of biological activities. Many of these activities can be excessive due to dysregulation of aldosterone activity, thus contributing to cardiovascular disease



(Abbreviations: LVH: Left ventricular hypertrophy; PAI-1: Plasminogen activator inhibitor-1). (*Source:* Modified from Struthers AD, MacDonald TM. Review of aldosterone and angiotensin-II-induced target organ damage and prevention. Cardiovasc Res. 2004;61:663-70, with permission)

It likely causes vascular and cardiac remodeling, endothelial dysfunction, inhibits norepinephrine reuptake and causes baroreceptor dysfunction (Flow chart 3). It expands intravascular and extravascular volume. Inhibition of aldosterone is believed to be favorable due to: (1) reduced collagen deposition and possibly anti-remodeling effects; (2) BP reduction; (3) prevention of hypokalemia and associated arrhythmias and (4) modulation of nitric oxide synthesis (Flow chart 3). The major mineralocorticoid in heart failure is cortisol and not aldosterone. Serum aldosterone levels are not consistently elevated in patients with heart failure in the absence of diuretics. Accordingly, it is not aldosterone blockade *per se*, but mineralocorticoid receptor blockade that is important. Spironolactone and eplerenone are thus mineralocorticoid receptor blockers more than simply aldosterone receptor blockers.

ACE inhibitors were originally believed to persistently suppress angiotensin II in patients with heart failure, a major determinant of aldosterone production by the adrenal glands. This notion probably led to some initial loss of interest in aldosterone receptor inhibitors for the treatment of systolic heart failure. We now know that ACE inhibitors do not persistently suppress angiotensin II, and that there is aldosterone escape. There is now much greater interest in studying aldosterone receptor blockers. Two landmark studies, the randomized aldosterone evaluation study (RALES) (Fig. 7)[62] and the myocardial infarction heart failure efficacy and survival study (EPHESUS) (Fig. 8)[63] have remarkably increased the role of aldosterone mineralocorticoid antagonists for the everyday treatment of systolic heart failure. The drugs spironolactone[62] and eplerenone[63] are now widely used to treat chronic systolic heart failure and post-myocardial infarction heart failure. Despite their greater use today, in the United States it is estimated that less than one-third of eligible patients hospitalized for heart failure receive appropriate, guideline-recommended aldosterone antagonist therapy.[64] Some of the reluctance to use aldosterone blockers in patients with systolic heart failure may be justified because of the advanced age of patients, the frequency of chronic renal insufficiency, other common comorbidities such as diabetes mellitus and the serious threat of hyperkalemia.[65] However, when used according to the protocol, hyperkalemia is seemingly not such a major problem. Careful follow-up of patients and frequent measurement of renal function and serum potassium are necessary to ensure safety when using aldosterone receptor blocking drugs.

The RAAS is likely an ancient (~400–600 million years) system that evolved in mammals in such a way as to allow them to adapt salt and volume depletion, as might have occurred during transition from the sea to land eons ago. The notion is that regulation of salt and water retention is adaptive, perhaps by protecting intravascular volume, BP and perfusion to vital organs. We now know that chronic stimulation of the RAAS in patients with heart failure can be maladaptive, and that pharmacologically blocking the RAAS can improve patient survival. Blockade of aldosterone membrane receptors is a widely accepted form of therapy for systolic heart failure. The RALES and EPHESUS studies provide strong evidence that aldosterone mineralocorticoid receptor blockade is an effective therapy for patients with advanced heart failure and early post-myocardial infarction heart failure, respectively. The role of nuclear aldosterone receptors is less clear, but given the complex array of regulatory properties that angiotensin II and aldosterone demonstrate, including inflammation, collagen synthesis, cytokine production, regulation of nitric oxide and cell adhesion molecules, one has to suspect that the activation

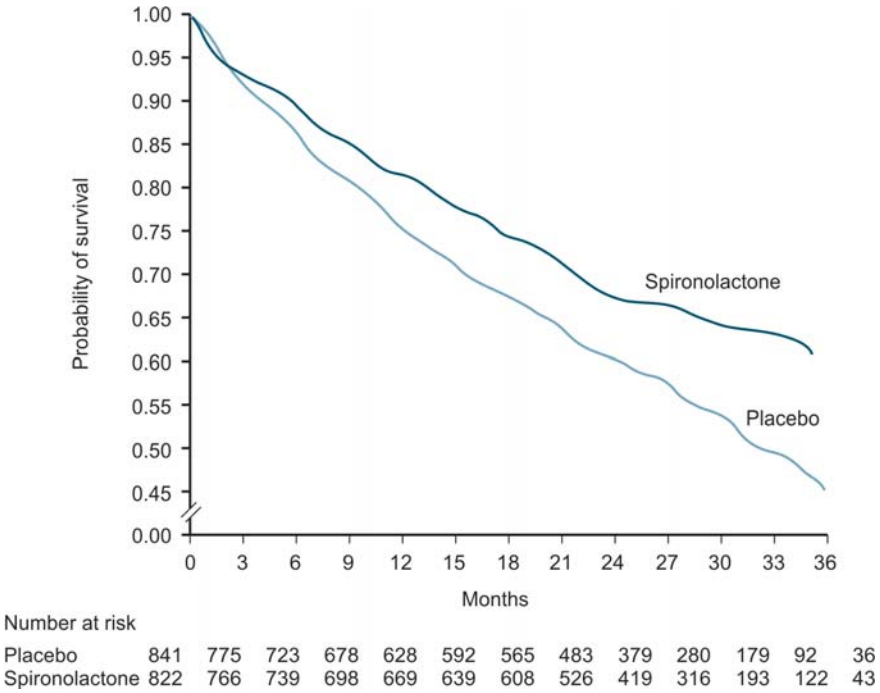


FIGURE 7: Survival curves of patients with advanced heart failure randomly allocated to spironolactone or placebo. Most patients were not receiving β-adrenergic blockers. There was a 30% reduction in mortality in patients randomized to spironolactone compared to patients in the placebo group. From the Randomized Aldactone Evaluation Study (RALES). (*Source:* Modified from Pitt B et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. N Engl J Med. 1999;341:709-17, with permission)

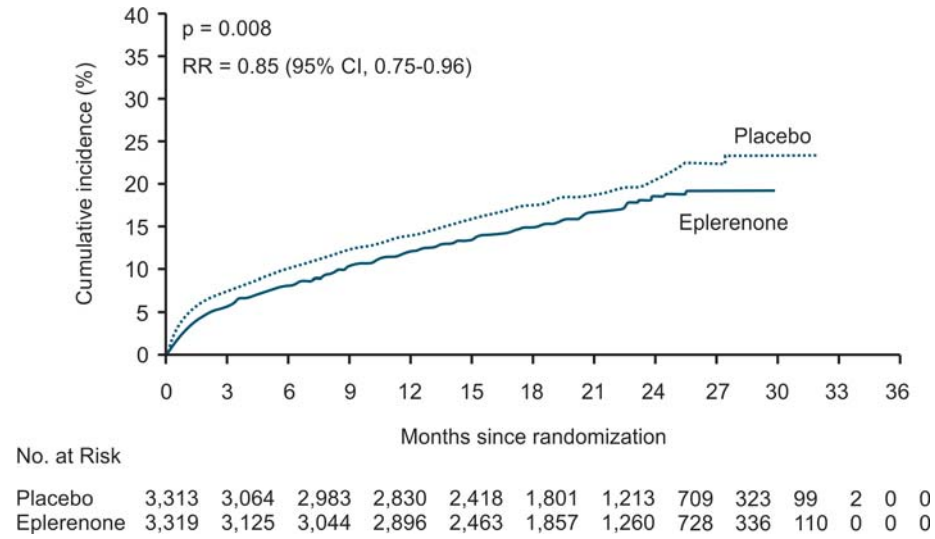


FIGURE 8: Kaplan-Meier estimates of the rate of death from any cause in the EPHESUS trial (Abbreviations: RR: Relative risk; CI: Confidence interval) (*Source:* Modified from Pitt B, Remme W, Zannad F, et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. N Engl J Med. 2003;348:1309-21, with permission)

of nuclear aldosterone receptors with resultant regulation of selective gene expression is also responsible for many of the biological activities of aldosterone, some of which are seen in systolic heart failure.

SPIRONOLACTONE AND EPLERENONE IN CHRONIC HEART FAILURE

The mechanism of action of spironolactone is complex, as aldosterone mineralocorticoid modulates many features of the heart failure syndrome. Although spironolactone is still used as an antihypertensive agent, it is not considered to be a "vasodilator" in the usual sense. Patients taking spironolactone need to be frequently and carefully monitored (patients in RALES were seen monthly for the first 12 weeks), as hyperkalemia and azotemia can occur with spironolactone,[65] particularly if nonsteroidal anti-inflammatory drugs are used concomitantly. Diabetes mellitus, chronic kidney disease, volume depletion, advanced age and use of other potassium sparing agents, and nonsteroidal anti-inflammatory drugs are all risk factors for the development of hyperkalemia when using RAAS blocking drugs.[61] With careful monitoring, however, serious hyperkalemia is uncommon.[62]

Because of the central importance of aldosterone in the pathophysiology of heart failure, it is not surprising that the aldosterone receptor blocker spironolactone has emerged as an important therapy. Spironolactone is an old drug that was primarily used in large doses to treat ascites, edema and refractory hypertension. Excessive mineralocorticoid, common in patients with heart failure, promotes sodium retention, loss of magnesium and potassium, SNS activation, parasympathetic

nervous system inhibition, myocardial and vascular fibrosis, baroreceptor dysfunction and impaired arterial compliance.[66] With the widespread emergence of ACE inhibitors, however, there was a common belief that ACE inhibitor therapy would also block aldosterone synthesis, so that there would be no need to add a drug-like spironolactone to an ACE inhibitor. However, it was eventually recognized that ACE inhibitors only transiently suppress the formation of aldosterone.[67] A small pilot study of 12.5–25 mg per day of spironolactone in conjunction with an ACE inhibitor, loop diuretic and digoxin-proved spironolactone was effective, well tolerated and did not cause serious hyperkalemia.[68] A much larger study was then launched.

The definitive RALES was published in 1999[62] and clearly demonstrated that spironolactone (25–50 mg per day) added to standard therapy (β-blockers were not yet in widespread use) was safe and reduced mortality by 30% (Fig. 7). Death from progressive heart failure and sudden death were both reduced by spironolactone. The patients who participated in RALES were primarily NYHA class III (70%) and IV (30%).

Eplerenone, a newer, more selective aldosterone mineralocorticoid receptor blocker, causes less gynecomastia and breast tenderness than spironolactone. It is more mineralocorticoid specific than spironolactone. EPHESUS[63] was conducted in patients who experienced a recent acute myocardial infarction with an EF of 40% or less who had heart failure, or had a history of diabetes mellitus. The patients in EPHESUS were randomly allocated to eplerenone or placebo in addition to standard therapy for acute myocardial infarction.

In EPHESUS, eplerenone (average dose 42.6 mg per day) reduced all-cause mortality by 15%, cardiovascular mortality by 17% and significantly lowered the need for subsequent hospitalization (Fig. 8). Sudden cardiac death was also reduced. As with RALES, serious hyperkalemia was unusual. The EMPHASIS-HF trial (Effect of Eplerenone versus Placebo on Cardiovascular Mortality and Heart Failure Hospitalization in Subjects with NYHA Class II Chronic Systolic Heart Failure) which employed eplerenone in a large double-blinded trial of patients with more mild (NYHA class II) heart failure was recently stopped prematurely when a favorable response was noted. This would suggest that eplerenone may be effective in patients with systolic heart failure and more mild symptoms.

Today, aldosterone mineralocorticoid antagonists are widely used to treat advanced heart failure and for selected patients with acute myocardial infarction. However, less than one-third of eligible patients hospitalized for heart failure are receiving guideline-recommended aldosterone receptor blocking drugs.[64] This is perhaps due in part to the need for more frequent and careful follow-up and the fear of hyperkalemia. There is a perception by some physicians that this class of drugs poses more risk than other RAAS blockers. Nevertheless, aldosterone receptor blockers are effective and safe when properly prescribed and monitored and their indications are seemingly expanding. There appears to be considerably less reverse remodeling in patients with mild-to-moderate heart failure and LV systolic dysfunction randomly assigned to eplerenone, even though there is a reduction in collagen turnover and a reduction in brain natriuretic factor (BNP).[69] Despite these surprising neutral effects on reverse remodeling, the results of the EMPHASIS-HF trial suggest that patients with mild-to-moderate systolic heart failure still derive a favorable effect on morbidity and mortality from eplerenone.

PHOSPHODIESTERASE TYPE 5 INHIBITORS

SILDENAFIL AND TADALAFIL

Phosphodiesterases are enzymes that hydrolyze the cyclic nucleotides—c-GMP and cyclic adenosine monophosphate (cAMP). At least 11 families of phosphodiesterase isoenzymes have been identified. Phosphodiesterase 5 (PDE 5) degrades c-GMP via hydrolysis, thus influencing c-GMP's ability to modulate smooth muscle tone,[70] particularly in the venous system of the penile corpus cavernosum and in the pulmonary vasculature. The discovery of sildenafil, a highly selective inhibitor of PDE 5, was initially aimed to be a novel treatment for coronary artery disease. The initial clinical studies in the early 1990s were not promising for this target, but the off-target effect of the enhancement of penile erections did not escape the notice of investigators. The use of PDE 5 inhibitors was then redirected toward erectile dysfunction and more recently pulmonary hypertension.

Nitric oxide (NO) activates soluble guanylate cyclase, stimulating the production of c-GMP. PDE 5 normally hydrolyzes c-GMP. Sildenafil inhibits PDE 5, leading to increased c-GMP and vasodilation in response to NO. For years it was known that PDE 5 was not present in normal cardiac myocytes, and the heart itself was not considered an appropriate target. This was recently challenged by Kass and his colleagues[71] who demonstrated that inhibiting PDE 5 in hypertrophied RVs induces a positive inotropic response.[71,72] In fact, PDE 5 is markedly upregulated in hypertrophied ventricles, and PDE 5 inhibition may lead to regression of RV hypertrophy.[72] PDE 5 has long been known to be highly expressed in the lung vasculature, and so it is not surprising that sildenafil may be beneficial for the treatment of patients with pulmonary hypertension. As of this writing, it is still not clear if normal cardiac myocytes express PDE 5, but hypertrophied and/or failing myocytes do express it, and PDE 5 inhibition can be clinically helpful in patients with pulmonary hypertension and some element of right ventricular hypertrophy or failing right ventricle.

Sildenafil and tadalafil are both PDE 5 inhibitors that are useful in patients with pulmonary arterial hypertension who have mild to moderately severe symptoms.[73] Preliminary data on sildenafil suggest that its use may also be safe and even beneficial in patients with disproportionate pulmonary hypertension and LV dysfunction.[74,75] Sildenafil citrate (Revatio®) is prescribed in doses of 20 mg TID and tadalafil (Adcirca®) is much longer acting and is prescribed in doses of 5 mg per day as needed to control pulmonary hypertension. Hypotension can occur with PDE 5 inhibitors, especially when they are used with nitrates. There is no specific antidote for PDE 5 induced hypotension. Sildenafil and tadalafil are not approved for use in patients with heart failure, but they are being investigated. A small case series (three patients) has recently implied that a combination of sildenafil and nitrates can be used in patients with heart failure and pulmonary hypertension,[76] although clearly more robust clinical trials are needed. Experimental data indicate that PDE 5 levels are increased in severely failing

hearts[77] and that sildenafil reduces myocardial remodeling.[78] Recent data also suggest that PDE 5 is regulated in the LV by oxidative stress.[79] Clearly this story is still unfolding and we have much to learn. Nevertheless, drugs such as sildenafil and tadalafil that selectively restore right ventricular contractility, limit right ventricular hypertrophy and reduce pulmonary artery remodeling are intriguing as potential therapy for right heart failure due to disproportionately increased pulmonary artery pressure. Perhaps PDE 5 inhibitors will also favorably affect left-sided systolic heart failure, particularly if there is associated pulmonary hypertension. More studies are needed, and use of these drugs for the treatment of heart failure remains investigational for now.

INTRAVENOUS VASODILATORS

NITROPRUSSIDE

Sodium nitroprusside can be dramatic in reversing the deleterious hemodynamics of acute systolic heart failure. Those who have had experience using the drug in this setting are often astonished how quickly the drug lowers PCWP and improves cardiac output, leading to prompt and often striking clinic improvement. The drug is usually started as doses of 10 mcg/min, and gradually titrated up to not more than 400 mcg/min, as needed to control hemodynamic abnormalities and symptoms. Some clinicians give nitroprusside according to body weight, with the typical dose starting at 10–20 mcg/kg/min. Our extensive experience with nitroprusside suggests that with low-dose infusion rates (less than 3 mcg/kg/min) used for less than 72 hours, toxicity is almost never observed.[80] The systolic BP should not be allowed to be less than 90 mm Hg or to a level that includes hypotensive symptoms. Invasive monitoring with a pulmonary artery catheter and an arterial catheter can be useful if the patient has marginal BP. When nitroprusside induces hypotension prior to the desired hemodynamic improvement, the additional administration of dopamine in doses greater than 3 mcg/kg/min will usually correct the problem.[81] Persistent or severe hypotension will nearly always dissipate as soon as nitroprusside is stopped.

METABOLISM AND TOXICITY OF NITROPRUSSIDE

Nitroprusside has been used to treat severe heart failure for many years,[82] although the Food and Drug Administration (FDA) has approved it only for severe hypertension and hypotensive surgery. It must be used carefully by experienced nurses and clinicians. Thiocyanate toxicity can occur, and thiocyanate levels should be checked as needed. Measurement of thiocyanate is a simple, inexpensive colorimetric test, normal levels being less than 10 mg/ml. Metabolic acidosis, anuria and a prolonged high dose of nitroprusside (> 400 mcg/min) can predispose to thiocyanate toxicity, prompting the measurement of thiocyanate levels. The thiocyanate ion is also readily removed by hemodialysis. When thiocyanate toxicity does occur, the patient may present with confusion, hyperreflexia and convulsions. Occasionally, mild hypoxemia occurs from nitroprusside due to ventilation-perfusion mismatch, but it is of little clinical consequence, as cardiac output rises and the delivery of oxygen to tissues increases. Coronary "steal" can occur when nitroprusside is used in the setting of acute myocardial infarction, and it should not be used routinely in this setting.[83] If intravenous vasodilator therapy is used for patients with acute myocardial infarction and severe heart failure, intravenous nitroglycerin may be preferred. Nevertheless, nitroprusside has been used successfully in this setting when given late.[82] If nitroprusside is used to treat severe heart failure related to acute myocardial infarction, it should be given later, perhaps 12 hours after admission to the hospital.[83]

NITROPRUSSIDE AND SEVERE HEART FAILURE

Nitroprusside quickly improves hemodynamics and symptoms in patients with severe heart failure.[84] Even patients with hypotension and shock may improve with nitroprusside,[85] as BP may stabilize or even improve with a large increase in cardiac output. Patients with severe mitral regurgitations or aortic regurgitation may also demonstrate dramatic reversal of serious hemodynamic perturbations with nitroprusside. Patients with severe aortic stenosis and worsening heart failure can be improved with nitroprusside used prior to aortic value replacement,[86] provided they are not hypotensive. It can also be used to stabilize acute heart failure in patients who demonstrate a ruptured interventricular septum following acute myocardial infarction. Recent data indicate that in patients hospitalized with advanced, low-output heart failure, those stabilized in the hospital with nitroprusside may have a more favorable long-term clinical outcome.[87]

INTRAVENOUS NITROGLYCERIN

Similar to nitroprusside, intravenous nitroglycerin has an immediate onset and offset of action. The infusion rate is usually initiated at 10–20 mcg/min and titrated slowly to 200–500 mcg/min as needed to control symptoms and improve hemodynamic parameters. It is not approved by the FDA for the treatment of heart failure, but has been widely used for this indication over the past 20 years. Intravenous nitroglycerin is endothelium dependent, and unlike nitroprusside, it has more effect on the venous circulation than on the arterial circulation. However, higher doses of intravenous nitroglycerin decrease SVR, as well as increase venous capacity. Therefore, cardiac output increases and BP can be maintained. PCWP is reduced. Mitral regurgitation improves. There are few data available on the effects of intravenous nitroglycerin on coronary circulation in patients with heart failure. Coronary blood flow appears to improve. This suggests that both the epicardial conductance vessels and the coronary arteriolar resistance vessels are favorably influenced by intravenous nitroglycerin.

LIMITATIONS OF INTRAVENOUS NITROGLYCERIN IN THE TREATMENT OF PATIENTS WITH HEART FAILURE

Intravenous nitroglycerin causes headache in about 20% of patients and, when severe, may require cessation of the infusion. Hypotension (10%), nausea and bradycardia occasionally occur. Some patients are relatively resistant to intravenous nitroglycerin and seemingly require very large doses to afford a hemodynamic

effect. The reason for this is not particularly clear, but very large doses in excess of 500 mcg/min are best avoided. Nitrate tolerance is said to occur when there is a robust initial hemodynamic response, but by 1–2 hours the dose of intravenous nitroglycerin must be increased to establish a continued hemodynamic response. About one-half of patients develop nitrate tolerance, and it cannot be predicted by baseline hemodynamic values (Fig. 5). The mechanism of resistance to intravenous nitroglycerin is not clear, but it is possibly prevented by the concomitant use of oral hydralazine (Fig. 2).

NESIRITIDE

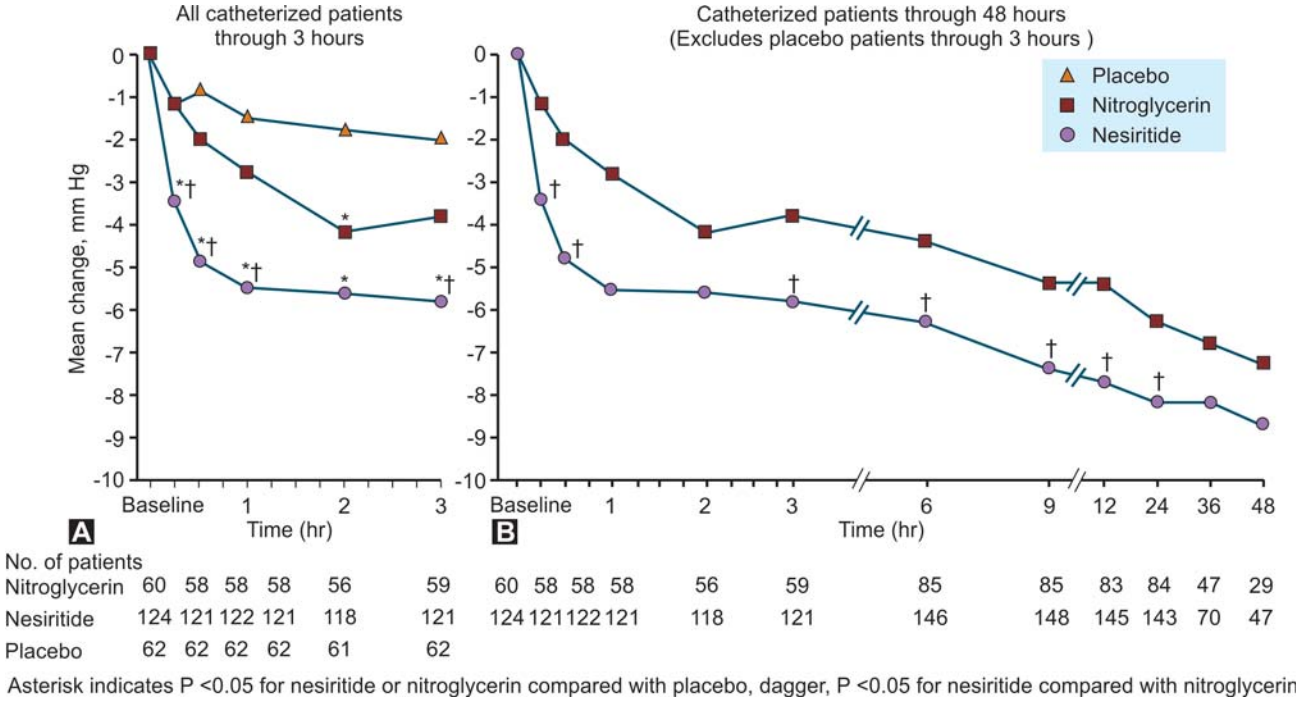
Nesiritide is a pure, human Brain Natriuretic Peptide (BNP) synthesized using recombinant DNA techniques. It has the same 32-amino acid sequence as endogenous BNP released from the heart. When infused intravenously into the circulation of patients with heart failure, the mean terminal elimination half-life of nesiritide is about 18 minutes. Plasma BNP levels increase about three-fold to six-fold with a nesiritide infusion. Human BNP is eliminated from the circulation through complex, multiple mechanisms. Most of the BNP is cleared by c-receptors on cell surfaces, but some is cleared by neutral endopeptidases in renal tubular and vascular cells, and a smaller amount is cleared by renal filtration that is proportional to body weight.

The largest clinical trial of nesiritide, Vasodilation in the Management of Acute CHF (VMAC), was a comparison study with intravenous nitroglycerin.[88] It demonstrated that nesiritide-improved hemodynamic function and self-reported symptoms are more effective than intravenous nitroglycerin or placebo (Figs 9A and B). On this basis, nesiritide was approved by the FDA for heart failure and became widely used for the treatment of acute heart failure. Nesiritide has venous, arterial and coronary vasodilator properties. Cardiac output improves and PCWP is reduced. Hypotension occurs in about 4% of patients, and unlike intravenous nitroglycerin, it can be prolonged (~20 min) because of nesiritide's relatively longer half-life. The effects of nesiritide on renal function are variable, but generally only a modest or neutral renal effect is observed, though worsening renal function has been reported.[89,90]

In 2005, Sackner-Bernstein and his colleagues reported that nesiritide may be associated with an increased risk of death after treatment for acute decompensated heart failure.[91] At about this time, infusions of nesiritide were also being widely performed in outpatient clinics, and the drug came under severe criticism.[92] Ultimately, a randomized controlled trial of nesiritide versus placebo was performed, which demonstrated that serial outpatient nesiritide infusions did not provide a demonstrable clinical benefit over standard therapy.[93] Rapid de-adoption of nesiritide was observed.[94] A large randomized mortality trial of nesiritide for acute heart failure has shown that the role of nesiritide for the treatment of acute decompensated heart failure will likely diminish.

ORAL β-ADRENERGIC BLOCKING DRUGS

There is a fundamental belief that the biologically powerful adrenergic nervous system compensates the failing heart by increasing myocyte size (hypertrophy), heart rate and force of contraction (inotropy). The SNS also activates the RAAS, thus conserving intravascular volume and redirecting blood flow to vital organs. However, an overly active SNS has repeatedly been shown to be essentially toxic to myocardial cells in both animals and humans.[95] There have been numerous large randomized



FIGURES 9A AND B: Changes in pulmonary capillary wedge pressure from baseline in response to intravenous nitroglycerin, nesiritide and placebo in patients with heart failure [*Source:* Modified from Publication Committee for the VMAC Investigators (Vasodilatation in the management of Acute CHF). Intravenous nesiritide vs nitroglycerin for treatment of decompensated congestive heart failure: A randomized controlled trial. JAMA. 2002;287:1531-40, with permission)

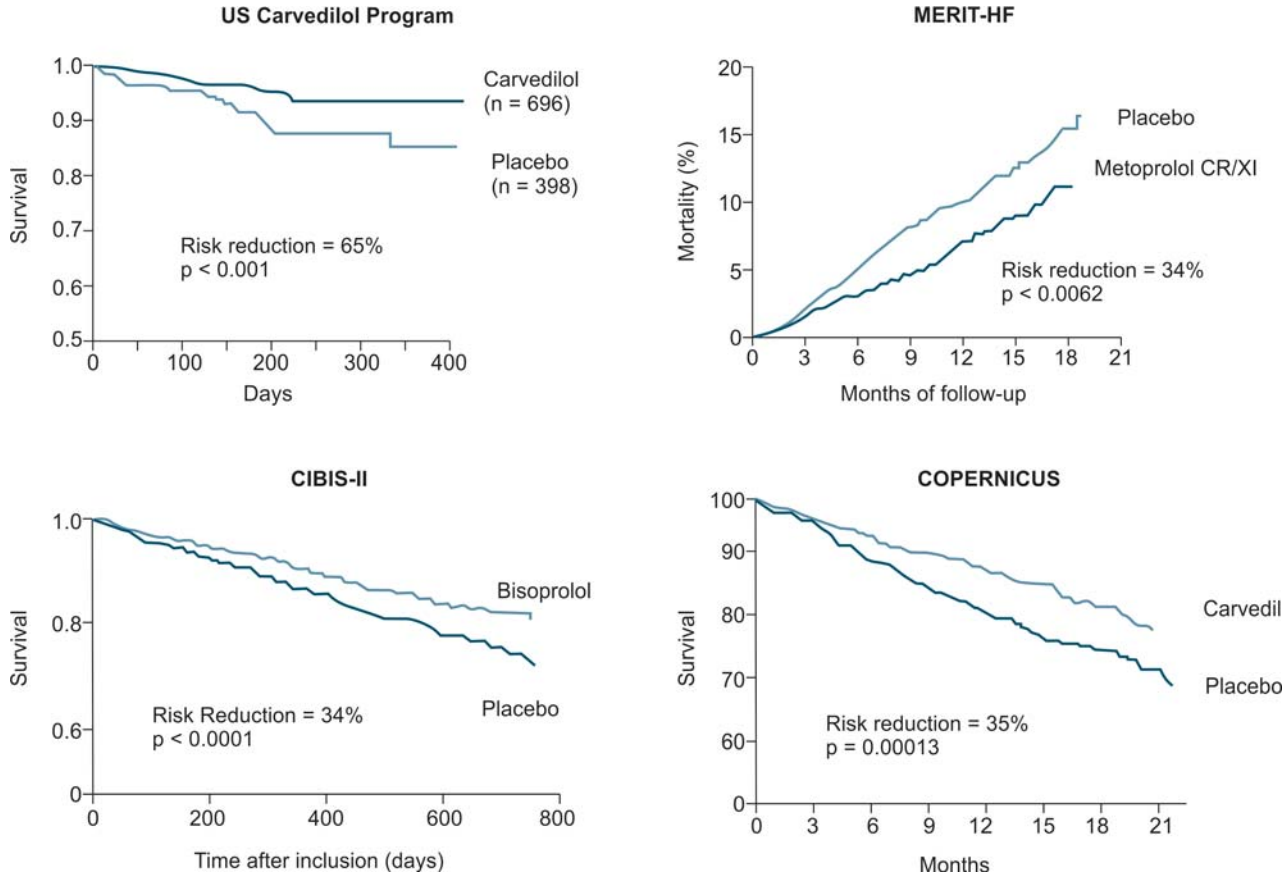


FIGURE 10: Placebo-controlled studies of beta blocker therapy (*Source:* Harry Krum. In: JD Hosenpud, BH Greenberg (Eds). Congestive Heart Failure, 3rd edition. Philadelphia: Lippincott Williams and Wilkins; 2007. pp. 510-20)

trials supporting the concept that blocking the SNS with β-adrenergic blocking drugs in patients with systolic heart failure slows the progression of systolic heart failure and improves patient survival (Fig. 10).

The importance of dysfunctional adrenergic activation in heart failure was first elucidated by the work of Braunwald and his colleagues at the National Institutes of Health in the 1960s.[96] Since then, there has been an enormous basic and clinical research effort testing the rather counterintuitive concept that blocking the β_1- and β_2-adrenergic receptors will benefit patients with systolic heart failure.[97] It is well known that β-adrenergic receptors downregulate in response to excessive sympathetic drive,[98] presumably in an attempt to protect the cardiac myocyte from overstimulation. Such biological behavior suggests that blocking the receptors pharmacologically may also protect the heart.[99] Moreover, pheochromocytoma (a classic example on long-term hyperadrenergic activity) is well known to express itself as dilated or hypertrophic cardiomyopathy.[100] This provides proof of concept that the overly active SNS and its dysfunctional status are central to the pathophysiology of heart failure,[101–104] similar to the overly active RAAS.

The first use of β-adrenergic blockers to treat patients with heart failure was the product of a series of carefully written case reports from Göteborg, Sweden.[105–107] This experience was a source of both great excitement and profound skepticism. Eventually, a small clinical trial [Metoprolol in Dilated Cardiomyopathy (MDC)] was launched, and showed only marginal benefit of metoprolol in patients with heart failure.[108] Other clinical trials were performed using bisoprolol [The Cardiac Insufficiency Bisoprolol Study (CIBIS) and CIBIS II][109,110] and metoprolol succinate [the Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF)].[111] Carvedilol, an α_1 and nonselective β-adrenergic blocker, was also demonstrated to improve survival in patients with moderate and even very severe heart failure [The Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) Trial].[112] Some would argue that the α_1-adrenergic receptor blockade induced by carvedilol provides an additional advantage to the standard β-adrenergic blockade,[113,114] but this has remained controversial. Today β-adrenergic blockers are widely used throughout the world to treat patients with systolic heart failure.[115] They are considered "evidence-based" therapy. The suggested initial dose and evidence-based maximal dose are shown in Table 2.

Although it is unusual nowadays to see patients with heart failure who are naive to either RAAS blockers or β-blockers, occasionally the issue of which class of drug to start first arises. Experience indicates that either RAAS blockers (i.e. ACE inhibitor or ARB) or a β-blocker may be initiated first,[116] but eventually full doses of both classes of drugs should be attempted. The titration schedule of β-adrenergic drugs should be slow, that is over several weeks. The magnitude of heart rate reduction is significantly associated with the survival benefit of β-blockers in patients with systolic heart failure, whereas

the dose of β-blocker is not.[116,117] There is also a strong correlation between change in heart rate and improvement in LV ejection fraction.[118] It appears as though decreased heart rate, improved chamber contractility and afterload reduction each contribute to the improved LV ejection fraction with use of carvedilol.[119]

β-adrenergic blocking drugs are now widely used to treat all stages of heart failure. Some patients admitted to the hospital with NYHA class III or IV systolic heart failure may not tolerate β-blockers because of symptomatic hypotension or low cardiac output, but most hospitalized patients with acute heart failure do tolerate these drugs. The continuation of β-blocker therapy in patients hospitalized with acute decompensated systolic heart failure is associated with lower postdischarge mortality risk and improved treatment rates.[120] Withdrawal of β-blocker therapy in the hospital is associated with a higher risk. β-blocker therapy before and during hospitalization for acute systolic heart failure is associated with improved outcomes.[121] In our experience, the most common documented cause of discontinuance of β-blockers in patients with heart failure is failure to restart β-blockers after they have been stopped during hospitalization.[122]

Not all patients with systolic heart failure improve with β-blocking therapy. One possibility is that functional improvement from β-blockers may be related to changes in myocardial contractile protein gene expression,[123] which could vary from patient to patient. Another possibility is that β-blocking drugs are quite different from each other. Metoprolol and bisoprolol are both β-receptor subtype selective (i.e. β_1). Bucindolol, labetalol and carvedilol are each nonselective, and labetalol and carvedilol have α_1-blocking properties that produce ancillary vasodilation. Bucindolol, although not available, has been intensely studied and has mild vasodilator properties, probably mediated by c-GMP. Additionally, bucindolol has meager "inverse agonism", so there is less negative chronotropism and inotropic effects. Bucindolol can also lower systemic norepinephrine levels substantially in some patients, and therefore has the potential to be a powerful sympatholytic agent. The norepinephrine lowering effects of bucindolol, as well as the clinical response to the drug, are strongly influenced by the presynaptic α_2c-adrenergic receptors, which modulate exocytosis and exhibit substantial genetic variation in humans. It is believed that a α_2c-adrenergic receptor polymorphism affects the sympatholytic effects of bucindolol in patients with systolic heart failure.[124] Patients with the α_2c-Del 322-325 polymorphism appear to have a marked increased in the sympatholytic response to bucindolol, and these carriers exhibit no evidence of clinical efficacy when treated with bucindolol. This concept is consistent with observations from other studies that indicate a marked decrease in plasma norepinephrine levels as a consequence of certain drug therapy, such as moxonidine, is associated with increased mortality and more heart failure hospitalizations. This also seems true with regard to the response to bucindolol where carriers of the α_2c-Del 322-325 variant exhibit very low plasma norepinephrine levels during bucindolol use and a poor response to treatment. The frequency of this genetic variant is ~0.04 in whites and ~0.40 in blacks.

In addition to their favorable effects on LV performance and patient survival, β-adrenergic blockers, like RAAS blockers, slow the progression of LV remodeling. This occurs in patients with heart failure secondary to acute myocardial infarction and in patients with chronic heart failure from dilated cardiomyopathy. LV end-diastolic volume tends to improve the LV becomes less spherical and assumes a more natural ellipsoid shape. Mitral regurgitation is ameliorated or improved, and on an average the LV ejection fraction goes up by about 5–7 ejection fraction units. In some cases there is spectacular reverse remodeling, and in other cases this is less apparent or may not be seen at all. Reverse remodeling of the LV is associated with improved survival. We now have three major heart failure therapeutic strategies aimed at producing reverse remodeling: (1) RAAS blocking drugs; (2) Cardiac Resynchronization Therapy (CRT) and (3) β-adrenergic blocking drugs. Of course, coronary revascularization can also improve LV size and performance in selected patients. These therapies have proven to be the powerful drivers of improved patient survival.

CONCLUSION

Neurohumoral modulating drugs now have a central role in the treatment of patients with systolic heart failure. This was not the case 35 years ago when only digitalis and diuretics were used. Annualized mortality has fallen from ~20% to less than 10% per year commensurate with the use of RAAS and SNS blocking drugs. Of course, ICDs and CRT have also importantly contributed to this mortality reduction. The total cardiovascular death rate burden has fallen substantially in accordance with the widespread use of these therapies. Although, the incidence of ST segment elevation myocardial infarction (STEMI) has also fallen dramatically, incident heart failure continues to increase. There is now much better treatment for hypertension and hyperlipidemia. Paradoxically, as people live longer, we are now seeing a wave of heart failure in the elderly, the fastest growing segment of our population. The scourge of heart failure has not gone away, but has rather been shifted to people in their 70s, 80s and 90s. In the end, prevention of heart failure by lifelong control of known risk factors and mechanistic enlightenment although additional genomic studies may reduce the burden of heart failures even more, as systolic heart failure is likely a largely preventable disorder.

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Chapter 6

Positive Inotropic Drugs

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Chapter Outline

- Intravenously Administered, Short-term Positive Inotropic Therapy
  - Adrenergic Receptor Agonists
  - Phosphodiesterase Inhibitors
  - Other Intravenously Administered Positive Inotropic Interventions
  - Orally Administered Positive Inotropic Agents

INTRODUCTION

Positive inotropic drugs (aka, positive inotropes) are agents that increase the velocity and strength of contraction of the cardiac myocyte and as a consequence, the myocardium and the heart as an organ unit; a few of the measurements of contractility or inotropy include Δ LV systolic upstroke pressure/Δ time, peak slope of LV developed pressure and end-systolic elastance. This chapter will focus on pharmacologic agents used primarily to augment inotropy. While the positive inotropic drugs also increase the amount or magnitude of contraction, this effect can also be attained to a certain extent by various non-inotropic agents (e.g. unloading vasodilating drugs) and thus, is not a unique property of positive inotropes.

Positive inotropic drugs are, therefore, generally directed at patients whose overall cardiovascular function is compromised by loss of cardiac contractility resulting in symptoms and signs of depressed stroke volume, cardiac output, hypoperfusion of vital organs and systems and often, hypotension.

In general, positive inotropes enhance cardiac contractility via modulation of calcium handling by the cardiomyocyte. The cellular mechanisms of action of the major inotropic drugs are illustrated in Figure 1.

Enhancement of cardiac contractility by positive inotropes with consequent improvement of compromised hemodynamics is not achieved without a cost. Unless the agent also possesses substantial cardiac unloading properties (preload and afterload reduction) or substantially evokes other favorable effects (e.g. improvement of autonomic balance), positive inotropes increase the oxygen and metabolic demands of the heart. This unfavorable property is exacerbated by other pharmacologic effects not uncommonly associated with inotropic agents such as positive chronotropy (increase in heart rate), cardiac dysrhythmias and a rise in vascular resistance afterload. These undesirable effects can be particularly troublesome in the setting of occlusive coronary artery disease, where the oxygen metabolic supply can be limited. For these reasons, intravenously administered inotropic therapy should generally be reserved for acute, short-term intervention. Chronic oral inotropic therapy is, thus far, relegated to an agent (currently digoxin) with a mild positive inotropic effect, accompanied by other favorable properties (refer to the digoxin section below). The development of newer inotropic agents to expand these application profiles has, to date, been mired in adverse effects and outcomes.

INTRAVENOUSLY ADMINISTERED, SHORT-TERM POSITIVE INOTROPIC THERAPY

The agents placed under this heading represent a spectrum of pharmacologic properties in addition to their positive inotropic effects. The predominant distinguishing feature among these agents is their effect on vasculature, which can range from vasodilatation to balanced vascular tone to vasoconstriction (Fig. 2 and Table 1). The pharmacologic mechanisms for their positive inotropy center on increasing intracellular cyclic adenosine monophosphate (cAMP) by either adrenergic receptor stimulation or inhibition of cAMP degradation (Fig. 1).

ADRENERGIC RECEPTOR AGONISTS

Although the adrenergic agonists can evoke tachycardia and dysrhythmias, they do have short elimination half-lives, an ideal pharmacologic property in the monitored critical care setting where a quick "turn on" and "turn off" of cardiovascular effects allow immediate and tightly controlled hemodynamic support.

The catechols (3,4-hydroxyphenyl ring) are the major drug group in the adrenergic family used for positive inotropic therapy. The molecular structures of those most commonly employed clinically are shown in Figure 3.

The adrenergic agonists evoke most of their pharmacologic effects through stimulation of beta- and alpha-adrenergic receptors. The myocardium is heavily populated with beta-receptors and to a lesser extent, alpha-receptors; all capable of augmenting cardiac contractility in varying degrees. Stimulation of β_1- and β_2-adrenergic receptors increases the inotropic (and chronotropic) state of the cardiomyocyte via mechanisms shown in Figure 1. Beta-adrenergic receptors are also located in other organs and regions of the body with the β_2-receptor being the

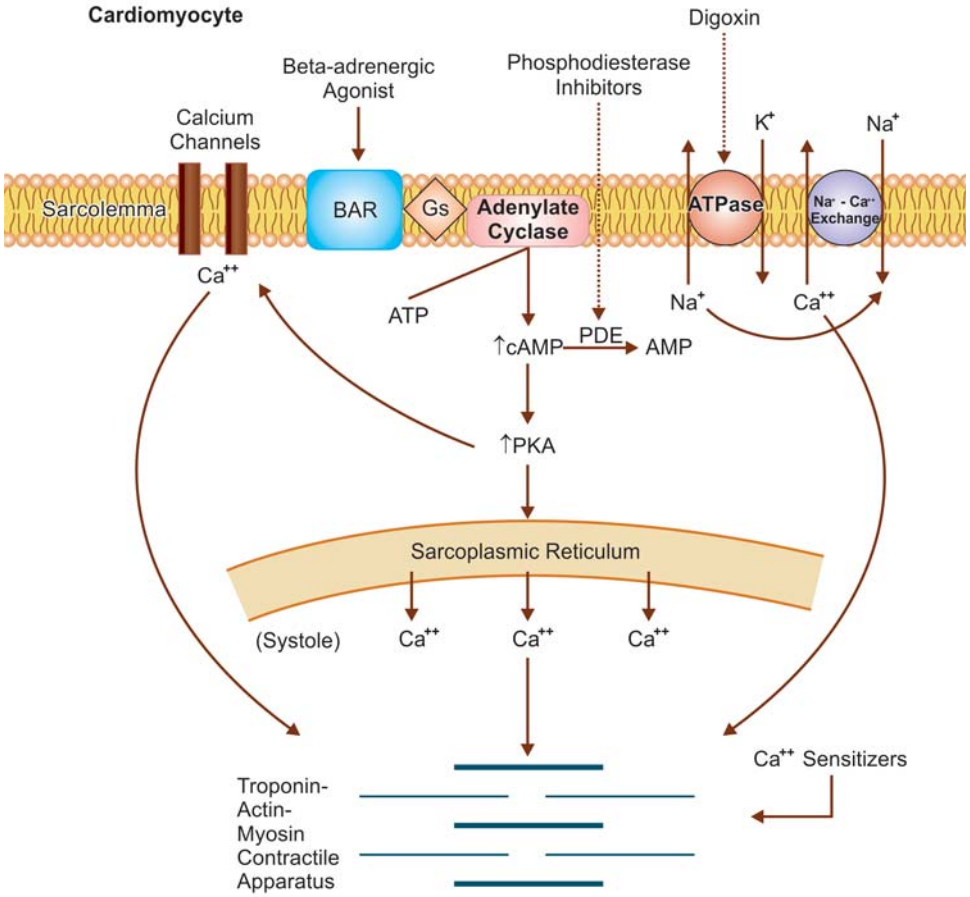


FIGURE 1: The major positive inotropic groups generally act through mechanisms that increase the concentration and availability of intracellular calcium for the actin-myosin contractile apparatus. Beta-adrenergic agonists attach to the beta-adrenergic receptor, activating the Gs protein-adenylate cyclase complex to convert ATP to cAMP. cAMP activates protein kinase A, which phosphorylates several intracellular sites resulting in an influx and release of Ca^{++} for systole. Phosphodiesterase inhibitors retard the breakdown of cAMP. Calcium sensitizers act by making the troponin-actin-myosin complex more responsive to available Ca^{++}. By blocking the Na/K ATPase pump, digoxin increases intracellular Na^{+} loading of the Na^{+}-Ca^{++} exchanger, resulting in less extrusion of Ca^{++} from the myocyte. Dashed arrow indicates inhibition. While this illustration depicts the major pharmacologic actions of these positive inotropic groups, their comprehensive mechanisms are considerably more numerous and complex. (Abbreviations: ATP: Adenosine triphosphate; cAMP: Cyclic adenosine monophosphate; AMP: Adenosine monophosphate; PDE: Phosphodiesterase; BAR: Beta-adrenergic receptor; PKA: Protein kinase A)

TABLE 1

The hemodynamic profiles of the agents currently employed to deliver short-term inotropic and vasoactive support

	Phosphodiesterase Inhibitor	Adrenergic agonists				
		Dopamine				
	Milrinone	Dobutamine	Low dose	Higher dose	Norepinephrine	Phenylephrine
Contractility (inotropy)	↑	↑↑↑	↑	↑↑	→↑	↗
Cardiac output	↑↑	↑↑↑	↑	↑	→↑	↗
Heart rate (chronotropy)	→↑	→↑	→↑	↑↑	→↑	→↗
LV filling pressure	↓↓↓	↓↓	↓	→↑	→↑	→↑
Systemic blood pressure	→↓	→↑	→	↑↑	↑↑↑	↑↑↑
Systemic vascular resistance	↓↓↓	↓↓	→	↑↑	↑↑↑	↑↑↑
Pulmonary vascular resistance	↓↓↓	↓↓	→	→↑	↑	↑

↓ decrease; → minimal to no change; ↗ mild increase; ↑ increase

most ubiquitous, accounting for concomitant vasodilatation and bronchodilatation during β_2-receptor agonism. Alpha-adrenergic receptors are predominantly located in the vasculature, such that their stimulation evokes vasoconstriction in excess of any positive inotropic effect. The cardiovascular effects of adrenergic agents used clinically for inotropic and hemodynamic support are individually presented under the heading of each and summarized in Table 1.

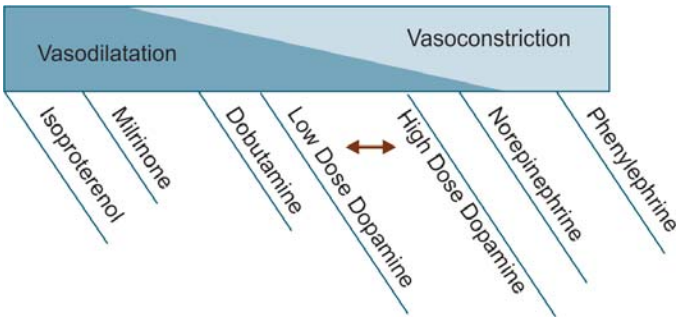


FIGURE 2: The spectrum of net vascular properties of the agents currently available for short-term positive inotropy and cardiovascular support. The vascular effects and responses are a major determinant for selection in individual patients

Dobutamine

Dobutamine is presented first because at this time, it is the agent most commonly used for short-term intravenous inotropic support and its net cardiovascular effects in the setting of left ventricular systolic failure result predominantly from positive inotropic enhancement of depressed cardiac contractility.

Dobutamine was developed from methodical manipulation and substitutions on the basic catechol-phenylethylamine molecule.[1] Out of over 15 molecules formulated and then tested in the animal model, dobutamine achieved the greatest augmentation of cardiac contractility and performance with the least net vasoactivity and chronotropy.

Dobutamine, a racemic compound (+ and – enantiomers), activates myocardial β_1- and β_2-adrenergic receptors and, via cAMP and the downstream mechanisms depicted in Figure 1, increases the velocity and extent of myocardial contraction. In chronic heart failure, the number and inotropic responsiveness of β_1-receptors are reduced[2] such that dobutamine's cardiac effects in this clinical setting are, in large part, rendered by agonism of β_2-receptors. Beta-receptor stimulation also accounts for the chronotropic properties of dobutamine.

In the setting of systolic heart failure, dobutamine generally evokes a mild net vasodilatory effect, reducing vascular resistance, through arteriolar β_2-receptor stimulation exceeding the modest vasoconstricting effects of its alpha-receptor agonism. Studies by Binkley and his colleagues[3–5] indicate that the cardiovascular pharmacology of dobutamine in human heart failure is considerably more complex. Dobutamine's favorable effects on aortic impedance and vascular-ventricular coupling allow further enhancement of ventricular contractility and performance.[4,5] In the total artificial heart model (calf), dobutamine increases cardiac output in the absence of myocardium and positive inotropic mechanisms.[5] This response is likely rendered by the vascular properties of dobutamine; its dextro-isomer (+enantiomer) reduces systemic vascular resistance and afterload via β_2-receptor stimulation and its levo-isomer (–enantiomer) reduces venous capacitance with enhanced venous return via alpha-receptor agonism.[5,6]

The major clinical indication for dobutamine administration is short-term inotropic support in patients compromised by ventricular systolic dysfunction, which has resulted in a problematic reduction in blood pressure and systemic perfusion (Table 2). "Short-term" until the patient recovers adequately or

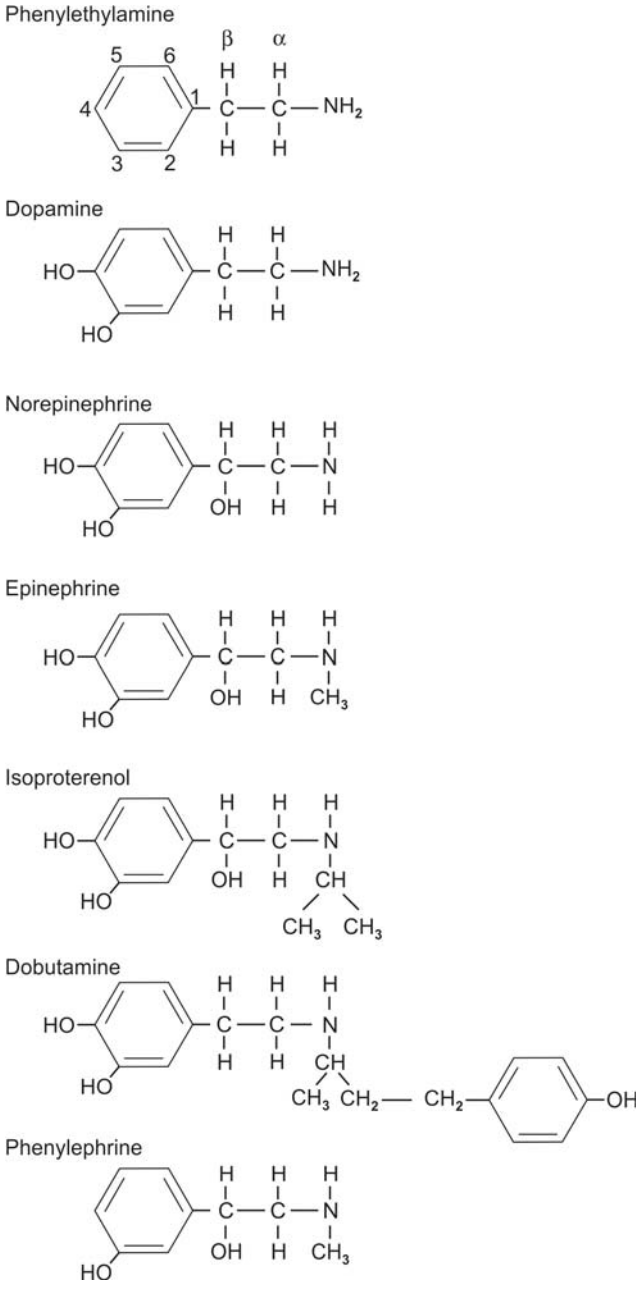


FIGURE 3: The phenylethylamine molecule is the basic structure for the adrenergic compounds under discussion. Variations in the hydroxyl attachment at the β site and the groups at the amino end determine the pharmacologic properties and consequent clinical applications of the catechols. Very little modification of the molecular structure is needed to change a strong vasodilator (isoproterenol) to a strong vasopressor (norepinephrine). Deletion of the 4-hydroxyl group from the epinephrine molecule results in phenylephrine, a powerful vasoconstrictor

is moved into more advanced interventions (e.g. mechanical support, remedial cardiac surgery). The typical patient presents with decompensated chronic or acute systolic heart failure, reduced stroke volume and cardiac output, elevated ventricular filling pressures, mild-to-moderate reduction in systemic blood pressure (systolic blood pressure 70–100 mm Hg) and impaired systemic perfusion (e.g. prerenal azotemia, elevated liver enzymes, impaired mentation); the clinical setting of "cold and wet".[7] The non-inotropic spectrum of intervention in this general clinical setting can include diuretics for volume overload and

TABLE 2

The clinical applications of dobutamine administration

Major indication:

Short-term (hours to days) inotropic and hemodynamic support for patients with ventricular systolic dysfunction resulting in a depressed stroke volume and cardiac output, systemic hypoperfusion, mild-to-moderate systemic hypotension (systolic blood pressures of 70–100 mm Hg) and an elevated left ventricular diastolic filling pressure (> 18 mm Hg). This support is maintained until the patient recovers or is directed into more advanced cardiovascular support (e.g. intra-aortic balloon counterpulsation, ventricular assist device) and/or remedial intervention (e.g. coronary artery intervention, valvular repair or replacement, cardiac transplantation).

Additional considerations:

A. Pharmacologic support as needed for patients with severe heart failure undergoing major diagnostic or surgical procedures
B. Cardiovascular hemodynamic support for the heart failure patient through the course of a major illness
C. Pharmacologic bridge in severe heart failure to standard therapies (e.g. angiotensin-converting enzyme inhibitor, beta-adrenergic blocker)
D. As a continuous infusion via indwelling central venous catheter to provide the only means of stabilizing an unstable or decompensated heart failure patient to allow discharge from the hospital (to extended care, home or hospice)
E. For hemodynamic support during weaning from cardiopulmonary bypass and during recovery from cardiac surgery
F. To facilitate recovery of myocardial stunning in the setting of low output cardiac failure
G. As a means of improving renal function and urine output in patients hospitalized for low output, systemic hypoperfusion and volume-overloaded congestive heart failure when renal responsiveness to standard therapy and diuretics is impaired
H. For hemodynamic support during management of cardiac transplant rejection complicated by hemodynamic decompensation
I. To augment systolic function of problematic systolic failure of the right ventricle
J. To assess ventricular (right or left) contractile reserve
K. To evaluate the severity of low-flow, low-gradient aortic valvular stenosis
L. As pharmacologic stress for myocardial perfusion imaging

elevated ventricular filling pressures (> 18 mm Hg), vasopressor infusion (e.g. moderate- to high-dose dopamine, norepinephrine, phenylephrine) for marked hypotension and shock, and inodilator or vasodilator therapy (e.g. milrinone, nitroprusside, nitroglycerin,) for patients with systemic systolic blood pressure more than 90–100 mm Hg. It is not unusual to administer two of these agents simultaneously to achieve and maintain optimal clinical and hemodynamic stability on the way to more definitive intervention.

In the appropriate patient, namely the patient with ventricular systolic dysfunction resulting in a fall in stroke volume and cardiac output, an elevation in left ventricular end-diastolic filling pressure, systemic hypoperfusion and mild-to-moderate reduction in systemic blood pressure, dobutamine increases stroke volume, cardiac output, systemic systolic blood pressure and pulse pressure, and systemic perfusion, while decreasing pulmonary and systemic vascular resistance and left ventricular filling pressure[8–10] (Fig. 4). In patients with concomitant mitral regurgitation, the decrease in systemic vascular resistance, ventricular volume and mitral orifice area likely accounts for the reduction in mitral regurgitation with additional augmentation of stroke volume and cardiac output during dobutamine administration.[10] While there appears to be a dose-related separation of positive inotropy and beneficial hemodynamic effects from positive chronotropy, higher dosing will evoke a faster heart rate and can provoke ectopic beats and tachydysrhythmias[8] (Fig. 4).

Regional blood flow studies in patients with decompensated chronic heart failure revealed that dobutamine increases limb blood flow proportional to any increase in cardiac output with a less predictable augmentation in renal blood flow and no statistical change in hepatic-splanchnic flow.[11] Dobutamine favorably affects renal function, glomerular filtration rate and urine output.[8]

In patients with ventricular systolic dysfunction and patent coronary arteries, dobutamine increases coronary blood flow proportional to or greater than the increase in cardiac output and myocardial oxygen consumption.[12,13] This favorable effect on myocardial energetics is likely related to several mechanisms, including dobutamine-induced increase of coronary perfusion pressure (drop in left ventricular diastolic pressure more than the reduction in systemic diastolic pressure) and coronary diastolic perfusion time and a reduction in coronary vascular resistance.[8,12–14] The decrease in systemic and pulmonary vascular resistance, ventricular systolic (+diastolic) volume and ventricular afterload with dobutamine reduces myocardial oxygen consumption. Positive inotropy by itself generally causes an increase in myocardial oxygen consumption. At doses short of provoking a clinically significant rise in heart rate (> 10% above baseline), the coronary blood flow and myocardial oxygen delivery are equal to or exceeds the increase in myocardial oxygen consumption evoked by the positive inotropic effects of dobutamine.[12,13] However, these favorable coronary-myocardial energetic properties of dobutamine can be disrupted in the setting of occlusive coronary artery disease, whereby fixed obstructive lesions can prevent augmentation of coronary blood flow to match the rise in contractility and oxygen consumption. Any substantial elevation in the heart rate imposes a particular threat to coronary perfusion and the balance of oxygen demand and delivery by increasing myocardial oxygen consumption without an increase (or even a decrease) in coronary flow through shortening of the coronary diastolic perfusion time.[14] The positive chronotropic (in addition to inotropic) effect of high-dose dobutamine is now regularly employed during dobutamine stress myocardial imaging to elicit evidence of ischemia in patients with suspected occlusive coronary artery disease.

The chronotropic properties are of extreme importance in all patients, but particularly in patients with occlusive coronary disease where tachycardia will overtake the aforementioned favorable coronary-myocardial effects to provoke myocardial ischemia. For these reasons, proper patient and dose selection is of marked importance in patients with ventricular systolic dysfunction and occlusive coronary artery disease. Using these pharmacotherapeutic considerations as a guide, dobutamine can be safely administered to heart failure patients with occlusive coronary disease to attain and maintain a stable clinical and hemodynamic short-term course until the patient is directed to more advanced management (e.g. intra-aortic balloon counterpulsation, coronary angiography and intervention, coronary bypass surgery).[15–22] During this short-term "pharmacologic bridge", dobutamine, for safe effective therapy, has to

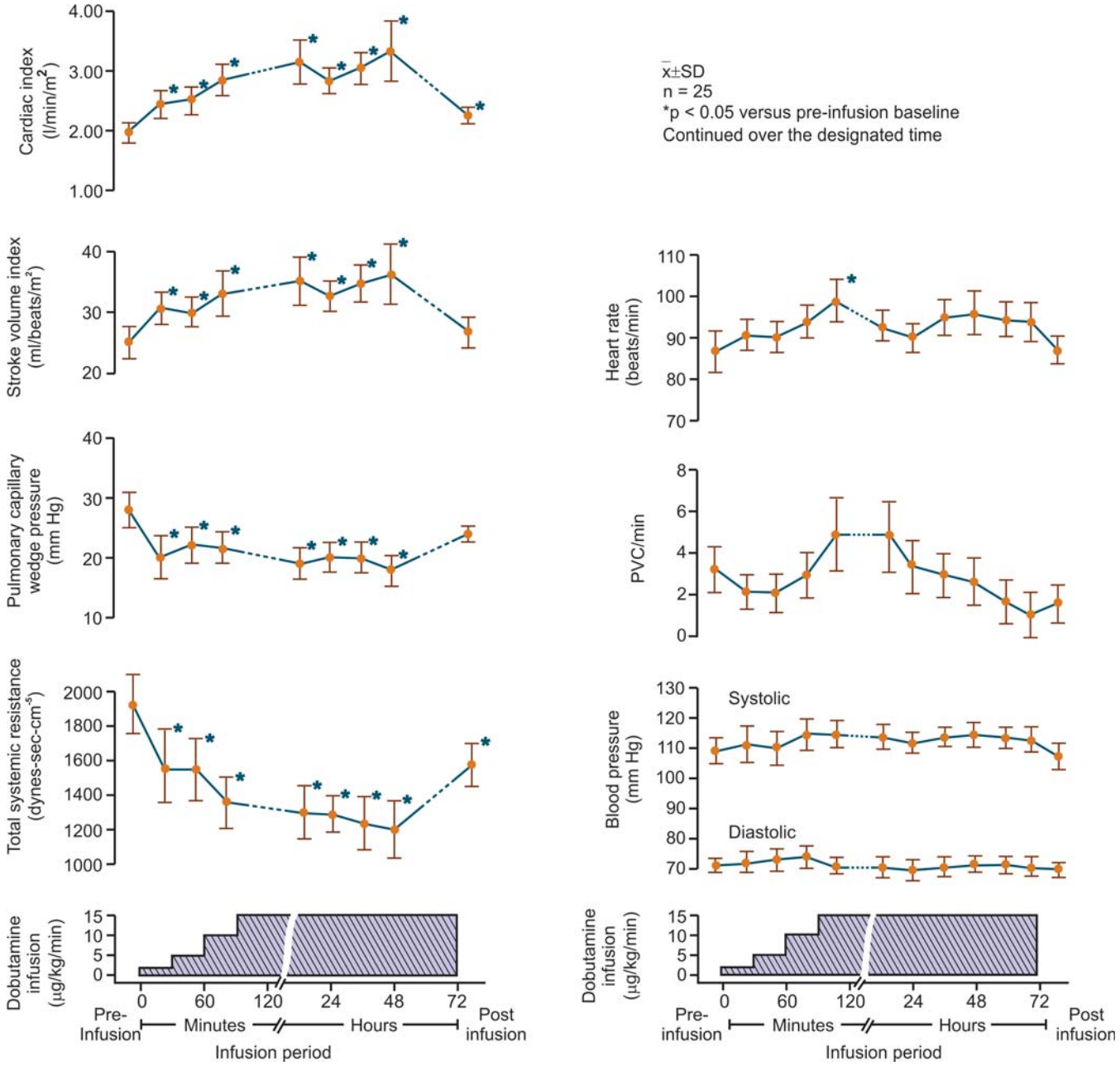


FIGURE 4: Pharmacodynamic curves for the dose-response and sustained infusions (72 hours) of dobutamine in chronic low output congestive heart failure. The infused dose is presented in the bottom panel (*Source:* Modified from reference 8, with permission)

be able to favorably affect the determinants of oxygen metabolic consumption and delivery (reduce elevated ventricular diastolic pressures, vascular resistance, ventricular volume and wall stress and increase coronary perfusion pressure and time) equal to and greater than the rise in myocardial oxygen consumption of positive inotropy. Nevertheless, even with proper patient and dose selection, some patients with occlusive coronary artery disease can develop myocardial ischemia + infarction during dobutamine administration.[16–18]

Dobutamine may have a favorable effect on myocardial stunning beyond the simple increase in coronary blood flow and myocardial perfusion of the affected region or whole heart.[23–25]

Clinical indications and applications: The most common clinical scenarios for appropriate dobutamine administration (to improve and stabilize hemodynamic and clinical status) include patients managed for decompensated, hypoperfused, often hypotensive chronic systolic heart failure, acute systolic heart failure (e.g. acute myocardial infarction, acute myocarditis), or immediately following cardiac surgery + cardiopulmonary bypass. The various considerations for the administration of dobutamine are presented in Table 2.

Administration and dosing: Although the usual dose range for dobutamine is 2.0–15.0 mcg/kg/min, many patients can experience clinical and hemodynamic benefit at a lower starting dose of 0.5–1.0 mcg/kg/min and do so with minimal to no increase in heart rate or dysrhythmias. Dosing can be advanced by 1.0–2.0 mcg/kg/min increments every 12–15 or more minutes until the desired clinical and hemodynamic effects are attained, but short of increasing heart rate more than 10% above baseline,

provoking dysrhythmias or eliciting side effects. In the absence of beta-adrenergic blockade, the inability to improve hemodynamics, stroke volume, cardiac output and clinical parameters in symptomatic systolic heart failure during incremented dobutamine infusion rates up to 15 mcg/kg/min portends a poor prognosis.[8]

Once the decision is made to discontinue the dobutamine infusion, maintenance doses of less than or equal to 2.0 mcg/kg/min can usually be stopped without difficulty. Higher infusion rates over an extended period generally require weaning over 12–72 hours to avert clinical and hemodynamic deterioration with more abrupt discontinuation.[8,26] Prolonged, higher dose infusions in patients treated for decompensated chronic systolic heart failure often require a longer weaning period or incremental oral dosing of hydralazine to achieve withdrawal of dobutamine without difficulty.[26] Although tolerance can occur to a mild-moderate degree during a prolonged continuous infusion, it is generally not enough to facilitate weaning.[27]

The pharmacokinetic and pharmacodynamic properties of dobutamine endorse its application as a short-term positive inotropic agent. In heart failure patients, its half-life averages 2.37 + 0.07 minutes[28] indicating that steady state for any dose is achieved in about 12–13 minutes, an invaluable characteristic if positive inotropy is urgently needed. And most of the drug is eliminated within 12–13 minutes upon discontinuation of the infusion, allowing a rapid dissipation of adverse effects if encountered during the infusion. In human heart failure, there is a direct near-linear relationship between the infusion dose of dobutamine, its plasma levels and hemodynamic responses[29] (Fig. 5).

Concomitant administration of a phosphodiesterase inhibitor (e.g. milrinone) enhances the inotropic effect of dobutamine by retarding the breakdown of intracellular cAMP generated by dobutamine.[30] The inotropic and hemodynamic effects of dobutamine are predictably blunted in patients receiving beta-adrenergic blocking agents, particularly the nonselective adrenergic blockers (e.g. carvedilol);[31,32] this interaction can be readily overcome with incremental dosing of dobutamine,[33] which competitively replaces the adrenergic blocker at the receptor site. It is usually not necessary to replace dobutamine with a non-adrenergic agent (e.g. milrinone) in most of these patients.

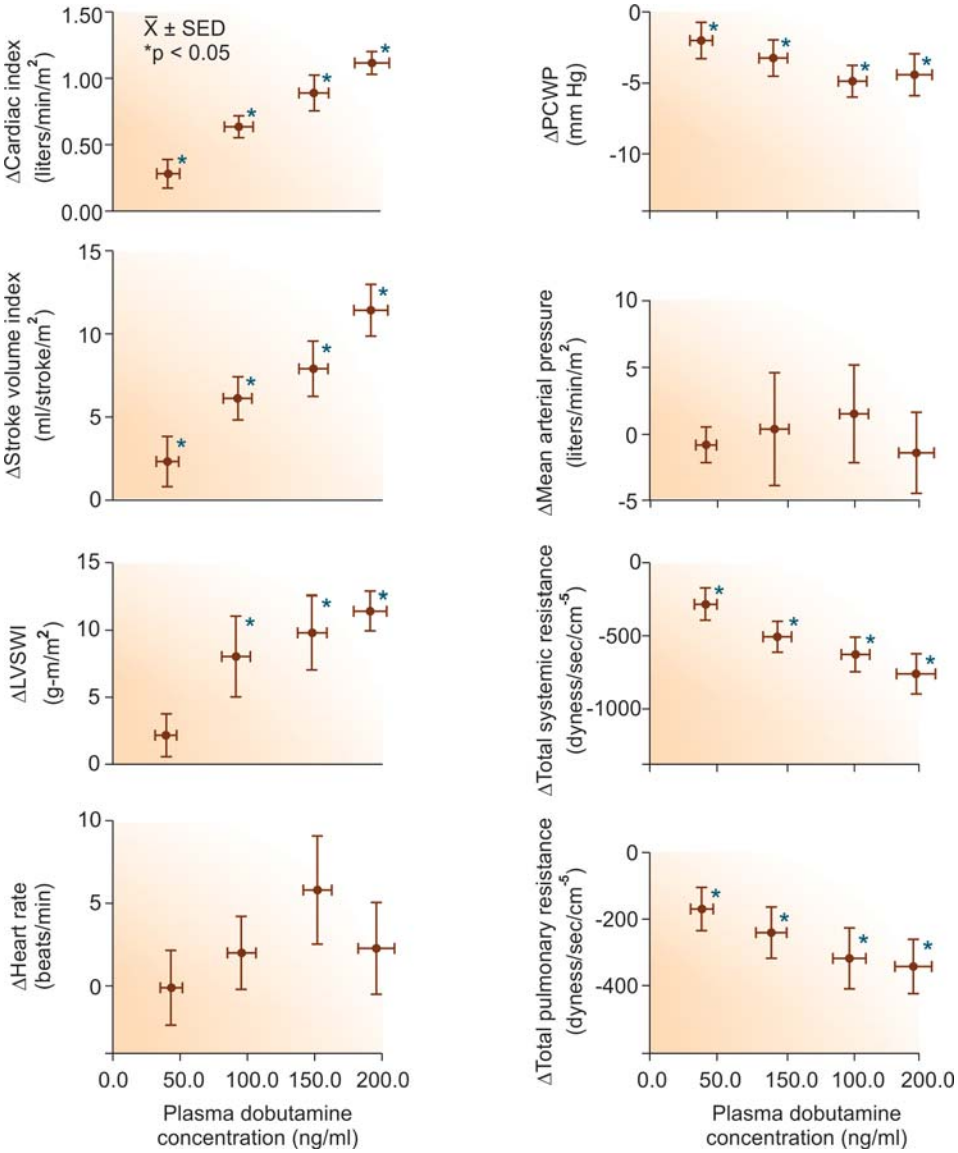


FIGURE 5: Graphs depicting the relationship of dobutamine infusion dose, plasma concentration and hemodynamic effects in patients with moderate-to-severe heart failure. The infusion rates for the 4 data points of each graph are 2.5, 5.0, 7.5 and 10.0 mcg/kg/min incremented every 20–30 minutes. Key: Δ: Change in; LVSWI: Left ventricular stroke work index; *: Indicates a significant change from baseline. (*Source:* Modified from ref 29)

Adverse and undesirable effects: The most common adverse effects of dobutamine are tachycardia and dysrhythmias. From comparative studies and registries, it is clear that improper patient and/or dose selection will evoke sinus tachycardia, atrial and ventricular dysrhythmias, other undesirable effects and adverse clinical outcomes.[34–37] In retrospective studies, the apparent dobutamine-induced adverse effect on outcomes is largely attributable to its administration in a more ill and compromised patient population than that served by the comparator.[37–39] Nevertheless, these reports[34–39] serve to emphasize the importance of proper patient, drug and dose selection.

Other side effects, also generally dose related, include headache, tremor, anxiety, palpitations and nausea. A hypertensive response (elevated systemic systolic blood pressure) can be observed when dobutamine is administered to patients with a history of systemic hypertension or peripheral vascular disease. Patients with high-grade occlusive coronary artery disease can experience angina, myocardial ischemia and infarction, particularly in patients who don't meet the primary indication for use (Table 2) and/or receive excessive initial dosing or excessively rapid advancement of dose. Dobutamine infusions can lower plasma potassium concentrations.[40] Less common side effects include generalized erythema/flushing, eosinophilia and hypersensitivity myocarditis;[41,42] reactions likely related to a bisulfite adjuvant. Dobutamine has been reported to induce stress cardiomyopathy (aka, Takotsubo cardiomyopathy) in patients undergoing pharmacologic stress testing with this agent.[43]

Dopamine

While dopamine, an endogenous precursor of epinephrine and norepinephrine, is the simplest molecule of the adrenergic agents, it has the most complex pharmacology (Figs 2 and 3 and Table 1). In general, dopamine elicits its pharmacodynamic effects through stimulation of dopaminergic receptors (D_1 and D_2) and adrenergic receptors (β_1, β_2 and α) and through the neuronal release and reduced neuronal uptake of endogenous norepinephrine.[44–46] At lower infusion rates (< 4.0 mcg/kg/min) in human heart failure, dopamine behaves as a mild vasodilator (dopaminergic), particularly of visceral and renal arterial-arteriolar vascular beds. With increased dosing, this effect is overtaken by dopamine's agonism of adrenergic receptors directly and through its release of norepinephrine from nerve endings; vasodilatation gives way to a net-balanced vascular effect and some positive inotropy at moderate dosing (4.0–8.0 mcg/kg/min) and to considerable vasoconstriction and some retained inotropy at higher doses (> 8.0 mcg/kg/min).

In states of low cardiac output, systemic hypoperfusion, and adequate or elevated left ventricular filling pressures, dopamine at less than 4.0 mcg/kg/min can augment ventricular contractility, stroke volume and cardiac output, and reduce systemic and pulmonary vascular resistance; all to a modest degree without a substantial change in systemic blood pressure.[11,47–50] As infusion rates move to more than 4.0 mcg/kg/min, vascular resistance, stroke volume and cardiac output plateau and there occurs a substantial dose-related rise in systemic blood pressure. Positive chronotropy and provocation of dysrhythmias are also dose related and can become an undesirable effect at more than or equal to 6.0 mcg/kg/min. Ventricular filling pressure can drop in some patients, but generally does not change or can increase with higher dosing. Indices of ventricular contractility (positive inotropy) are blunted at higher dosing and during continuous infusion,[11] presumably secondary to the rise in blood pressure, vascular resistance and ventricular afterload and depletion of myocardial norepinephrine stores from dopamine-induced release (and reduced uptake) at nerve endings during high-dose or prolonged infusions.

The vasoconstricting properties of moderate to high doses of dopamine are employed clinically to increase and stabilize systemic blood pressure in cardiogenic or vasodilatory (e.g. septic) hypotension and shock.[51–55] This clinical application predominates over its use as a primary inotropic agent and represents its principal indication (vasopressor). Interestingly, the results of a recently performed multicenter trial on shock showed that dopamine offers little advantage over norepinephrine and may even be less effective in the cardiogenic subgroup.[55] (see Norepinephrine on the next page).

Much of the appeal for dopamine administration in problematic hypotension and shock emanates from what are believed to be favorable dopaminergic renal effects. It has been shown that dopamine, particularly at lower doses (< 5.0 mcg/kg/min), can augment renal blood flow equal to or greater than the percentage increase in cardiac output.[11,56–58] Whether this augmentation in renal blood flow evokes an increase in glomerular filtration rate, natriuresis and diuresis in heart failure, hypotension or shock remains controversial and burdened by conflicting published results.[11,47,56–61]

The most common adverse effects of dopamine administration are similar to those of dobutamine, namely positive chronotropy and dysrhythmias, both dose related.[11] Dopamine crosses the blood-brain barrier to provoke nausea and vomiting in some patients. Intense vasoconstriction by dopamine can lead to ischemia of digits and various organ systems. Subcutaneous infiltration at the infusion site can provoke pain and ischemic changes, potentially reversible with local instillation of phentolamine. Dopamine has been reported to depress minute ventilation in heart failure.[62]

Other Adrenergic Agents

These agents are used in various clinical settings for various indications. Due to over-riding vascular effects, they are not employed as primary positive inotropic drugs.

Isoproterenol: This drug is perhaps the purest beta-adrenergic receptor agonist (β_1 and β_2) available for clinical use. However, its positive inotropic properties are largely overshadowed by strong vasodilatory and positive chronotropic effects (Table 1). Its principal clinical application is rather narrow, namely to increase heart rate in the short term (until recovery or definitive intervention) in patients with problematic bradycardia or inadequate heart rate response; particularly in clinical situations where intravenous atropine is contraindicated, inadequate or ineffective. In view of other available, generally safer vasodilating agents (e.g. milrinone, nesiritide, nitrates), isoproterenol is rarely used as a primary vasodilating agent. Adverse effects

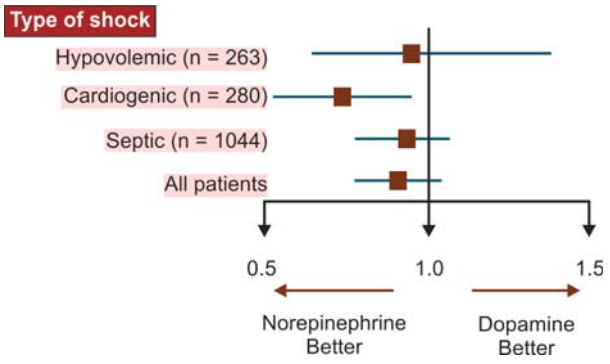


FIGURE 6: A forest plot showing the hazard ratio (± 95% confidence intervals) of norepinephrine versus dopamine support during shock management of the three major shock subgroups studied. While there were no differences between the two treatments for all shock patients combined or for septic and hypovolemic subgroups, the hazard ratio of the cardiogenic shock subgroup favored norepinephrine over dopamine based on dysrhythmic events during treatment and mortality at 28 days following the shock episode (*Source:* Modified from reference 55)

include flushing, tremor, anxiety, tachycardia, dysrhythmias and hypotension.

Epinephrine: This endogenous catecholamine stimulates β_1, β_2 and α_1 adrenergic receptors. Epinephrine differs from dobutamine in that its administration is modulated by neuronal uptake and its β_2 and α_1 effects are more intense than those of dobutamine. In cardiovascular medicine, epinephrine is most often employed during cardiopulmonary resuscitation or as a global hemodynamic support drug during withdrawal for cardiopulmonary bypass and recovery from cardiac surgery. Adverse effects include those described above for dobutamine, dopamine and isoproterenol.

Norepinephrine and phenylephrine: These agents are predominant α_1-adrenergic agonists with mild beta-receptor agonism and thus, they are viewed as vasopressors (Fig. 2 and Table 1). As such, these compounds are used for vasoconstriction to increase and stabilize systemic blood pressure in states of marked hypotension and shock (vasodilatory and cardiogenic).[55,63] The results of a large multicenter trial (1,679 patients) conducted in Europe on the treatment of shock states showed no difference in overall mortality at 28 days (primary endpoint) between dopamine and norepinephrine when used to stabilize blood pressure and clinical status.[55] However, for comparable blood pressure responses, dopamine appeared to be more chronotropic and arrhythmogenic. In the cardiogenic subgroup of 280 patients, the 28-day survival outcome favored norepinephrine as the preferred stabilizing vasopressor[55] (Fig. 6).

Norepinephrine dosing in hypotension and shock generally ranges 0.02–0.40 mcg/kg/min. In addition to the adverse effects described for dopamine, norepinephrine can evoke dose-related systemic hypertension and bradycardia.

More intense vasoconstriction with minimal positive inotropy is rendered by phenylephrine.

PHOSPHODIESTERASE INHIBITORS

Drugs under this grouping are often referred to as "inodilators" because vasodilation is a major component of their pharmacology. In fact, amrinone, studied early in this category, is principally a vasodilator with little to no ability to augment ventricular contraction beyond its unloading effects on the ventricle.[64–66] Thrombocytopenia during prolonged administration tempered its clinical application. As a therapeutic modality, amrinone has largely been replaced by milrinone.

Milrinone

While milrinone can elicit some positive inotropy through other cellular mechanisms (e.g. activation of the calcium release channel), its cardiovascular effects are principally rendered through inhibition of Phosphodiesterase III (PDE III) with consequent impairment of the breakdown metabolism of cAMP[67] (Fig. 1).

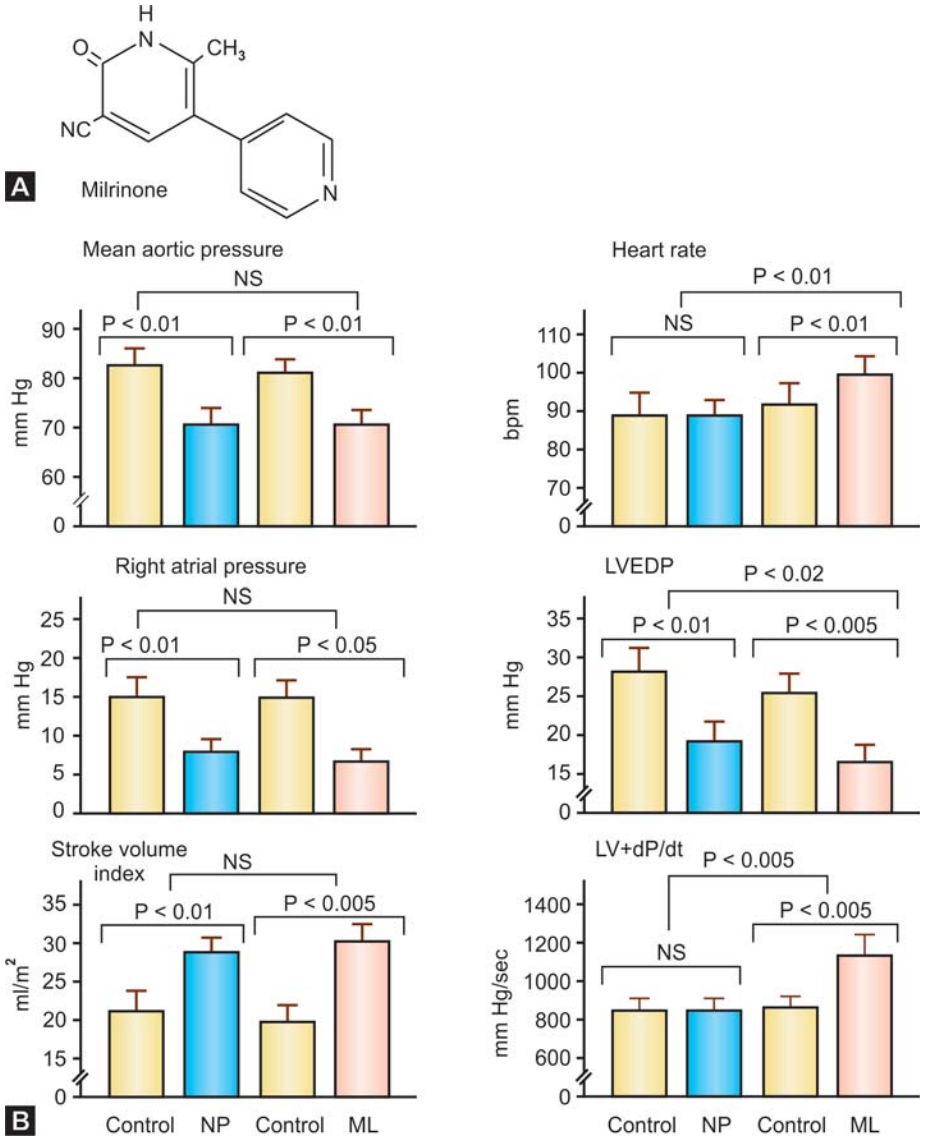
In contrast to dobutamine, a positive inotrope with mild vasodilating properties, milrinone is a vasodilator with mild positive inotropic properties. Therefore, for any matched degree of enhanced contractility, milrinone evokes a greater reduction in pulmonary and systemic vascular resistance, systemic blood pressure and ventricular filling pressures[68–73] (Figs 7A and B). As a vasodilator, proper dosing of milrinone can improve hemodynamics with little to no increase in myocardial oxygen consumption.[73,74] Its ability to lower pulmonary vascular resistance and pressure makes it a favorable agent for augmentation of central hemodynamics in patients with elevated pulmonary artery pressures.[71,72] Bolus milrinone has become one of the vasodilating agents used to determine reversibility of pulmonary hypertension in patients with advanced heart failure under evaluation for cardiac transplantation.[75,76]

In patients with severe low output congestive heart failure, milrinone augments the hemodynamic effects of dobutamine and vice versa. It is not unusual to employ this combination in patients with markedly compromised hemodynamics, generally in the setting of advanced, end-stage heart failure, as a pharmacologic bridge to placement of a ventricular assist device and/or cardiac transplantation. Parenthetically, without these advanced interventions, the requirement for this drug combination to clinically stabilize the patient portends a poor outcome.

Since, milrinone does not act through adrenergic receptors, it can augment hemodynamics in patients on beta-adrenergic antagonists; this is particularly important for the nonselective beta-blockers (e.g. carvedilol), which competitively interfere with low-dose dobutamine.[77]

While vasodilatation is a favorable property of milrinone when administered properly to the appropriate patient, vasodilation also renders its limitations. This agent is generally not employed in patients with systemic systolic blood pressure less than 90 mm Hg and thus, milrinone is not a first-line agent for the management of low output hypotension or shock. Extensive vasodilatation, hypotension and its cellular PDE III inhibition can elevate heart rate and provoke dysrhythmias.[78] Some patients experience a generalized warmth and flushing at moderate-to-high infusion rates or during bolus administration. Fluid retention is not uncommon during continuous infusions.[78]

Milrinone is generally started at 0.20–0.30 mcg/kg/min and gradually advanced as needed to achieve the intended hemodynamic and clinical endpoints and short of evoking tachycardia, dysrhythmias or hypotension. Milrinone has a half-life of



FIGURES 7A AND B: (A) The molecular structure of milrinone. (B) Comparison of the hemodynamic effects of milrinone (ML) at the maximal dose administered and nitroprusside (NP) at the dose selected to match the reduction in mean aortic pressure by milrinone. For comparable ventricular unloading, milrinone evoked positive inotropy (increased + dP/dt—change in LV developed systolic pressure over change in time) and positive chronotropy. (Abbreviations: LVEDP: Left ventricular end-diastolic pressure; NS: Not statistically significant). (*Source:* Modified from reference 69)

1–3 hours[79,80] and thus, the onset of action and equilibration is not as prompt as that seen with the catechol inotropes. Although infrequently required, an initial bolus dose of 20–80 mcg/kg infused over 10–15 minutes accelerates the onset of action in situations where a more rapid effect is needed.[81] The lengthy elimination half-life (1–3 hours) results in a more prolonged recovery from adverse effects once milrinone is discontinued. Some pharmacodynamic tolerance can occur with prolonged administration.

OTHER INTRAVENOUSLY ADMINISTERED POSITIVE INOTROPIC INTERVENTIONS

A number of additional pharmacologic interventions are known to enhance myocardial contractility.

Calcium Sensitizers

Calcium sensitizers (e.g. levosimendan) augment cardiac contractility by modulating intracellular mechanisms of contraction at the same concentrations of intracellular calcium (Fig. 1).

Levosimendan: Although some of its positive inotropic effect is probably rendered through phosphodiesterase inhibition, levosimendan is reported to enhance myocardial contractility through sensitization of the contractile apparatus to available calcium by increasing or stabilizing calcium binding to troponin C.[82,83]

Levosimendan behaves as an inodilator in human heart failure; it reduces vascular resistance and ventricular filling pressures, and by unloading the ventricle and some positive inotropy, it augments stroke volume and cardiac output.[84–87] Compared to dobutamine, levosimendan predictably causes a greater reduction in systemic blood pressure and B-type natriuretic peptide during infusions, but with identical all-cause mortality and comparable secondary clinical outcomes at 180 days postinfusion.[86] As a predominant vasodilator, levosimendan should theoretically have a favorable effect on myocardial energetics and oxygen balance; although this consideration has not been adequately studied in human systolic heart failure. For patients on nonselective adrenergic blockers (e.g. carvedilol), levosimendan can render its hemodynamic effects without having to compete for adrenergic receptors.[88] Because of its

prominent vasodilating properties, levosimendan should not be considered a first-line drug for low output hypotension or shock.

Levosimendan itself has an elimination half-life of 1–2 hours, but a primary active metabolite (OR-1896) has a half-life of more than 75 hours. A sustained hemodynamic effect long after the infusion, which stopped may be favorable in some instances, but when accompanied by tachycardia, dysrhythmias, hypotension or other undesirable effects, the lengthy and somewhat unpredictable elimination is a shortcoming, particularly in critical care.

Levosimendan is available for clinical use in some countries of Europe, Asia and South America.

Additional Intravenously Administered Positive Inotropes

Preliminary studies of istaroxime, an inhibitor of sarcolemmal Na/K ATPase and activator of calcium ATPase of the sarcoplasmic reticulum, show promise as an agent to enhance cardiac systolic and diastolic performance.[89]

Intravenously administered thyroxine or triiodothyronine can improve hemodynamics and blood pressure with a reasonable safety margin, even in patients with advanced, end-stage heart failure and cardiogenic shock.[90,91] Historically, intravenously administered glucagon has been used to augment myocardial contractility in patients with low output hypotension or shock refractory to adrenergic stimulation or treated with moderate to high doses of beta-adrenergic blocking agents.

ORALLY ADMINISTERED POSITIVE INOTROPIC AGENTS

Oral inotropes have not fared well over the past two decades as intervention to improve myocardial contractility and performance. While digitalis (currently digoxin) has been used for over 200 years to treat cardiac failure and "dropsy", this coveted role has been reined in by the Digitalis Investigation Group (DIG) trial published in 1997.[92] Many orally administered, non-digitalis agents have been formulated over the past four decades to replace digoxin in the therapeutics of human heart failure; examples include amrinone, milrinone, vesnarinone, pimobendan and butopamine. But all were found to be ineffective, to provoke undesirable effects or to adversely affect outcomes.

Digitalis-Digoxin

Most of the enhancement of myocardial contractility by digoxin appears to be generated by inhibiting the Na/K ATPase pump of the cardiomyocyte sarcolemma (Fig. 1). This inhibition results in elevation of intracellular sodium, which increases (via blunting of the sodium-calcium exchanger) the intracellular calcium available for contraction.[93] Digitalis may also direct calcium into the myocyte via modulation of the voltage-sensitive sodium channels.[93]

Some of the clinical benefits of digitalis therapy in heart failure likely occur through alteration of sympathetic tone. Heart failure increases sympathetic nervous system tone and reduces parasympathetic tone, resulting in a number of undesirable effects including increased vascular resistance, tachycardia, renin release and diminished baroreceptor sensitivity; many of these undesirable responses are favorably suppressed or reversed by chronic digitalis administration.[94–101] It is likely that any clinical or hemodynamic benefit noted during chronic digoxin administration is attributable to a varying combination of a direct effect on the cardiomyocyte and improvement of autonomic tone and balance.

Intravenously administered digoxin in heart failure evokes a modest increase in mean stroke volume, cardiac output and systemic blood pressure, a modest decrease in heart rate and ventricular filling pressures, and little change in vascular resistance; although individual responses can vary widely with better hemodynamic effects noted in the more hemodynamically compromised patients.[101–103] The nonpredictable variability of hemodynamic responses and potential undesirable effects (e.g. dysrhythmias) for a drug with a relatively low therapeutic index and long elimination half-life have limited the use of intravenous digoxin and its congeners. Intravenous digoxin is reserved as an option to slow an elevated ventricular rate in patients with decompensated heart failure and rapidly conducting atrial fibrillation or flutter.

The results of noncontrolled or relatively small (low number of enrolled patients) studies over the years have suggested that long-term, orally administered digoxin in heart failure can favorably affect clinical status, augment ventricular ejection fraction, increase exercise performance, and improve hemodynamics at rest and during exercise.[104–111] Again, the clinical and hemodynamic responses are individually quite variable with improvement more noteworthy in patients with severe decompensation.[105–107,110]

Two digoxin withdrawal studies, both double blind, randomized and placebo controlled, published in 1993 provide evidence supporting the merits of chronic digoxin administration in patients with mild-moderate heart failure (FC II-III) and sinus rhythm.[111,112] The Prospective Randomized Study of Ventricular Failure and the Efficacy of Digoxin (PROVED) study[111] was performed in patients chronically treated with diuretics and digoxin and the Randomized Assessment of the effect of Digoxin in Inhibitors of the Angiotensin-Converting Enzyme (RADIANCE) study[112] in patients chronically treated with diuretics, digoxin and angiotensin-converting enzyme inhibitors. In both studies, compared to continued digoxin therapy, the patients randomized to withdrawal of digoxin to placebo experienced, over a three-month period, a reduction in left ventricular ejection fraction, clinical status, functional capacity and exercise performance and an increase in heart rate and body weight. This deterioration was most notable in patients with more severe heart failure, but also occurred in patients with a milder course.[113,114] Both trials were performed prior to standard background beta-blocker therapy.

Studies examining the use of digoxin in patients with ventricular dysfunction following acute myocardial infarction showed minimal benefit and a high potential for adverse outcomes.[115–121]

The DIG trial[92] has overshadowed all prior studies regarding the use of digitalis chronically in patients with heart failure and sinus rhythm, and has now provided the framework for current digoxin use. Six thousand eight hundred patients with symptoms

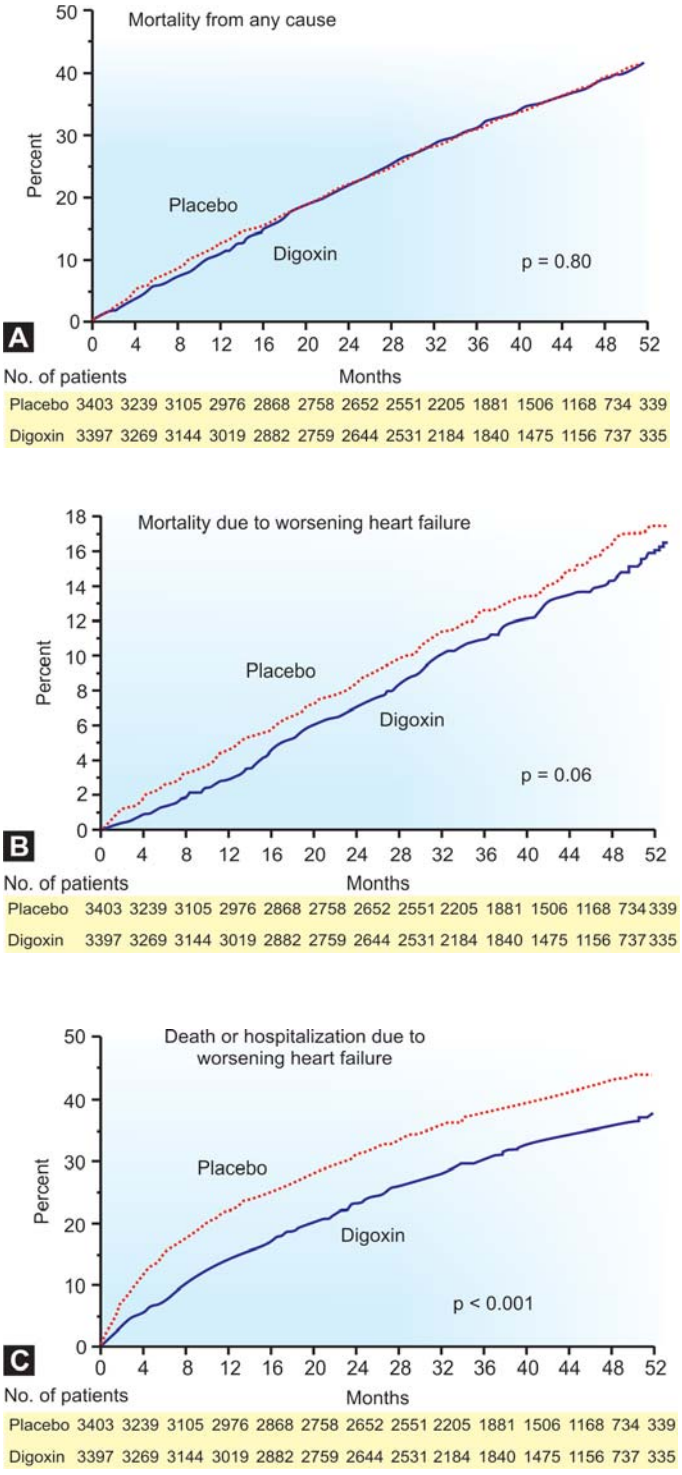
and signs of heart failure, LV ejection fraction less than or equal to 0.45 and in sinus rhythm were randomized 1:1 to digoxin (median dose 0.25 mg/day) or placebo. Patients with heart failure and ejection fraction, more than 0.45 were enrolled in a parallel ancillary study. About 95% of the study population was chronically taking an angiotensin-converting enzyme inhibitor, 82% a diuretic and 78% both agents. Chronic digoxin therapy in the DIG Trial had no effect on total mortality, but tended to reduce mortality attributable to heart failure and statistically reduced the combined endpoints of heart failure mortality or hospitalization for heart failure[92] (Fig. 8). While this benefit was greatest in patients with lower ejection fractions and worse clinical status, modest improvement was also noted for patients with an LV ejection fraction more than 0.45.[92,122,123]

The DIG Trial has since undergone considerable scrutiny, re-analysis and post-hoc analysis. Major limitations of the trial include absence of concomitant beta-blocker therapy and in retrospect, excessively high digoxin dosing and serum levels. Two percent of digoxin-treated patients in the trial were hospitalized for suspected digoxin toxicity compared to 0.9% for placebo ($p < 0.001$). Higher serum concentrations of digoxin (> 1.2 ng/ml) were associated with increased mortality over a mean follow-up of 37 months.[124] Importantly, improved heart failure mortality and hospitalization outcomes were maintained at lower digoxin levels (< 1.0 ng/ml).[124–126] The initial concern for a higher digoxin-related mortality for women[127] was later shown to be related to higher serum digoxin concentrations; outcomes improved at less than 1.0 ng/ml with a progressive rise in mortality and morbidity at levels more than or equal to 1.2 ng/ml.[128]

The DIG Trial was performed prior to routine beta-adrenergic blocker therapy in heart failure.[92] The results of two retrospective studies on populations far smaller than that of the DIG Trial suggest that chronic digoxin therapy may be of little benefit in heart failure patients in sinus rhythm on current, optimal therapeutic management including angiotensin-converting enzyme inhibition or angiotensin receptor blockade, beta-adrenergic blockade, diuretic, spironolactone and biventricular pacing for ventricular resynchronization.[129,130]

Indications and application: For the overall heart failure population, long-term digoxin administration has a Class IIa indication (level of evidence: B) from the 2009 ACC/AHA Task Force, which stated "Digitalis can be beneficial in patients with current or prior symptoms of heart failure and reduced left ventricular ejection fraction to decrease hospitalizations in heart failure.[131] Chronic digoxin therapy remains an option to control ventricular rate in the heart failure patient with atrial fibrillation, although this consideration has been challenged.[132]

With the exception of blocking AV nodal conduction in rapidly conducting atrial fibrillation or flutter in heart failure patients for whom other AV blocking agents (e.g. beta-adrenergic blockers, calcium channel blockers) may be problematic, there is hardly ever a need for accelerated or high-dose digoxin administration (historically termed "digitalization"). The initial and maintenance oral dose is 0.0625–0.25 mg/day. The 0.125 mg/day dose has largely replaced 0.25 mg/day as the standard maintenance dose because at the lower dose, serum digoxin levels (drawn > 8 hours after dosing) typically remain less than or equal to



FIGURES 8A TO C: Graphs showing selected results of the Digitalis Investigation Group (DIG) Trial. (A) Long-term digoxin therapy did not impact total mortality. (B) Digoxin tended to favorably affect heart failure mortality at borderline statistical significance. (C) Chronic digoxin administration favorably affected ($p < 0.001$) the combined outcomes of mortality or hospitalization when attributable to worsening heart failure (*Source:* Modified from reference 92)

1.0 ng/ml in patients with normal renal function and clearance. Fifty to eighty percent of orally administered digoxin is absorbed with an elimination half-life of 36–48 hours, largely via renal excretion. Dose reduction or discontinuation becomes important in patients with renal dysfunction and/or during

TABLE 3

A partial list of agents known to affect, through a number of different mechanisms, serum digoxin concentrations

A. Decrease levels
- Cholestyramine
- Sucralfate
- Kaolin-pectin
- Antacids
- Salbutamol
- Rifampin
- Thyroxine

B. Increase levels
- Antiarrhythmic agents
  - Amiodarone
  - Propafenone
  - Quinidine
- Calcium channel blocking agents
  - Verapamil
  - Diltiazem
  - Dihydropyridines (e.g. nifedipine)
- Potassium-sparing diuretics
  - Spironolactone
  - Triamterene
  - Amiloride
- Antimicrobials
  - Macrolides (-mycin)
  - Tetracycline
  - Itraconazole
- Other
  - Captopril
  - Carvedilol
  - Cyclosporine
  - Indomethacin
  - Omeprazole
  - St. John's wort

concomitant administration of medications known to elevate digoxin concentrations (Table 3).

Digoxin's direct effect on sinoatrial and atrioventricular nodal cells and its autonomic properties (reducing sympathetic tone and enhancing parasympathetic tone) leads to many of the manifestations of digoxin toxicity, generally at serum levels more than 2.0 ng/ml, including sinus bradycardia and AV nodal blockade. Other digoxin-toxic dysrhythmias include atrial tachycardia with AV block ("PAT with block"), ventricular ectopic beats, ventricular tachycardia and fibrillation, and accelerated conduction over accessory bypass tracts. Nausea, vomiting, mental disturbances and visual aberrations are some of the systemic manifestations of toxicity. Digitalis, a sterol molecule, is a common cause of gynecomastia and breast discomfort in men taking this agent long term. To suppress some of the problematic toxic dysrhythmias, the intravenous administration of atropine, potassium and/or magnesium when appropriate, can be employed until serum digoxin concentrations fall to acceptable levels and the adverse effects dissipate. Severe, life-threatening toxicity often necessitates the administration of anti-digoxin Fab-fragment immunotherapy.[133,134]

Other Orally Administered Positive Inotropic Agents

Hydralazine has positive inotropic properties in human heart failure in addition to its well-established vasodilating, ventricular unloading effects.[12,26,135] These inotropic and hemodynamic effects can be employed to wean dobutamine (and perhaps, milrinone and low-dose dopamine) from heart failure patients who appear hemodynamically dependent on the intravenous inotrope.[26]

Absolute and relative hypothyroidism can play a major role in the clinical course and outcomes in heart failure.[136–141] Thyroid hormone replacement enhances myocardial contractility through a number of mechanisms and is of particular clinical importance in these specific patient groups. Whether thyroid hormone intervention merits consideration as a means of augmenting cardiac performance and clinical outcomes in patients with heart failure beyond these groups remains unanswered.

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Chapter 7

Antilipid Agents

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Chapter Outline

- Appropriate Uses
- Statins
  - Efficacy
  - Muscle Safety
  - Statin Drug Interactions
  - Renal Excretion
  - Managing Muscle Symptoms
  - Liver Safety
- Add-on to Statin Therapy
- Bile Acid Sequestrants
  - Efficacy
  - Safety
- Ezetimibe
  - Efficacy
  - Safety
- Niacin
  - Efficacy
  - Flushing
  - Safety
- Triglyceride-lowering Therapy
- Fibrates
  - Efficacy
  - Safety
- Omega-3 Fatty Acids
  - Efficacy
  - Safety
- Drugs in Development

Over 150 years ago, Virchow and his colleagues described the accumulation of lipid as the hallmark of the atherosclerotic plaque. Since then, an extensive body of evidence has shown a direct relationship between blood cholesterol levels and atherosclerotic cardiovascular diseases. Causality has been proven in numerous clinical trials showing that lowering total and low density lipoprotein cholesterol (LDL-C) slows the development of atherosclerotic disease and prevents clinical events. The large majority of clinical data comes from statin trials. Other lipid modifying drugs have demonstrated more modest cardiovascular benefits. This chapter will review appropriate uses, mechanisms of action, lipid-modifying efficacy, cardiovascular benefits and safety for each class of lipid-modifying drugs.

APPROPRIATE USES

The National Cholesterol Education Program Adult Treatment Panel (NCEP ATP III) has identified two lipid targets for the prevention of cardiovascular diseases, LDL-C and non-high-density lipoprotein cholesterol (non-HDL-C) (Table 1).[1] The first target of therapy is *LDL-C*, with treatment goals based on the risk of a coronary heart disease event in the next 10 years. The second target of therapy is non-*HDL-C*. Non-HDL-C is calculated by subtracting HDL-C from total cholesterol and reflects circulating levels of atherogenic apolipoprotein-B containing lipoproteins. The non-HDL-C goal is 30 mg/dL higher than the LDL-C goal. Although the NCEP ATP III guidelines recommended using non-HDL-C when triglycerides are 150–500 mg/dL, recent evidence suggests that this recommendation can be simplified to using the non-HDL-C goal when triglycerides are less than 500 mg/dL.[2]

In those with triglyceride levels more than 500 mg/dL, prevention of pancreatitis is the initial objective. Once triglycerides are less than 500 mg/dL, attention can then turn to addressing LDL-C and non-HDL-C levels for cardiovascular prevention. Although low levels of HDL-C and high levels of triglycerides are markers of increased cardiovascular risk, specific treatment targets have not been identified due to the lack of evidence that pharmacologically altering the levels of these two factors *per se* reduces cardiovascular risk.[3] Cardiovascular prevention efforts in patients with low HDL-C should focus on lifestyle and drug therapy to achieve LDL-C and non-HDL-C goals. In the NCEP ATP III 2004 update, statins were recommended as first line therapy for cardiovascular prevention.[4]

Similar treatment strategies are used to lower LDL-C and non-HDL-C. All patients should be advised to undertake therapeutic lifestyle changes. *Statins* are the drugs of choice based on an extensive record of safely reducing cardiovascular events and overall mortality. Bile acid sequestrants and niacin also reduce cardiovascular risk, although they are less effective and have more adverse effects than statins. Ezetimibe is a well tolerated

TABLE 1

Overview of lipid treatment goals and strategies

	1st target LDL-C	*Triglycerides (mg/dL)* < 500 *2nd target* Non-HDL-C	> 500
Objective	*Prevent CVD*	*Prevent CVD*	*Prevent pancreatitis*
Treatment goals	*LDL-C goal* *High risk:* CHD/CHD risk equivalents* < 100 (optional < 70) mg/dL *Moderately high risk:* > 2 risk factors** with 10-20% 10-year CHD risk†< 130 mg/dL (optional < 100 mg/dL) *Moderate risk:* > 2 risk factors** with < 10% 10-year CHD risk < 130 mg/dL *Lower risk:* 0–1 risk factor < 160 mg/dL (consider drug therapy LDL > 190 mg/dL/optional LDL > 160 mg/dL)	Non-HDL-C goal 30 mg/dL higher than LDL goal	Triglycerides < 500 mg/dL
Lifestyle	Therapeutic lifestyle changes	Therapeutic lifestyle changes	Therapeutic lifestyle changes Very low-fat (< 15%) diet
Drug 1st choice	Statins	Statins	Fibrates
Drug add-on or 2nd choice	Niacin bile-acid sequestrant Ezetimibe	Niacin Ezetimibe Fibrate	Omega-3 fish oil Niacin Statins (high dose)

* Coronary heart disease (CHD) includes a history of myocardial infarction, stable or unstable angina, coronary artery revascularization, or clinically significant myocardial ischemia; CHD risk equivalents include other cardiovascular disease, including peripheral arterial disease, abdominal aortic aneurysm, carotid artery disease (stroke of carotid or intracerebral origin, transient ischemic attack, or > 50% carotid artery stenosis), diabetes, and > 2 risk factors with > 20% 10-year CHD risk

** Risk factors include age (men > 45 years, women > 55 years), cigarette smoking, hypertension (blood pressure > 140/90 mm Hg or antihypertensive therapy), low HDL-C (< 40 mg/dL) and family history of premature CHD (onset in male first degree relative < 55 years; first degree female relative < 65 years)

† 10-year risk of nonfatal myocardial infarction and CHD death estimated by Framingham Scoring

drug that lowers LDL-C and non-HDL-C but has yet to be established whether ezetimibe reduces cardiovascular risk.

Fibrates are generally the first choice for triglyceride-lowering to prevent pancreatitis. However, fibrates reduce cardiovascular risk less than statins and have safety concerns when used in combination with statins. High doses of omega-3 fish oil, niacin or statins also effectively lower elevated triglycerides. The mechanisms of action, efficacy and safety for each class of drug will now be reviewed.

STATINS

Statins are the foundation of cardiovascular risk reduction. Consistent evidence from more than 100,000 clinical trial participants has shown statins reduce the risk of coronary heart disease and stroke in direct proportion to the magnitude of LDL-C lowering. Statins inhibit 3-hydroxy-3-methylglutarul coenzyme A (HMG CoA) reductase, the rate-limiting step in cholesterol synthesis (Fig. 1). A lower concentration of intracellular cholesterol upregulates LDL receptors on the cell surface and enhances removal of circulating LDL-C. Downstream products of HMG CoA also influence inflammatory, thrombotic and vasodilatory factors, although the impact of these "pleiotropic" effects on clinical cardiovascular events remains to be determined.[5]

EFFICACY

A dose of statin should be used that will lower LDL-C by at least 30–40%. Starting doses of statins generally achieve this degree of LDL-C lowering (pitavastatin 2 mg, atorvastatin 10 mg, lovastatin or pravastatin 40 mg, rosuvastatin 10 mg, simvastatin 40 mg and fluvastatin 80 mg) (Table 2). Reducing LDL-C by more than or equal to 50% or more may be desirable, but usually requires the highest doses of atorvastatin (40–80 mg), rosuvastatin (20–40 mg), or a statin used in combination with another LDL-C lowering agent. Each doubling the statin dose will result in an additional 6% reduction in LDL-C and non-HDL-C ("rule of sixes"). Moderate doses of statins lower triglycerides by about 15–20%, while the highest doses of atorvastatin, rosuvastatin, and simvastatin can lower triglycerides by up to 30%. Statins modestly raise HDL-C by 2–10%. Although HDL-C and triglyceride levels predict cardiovascular risk, it does not appear that the increases in HDL-C or decreases in triglyceride decreases from statin, or any other drug, therapy contribute further cardiovascular reduction beyond that obtained from LDL-C lowering.[3]

MUSCLE SAFETY

The majority of patients tolerate statins without difficulty.[6] Although commonly reported, muscle complaints are usually not related to statin use. Rhabdomyolysis occurs very rarely

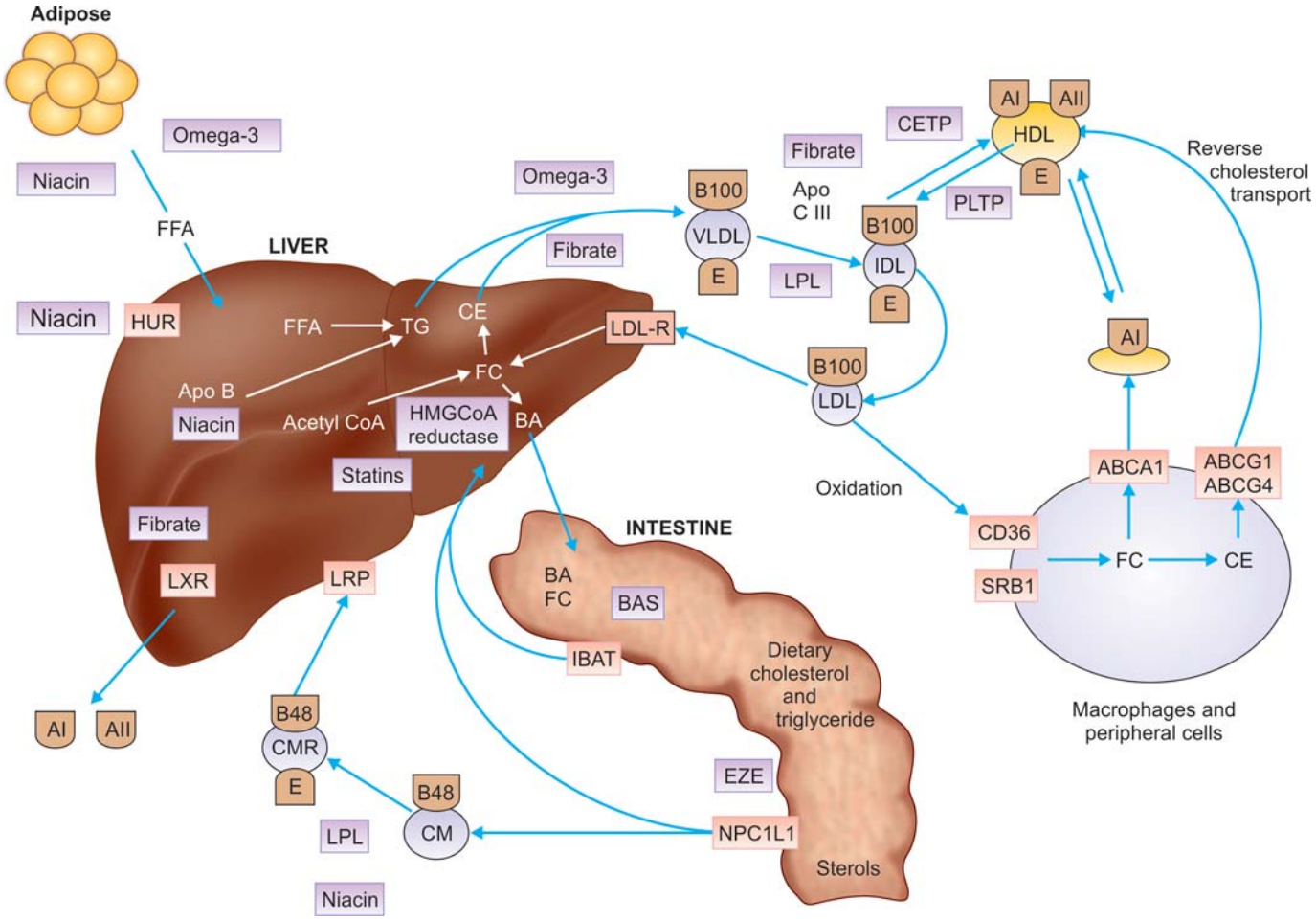


FIGURE 1: Overview lipid-modifying drug mechanisms

Statins inhibit the rate-limiting step in cholesterol synthesis, 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGCoA reductase) which binds acetyl CoA to free cholesterol to create cholesterol esters. Reduction in intrahepatic free cholesterol (FC) increases the number of LDL-receptors (LDL-R) on the cell membrane, faciliating removal of LDL-C from plasma. *Bile-acid sequestering agents (BAS)* and *ezetimibe (EZE)* lower plasma LDL-C by lowering intracellular free cholesterol levels. BAS bind bile acids via the intestinal bile acid transporter (IBAT), interrupting the enterohepatic circulation of bile acid FC. EZE acts on the Niemann-Pick C1-Like 1 (NPC1L1) transporter in at the intestinal wall to prevent absorption of dietary and biliary cholesterol. EZE also blocks uptake of plant sterols. *Dietary sterol/stanols* competitively inhibit the uptake of cholesterol in the intestine. The efficacy of all three intestinally active agents is limited since there is a compensatory increase in hepatic cholesterol synthesis. *Niacin* acts through a unknown and known mechanisms, including partially inhibiting the release of free fatty acids (FFA) from adipose; increasing lipoprotein lipase (LPL) activity thereby enhancing removal of chylomicron (CM) triglyceride from plasma; decreasing apolipoprotein B (apo B) synthesis which lowers very low density lipoprotein cholesterol (VLDL-C) and intermediate density lipoprotein cholesterol (IDL-C), and thus plasma triglcyerides; and increasing high density lipoprotein cholesterol (HDL-C) levels through decreased hepatic uptake, likely through the holouptake receptor (HUR) and catabolism. Increased levels of HDL-C may increase reverse cholesterol transport from peripheral cells to the liver. *Fibrates* lower triglyceride levels by decreasing VLDL secretion and increasing catabolism of triglyceride-rich particles via several mechanisms, including reduced apolipoprotein C (apo C) production which upregulates lipoprotein-lipase-mediated lipolysis and increased cellular FFA uptake as well as increasing FFA catabolism. Fibrates increase HDL-C induce apolipoprotein A-I and A-II (AI & AII) synthesis via the liver X receptor/retinoid X receptor heterodimer (LXR), *Omega-3 fatty acids (O-3)* reduce the rate of VLDL synthesis through a number of putative mechanisms inhibiting release of FFA from adipose, inhibiting FFA synthesis, and increasing apo B degradation (Abbreviations: ABC: ATP-binding cassette; B48 or B100: Apolipoprotein B48 or B100; CETP: Cholesterol ester transfer protein; CMR: CM remnant; E: Apolipoprotein E; LRP: LDL receptor-related protein 1; PLTP: Phospholipid transport protein; SRB-1: Steroid receptor binding protein)

and generally in patients with multiple factors predisposing to decreased clearance such as advanced age, diminished renal function, and medications interfering with statin metabolism. Notably, currently marketed statins are much safer than low-dose aspirin, which has more than 200-fold higher rate of major bleeding than statins have of inducing rhabdomyolysis. In properly selected patients participating in long-term clinical trials of statin therapy, myopathy (muscle symptoms with creatine kinase elevations more than 10 times the upper limit of normal) and rhabdomyolysis occurred in less than 0.2% of subjects, with the exception of a higher rate of approximately 0.9% observed with simvastatin 80 mg.[7,8] The higher rate of muscle injury with simvastatin 80 mg has resulted in a communication from the US Food and Drug Administration regarding the safety of this dose.[7,8]

STATIN DRUG INTERACTIONS

Risk of myopathy and rhabdomyolysis is related to circulating drug levels. Three statins are metabolized by hepatic cytochrome P450 enzyme (CYP) 3A4 and have the most potential for drug

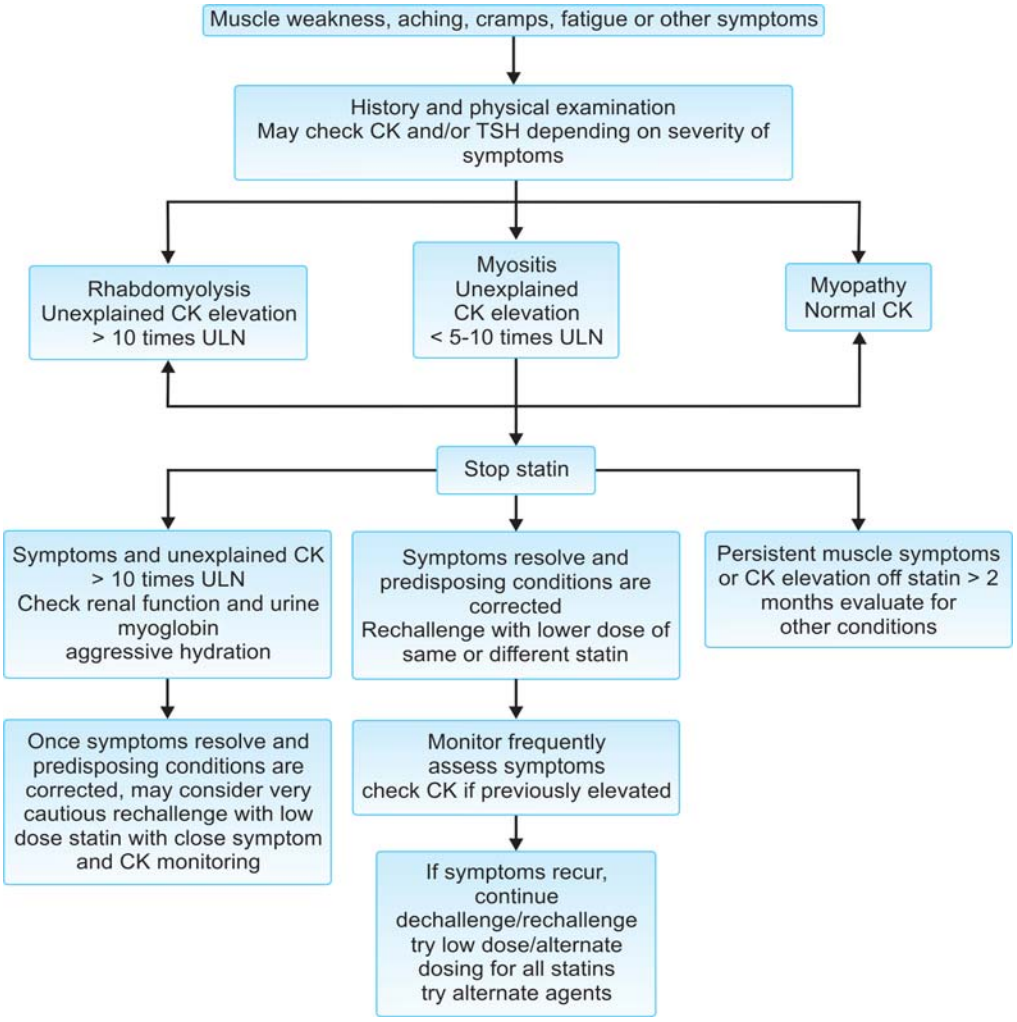
TABLE 2

Percent change in lipids and lipoproteins from baseline for various doses of statins, and statins coadministered with ezetimibe, niacin or fenofibric acid. Doses achieving a 30% to less than 50% reduction in LDL-C are highlighted in light gray and doses achieving more than or equal to 50% reductions are highlighted in dark gray.[14,27-33]

Statin dose	*Fluvastatin*	*Pitavastatin*	*Pravastatin*	*Simvastatin*	*Atorvastatin*	*Rosuvastatin*	*Simvastatin + Ezetimibe 10 mg*	*Rosuvastatin + Fenofibric acid 135 mg*	*Lovastatin + ER Niacin 2 gm*
					LDL-C				
2 mg		-36							
4 mg		-43							
10 mg	NR		-20	-28	-37	-46	-46	-37	NR
20 mg	-22		-24	-35	-43	52	-50	-39	NR
40 mg	-25		-30	-39	-48	-55	-56	NR	-42
80 mg	-35		-37	-46	-51	NA	-59	NA	NA
					Non-HDL-C				
2 mg		-33							
4 mg		-36							
10 mg	NR		-19	-26	-34	-42	-42	-45	NR
20 mg	NR		-22	-33	-40	-48	-47	-45	NR
40 mg	NR		-27	-36	-45	-51	-51	NR	NR
80 mg	NR		NR	-42	-48	NA	-55	NA	NR
					Triglycerides				
2 mg		-19							
4 mg		-18							
10 mg	NR		-8	-12	-20	-20	-24	-47	NR
20 mg	-12		-8	-18	-23	-24	-26	-43	NR
40 mg	-14		-13	-15	-27	-26	-29	NR	-44
80 mg	-19		-19	-18	-28	—	-26	NA	NR
					HDL-C				
2 mg		+7							
4 mg		+5							
10 mg	NR		+3	+5	+6	+8	+8	+20	NR
20 mg	+3		+4	+6	+5	+10	+9	+19	NR
40 mg	+4		+6	+5	+4	+10	+9	NR	+30
80 mg	+11		+3	+7	+2		+7	NA	NR

(Abbreviations: ER: Extended release; NA: Dose not approved; NR: Not reported).

FLOW CHART 1: An approach to managing muscle and other symptoms in statin-treated patients



(Abbreviations: CK: Creatine kinase; TSH: Thyroid stimulating hormone; ULN: Upper limit of normal range).

interactions—atorvastatin, lovastatin and simvastatin (remember as "A, L, S") (Table 3). Avoid concomitant use of these three statins with potent inhibitors of CYP3A4, including use with azole antifungals (ketoconazole and itraconazole; alternative—fluconazole), macrolide antibiotics (erythromycin and clarithromycin; alternative—azithromycin), rifampicin and protease inhibitors (alternative—indinavir) (Table 4). Lower doses of simvastatin and lovastatin are recommended for patients receiving weaker CYP3A4 inhibitors amiodarone, calcium channel blockers diltiazem and verapamil (alternatives—amlodipine and nifedipine). Interactions with some antidepressants (alternatives—paroxetine and venlafaxine) have also been reported. Alternatives to CYP3A4 metabolized statins include rosuvastatin, which is minimally metabolized, pravastatin which has no cytochrome P450 metabolism, fluvastatin, which is metabolized by the 2C9 pathway and pitavastatin which has no significant CYP3A4, 2C9 or 2C8 metabolism. All statins are glucuronidated, increasing the potential for interaction with gemfibrozil. Cyclosporine raises blood levels of virtually all statins by both cytochrome P450 and other pathways, and low doses of statins should be titrated carefully, if needed.

RENAL EXCRETION

Although statins are primarily metabolized by the liver, some statins have relatively greater renal excretion—lovastatin, pitavastatin, pravastatin, rosuvastatin and simvastatin. Dose adjustment may be considered in those with markedly impaired renal excretion. All statins should be used with caution in patients with a glomerular filtration rate less than 30 since substantially impaired renal excretion is also a marker for other patient characteristics that may increase the potential for adverse muscle effects, including advanced age, frailty and polypharmacy.

MANAGING MUSCLE SYMPTOMS

An approach to the management of muscle and other symptoms in statin-treated patients is provided in Flow chart 1. Persistent muscle pain or weakness affecting the proximal muscles is the most common manifestation of statin intolerance. Intermittent or nocturnal muscle cramps and localized joint pain are not uncommon. Generalized fatigue may be the presenting complaint for elderly patients. The general approach is to discontinue the statin until symptoms resolve, and then rechallenge

TABLE 3

Summary of comparative pharmacokinetics of statins in healthy volunteers

	Atorvastatin	*Fluvastatin*	*Lovastatin*	*Pitavastatin*	*Pravastatin*	*Rosuvastatin*	*Simvastatin*
Major metabolic enzyme	CYP3A4	CYP2C9	CYP3A4 Glucuronidation	Minimal CYP450 Glucuronidation	No CYP450 Glucuronidation	Some CYP 2C8 Glucuronidation	CYP3A4 Glucuronidation
Renal excretion (%)	≤ 2	< 6	≥ 10	15	20	10	13
Absorption (%)	30	98	30–31	51	34	40–60	60–80
Prodrug	No	No	Yes	No	No	No	Yes
t_{max} (h)	1.0–2.0	0.5–1.0	2.0–4.0	1.0	1.0–1.5	3.0–5.0	1.3–3.0
$T_{1/2}$ (hours)	14–15	3.0	2.0	12	2.0	20	1.4–3.0
Lipophilicity (logP)	4.06	3.24	4.30	—	–0.23	—/33	4.68
Protein binding (%)	> 98	> 98	> 95	99	43–54	88	95
Affinity for Pgp transporter	Yes	No	Yes		Yes	No	Yes
Hepatic first-pass metabolism (%)	20–30	40–70	40–70	—	50–70	50–70	50–80
Systemic active metabolites (no.)	Yes (2)	No	Yes (3)	No	No	Minimal	Yes (3)
Bioavailability (%)	12–14	29	< 5	51	18	20	<5

TABLE 4

Selected clinically relevant statin drug interactions

Drug interactions	*Atorvastatin*	*Fluvastatin*	*Lovastatin*	*Pitavastatin*	*Pravastatin*	*Rosuvastatin*	*Simvastatin*
Gemfibrozil Alternative: Fenofibrate	+	+	++	+	++	+	++
Cyclosporine	++		++	++	++	++	++
HIV protease inhibitors Alternative: Indinavir	+		+	+		+	+
Ketoconazole, itraconazole Alternative: Fluconazole	+		+				+
Erythromycin, clarithromycin, telithromycin Alternative: Azithromycin	+	+	++				+
Rifampicin	+		+	+			+
Diltiazem, verapamil Alternatives: Amlodipine, nifedipine			+				+, ++
Amiodarone			+				+
Digoxin	+						+
Fluoxetine, fluvoxamine, sertraline, nefazodone Alternative: paroxetine, venlafaxine	+		+				+

with a low dose of the same or another statin. Creatine kinase levels are usually normal in statin-intolerant patients but may be helpful if symptoms are severe. Patients with recurrent muscle symptoms on statin rechallenge may tolerate alternate dosing strategies including alternate day or weekly dosing intervals, with up-titration as tolerated. For example, rosuvastatin 5–10 mg once a week, or 2.5 mg every other day, can lower LDL-C by 25%. Patients reliably developing muscle symptoms after a discrete time period, for example, 3 months, may tolerate a statin, if taken for 2½ months with a 2 week statin-free holiday. Regular or extended-release fluvastatin 80 mg is also an option. Even a low dose of a statin will be more effective than alternative LDL-C lowering therapies. Additional strategies include improving diet and lifestyle habits plant stanol/sterol supplementation, ezetimibe and bile acid sequestering agents.

Coenzyme Q10 has been shown in a few, but not most, randomized studies to improve statin tolerance when given in higher doses of 100–200 mg/day. Vitamin D supplementation has also been proposed for Vitamin D deficient patients suffering muscle symptoms, but randomized trials have not yet been performed. Red yeast rice, which contains a low dose of naturally occurring lovastatin, may be tolerated by some patients otherwise intolerant of statins, although the usual cautions regarding efficacy and safety apply as they do to other over-the-counter remedies.

Creatine kinase levels should not be monitored on a routine basis in statin-treated patients, although creatine kinase levels should be evaluated in patients developing severe or recurrent muscle symptoms. Muscle symptoms that fail to resolve within 2 months of statin discontinuation are likely due to another etiology. Rheumatologic disorders (including polymyalgia rhuematica), hypothyroidism, chronic sleep deprivation, sleep apnea, underlying muscle disorders, among others, are not uncommon. These conditions may also lower the threshold for statin-related muscle symptoms and once treated, statin therapy can then be resumed.

LIVER SAFETY

Abnormal liver function tests are also common among patients receiving statins but are not usually related to statin use. Persistent elevations in hepatic alanine transaminase (ALT; which is the most specific test for drug-related hepatotoxicity) in long-term clinical trials are uncommon and related to increasing statin dose. Over a period of 2–5 years, persistent ALT elevations greater than 3 times the upper limit of normal occurred in approximately 1% of study participants receiving 80 mg of atorvastatin or simvastatin. Persistent ALT elevations less than 3 times the upper limit of normal are usually due to non-alcoholic steatohepatitis, or fatty liver, related to insulin resistance. As long as a stable pattern of ALT elevation has been established, statins can still be used in these patients for cardiovascular prevention with regular ALT monitoring. Often ALT levels improve with long-term statin therapy. In patients with unexplained ALT elevations greater than 3 times the upper limit of normal, the statin should be discontinued along with other potential hepatotoxic prescription and over-the-counter agents. The patient monitored until levels return to baseline or an etiology is established. Except for bile acid sequestrants, statins and other lipid-lowering therapies are generally contraindicated in patients with severe liver disease and the value of preventive therapy should be carefully evaluated in such patients.

ADD-ON TO STATIN THERAPY

Consideration may be given to adding a second agent to a statin in patients who have not achieved their LDL-C and non-HDL-C goals and for whom more aggressive therapy is deemed appropriate. It should be noted, however, at this time there is insufficient clinical trial evidence that adding a second agent to statin therapy will result in additional cardiovascular event reduction. Until evidence from ongoing trials is available, selection of one agent over another can only be guided by considerations of LDL-C and non-HDL-C lowering efficacy, safety and cost.

Ezetimibe, bile acid sequestrants and niacin 2 gm will lower LDL-C, an additional 15% when added to statin therapy (Table 5). Niacin is more effective than other agents for lowering non-HDL-C due to greater increases in HDL-C. Bile acid-sequestrants are less effective for lowering non-HDL-C due to

TABLE 5

Lipid lowering options for patients who have not achieved LDL-C and non-HDL-C goals on statin therapy[11,34-36]

	Percent changes from baseline			
Drug	*LDL-C*	*Non-HDL-C*	*Triglyceride*	*HDL-C*
Double statin dose	–6%	–6%	–2 to –12%	–2 to +2%
Ezetimibe 10 mg	–15 to –20%	–12%	–9%	NS
Niacin 2 gr	–1 to –8%	–15 to –31%*	–24%	+18 to +21%
Bile acid binding agent Colestipol 2 scoops (6 gr) Cholestyramine 2 scoops (8 gr) Coleselvalam 6 tabs or suspension (3.75 gr)	–6 to –16%	–5 to –8%	0 to +23%	+1 to +7%
Fenofibrate 145 mg Fenofibric acid 135 mg	–6 to +4%	–3 to –23%*	–15 to –27%	+10 to +13%
Gemfibrozil 600 mg BID	+7%	+2%	–18%	0%
Marine omega-3 fatty acids	–6 to +10%	–7 to –9%	0 to –27%	+2 to +4%

*Calculated by subtracting mean HDL-C from mean total cholesterol

their very low density lipoprotein cholesterol (VLDL-C) raising effects. Fibrates have variable effects on LDL-C, and may raise it in patients with elevated triglyceride levels. Fenofibrate will lower LDL-C and non-HDL-C somewhat more than gemfibrozil, and appears to be safer than gemfibrozil when used with a statin. Omega-3 fatty acids may increase LDL-C and have modest effects on non-HDL-C, despite significant triglyceride lowering.

The term "residual risk" has been used to describe patients who have achieved their LDL-C and non-HDL-C goals on statin therapy yet still experience a cardiovascular event. Typically, these patients have low HDL-C and elevated levels of triglycerides, LDL-C particles and apolipoprotein B. An evidence-based strategy has yet to be determined for these patients since drug-related changes in HDL-C and triglyceride have not been associated with cardiovascular risk reduction.[3] Fenofibrate added to moderate dose simvastatin therapy did not result in additional cardiovascular risk reduction in the action to control cardiovascular risk in diabetes (ACCORD) trial, although a subgroup analysis did suggest those with elevated triglycerides and low HDL-C levels experienced greater risk reduction.[9] It should be noted, however, that high-dose statin therapy reduces cardiovascular risk compared to moderate dose statin therapy regardless of the type of lipid disorder present.[10] Two ongoing clinical trials are evaluating the additive benefit of extended-release niacin to background statin therapy. Until clinical trial data are available, it is just as likely that the residual lipid abnormalities present in the inflammatory state of insulin resistance and obesity are just as likely to be markers, rather than causes, of increased cardiovascular risk.

BILE ACID SEQUESTRANTS

Bile acid sequestrants interrupt the enterohepatic recirculation of cholesterol-rich bile acids by irreversibly binding them in the intestinal lumen (Fig. 1). Bile acid sequestrants are not systemically absorbed. Cholestyramine and colestipol modestly decrease CHD risk in long-term clinical trials, as would be expected from their modest effect on LDL-C. No long-term clinical outcomes data are available for colesevelam.

EFFICACY

As monotherapy, bile acid sequestrants at the recommended dosage [colestipol 2 scoops (6 gr), cholestyramine 2 scoops (8 gr) or colesevelam 6 tabs or suspension (3.75 gr)] will lower LDL-C by about 15% and non-HDL-C by about 10%.[11] Bile acid sequestrants increase triglycerides on average by 15–30% and the largest triglyceride increases occur in patients with more severe hypertriglyceridemia. Bile acid sequestrants are contraindicated in those with triglyceride levels more than 400 mg/dL and should be used with caution when triglycerides are 200–400 mg/dL. Colesevelam has been shown to reduce hemoglobin A_{1C} levels by about 0.5% in diabetics with inadequate glycemic control, with greater benefit in those with hemoglobin A_{1C} levels more than 8.0%.[12] Notably, average triglyceride levels were less than 200 mg/dL in these studies.

SAFETY

Adverse intestinal effects, such as bloating, constipation and bowel obstruction, limit their use, although these effects are less common with colesevelam.[13] Colestipol and cholestyramine decrease the absorption of anionic drugs and vitamins (vitamins A, D and K, and folic acid) and should be administered 1 hour after or 4 hours before estrogen, progestin, warfarin, digoxin, thyroxine, phenobarbitol, propranolol, thiazide diuretics, tetracycline, vancomycin, penicillin G, niacin or ezetimibe. Colesevelam has much higher specificity for bile acids than the other sequestrants and does not interfere with the absorption of warfarin, digoxin or several other anionic drugs.

EZETIMIBE

Ezetimibe also acts in the intestine. Ezetimibe selectively inhibits uptake of cholesterol by blocking Niemann-Pick C1-Like 1 receptor, a critical mediator of cholesterol absorption, at the brush border of the small intestine (Fig. 1). By reducing cholesterol absorption from bile acids and diet, ezetimibe reduces intracellular cholesterol levels which in turn up-regulates LDL receptors to lower plasma cholesterol levels. Statins and bile acid sequestrants act similarly through this final cholesterol-lowering pathway. Ezetimibe and its active metabolites undergo extensive enterohepatic recirculation limiting systemic exposure. Ezetimibe has no effect on the metabolism of statins, fibrates, warfarin or a number of other drugs studied. Combination of ezetimibe with cyclosporine increases the blood concentrations of both drugs.

EFFICACY

As monotherapy, ezetimibe lowers LDL-C and non-HDL-C by about 20%. When used with a statin, ezetimibe lowers LDL-C by 15–20% with a lesser effect on non-HDL-C (Table 4).[14] A combination of tablet of ezetimibe 10 mg and simvastatin 80 mg lowers LDL-C by about 60%, similar to the highest doses of atorvastatin and rosuvastatin.

SAFETY

Ezetimibe has minimal adverse effects and does not appear to increase the risk of myopathy when used in conjunction with a statin.[13] No dose adjustments are needed in patients with renal or hepatic insufficiency. Statin-ezetimibe combinations cause persistent hepatic ALT elevations greater than 3 times the upper limit of normal at a rate similar to atorvastatin 80 mg. The value of ezetimibe when added to statin therapy for cardiovascular prevention is unclear. Two of three surrogate endpoint trials showed ezetimibe had no additional effect on carotid intimal medial thickness over statin therapy alone, and one long-term endpoint trial demonstrated a less than expected cardiovascular risk reduction benefit from the combination of ezetimibe and simvastatin compared to placebo.[15] Methodologic problems limit conclusions from the surrogate endpoint trials and the aortic stenosis population studies in the clinical endpoint trial may have unique characteristics. Two large outcomes trials better designed to evaluate ezetimibe added to statin therapy are

ongoing. Until data are available from these trials, ezetimibe can still be considered an option if LDL-C and non-HDL-C goals have not been met on maximal statin therapy, or in the statin intolerant patient.

NIACIN

Niacin can improve all lipid parameters, although effects are highly variable between patients. Therefore, niacin should only be continued in those experiencing a significant therapeutic response in the targeted lipid parameter(s) until clinical trial data are available regarding its cardiovascular risk reduction benefits added to a statin. Not all of niacin's mechanisms of action have been elucidated. Niacin lowers LDL-C and VLDL-C by decreasing apolipoprotein B synthesis. Triglyceride reductions result from partial inhibition of fatty acid release from adipose tissue, leading to decreased hepatic triglyceride synthesis, as well as through increased lipoprotein lipase activity which increases the rate of chylomicron triglyceride removal from plasma (Fig. 1). Niacin-induced increases in HDL-C levels are likely related to decreased triglyceride levels, and may result from decreased hepatic uptake and catabolism of HDL-C. Niacin undergoes extensive first pass metabolism in the liver, through enzymatic pathways separate from those metabolizing statins, and is rapidly excreted in urine. Niacin has few important drug interactions although it is extensively bound to cholestyramine.

In the Coronary Drug Project trial, niacin reduced the risk of coronary heart disease by 17% over a period of approximately 6 years. This is about the risk reduction expected from a 15% reduction in LDL-C and non-HDL-C from the average 2 gm of niacin used in this trial.[5,16] Six trials of niacin used in combination with a colestipol or a statin have demonstrated a benefit on coronary or carotid atherosclerotic plaque.[17,18] Two of these very small trials reported a significant reduction in cardiovascular events. A trial is underway to evaluate whether niacin-induced HDL-C increases and triglyceride reductions further reduce cardiovascular events over LDL-C lowering. Another trial is evaluating the incremental cardiovascular benefit of adding niacin combined with laropriprant, described below, to background statin therapy.

EFFICACY

One gram of niacin will raise HDL-C by 15% and lower triglycerides by 25%, but has little effect on LDL-C or non-HDL-C levels. At the 2 gm dose, niacin will lower LDL-C by about 15%, and further increase HDL-C (+ 25%) and lower triglycerides (- 30%). Niacin 2 gm will also lower lipoprotein by about 20%, although it is not known whether this will further reduce cardiovascular risk. When added to a statin, niacin retains the HDL-C raising and non-HDL-C and triglyceride lowering properties for niacin monotherapy, although some attenuation of LDL-C lowering may occur.

Extended-release niacin in doses greater than 2 gm/day are not recommended due to serious concerns about hepatoxicity. Immediate-release, or crystalline, niacin more than 3 gm/day may further lower LDL-C (> 20%), raise HDL-C (> 35%), and lower triglycerides (> 40%). Nicotinamide and inositol hexanicotinate, marketed as "no-flush" niacin, have no lipid effects.

FLUSHING

Immediate-release, or crystalline, niacin may have substantial cutaneous effects, such as flushing and itching, that are reduced with extended-release niacin formulations. Nicotinic acid receptors in the skin release prostaglandin D_2 which results in vasodilatation and histamine release. Tachyphylaxis to these effects develops with consistent dosing over a period of weeks to months. A higher dose of aspirin (325 mg), ibuprofen 200 mg, or another nonsteroidal anti-inflammatory drug (NSAID) taken 30–60 minutes prior to niacin administration can alleviate flushing, redness, itching, rash and dryness.[19] These drugs should be limited to short-term use due to concerns about gastrointestinal and cardiovascular toxicity with long-term NSAID use. Laropriprant, which reduces niacin flushing by blocking prostaglandin D_2 release, is under development.

Niacin adherence may be improved titrating the dose gradually over a period of weeks to months. The starting dose of extended release niacin is 500–1000 mg at bedtime, and for immediate-release niacin is 125–250 mg twice daily. Niacin should be retitrated when switching between brands or forms of niacin or after missing more than three doses. Patients find it helpful to hear a description of niacin flushing symptoms prior to the first use: flushing usually starts 30–120 minutes after ingestion of extended-release niacin, and 15–30 minutes after the ingestion of immediate-release niacin; episodes typically last 5–60 minutes. During a flushing episode, chewing as aspirin or taking diphenhydramine may decrease severity. Flushing rates usually substantially diminish after 4 weeks of extended-release niacin use, and rarely occur after 1 year of use. Ingestion with a snack or meal slows absorption. Spicy foods, alcohol, hot beverages and hot baths or showers can exacerbate flushing.

SAFETY

Doses of extended-release niacin greater than 2 gm/day are contraindicated due to a very high rate of serious hepatotoxicity, including liver failure, reported with the sustained-release formulation of niacin at 1.5-3 gm/day. Sustained-release niacin, which is available over the counter, should be avoided, especially in doses of more than 1.5 gm daily. In contrast, immediate-release niacin appears to have no significant hepatotoxcity in doses up to 3 gm/day. Rates of persistent hepatic transaminase elevations with extended-release niacin-statin combinations appear to be similar to that of moderate-dose statins (< 1%).

No evidence of serious hepatoxicity has been reported to date for extended-release niacin used with moderate dose statins. Few data are available for extended release niacin used with the highest doses of statin, or the long-term safety of higher doses of immediate-release niacin used concomitantly with a statin.

Serum ALT should be monitored every 6–12 weeks during the first 6–12 months of niacin treatment, and every 6 months thereafter. Niacin should be discontinued if hepatic transaminase levels are persistently more than 3 times the upper limit of normal, bilirubin is more than 3 mg/dL, prothrombin time is elevated, or symptoms of nausea, vomiting or malaise are present. Niacin rechallenge should be undertaken only with careful monitoring, if at all.

Rhabdomyolysis has not been reported for niacin monotherapy and has been rarely reported with niacin used in combination with a statin. Although few patients have been studied in long-term clinical trials, the myopathy rate of niacin combined with a statin appears to be similar to that of a statin alone. The exception is for patients of Chinese descent who are significantly increased risk of myopathy when niacin more than or equal to 1 gm is used concomitantly with simvastatin more than or equal to 40 mg.[8] In patients of Chinese descent, simvastatin 80 mg should not be used with niacin.

Niacin may worsen insulin resistance and cause diabetes, especially in those with impaired fasting glucose or abnormal glucose tolerance. Fasting glucose levels should be monitored after each dose titration and annually thereafter. Although niacin reduces cardiovascular events in patients with diabetes, diabetic therapy may need intensification to maintain patients at their hemoglobin A_{1c} goals.

Uncommon adverse effects of niacin include intermittent atrial fibrillation, exacerbation of gout (consider allopurinol if a history of gout and serum uric acid levels exceed 10 mg/dL), hyperpigmentation of skin-fold areas (acanthosis nigricans), upper gastrointestinal bleeding (niacin is contraindicated in patients with active peptic ulcer disease), mildly decreased platelet counts, and rarely blurred vision (cystoid macular degeneration reported with niacin > 3 grams).

TRIGLYCERIDE-LOWERING THERAPY

Triglycerides are not a target of therapy for cardiovascular risk reduction. Although those with triglyceride levels more than 150 mg/dL are at increased cardiovascular risk, adjustment for low HDL-C levels and insulin resistance eliminates the majority of the risk associated with elevated triglycerides. Nor are triglyceride changes from drug therapy associated with reduced cardiovascular risk.[3] In those with severe hypertriglyceridemia (> 500 mg/dL), triglycerides are the target of therapy to prevent pancreatitis.

Patients should fast for at least 8 hours prior to obtaining the blood sample for triglyceride measurement. Secondary causes of hypertriglyceridemia should be evaluated in all patients. Particular attention should be paid to detecting undiagnosed or poorly controlled diabetes or hypothyroidism. Once these conditions are adequately treated, triglyceride levels usually fall to less than 500 mg/dL.

All patients should see a dietitian for counseling on a diet very low in fat (< 15%) and refined carbohydrates, and obese patients should be counseled to lose weight. When triglycerides are more than 1000 mg/dL, a triglyceride-lowering drug is usually started simultaneously with diet and lifestyle changes. Fibrates are considered first-line therapy and lower triglycerides by 20–50%. Higher doses of niacin, omega-3 fish oil and statins also lower triglycerides. Bile acid sequestrants are absolutely contraindicated in severely hypertriglyceridemic patients since they can markedly exacerbate hypertriglyceridemia. Ezetimibe has only modest triglyceride-lowering effects. Once triglyceride less than 500 mg/dL are achieved, attention should then turn to treating LDL-C and non-HDL-C to reduce cardiovascular risk.

FIBRATES

Fibrates are nuclear peroxisome proliferator-activated (PPAR) receptor-α agonists that upregulate the gene for lipoprotein lipase and downregulate the gene for apolipoprotein C-III, an inhibitor of lipoprotein lipase. Lipoprotein lipase increases triglyceride hydrolysis (which decreases VLDL-C secretion) and increases catabolism of triglyceride-rich particles (Fig. 1). Fibrates modestly raise HDL-C by lowering triglycerides and by increasing synthesis of apolipoproteins A-I and A-II. Fibrates variably influence LDL-C levels depending on the type of dyslipidemia and which fibrate is used.

Gemfibrozil undergoes glucuronidation in the liver and is 70% renally excreted. Gemfibrozil potently inhibits glucuronidation of other drugs, including all statins. Fenofibrate is also metabolized via glucuronidation and is primarily renally excreted. However, fenofibrate and fenofibric acid, its active metabolite, are much less potent inhibitors of glucuronidation than gemfibrozil, and have little effect on statin levels. Fibrates may substantially increase prothrombin time and international normalized ratios in patients receiving warfarin. Warfarin dose may need to be decreased by 25–35%.

Fenofibrate very modestly reduces cardiovascular risk to the degree expected from the magnitude of its modest LDL-C and non-HDL-C changes.[9,16] Conversely, gemfibrozil reduces cardiovascular risk more than expected from the minimal changes observed in LDL-C and non-HDL-C. The risk reduction with gemfibrozil is independent of triglyceride changes and has been largely attributable to the use of gemfibrozil itself.[20]

EFFICACY

Lipid effects may vary substantially depending on the type and severity of the dyslipidemia present. As monotherapy, fenofibrate is slightly more effective than gemfibrozil for lowering LDL-C (11% vs 1%, respectively) and non-HDL-C (18% vs 13%), although both may increase LDL-C levels in hypertriglyceridemic patients.[21] Both drugs lower triglycerides by about 45% and raise HDL-C by about 10%.

SAFETY

Fibrates increase the risk of myopathy, abnormal transaminase levels, and creatinine elevations.[22] Fibrate monotherapy increases the risk of myopathy five-fold (number needed to harm 3500) over statins alone. The risk for gemfibrozil is two-fold higher than for fenofibrate. When used with a statin, gemfibrozil has a 33-fold higher risk of myopathy than fenofibrate, in part due to greater inhibition of glucuronidation. Gemfibrozil increases blood levels of all statins, with a lesser impact on fluvastatin. Fenofibrate appears to have little impact on statin blood levels, and so is the drug of choice for combination with low-to-moderate dose statins. Fenofibrate has not been evaluated with the highest doses of statins. Although fenofibrate-statin combinations have acceptable muscle safety, it should be noted their value has not yet been demonstrated in clinical outcomes trials.

In patients at increased risk for myopathy, the potential benefits of fibrates should be carefully weighed against their

risks, especially in combination with a statin. Myopathy risk characteristics include advancing age, female sex, renal or hepatic dysfunction, hypothyroidism, debilitation, surgery, trauma, excessive alcohol intake or heavy exercise. Extensive patient education and regular creatine kinase monitoring should be considered in such cases. For severely hypertriglyceridemic patients for whom the safety of fibrates is a concern, high doses of marine omega-3 fatty acids (> 3 gm) should be strongly considered.

Rises in creatinine levels can occur in patients taking fenofibrate, although the clinical significance of this is unclear. Fenofibrate often improves proteinuria with long-term use, and no cases of renal failure have been reported. However, the dose of fenofibrate should be reduced if creatinine rises above the normal range, and the patient carefully monitoring for adverse effects. Fenofibrate dose should be reduced in patients with glomerular filtration rates less than 60 ml/min/1.73 m^2, and fenofibrate completely avoided when it is less than 15 ml/min/1.73 m^2. Fenofibrate is nondialyzable and must be avoided in dialysis and renal transplant patients. A reduced dose of gemfibrozil can be used in these patients. Gemfibrozil also has significant renal excretion and concomitant use with statins with renal clearance should be avoided. The maximum dose for elderly patients is one-third of the full dose of fenofibrate.

Although gemfibrozil more frequently increases hepatic transaminase levels than fenofibrate, the rates of hepatic and total adverse events are lower for gemfibrozil than fenofibrate. Both fibrates are contraindicated in the setting of severe liver disease. Fibrates predispose to gallstones but are only contraindicated in untreated gallbladder disease. Increased risk of deep vein thrombosis and pulmonary embolism has been observed in some fibrate trials, but no increase was observed when fenofibrate was added to simvastatin in the ACCORD trial.[9] Unlike the earlier fenofibrate intervention and event lowering in diabetes (FIELD) trial of fenofibrate monotherapy,[23] no increase in coronary mortality was noted in ACCORD.

OMEGA-3 FATTY ACIDS

The omega-3 fatty acids eicosopentanoic acid (EPA) and docohexanoic acid (DHA) in doses more than 3 gm daily can lower triglyceride levels about as much as a fibrate.[24] EPA and DHA come from marine sources (fish and seaweed) and are the only omega-3 fatty acids that lower triglycerides. α-linolenic acid is an omega-3 fatty acid derived from land-based plant sources is minimally converted to EPA and DHA and has minimal lipid effects.

EPA and DHA, including intake from fatty fish once or twice a week, have been shown to reduce the risk of coronary death, although the mechanisms through which this occur is unclear.[25] Triglyceride-lowering *per se* does not appear to reduce cardiovascular risk in studies to date.[3] The mechanisms through which omega-3 fatty acids lower triglycerides have not been fully elucidated, but the ultimate result is a reduced rate of VLDL-triglyceride secretion (Fig. 1). EPA and DHA are rapidly absorbed with a long half-life due to extensive incorporation into cell membranes. Omega-3 fatty acids have no effects on cytochrome P450 metabolism and no apparent drug interactions.

EFFICACY

A 3–4 gm dose of EPA/DHA is needed to lower triglycerides by 30–45%. Very concentrated fish oil is available over-the-counter or by prescription (four 1 gm capsules = 3.4 gm EPA + DHA). Care must be taken with over-the-counter preparations to ensure they are highly purified and free of significant contamination.

SAFETY

The most common adverse effects of omega-3 fish oil are fishy eructation, nausea and intestinal complaints. Pharmaceutical grade fish oil is highly refined and has fewer adverse gastrointestinal effects. Environmental toxins such as mercury, dioxins, polychlorinated biphenyls, may be present in fish oil and oily fish, and premenopausal women and children should limit consumption. Doses of omega-3 fatty acids less than 6 gm daily do not increase glucose levels or the risk of bleeding with aspirin or anticoagulants.

DRUGS IN DEVELOPMENT

Several drugs with novel mechanisms influencing the metabolism of LDL-C, VLDL-C and HDL-C are in development.[26] Several at-risk populations may benefit from LDL-C and non-HDL-C lowering agents, including those who are intolerant of statins, those with familial hypercholesterolemia or other forms of severe hyperlipidemia, and those needing additional lipid modification to reach their treatment targets. Although low HDL-C levels are a marker for increase risk, it remains to be determined whether raising HDL-C pharmacologically will reduce cardiovascular events. The long-term safety of these new agents will need to be established, and clinical trials evaluating their additive benefit over current evidence-based therapies will likely be required before they are approved for clinical use.

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Chapter 8

Antithrombotic and Antiplatelet Agents

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Chapter Outline

- Clotting, A Primer
- Antithrombotic Agents
  - The Heparins and Indirect Xa Inhibitors
    - Limitations, Monitoring and Adherence
  - Low Molecular Weight Heparins
    - Advantages and Indications
    - Limitations, Monitoring and Adherence
  - Fondaparinux
    - Advantages and Indications
    - Limitations, Monitoring and Adherence
  - Idrabiotaparinux
- AVE5206
- Vitamin K Antagonists (VKA)
  - Warfarin
    - Mechanism and Indications
    - Limitations, Monitoring and Adherence
- ATI-5923
- Direct Factor XA Inhibitors
  - Rivaroxaban
    - Efficacy
  - Apixaban
    - Efficacy
- Direct Thrombin Inhibitors
  - Hiurdin
  - Bivalirudin
    - Limitations and Monitoring
  - Argatroban
    - Limitations and Monitoring
  - Ximelagatran
  - Dabigatran
- Antiplatelet Agents
  - Inhibitors of Platelet Adhesion
  - Inhibitors of Platelet Activation
  - Inhibitors of Platelet Aggregation

INTRODUCTION

Arterial and venous thromboses are a major cause of death and disability worldwide. A majority of myocardial infarctions (MI) and cerebrovascular accidents (CVA) are caused by unregulated arterial thrombosis after rupture of an atherosclerotic plaque. Venous thromboembolism (VTE)—deep vein thrombosis (DVT) and pulmonary embolism (PE)—and embolic stroke secondary to atrial fibrillation (AF) are the result of pathologic venous clot. As prevention and treatment of these entities are fundamental to the discipline, anticoagulants are an elemental component of the cardiologist's armamentarium. Warfarin, heparin and aspirin have been the standards of antithrombotic and antiplatelet therapeutics, but in the past 15 years low molecular weight heparins (LMWH) and the platelet ADP receptor antagonist clopidogrel have markedly altered the standards of treatment. A new wave of antithrombotic and antiplatelet drugs have been developed that, if approved, may similarly alter the standards of care. In this chapter, we have focused on the mechanisms and potential applications of these new agents, contrasting with the current standards.

CLOTTING, A PRIMER

Prior to discussing individual agents, a brief update on thrombosis: the classic, waterfall cascade, as described by Davie and Ratnoff in 1964,[1] served as a useful basis for understanding the mechanisms underlying clotting (Fig. 1). The addition of an "extrinsic" pathway, triggered by tissue factor (TF) activation of factor VII after endothelial injury, and recognition of factors V and VIII as cofactors transformed the linear cascade into a Y. This new schema placed factor Xa (fXa) in a central position as the first, integrative step of a common pathway. Conveniently, the activated partial thromboplastin time (aPTT) and prothrombin time (PT) are well suited to interrogate for gross abnormalities in the enzymes constituting the intrinsic and extrinsic portions of the cascade. This new formulation has provided an intuitive framework that allows medical students and non-specialist physicians to understand clotting disorders and apply antithrombotic and antiplatelet drugs rationally.

Subsequent research has revealed additional components of the clotting system and highlighted the importance of feedback and inhibition (Fig. 2). Two developments deserve specific mention: First, thrombin has been recognized as an integrating

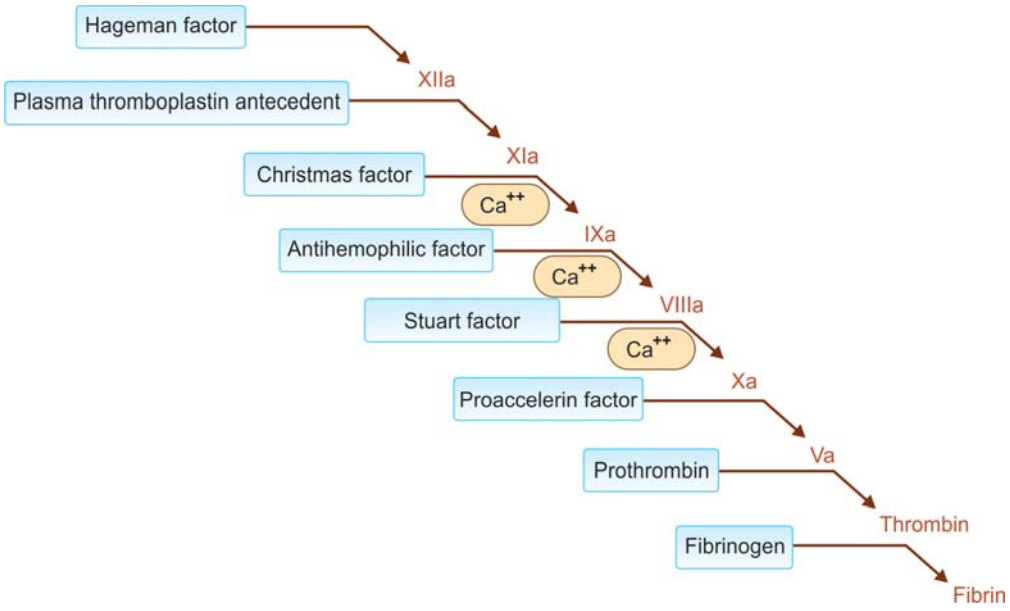


FIGURE 1: Classic waterfall cascade: initially conceived as a linear series of reactions in which each enzyme activated the next to produce fibrin. Original enzyme names are denoted in black with conversion to active enzyme in red using current nomenclature. Although TF and factor VII were not recognized as part of the original clotting cascade, it depicted the sequence of reactions of the intrinsic pathway quite accurately

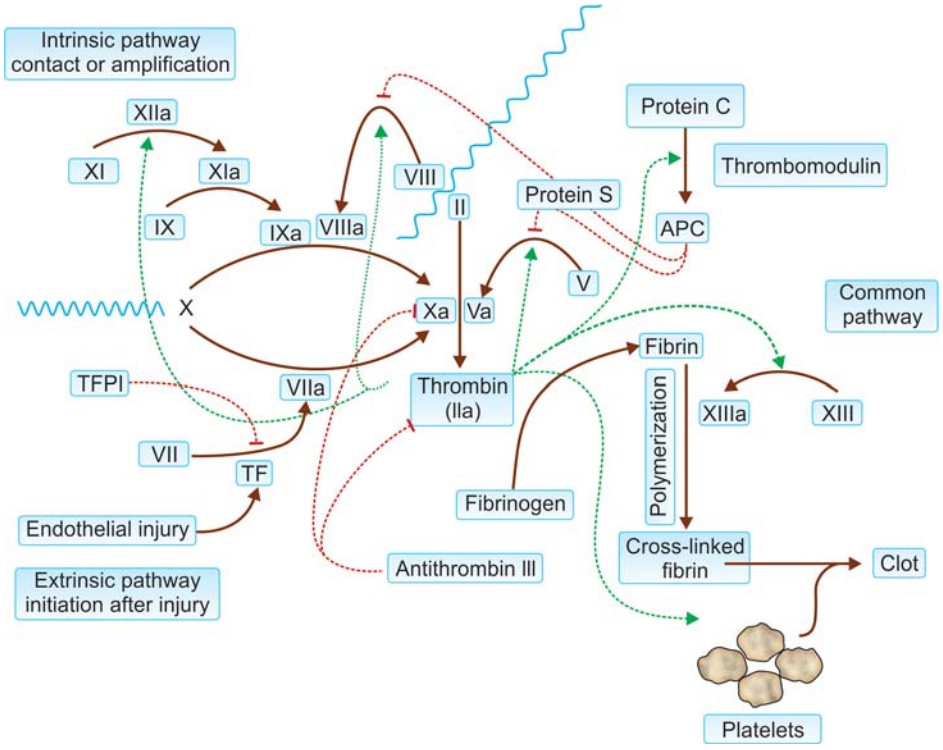


FIGURE 2: Clotting cascade as currently understood: the intrinsic pathway (upper left) proceeds through factors XI, IX and VIII to activation of fX. Activation of fXI can occur through fXIIa, as occurs after addition of a negatively charged trigger in the aPTT, or through thrombin feedback. After endothelial injury, exposed tissue factor complexes with and activates fVII via the extrinsic pathway, which activates fX in turn. The common pathway integrates procoagulant signal and leads to conversion of fibrinogen to fibrin by thrombin. Thrombin and fXa, the two principal anticoagulant targets, are components of the common pathway. *Legend*: Inactive pro-enzymes are gray. Active enzymes are black and denoted with an a. Black arrows signify activation reactions. Molecules astride the arrows are activating protases. Enzymes depicted in smaller type act as cofactors for coagulation proteases. Green, dotted arrows signify action by thrombin as an activating enzyme. Antithrombotic molecules are written in red and their sites of action are denoted by red dotted lines

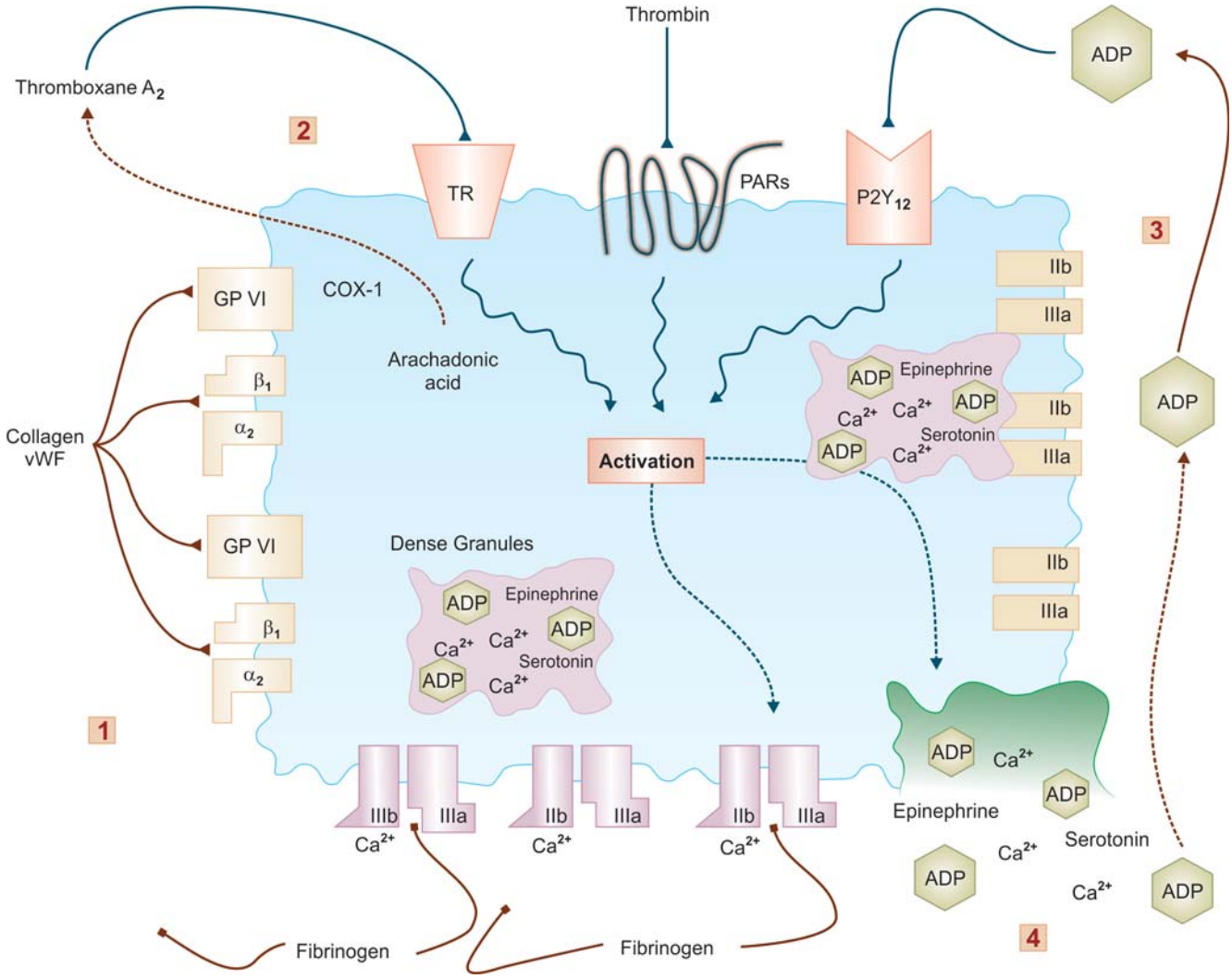


FIGURE 3: Mechanisms of platelet activation: proceeding clockwise, the first step in activation is adhesion (1). After injury, exposed components of the extracellular matrix and subendothelium, such as collagen and vWF, bind to GPVI and integrin $\alpha_2\beta_1$ on the platelet surface. Binding arrests platelet movement at sites of injury and begins the sequence of platelet activation through intracellular signal transduction. Platelet activation and recruitment occur through several signaling pathways. The three major pathways are depicted here (2). Thromboxane A_2, generated from arachidonic acid by COX-1, signals through the thromboxane receptor (TR). The ADP, released from platelets, signals through the $P2Y_{12}$ receptor. Thrombin cleaves the PAR-1 and PAR-4 receptors, leading to intracellular signaling. Of the three, thrombin is the most powerful activating agent. *Activation* (3) occurs through a number of intracellular pathways in response to thrombin, TxA_2 or ADP signaling. As a result, dense granules are released and conformational changes of GP IIb/IIIa occur, making them highly avid for fibrinogen. Other cellular changes, including platelet flattening and exposure of negatively charged phospholipids, also result. The final step is *aggregation* (4). Divalent fibrinogen molecules bind to the GP IIb/IIIa receptors of adjacent platelets. Given the high density of this receptor on the platelet surface, adjacent platelets become multiply interconnected, forming a platelet plug[3]

enzyme in the coagulation pathway. In addition to its principal role converting fibrinogen to fibrin, it forms positive feedback loops to the intrinsic arm of the clotting cascade, activating factors V, VIII and XI (as well as XIII). Rather than an orphan arm of the clotting cascade, the intrinsic pathway is now viewed as the site of feedback amplification in thrombosis—after initiation via the quickly inhibited extrinsic pathway—and a promising target for future anticoagulants.[2] Understanding of the central role played by thrombin has lead to the development of new direct thrombin inhibitors (DTI) that show promise in treating venous and arterial thrombi. The second development is discovery of multiple platelet signaling pathways. The recognition of additional activating pathways—unaffected by aspirin—has lead to the development of new antiplatelet agents that are essential for treatment of arterial thrombi.

Arterial and venous thrombi are composed of identical components; platelet aggregates, fibrin and jailed red cells, but the relative proportions in each are distinct.

Arterial thrombi are composed primarily of platelet aggregates and fibrin, in contrast to platelet-poor venous thrombi. Under the high-shear conditions of the arterial circulation, platelets serve as the stable foundation for clot propagation (Fig. 3). Platelet movement is arrested at sites of injury by adherence of constitutively expressed platelet receptors GPVI, GPIb and $\alpha_2\beta_1$ to newly exposed, subendothelial von Willebrand Factor (vWF) and collagen. Receptor binding

initiates platelet activation. Adherent platelets release dense granules that contain ADP and ionized Ca, synthesize and release thromboxane A_2 (TXA_2). The adherent platelet also alters its conformation, flattening against the damaged vessel wall to provide a phospholipid and Ca^{2+} rich surface on which the clotting cascade can function efficiently. Via their respective receptors, ADP, TXA_2 and thrombin activate and recruit additional platelets at the site of injury. In activated platelets, conformational change of the abundant cell-surface receptor GPIIb/IIIa markedly increases its affinity for fibrinogen.[4] The plug is reinforced as fibrinogen molecules, produced via the clotting cascade, cross-link platelets.

ANTITHROMBOTIC AGENTS

THE HEPARINS AND INDIRECT Xa INHIBITORS

Unfractionated heparin (UFH) is the prototype intravenous anticoagulant. Derived from porcine intestinal mucosa, UFH is a polysaccharide with average molecular weight of 15 kDa. A specific pentasaccharide sequence within this polymer binds to antithrombin III (AT), inducing a conformational change that allows direct and potent fXa inhibition. The AT-heparin complex also inhibits thrombin. The UFH does not enhance AT inhibition of thrombin, but rather serves as a physical bridge, approximating the two molecules. A heparin must have 18 or more saccharide units (MW ~ 5.4 kDa) to facilitate AT-thrombin interaction. Given the average size of a UFH molecule, the vast majority can inhibit thrombin and fXa (an inhibition ratio of 1:1). Prothrombinase bound Xa or fibrin bound thrombin are relatively inaccessible to the AT-heparin complex due to its large size.[5]

Indications

Unfractionated heparin can be used in any situation in which parenteral anticoagulation is required. UFH is well suited to short-term or high-risk anticoagulation due to its short half-life (1–2 hrs) and potential for reversal with protamine. This salmon sperm derived protein binds avidly to long-chain heparins, forming complexes that are cleared via the kidney, extinguishing its anticoagulant effect. UFH is appropriate for a wide range of situations, including anticoagulation during acute coronary syndrome (ACS), maintenance of anticoagulation for high-risk patients in the perioperative setting and DVT prophylaxis. In many of these situations, heparin has been replaced by LMWH due to ease of administration. There are a small number of indications in which heparin is the current standard of care (bivalirudin, discussed below, may replace UFH for indication 4):

1. Patients with a high bleeding risk with indication for short-term anticoagulation.
2. Patients with renal impairment; as LMWH is cleared by the kidneys, it is contraindicated in patients with CrCl < 30 ml/min. UFH is not dependent on renal excretion.
3. Massive PE or extensive DVT; LMWH was not studied in these populations.
4. PCI; short half-life, ease of point-of-care monitoring with aPTT or activated clotting time (ACT).
5. Cardiopulmonary bypass (CPB) and other extracorporeal circuits due to experience and full reversibility.

Limitations, Monitoring and Adherence

The UFH is extensively bound to plasma proteins (including platelet factor 4 (PF4) and high molecular weight vWF multimers) whose concentrations vary from patient to patient. The effect on individual patients is variable and UFH must be monitored to achieve appropriate anticoagulation. As a strictly parenteral and subcutaneously (SQ) administered anticoagulant, out of hospital uses are rare and monitoring occurs as a part of inpatient care. The aPTT should be tested 4–6 hours after the initiation of therapy. Once the therapeutic aPTT is reached, usually 1.5–2 times reference, UFH can be safely monitored on a daily basis so long as dosing remains constant. The UFH also requires regular monitoring of platelet count due to the risk of heparin-induced thrombocytopenia (HIT, also known as HTTS).

The HIT is a principal adverse effect of UFH given its potential severity. Antibodies against the heparin-PF4 complex cause HIT by activating the cascade of platelet activation described above. The indiscriminate activation of platelets causes an initial drop in platelet count, usually occurring by week two of therapy, and is followed by widespread arterial thrombosis if the condition is not recognized and UFH withdrawn.[6] Other limitations of UFH include a greater risk of subtherapeutic anticoagulation, resulting less efficacious anticoagulation. When compared to LMWH in the treatment of acute VTE, meta-analyses have found increased total morality and risk of patient bleeding.[7] Although a lesser concern, long-term treatment with UFH has been associated with osteoporosis, through a direct inhibitory effect on osteoblasts.

LOW MOLECULAR WEIGHT HEPARINS

Low molecular weight heparins (LMWH) including enoxaparin, dalteparin and nadroparin are commercial preparations produced by controlled depolymerization (shortening) of UFH to an average MW of 5 kDa. Due to its shorter average molecular length, few molecules are able to bridge AT to thrombin. Therefore, LMWH exerts majority of its effect through indirect inhibition of fXa with an anti-Xa/anti-IIa ratio of ~3.8. In contrast to heparin, exclusively renal excretion occurs in a dose-dependent fashion.

Advantages and Indications

The LMWH has high (90%) bioavailability, which translates to predictable plasma levels after SQ administration. The half-life of most LMWH is approximately 4 hours, which allows daily or BID administration. These properties allow weight-based administration without a daily monitoring requirement, a significant convenience and cost advantage. The LMWH is also better suited for long-term therapy, as patients can self-administer SQ injections. Furthermore, when compared to UFH, incidences of HIT and osteoporosis are significantly lower.[8]

Most studies comparing LMWH to UFH have measured asymptomatic venous thrombosis as a primary endpoint, rather than fatal thromboembolism, due to low incidence of the latter.

The LMWH has been found non-inferior to UFH with respect to prevention of DVT in a wide range of clinical settings, with equivalent safety profiles. The LMWH, specifically enoxaparin, has shown equivalency with UFH in ACS. The appropriate use of LMWH in the catheterization lab remains unsettled, due to potential increased bleeding risk, and falls outside the scope of this chapter. A full discussion can be found in other sections of this text. On the strength of these studies, LMWH have the following FDA indications:[9,10]

- Prophylaxis of DVT in patients undergoing abdominal surgery (40 mg SQ daily), total knee replacement or total hip replacement (30 mg SQ BID) and medically ill patients (40 mg SQ daily) with limited mobility.
- Inpatient treatment of acute DVT with or without PE.
- Outpatient treatment of acute DVT without PE.
- Prophylaxis of recurrent ischemia in patients with unstable angina and NSTEMI in conjunction with aspirin.[11]
- Treatment of acute STEMI with thrombolysis in conjunction with aspirin; whether managed medically or subsequent PCI.[12]
- Extended treatment of VTE in patients with cancer (dalteparin).

Despite the lack of US clinical indication, LMWH are used (off-label) for treatment of VTE in pregnancy and for "bridging" during temporary discontinuation of warfarin in patients with prosthetic heart valves who are preparing to undergo a surgical procedure.

Limitations, Monitoring and Adherence

Two important situations exist in which weight-based dosing does not produce levels of anticoagulation; in patients with renal failure (CrCl < 30 ml/min) and individuals more than 100 kg of weight. The LMWH is contraindicated in these situations given the difficulty of monitoring. Unlike UFH, the aPTT does not reflect the level of anticoagulation after administration of LMWH. When monitoring is required, an anti-fXa level is the most accurate measure of anticoagulation, but this test is infrequently available. The LMWH is only partially reversible with protamine (~ 60%); therefore it is relatively contraindicated in settings that may require rapid reversal, such as PCI. Finally, LMWH carries a black box warning due to increased risk of epidural hematoma in patients who are under treatment or will be treated with LMWH. Repeated attempts at spinal puncture, concurrent treatment with other medications affecting hemostasis, including NSAIDs, and indwelling spinal catheters further increase the risk for this complication.

FONDAPARINUX

Fondaparinux is a synthetic analogue of the ATIII binding pentasaccharide sequence found in heparins, producing equivalent fXa inhibition to LMWH. Administered in IV form only, it is 100% bioavailable.

Advantages and Indications

Although theoretic advantages of fondaparinux exist, including more predictable dosing, evidence is lacking that fondaparinux is superior to LMWH. Nevertheless, the drug is broadly approved for treatment of acute DVT, PE[13] and DVT prophylaxis in a manner similar to LMWH. The OASIS-5 study compared outcomes of ACS patients treated with 6 days of either fondaparinux to LMWH. The investigators found fondaparinux non-inferior at 9 days with respect to patient outcomes with fewer bleeding episodes and improved 30 days mortality.[14] Based on these findings, fondaparinux receives a class 1 indication as alternative therapy to either UFH or LMWH in the recent ACCF/AHA Focused Update of the Guidelines for the Management of Patients with Unstable Angina/Non-ST Elevation Myocardial Infarction.[14a] However, guiding catheter thrombosis and other intra-procedural thrombotic effects were increased in patients treated solely with fondaparinux who underwent subsequent PCI.[15] This finding greatly tempered enthusiasm for the drug as a potential UFH replacement in ACS. Recently, the CALISTO trial demonstrated a beneficial effect of fondaparinux 2.5 mg daily (over 45 days) for the treatment of symptomatic superficial thrombophlebitis, when compared to placebo.[16] Fondaparinux has been used for the treatment of HIT, as thrombocytopenia and thrombosis are less likely than with LMWH. In theory, the small molecule is less likely to activate preformed PF4 antibodies, but case reports of HIT after fondaparinux use do exist.[17] Finally, as a synthetic molecule, there is no risk for bacterial contamination, as has occurred with UFH.

Limitations, Monitoring and Adherence

Overall, similar to LMWH, fondaparinux is principally cleared by the kidneys, and is contraindicated in patients with CrCl less than 30. Unlike LMWH, it is contraindicated in patients less than 50 kg, which may exclude a large number of elderly patients and women.

IDRABIOTAPARINUX

Idrabiotaparinux is a hypermethylated fondaparinux derivative with half-life of 130 hours, designed as a once weekly drug. Like fondaparinux, it is primarily excreted via the kidney.[18] Originally developed as idraparinux, the drug was tested as extended therapy for prevention of VTE in patients with acute DVT or PE.[19] In this study, idraparinux 2.5 mg SQ weekly was equivalent to standard therapy (LMWH and warfarin) with less observed bleeding in patients with DVT, but inferior to standard therapy after PE. A study of extended prophylaxis versus placebo (12 months) found reduced thromboembolism but with increased risk of major bleeds, including intracranial hemorrhage (ICH).[20] Subsequently, an open label trial of idraparinux in AF was stopped early given increased major bleeding events, also including ICH.[21] The development of idraparinux was halted due to the increased risk of bleeding, long half-life and irreversibility.

Renamed idrabiotaparinux after addition of a biotin moiety, the compound was now reversible by IV administration of avidin, a protein derived from eggs. Like protamine, avidin binds tightly to idrabiotaparinux, leading to rapid clearance. An initial bioequivalence study found the two molecules equivalent, with respect to clinical outcome, in treatment of acute DVT. Fewer major bleeding episodes were reported in the idrabiotaparinux group.[22] Avidin produced marked (~ 80%) and sustained

reduction in anti-Xa levels, a surrogate for effect as a reversal agent. Based on this finding, new studies of idrabiotaparinux are underway in the treatment of PE (CASSIOPEA study; NCT00345618) and AF (BOREALIS-AF; NCT00580216).

AVE5206

AVE5206 is a "hemisyntheic" molecule produced by depolymerization of heparin with an enzyme that selectively spares bonds included in the AT-binding sequence. This ultra low molecular weight heparin has a molecular weight of 2.4 kDa and anti-Xa/IIa ratio of ~ 80.[23] Like fondaparinux, the lower molecular weight and more specific AT binding are thought to produce higher bioavailability by lowering non-specific binding. Initial in vitro comparison to enoxaparin showed greater anti-Xa activity. Equivalent in vivo activity was observed in a rat model of venous thrombosis and canine model of arterial thrombosis. An initial dose finding study in post-total knee replacement patients showed that AVE5026 prevented DVT in a dose-dependent manner. Once daily 20 mg and 40 mg SQ doses were significantly more efficacious than enoxaparin 40 mg SQ daily, which is lower than the FDA-approved dose.[24] The rates of bleeding in these groups were comparable. The performance of this drug in other clinical settings remains untested.

VITAMIN K ANTAGONISTS (VKA)

WARFARIN

Warfarin is the oral anticoagulant against which all newer anticoagulants are measured. Despite its many drawbacks (see below), it has been successfully used to treat a wide range of thrombotic conditions. A significant infrastructure for monitoring now exists and clinicians are comfortable with use of the drug.

Mechanism and Indications

Warfarin sodium is a dicumarol[25] derivative that blocks addition of g-carboxyglutamic acid (Gla) to factors II, VII, IX, X, protein C and protein S by the vitamin K epoxide reductase (VKOR) enzyme complex. Inhibition of this reaction impairs the final, activating step in hepatic synthesis of these vitamin K-dependent clotting factors (Fig. 4).

The VKA are currently indicated for the treatment of the following conditions:

- Antiphospholipid antibody syndrome (APLAS)
- Primary prevention of stroke or systemic embolism in patients with atrial fibrillation
- Secondary prevention of recurrent CVA
- Secondary CAD prophylaxis after ACS or MI
- Heparin-induced thrombocytopenia (HIT)
- Impaired LV function[26]
- Peripheral arterial occlusive disease
- Prosthetic cardiac valve[27]
- Endocarditis without intra-cerebral abscess[28]
- Protein C deficiency
- Protein S deficiency
- Pulmonary embolism—acute treatment and secondary prophylaxis
- Venous thromboembolism (VTE, including DVT)—acute treatment and secondary prophylaxis

Given the extensive number of indications, a dosing discussion for each is beyond the scope of this chapter and best obtained from disease specific resources, such as AHA/ACC guidelines (e.g. AF, heart failure, valvular heart disease, etc.), ACCP evidence-based clinical practice guidelines (e.g. PE, VTE, etc.)[29] and Micromedex.

Limitations, Monitoring and Adherence

The significant cost and burden of monitoring, numerous drug interactions and a narrow therapeutic window make warfarin therapy challenging for patients and providers. Recent studies have shown that, on average, the typical patient on long-term anticoagulation for AF is within the therapeutic range just over 50% of the time. In specialized anticoagulation clinics, this percentage increases to 63%.[30] This difference has clinical significance, as a 10% improvement of time in therapeutic range (TTR) correlates with a 29% reduction in all-cause mortality.[31,32]

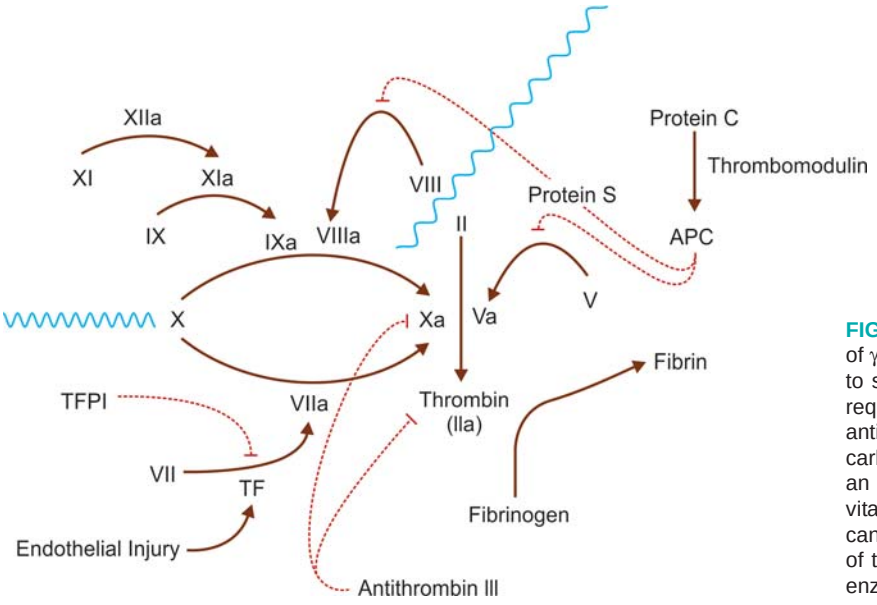


FIGURE 4: Sites of warfarin effect: vitamin K is a cofactor of γ-glutamyl carboxylase, which adds a carboxyl moiety to several proteases of the clotting cascade. Proteases requiring carboxylation are II (prothrombin), VII, IX, X and anticoagulant proteins C and S. Without addition of the carboxyl group, these enzymes are inactive. Warfarin is an inhibitor of vitamin K epoxide reductase (VKOR). If vitamin K remains oxidized through inhibition of VKOR, it cannot function as a cofactor and hepatic carboxylation of these enzymes is decreased. The names of affected enzymes are blurred in the figure

Conversely, elevated INR (especially > 4.0) places patients at risk for bleeding complications.[33] Patient adherence is an additional barrier to successful therapy with VKAs. A significant number of patients (22–33%) newly started on warfarin therapy for AF discontinue treatment by the end of year one. Several factors are associated with poor adherence to warfarin; younger age, males, poverty and homelessness, but also higher educational achievement and employment.[34] The difficulty of maintaining patient adherence and concerns about bleeding complications dissuade many clinicians from initiating warfarin therapy when treatment is indicated.

These reasons have spurred the search for new, oral anticoagulants that will maintain treatment efficacy, improve patient adherence, minimize monitoring and maximize safety. The following sections discuss new therapies that have shown promise as potential replacements for warfarin.

ATI-5923

ATI-5923 also known as tecarfarin, this new VKA also acts as a VKOR and is a structural analogue of warfarin. As such, it can be monitored via the INR. Unlike warfarin, it is a single enantiomer that is highly protein bound and metabolized by carboxyesterases in the liver to a single, inactive metabolite. This single enantiomer is not metabolized by the CYP450, potentially avoiding the many drug-drug interactions that complicate warfarin therapy. A phase IIA study of tecarfarin found that, over a 6–12 period, patients had a TTR exceeding 71%. More impressive, patients were found to be in the extremes on INR (< 1.5 or > 4.0) at a 1.2% rate.[35] The authors of this study argue that this medication may offer the same proven efficacy of warfarin with more predictable patient response and fewer complex drug interactions. Recently, investigators administered tecarfarin and warfarin to healthy volunteers in before and after fluconazole, a potent CYP2C9 and CYP3A4 inhibitor. They found that the serum levels of tecarfarin were unaffected while levels of warfarin increased 213% when given in conjunction with fluconazole.[36] Despite these promising preliminary results, the results of a phase II/III trial in 600 patients with prosthetic heart valves (EmbraceAC) did not demonstrate improved TTR in tecarfarin when compared to warfarin.[37]

DIRECT FACTOR Xa INHIBITORS

The direct fXa inhibitors are a new class of (primarily) orally formulated anticoagulants that have pharmacologic profiles similar to that of LMWH. The promise of this class lies in its potential to replace warfarin for long-term indications without need for routine monitoring or "bridging" during the peri-operative period. Early studies indicate that the direct fXa inhibitors may also replace LMWH in some settings such as postoperative DVT prophylaxis.[38] It remains to be seen whether the therapeutic index of these drugs is wide enough to permit use of in a broad range of clinical settings.

RIVAROXABAN

Rivaroxaban, an oral agent, is the prototype drug in this class and was approved by the FDA in late 2011 for prevention of stroke and systemic embolism in persons with atrial fibrillation.

Mechanism

In contrast to the heparins, this new class of inhibitors directly inhibits fXa without involvement of AT III. Direct inhibitors can bind to the prothrombinase complex, not accessible AT III-mediated indirect inhibitors, with resultant reduction in thrombin generation. Rivaroxaban binds to the S1 side pocket of fXa rather than the active site.[39] The small molecule binds rapidly and reversibly, inhibiting fXa in a dose-dependent manner. Rivaroxaban prolongs PT to a greater extent than aPTT, but due to variable interaction with assay reagents these values cannot be used reliably for monitoring. The compound has high oral bioavailability (> 80%), reaches maximum concentration in 2–4 hours with a 7–11 hour terminal half-life. These properties permit daily, weight-based dosing, obviating the need for monitoring in many patients.

Efficacy

The first phase III studies compared oral rivaroxaban to SQ enoxaparin in orthopedic postoperative DVT prophylaxis. The RECORD1 study demonstrated that rivaroxaban treatment for 1 month after THA reduced asymptomatic and major VTE with rates of bleeding equivalent to once daily LMWH, an EU-approved dosing regimen.[40] In the RECORD 4 study, rivaroxaban provided superior protection from VTE when compared to enoxaparin 30 mg SQ BID (FDA approved dose) after TKA.[41] There were trends toward increased bleeding in the rivaroxaban groups, but they did not reach significance. Based on these studies, rivaroxaban is approved in the EU and Canada for VTE prophylaxis after orthopedic surgery at the 10 mg daily dose.[42] Methodological concerns regarding two additional RECORD studies[43,44] and evidence of increased bleeding in rivaroxaban-treated groups, when adjusted for covariates, has led the FDA to delay drug approval.[45]

Phase three studies of rivaroxaban have now been completed. ROCKET AF is the most significant of these trials.[46] In this non-inferiority study, fixed dose oral rivaroxaban (20 mg daily) was compared to adjusted dose warfarin for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation. Over 14,000 patients were enrolled and median follow up was 590 days. The patients included in this study were at high risk of stroke, as evidenced by mean $CHADS_2$ score of 3.5. Rivaroxaban was found to be noninferior to warfarin in the intention-to-treat analysis with significant reductions in intracranial hemorrhage and fatal bleeding. The absolute number of strokes and systemic emboli observed in the rivaroxaban arm was lower than in the warfarin arm, but debate persists regarding the statistical significance of this finding.[47] The EINSTEIN study of rivaroxaban for the treatment of acute symptomatic DVT was reported in late 2010.[48] In the open-label, randomized portion of the non-inferiority study, rivaroxaban (15 mg orally BID for 3 weeks, followed by 20 mg daily) was found to be non-inferior to standard therapy with subcutaneous enoxaparin followed by VKA. In the rivaroxaban treatment arm, there was no increase in the incidence of major bleeding and fewer recurrent DVT were observed. Superiority was reported with respect to

recurrent VTE in a randomized, double-blind extension study (versus placebo), but at the expense of increased major and clinically relevant bleeding episodes. The most recently reported phase III trial is ATLAS ACS 2-TIMI 51, a double-blind, placebo controlled evaluation of rivaroxaban for secondary prevention of death from cardiovascular causes, MI or stroke after acute coronary syndrome (ACS).[49] The authors reported a reduction in the primary, composite endpoint in both the 2.5 mg PO BID and 5 mg PO BID treatment arms. When compared to placebo, significantly lower rates of death secondary to cardiovascular causes and significantly lower rates of all-cause death were observed in the 2.5 mg PO BID treatment arm. Significantly higher rates of TIMI major bleeding and ICH were reported in rivaroxaban-treated patients. Finally, the MAGELLAN study of VTE prevention in medically ill patients has been presented in abstract, but has not been published in a peer-reviewed journal at the time of writing.[50]

Limitations, Monitoring and Adherence

Rivaroxaban undergoes hepatic metabolism (via CYP3A4/A5 and CYP2J2) and renal excretion of active and inactive metabolites. Initial studies of rivaroxaban have found minimal interaction with clinically important medications; atorvastatin, ASA and NSAIDs, clopidogrel, ranitidine and digoxin. However, strong inhibitors of CYP3A4 and P-glycoprotein, such as azole antimycotics and protease inhibitors (PI), significantly raise plasma concentrations of rivaroxaban.[34] Due to significant renal excretion, rivaroxaban is contraindicated in patients with creatinine clearance < 30 ml/min, similar to LMWH. Drug levels were unaltered in patients with Child-Pugh A hepatic impairment, but patients with more severe liver disease have not been studied. A weight-based daily dose can be administered to all patients without significant liver or kidney impairment.

APIXABAN

Apixaban is a second direct fXa inhibitor in advanced stages of testing. Like rivaroxaban, the molecule is a selective, reversible fXa inhibitor that reaches maximum plasma concentrations quickly (~ 3 hrs) after administration, and has a prolonged half-life (8–14 hrs). About 50% of absorption occurs after oral administration. The drug is metabolized, predominantly, through non-hepatic pathways with renal excretion a major (~ 30%) route of elimination.[51,52] CYP3A4 mediates hepatic metabolism. Uses of potent inhibitors (azole antifungals, macrolide antibiotics and PI) are contraindicated in conjunction with apixaban.[53] The advantages (oral dosing without routine monitoring) and disadvantages (possible increased bleeding, limitation of use in renal impairment and drug interactions) of apixaban appear similar to those of rivaroxaban.

Efficacy

Its development has followed a trajectory similar to that of rivaroxaban. Dose ranging studies for DVT prophylaxis after orthopedic surgery,[54] DVT treatment[55] and ACS[56] demonstrated prevention of thrombosis efficacy and acceptable safety profile. An initial comparison of apixaban (2.5 mg PO BID) to enoxaparin (30 mg SQ BID) after TKA did not demonstrate non-inferiority due to an unexpectedly low event rate.[57] Nevertheless, less bleeding was observed in the apixaban group and the drugs' safety profiles were comparable. A follow-up, post-TKA study in comparison to enoxaparin 40 mg SQ daily over 10–14 days, demonstrated a significant decrease in rate of VTE without an increase in bleeding.[58] Ongoing trials will compare apixaban to enoxaparin in post-THA (ADVANCE-3; NCT00423319), prevention of VTE in patients with metastatic cancer (NCT00320255) and medically ill patients (ADOPT; NCT00457002).

Two phase III stroke prevention studies with apixaban have recently been reported. The first, AVERROES, compared apixaban 5 mg twice daily with aspirin for stroke prevention in patients with atrial fibrillation in whom warfarin therapy was "unsuitable".[59] The rate of stroke or systemic embolism in patients treated with apixaban was significantly reduced when compared to patients treated with ASA (relative risk 0.45). The rates of major bleeding and intracranial hemorrhage were not increased in the apixaban treatment arm. A decreased rate of all-cause death (non-significant) was observed in the apixaban treatment arm. This result was not surprising in light of the well established superiority of therapeutic anticoagulation, in comparison to aspirin, in patients with atrial fibrillation and elevated risk of stroke. The subsequent ARISTOTLE study compared apixaban 5 mg twice daily to warfarin in patients with atrial fibrillation.[60] The mean stroke risk of the large study population (CHADS2 2.1) was lower than that of ROCKET AF. Apixaban was superior to warfarin in the prevention of stroke and systemic embolism with rates of major bleeding that were significantly decreased. Additionally, the rates of death from any cause were significantly decreased in the apixaban treatment arm. A placebo-controlled trial of apixaban for secondary prevention of recurrent ischemic events after ACS did not show a reduction of events and was associated with an increase in of major bleeding.[61]

Finally, studies of acute DVT treatment (AMPLIFY and AMPLIFY-EXT; NCT00633893 and NCT00643201, respectively) are underway.

Several other direct fXa inhibitors are in various stages of development. Below are brief summaries of three:

- Edoxaban (DU-176b) has reached late-stage testing in a number of clinical settings. Phase II studies showed efficacy in TKA, THA (v. dalteparin) and AF.[62] In the ENGAGE-AF TIMI 48 trial (NCT00781391), two doses of edoxaban will be compared to standard warfarin therapy for stroke prevention in AF. Phase III trials of DVT prophylaxis after THA, TKA, hip fracture and acute treatment of symptomatic DVT/PE are underway.
- Betrixaban is at an earlier stage of development, but has shown efficacy in prevention of DVT after TKA.[63] Extrarenal clearance sets betrixaban apart from other drugs in the class. A preliminary study in patients with mild, moderate and severe renal impairment is underway (NCT00999336).
- Otamixaban is parenteral in formulation. It was developed as a potential replacement for heparin in ACS. The phase II SEPIA-ACS TIMI 42 trial compared five doses of otamixaban doses to heparin plus eptifabitide. Intermediate doses showed efficacy and bleeding rates comparable to standard therapy. Lower doses of otamixaban were

associated with increased thrombotic complications while the highest dose was associated with excess bleeding.[64]

DIRECT THROMBIN INHIBITORS

Thrombin is a key point of propagation in thrombosis and hemostasis (as discussed above). Not only does active thrombin convert fibrinogen to fibrin but also creates a positive feedback loop by activating factors V, VIII and XI. It also acts as a potent activator of platelets.[65] Given this central location in the clotting cascade, it is an attractive anticoagulant target. UFH indirectly inhibits thrombin, mediated by AT III, but this complex has limited activity against fibrin-bound thrombin. The inability to inhibit fibrin-bound thrombin, the site of clot propagation, is a potentially significant limitation. The direct thrombin inhibitors (DTI) are designed to overcome this limitation.

Thrombin's activity can be inhibited at three separate locations on the molecule: (1) the active, catalytic site; (2) exosite 1, the dock for substrates such as fibrin and (3) exosite 2, the heparin binding domain. Two classes of DTI are distinguished by their mechanism of inhibition. The bivalent DTI are derived from hirudin, a naturally occurring compound that was isolated from the leech in 1905—the first anticoagulant. The bivalent DTI, as the name suggests, exert their inhibitory effect through binding to exosite 1 and the catalytic site. Univalent DTI, in contrast, are small synthetic molecules that bind only to the active site.[66] None of the DTI bind at exosite site 2, the heparin-binding site. The bivalent DTI are parenteral in formulation and have limited clinical application outside the catheterization lab. The first oral DTI, dabigatran, has been approved by the FDA and, along with the direct fXa inhibitors, may significantly change standards of anticoagulation.

HIURDIN

Hiurdin, isolated from *Hirudo medicinalis*—the medicinal leech, is not used as a commercial anticoagulant. Two recombinant hirudins (r-hirudin or lepirudin and desulfato-hirudin or desirudin) differ at a single amino acid and are used in clinical practice. Referred to generically as hirudin, the three molecules are pharmacologically interchangeable.

Mechanism and Monitoring

Hirudin forms an irreversible 1:1 complex with thrombin and interacts minimally with plasma proteins. Hirudin has a short half-life in patients with normal renal function. Therapeutic levels are reached in 30–60 minutes after beginning IV infusion. Excretion is predominantly renal. Functional half-life is extended in patients with renal dysfunction and can reach 5 days in patients with absent kidney function. The aPTT is the test for choice of monitoring hirudin anticoagulation, but the response is linear only to 60–70 seconds. Beyond that point, the aPTT will underestimate the level of coagulation. If higher levels of anticoagulation are desired, such as during CPB, the ecarin clotting time (ECT), a thrombin-based measure of clotting, is the appropriate test. Both tests have the potential to underestimate degree of anticoagulation in patients with reduced levels of prothrombin (e.g. severe liver disease, diffuse intravascular coagulation (DIC) or concurrent VKA treatment), and in patients with fibrinogen depletion (e.g. post-thrombolysis or hemodilution during CPB).[67]

Indications

Hirudins have two specific indications. Based on the HAT trials, lepirudin is approved for treatment of HIT complicated by thrombosis. In these studies, the incidence of new thrombosis was significantly lowered, by 93%, in the hirudin groups as compared to historical controls.[68,69] The risks for limb amputation or death were equivalent in the two groups. Current standards advocate immediate heparin withdrawal, regardless of thrombosis at the time of diagnosis; followed by immediate parenteral anticoagulation until a therapeutic INR has been reached with a VKA.[70] In this setting, the use of hirudin is appropriate in patients with preserved renal function. Given its ability to inhibit clot-bound thrombin, lepirudin was also studied as an alterative to heparin during PCI.[71] In these studies, hirudin was more effective in prevention of ischemic endpoints but not significantly better than heparin in prevention of cardiovascular death or MI at 1 week. Higher rates of bleeding and increased transfusion requirements observed in the studies negated the potential beneficial effects. Hirudin is an appropriate alternative during PCI in patients with HIT and has demonstrated efficacy in this population.[72] The second, but little used, indication for desirudin is prophylaxis and treatment of DVT.[73] This is appropriate only in patients with confirmed or suspected HIT/HTTS given the often-used alternatives. Hirudin has been employed in CPB complicated by HIT, where it provided effective anticoagulation but increased postoperative blood loss.[74,75]

Limitations

The two primary limitations of hirudins are mutually reinforcing. The extreme dependence on normal renal function to maintain predictable anticoagulation can make avoiding over anticoagulation difficult. Given the increased rate of bleeding, for which the greatest risk factor is impaired renal function, treatment of elderly or critically ill patients is challenging and requires close monitoring. There is no antidote to hirudin. When bleeding is life-threatening and occurs after hirudin use, only specific HD filters are effective for removal.[76] Greater than 44% of patients exposed to lepirudin develop antibodies, which have little clinical effect and may enhance the antithrombotic effect.[77] Despite the frequent development of antibodies, the risk of true anaphylactic reaction is extremely low (estimated at 0.015% after first exposure) and manifests within minutes of IV administration.[78]

BIVALIRUDIN

Bivalirudin (Angiomax, formerly Hirulog) is a synthetic, bivalent DTI and hirudin analogue. Unlike hirudin, the molecule is cleaved after binding, producing transient inhibition of thrombin.[79] Bivalirudin has a lower affinity for thrombin than hirudin by 1000-fold and does not spur antibody formation. The drug is degraded by proteolytic and hepatic mechanisms. Because it is cleared by glomerular filtration alone, dose adjustment is required in patients with renal impairment.

Indications and Efficacy

Due to short half-life and IV formulation, bivalirudin is administered as a continuous infusion after an initial bolus. The principal indication is as an alternative anticoagulant during PCI. Bivalirudin can also be used for treatment of HIT/HTTS, but its mode of administration makes use impractical in non-critical care settings. Current FDA indications are:[80]

- Use as an anticoagulant in patients with unstable angina undergoing percutaneous transluminal coronary angioplasty (PTCA).
- Use as an anticoagulant in patients undergoing percutaneous coronary intervention (PCI) with provisional use of glycoprotein IIb/IIIa inhibitor (GPI) is indicated.
- Bivalirudin is indicated for patients with or at risk of HIT/HITTS undergoing PCI.

Bivalirudin has been studied in conjunction with optimal antiplatelet therapy, including aspirin (and clopidogrel, if indicated). The drug has not been studied in patients with ACS who are not undergoing intervention.

Discussion regarding the choice of heparin versus bivalirudin in PCI can be found in other chapters, but the studies supporting these indications are discussed briefly below. The REPLACE-2 study was the first to evaluate bivalirudin as compared to standard therapy; heparin and scheduled glycoprotein IIb/IIIa inhibitor (GPI), during scheduled PCI.[81] The study found that bivalirudin, with optional use of GPI for intra-procedural complication, was non-inferior to the standard of care with respect to the primary endpoint through 6 months. Significantly lower rates of bleeding were noted in the bivalirudin-treated group. Patients with unstable angina or NSTEMI were randomized to one of three groups in the ACUITY trial; bivalirudin alone, bivalirudin plus GPI or heparin plus GPI.[82] Bivalirudin alone was equivalent to either GPI-containing regimen with respect to MI, revascularization and death at 30 days and 1 year. As in the REPLACE-2 study, rates of bleeding were significantly lower in the unaccompanied bivalirudin group. This result underlines the import of thrombin in pathologic platelet activation. Most recently, the HORIZONS-AMI trial evaluated bivalirudin alone in comparison to heparin and GPI in STEMI.[83] Significantly lower rates of bleeding during hospitalization, cardiac and all cause death at 30 days were observed in the bivalirudin group. Increased acute stent thrombosis was observed at 24 hours in bivalirudin treated patients, but a significant difference was not observed at 30 days. Bivalirudin has shown efficacy comparable to heparin when used during on-pump and off-pump CABG, with lower rates of bleeding and decreased transfusion requirements.[84–87]

Limitations and Monitoring

The two main limitations of bivalirudin are its exclusively parenteral formulation and its route of excretion, requiring dose adjustment patients with renal dysfunction. Assuming normal renal function, the half-life of bivalirudin is approximately 25 minutes. Coagulation parameters return to normal 1 hour after cessation of IV infusion. In patients with moderate, severe or dialysis-dependent renal impairment, clearance is prolonged by 20%, 60% and 80%, respectively.[88] The drug is 25% cleared by hemodialysis. As with all anticoagulants, it confers an increased risk of bleeding, but the lower rates of bleeding in the aforementioned trials make it an appropriate alternative during PCI, PTCA or CABG. The aPTT can be used for monitoring at lower levels of anticoagulation; up to 3 times the upper limit of normal. Above this limit, the test is no longer sensitive.[89] In practice, the ACT is used for monitoring during catheterization and coronary bypass due to the high levels of anticoagulation required. In this setting, target ACT range is over 200 seconds.[90]

ARGATROBAN

Argatroban is a synthetic, small molecule derived from L-arginine. This univalent DTI, as a prototype of the class, reversibly inhibits only the active site of thrombin. Argatroban otherwise behaves similarly to bivalirudin, inhibiting both free and clot-bound thrombin. The molecule is metabolized in the liver and excreted, principally, in the feces without significant renal involvement.[91] Argatroban is administered intravenously. The plasma half-life is 45 minutes and steady-state anticoagulation is reached in 1–3 hours.

Indications and Efficacy

Argatroban has two FDA indications and is used principally in patients with HIT and significant renal dysfunction:

- Prophylaxis or treatment of thrombosis in patients with HIT
- Use during PCI in patients with documented or at risk for HIT.

The principal data for efficacy of argatroban in HIT are derived from two, historically controlled prospective studies.[92,93] In these studies, prompt treatment with intravenous argatroban (to an INR of 1.5–3 for 5–7 days) resulted in a significant decrease in new thrombosis (28% vs 38.8%) when compared to historical HIT controls treated with placebo. Authors reported a decrease in thrombosis-related death in the argatroban-treated HITTS group, but treatment with argatroban produced no difference in all-cause mortality in either group. A subsequent subgroup analysis of this data, with respect to demographic variables and platelet count, found no differences in treatment effect or rates of bleeding.[94] A subsequent comparison of argatroban to desirudin in the treatment of HIT was recently abandoned due to low enrollment.[95] An initial, retrospective study of argatroban demonstrated acceptable rates of adverse events; death, MI, urgent revascularization or major bleeding, when argatroban was used for PCI in patients with HIT.[96] As was observed with bivalirudin, the addition of GPI did not improve clinic outcomes. A subsequent, single-center study of argatroban use in patients with ACS, STEMI or NSTEMI and history of HIT reported fewer adverse outcomes and a low rate of bleeding when used for PCI in a cohort of patients with HIT.[97] Argatroban has shown promise in a number of additional clinical situations where HIT is a consideration; mechanical heart valves,[98] left ventricular-assist devices and pre-heart transplant,[99,100] thrombolysis after stroke[101] and renal replacement therapy.[102,103]

Limitations and Monitoring

The principal advantage of argatroban is ease of use in patients with impaired renal function. In treatment of HIT[104] and during

PCI,[105] no dose-adjustment of argatroban for renal dysfunction is required. Argatroban treatment of HIT in patients with mild hepatic dysfunction is possible with dose adjustment,[106] but other treatment options likely obviate use in this clinical scenario. In patients with HIT, the level of anticoagulation can be safely monitored using the aPTT so long as the desired therapeutic range in less than 3 times the upper limit of normal. A target ACT of 300–450 seconds is recommended in PCI but is derived from a small evidence base. A retrospective analysis of ACT in PCI showed that times greater than 450 seconds were associated with greater risks of bleeding, without improvement in thrombotic outcome.[107] Argatroban also prolongs the INR, a fact that can complicate transition to long-term warfarin therapy. When an infusion rate of 2 mcg/kg/min or less is used, the INR directly attributable to warfarin can be calculated from the following equation: 0.19 + 0.57 (Measured INR). In patients transitioning from argatroban to warfarin, a measured INR of 5 or less is not associated with increased bleeding.[108]

Allergic reactions after argatroban administration have manifested in a variety of clinical settings. Greater than 95% of these reactions occurred in patients who were concomitantly treated with thrombolytic therapy (e.g. streptokinase) or iodine-based contrast media. Coadministration with other antithrombotic or antiplatelet agents is associated with an increased risk of bleeding. Although partially metabolized by CYP450 enzymes, no clinically significant drug interactions have been identified.

XIMELAGATRAN

Ximelagatran was the first oral, univalent direct thrombin inhibitor to reach advanced stages of pre-clinical testing.[109] By 2005, phase III trials of ximelagatran had demonstrated efficacy in several clinical settings: postoperative DVT prophylaxis,[110–114] acute DVT treatment,[115] secondary prevention of ACS[116] and stroke prevention in patients with AF.[117] Ximelagatran had received approval in several European and South American countries for postoperative VTE prophylaxis. A British meta-analysis comparing ximelagatran to standard dose enoxaparin showed improved VTE prophylaxis, but increased serious bleeding.[118] Despite these promising results, development was halted in 2006 (and the drug was withdrawn from foreign markets) when significant hepatotoxicity and fulminant liver failure were noted in extended (> 35 days) phase III trials.

This episode merits discussion due to the increased scrutiny that future anticoagulants will face during the approval process. No elevations in liver enzymes were observed during the first trials of ximelagatran, in which the drug was tested for 2 weeks or less. The Thrive III study, in which ximelagatran was tested for an extended period (18 months) versus placebo, was the first to report significant ALT elevations.[119] The first case of fatal hepatotoxicity was reported in the SPORTIF V trial, which also confirmed that ximelagatran was as effective as warfarin for stroke prevention in AF with less bleeding.[120] The same year, an analysis of hepatotoxicity in extended clinical trials found ALT elevation in approximately 8% of treated patients. It was suggested that monitoring of ALT during the first 6 months of therapy would be sufficient to identify at-risk patients.[121] Further follow-up indicated that liver dysfunction could develop after withdrawal of ximelagatran and that elevation of ALT was not a consistent predictor of severe hepatic dysfunction.[122] The mechanism of hepatocyte injury remains unknown but genomic studies indicate a possible association with major histocompatability complexes (MHC). Taken together, these findings indicate an idiosyncratic toxicity rather than a class effect.

DABIGATRAN

Dabigatran is a univalent, oral DTI that potently inhibits thrombin, similar to ximelagatran. Like rivaroxaban, dabigatran is approved in the EU (Pradaxa) and Canada (Pradax) for perioperative DVT prophylaxis in orthopedic patients. The structure of dabigatran etexilate, the orally formulated pro-drug, is distinct from ximelagatran. Metabolism proceeds through plasma esterases, rather than hepatic enzymes.[123] Preclinical testing and surveillance during clinical trials have revealed no hepatotoxicity. It is theorized that rapid plasma metabolism quickly lowers inactive precursor concentrations, preventing a ximelagatran-like toxicity.[124] The drug reaches peak plasma concentrations in 1.5 hours and exhibits a 14–17 hour half-life. Twice-daily dosing is standard. Dabigatran is contraindicated in severe renal impairment as 80% of active drug is cleared via the kidneys. To date, clinical trials have excluded patients with renal dysfunction and no reliable dose-reduction regimes have been examined. Greater than 60% of the drug is removed during hemodialysis,[125] but safety in this population cannot be recommended without further investigation.

Efficacy

Initial studies found dabigatran effective for postoperative VTE prevention in orthopedic patients and comparable to daily enoxaparin over a wide dose range.[126] In the RE-MODEL trial, dabigatran 150 mg or 220 mg orally BID were non-inferior to enoxaparin SQ 40 mg daily for VTE prevention after TKR.[127] Similarly, dabigatran was non-inferior to enoxaparin for VTE prevention after THR in the RE-NOVATE trial.[128] The three preceding trials reported safety profiles of dabigatran that were comparable to daily enoxaparin and formed the basis for approval in the EU and Canada. It is questionable whether US approval is imminent for this indication, as RE-MOBILIZE found dabigatran inferior to US standard, BID enoxaparin dosing after TKR.[129] A second trial of dabigatran 220 mg orally BID is ongoing (RE-NOVATE II; NCT00657150).

Following recent positive trials, dabigatran became the first, FDA-approved oral and anticoagulant since warfarin in fall of 2010. The most important of these trials is the RE-LY trial, in which dabigatran was compared to dose adjusted warfarin for stroke prevention in patients with AF and elevated $CHADS_2$ risk score.[130] Two doses of dabigatran were used in the trial. The first, 110 mg orally BID, was non-inferior to warfarin with respect to embolic stroke and all-cause mortality while the yearly rate of major bleeding significantly decreased. The second dose, dabigatran 150 mg orally BID, was superior to warfarin and reduced rates of stroke and systolic embolism. The mortality rate in patients treated with dabigatran approached statistical superiority ($p = 0.051$) when compared to warfarin while rates of major bleeding were equivalent. In both doses, lower rates

of ICH were observed. Based on these findings, the FDA advisory panel has unanimously recommended approval the 150 mg PO BID dose of dabigatran for stroke prevention in AF.[131] Additional recommendations include: manufacture of a 75 mg tablet for daily use in renal impairment, use of 110 mg PO BID dose for patients with elevated bleeding risk and phase IV testing of higher dose dabigatran in this clinical setting. Finally, dabigatran 150 mg orally BID has demonstrated equivalence to standard therapy (SQ enoxaparin followed by dose adjusted warfarin) in 6 month treatment of acute VTE, both DVT and PE in the RE-COVER study.[132] A duplicate trial (RE-COVER II; NCT00680186) and two extension studies (RE-MEDEY, comparison to warfarin for 18 months; NCT00329238) and (RE-SONATE; NCT00558 259) may determine whether dabigatran replaces warfarin as the drug of choice for treatment and long-term prevention of VTE.

A site-by-site, post-hoc analysis of the RE-LY data with respect to time in therapeutic range (TTR) —in warfarin-treated patients—demonstrated that outcome discrepancies were greatest at the treatment centers with the poorest TTR.[133] This analysis suggests that the advantages of dabigatran were accentuated at sites where warfarin monitoring was most problematic. Dabigatran should immediately fill a need for patients with inadequate access to an anticoagulation clinic or for whom increased bleeding risk makes warfarin therapy unacceptable.

Limitations and Monitoring

As noted above, no excess ALT elevations, or hepatic toxicity, were noted in these studies. The main adverse effect in dabigatran treated groups was dyspepsia. The authors of the RE-LY study postulate that the acidity of dabigatran which facilitates absorption may be the cause of dyspepsia and increased rates of gastrointestinal (GI) bleeding. It was specifically formulated with tiny, acidic pellets inside a capsule to mitigate the effects of proton pump inhibitors (PPIs).[134] Two excess MI were observed per 1,000 patients in the RE-LY trial, but the significance of this finding is unclear given reductions in MI observed in trials of ximelagatran. An ongoing trial of dabigatran for secondary prevention of ACS (RE-DEEM; NCT00621855) should provide a definitive answer. Dabigatran etexilate is a P-glycoprotein efflux substrate. Plasma concentrations increase when administered in conjunction with P-glycoprotein inhibitors amiodarone and verapamil. Use of the strong P-glycoprotein inhibitor quinidine is contraindicated with dabigatran. At present, no other medications are known to interact with dabigatran. Monitoring of dabigatran is not needed in patients with normal renal function. Interestingly, subgroup analysis indicated that mild renal impairment correlated with improved outcomes in the RE-LY trial. Recommendations regarding dosing in renal impairment have yet to be finalized. Although monitoring of anticoagulation should not be required for the vast majority of patients, the ECT and thrombin time (TT) were found to be the most sensitive and precise in the therapeutic range.[135] Concern has been raised regarding the lack of an established reversal agent for dabigatran in cases of uncontrolled bleeding, especially amongst elderly patients.[135a]

ANTIPLATELET AGENTS

Platelets instigate and catalyze arterial thrombosis in a stepwise process (Fig. 5). Each step presents a potential therapeutic target for inhibition of thrombosis. At injury outset, platelets adhere to subendothelial matrix components, minimizing the breach in the endothelial wall. Although few therapeutics that interrupt adherence have been studied, development potential will be discussed briefly. Also exposed by endothelial injury, TF binds factor VII, initiates the clotting cascade and generates thrombin, which is a potent activator of platelets. ADP and TxA_2 are also crucial signals that lead to platelet activation and recruitment. The most established antiplatelet therapies, aspirin (an inhibitor of TXA_2 synthesis) and clopidogrel (an ADP/$P2Y_{12}$ antagonist), aim to disrupt this second step. New therapeutics aim to improve ADP inhibition and inhibit thrombin signaling. Once activated, intracellular signaling produces a conformational change in the GP IIb/IIIa ($\alpha_{IIb}\beta_3$) receptor that favors fibrinogen binding (as well as vWF and fibronectin). *Aggregation* is the result of avid platelet binding, via the abundant $\alpha_{IIb}\beta_3$, to many fibrinogen molecules. The two $\alpha_{IIb}\beta_3$ binding regions of fibrinogen produce extensive platelet cross-linking. This final step is inhibited by the parenteral glycoprotein IIb/IIIa inhibitors (GPI), which will be discussed only briefly in this section, due to their limited use outside the catheterization lab.

INHIBITORS OF PLATELET ADHESION

At present, there are no clinically available inhibitors of platelet adhesion. In vitro and animal models have demonstrated that inhibition of multiple receptors can reduce platelet adhesion to the subendothelial matrix.[136] Animal models have demonstrated protection from arterial thrombosis when adhesion is inhibited. For example, murine GPVI knockout mice demonstrate only a moderate bleeding phenotype but significant protection from experimentally induced, arterial thrombosis.[137] A monoclonal antibody directed against the murine GPVI receptor led to a long-term prevention from thrombosis.[138] Together, these findings make inhibitors of adhesion an attractive target for drug development. Molecules currently under investigation include naturally derived compounds, including those from the leech and the mosquito, as well as synthetic molecules.

Aegyptin, a mosquito derived molecule, displays high in vitro affinity for vWF and binds, with lower affinity, to the GPVI and $\alpha_2\beta_1$-binding sites of collagen. In vivo, the molecule prevents platelet aggregation and thrombosis after laser-induced carotid injury in rats without excess bleeding.[139] Saratin, a leech derived compound, prevents platelet and vWF binding to collagen under high-shear conditions.[140] A small molecule inhibitor of integrin $\alpha_2\beta_1$ has also shown efficacy in an animal model of arterial thrombosis.[141] Finally, ARC1779 is an intravenous, oligonucleotide-based aptamer that inhibits the A1 domain of vWF and prevents binding to platelet GP1b. Of current adhesion inhibitor candidates, it has reached most advanced stage of development. Administration of ARC1779 prevented occlusive thrombi in a simian model of carotid injury.[142] A human dose-ranging study demonstrated a dose-dependent inhibition of platelet function without increased bleeding in a cohort of healthy subjects.[143] An ex vivo study of

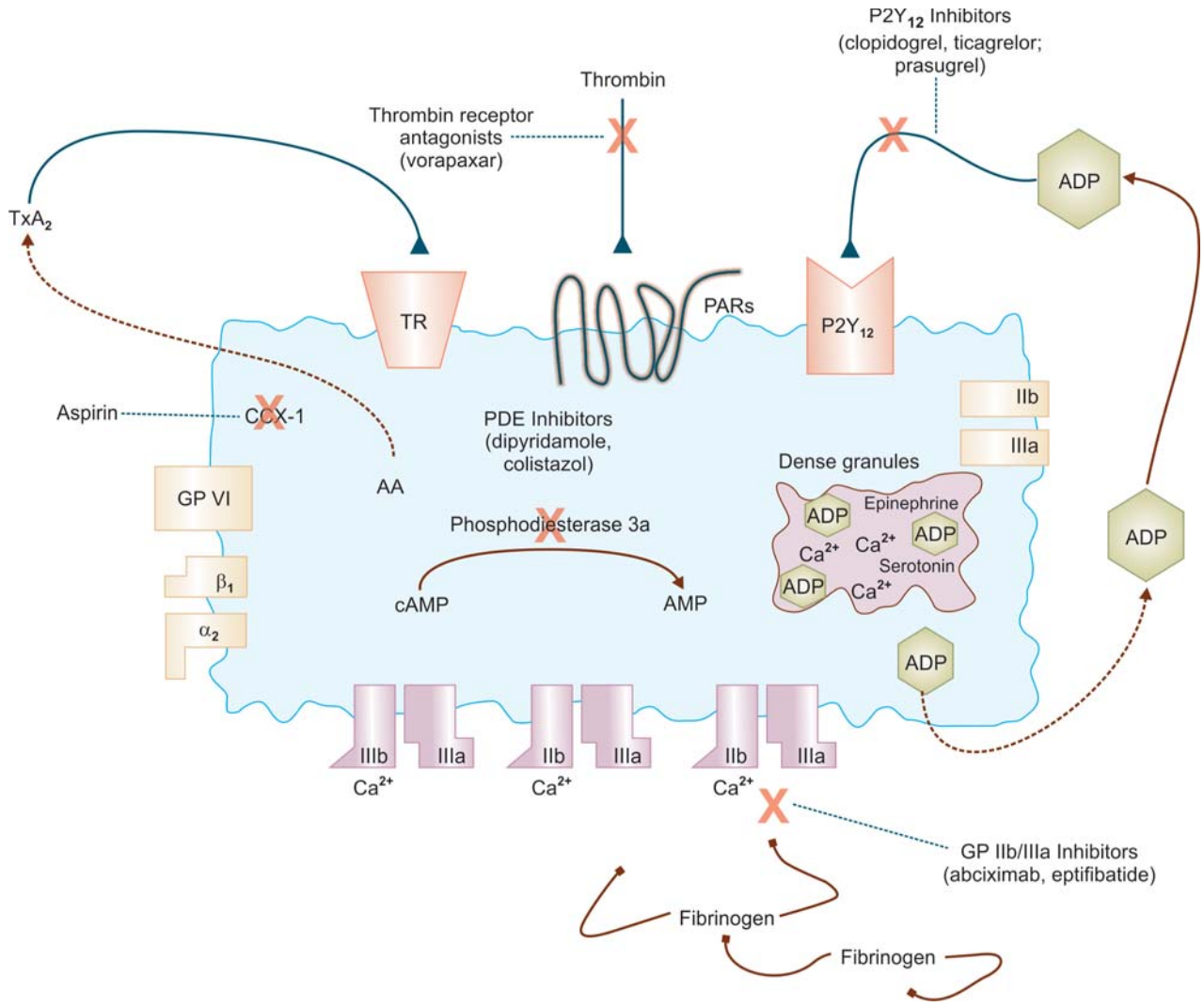


FIGURE 5: Antiplatelet agents: Depicted at right are the major sites of action of the five extant classes of antiplatelet drugs. Aspirin is the major inhibitor of the TxA_2 pathway. Clopidogrel and ticagrelor inhibit $P2Y_{12}$ activation by ADP. GP IIb/IIIa inhibitors inhibit fibrinogen binding and platelet aggregation

blood drawn from acute MI subjects demonstrated that ARC1779 reduced platelet activation to the level of controls despite a twofold increase in vWF activity.[144] The drug has also been administered experimentally, with apparent success, to a patient with refractory thrombotic thrombocytopenia purpura.[145]

INHIBITORS OF PLATELET ACTIVATION

TXA_2 Pathway Inhibitors

Aspirin or acetylsalicylic acid (ASA) is the prototype TXA_2 pathway inhibitor. NSAIDs ibuprofen and naproxen, which reversibly inhibit cyclooxygenase (COX), and selective COX-2 inhibitors, such as celecoxib, are members of the class, as are ridogrel and terbogrel, which combine a TxA_2 synthase inhibitor and TxA_2/prostaglandin endoperoxide receptor antagonist. While these combination drugs have theoretic advantages over aspirin, they have not proven clinically more efficacious[146] and have produced untoward side effects.[147]

Mechanism: ASA, a modification salicylic acid, was first synthesized in 1897 by Felix Hoffman of Bayer and subsequently marketed as Aspirin.[148] Widely used as a pain reliever, its effect on platelets and bleeding were not described until 1967.[149,150] Vane and others reported impaired prostaglandin synthesis as the biochemical mechanism of ASA shortly thereafter.[151] Aspirin acts by irreversibly acetylating cyclooxygenase-1 (COX-1), inhibiting the synthesis of prostaglandin H_2, a TxA_2 precursor. ASA is rapidly absorbed and reaches peak plasma levels in less than 1 hour. Enteric-coated ASA is absorbed at a slower rate and peak plasma levels are reached in 3–4 hours, hence the instruction to chew ASA when administered for ACS. The half-life of ASA is short, 15–20 minutes, but given irreversible platelet inactivation the functional duration of action is 5–10 days, the life span of a platelet.[152]

Indications and efficacy: The first published reports of ASA use for prevention of heart disease predate the mechanistic discoveries by nearly two decades.[153] Lawrence Craven, a general practitioner in Glendale, CA, had reasoned that ASA may prevent MI when administered daily at moderate dose, given its propensity cause bleeding. It became his practice to advise daily aspirin to overweight and sedentary men between

the ages of 45 and 65.[154] Indeed, ASA has proven a highly effective therapy in prevention of thrombotic outcomes.[155,156] A recent meta-analysis estimated that daily ASA use in high-risk patients reduced serious vascular events, including MI and CVA, by one quarter.[157] The current indications for ASA use include:

- 325 mg daily for 1 month followed by 81 mg daily for life—ACS, including STEMI, NSTEMI and UA[158–160]
- 325 mg daily for 1 month followed by 81 mg daily for life—following PCI
- 81 mg daily for life—for secondary prevention of MI in patients with CAD, PAOD or documented pulmonary artery disease
- 81 mg daily for life—after CABG, carotid endarterectomy or peripheral vascular bypass[161]
- 1300 mg daily—for symptomatic intracranial arterial stenosis[162]
- 81–325 mg daily—prevention of embolic stroke in patients with AF and $CHADS_2$ score of 1 or contraindications to warfarin use[163]
- 50–325 mg daily, preferably in combination with dipyridamole 200 mg twice daily—secondary prevention of CVA after stoke or TIA[164]
- 325 mg once—administered 24–48 hours after acute stroke (of note, ASA is not recommended within 24 hours of thrombolytic therapy)[165]
- 81–162 mg daily—for patients with heart failure and reduced ejection fraction[166]
- 100 mg daily—for patients with polycythema vera and no contraindication to ASA use.[167]

The recently published CURRENT-OASIS 7 study stratified patients with ACS, scheduled to undergo early-invasive PCI, to either low or full dose ASA from the outset of therapy. The investigators found that use of low dose ASA did not alter the rates of death, MI or CVA at 30 days.[168] This result is provocative, but will likely not alter recommendations until long-term follow-up data is available. The concept of aspirin resistance; that certain individuals are resistant to the platelet inhibitory effects of ASA, has generated much discussion in the past decade. The topic is plagued by non-standard testing, conflicting results of observational or retrospective trials and possible confounding by suboptimal patient adherence. No recommendations will be included here due to lack of consensus regarding testing and treatment.[169]

Of note, ASA is not formally indicated for primary prevention. In 2009, the US Preventative Services Task Force recommended encouragement of daily, low-dose ASA use for primary prevention of cardiovascular disease (CVD) in men aged between 45 and 79 years and women between 55 and 79 years without mention of risk factors or diabetes (DM).[170] Recently published meta-analyses and RCT have questioned the benefit of ASA for primary prevention due to a poor risk-benefit ratio.[171–177] Given these contradictory recommendations, a 2010 position statement of the American Diabetes Association (ADA) and American Heart Association was released.[178] The final statement included the provision that recommendation of low dose (75–162 mg) ASA in patients with DM and an elevated ten-year risk for CVD is "reasonable". It continued that ASA should *not* be recommended for primary prevention in men with age less than 50 years and women less than 60 years with DM without additional CVD risk factors.

Limitations and adverse effects: The main adverse effect of ASA is bleeding, most commonly GI, although rates are low. The yearly risk of major GI bleed is 0.05–0.1% among patients treated with low-dose ASA, twice the baseline rate.[179] Factors that increase the risk of bleeding are increasing age, previous GI bleeding (GIB) or peptic ulcer disease and concomitant use of warfarin, NSAIDs or steroids. The most recent AHA/American College of Gastroenterology guidelines advocate GI prophylaxis for any patient prescribed long-term antiplatelet therapy.[180] For patients on dual antiplatelet therapy, such as ASA and clopidogrel after drug-eluting stent (DES) placement, a PPI is the recommended agent to prevent GI bleeding. For patients on single antiplatelet therapy, PPI is recommended when gastroesophageal reflux disease or the above risk factors are present. After the publication of this guideline, the FAMOUS trial, an RCT of famotidine for prevention of GI sequelae in patients on chronic low-dose ASA, reported protection from ulcer, esophagitis and GIB versus placebo.[181]

Increased postoperative bleeding, but not death, has also been reported after CABG in patients with preoperative ASA use. A systematic review found that this effect was observed only in conjunction with doses greater than or equal to 325 mg daily.[182] This finding would indicate that continuation of low-dose ASA, rather than cessation 5 days prior, would be appropriate therapy for patients undergoing CABG. Cessation of antiplatelet therapy after MI or stent placement, especially within the recommended treatment windows, is associated with elevated risk of thrombosis.[183] Prior to any procedure that requires cessation of antiplatelet therapy, consultation with the primary (or consulting) cardiologist should be obtained to minimize this risk. "Rebound hypercoagulability" leading to increased rates of ischemic stroke has also been reported.[184]

A final precaution is aspirin sensitivity; a non-IgE mediated hypersensitivity-like reaction to ASA that is noted in concert with nasal polyps, asthma and chronic hyperplastic eosinophilic sinusitis.[185] Patients with this condition have respiratory exacerbations resembling asthma attacks within 3 hours of ASA (or other COX-1 selective NSAID) ingestion. The incidence is low, ~ 2.5% in the general population, but above 10% in patients who carry an asthma diagnosis. Aspirin desensitization, followed by daily use, effectively abolishes symptoms for patients who require daily use.

Inhibitors of ADP/$P2Y_{12}$ Signaling

Clopidogrel: Clopidogrel (Plavix) is the prototype $P2Y_{12}$ inhibitor, a second-generation thienopyridine. The first generation drug of this class, ticlopidine, is discussed subsequently.

Mechanism: Thienopyridines selectively and irreversibly inhibit the $P2Y_{12}$ receptor, reducing ADP-dependent platelet aggregation.[186] After ingestion, 15% of clopidogrel is converted to an active metabolite by the hepatic CYP system. Within 2 hours of a 300 mg oral dose, the active metabolite produces 40% inhibition of ADP-induced platelet aggregation.[187] Due to irreversible $P2Y_{12}$ inhibition, platelet inhibition is maintained for 48 hours, despite the 8-hour half-life of the active metabolite. After loading, daily administration of 75 mg increases platelet

inhibition to approximately 60%, the maximum achievable. A larger loading dose; 600 mg, achieves maximum platelet inhibition in 2 hours.[188,189] Loading doses above 600 mg do not appear to produce provide additive benefit.[190] Clinically, loading with 600 mg prior to PCI improves 30-day clinical outcome without increasing rates of bleeding.[191,192]

Indications and efficacy: Clopidogrel was approved on the basis of a single large trial, in which it (75 mg daily) was compared directly with ASA 325 mg daily for secondary prevention of CVD in patients with symptomatic peripheral arterial disease (PAD), recent MI or recent ischemic stroke (both < 35 days).[193] The CAPRIE study reported a significant decrease in recurrent MI, stroke or vascular death favoring clopidogrel at nearly 2 years. Also reported was a trend toward fewer episodes of major bleeding in the clopidogrel group. Subgroup analysis, however, demonstrated that differential outcomes in PAD accounted for a majority of the observed effect.[194] Differences in outcome were minimal when analysis was limited to patients with recent MI. Clopidogrel was approved in 1997 for secondary prevention of CVD as an alternative to, but not replacement for, ASA. Clopidogrel has proven broadly efficacious in prevention of recurrent CVD.[195] Based on subsequent trials, notably PCI-CURE and CREDO, dual antiplatelet therapy (ASA plus clopidogrel) has become the standard of care after PCI.[196,197] Current indications for clopidogrel include:

1. ACS:
   - For patients with NSTEMI or unstable angina, a 300 mg loading dose followed by 75 mg daily in combination with daily ASA
   - For patients with STEMI; 75 mg daily in combination with ASA, with or without thrombolytics. Loading dose is optional in this setting, but 600 mg appears appropriate for patients proceeding to PCI
2. Secondary prevention of CVD with documented MI, stroke or PAD.

CHARISMA, a trial of clopidogrel plus ASA for primary and secondary prevention, found that medical management with long-term dual antiplatelet therapy did not benefit a high-risk population when compared to low-dose ASA.[198] Dual antiplatelet therapy may improve secondary prevention in the highest risk patients, but increased bleeding has limited wide use. Current indications do not specify duration of dual antiplatelet therapy, but the recommended minimum length of therapy for patients implanted with bare metal stents is 1 month.[199] Optimal duration of dual antiplatelet therapy after DES remains uncertain due to reports of stent thrombosis beyond 1 year.[200] However, a recent study suggests that no clinical benefit was derived from dual antiplatelet therapy beyond 12 months in conjunction with DES.[201] The importance of 12 months of uninterrupted dual antiplatelet therapy after DES is undisputed and has become a point of emphasis.

Limitations and adverse effects: Incidence of bleeding increases when clopidogrel is added to ASA as part of dual antiplatelet therapy.[202–204] In the CHARISMA trial, risk of bleeding was highest during the first year of therapy.[205] This was predominantly moderate bleeding, but maintained a strong association with increased mortality. As discussed above, PPI is currently indicated for all patients receiving dual antiplatelet therapy. Concern has arisen that concomitant use of PPI and clopidogrel attenuates the effect of the latter.[206] Inhibition of CYP450 2C19 by omeprazole, reducing the conversion of clopidogrel to its active metabolite, is the most frequently postulated mechanism for this effect. No adverse affect was observed, retrospectively, when clopidogrel was prescribed in conjunction with pantoprazole, which does not inhibit 2C19.[207] At present, the ACC/AHA does not find the data sufficient to recommend a change in clinical practice. Low rates of several life-threatening adverse events have been reported in association with clopidogrel.[208] The most important of these events is TTP, which can occur after as little as 2 weeks of treatment.

A black box warning was recently added to clopidogrel, warning of adverse events among patients with genetic polymorphisms of 2C19 that impair metabolism. In a sample of 162 healthy subjects, at least one reduced-function 2C19 allele was associated with impaired in vitro platelet aggregation and reduced blood levels of the active clopidogrel metabolite.[209] Investigators then analyzed data from the previously completed TRITON-TIMI 38 trial with respect to the presence or absence of a reduced function 2C19 allele in patients treated with clopidogrel. The reduced function allele was associated with a 4.1% absolute increase in rate of stroke, MI or death from cardiovascular causes when compared to 'noncarriers'. The incidence of this allele in the general population is 2% and 30% for homozygotes and heterozygotes respectively. An ACCF/AHA response did not advise routine CYP testing or alteration of clinical practice, citing a paucity of prospective outcome data or predictive value of routine genetic testing. [210] They emphasized the importance of clinical judgment and advised that the use of prasugrel or double-dose of clopidogrel would be reasonable for selected patients.

Ticlopidine was the first available $P2Y_{12}$ inhibitor. In patients with recent embolic stroke or cerebral ischemia, ticlopidine (250 mg twice daily) was superior to ASA in secondary prevention of stroke, MI or CV death.[211,212] Excess rates of bleeding were not observed in these studies. Due to higher rates of potentially fatal adverse effects, including neutropenia, thrombocytopenia, aplastic anemia and TTP, ticlopidine has largely been replaced by clopidogrel. It remains clinically available for dual antiplatelet therapy after PCI in patients with documented clopidogrel allergy. Ticlopidine is also approved for secondary prevention of ischemic stroke in patients with aspirin intolerance, but clopidogrel offers comparable efficacy with improved safety.[59]

Prasugrel

Prasugrel (Effient) is a third generation thienopyridine. Like clopidogrel, an active metabolite irreversibly inhibits the $P2Y_{12}$ receptor. In contrast to clopidogrel, the liver converts prasugrel more efficiently to its active metabolite. Whereas clopidogrel reaches peak effect in 4–6 hours, producing 60% inhibition of platelet aggregation, prasugrel produces complete inhibition of platelet aggregation by 1 hour.[213] Despite structural similarities, prasugrel is unaffected by common polymorphisms of 2C19 and 2C9, another CYP450 enzyme implicated in reduced clopidogrel metabolism.[214,215] These pharmacologic distinctions have

correlated with increased in vivo platelet inhibition when compared to clopidogrel.[216]

Indications and efficacy: Prasugrel was approved for clinical use in 2009 on the basis of TRITON-TIMI 38 trial data. Prasugrel is currently indicated for:

- Patients with unstable angina or NSTEMI
- Patients with STEMI when managed with immediate or delayed PCI.

The original study compared prasugrel (60 mg loading dose followed by 10 mg daily) to clopidogrel (with 300 mg bolus followed by 75 mg daily) when used in patients presenting with ACS and planed PCI.[217] Prasugrel was associated with a significant decrease in the primary end-point at 15 months: death from cardiovascular causes, nonfatal MI and nonfatal stoke. Rates of urgent vessel revascularization and stent thrombosis were also reduced through 15 months. Increased rates of major bleeding were observed in the treatment group. An editorial accompanying the article observed a one-to-one correlation between cardiovascular deaths prevented and episodes of fatal bleeding.[218] Subgroup analyses of the TIMI 38 data describe superior efficacy in a number of specific populations; STEMI, DM and in conjunction with GPI, with or without stent use.[219] No differences in clinical outcome were observed in prasugrel patients treated with PPI.[220]

Limitations and adverse effects: A class III recommendation (indicating harm) regarding prasugrel has been included in the most recent STEMI and UA/SNTEMI guidelines.[160,281] It should not be used in patients with *"history of stroke and transient ischemic attack for whom primary PCI is planned, prasugrel is not recommended as part of a dual-antiplatelet therapy regimen."* Prasugrel received an extensive black box warning based on the increased risks for bleeding. Treatment with prasugrel is contraindicated in patients with age more than 75 years, except for those at highest risk, due to increased risk of fatal and ICH. The drug is contraindicated if urgent CABG is 'likely' and should be discontinued 7 days prior to any surgery. Dose adjustment of maintenance therapy is suggested for patients weighing under 60 kg or with a 'propensity to bleed'.[221] Limited experience with this drug limits estimation of TTP rates in comparison to clopidogrel.

Two additional $P2Y_{12}$ inhibitors have reached phase III testing. These new agents are non-thienopyridine agents that potently and reversibly inhibit ADP signaling.

Ticagrelor: (Brillanta, formerly AZD 6140) is an oral, reversible ATP analogue that acts as a $P2Y_{12}$ inhibitor. Unlike the thienopyridines, this drug inhibits the $P2Y_{12}$ receptor as a non-competitive inhibitor to ADP.[222,223] Ticagrelor is a direct acting compound that does not require metabolism for activation. Excretion of ticagrelor and a single active metabolite occur via the fecal route with negligible renal involvement.[224]

Efficacy: The PLATO study compared ticagrelor to clopidogrel in patients admitted to the hospital with ACS irrespective of ST elevation.[225] At 12 months patients in the ticagrelor group had significantly lower rates of a composite end point (death from vascular causes, MI and stroke). All-cause death and MI, but not stroke, were reduced in the ticagrelor group as well. Authors theorized that intensive $P2Y_{12}$ inhibition by ticagrelor produced the observed benefit. The RESPOND study supports this assertion. In the study, clopidogrel non-responders, as described by Gurbel et al.,[226] were switched to ticagrelor. Platelet reactivity decreased by greater than 10% in all patients and over 30% in three quarters of patients treated with ticagrelor.[227] Although mechanistically plausible, platelet reactivity after administration of clopidogrel and ticagrelor has not been directly correlated to clinical outcome.

Limitations and adverse effects: The overall rates of bleeding observed in PLATO were comparable, but higher rates of intracranial bleeding were noted in association with ticagrelor. Three additional major adverse effects were noted in the ticagrelor group; dyspnea, which drove increased rates of drug discontinuation, asymptomatic cardiac pauses and increased levels of creatinine and uric acid. Concern that dyspnea was indicative of pulmonary disease prompted ONSET/OFFSET. In this small study, stable CAD patients treated with ASA were randomized to ticagrelor, clopidogrel or placebo for 6 weeks, including a loading dose for patients not in the placebo arm. A 40% incidence of dyspnea was noted among ticagrelor-treated patients, including three who discontinued therapy. However, no changes in pulmonary function tests, transthoracic echocardiography, EKG or BNP were noted in patients with dyspnea, as compared to controls.[228]

Currently available clinical data appears to favor ticagrelor over prasugrel for use in high-risk or clopidogrel-resistant patients.[229] In July 2010, the FDA advisory panel overseeing approval of ticagrelor recommended approval of the drug.[230] Contingent on approval, two post-approval studies will be required: (1) of patients with moderate and severe hepatic impairment and (2) of the US patients with ACS, as subgroup analysis of PLATO failed to demonstrate benefit for American subjects.

Cangrelor is an intravenous inhibitor of the $P2Y_{12}$ receptor with a 3–6 minute half-life and 60-minute duration of action after cessation of infusion. Two randomized, placebo-controlled trials of cangrelor were recently reported.[231,232] Parenteral cangrelor was administered at or before PCI in comparison to a 600 mg loading dose of oral clopidogrel. Treatment with cangrelor did not lead to a significant decrease in the primary end point; death from any cause, MI or ischemia-driven revascularization at 48 hours, in either study. Secondary endpoints were met but at the cost of increased major bleeding. The continued development of cangrelor as an intra-procedural $P2Y_{12}$ inhibitor is uncertain. A phase II trial of cangrelor use in the pre- and post-surgical settings is underway (BRIDGE; NCT00767507). A second direct parenteral $P2Y_{12}$ inhibitor, elinogrel, has reached phase II testing of use in patients with non-urgent PCI (INNOVATE-PCI; NCT00751231).

Phosphodiesterase (PDE) Inhibitors

Dipyridamole: The prototype drug in the class, acts by increasing intracellular levels of cyclic adenosine monophosphate (cAMP). Increased cAMP levels, in turn, reduce platelet activation by inhibiting calcium mobilization. Several in vitro mechanisms of action have been demonstrated; inhibition of platelet PDE, reduction of adenosine uptake by platelets and

stimulation of prostacyclin (PGI_2) release by endothelial cells.[233] The dug also acts as a direct vasodilator (used as Persantine in stress echocardiography and thallium imaging) through inhibition of endothelial cyclic guanosine monophosphate phosphodiesterase (cGMP-PDE). Inhibition of cGMP-PDE potentiates the vascular effects of nitric oxide.[234] The mechanism of dipyridamole at clinical dosages remains indeterminate.

Indications and efficacy: Dipyridamole was introduced in 1959 for treatment of angina. The antiplatelet properties of the drug were discovered later, leading to its repurposing as an antithrombotic agent. It has proven ineffective as a lone anticoagulant.[235] Discussion of use in stress testing can be found elsewhere. The current indications for dipyridamole are:

- 100 mg four times daily in conjunction with warfarin to reduce thrombotic complications after implantation of a mechanical heart valve.[236]
- Extended-release dipyridamole (ERDP) 200 mg in conjunction with ASA 25 mg used twice daily for secondary prevention of stroke after TIA or completed ischemic stroke due to thrombosis.

Combination ERDP-ASA, marketed as Aggrenox, is the preferred agent for stroke prophylaxis and accounts for nearly all use.[237] This recommendation is based on two foundational trials. The ESPS 2 study reported a roughly 20% reduction in recurrent ischemic stroke in patients treated with the ERDP-ASA combination, compared to low-dose ASA.[238] The combination did not effect rates of bleeding, MI or death. The ESPRIT study reported a 1% absolute risk reduction in yearly stroke rate among patients treated with ERDP-ASA when compared to ASA alone.[239] A subsequent comparison of ERDP-ASA and clopidogrel for prevention of recurrent ischemic stroke demonstrated equivalent efficacy.[240]

Limitations and adverse effects: Headache is principal adverse effect of dipyridamole treatment, affecting one-third of treated patients and a leading cause of drug discontinuation. A pilot study has reported decreased rates of headache in patients in whom the dose of dipyridamole, as a component of ERDP-ASA, was titrated over 2 weeks.[241] Increased rates of diarrhea and other GI complaints have been reported in association with Aggrenox. The risks of ERDP-ASA beyond headache are similar to those of ASA alone. The ECDP-ASA administration is contraindicated in patients with severe hepatic impairment or severe renal impairment (GFR < 10 ml/min).

Cilostazol: Cilostazol is an inhibitor of platelet PDE3A that, like dipyridamole, also acts as a vasodilator. Thrombin activates PDE3A (via PAR-1, below), reducing the intracellular cAMP concentration and promoting platelet activation.[242] Given the antagonism of thrombin signaling in platelets, it is not surprising that cilostazol exerts antiplatelet effects. The principal route of drug metabolism is hepatic (CYP3A4 and 3A5) and fecal excretion predominates.[243]

Indications and efficacy: Cilostazol was granted FDA approval in 1999 for a single clinical indication: 50–100 mg twice daily for treatment of symptomatic claudication. In randomized, placebo controlled trials, cilostazol treatment produced significant increases in pain-free walking distance for patients with disabling disease (but without limb ischemia or pain at rest).[244,245] Current ACCP guidelines advocate for cilostazol use only in patients with moderately disabling disease who are ineligible for surgical or catheter-based treatment.[246] They specifically recommend against use in patients with mild disease as exercise therapy and lifestyle modifications may be similarly efficacious. While cilostazol use is associated with symptomatic improvement, it has no proven benefit in secondary prevention of cardiovascular events.[247]

More recently, cilostazol has been tested as an adjunctive antiplatelet therapy after PCI. The addition of cilostazol to dual antiplatelet therapy after bare metal stent placement was associated with decreased angiographic stenosis at 6 months.[248] No reduction in MI or mortality was reported in the association with the reduction in stenosis. The effect was most pronounced in diabetic subjects, long lesions and small-diameter vessels, situations in which DES would be preferentially used. Addition of cilostazol to clopidogrel and ASA, dubbed triple therapy, was subsequently shown to reduce stenosis in patients with long (> 25 mm) lesions and DES placement.[249] No MI or mortality benefit was demonstrated, but triple therapy was associated with reduced target vessel revascularization. A similar effect was observed in diabetic patients treated with cilostazol in addition to standard therapy.[250] A more recent retrospective analysis of patients treated for ACS with primary PCI and DES in Korea reported improved clinical outcomes, including cardiac and total death, among patients treated with triple therapy for at least 1 month.[251] In vitro measures of platelet reactivity are decreased after 30 days of cilostazol when compared to dual antiplatelet therapy.[252] Prospective trials of triple therapy in a heterogeneous population showing clinical benefit are needed before cilostazol use after PCI becomes standard practice.

Limitations and adverse effects: The principal adverse effects of cilostazol are headache and diarrhea, as with dipyridamole. Palpitations are the unique side effect associated with cilostazol. As a PDE3A inhibitor, like milrinone, cilostazol acts as a dromotropic agent, increasing conduction velocity of the AV node. Cilostazol has been used for treatment of bradyarrhythmia, including slow AF.[253,254] Caution should be exercised when cilostazol is used in concert with inhibitors of CYP3A4/5 such as macrolide antibiotics, selective serotonin reuptake inhibitors, azole antifungals and warfarin. Additionally, grapefruit juice was associated with purpura in a patient using cilostazol.[255]

Thrombin Receptor Antagonists

Thrombin signaling via PARs appears to be the most potent of the three parallel platelet activation pathways. The PARs do not employ ligand-receptor binding. Rather, thrombin cleaves an exposed, N-terminal portion of the PAR, which leads to conformational change and exposure of a previously buried protein moiety. The newly exposed moiety is mobile and acts as a tethered ligand, activating the PAR.[256] After tethered ligand binding, the intracellular portion of the receptor effects platelet activation; shape change, TxA_2 synthesis and release, activation of $\alpha_{IIb}\beta_3$, through G-protein signaling. An excellent review of thrombin signaling through PARs can be found.[121]

Vorapaxar: Vorapaxar (SCH 530348) is an oral inhibitor of PAR_1 and prototype thrombin receptor antagonists (TRA). Vorapaxar was derived from himbacine, a compound isolated from the bark of the Australian magnolia.[257] Vorapaxar dose-dependently

inhibited platelet aggregation in vitro and does not affect traditional measures of coagulation. The drug is rapidly absorbed but slowly eliminated with a half-life of 165–311 hours. Return of platelet function occurs, on average, 1 month after drug cessation.[258] The drug is excreted in the feces and dose adjustment for renal function in not required.

Efficacy: A large phase II has demonstrated that coadministration of vorapaxar with standard dual antiplatelet therapy does not increase bleeding risk.[259] In this placebo-controlled trial, a loading dose of vorapaxar was administered prior to planned PCI and a lower, maintenance dose for 2 months thereafter. A second, smaller phase II trial confirmed the safety of vorapaxar after PCI in patients with NSTEMI.[260] In this trial, standard therapy was defined as ASA, ticlopidine and heparin during catheterization. A significant reduction in periprocedural MI was reported in the treatment group. Phase III studies are underway to determine whether promising preclinical and animal studies translate to reduced MI and death in a clinical setting. The first, TRA 2°P-TIMI 50, will compare a 2.5 mg daily dose to placebo in secondary prevention of CVD over a period of 2.5 years (NCT00526474).[261] The second, TRA*CER, will randomize patients presenting with high-risk NSTEMI to placebo or 40 mg oral vorapaxar followed by 2.5 mg daily for at least 1 year (NCT00527943).[262]

A second TRA, atopaxar (E5555), is also in development. Recently released phase II data indicate that, when used in patients with ACS, atopaxar does not increased major bleeding.[263] Higher doses fully inhibited platelet function but were also associated with dose-dependent increased in liver function tests and QTc.

INHIBITORS OF PLATELET AGGREGATION

Three glycoprotein IIb/IIIa inhibitors (GPI) have received FDA approval for use in ACS or adjunctive therapy during PCI. In aggregate, these agents significantly reduce death and MI through 6 months.[264] Oral GPI have shown no clinical benefit and are associated with increased mortality.[265,266] Despite initial widespread use, the clinical indications for GPI use have become more limited. In 2004, GPI were found to provide no benefit compared to placebo when given in combination with ASA and clopidogrel prior to PCI, as had become standard.[267,268] The utility of GPI was called into further question in 2007 when bivalirudin was shown to obviate the need for either heparin or GPI during PCI, as discussed above. A complete discussion of GPI indications and use is located in sections discussing catheterization and PCI. Each agent is briefly introduced below in conjunction with significant adverse effects or limitations. All GPI are contraindicated in patients with an active bleed or elevated risk for severe bleeding.

The first approved agent, *abciximab* (*ReoPro*), is a chimeric protein composed of Fab (fragment, antigen binding) regions from the murine 7E3 antibody and the Fc of human immunoglobulin. The first trial of abciximab in conjunction with coronary stenting found a marked improvement in clinical outcome at both 30 days and 6 months.[269] Abciximab has demonstrated benefit over placebo in patients with elevated troponin at the time of PCI.[270] Abciximab is not cleared by the kidneys and is safe in patients with CKD or ESRD. In EPIC, the first GPI trial, abciximab use was associated with a 50% increase in major bleeding, an absolute 11% incidence. Improvements in catheterization technique have decreased bleeding risk, but it remains the major adverse event associated with GPI. The high affinity binding of abciximab may play a role. The dissociation half-life from platelets is 4 hours, but it persists in blocking 13% of $\alpha_{IIb}\beta_3$ at 15 days.[271] Finally, abciximab doubles the risk of severe thrombocytopenia (defined as plt < 20,000).

Eptifibatide: Eptifibatide (Integrilin) is small molecule GPI modeled after a component of pigmy rattlesnake (Sistrurus miliarius barbouri) venom. A peptide-based compound, eptifibatide binds tightly to $\alpha_{IIb}\beta_3$, producing dose-dependent reversible inhibition. Significantly lower rates of MI and death occurred in patients with ACS who were treated with eptifibatide, in addition to heparin and ASA, with or without subsequent PCI.[272,273] The ESPRIT trial demonstrated reduced rates of MI and death at 1 year when used in conjunction with standard therapy during PCI.[274,275] Subsequently no benefit was reported with scheduled eptifibatide prior to PCI as compared to provisional use after procedural thrombotic complication.[276] As with abciximab, eptifibatide use is associated with increased risk of bleeding. In particular, the incidence pulmonary hemorrhage after eptifibatide (0.33%) is higher than after abciximab (0.14%). Renal clearance accounts for greater than 50% of eptifibatide elimination. Therefore, the dose must be adjusted in patients with CrCl less than 50 ml/min. It is contraindicated in patients with creatinine above 4 mg/dL or in ESRD.

Tirofiban: Tirofiban (Aggrastat) is a second small molecule, non-peptide GPI.[277,278] Although never compared directly with eptifibatide, it is used interchangeably due to similar mechanisms of action and clearance. When compared directly to abciximab, tirofiban use was associated with increased rates of MI.[279]

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Section 3

DIAGNOSIS

Chapter 9

History

Kanu Chatterjee

Chapter Outline

- The History
  - General Approach
  - Analysis of Symptoms

The history and physical examination are essential, not only for the diagnosis of cardiovascular disorders but also to assess its severity, to establish a plan of its management and to assess the prognosis. Appropriate history and physical examination are also essential to decide what tests are necessary for a patient as presently a plethora of tests is available for the diagnosis and management of the same cardiac disorder. For example, for the diagnosis of the etiology of chest pain due to coronary artery disease, one can perform many noninvasive, semi-invasive and invasive tests to establish or exclude the presence of obstructive coronary artery disease. It should also be appreciated that "history and physical examination" are cost-effective. Many tests that are frequently performed today are unnecessary and are much more expensive. During examination of the patient, the physician can gain the confidence of the patient and of the family and can establish a good rapport that is necessary for the appropriate management of the problem of the patient. During examination, the physician has the opportunity to demonstrate sincerity which facilitates to gain trust of the patient and the family.

In today's electronic age the patients and their relatives are often more familiar than the physicians about the recent developments in the diagnostic techniques and therapies. It is thus preferable (but some times impossible) to have this knowledge before examining the patient. In today's health care environment there are severe constraints on time available for taking appropriate history and to do adequate physical examination.[1] Frequently, the physicians have to order the "tests" because of time constraints even before examining the patient. Furthermore, there is a growing concern about malpractice suits and the medical and paramedical personnels are frequently forced to perform the investigations, which are otherwise would not have been necessary.

THE HISTORY

GENERAL APPROACH

During taking history, it is desirable to allow the patient to present the symptoms without interruption. Frequent interruptions give the impression that the physician is in hurry and impatient and disinterested. While taking history, the physician can observe the manner in which the patient describes the symptoms and the patient's emotional state and mood.

After the patient describes the symptoms, it is appropriate to discuss with the patient and the family to ascertain the chronology of symptoms and their severity. The patient may present with many symptoms. It is pertinent to enquire about each symptom. The major symptoms associated with cardiovascular disorders are chest pain or discomfort, dyspnea, palpitations, dizziness and syncope.

ANALYSIS OF SYMPTOMS

Chest Pain or Discomfort

Chest pain is one of the very common presenting symptoms that patients present to the cardiologists for their expert views for the diagnosis of its etiology and management. The chest pain or discomfort can be caused by various cardiac and noncardiac causes, which are summarized in Tables 1 to 4.

"Cardiac pain" may be due to myocardial ischemia or it can be nonischemic in origin. The cardiac pain resulting from myocardial ischemia is called "Angina pectoris". The precise mechanism of cardiac pain due to myocardial ischemia has not been elucidated. It has been postulated that small nonmedullated sympathetic nerve fibers, which are present in the epicardium along the coronary arteries, serve as the afferent pathways for angina pectoris. The afferent impulses enter the spinal cord in C8 to T4 segments, and are transmitted to the sympathetic

TABLE 1

Cardiac chest pain

• Coronary artery disease
• Acute coronary syndromes
• Stable angina
• Ischemic cardiomyopathy
• Noncoronary artery disease
• Aortic dissection
• Acute pulmonary embolism

TABLE 2

Noncardiac chest pain

Pulmonary

- Pleuritis
- Pneumonia
- Tracheobronchitis
- Pneumothorax
- Mediastinitis
- Tumor

TABLE 3

Cardiac causes of chest discomfort

- Aortic Stenosis
- Aortic regurgitations
- Hypertrophic cardiomyopathy
- Restrictive cardiomyopathy
- Pulmonary hypertension

TABLE 4

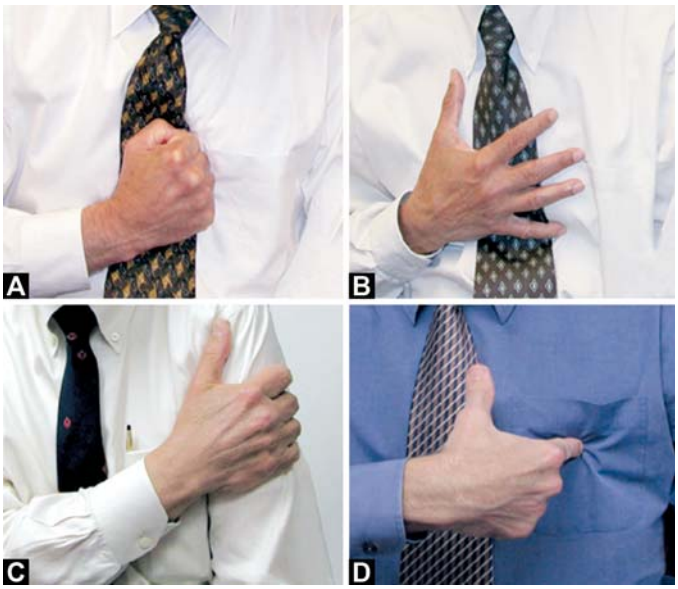
Noncardiac chest pain

Musculoskeletal

- Costochondritis
- Intercostal muscle cramps
- Cervical disc disease

Other causes

- Herpes zoster
- Emotional
- Chest wall tumor
- Disorders of breast



FIGURES 1A TO D: Illustrations of (A) the Levine Sign, (B) the Palm Sign, (C) the Arm Sign, (D) the Pointing Sign [*Source:* Marcus GM, et al. Am J Med. 2007;120:83-9 (Ref 3)]

ganglia of the same segments. The impulses then travel by spinothalamic tract to the thalamus. The pain perception requires activation of the specific cortical centers.

Angina pectoris is a symptom of both of chronic coronary artery disease and of acute coronary syndromes. For the diagnosis of angina pectoris, it is imperative to inquire about the character, location, site of radiation, duration, and precipitating and relieving factors of the chest discomfort.

The character of the discomfort is usually not severe pain. More frequently, it is described as "heaviness", "pressure", "tightness", "squeezing" or "band across the chest". Sometimes the patients have difficulty describing precisely the character of the chest discomfort. The character of angina pectoris is usually "dull and deep" and not "sharp and superficial". The "elephant sitting on the chest" is a typical textbook description, and frequently a knowledgeable patient uses this phrase to describe the character of the chest discomfort. However, such description is rather infrequently associated with coronary artery disease.

The location of the chest discomfort can be retrosternal, epigastric or left pectoral. It is infrequently located in the left axilla. Occasionally the initial location of angina can be left arm and hands, interscapular or left infrascapular area. When the character of pain is stabbing and pleuritic and it is positional or reproducible with palpation, it is unlikely to be angina and the likelihood ratio is 0.2:0.3.[2] When chest pain is much localized and can be indicated by one or two finger tips, it is unlikely to be angina pectoris.

The radiation of angina pain may be to one or both shoulders, one or both arms and hands, one or both sides of the neck, lower jaw and interscapular area. The radiation can also occur to armpits, epigastrium and subcostal areas. The radiation is usually from the center to the periphery (centripetal) and rarely from the periphery to center (centrifugal). The radiation to one or both shoulders is associated with the likelihood ratios of 2.3:4.7.[2]

Patient's gestures during describing the chest discomfort have been thought to be useful in the diagnosis of its etiology. The prevalences, specificities and positive predictive values of the Levine Sign, the Palm Sign, the Arm Sign and the Pointing Sign (Figs 1A to D) have been assessed in a prospective observational study.[3] The prevalence of the Levine, Palm, Arm and Pointing Signs was 11%, 35%, 16% and 4%, respectively. The specificities of Levine Sign and Arm Sign were 78% and 86%, respectively, but the positive predictive values were only 50% and 55%, respectively. The Pointing Sign had a specificity of 98% for nonischemic chest discomfort.

The intensity of angina increases slowly and reaches its peak in minutes, not instantaneously. Similarly it is relieved gradually, not abruptly. Analysis of the duration of chest discomfort is also helpful to decide whether it is ischemic or nonischemic pain. When the duration is extremely short, only 1–2 seconds, it cannot be angina pectoris. Similarly, if the chest pain lasts continuously without remission for several hours and without evidence for myocardial necrosis, it is unlikely to be angina.

The precipitating and relieving factors of the chest discomfort should be analyzed to determine its etiology. The classic angina (Heberden's angina) is precipitated by exercise or by emotional stress and is relieved when the exercise is discontinued. It tends to occur often after meals. The original description of classic angina pectoris by William Heberden is shown in Figure 2.[4]

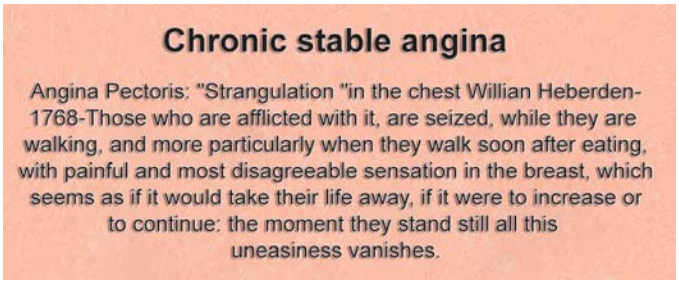


FIGURE 2: Description of effort angina by Sir William Heberden in 1768 (Ref 4)

The effort angina is also relieved with sublingual nitroglycerin. The time for relief after using nitroglycerin sublingually is not instantaneous. It takes a few seconds (usually 30 seconds or longer). It should be appreciated that chest pain due to esophageal spasm is also relieved by nitroglycerin.

Exposure to cold weather precipitates angina more easily in patients with classic angina. Similarly, carrying heavy objects and heavy meals are also frequent precipitating factors. The character location and radiation of chest discomfort are similar in the different clinical subsets of angina. However, some distinctive features can be recognized in various subsets.

In patients with vasospastic angina, angina occurs at rest and usually not during exercise. The duration is variable. It tends to have cyclic phenomenon and, in the individual patient, it tends to occur more or less at the same time.

In patients with acute coronary syndromes, the duration is usually longer. In patients with ST Segment Elevation Myocardial Infarction (STEMI), the relief of chest pain may not occur until reperfusion therapy is established.

The atypical presentations frequently called "anginal equivalents" are dyspnea, indigestion and belching, and dizziness and syncope without chest pain. The atypical presentations are more common in diabetics, women and the elderly. The few clinical features of angina are summarized in Tables 5 and 6. The chest pain due to acute pericarditis, acute pulmonary embolism or acute aortic dissection may be similar to that of acute coronary syndromes.

The pericardial pain is usually superficial and sharp and may have a pleuritic quality. It can radiate to both shoulders and infraspinatus areas. Generally, pericardial pain is worse in supine position and less severe in sitting and leaning forward position. Occasionally pericardial pain waxes and wanes with cardiac systole and diastole.

The location of pain of acute pulmonary embolism can be retrosternal and may not have a pleuritic quality. It is frequently associated with tachypnea.

The chest pain resulting from acute aortic dissection is usually severe. The location can be anterior chest. Radiation to the back is common. The downward radiation along the spine is very suggestive of aortic dissection. The onset of pain is frequently instantaneous and the maximal severity may occur at the onset. The character of the pain is "shearing or tearing". A few clinical features of pain of acute pericarditis, pulmonary embolism and acute aortic dissection are summarized in Table 7.

TABLE 5

The clinical features of stable angina

Location
• Usually retrosternal, can be epigastric, interscapular
Localization
• Usually diffuse, difficult to localize
• When is very localized (point sign)—unlikely to be angina
Quality
• Pressure, heaviness, squeezing, indigestion
Radiation
• One or both arms, upper back, neck, epigastrium, shoulder
• Lower jaw (upper jaw, head, lower back, lower abdomen or lower extremities radiation is not feature of angina)
Duration
• Usually 1–10 minutes (not a few seconds or hours)
Precipitating factors
• Physical activity, emotional stress, sexual intercourse
Aggravating factors
• Cold weather, heavy meals
Relieving factors
• Cessation of activity, nitroglycerin (if relief is instantaneous it is unlikely to be angina)
Associated symptoms
• Usually none, occasionally dyspnea

TABLE 6

Few clinical features of chest pain in acute coronary syndromes

Location
• Same as stable angina
Quality
• Same as stable angina
Duration
• Usually longer than stable angina
Relieving factors
• Usually unrelieved by rest or nitroglycerin
Associated symptoms
• Dyspnea, sweating, weakness, nausea, vomiting presyncope or syncope

The severity of angina is assessed by the Canadian Cardiovascular Society (CCS) Functional Classification[5] (Table 8) or Specific Activity Scale[6] (Table 9). The use of CCS is most frequently used to assess the severity of angina, and has been proven to be useful to assess its prognosis.[7] The Specific Activity Scale, which is a more quantitative assessment of the severity of angina, is not used in the clinical trials.

In patients with suspected or documented coronary artery disease, inquiries should be made about the risk factors. The modifiable and nonmodifiable risk factors for atherosclerotic coronary artery diseases are summarized in Table 10.

TABLE 7

Few clinical features chest pain due to acute pericarditis, acute pulmonary embolism and acute aortic dissection

Acute pericarditis

Location

- Anterior chest, superficial

Character

- Sharp, can be pleuritic

Radiation

- Supraspinatus areas, shoulders, back

Relieving factors

- Worse in supine position, less severe in sitting and leaning forward position, relieved by analgesics, non steroidals and steroids

Acute pulmonary embolism

Location

- Usually retrosternal

Quality

- Deep, may be similar to acute coronary syndromes

Associated symptoms

- Tachypnea and dyspnea

Acute aortic dissection

Location

- Chest, back

Quality

- Shearing, tearing

Onset

- Instantaneous

Radiation

- Downwards along the spine

TABLE 8

Canadian cardiovascular society (CCS) functional classification

Class I

- Ordinary physical activity, such as walking and climbing stairs, does not cause angina
- Angina with strenuous or rapid or prolonged exertion at work or recreation

Class II

- Slight limitation of ordinary activity. Walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, in cold, in wind or when under emotional stress, or only during the few hours after awakening
- Walking more than two blocks on the level, and climbing more than one flight of ordinary stairs at a normal pace and in normal conditions

Class III

- Marked limitation of ordinary physical activity
- Walking 1–2 blocks on the level and climbing more than one flight in normal conditions

Class IV

- Inability to carry on any physical activity without discomfort—anginal syndrome may be present at rest

Smoking, hypertension, diabetes, obesity, metabolic syndrome, hyperlipidemia and physical inactivity are risk factors for coronary artery disease. History of peripheral vascular and cerebrovascular disease and stroke is also associated with a higher risk of coronary artery disease. These risk factors are modifiable.

Older age, male gender and family history of atherosclerotic cardiovascular disease are also risk factors for coronary artery disease, but these risk factors are not modifiable.

TABLE 9

Specific activity scale

Class I

- Patients can perform to completion any activity requiring ≤ 7 metabolic equivalents [e.g. can carry 24 lbs up eight steps; carry objects that weigh 80 lbs, do outdoor work (shovel snow, spade soil); do recreational activities (skiing, basketball, squash, handball, jog/walk 5 mph)]

Class II

- Patients can perform to completion any activity requiring ≤ 5 metabolic equivalents (e.g. have sexual intercourse without stopping, garden, rake, weed, roller skate, dance fox trot, walk 4 mph on level ground), but cannot and do not perform to completion activities requiring ≥ 7 metabolic equivalents

Class III

- Patients can perform to completion any activity requiring ≥ 2 metabolic equivalents (e.g. shower without stopping, strip and make bed, clean windows, walk 2.5 mph, bowl, play golf, dress without stopping), but cannot and do not perform to completion any activities requiring ≥ 5 metabolic equivalents.

Class IV

- Patients cannot or do not perform to completion activities requiring ≥ 2 metabolic equivalents. Cannot carry out activities listed above (Specific Activity Scale Class III)

TABLE 10

Cardiac and pulmonary causes of dyspnea

Differential diagnosis of dyspnea	
Cardiac	Pulmonary
CHF	COPD
CAD	Asthma
Cardiomyopathy	Restrictive lung diseases
Valvular dysfunction	Hereditary lung diseases
LVH	Pneumothorax
Pericardial diseases	
Arrhythmias	
Congenital HD	

(Abbreviations: CHF: Congestive heart disease; HD: Heart disease; CAD: Coronary heart disease; LVH: Left ventricular hypertrophy

Dyspnea

Dyspnea is an uncomfortable sensation of breathing. It is also defined as "labored" breathing. The precise mechanism of dyspnea has not been established. It has been suggested that activation of the mechanoreceptors in the lungs, pulmonary artery and heart and activation of the chemoreceptors are involved in inducing dyspnea. Dyspnea can occur during exertion (exertional), during recumbency (orthopnea) or even with standing (platypnea).

There are both cardiac and noncardiac (Table 10) causes of dyspnea. Pulmonary disease, such as chronic obstructive lung disease, is one of the common noncardiac causes of dyspnea. Many patients have both cardiac and pulmonary disease. It is not uncommon in clinical practice to encounter patients who have coronary artery disease and chronic obstructive

pulmonary disease. In such patients, to determine the cause of dyspnea appropriate history and physical examination are essential. To distinguish between cardiac and noncardiac dyspnea, the measurements of serum B-type Natriuretic Peptide (BNP) or N-Terminal ProBNP (NTBNP) is helpful. In noncardiac dyspnea, the natriuretic peptide levels are normal, and in patients with heart failure, they are substantially elevated.

Exertional dyspnea can be caused by both cardiac and noncardiac causes. Exertional dyspnea is an important symptom of chronic heart failure. However, it is also a symptom of chronic pulmonary diseases and of metabolic disorders such as obesity and hyperthyroidism. Dyspnea is also a common symptom of anxiety disorders. Cardiac dyspnea gets worse with physical activity. Dyspnea of functional origin frequently improves after exercise.

Orthopnea is defined when patients develop dyspnea lying flat and feel better when the upper part of the torso is elevated. Although orthopnea is a symptom of heart failure, it also occurs in patients with pulmonary disease such as emphysema and chronic obstructive pulmonary disease.

Paroxysmal nocturnal dyspnea is virtually diagnostic of cardiac cause. After being in the recumbent position for about 15 minutes to 2 hours, the patient develops shortness of breath and has to sit or stand up to get relief. The hemodynamic mechanism is that after assuming the recumbent position, there is an increase in the intravascular and intracardiac volumes, which is associated with an increase in pulmonary venous pressure and transient hemodynamic pulmonary edema. The sitting and/or upright position is associated with a reduction of intravascular and intracardiac volumes due to decreased venous return and reduction of pulmonary venous pressure and relief of dyspnea. Left ventricular systolic and diastolic heart failure and aortic and mitral valve diseases are the common causes of paroxysmal nocturnal dyspnea.

Sleep-disordered breathing, which may be associated with dyspnea, can occur in cardiac patients. Cheyne-Stokes respiration is a specific type of periodic breathing that is characterized by alternating periods of apnea and hyperpnea. During hyperpneic phases there is a progressive decrease in PCO_2 with increased pH, which inhibits the respiratory drive; during apneic phase CO_2 accumulates with an increase in respiratory acidosis and the respiratory center is stimulated and breathing is initiated. It appears that chemoreceptors-mediated stimulation of the respiratory centers is blunted in patients with Cheyne-Stokes respiration. Patients feel shortness of breath during the hyperpneic phase. Central, obstructive and mixed types of sleep apnea are observed in patients with heart failure. The hemodynamic causes of sleep-disordered breathing in heart failure have not been clearly elucidated. Initially, the Cheyne-Stokes respiration was thought to be due to low cardiac output;[8] however, there does not appear to be a good correlation between any hemodynamic changes of systolic heart failure and Cheyne-Stokes respiration. History of sleep-disordered breathing should be enquired as it is associated with worsening heart failure, pulmonary hypertension, and increased risks of arrhythmias and sudden cardiac death.

Wheezing due to constriction of the bronchial smooth muscles associated with dyspnea does not always imply pulmonary diseases. It may be caused by hemodynamic pulmonary edema in patients with systolic and diastolic heart failure and valvular heart diseases (cardiac asthma).

There are many cardiac conditions which can be associated with episodic severe dyspnea. In between the episodes of dyspnea, these patients are relatively asymptomatic and may have good exercise tolerance. In patients with episodic dyspnea, intermittent severe mitral regurgitation due to papillary muscle dysfunction should be considered in the differential diagnosis. Intermittent mitral valve obstruction due to left atrial myxoma or ball valve thrombus is a rare cause of this syndrome. In patients with left atrial myxoma, dyspnea may be positional and may be associated with syncope. Another cause of episodic severe dyspnea is "stiff heart syndrome".[9] These patients usually have normal left ventricular ejection fraction and have history of hypertension and coronary artery disease (diastolic heart failure). Fluid retention, either from the increased salt intake or from the lack of use of the diuretics, precedes the onset of dyspnea.

Atrial or ventricular tachyarrhythmias usually do not produce episodic severe dyspnea in absence of valvular or myocardial disease. However, it can occur in patients with left ventricular dysfunction and in patients with mild-to-moderate mitral stenosis.

In patients with massive or submassive pulmonary embolism, tachypnea and dyspnea are common presenting symptoms. There may be associated chest pain and wheezing. Patients with pulmonary embolism prefer the supine position as opposed to patients with hemodynamic pulmonary edema who prefer the upright position. Arterial desaturation may be present in both conditions. A plain chest X-ray may be useful to establish the diagnosis. In patients with pulmonary embolism, the chest X-ray is clear and does not demonstrate radiologic evidences of pulmonary venous hypertension. In patients with hemodynamic pulmonary edema, prominent upper lobe vessels, perihilar haziness, and Kerley lines and frank pulmonary edema may be present (Fig. 3).

A careful cardiovascular examination may also reveal the etiology of dyspnea. For example, evidence of valvular and

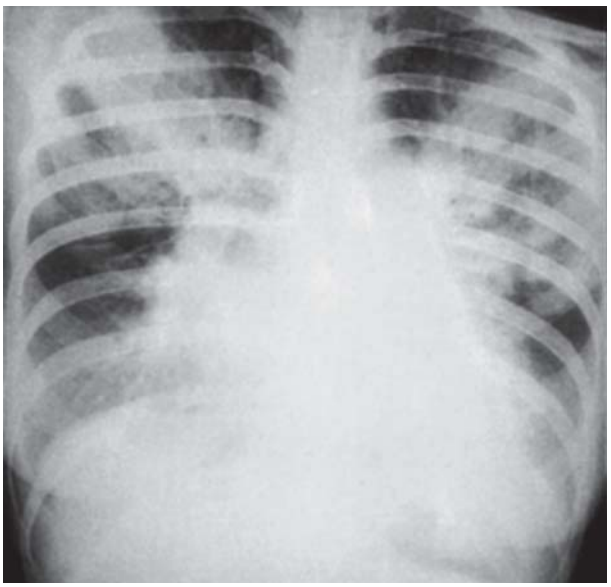


FIGURE 3: A plain chest X-ray of a patient with acute severe mitral regurgitation showing florid hemodynamic pulmonary edema

TABLE 11

Cardiac cause of dyspnea

Dyspnea
Cardiac or noncardiac dyspnea
Physical examination:
Signs of heart failure—diagnostic of cardiac cause, e.g. S3, elevated JVP, positive HJR
Presence of cardiac pathology:
Very suggestive of cardiac cause
Chest X-ray:
Very helpful when findings of pulmonary venous congestion or pulmonary hypertension are present
ECG:
Normal electrocardiogram
A negative predictive value has over 90%

(Abbreviations: JVP: Jugular venous pressure; HJR: Hepatojugular refulx

myocardial heart diseases suggests cardiac cause of dyspnea (Table 11). The presence of S3 gallop usually indicates increased left ventricular diastolic pressures except in young people and patients with chronic primary mitral regurgitation. In patients with heart failure, presence of S3 is also associated with the increased levels of B-type natriuretic peptides. The presence of characteristic physical findings of significant valvular heart disease also suggests cardiac dyspnea. The absence of these signs, however, does not exclude cardiac dyspnea.

Palpitation

Palpitation is perceived as an uncomfortable sensation in the chest associated with heartbeats. The most frequent cause of palpitation is premature atrial or ventricular contractions. The premature beat itself is not felt; the normal beat following the compensatory pause is felt as a strong beat. The patients usually describe this uncomfortable sensation as “a thump”, “skipped beat”, “the heart is coming out of chest”, “heart stops” and “heart stops beating”.

The frequent premature beats may also be associated with other symptoms such as dizziness, sinking feeling, shortness of breath and chest pain. The chest pain can be troublesome and anxiety provoking. The mechanism of chest pain remains unclear; it is possible that the beat following the compensatory pause is associated with activation of myocardial afferent stretch receptors causing chest pain. The same mechanism can be hypothesized for dyspnea associated with premature beats.

During taking history about palpitation, it is desirable to enquire about the duration, whether it is regular or irregular, fast or slow, and the mode of onset and termination. It is sometimes easier for the patient to recognize the type of arrhythmia if the physician taps with the fingers to describe the type of arrhythmia. If it is fast and irregular, the likely diagnosis is atrial fibrillation; although rarely it can be due to multifocal atrial tachycardia. A fast irregular palpitation can be due to atrial flutter or very frequent premature beats.

An abrupt onset and abrupt termination of fast regular or irregular tachycardia is a common feature of supraventricular tachycardia, although it may also occur in ventricular tachycardia. The associated symptoms of supraventricular tachycardia, besides palpitation, are dyspnea, chest pain, presyncope or even syncope. Some patients also experience polyuria during prolonged episodes of supraventricular tachycardia. The mechanism of polyuria is probably due to stimulation of release of atrial natriuretic peptide and suppression of vasopressins. The vasodilatory effects of atrial natriuretic peptides may also contribute to hypotension and presyncope.

Syncope

Syncope is defined as transient loss of consciousness. Patients with presyncope complain of dizziness and near fainting, although they do not loose consciousness completely. The mechanism of cardiac syncope is reduced cerebral perfusion resulting from decreased cardiac output and hypotension.

A large number of cardiac and noncardiac conditions can cause syncope (Chapter “Syncope”). Dysrhythmias, abnormalities of function of the autonomic nervous system, anatomic conditions such as left or right ventricular outflow obstruction, vascular disorders such as severe pulmonary arterial hypertension, acute coronary syndromes, aortic dissection and acute massive or submassive pulmonary embolism can be associated with syncope.

Acute coronary syndromes, aortic dissection or pulmonary embolism do not cause recurrent syncope. However, when syncope is the presenting symptom in these patients, the prognosis is poor.

A careful history is helpful for the diagnosis of the cause of syncope. Inquiry should be made about the circumstances in which syncope occurred, whether it was accompanied or preceded by palpitation, whether it occurs during exertion or it can also occur at rest, and whether it occurs only during upright position or it is unrelated to body position.

Stokes-Adams-Morgagni syndrome occurs due to ventricular asystole (cardiac standstill) in patients with advanced atrioventricular block. The syncope is unrelated to body position or exertion. The onset is sudden and recovery is also abrupt. During asystole the skin is pale and white and with the return of circulation, the skin appears red and flushed. There are no premonitory symptoms and after recovery of consciousness, the patients are not confused and are immediately aware of the surroundings. Stokes-Adams-Morgagni syndrome may be familial, suggesting a genetic abnormality may be present.

Vasovagal or neurocardiogenic syncope occurs during upright position and frequently after remaining in a standing position for a few minutes. The onset is not abrupt and premonitory symptoms, such as nausea, abdominal discomfort and urge for bowel movement, may precede syncope. The recovery of consciousness is gradual and patients may appear confused after recovery of consciousness.

Syncope resulting from supraventricular tachyarrhythmias is usually not of abrupt onset. Supraventricular tachycardia more frequently causes presyncope rather than frank syncope. It is associated with fast palpitations and usually occurs during upright position. Some patients with brady-tachy syndrome give history of syncope after the fast palpitations stop and the mechanism appears to be due to prolonged sinus node recovery time. Paroxysmal Orthostatic Tachycardia Syndrome (POTS) syncope usually occurs in patients during exercise and is caused by inappropriate sinus tachycardia.

There are other types of syncope which are due to stimulation of the parasympathetic nervous system that is associated with cardioinhibitory and vasodepressor response. The history of syncope precipitated by sudden movement of the head, rubbing or shaving the neck, or wearing a tight collar suggests carotid sinus syncope. The history of syncope while swallowing or drinking cold water (glossopharyngeal syncope) is due to stimulation of the ninth cranial nerves, and it may also be associated with neuralgic pain.[10]

Micturition syncope occurs during or immediately after voiding and is caused by reflex stimulation of the parasympathetic nervous system.[11] The posttussive syncope, also known as cough syncope, occurs during or immediately after paroxysms of violent cough.[12] The mechanisms of cough syncope remain unclear. A decrease in cardiac output due to decreased venous return resulting from increased intrathoracic pressure during paroxysms of prolonged cough is a potential mechanism.

In patients with orthostatic hypotension, syncope occurs in the upright position and the onset is gradual. Enquiries should be made about the use of antihypertensive drugs and sublingual nitroglycerin preceding syncope. Orthostatic hypotension may also occur in patients with diabetes, amyloidosis and other disorders of autonomic function and there may be history of impotence, sphincter disturbances and anhidrosis.

A history of presyncope, blurring of vision with or without arm claudication during exercise of the upper extremities is very suggestive of "subclavian steal" syndrome.[13]

Syncope due to anatomic causes (aortic stenosis, hypertrophic obstructive cardiomyopathy, pulmonary hypertension) usually occurs during exercise. The mechanism appears to be the inability to increase cardiac output during exercise and disproportionate decrease in metabolically mediated peripheral vascular resistance.

The convulsive disorders, such as epilepsy, can also cause syncope. It can occur in any position. There is usually a history of prodromal aura preceding the seizure. Urinary and bowel incontinence and biting of tongue and other involuntary injuries support the diagnosis of epilepsy.

Edema

Patients with edema present with the symptom of "swelling", usually of the lower extremities. Both cardiac and noncardiac conditions may be associated with edema. Enquiries should be made regarding the initial location and progression of edema. Right heart failure with systemic venous hypertension causes dependant edema such as in the ankles, feet and legs. In patients with worsening right heart failure, edema can extend to the thighs, genitalia and abdomen. In patients who are bedridden, edema can be predominantly in the back.

Chronic venous insufficiency may also be associated with lower extremity edema and a bluish discoloration of the skin may be present. In patients with idiopathic lower extremity edema, symptoms and signs of systemic venous hypertension are absent.

Generalized edema is uncommon in heart failure and usually suggests permeability edema such as in patients with hypoalbuminemia.

The history of edema localized in the upper extremity should raise the suspicion of upper extremity venous obstruction such as subclavian, innominate and superior vena cava thrombosis. These patients may also complain of facial edema with bluish discoloration.

Non-pitting lymphedema of the upper extremity is occasionally observed in patients who had a mastectomy and axillary lymph node removal for breast malignancy.

Cough

The paroxysms of cough may be the presenting symptoms of cardiac and noncardiac patients. Patients with left heart failure may complain of nocturnal cough with or without dyspnea. Paroxysms of nonproductive cough are bothersome complications of angiotensin-converting enzyme inhibitor therapy.

Cough with or without expectoration is also a frequent presenting symptom of pulmonary diseases.

Hoarseness with or without cough is a rare complication of mitral stenosis (Ortner's syndrome). A markedly enlarged left atrium and pulmonary artery compress the left recurrent laryngeal nerve causing hoarseness.[14] Hoarseness also occurs in patients with aortic aneurysm if it compresses the left recurrent laryngeal nerve.

Hemoptysis

Hemoptysis is an uncommon presenting symptom of cardiac patients. Patients with hemodynamic pulmonary edema may present with history of frothy pink, blood-tinged sputum. These patients also have dyspnea.

Rarely, in patients with mitral stenosis and severe pulmonary hypertension, profuse hemoptysis (pulmonary apoplexy) can occur due to rupture of the bronchopulmonary venous anastomotic vessels. If profuse hemoptysis occurs in a patient instrumented with a balloon flotation catheter, pulmonary artery rupture should be suspected.

Recurrent hemoptysis may be a presenting symptom in patients with precapillary pulmonary arterial hypertension and Eisenmenger's syndrome. The thrombosis *in situ* of pulmonary vessels appears to be the mechanism.

Hemoptysis associated with pleuritic chest pain should raise the suspicion of pulmonary embolism.

Patients on anticoagulation therapy may present with hemoptysis. It should be appreciated, however, that frank hemoptysis is an uncommon presenting symptom of cardiac patients and primary bronchopulmonary disease, such as malignancy, should always be suspected.

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Chapter 10

Physical Examination

Kanu Chatterjee

Chapter Outline

- General Appearance
  - Examination of the Skin
  - Examination of the Musculoskeletal System
- Measurement of Arterial Pressure
  - Examination of the Jugular Venous Pulse
  - Estimation of Jugular Venous Pressure
  - Jugular Venous Pulsations
  - Arterial Pulse
  - Examination of the Precordial Pulsation
- Auscultation
  - Third (S3) and Fourth (S4) Heart Sounds
  - Auscultation of Heart Murmurs
  - Pulmonary Outflow Obstruction
  - Diastolic Murmurs
  - Continuous Murmurs

The physical examination, like taking history, is an integral part of evaluation of a patient with suspected or established cardiovascular disorders. It also allows the physician to decide about what investigations are appropriate for establishing the diagnosis and for assessing the management strategies and prognosis.

GENERAL APPEARANCE

The physical examination starts with the inspection of the general appearance of the patient. During inspection, the physician has the opportunity to observe the patient's expression, skin color, posture and general health status. If the patient is restless and anxious, it may indicate that the underlying disorder is severe or it might be due to anxiety. In a patient presenting with chest pain, pale skin, diaphoresis, restlessness may suggest acute coronary syndrome. Pale skin may indicate anemia or peripheral vasoconstriction. Spontaneous diaphoresis is due to excessive activation of the sympathetic adrenergic system.

The presence and type of dyspnea can be determined during inspection. Tachypnea with labored breathing and inability to lie down is usually due to cardiac dyspnea associated with pulmonary venous congestion. In contrast, "puffing"—breathing with prolonged expiration—indicates chronic obstructive pulmonary disease. During inspection, the type of disordered breathing can also be diagnosed. For example, Cheyne-Stokes respiration, which is common in patients with advanced heart failure, can be apparent.

During inspection, the nutritional status of the patient can be determined. Obesity or cachexia can easily be recognized. Obesity is a risk factor for metabolic syndrome, coronary artery disease and heart failure. Cachexia is indicative of severe end-stage heart failure or other systemic disorders such as malignancy. The fragility may also be obvious during inspection of the general appearance of the patient. It is associated with increased morbidity following cardiac and noncardiac surgery.

Mental status evaluation can be performed during inspection of the patient. Mental confusion may indicate reduced cerebral perfusion due to reduced cardiac output such as in patients with cardiogenic shock. It may also be due to primary cerebrovascular diseases such as subdural hematoma. In patients with sleep-disordered breathing, somnolence and mental confusion during the day is common.

Abnormal gait, dysphasia, dysarthria, motor weakness and other manifestations of neurologic deficits can be detected during inspection of the general appearance. These neurologic abnormalities may indicate prior cardioembolic stroke.

The Parkinsonian gait and other manifestations of Parkinsonism may indicate Shy-Drager syndrome in patients with orthostatic hypotension and syncope.[1] The patients with pseudohypertrophic muscular dystrophy, which can be associated with dilated cardiomyopathy, have characteristic abnormality of the gait. The patients with Friedreich's ataxia with ataxic gaits are occasionally associated with hypertrophic cardiomyopathy.

EXAMINATION OF THE SKIN

Examination of the color of the skin can reveal presence of cyanosis, jaundice and slaty, and bronze discoloration.

Cyanosis is characterized by bluish discoloration of the skin and mucous membrane. Most frequently cyanosis is due to presence of abnormal amount of reduced hemoglobin. If the amount of reduced hemoglobin is less than 4 g/dL, cyanosis does not develop. Cyanosis can be central or peripheral or mixed. The central cyanosis is due to intracardiac or intrapulmonary right-to-left shunt. The amount of desaturated hemoglobin is increased in central cyanosis and best recognized inspecting the buccal mucous membrane, tongue and

oropharyngeal mucous membrane. The desaturation does not improve with supplemental oxygen treatment in patients with intracardiac right-to-left shunt. In Eisenmenger's syndrome due to atrial or ventricular septal defects, central cyanosis and clubbing are present in fingers and toes. However, in Eisenmenger's syndrome, due to patent ductus arteriosus, cyanosis and clubbing are present only in the toes (differential cyanosis) because desaturated blood is shunted to descending thoracic aorta via patent ductus arteriosum. The peripheral cyanosis usually reflects reduced cardiac output. A sluggish peripheral circulation, irrespective of the mechanism, can be associated with peripheral cyanosis as there is increased time available for oxygen extraction.

The bluish discoloration of the skin is also a manifestation of methemoglobinemia and argyria. Methemoglobinemia may be hereditary or acquired resulting from overdose of nitrates, nitrites or nitroprusside.

Argyria is characterized by slate-blue discoloration of the skin and results from the deposition of melanin stimulated by silver iodide.[2]

Jaundice due to hyperbilirubinemia is occasionally seen in patients with severe right heart failure associated with congestive hepatopathy. Patients with portopulmonary hypertension may also have jaundice. Malfunctions of the prosthetic valves can be associated with hemolysis and jaundice. The cardiologists are frequently consulted for preoperative clearance of the patients before liver transplantation and these patients usually have jaundice.

Bronze discoloration of the skin in unexposed areas suggests primary or secondary hemochromatosis. However similar discoloration of the skin is also observed in patients on long-term amiodarone treatment after exposure to sun.

A butterfly rash of the face is seen in patients with lupus erythematosus, which can be associated with valvular heart disease (Libman-Sachs endocarditis) and precapillary pulmonary arterial hypertension. A malar flush with cyanotic lips is seen in some patients with severe mitral stenosis.

However, it can also be seen in patients with chronic severe precapillary pulmonary arterial hypertension.

Palmer and planter keratoses and woolly hair are characteristic features of Naxos Disease, a genetically inherited form of arrhythmogenic right ventricular dysplasia/cardiomyopathy.[3]

Telangiectasia of tongue, buccal mucosa and lips may indicate Osler-Weber-Rendu syndrome, which is associated with pulmonary arteriovenous malformations.[4]

Tendon xanthoma, xanthoma within palmer creases and subcutaneous lipid nodules indicate familial hyperlipidemia, which is associated with premature coronary artery disease.

Multiple cutaneous lentigines may indicate LEOPARD syndrome, which is associated with conduction defects and congenital pulmonary stenosis.[5]

Petechiae and purpuric rash with or without Osler and Janeway nodes are features of bacterial endocarditis. Funduscopic examination may reveal "Roth spots" (retinal hemorrhagic areas with clear centers).

Carcinoid heart disease may be associated with blotchy cyanotic discoloration and also episodes of diarrhea.

Livido reticularis is a common skin manifestation of many conditions such as lupus erythematosus and the blue toes syndrome. The blue toes syndrome is due to cholesterol emboli and is characterized by cyanosis of the toes and preserved peripheral pulses and is a complication of left heart catheterization and descending aortic surgery.[6]

Diabetes can be associated with atrophic skin lesions in the legs, called necrobiosis diabeticorum and it is rather an uncommon complication of diabetes.

Lyme disease, which can be associated with pericarditis, heart block and myocarditis, is characterized by an annular skin rash with a clear central area.

Tightening of the skin, flexion contractures of the fingers causing claw-like deformity of hands are features of advanced scleroderma. The CREST syndrome (calcinosis, Raynaud phenomenon, esophageal motility disorder, sclerodactyly and telangiectasia) is a variant of scleroderma. Both scleroderma and CREST syndrome are causes of precapillary pulmonary hypertension. A few conditions of abnormalities of skin that can be associated with cardiovascular disorders are summarized in Table 1.

EXAMINATION OF THE MUSCULOSKELETAL SYSTEM

The majority of congenital heart disease with musculoskeletal abnormalities is encountered in the pediatric population. In adult cardiology practices a few conditions, although distinctly uncommon, may be seen (Chapter "Congenital Heart Disease in the Adult Patient") (Table 2).

Patients with Marfan's syndrome are tall and usually have kyphoscoliosis and pectus deformities. The arm span exceeds the height, and the upper head to pubis segment is longer than lower pubis to feet segment. The lax joints, arachnodactyly and high-arched palate are also features of Marfan's syndrome.

Marfan's syndrome is associated with aortic regurgitation and mitral regurgitation. It can also be associated with aortic root disease. The patients with Ehler-Danlos syndrome, which can be associated with mitral regurgitation due to mitral valve prolapse, arterial dilatation and aortic root disease, have hyperextensible joints and friable hyperelastic skin.

The Turner's syndrome, which is associated with coarctation of aorta, has a webbed neck, small jaw, high-arched palate, hypertelorism and low-set ears.

The Holt-Oram syndrome is characterized by the secundum atrial septal defect and absent thumbs with or without hypoplastic radial bones.

The patients with Down syndrome (trisomy 21) may have various congenital heart defects, including ventricular septal defect and endocardial cushion defects. The musculoskeletal abnormalities include a small head, slanting eyes with epicanthal folds, hypertelorism and low-set ears.

The cardiac involvement can occur in various types of acquired musculoskeletal arthritic disorders.

In patients with rheumatoid arthritis, aortic regurgitation and heart block can be observed. The coronary artery small vessel disease can cause myocardial microinfarcts.

Ankylosing spondylitis can be associated with aortic regurgitation, mitral regurgitation and atrioventricular block.[7] Valvular involvements due to verrucous endocarditis (Libman-Sacks endocarditis) and pulmonary arterial hypertension are cardiac complications of systemic lupus erythematosus.

TABLE 1

Skin abnormalities and cardiovascular disorders

- Cyanosis
  Central—intracardiac and intrapulmonary right-to-left shunt
  Peripheral—low cardiac output, increased peripheral oxygen extraction
- Methemoglobinemia—bluish discoloration of the skin
  Hereditary (rare) and acquired (nitrate and nitrite toxicity)
- Jaundice—yellow discoloration
  Prosthetic valve malfunction-hemolysis
  Portopulmonary hypertension
  Severe congestive hepatopathy
- Bronze discoloration—slaty color of the skin
  Primary or secondary hemochromatosis
  Atrial or ventricular arrhythmias
  Restrictive cardiomyopathy, dilated cardiomyopathy
- Amiodarone skin toxicity—benign
- Butterfly rash of the face—lupus erythematosus
  Valvular disease (Libman-Sack endocarditis)
  Pulmonary arterial hypertension
- Malar flush of the face—
  Severe mitral stenosis
  Severe precapillary pulmonary hypertension
- Planter and palmer keratosis and wooly hair—naxos disease
  Arrhythmogenic right ventricular dysplasia
- Telangiectasia of lips, tongue and buccal mucous membrane—
  Osler-Weber-Rendu syndrome
  Arteriovenous malformations
- Xanthomatosis—tendon xanthoma, xanthoma in the palmer crease, with or without xanthelasma—familial hyperlipidemia
  Premature coronary artery disease
- Cutaneous lentiginosis—LEOPARD syndrome
  Conduction defects, congenital pulmonary stenosis
- Petechiae and purpuric skin rash—bacterial endocarditis
  Valvular heart disease
- Blotchy cyanosis—carcinoid heart disease
  Right-sided valvular heart disease
- Livid reticularis—reticular purplish skin rash
  Lupus erythematosus
  Valvular heart disease, pulmonary hypertension
  Blue toes syndrome
  Cholesterol emboli
- Atrophic skin lesions—necrobiosis-diabeticorum
  Increased risks of cardiovascular disease
- Annular skin rash with clear center—lyme disease
  Heart block, myocarditis
- Tightening of the skin, flexion contractures of the fingers, telangiectasia-Scleroderma, CREST syndrome
  Pulmonary arterial hypertension

There is higher association of straight back, pectus excavatum and scoliosis with mitral valve prolapse syndrome.

Finger and toes should be examined for clubbing. The drumstick type of clubbing is seen in cardiovascular diseases such as congenital cyanotic heart disease and bacterial endocarditis.

The bacterial endocarditis can be also associated with splinter hemorrhage, Janeway and Osler nodes and valvular regurgitations.

The Heberden's nodes, which are usually seen in the fingers, result from osteoarthritis and are not associated with cardiovascular disorder.

TABLE 2

A few musculoskeletal abnormalities associated with cardiovascular disorders

- Marfan's syndrome
  Aortic regurgitation, mitral regurgitation, aortic disease
- Ehler-Danlos syndrome
  Mitral regurgitation, aortic disease
- Turner's syndrome
  Coarctation of aorta
- Holt-Oram syndrome
  Atrial septal defect
- Down's syndrome
  Ventricular septal defect, atrioventricular cushion defects
- Rheumatoid arthritis
  Aortic regurgitation, heart block
- Ankylosing spondylosis
  Aortic and mitral valve disease, heart block
- Clubbing of the fingers and toes
  Congenital cyanotic heart disease, bacterial endocarditis
- Straight back syndrome
  Mitral valve prolapse
- Clubbing of fingers and toes
  Congenital cyanotic heart disease, bacterial endocarditis

MEASUREMENT OF ARTERIAL PRESSURE

At present, in most institutions, automated techniques are used for the measurement of blood pressure. The various techniques of measuring blood pressure, their advantages and disadvantages and pitfalls are discussed in the section of clinical hypertension.

The cuff technique is preferable to digital technique. The cuff wrist systolic pressure is higher than the arm systolic pressure and the wrist diastolic pressure is lower than the arm diastolic pressure.

The blood pressure measured by the physician is usually higher than when it is measured by the nurses.

Higher blood pressure recorded by physicians is sometimes referred as "White coat hypertension". Controversy exists about the prognostic significance of white coat hypertension.

When blood pressure is determined by auscultatory methods, the Korotkoff Phase I indicates systolic blood pressure. The disappearance of the sound (Korotkoff V) indicates diastolic blood pressure. Occasionally Korotkoff sounds disappear soon after the first sound and reappear after the release of cuff pressure. The difference of pressure at the first appearance and the reappearance of the Korotkoff sounds is called auscultatory gap. The mechanism and significance remain unclear.

The blood pressure should be recorded initially 2–3 times at 1–5 minutes intervals. The first recorded blood pressure is frequently higher than the second or the third time recording. The lowest recorded blood pressure should be used to determine the blood pressure. The mechanism of this phenomenon is not clear but it may be due to conditioning of the muscular and vascular receptors.

During the initial visit, it is desirable to determine blood pressure in both arms. The difference between the two arms pressure should be less than 10 mm Hg. In a considerable number of subjects, the pressure difference exceeds 10 mm Hg

in absence of any cardiovascular abnormalities.[8] A significant difference in the pressure in the two arms may occur in subclavian artery obstruction, supravalvular aortic stenosis, presubclavian coarctation, pseudocoarctation and aortic dissection.

Simultaneous palpation of radial and femoral arteries may reveal a delayed onset and decreased amplitude of femoral pulse, which may indicate coarctation or pseudocoarctation of aorta and abdominal aortic and femoral atherothrombotic obstruction.

In patients with stiff calcified upper extremity arteries, cuff pressure may be much higher than the intraarterial pressure (pseudohypertension). After obliterating the pulse during pressure measurement, if the radial pulse is still palpable, it indicates stiff arteries (Osler maneuver).[9]

EXAMINATION OF THE JUGULAR VENOUS PULSE

Careful examination of the jugular venous pulse and pressure provides information regarding the hemodynamic changes in the right side of the heart. There is controversy regarding whether external or the internal jugular veins should be examined. It has been suggested that for estimation of jugular venous pressure it is easier and preferable to examine the external jugular vein.[10] However, it has also been suggested that if pulsation is present and visible, the examination of the internal jugular veins is preferable to that of the external jugular veins as the internal jugular veins are in a direct line with the superior vena cava.[11] The external jugular veins are not in a direct line with the superior vena cava and it drains into superior vena cava after negotiating two 90 degree angles.[11] Thrombus formation in the external jugular venous bulb is not uncommon, particularly in older people which may cause its partial obstruction. The lateral movement of the head may also cause partial obstruction of the external jugular veins due to contraction of the platysma muscles and cause a spurious increase in venous pressures. Occasionally the left internal jugular venous pressure is higher than the right internal jugular venous pressure because of the compression of the left innominate vein by the unfolded aorta. During inspiration, with the descent of the aorta and decompression of the left innominate vein, the pressures of both internal jugular veins are equal. However, in some elderly patients, the partial compression of the left innominate vein by the aorta may persist, impairing transmission of right atrial pressure to the left innominate vein and causing unequal pressures between right and left internal jugular veins. The right internal jugular vein is in direct line with the right innominate vein and superior vena cava. Thus it is preferable to examine the right internal jugular vein.

ESTIMATION OF JUGULAR VENOUS PRESSURE

The jugular venous pressure can be estimated by examining either external or internal jugular veins (Fig. 1). Conventionally the upper torso is elevated to 30–40 degrees and the top of the venous pulsation is determined and 5 cm is added to the height assuming that right atrium is located 5 cm below the sternal angle (angle of Louis).[12] However, a computerized tomographic study to determine the distance between the sternal angle and level of the right atrium demonstrated that the distance varies according to the body position.[13] In the supine position, the

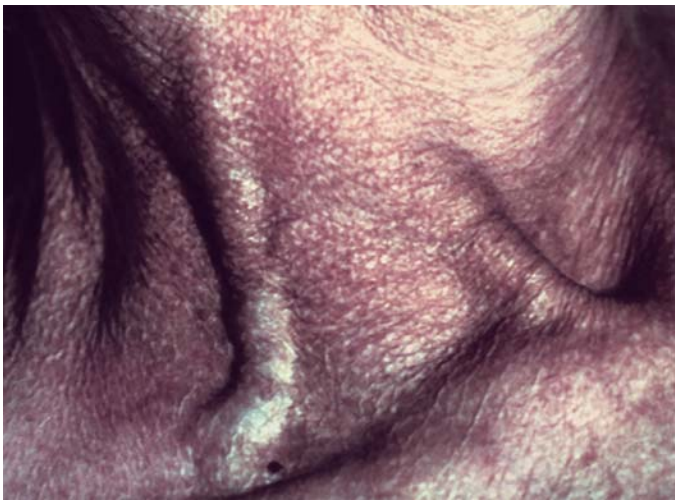


FIGURE 1: The courses of the external and internal jugular veins. The external jugular vein runs from lateral to the medial side of the neck across the sternocleidomastoid muscle. The internal jugular vein starts at the root of the neck in between the two heads of the sternocleidomastoid muscle runs superiorly toward the angle of the jaw

average vertical distance was 5.4 cm. However, with upper torso elevated to 30, 45 and 60 degrees the average vertical distance was 8, 9.7 and 9.8 cm respectively.[13] Thus, it has been suggested that 10 cm should be added rather than 5 cm, if the torso is elevated to 45 degree or greater.[14]

The methods of qualitative measurement of jugular venous pressure have been proposed.[11] With upper torso elevated to 30–40 degrees, if the venous pulse, the central venous pressure is usually between 7–10 cm water which is in the normal range. If the top of the venous column is more than 3 cm, the venous pressure is likely to be increased.[15]

The other qualitative techniques have been proposed. In the supine position or torso slightly elevated such as with one pillow, and the head turned very slightly to the opposite side of the neck that to be examined, the external jugular vein can be more easily recognized when a beam of light is shined across the neck. When light pressure is applied at the root of the neck, the external jugular vein is distended as the venous return is obstructed and it can be easily seen as it runs across the midportion of the sternocleidomastoid muscle, which is approximately at the same level as the sternal angle. When the inflow to the vein is obstructed by exerting pressure at the angle of the jaw, the top of the venous pulse represents the transmitted right atrial pressure and thus a rough estimation of right atrial pressure is feasible by this technique.[11] If the external jugular venous pulse is not visible in supine position above the clavicle, particularly during abdominal compression, it is very likely that the central venous and right atrial pressures are low. When the external jugular venous pulse is visible and collapses during inspiration, it is likely that that the right atrial pressure is normal. When the venous pulse does not collapse during inspiration, it is assumed that the central venous and right atrial pressures are elevated.[11]

It should be appreciated that the external jugular venous pulse may not be recognized in patients with a fat and short neck. Kinking and thrombotic obstruction of the external jugular veins may also cause a spuriously higher central venous pressure.

Sometimes central venous pressure can be estimated by examining the veins on the dorsum of the hands. These veins are distended when the hands are below the level of right atrium. The hands and arms are gently raised from the dependant position. If the right atrial pressure is normal, the veins of the dorsum of the hands collapse when the hands are at the level of sternal angle of Louis. When the right atrial pressure is high, the veins do not collapse even when the hands are raised above the sternal angle. Like external jugular veins, the veins of the upper extremity can be partially obstructed by thrombi and they are also tortuous which can impede the outflow that may be associated with spurious measurements of central venous pressures.

Thus, whenever possible, internal jugular veins should be examined not only for analysis of the character of the venous pulse but also for estimation of the central venous pressure.

Elevated central venous pressure suggests that the right atrial pressure is elevated. The upper limit of normal right atrial pressure in the supine position is about 7 mm Hg. The central venous pressure estimated in centimeter water which is converted to mm Hg by multiplying it by 0.74. In a number of clinical conditions right atrial pressures are elevated. It might be caused by obstruction of the tricuspid valve. In absence of tricuspid valve obstruction it reflects elevated right ventricular diastolic pressure, which results from right ventricular systolic or diastolic failure. In adult patients, the most common cause of right ventricular failure is left ventricular failure. Elevated jugular venous pressure is associated with a worse prognosis of patients with systolic heart failure.[16] Some of the causes of increased central venous pressure are summarized in Table 3.

In some patients the jugular venous pulsations are not visible because of the variety of reasons. In these patients venous pressures can be approximately estimated by determining the changes of the size of the inferior vena cava during inspiration. A decrease in the diameter of the inferior vena cava by 50% or greater during inspiration suggests normal right atrial pressure.[17] Lack of respiratory variation of the size of the inferior vena cava suggests increased right atrial pressure.

TABLE 3

A few causes of increased central venous and right atrial pressures

- Tricuspid valve obstruction—
  - Rheumatic tricuspid valve stenosis (usually associated with mitral and/or aortic valve disease)
  - Right atrial myxoma
  - Carcinoid heart disease
  - Neoplastic disease
- Right ventricular failure—
  - Systolic—
    - Primary-RV infarction
    - Secondary-pulmonary hypertension
  - Diastolic—
    - Right ventricular hypertrophy
  - Pericardial disease
  - Pericardial effusion
  - Constrictive pericarditis
- Primary tricuspid regurgitation—
  - Traumatic
  - Ruptured chordae
  - Ebstein's anomaly
  - Carcinoid heart disease
  - Rheumatic heart disease
  - Neoplastic disease
- Generalized volume overload—
  - Glomerulonephritis
  - Anemia
  - Large atriovenous communications
  - Isolated right ventricular volume overload
  - Atrial septal defects

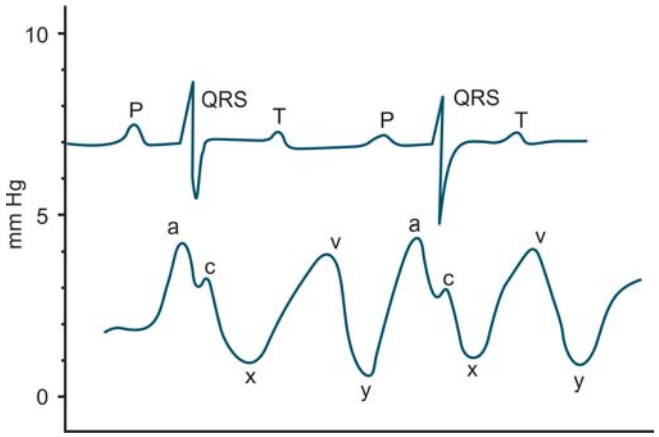


FIGURE 2: The schematic illustrations of right atrial pressure waveforms, which reveal three positive "a", "c" and "v" waves and two negative waves "x" and "y" descent. The "a" wave occurs during atrial systole following P wave of the electrocardiogram. The "c" wave occurs at the onset of right ventricular systole when the closed tricuspid valve bulges into the right atrium. It occurs just after the QRS complex of the electrocardiogram. The "x" descent is related to atrial relaxation. The peak of the "v" wave coincides with the end of right ventricular systole. It coincides with the end of the T-wave of the electrocardiogram. The "y" descent is caused by the opening of the tricuspid valve and during the rapid filling phase (P = P wave; QRS = QRS complex; T-wave. Normally the magnitude of "a" wave is greater than "v" wave and is less than 7 mm Hg)

JUGULAR VENOUS PULSATIONS

The jugular venous pulse characters are best analyzed by examining the internal jugular veins. When the right atrial pressure waveforms are recorded during cardiac catheterization, three positive waves (a, c and v) and two negative waves (X and Y descents) are recognized. The "a" wave occurs during atrial systole with increased right atrial pressure due to atrial contraction (Fig. 2). The "c" wave is related to bulging of the closed tricuspid valve into the right atrium at the beginning of the right ventricular systole. The "x" descent is primarily due to atrial relaxation with a fall in right atrial pressure. The downward descent of the tricuspid valve apparatus also contributes to the genesis of the "x" descent.

After complete relaxation of the right atrium and the nadir of "x" descent, the right atrial pressure rises as the systemic venous return to the right atrium continues. With the onset of right ventricular systole when the tricuspid valve closes, the right atrial pressure rises and the "v" wave begins. The right atrial pressure continues to rise as the systemic venous return to the right atrium continues.

The peak of the "v" wave coincides with the end of the right ventricular systole and can be recognized by timing with the down slope of the carotid pulse. The "y" descent begins

with the opening of the tricuspid valve and continues during the rapid filling phase of the right ventricle with a concurrent pressure decline in the right atrium.

The jugular venous pulsations closely reflect transmitted right atrial pressure changes. It should be recognized that there are delays in the transmission of the right atrial pulse waves to the jugular veins (60–110 m/sec).[18]

It should be appreciated that in the jugular venous pulse the right atrial "c" wave is not transmitted. Occasionally during the jugular venous "x" descent transmitted carotid pulse induces an artifact. In absence of sinus rhythm, there is no "a" wave or "x" descents.

At the bedside, it is necessary to distinguish between jugular venous pulsation and carotid arterial pulsation. During inspection, the venous pulsation is characterized by the dominant inward movement, whereas the arterial pulse is characterized by the dominant outward movement. In the jugular venous pulse, an undulating character with two peaks and two troughs is recognized. In the carotid artery pulse there is one positive wave. Furthermore, a gentle pressure at the root of the neck obliterates the venous pulsation and the arterial pulsation becomes more obvious. The jugular venous pulsations and pressures can be varied with changes in the body position such as during sitting and standing. The changes in arterial pulsation do not occur with changes in the body position. There are respiratory variations in the jugular venous pulse. In the arterial pulse, there are respiratory changes.

A number of clinical conditions are associated with a prominent "a" wave (increased amplitude) in the jugular venous pulse. The increased amplitude of the "a" wave is primarily due to increased resistance of the right atrial emptying during right atrial systole. However, shortening of the right ventricular filling time may also be contributory.[19,20]

A prominent "a" wave is observed in patients with tricuspid valve obstruction. In absence of tricuspid valve obstruction, a prominent "a" wave results from increased resistance to right ventricular filling during atrial systole, which is almost always due to right ventricular hypertrophy. In patients with pulmonary arterial hypertension and in patients with systolic heart failure due to dilated cardiomyopathy, shortening of the right ventricular filling time is also a contributing mechanism.[19,20]

In a few arrhythmias, abnormalities of "a" wave can be appreciated. In patients with a very short PR interval, a prominent presystolic "a" wave is recognized. In atrioventricular nodal reentrant tachycardia and ventricular tachycardia with retrograde conduction, atria contract during ventricular systole due to almost simultaneous activation of atria and ventricles. In atrioventricular dissociation or complete heart block, right atrial systole can occur during ventricular systole and as right atrium contracts when the tricuspid valve is closed, a prominent "a" wave, often called cannon wave, is observed. In these patients the cannon waves occur irregularly but the arterial pulse is regular. In patients with a markedly prolonged PR interval, if atrial systole occurs during preceding ventricular systole, a prominent "a" waves occur due to a similar mechanism. The most common causes of prominent "a" waves, however, are atrial and ventricular premature beats. A few clinical conditions which can be associated with a prominent "a" wave are summarized in Table 4.

TABLE 4

A few conditions that can be associated with a prominent "a" wave

- Tricuspid valve obstruction—
  - Rheumatic tricuspid stenosis
  - Right atrial myxoma
  - Right atrial mass
- Increased resistance distal to the tricuspid valve—
  - Right ventricular hypertrophy—
    - Pulmonary valve stenosis
    - Pulmonary arterial hypertension
  - Left ventricular hypertrophic cardiomyopathy
- Dysrhythmias—
  - Atrial or ventricular premature beats
  - Atrioventricular dissociation and complete heart block
  - Markedly prolonged PR interval
  - Very short PR interval (accessory pathway)
  - Atrioventricular reentrant tachycardia
  - Ventricular tachycardia with retrograde atrial activation

In a few rare conditions, the "a" wave may be absent. In patients with giant silent right atrium and severe Ebstein's anomaly, the "a" waves may not be recognized.

A prominent tall "v" wave (Lancisi sign) followed by a sharp "y" descent are characteristic features of moderate-to-severe tricuspid valve regurgitation and can be easily recognized by examining the internal jugular venous pulse. The onset of the regurgitant "v" wave is earlier and occurs with the beginning of right ventricular ejection, which coincides with the carotid pulse upstroke. The amplitude of the "v" wave is related to regurgitant volume and right atrial compliance. It should be recognized that in presence of a markedly enlarged right atrium, even severe tricuspid regurgitation may not cause a prominent "v" wave. The sharp "y" descent following the large "v" wave results from the increased transtricuspid pressure gradient at the onset of right ventricular filling, which causes a rapid decline in right atrial pressure.

In some patients with atrial septal defect, without pulmonary hypertension and tricuspid regurgitation, a prominent "v" wave may occur. The mechanism remains unclear. It has been postulated that the concomitant systemic venous return and left-to-right shunting across the defect may cause an increase in the right atrial pressure during systole causing a prominent "v" wave.

In occasional patients with a large arteriovenous fistula for hemodialysis, a prominent "v" wave is seen due to shunting of a large volume of arterial blood to the systemic venous system.[14]

A prominent "x" descent is observed in some patients with atrial septal defect. In the very early stage of cardiac tamponade, a prominent "x" descent may be seen. In severe cardiac tamponade, the "x" descent is attenuated. An attenuated "x" descent also occurs in severe tricuspid regurgitation.

A sharp "y" descent preceded by a large "v" wave is a characteristic of severe tricuspid regurgitation. A sharp "y" descent without a prominent "v" wave occurs in constrictive pericarditis, restricted cardiomyopathy and severe right heart failure with markedly increased jugular venous pressure. In both constrictive pericarditis and restrictive cardiomyopathy, the

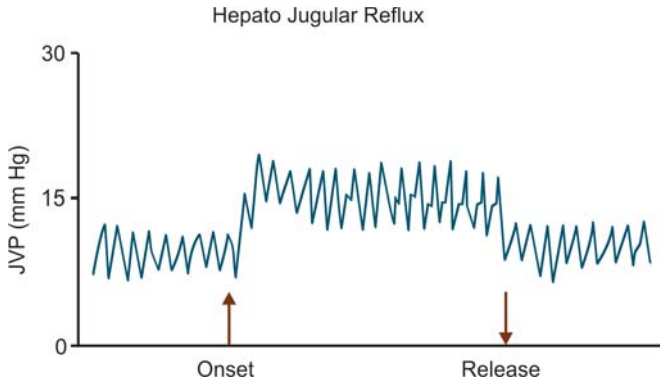


FIGURE 3: Schematic illustration of positive hepatojugular reflux. With the onset of abdominal compression the jugular venous pressure rises and remains elevated during the period of compression. (Abbreviation: JVP: Jugular venous pressure)

mean jugular venous pressures are elevated and the amplitude of the "a" and "v" waves are similar. The most striking feature is the sharp "y" descent in the jugular venous pulse.

Bedside distinction between constrictive pericarditis and restrictive cardiomyopathy is difficult. In constrictive pericarditis, the precordium is quiet. In restrictive cardiomyopathy, a left parasternal (right ventricular) lift may be present if there is pulmonary hypertension and secondary tricuspid regurgitation. In these patients the intensity of the pulmonic component of the second heart sound is increased. In constrictive pericarditis, a pericardial knock can be heard along the lower left sternal border. In restrictive cardiomyopathy with pulmonary hypertension and severe tricuspid regurgitation, hepatic pulsation may be present. It should be appreciated that pulsatile hepatomegaly may be present in constrictive pericarditis.[21] Although the mechanism remains unclear, pulsatile hepatomegaly is no longer appreciated after successful pericardiectomy.[21]

The hepatojugular reflux, also called abdominojugular reflux, is assessed during sustained abdominal compression by applying firm pressure over the abdomen for 10–15 seconds. Normally during abdominal compression, the jugular venous pressure increases transiently by 1–3 cm. In patients with right ventricular failure, the jugular venous pressure increases by more than 3 cm and remains elevated (Fig. 3). The mechanism of the positive hepatojugular reflux remains unclear. It is likely that the failing right ventricle is unable to respond normally during volume load (increased preload) and abdominal compression. Furthermore, abdominal compression increases the level of the diaphragm which increases right ventricular afterload.[22] In adults, in absence of isolated right heart failure, a positive hepatojugular reflux is associated with pulmonary capillary wedge pressure of 15 mm Hg or higher.[23] It is likely due to decreased right ventricular compliance in patients with left heart failure due to dilated cardiomyopathy.

Kussmaul's sign is defined as when there is a lack of fall or an increase in the jugular venous pressure during inspiration. It occurs in a number of clinical conditions (Table 5). The mechanism of Kussmaul's sign in constrictive pericarditis remains unclear. It is possible that during inspiration, with the descent of the diaphragm, there is partial obstruction of the venae cavae. The physical findings of constrictive pericarditis are summarized in Table 6. In addition to elevated jugular venous pressure and Kussmaul's sign, the precordium is quiet, and the features of significant pulmonary hypertension are absent. In restrictive cardiomyopathy, in conditions associated with partial obstruction of the venae cavae, and the space occupying lesions of the right atrium and right ventricle the jugular pressure increases during the venous return to the right atrium. In patients with acute pulmonary embolism, right ventricular myocardial infarction and chronic severe tricuspid regurgitation Kussmaul's sign may be present. However, in clinical practice, the two common causes are constrictive pericarditis and restrictive cardiomyopathy. The clinical features of restrictive cardiomyopathy are summarized in Table 7. In addition to Kussmaul's sign, the evidences of pulmonary hypertension, a prominent left parasternal lift, secondary tricuspid regurgitation and occasionally systolic pulsation of the liver are present.

TABLE 5

A few conditions in which Kussmaul's sign can be present

- Constrictive pericarditis
- Restrictive cardiomyopathy
- Right ventricular myocardial infarction
- Massive pulmonary embolism
- Partial obstruction of the venae cavae
- Right atrial and right ventricular tumors

TABLE 6

Constrictive pericarditis—physical findings

- Elevated jugular venous pressure
- Sharp "Y" descent
- Kussamul's sign
- Accemtuated reduction of arterial
- Pulse amplitude during inspiration
- Quiet precordium
- Distant heart sounds
- Pericardial knock
- Absence of pulmonary hypertension
- Pulsus paradoxus is uncommon

TABLE 7

Restrictive cardiomyopathy—physical findings

- Kussamul's sign
- Active precordium-sustained RV and LV impulse
- Apical impulses
- Signs of pulmonary arterial hypertension
- Right and left sided S3 gallops

(Abbreviations: RV: Right ventricle; LV: Left ventricle)

ARTERIAL PULSE

The contour, character and amplitude of the arterial pulses are related to left ventricular stroke volume, left ventricular velocity of ejection, aortic dP/dT, systemic vascular resistance, and the capacity and compliance of the arterial vascular system. The antegrade pulse wave (percussion wave) velocity is about

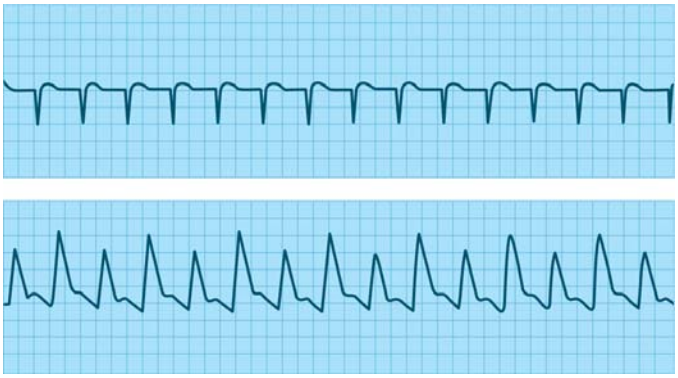
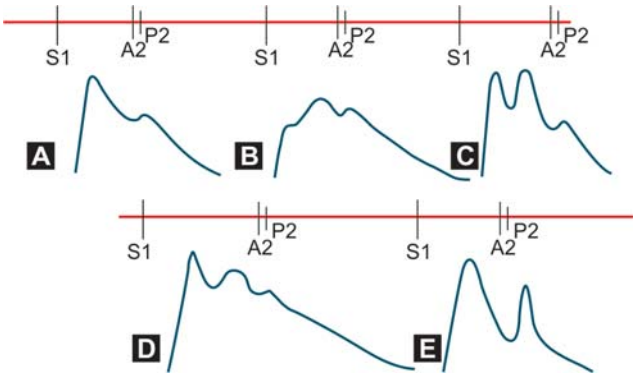


FIGURE 4: The characteristic "strong and weak alternating sequences of arterial pulses" in a patient with systolic heart failure are illustrated. The upper panel is an electrocardiogram showing normal sinus rhythm. The lower panel is directly recorded arterial pressure, showing alternating higher and lower arterial pressure



FIGURES 5A TO E: The characters of the normal (A), anacrotic (B), bisferiens (C and D) and dicrotic (E) pulse are illustrated. (Abbreviations: S1: First heart sound; A2: Aortic valve closure sound; P2: Pulmonary valve closure sound)

4 m/sec and the reflected pulse wave (tidal wave) propagates centrally from the periphery with similar velocity. As the antegrade pulse wave propagates to the periphery, it fuses with the reflected wave causing its peripheral amplification. The onset of the reflected wave occurs at the site where the antegrade pulse wave meets the resistance usually at the bifurcation of aorta. If the resistance occurs more proximally as in coarctation of aorta, the fusion of the percussion and tidal waves occur earlier and it may occur during systole. The central propagation of the reflected wave is faster with increased stiffness of the aorta as with aging and the fusion of the percussion and tidal waves occur during systole—a major determinant of systolic hypertension.

Examination of the volume and contours of arterial pulses provides important diagnostic clues regarding the underlying etiology of the pathophysiologic condition. Decreased amplitude may reflect reduced stroke volume irrespective of its etiology. Pulsus alternans in presence of regular rhythm indicates reduced left ventricular ejection fraction (Fig. 4). It should be recognized that pulsus alternans should be diagnosed only in presence of a regular rhythm. The strong beat results from the decreased afterload resulting from lower arterial pressure in the preceding cardiac cycle. The strong beat is associated with a higher arterial pressure which increases the afterload for the next beat and the stroke volume decreases and the phenomenon continues. Frequently pulsus alternans is initiated by a premature beat. Following a premature beat, left ventricular preload is increased due to the longer duration of diastole and stroke volume and the arterial pressure increase. As the increase in arterial pressure is associated with increased left ventricular afterload, the stroke volume and arterial pressure decrease and the sequence of the strong and weak beats of pulsus alternans continue despite no further appreciable changes in preload.

It should be appreciated that the absence of pulsus alternans does not exclude systolic heart failure. However, the presence of pulsus alternans is almost diagnostic of reduced left ventricular ejection fraction although it is present in only about 10% of patients with chronic systolic heart failure. In patients with acute coronary syndrome, in approximately 25% of patients pulsus alternans can be appreciated.[24]

The different pulse contours and characters are illustrated in Figures 5A to E.

The carotid pulse contour is similar to that of central aortic pressure waveform. The delay in the upstroke of the carotid pulse compared to the onset of the central aortic pulse wave is only about 20 m/sec. Thus, the examination of the carotid pulse provides an accurate assessment of the central aortic pulse.

The normal carotid pulse upstroke occurs immediately after the first heart sound. At the bedside, it is felt almost at the same time with the first heart sound. The anacrotic wave, which can be almost always recorded in the central aortic pressure tracing in its ascending limb, is not appreciated in the normal carotid pulse. The peak of the normal carotid pulse occurs in early systole and long before the second heart sound. Normally the dicrotic notch or the dicrotic wave is not appreciated (Fig. 5A).

The anacrotic pulse is characterized by the presence of a prominent positive wave during the ascending limb of the arterial pulse (Fig. 5B). It is appreciated best by examining the central arterial pulse such as the carotid pulse. The anacrotic pulse is an important physical finding of fixed left ventricular outflow tract obstruction such as aortic valve stenosis. The more severe the aortic stenosis the earlier is the anacrotic wave in the ascending limb of the carotid pulse. In very severe aortic stenosis the anacrotic wave is absent. A clinically appreciable anacrotic pulse in radial artery almost always suggests hemodynamically significant aortic valve stenosis.

The pulsus bisferiens is characterized by two peaks: (i) prominent percussion and (ii) tidal waves during systole (Fig. 5C). It is appreciated in patients with hemodynamically isolated, aortic regurgitation and in patients with mixed aortic valve disease when aortic regurgitation is the predominant lesion. It should be recognized that an absence of pulsus bisferiens does not exclude significant aortic regurgitation. The Corrigan or "water-hammer" pulse is appreciated in patients with significant aortic regurgitation. The maneuver that demonstrates the presence of water-hammer pulse is when the arm raised abruptly and filling for the changes of the radial pulse in its rise and fall. The characteristic features of the water-hammer pulse are an abrupt, very rapid upstroke of the radial pulse and a very rapid collapse of the pulse. The bounding pulse is also a feature of severe aortic regurgitation. However, it is also present in patients with severe chronic anemia, in patients with a large left-to-right shunt due to a patent ductus arteriosus and in patients with large arteriovenous fistulae.

In patients with acute severe aortic regurgitation, these changes in the arterial pulse are not observed. The pulse amplitude may be decreased.

In patients with hypertrophic obstructive cardiomyopathy, pulsus bisferiens is rarely appreciated although it can be recorded in the central aortic pressure tracing. The first peak is due to percussion wave (spike) and the second peak is due to delayed slow ejection (dome) resulting from left ventricular outflow tract obstruction (Fig. 5D).

The dicrotic pulse is characterized by an accentuated dicrotic wave which occurs in diastole (Fig. 5E). It may be observed in patients with high cardiac output as in sepsis and also when the systemic vascular resistance is high as in low output states. It is also occasionally appreciated in the immediate postoperative period after aortic valve replacement. The precise mechanisms of dicrotic pulse in these patients remain unclear.

The pulsus paradoxus is characterized by a fall in arterial pressure during inspiration more than 10 mm Hg. Normally systolic arterial pressure falls during inspiration by an average of 8–12 mm Hg. In cardiac tamponade there is a substantially greater decrease in the arterial pressure during inspiration (Fig. 6). The magnitude of the pulsus paradoxus can be better appreciated if the blood pressure is recorded by the sphygmomanometer. The cuff pressure should be decreased slowly. The systolic pressure at expiration is noted. With a further reduction of cuff pressure, the systolic pressure during inspiration is noted and the difference between these two systolic blood pressures provides an estimate of pulsus paradoxus. More severe the tamponade, a greater fall in arterial pressure occurs during inspiration.

EXAMINATION OF THE PRECORDIAL PULSATION

Precordial cardiovascular pulsations are best appreciated with the patient in supine position with the upper torso elevated not more than 45 degree. During inspection, the left ventricular apical impulse is usually visible over the left fifth intercostal space medial to the anterior axillary line. In patients with severe volume overload of the left ventricle, such as due to severe mitral or aortic regurgitation, an accentuated left ventricular apical impulse along with pulsation of the entire precordium may be visible.

The leftward displacement of the cardiac impulse can be caused by right-side tension pneumothorax, left-side pulmonary fibrosis, massive right pleural infusion and absent left precordium.

A visible subxiphoid impulse is usually due to right ventricular failure with or without hypertrophy.

An ascending aortic aneurysm may be associated with a visible pulsation over the right second intercostal space. The pulsation in the suprasternal notch may be caused by the aneurysm of the arch of the aorta. However the most common cause of supraclavicular pulsation is the kinked carotid artery.

A visible pulsation over the left second or third intercostal space is usually due to dilated pulmonary artery, which may result from pulmonary artery hypertension, poststenotic dilatation and increased flow. The retraction of the ribs in the left axilla (Broadbent's sign) is usually due to adhesive pericarditis, which is not associated with any clinical relevance.

The left parasternal impulse is best appreciated over the third and fourth interspace along the sternal border with patient in the supine position and the upper torso slightly elevated. A sustained palpable impulse during systole, also called right ventricular lift, usually indicates right ventricular systolic or diastolic failure with or without hypertrophy. Right ventricular lift is usually secondary to pulmonary hypertension. Thus other physical findings of pulmonary hypertension, such as increased intensity of the pulmonic component of the second heart sound (P2) and tricuspid regurgitation, may be present. Occasionally a palpable right ventricular gallop is also appreciated along with sustained right-left parasternal lift.

An easily palpable systolic but not sustained, right ventricular impulse is appreciated in some patients with severe

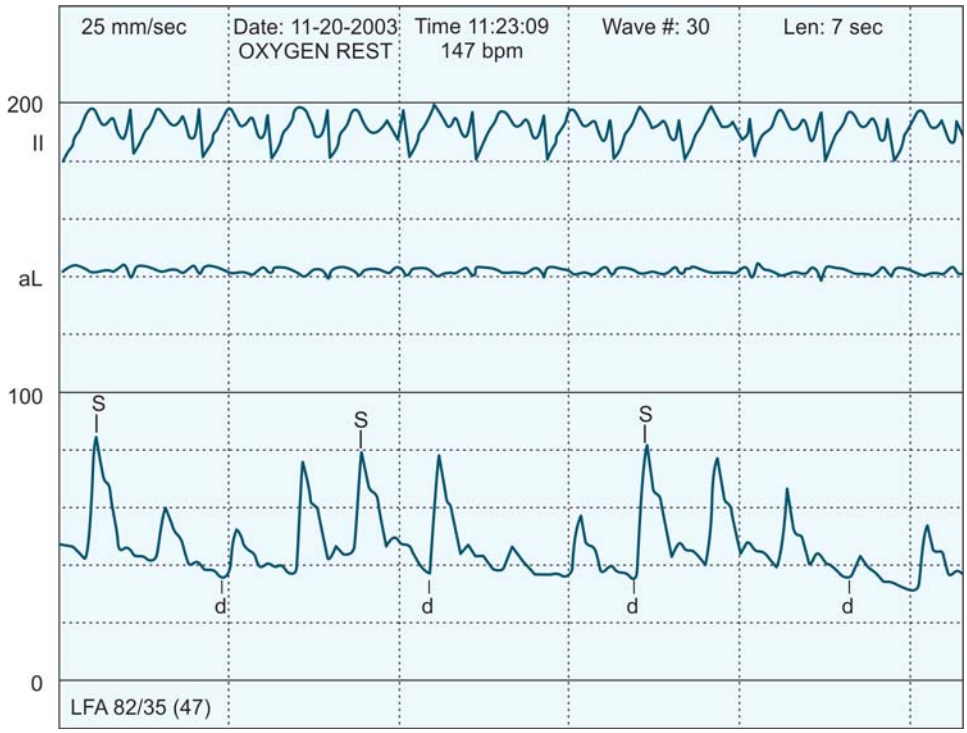


FIGURE 6: The marked decrease in the systolic blood pressure during inspiration (pulsus paradoxus) in a patient with tamponade is illustrated. The upper two panels are electrocardiogram showing normal sinus rhythm. The lower panel is directly recorded arterial pressure showing a marked decrease in arterial pressure during inspiration

tricuspid regurgitation.[25] A sustained left parasternal systolic lift is occasionally palpable in patients with severe mitral regurgitation. This impulse is due to atrial expansion during ventricular systole.[26]

Very rarely an outward diastolic and systolic right ventricular impulse, associated with constrictive pericarditis, is felt over the lower left parasternal area.[27] The diastolic impulse coincides with the pericardial knock. The mechanism for this unusual precordial impulse in constrictive pericarditis is unknown.

The left ventricular apical impulse, also called apex beat, is examined with the patient in a partial left lateral decubitus position. It is normally located in the fourth or fifth intercostal space just medial to the left mid-clavicular line. Normally it is localized and not more than 2–3 cm in diameter. The left ventricular apical impulse is usually the Point of Maximal Impulse (PMI). However, the amplitude of the epigastric or lower left sternal impulse, which is usually of right ventricular in origin, may be greater than the left ventricular apical impulse. In a number of clinical conditions when the right ventricle is markedly dilated, such as in patients with a large atrial septal defect or severe mitral stenosis, the left ventricular apical impulse may not be palpable as the left ventricle is displaced posteriorly.

The location of the left ventricular apical impulse can be displaced laterally due to left or right ventricular enlargement, right tension pneumothorax or a large pleural effusion. In patients with complete congenital absence of the left pericardium, the left ventricular apical impulse is displaced laterally in the supine position but it is moved medially in the left lateral decubitus.[28]

The genesis of the left ventricular apical impulse remains unclear. It appears to be related to the phenomenon of cardiac torsion. The normal character of the left ventricular apical impulse results from the counterclockwise movement of the basal segments as viewed from the base and clockwise movement of the apical segments.[29] The torsion characteristics are altered in various pathologic conditions.

An apex cardiogram (rarely performed in the present era) provides insights into the pathophysiological correlates of left ventricular function and hemodynamics. The initial upstroke of the left ventricular apex cardiogram coincides with the onset of the isovolumic phase of the left ventricular systole. The left ventricular ejection starts at the E point of the apex cardiogram. The normal left ventricular apical impulse during palpation coincides with the beginning of ejection, and it occurs almost simultaneously with the carotid pulse upstroke or the first heart sound. The normal character of the apical impulse is usually associated with a normal left ventricular ejection fraction. The hyperdynamic apical impulse has increased amplitude (more easily palpable) but maintains the normal characters.

TABLE 8

Cardiovascular physical examination

Palpable precordial impulses
• Prominent systolic left parasternal impulse
– RV failure
• Sustained LV apical impulse
– Reduced LVEF
– Increased LV mass
• Palpable PA impulse
– Left to right shunt
– Pulmonary hypertension
– Pulmonary stenosis

(Abbreviations: LV: Left ventricle; RV: Right ventricle; LVEF: Left ventricle ejection fraction; PA: Pulmonary artery)

A sustained apical impulse is diagnosed when the impulse is felt during the entire ejection phase. The most common cause of a sustained left ventricular apical impulse is reduced left ventricular ejection fraction. A significant left ventricular hypertrophy as in patients with hypertrophic cardiomyopathy or severe aortic regurgitation can be associated with a sustained left ventricular apical impulse. Rarely in patients with severe obstructive hypertrophic cardiomyopathy will have the apical impulse bifid outward movement.[30] A few clinical conditions and mechanisms of precordial impulses are summarized in Table 8.

A palpable presystolic "a" wave or an early diastolic palpable S3 gallop is almost always associated with an abnormally elevated left ventricular diastolic pressure. The features of the left ventricular apical impulse as recorded by the apex cardiogram are illustrated in Figure 7.

AUSCULTATION

The heart sounds are schematically illustrated in Figure 8. The analysis of the heart sounds should precede analysis of the heart murmurs. The high-frequency heart sounds such as first (S1) and second (S2) and murmurs such as due to aortic and

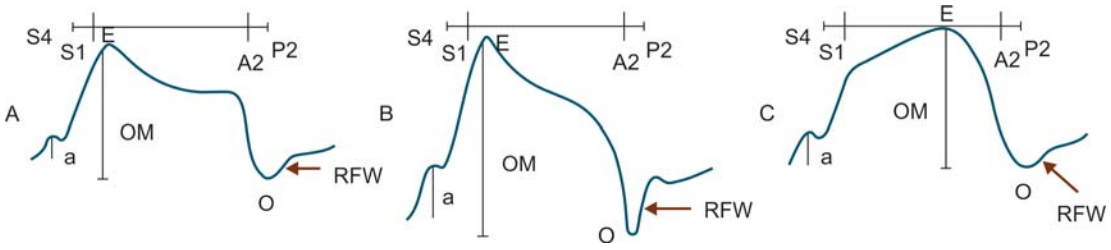


FIGURE 7: The schematic illustration of the apex cardiogram. The "E" point reflects the beginning of the ejection. The "O" point coincides with the end of the rapid filling phase and S3. The hyperdynamic impulse is characterized by normal duration of the apical impulse but the amplitude is increased. A sustained apical impulse is characterized by the continued ejection phase after the "E" point. (Abbreviations: A: Normal apical impulse; B: Hyperdynamic apical impulse; C: Sustained apical impulse; OM: Outward movement; "a": Presystolic "a" wave; S4: Fourth heart sound; A2: Aortic component of the second heart sound; P2: Pulmonic component of the second heart sound; RFW: Rapid filling wave)



FIGURE 8: The schematic illustration of the heart sounds. S4 is the presystolic low pitch atrial sound. The S1 consists of higher pitch mitral (M1) and tricuspid valve (T1) closure sounds. The S2 consists of higher pitch closure sounds of aortic (A2) and pulmonary (P2) valves. The S3 is a lower pitch early diastolic filling sound. The wide splitting of S2 is defined when the interval between A2 and P2 is longer than normal. The A2 precedes P2 and during inspiration the interval between A2 and P2 widens. The paradoxical splitting is defined when P2 precedes A2 during the expiratory phase of the respiratory cycle and during inspiration the P2-A2 interval shortens. The "fixed splitting" is defined when the A2-P2 interval remains relatively unchanged during expiration and inspiration. (Abbreviations: S4: Fourth heart sound; M1: Mitral valve closure sound; T1: The tricuspid valve closure sound; A2: The aortic valve closure sound; P2: The pulmonary valve closure sound; S3: The third heart sound)

mitral regurgitation are better appreciated with the use of the diaphragm of the stethoscope.

The lower frequency heart sounds such as third (S3) and fourth (S4) and mid-diastolic rumbles are better heard with the bell of the stethoscope.[24]

The precise mechanisms of the genesis of the heart sounds remain unknown. The classic hypothesis for the origin of S1 is that its high-frequency components are related to the mitral and tricuspid valve closures.[31] Another hypothesis is that the high-frequency components of S1 are due to movement and acceleration of blood flow in the left ventricle and ejection of blood into the aorta.[32] In support of the classic hypothesis, in right bundle branch block, the first and the second components of S1 coincide with mitral and tricuspid valve closures.[33]

The S1 occurs just before the upstroke of the carotid pulse at the beginning of the isovolumic systole. At the bedside S1 and S2 are best recognized by timing with carotid pulse upstroke and down stroke, respectively.

The maximal intensity of S1 is appreciated over the cardiac apex. The rate of mitral valve closure is the major determinant of the intensity of S1. Left ventricular contractile function influences the rate of mitral valve closure. The position of the mitral valve before its complete closure also contributes to the intensity of S1. The longer the distance from the open to the close position, louder is S1. The shorter distance is associated with reduced intensity of S1. The mobility of the mitral valve leaflets also determines the intensity of S1. The calcified immobile mitral valve is associated with reduced intensity of S1. The PR interval influences the intensity of S1. A very short PR interval as in patients with accessory pathway, the S1 is louder than normal. The first-degree atrioventricular block is associated with decreased intensity of S1. The changing intensity of S1 can occur in AV dissociation and atrial fibrillation.

The most common cause of widely split S1 is right bundle branch block but it may also occur in atrial septal defect. In patients with severe mitral stenosis, rarely reversed splitting of S1 is appreciated. A relatively loud S4 and S1 may appear as splitting of S1 (pseudo splitting of S1). However, when the bell of the stethoscope is used, S4 and S1 can be easily appreciated. When the diaphragm is used, S1 appears as single. A systolic ejection sound following S1 may also appear as splitting of S1. However, in splitting of S1, the interval between the first and the second component is narrower than the interval between S1 and ejection sound. Furthermore, the splitting of S1 is best heard along the lower left sternal border. In contrast, the aortic ejection sound is heard over the right second interspace, along the left sternal border and over the cardiac apex. A Midsystolic Click (MSC) following S1 may appear as widely split S1. However, S1-MSC interval is much longer than splitting of S1. The S1-MSC interval varies with maneuvers (supine and standing); the interval between the two components of S1 usually remains unchanged.

In Ebstein's anomaly the closure of the tricuspid valve is characterized by a scratchy sound which is termed as "sail sound". The sail sound is widely separated from M1 partly due to the abnormality of the tricuspid valve and partly due to the presence of right bundle branch block.[34]

The auscultatory alternans is a sign of large pericardial effusion, although it may also occur in association with electrical alternans. The clinical conditions that can be associated with altered intensity and splitting of S1 are summarized in Table 9.

There are two components of the second heart sound (S2): (i) one related to closure of the aortic valve designated as A2 and (ii) the other to closure of the pulmonary valve designated as P2. At the bedside, S2 occurs with the downslope of the carotid pulse. The A2 coincides with the dicrotic notch of aortic

TABLE 9

A few clinical conditions that can be associated with altered intensity and splitting of the first heart sound

- Increased intensity—
  - Mitral valve obstruction
  - Short PR interval
  - Enhanced left ventricular contractile function
  - Holosystolic mitral valve prolapse
- Decreased intensity—
  - Long PR interval
  - Decreased left ventricular contractile function
  - Increased left ventricular diastolic pressure
  - Premature closure of the mitral valve (severe acute aortic regurgitation)
  - Immobile mitral valve
  - Large pericardial effusion
- Changing intensity—
  - AV dissociation
  - Atrial fibrillation
- Wide splitting—
  - Right bundle branch block
  - Premature ventricular contractions
  - Ventricular tachycardia
  - Atrial septal defect
- Reversed splitting—
  - Severe mitral stenosis
  - Auscultatory alternans
  - Tamponade
  - Electrical alternans

pressure tracing and P2 with the dicrotic notch of pulmonary artery pressure tracing. The ventricular ejection ends before the closure of the aortic and pulmonary valves. The intervals between the end of ejection and the closure of the aortic and pulmonary valves are called "the hang out times". The hang out times are influenced by stroke volume and aortic and pulmonary artery compliance. Normally aorta is stiffer than the pulmonary artery. The aortic hang out time is thus shorter than the pulmonary artery hang out time. The differences between the aortic and pulmonary hang out times account for most of the normal A2-P2 intervals. In pulmonary artery hypertension, the pulmonary artery stiffness increases and the pulmonary artery hang out time shortens and the splitting of S2 becomes narrower despite increased resistance to right ventricular ejection.

The isolated changes in left or right ventricular stroke volume influence aortic and pulmonary hang out times, respectively. In patients with significant aortic regurgitation or a patent ductus arteriosus with a large left-to-right shunt, there is a selective increase in left ventricular stroke volume that prolongs the aortic hang out time. In patients with atrial septal defects with large left-to-right shunts, right ventricular stroke volume increases without a significant change in left ventricular stroke volume. Thus the pulmonary artery hang out time is prolonged.

The intensity of the components of S2 is primarily determined by the pressures beyond the semilunar valves against which they close. Normally the aortic pressure is higher than the pulmonary artery pressure, and thus A2 is louder than P2. In pulmonary arterial hypertension, the intensity of P2 is increased as the pulmonary arterial pressure increases.

There are a number of clinical conditions in which the intensity of A2 is altered. The intensity of A2 is increased in systemic hypertension, adult type of coarctation of aorta and ascending aortic aneurysm. The intensity of P2 is increased in pulmonary arterial hypertension, irrespective of its cause. The decreased intensity of A2 may be caused by a lack of appropriate coaptation of the aortic valve. In calcific aortic stenosis, the mobility of the aortic valve is markedly restricted which is associated with decreased intensity of A2. In patients with severe aortic stenosis or regurgitation, aortic diastolic pressure may decrease and the intensity of A2 is reduced.

The decreased intensity of P2 is recognized in patients with pulmonary valve stenosis and congenital absence of the pulmonary valves. Significant pulmonary regurgitation following corrective surgery is also associated with reduced intensity of P2.

The physiologic splitting of the second heart sound is defined when the A2-P2 interval increases during inspiration. During inspiration with increased systemic venous return, right ventricular stroke volume is increased. The inspiratory increase in the A2-P2 interval results primarily due to the increased pulmonary hang out time, although slight prolongation of right ventricular ejection time may also be contributory. The paradoxical or reversed splitting of S2 is defined when A2 follows P2 during expiration and the P2-A2 interval decreases during inspiration. The most common cause of paradoxical splitting of S2 is left bundle branch block.

It is also appreciated in patients with right ventricular pacing and accessory pathway with right ventricular connection. Paradoxical splitting also occurs when there is a selective increase in left ventricular stroke volume as in patients with severe aortic regurgitation or with a large patent ductus arteriosus. The increase in left ventricular stroke volume is associated with prolongation of left ventricular ejection time as well as increased aortic hang out time. A substantial increase in left ventricular outflow resistance, such as severe aortic stenosis, hypertrophic obstructive cardiomyopathy and hypertension, may also be associated with paradoxical splitting of S2.

The fixed splitting of S2 is defined when the variation in the A2-P2 interval is 20 m/sec or less during the inspiratory and expiratory cycles of respiration. The secundum type of atrial septal defect is the most common cause of fixed splitting of S2. During inspiration the magnitude of left-to-right shunt decreases and during expiratory phase the left-to-right shunt increases. A large atrial septal defect is associated with shortening of left ventricular ejection time without any change in right ventricular ejection time.[35] However, the increase in pulmonary artery hang out time due to decreased pulmonary vascular impedance appears to be the principal mechanism of the "fixed splitting" of S2.

Severe right ventricular failure may also be associated with fixed splitting of S2. Right ventricle is unable to handle the inspiratory increase in the systemic venous return. Thus, there is very little variation in right ventricular ejection time during the respiratory cycle.

The wide splitting of S2 is most common in patients with conduction abnormalities such as right bundle branch block.

TABLE 10

A few clinical conditions that may be associated with changes in intensity and splitting of the second heart sound

Increased intensity of A2:	Systemic hypertension
	Coarctation of the aorta
	Ascending aortic aneurysm
Decreased intensity of A2:	Calcific aortic stenosis
	Severe aortic regurgitation
Increased intensity of P2:	Pulmonary arterial hypertension
	Peripheral pulmonary artery branch stenosis
	Idiopathic dilatation of the pulmonary artery
Decreased intensity of P2:	Pulmonary valve stenosis
	Congenital absence of pulmonary valve
Wide splitting of S2:	Right bundle branch block
	Left ventricular pacing
	Accessory pathway with left ventricular preexcitation
	Premature beats of left ventricular origin
	Fascicular tachycardia
	Right ventricular outflow obstruction
	Pulmonary arterial hypertension
Wide and "fixed" splitting of S2:	Atrial septal defects
	Common atrium
	Right ventricular failure
Reversed (paradoxic) splitting of S2:	Left bundle branch block
	Right ventricular pacing
	Accessory pathway with right ventricular preexcitation
	Premature beats of right ventricular origin
	Right ventricular tachycardia
	Severe aortic regurgitation
	Large patent ductus arteriosus
	Left ventricular outflow obstruction
	Systemic hypertension
	Severe tricuspid regurgitation (rare)
Single S2:	Eisenmenger syndrome with ventricular septal defect
	Single ventricle

(Abbreviations: A2: Aortic component of the second heart sound; P2: Pulmonic component of the second heart sound; S2: Second heart sound)

It is also appreciated in some patients with accessory pathways with initial activation of the left ventricle.

A single S2 can occur when A2 and P2 are fused due to almost equal right and left ventricular ejection time as in patients with Eisenmenger's syndrome with ventricular septal defect or a single ventricle. In some conditions A2 may be absent such as severe aortic regurgitation resulting from bacterial endocarditis. In congenital absence of the pulmonary valve, P2 is absent. In patients with severe right ventricular outflow obstruction, the intensity of P2 is markedly reduced and S2 may appear single. A few clinical conditions which may be associated with changes in the intensity and splitting of S2 are summarized in Table 10.

THIRD (S3) AND FOURTH (S4) HEART SOUNDS

The S3 and S4 are low pitch sounds and originate in the ventricles. They are often termed ventricular filling sounds and are associated with ventricular filling and an increase in ventricular dimensions. The S3 occurs with the beginning of passive ventricular filling after the relaxation is completed. It coincides with end of the rapid filling phase of the apexcardiogram. The S4 occurs during atrial systole. Both S3 and S4 are better appreciated with the bell of the stethoscope. The S3 is close to the second heart sound and occurs after the down stroke of the carotid pulse. The S4 is close to the first heart sound and occurs just before the upstroke of the carotid pulse.

The left ventricular S3 and S4 are best heard over cardiac apex in the left lateral decubitus position. The right ventricular S3 and S4 are best heard along the lower left sternal border. Occasionally right ventricular filling sounds are also heard over the lower right sternal border. The intensity of right ventricular S3 and S4 increases during inspiration. The S3 can be appreciated in healthy adults younger than 40 years old. It is considered abnormal if it is heard in subjects older than 40 years. The S4 is usually abnormal in children and young adults. With decreased left ventricular compliance as occurs with aging, S4 can be appreciated in many older individuals without any cardiac abnormality.

It may be sometimes difficult to distinguish between splitting of S2 from S2-S3 when S3 is present. Similarly, splitting of S1 may be difficult to distinguish from S4-S1. The bell-diaphragm technique of auscultation may be useful. As both S3 and S4 are low pitch sounds, when the bell of the stethoscope is used, these sounds become more obvious. When the diaphragm of the stethoscope is used, S3 and S4 low pitch sounds are either no longer heard or become very muffled. As the M1 and T1 components of S1 and A2 and P2 components of S2 are high-pitch sounds, they become sharper and more easily heard.

When S3 or S4 are louder and have relatively higher pitch, they sound like gallops (like horse's gallop) and are called gallop sounds. The S3 and S4 are ventricular and atrial gallops, respectively. The gallop sounds usually reflect elevated ventricular end-diastolic pressures. Left ventricular S3 gallop is also associated with elevated plasma levels of B-type natriuretic peptide.[36,37] Both presence of S3 and elevated jugular venous pressure are also associated with worse prognosis in patients with systolic heart failure.[38]

Pericardial Knock

It is a common auscultatory finding in constrictive pericarditis. It occurs in diastole and its timing is earlier than that of S3.

Ejection Sounds

The ejection sounds are related to the opening of the semilunar valves at the beginning of the ventricular ejection. The aortic ejection sound is related to the opening of the aortic valve and the pulmonary ejection sound is that of opening of the pulmonary valve. The intensity of the aortic ejection sound does not vary during the respiratory phase. The intensity of the pulmonary ejection sound however decreases during inspiration. During inspiration there is a slow upward movement of the pulmonary valve before it starts opening. This slow ascent of the pulmonary valve is associated with decreased intensity of the pulmonary ejection sound as the sudden "halting" is the mechanism of the ejection sound.

The conditions that may be associated with aortic ejection sound are aortic valve stenosis, aortic regurgitation and bicuspid aortic valve. The conditions that may be associated with pulmonary ejection sound are pulmonary valve stenosis, pulmonary hypertension, pulmonary regurgitation and idiopathic dilatation of the pulmonary artery.

In some patients with hypertrophic obstructive cardiomyopathy, a nonejection sound is heard which is called pseudoejection sound. It coincides with anterior systolic motion of the mitral valve.[39] This sound occurs later than aortic ejection sound. It has been suggested that it may result from the contact of the mitral valve with the interventricular septum during systole or from the deceleration of blood flow in the left ventricular outflow tract.

Midsystolic Click

The prolapse of the mitral valve is the most common cause of midsystolic clicks. The S1-MSC interval is longer than the S4-S1 or M1-T1 intervals. In mitral valve prolapse, in a given patient the click diameter of the left ventricle is fixed. The S1-MSC intervals vary with changes in left ventricular volumes. During the supine position the S1-MSC interval is longer because the left ventricular end-diastolic volume is larger and the click diameter is reached later. The duration of the late systolic murmur is shorter. In the upright position the left ventricular end-diastolic volume is smaller and the click diameter is reached earlier and the S1-MSC interval is shorter. The duration of the late systolic murmur is longer. Following a post-ectopic beat, the click diameter is reached earlier because of more rapid ejection due to post-ectopic potentiation and the S1-MSC interval is shorter and the duration of the late systolic murmur is longer. In Figure 9, the auscultatory findings of mitral valve prolapse are schematically illustrated. In Table 11, the maneuvers that change the S1-MSC interval and the duration of the late systolic murmur are summarized.

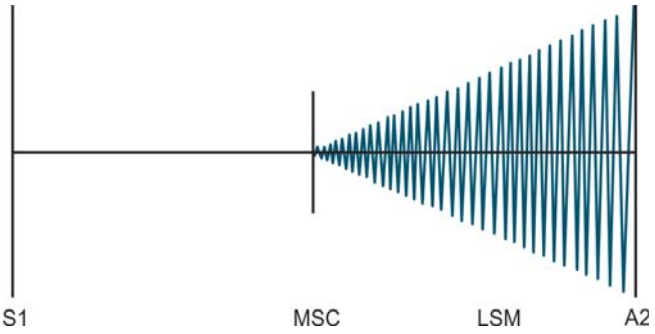


FIGURE 9: The schematic illustration of the auscultatory findings of midsystolic click—late systolic murmur syndrome due to mitral valve prolapse. (Abbreviations: S1: The first heart sound; MSC: Midsystolic click; LSM: Late systolic murmur)

TABLE 11

The maneuvers that influence the S1 and midsystolic click interval and the duration of the late systolic murmur in mitral valve prolapse are summarized

MSC-LSM	
Supine S1	MSC increased, LSM shorter
Standing S1	MSC shorter, LSM longer
Squatting S1	MSC increased, LSM shorter
Post-PMB S1	MSC shorter, LSM longer

S1-MSC = the first heart sound midsystolic click interval;
LSM = late systolic murmur;
PMB = post-premature beat

(Abbreviations: MSC: Midsystolic click; S1: First heart sound)

In some patients with mitral valve prolapse, brief musical systolic murmurs often preceded by clicks are heard in mid-systole or late systole. These murmurs are called systolic "whoop" or "precordial honk".[40]

Early Diastolic High-Frequency Sounds

The high-pitch sounds associated with the opening of the mitral or tricuspid valves are called opening snaps and occur in early diastole. These sounds coincide with their rapid opening to the maximal open position and are appreciated in patients with mitral or tricuspid valve stenosis. The opening snaps are best heard with the diaphragm of the stethoscope.

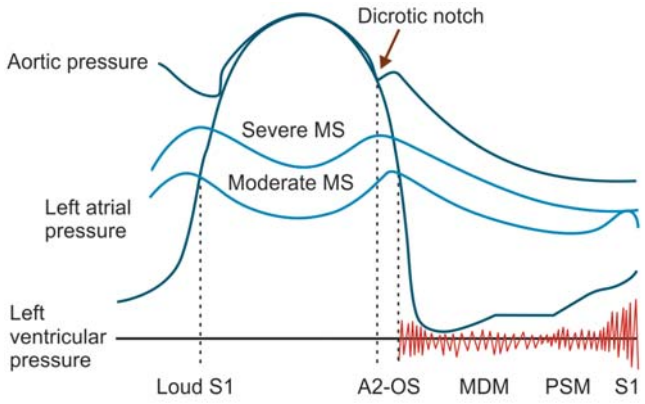


FIGURE 10: The schematic illustrations of aortic, left atrial and left ventricular pressure tracings in patients with mitral stenosis. The A2-OS interval is shorter in patients with more severe mitral stenosis than in patients with milder mitral stenosis. (Abbreviations: A2: Aortic valve closure; OS: Opening snap; MDM: Mid-diastolic murmur; PSM: Pre-systolic murmur; MS: Mitral stenosis; S1: The first heart sound)

The opening snap of mitral stenosis is better appreciated over the mitral area just medial to the apex with the patient in the left lateral position. It can be widely transmitted and can be heard over the left second intercostal space. The opening snap following A2 can be mistaken as widely split S2. However, widely split S2 is uncommon in absence of right bundle branch block. Furthermore, if the intensity of P2 is increased, three high-pitch sounds, A2, P2 and opening snap, can be appreciated over the left second intercostal space particularly during inspiration.

A mobile mitral valve leaflet is necessary for the genesis of the opening snap. It is absent in patients with a heavily calcified immobile mitral valve.

However, opening snap is present in the majority of patients with mitral stenosis and its presence along with a loud S1 provides a clue to its diagnosis.

The interval between A2 and the opening snap (A2-OS) is inversely related to the severity of mitral stenosis. The shorter the A2-OS interval, more severe is the mitral stenosis. With severe mitral stenosis, the gradient across the mitral valve is increased and the interval between closing pressure of the aortic valve and opening pressure of the mitral valve is shorter (Fig. 10). When the mitral stenosis is mild the A2-OS interval is longer. It should be appreciated that A2-OS interval should be assessed when the heart rate is relatively normal. Tachycardia is associated with a shorter A2-OS interval for the same severity of mitral stenosis.

As the A2-OS interval is also related to the closing pressure of the aortic valve, the conditions that are associated lower aortic valve closing pressure such as severe aortic stenosis or regurgitation. The A2-OS interval is shorter despite mild mitral stenosis. Thus, severity of mitral stenosis cannot be assessed in patients with coexisting aortic stenosis or regurgitation.

The tricuspid valve opening snap is usually heard in significant tricuspid valve stenosis. It is localized and associated with low pitch mid-diastolic murmur and best heard over the lower left sternal border.

Occasionally, tricuspid opening snap is appreciated in patients with an atrial septal defect and a large left-to-right shunt.[41]

In atrial myxoma, the movement of the tumors into the ventricle with the opening of the mitral or tricuspid valve may be associated with a high-pitch sound, which is termed as "tumor plop". Similarly, the movement of large mobile vegetation can be associated with a similar sound, which is called "vegetation plop".

A high-frequency sound associated with a rapid inward movement of the prolapsed mitral valve may appear as opening snap.[42]

In occasional patients with hypertrophic cardiomyopathy with a small left ventricular cavity, high-pitch sounds are heard in early diastole coinciding with the time of contact of the anterior leaflet of the mitral valve to the interventricular septum.[43] This sound is often termed "opening slap".

The friction rub associated with pericarditis is produced by the friction of the parietal and visceral layers of the pericardium, and has a scratchy quality. It can be heard during atrial systole, ventricular systole and the rapid filling phase (three-component rub). However, it can be heard only during one or two phases of the cardiac cycle. A firm pressure with the diaphragm of the stethoscope frequently increases its intensity. The intensity may also increase during held inspiration with the patient leaning forward. The pericardial rub may be localized or widespread. Occasionally it is heard only along the lower right sternal border.

Overt hyperthyroidism is occasionally associated with a superficial "scratchy" high-pitch sound, which is called Means-Lerman scratch.

Mediastinal emphysema can cause crunching sounds, which are called mediastinal crunch. It occurs not infrequently after open heart surgery and it is benign.

Superficial scratchy sounds during systole due to the movement of the transvenous pacemakers or balloon floatation catheters across the tricuspid valve can be heard in some patients along the lower left sternal border and should not be confused with tricuspid regurgitation murmur or pericardial friction rub.

The pacemaker sounds are high-frequency sounds which occur due to stimulation of the intercostal muscles and they are unrelated to the cardiac cycle.

The presence of a relatively large amount of air (not small air bubbles) in the right ventricular cavity is associated with loud sloshing noises, which can be heard over the entire precordium. These noises sound like loud peculiar murmur and are called "mill wheel murmur".[44]

Artificial Valve Sounds

The opening and closing sounds of both mechanical and bioprosthesis are high-pitch sounds. The closing and opening sounds of mechanical prosthesis have a "clicky" character and there may be multiple clicks. The intensity of the closing clicks is louder than that of opening clicks in bileaflet mechanical prosthesis. With ball and cage mechanical valves, the closing and opening clicks are loud and may be of similar intensity. The closing or opening sounds with bioprosthesis do not have a "clicky" character but the closing sound is much louder.

TABLE 12

The timing and characters of the various types of murmurs

Systolic murmurs
- Ejection systolic starts after S1 and does not extend to S2
- Pansystolic starts with S1 and extends to S2 (mitral, tricuspid regurgitation, VSD)
- Early systolic starts with S1 and does not extend to S2 (mitral, tricuspid regurgitation, VSD)
- Late systolic starts after S1 and extends to S2 (mild MR or TR)

Diastolic murmurs
- Early diastolic starts with S2 (AI, PI)
- Mid diastolic starts after S2 (MS, TS, AFM)
- Presystolic starts after S2 and extends to S1 (MS, AFM)
- Continuous murmurs—encompass both systole and diastole (arteriovenous communication—PDA, AV fistula, mammary shuffle)

Abbreviations: PDA: Patent ductus arteriosus; AV: Atrioventricuar; AFM: Austin-Flint murmur; TS: Tricuspid stenosis; MS: Mitral stenosis; AI: Aortic insufficiency; PI: Pulmonary insufficiency; MR: Mitral regurgitation; TR: Tricuspid regurgitation; VSD: Ventricular septal defect; AS: Aortic stenosis; PS: Pulmonary stenosis

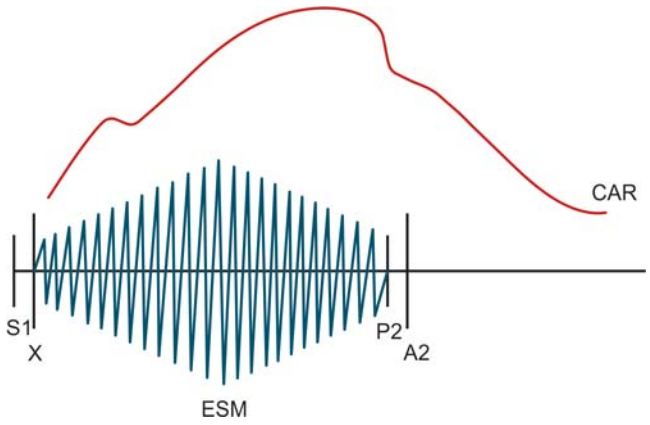


FIGURE 11: The schematic illustrations of the characters of the ejection systolic murmur and changes in carotid pulse in aortic valve stenosis. (Abbreviations: S1: First heart sound; A2: Aortic valve closure sound; P2: Pulmonary valve closure sound; ESM: Ejection systolic murmur; X: Aortic ejection sound; CAR: Carotid pulse)

The changes in the normal sounds associated with prosthetic valves may indicate their malfunction. However, malfunction of the prosthetic valve can exist without any changes in the prosthetic sounds.

AUSCULTATION OF HEART MURMURS

The various types of cardiac murmurs and some of their causes are summarized in Table 12. In clinical practice, significant valvular heart disease is first diagnosed by detecting a murmur. Detection of murmur by auscultation has a sensitivity of 70% and a specificity of 98%.[45] The guidelines recommend that all patients with suspected valvular heart disease should have echocardiography for establishing the cause of the murmur.[46]

The murmurs can be systolic, diastolic or continuous. The systolic murmurs are further classified as midsystolic (ejection) murmurs or regurgitant murmurs. The ejection systolic murmurs are related to left or right ventricular ejection to aorta or pulmonary artery, respectively. By definition, ejection systolic murmur begins after S1 and at the end of isovolumic systole. The interval between S1 and the onset of the murmur is related to the duration of the isovolumic systole. It ends at the end of ejection and before the closure of the semilunar valves, i.e. before A2 and P2. The interval between the end of the murmur and A2 or P2 is related to the duration of aortic or pulmonary hang out times. The intensity of the ejection systolic murmur increases (crescendo) during acceleration of blood flow in early systole and the intensity decreases (decrescendo) with deceleration of flow in late systole (the crescendo-decrescendo murmurs).

The regurgitant systolic murmurs are classified into: (1) holosystolic or pansystolic—the murmur starts with S1 and terminates at or after S2; (2) the early systolic murmur starts with S1 and ends before S2 and (3) the late systolic murmur starts after S1 and terminates at S2.

The diastolic murmurs are classified into: (1) early diastolic murmur which begins with S2 and terminates before S1; (2) mid-diastolic murmur which starts after S2 and ends at or before S1 and (3) late diastolic or presystolic murmur which starts in late diastole after S2 and terminates at S1.

The continuous murmurs begin in systole and continue into diastole.

The intensity of a murmur is conventionally graded into six grades. Grade I is the faintest murmur that can be heard. Grade II is also a faint murmur but can be heard easily. Grade III is a moderately loud murmur. Grade IV murmur is a loud murmur associated with a palpable thrill. Grade V is a very loud murmur but cannot be heard without the stethoscope. Grade VI is the loudest murmur and can be heard without a stethoscope.

It should be appreciated that the grading of the murmurs is purely subjective and depends on many factors including the hearing of the auscultators. Furthermore, the intensity of the murmur does not always correlate with the severity of valvular heart disease.

Ejection Systolic Murmurs

The ejection systolic murmurs may result from fixed or dynamic obstruction of the left ventricular outflow tract. The murmurs are of harsh quality. The fixed obstruction may be at the level of aortic valve, or it can be supravalvular or subvalvular. The characters and duration of the murmur may be similar in valvular, supravalvular and subvalvular aortic stenosis. However, there are other distinctive features of valvular, supravalvular and subvalvular aortic stenosis. Aortic valve stenosis is frequently associated with an anacrotic carotid pulse, delayed upstroke and delayed peak (Fig. 11). The murmur radiates to both carotids. In mild to moderately severe aortic valve stenosis, an ejection sound may be heard at the onset of the ejection systolic murmur. In severe aortic stenosis, aortic ejection sound is usually absent. In older patients with calcific trileaflet aortic valve stenosis, the ejection systolic murmur may have a musical quality (Gallavardin sign), which is frequently heard over the cardiac apex or along lower left sternal border. This musical murmur is related to vibrations of the subvalvular structures. In supravalvular aortic stenosis, the right carotid pulse amplitude is frequently greater than that of the left. The intensity of the radiated murmur over the right carotid artery is often

TABLE 13

Physical findings of hemodynamically significant aortic valve stenosis

- Slow rising delayed peaking small amplitude carotid pulse
- Anacrotic carotid pulse
- Anacrotic radial pulse
- Late peaking harsh ejection systolic murmur
- Palpable systolic thrill
- Sustained left ventricular apical impulse
- Paradoxical splitting of S2 in absence of left bundle branch block or right ventricular pacing
- Evidence of pulmonary hypertension

greater than over the left. The supravalvular, valvular and subvalvular aortic stenosis may all be associated with murmurs of aortic regurgitation. The presence of an aortic ejection sound excludes the diagnosis of fixed supravalvular or subvalvular aortic stenosis. The physical findings of hemodynamically significant aortic valve stenosis are summarized in Table 13.

Aortic valve sclerosis is associated with a short ejection systolic murmur. The murmur is best heard over the right second intercostal space and generally is not loud. It may be heard along the left sternal border and over cardiac apex. In aortic sclerosis there is no significant aortic valve obstruction. The carotid pulse upstroke and S2 are normal and aortic regurgitation murmur is absent. A transthoracic echocardiogram is recommended to confirm the diagnosis. Aortic sclerosis is a risk factor for adverse prognosis due to a higher incidence of atherosclerotic cardiovascular disease.

In patients with bicuspid aortic valve without aortic stenosis, a short ejection systolic murmur preceded by an ejection sound is frequently heard and an early diastolic murmur of trivial aortic regurgitation may also be present. The carotid pulse and S2 are normal. A transthoracic echocardiogram is recommended to confirm the diagnosis.

In dynamic left ventricular outflow tract obstruction due to Hypertrophic Obstructive Cardiomyopathy (HOCM), an ejection systolic murmur is always present. The murmur is best heard along the lower left sternal border or over cardiac apex. The murmur does not radiate to the neck. The intensity of the murmur varies with maneuvers (Table 14) due to changes in the severity of obstruction. Standing from squatting position is associated with increased obstruction and increased intensity of the murmur. In patients with fixed aortic valve stenosis or mitral regurgitation the intensity of the murmur decreases. During the phase II of Valsalva maneuver, the severity of obstruction is increased and the intensity of the murmur also increases. The carotid pulse volume either remains unchanged or decreases. During the phase II Valsalva maneuver, in fixed aortic stenosis or mitral regurgitation, the intensity of the murmurs decreases. With amyl nitrate inhalation, in HOCM, the intensity of the murmur increases along with the increase in the outflow gradient. In patients with fixed aortic stenosis the intensity of the murmur also increases. In mitral regurgitation the intensity of the murmur decreases as the severity of mitral regurgitation decreases because of reduction in systemic vascular resistance.

TABLE 14

The influence of maneuvers on the intensity of the murmurs of hypertrophic obstructive cardiomyopathy, aortic valve stenosis and primary mitral regurgitation

Murmur	*HOCM*	*AS*	*MR*
Standing	++	-	-
Squatting	-	-	+
Handgrip	-/+	-/+	+
Valsalva	++	-	-
Amyl nitrite	++	+	-

Abbreviations: HOCM: Hypertrophic obstructive cardiomyopathy; AS: Fixed aortic valve stenosis; MR: Mitral regurgitation

++, markedly increased; -, decreased; +, increased; -/+, may decrease or increase

The murmur of dynamic left ventricular outflow obstruction has been rarely observed in patients with acute myocardial infarction or apical ballooning syndrome who can develop transient left ventricular outflow obstruction.[45]

Innocent Murmurs

The innocent murmurs are typical ejection systolic murmurs and are not associated with any other abnormal findings. The duration and intensity of innocent murmurs are variable. The innocent murmurs are related to increased flow across semilunar valves. The high cardiac output, such as with anemia, thyrotoxicosis and pregnancy, may be associated with flow murmurs. In over 80% of normal pregnant women, a pulmonary ejection systolic murmur can be heard.

The Still's murmur is a short, low-pitched vibrating murmur which is heard in children along the left lower sternal border in absence of any other abnormality. It is thought that it is caused by the vibrations of the attachments of the pulmonary valve leaflets.

In children another innocent ejection systolic murmur can be heard over the left second interspace which is thought to originate from the vibrations of the pulmonary trunk. The straight back syndrome may be associated with an innocent ejection systolic murmur.[47]

PULMONARY OUTFLOW OBSTRUCTION

An ejection systolic murmur is present in pulmonary valve, supravalvular or subvalvular stenosis. The pulmonary valve stenosis is associated with a harsh ejection systolic murmur which is best heard over the left second interspace. It is usually preceded by the pulmonary ejection sound. The intensity of the murmur increases during inspiration but that of the ejection sound decreases. The duration of the murmur correlates with the severity of stenosis. The longer the duration, more severe is the stenosis. The interval between A2 and P2 also correlates with the severity. The wider the interval, more severe is the stenosis. In pulmonary valve stenosis, the intensity of P2 is decreased as the pressure beyond the pulmonary valve is lower.

Occasionally the long ejection systolic murmur of pulmonary valve stenosis can be mistaken for the murmur of ventricular septal defect particularly when the intensity of P2 is decreased. The murmur of ventricular septal defect is a regurgitant murmur and starts with the first heart sound. It is

best heard along the lower left sternal border. In ventricular septal defect the S2 is normal, while in pulmonary stenosis S2 is widely split. Inhalation of amyl nitrite is sometimes useful for the differential diagnosis. The intensity of the murmur of ventricular septal defect is decreased; the murmur of pulmonary valve stenosis is increased.

The idiopathic dilatation of the pulmonary artery is associated with a relatively short ejection systolic murmur, an ejection sound and a widely split S2 with normal intensity of P2. There is occasionally an early diastolic murmur of mild pulmonary regurgitation. The auscultatory findings are similar in pulmonary hypertension; however, in pulmonary arterial hypertension the intensity of P2 is increased and the splitting of S2 is narrower.

Regurgitant Murmurs

The systolic regurgitant murmurs start with S1 and may or may not extend to S2. When the murmur extends to S2 or beyond, it is called pansystolic or holosystolic murmur. It is caused when blood flows from a chamber whose pressure throughout the systole is higher than the pressure in the chamber receiving the flow. Mitral or tricuspid valve regurgitation and unrestricted ventricular septal defect are the major causes of holosystolic murmurs. When the murmur does not extend to S2, it is termed early systolic regurgitant murmur. Mitral or tricuspid valve regurgitation and ventricular septal defect may be associated with early systolic murmurs. When the murmur starts after S1 and extends to S2, it is termed late systolic murmur. The late systolic murmurs are auscultatory findings of relatively mild mitral or tricuspid regurgitation.

Mitral regurgitation: The murmurs of mitral regurgitation are high pitched and best appreciated with the diaphragm of the stethoscope over cardiac apex with the patient in partial left lateral decubitus position. The intensity of the murmur in part determines radiation. The direction of radiation is along the direction of regurgitation jet from left ventricle to left atrium. When the regurgitant jet is directed posterolaterally, the murmurs radiate toward the left axilla, inferior angle of left scapula and thoracic spine. In some patients this murmur radiates up the spine and can be heard over the top of the head.

When the regurgitant jet is directed anteromedially against the interatrial septum, the murmur radiates toward the base and root of the neck. This radiated murmur can be mistaken as the murmur of aortic stenosis. However, other findings of aortic stenosis or mitral regurgitation provide clues for the diagnosis. A transthoracic echocardiogram should be always performed for establishing the diagnosis.

The physical findings of acute severe mitral regurgitation are different than those of chronic severe mitral regurgitation. Acute severe mitral regurgitation, e.g. due to ruptured chordae, is associated with sudden onset of dyspnea due to pulmonary edema. The physical findings are characterized by an early systolic regurgitant murmur, evidence for pulmonary hypertension, and a hyperdynamic left ventricular apical impulse and normal left ventricular ejection fraction (Fig. 12). The murmur terminates in mid-systole or late systole when the left atrial pressure equalizes with left ventricular systolic pressure. The cardiomegaly and S3 are usually absent.

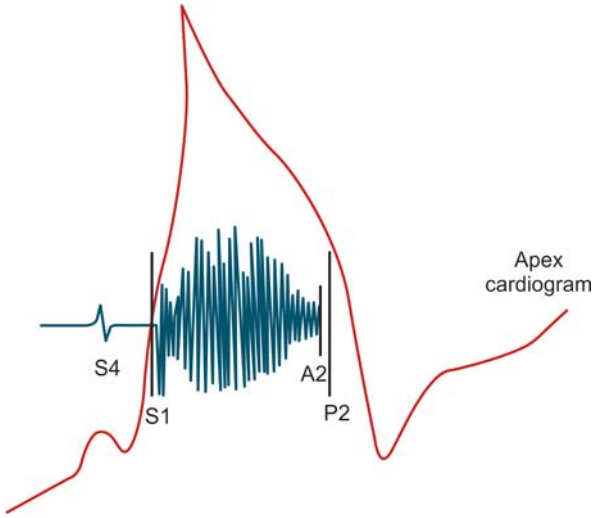


FIGURE 12: The schematic illustrations of physical findings of acute severe mitral regurgitation showing that the regurgitant murmur terminates before A2 because of equalization of left ventricular and left atrial pressures and cessation of regurgitation. Left ventricular apical impulse is hyperdynamic indicating normal ejection fraction. The intensity of P2 is increased indicating pulmonary hypertension

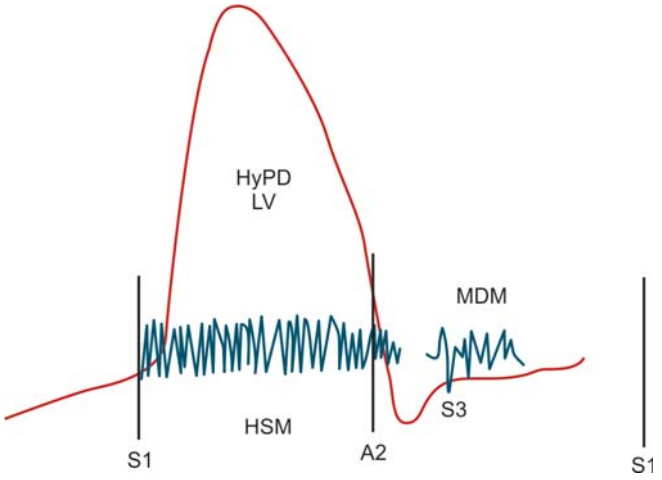


FIGURE 13: The schematic illustrations of physical findings of chronic severe mitral regurgitation showing that the high-pitched murmur is holosystolic (HSM) and extends beyond A2 as the left ventricular pressure remains higher than the left atrial pressure even after closure of the aortic valve. S3 is frequently present. Occasionally a low pitch mid-diastolic flow murmur (MDM) is heard. The left ventricular apical impulse is hyperdynamic (HyPD LV) indicating normal left ventricular ejection fraction

It should be appreciated that a short early systolic murmur may also be observed in patients with very mild mitral regurgitation such as due to mitral annular calcification.

The physical findings of chronic severe mitral regurgitation are characterized by a holosystolic murmur, a widely split S2 and an S3 (Fig. 13). The murmur frequently extends beyond A2 as the left ventricular pressure still remains higher than the left atrial pressure even after the closure of the aortic valve. The cardiac enlargement is also appreciated. The left ventricular apical impulse is hyperdynamic indicating normal ejection fraction. However, in patients with chronic severe primary mitral

regurgitation with continued volume overload, the left ventricular ejection fraction declines. When left ventricular ejection fraction is substantially reduced, it cannot be distinguished from secondary mitral regurgitation such as in patients with dilated cardiomyopathy. Chronic severe primary mitral regurgitation may be associated with postcapillary pulmonary hypertension.

The most common cause of late systolic murmur is prolapse of the mitral valve. The late systolic murmur resulting from mitral valve prolapse is usually preceded by clicks. The commonest etiology of mitral valve prolapse is the redundancy of the valve tissue with respect to the valve ring. The valve appears "floppy" (Barlow's syndrome). The onset of the prolapse that causes the late systolic murmur is not only related to the severity of mitral valve prolapse but also to the changes in ventricular volume. Standing, sitting and Valsalva maneuver cause an earlier onset of the click and the murmur because these maneuvers decrease left ventricular end-diastolic volume and with the onset of systole the prolapse occurs earlier.

Elevation of legs, squatting and handgrip, which is associated with increased left ventricular volume, delays the onset of the prolapse and the late systolic murmur.

Late systolic murmur due to mitral regurgitation can also occur from papillary muscle displacement in patients with ischemic heart disease.

In patients with pseudohypertrophic muscular dystrophy or Becker's muscular dystrophy, mitral valve prolapse and late systolic murmur are indications of cardiac involvement and result from fibrosis of the posterior left ventricular wall. The electrocardiogram almost always reveals a taller R wave in leads V1 and V2.

Tricuspid regurgitation: The tricuspid regurgitation murmur can be holosystolic, early systolic or late systolic. The early and late systolic murmurs indicate mild tricuspid regurgitation. The holosystolic murmur is usually associated with more severe tricuspid regurgitation. The murmurs of tricuspid regurgitation are best heard over the lower left parasternal area and the intensity increases during inspiration (Carvallo's sign, sometimes spelled Carvello's). During inspiration there is increased systemic venous return, which is associated with more severe tricuspid regurgitation. Presence of a right ventricular S3 and a mid-diastolic flow murmur, which also increase in intensity during inspiration, indicates more severe tricuspid regurgitation. These auscultatory findings are frequently detected in patients with atrial septal defect and a large left-to-right shunt.

The murmur of severe regurgitation may radiate to the right lower parasternal area and to the epigastrium.

Tricuspid regurgitation is most frequently secondary to pulmonary hypertension, which can be diagnosed at the bedside by the presence of a loud (Fig. 14).

Primary tricuspid regurgitation without associated pulmonary hypertension is encountered much less frequently. It can occur in patients with right-sided bacterial endocarditis, carcinoid heart disease, Ebstein's anomaly, traumatic ruptured chordae or prior right ventricular myocardial infarction. Rarely, it occurs in Uhl's syndrome.

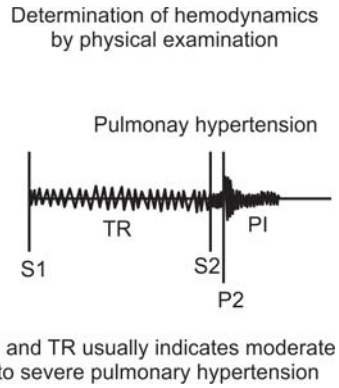


FIGURE 14: Schematic auscultatory findings of secondary tricuspid regurgitation. (Abbreviations: TR: Tricuspid regurgitation murmur; P1: Pulmonary insufficiency murmur; S1: First heart sound; A2: Aortic component of the second heart sound; P2: Pulmonary component of the second heart sound which is increased in intensity which indicates pulmonary arterial hypertension

TABLE 15

Tricuspid regurgitation—physical findings

- Elevated jugular venous pressure with prominent "V" wave and "y" descent
- Pansystolic murmur which increases in intensity during inspiration
- Systolic hepatic pulsation

A more frequent cause of primary tricuspid regurgitation is related to the right ventricular pacing electrode, which prevents complete closure of the tricuspid valve. Severe tricuspid regurgitation occurs when the pacing electrode perforates the tricuspid valve leaflets.

Late systolic murmur due to tricuspid valve prolapse is uncommon in absence of mitral valve prolapse. It may be preceded by clicks. The intensity of the murmur increases during inspiration.

The unrestricted ventricular septal defect is associated with a holosystolic murmur and it is best heard over the lower left third and fourth interspace. It is frequently associated with a palpable thrill. The intensity of the murmur does not vary with respiration. The muscular ventricular septal defect causes an early systolic murmur. The physical findings of tricuspid regurgitation are summarized in Table 15.

DIASTOLIC MURMURS

Early Diastolic Murmurs

Early diastolic murmurs result most frequently, either from aortic or pulmonary regurgitation. The aortic and pulmonary regurgitation murmurs start with or shortly after A2 or P2, respectively. These murmurs are of relatively higher pitched and best heard with the use of the diaphragm of the stethoscope.

Aortic regurgitation: Auscultation is essential for the diagnosis of aortic regurgitation. The detection of an early diastolic murmur during auscultation has a positive likelihood ratio of 8.8 for the presence of aortic regurgitation. When the early

diastolic murmur is absent during auscultation, the negative likelihood ratio is 0.2:0.3.[48] These findings indicate that when an early diastolic murmur is heard, the likelihood of presence of aortic regurgitation is very high.

The murmur is best heard when a firm pressure is applied with the diaphragm of the stethoscope and the patient leaning forward and during held expiration. Auscultation should be performed over the right second interspace, along left sternal border and over the cardiac apex for the detection of the murmur. The radiation of aortic regurgitation murmur is toward cardiac apex. Occasionally radiation occurs along the right sternal border when aortic regurgitation occurs due to aortic root or aortic cusp abnormalities.

The high-pitched early diastolic murmur of aortic regurgitation has a decrescendo configuration and a "blowing" quality. Occasionally the murmur can have a musical quality (diastolic whoop), which appears to be due to flail everted aortic cusp.

The duration of the murmur is variable. A pandiastolic regurgitation murmur indicates a persistent gradient between aortic diastolic and left ventricular diastolic pressures. When the murmur is of brief duration, the severity of aortic regurgitation can be mild or very severe. Not only the anatomic changes causing aortic regurgitation determine the severity of regurgitation and hence the duration of the murmur, the hemodynamic consequences of aortic regurgitation also influence the duration of the murmur. In patients with acute severe aortic regurgitation, the murmur can be short because of a rapid increase in left ventricular diastolic pressure, which equalizes with aortic diastolic pressure soon after the onset of the diastole. Due to a marked rapid increase in left ventricular diastolic pressure, S1 may be absent due to premature closure of the mitral valve. In acute severe aortic regurgitation, S4 may be absent because of a marked increase in left ventricular diastolic pressure, which may prevent effective left ventricular filling. The intensity of P2 is increased due to postcapillary pulmonary hypertension. The carotid pulse volume is decreased because of reduced forward stroke volume. Left ventricular impulse is not displaced and maintains normal character indicating normal ejection fraction. In acute severe aortic regurgitation, there is no left ventricular adaptation to severe volume overload and there is lack of left ventricular dilatation and hypertrophy.

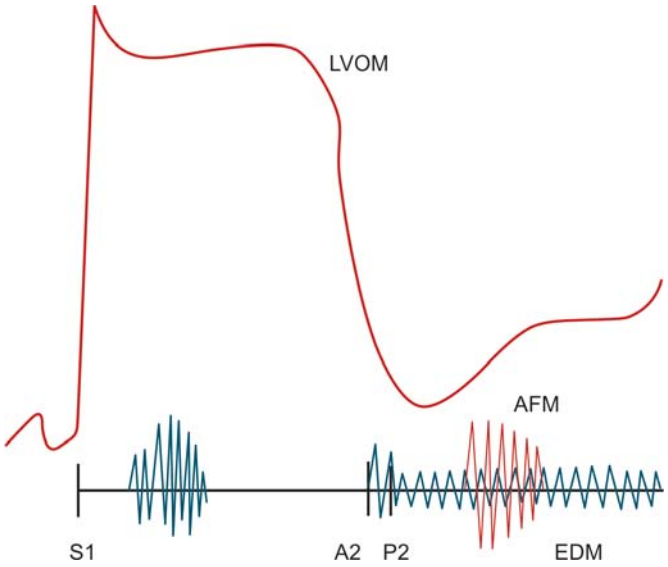


FIGURE 15: The schematic illustrations of physical findings in chronic severe aortic regurgitation showing a long early diastolic murmur, Austin Flint Murmur (AFM), reversed splitting of S2 and hyperdynamic left ventricular impulse. (Abbreviations: EDM: Early diastolic murmur; A2: Aortic component of second heart sound; P2: Pulmonic component of second heart sound; S1: First heart sound; LVOM: Left ventricular outward murmur)

The physical findings of chronic hemodynamically significant aortic regurgitation are illustrated in Figure 15 and Table 16. The early diastolic murmur is longer in duration and can be pandiastolic. A low-pitched mid-diastolic murmur, called "Austin Flint" murmur, may be heard. The intensity of A2 is usually decreased but it does not necessarily indicate severe aortic regurgitation. Reversed splitting of S2 in the absence of left bundle branch block results from a marked increase in left ventricular forward stroke volume and usually associated with significant aortic regurgitation. The increased flow may also be associated with an ejection systolic murmur. The decreased intensity of S1 indicates increased left ventricular end-diastolic pressure, which is more likely to occur in severe aortic regurgitation. Similarly presence of the physical findings of

TABLE 16

The differences in the physical findings in acute and chronic severe aortic regurgitation

	Acute	*Chronic*
Carotid pulse small volume	small volume	bisferiens quality, large volume, sharp upstroke
S1	decreased intensity or absent	decreased intensity or normal
S2	normal or decreased	normal or decreased
P2	increased	normal or increased
Apical impulse	normal and nondisplaced	displaced, normal or sustained
S4	absent	present
EDM	short	long or short
AFM	absent	present

Abbreviations: S1: First heart sound; S2: Second heart sound; P2: Pulmonic component of second heart sound; S4: Fourth heart sound; EDM: Early diastolic murmur; AFM: Austin Flint murmur

pulmonary hypertension and right heart failure indirectly suggest severe aortic regurgitation. The carotid pulse upstroke is sharp and may have a bisferiens character. Presence of a normal character of left ventricular apical impulse indicates normal ejection fraction. However, a sustained apical impulse does not necessarily indicate reduced ejection fraction as severe hypertrophy may also be associated with a sustained apical impulse. The apical impulse is usually displaced laterally and downward due to dilatation of the left ventricle.

Occasionally aortic regurgitation murmur is heard in patients with hypertension, aortic aneurysm and bicuspid aortic valve. Aortic regurgitation is mild in these conditions.

A diastolic murmur similar to aortic regurgitation can be heard in some patients with stenosis of the left anterior descending coronary artery (Dock's murmur).[49] This murmur is very localized and usually heard over the left second or third interspace just lateral to the left sternal border. It is caused by turbulent flow across a moderately severe stenosis. The murmur is absent after angioplasty or bypass surgery. For practical purposes, in all patients with suspected Dock's murmur, an echocardiographic study should be performed to exclude other commoner causes of early diastolic murmur.

Pulmonic regurgitation: Very mild or trivial pulmonary valve regurgitation is detected in many normal subjects by echo-Doppler studies and do not have any clinical significance.

In the adult patients, the most common cause of pulmonic regurgitation is pulmonary hypertension (Graham-Steel murmur).[50] It is high pitched and starts with a loud P2 and has a "blowing" quality. The duration is variable. The murmur may increase in intensity during inspiration. An echocardiographic study is essential to exclude aortic regurgitation.

Pulmonary regurgitation is common after repair of Tetralogy of Fallot and after pulmonary valvulotomy for pulmonary valve stenosis. The murmur is of lower pitch. The intensity of P2 is reduced as the pulmonary artery pressure is normal or low.

Pulmonic regurgitation can occur in patients with idiopathic dilatation of the pulmonary artery, with right-sided endocarditis and congenital absence of the pulmonary valve. In congenital absence of pulmonary valve, P2 is absent and a loud to-and-fro murmur may be heard.

Mid-Diastolic Murmurs

The mid-diastolic murmurs are low- or medium-pitched murmurs and have rumbling quality and thus these murmurs are frequently called "rumbles". An anatomic or functional obstruction of the atrioventricular valves is associated with mid-diastolic murmurs.

Mitral Stenosis

The characteristic auscultatory findings of mitral stenosis are a loud S1, a mid-diastolic murmur with or without presystolic accentuation. It is best heard with the bell of the stethoscope over the cardiac apex with the patient in the left lateral decubitus. The murmur originates in the left ventricular cavity explaining why it is best heard over the cardiac apex. The presystolic component of the mid-diastolic murmur can be present even in presence of atrial fibrillation. The mid-diastolic murmur due to mitral stenosis is preceded by the opening snap until the mitral valve is heavily calcified and immobile. The duration of the murmur correlates with the severity of mitral stenosis. The longer the duration, more severe is mitral stenosis. It should be appreciated however that low cardiac output is associated with shorter duration of the murmur and the intensity of the murmur is decreased even in presence of severe mitral stenosis. The mitral regurgitation murmur is frequently heard because of the presence of obligatory mitral regurgitation. A loud P2 and the Graham-Steel murmur can be present if there is significant pulmonary hypertension.

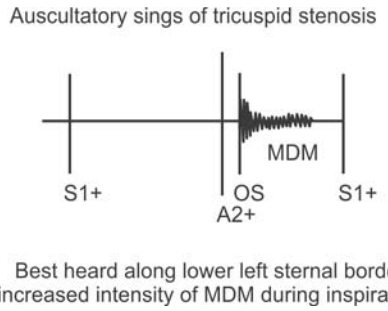


FIGURE 16: Schematic illustrations of auscultatory signs of tricuspid stenosis. Right sided opening snap (OS), mid-diastolic murmur (MDM) and increased intensity of the first heart sound (S1+). (Abbreviation: A2+: Aortic component of the second heart sound)

Tricuspid Stenosis

The auscultatory findings of tricuspid stenosis are very similar to those of mitral stenosis (Fig. 16). However, in tricuspid stenosis, the intensity of the murmur increases during inspiration because of increased gradient across the tricuspid valve (Carvallo'sign). The mid-diastolic murmur can be associated with an opening snap.

Isolated tricuspid valve obstruction is uncommon and it occurs in association with mitral and aortic valve disease in rheumatic valvular heart disease. The physical findings of tricuspid valve stenosis are summarized in Table 17.

When isolated tricuspid stenosis is present, right atrial myxoma or carcinoid heart disease should be suspected. An echocardiographic study is mandatory for the differential diagnosis.

Left and right atrial myxomas can be associated with the auscultatory findings, similar to those of mitral and tricuspid valve stenosis. The "tumor plop" sounds can be similar to opening snaps.

TABLE 17

Tricuspid stenosis—physical findings

- Elevated jugular venous pressure with prominent "a" wave and slow "y" descent
- Mid diastolic rumble which increases in intensity during inspiration
- Right sided opening snap
- Right sided presystolic murmur
- Presystolic hepatic pulsation

The echocardiographic evaluation is essential for establishing the correct diagnosis.

Austin Flint Murmur

It is a low-pitched rumbling murmur associated with aortic regurgitation. Controversy exists about the genesis of the murmur. Fluttering of the mitral valve and relative mitral stenosis due to movement of the mitral valve leaflets to the semi-closed position has been proposed as the potential mechanisms. It is however present most frequently in patients with hemodynamically significant aortic regurgitation.

Carey-Coombs Murmur

Acute rheumatic mitral valvulitis can be associated with a mid-diastolic murmur, which is transient. It is caused by swelling of the mitral valve leaflets and other signs of rheumatic carditis are usually present.

Increased flow across the atrioventricular valves can be associated with mid-diastolic murmurs. Severe mitral regurgitation and ventricular septal defects with large left-to-right shunts can cause left-sided mid-diastolic flow murmurs. An atrial septal defect with a large left-to-right shunt can be associated with a right-sided mid-diastolic flow murmur.

In patients with complete atrioventricular block, with a slow ventricular rate, a late diastolic murmur can be heard. This murmur is also called *Rytand's murmur*. The mechanism of this murmur remains unclear and diastolic mitral regurgitation has been postulated.[51]

CONTINUOUS MURMURS

The continuous murmurs begin in systole and extend to diastole. These murmurs result from blood flow from a higher pressure chamber or vessel to a lower pressure chamber or vessel.

In the adult patient, a patent ductus arteriosus and a venous hum are the usual causes of continuous murmurs. The venous hum can be easily diagnosed at the bedside. The venous hum is not heard in supine position. Pressure at the root of the neck also causes disappearance of the venous hum. The "mammary soufflé" associated with pregnancy is another cause of benign continuous murmur. Congenital or acquired arteriovenous fistulas also cause continuous murmurs. Following cardiac catheterization, an arteriovenous communication can occur at the site of insertion of the intravascular catheters, and a continuous murmur can be heard.

In patients with coarctation of aorta, a continuous murmur can be heard in the back overlying the area of constriction. In these patients, continuous murmurs can be heard over large tortuous intercostal arteries which can also be visible (Suzman's sign).[52]

The pulmonary arteriovenous malformations are usually silent, but occasionally a continuous murmur can be heard. Peripheral pulmonary artery branch stenosis can cause a continuous murmur.

Fistulous communication between an internal mammary artery graft to the vein accompanying the left anterior descending coronary artery is another rare cause of continuous murmur.[53]

The continuous murmurs associated with aortopulmonary window and truncus arteriosus and coronary arteriovenous fistulas are rarely encountered in adult patients.

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Chapter 11

Plain Film Imaging of Adult Cardiovascular Disease

Brad H Thompson, Edwin JR van Beek

Chapter Outline

- Chest Film Technique
- Overview of Cardiomediastinal Anatomy
- Cardiac Anatomy on Chest Radiographs
- Cardiac Chamber Enlargement
  - Left Ventricular Enlargement
  - Right Ventricular Enlargement
  - Left Atrial Enlargement
  - Right Atrial Enlargement
- Radiographic Manifestations of Congestive Heart Failure
- Cardiac Calcifications
- Acquired Valvular Heart Disease
  - Aortic Stenosis
  - Aortic Insufficiency
  - Mitral Stenosis
  - Mitral Regurgitation
  - Pulmonary Valve Stenosis
  - Pulmonary Valve Insufficiency
  - Tricuspid Insufficiency
- Pericardial Disorders
  - Pericardial Effusion
  - Pericardial Cysts
  - Congenital Absence of the Pericardium

INTRODUCTION

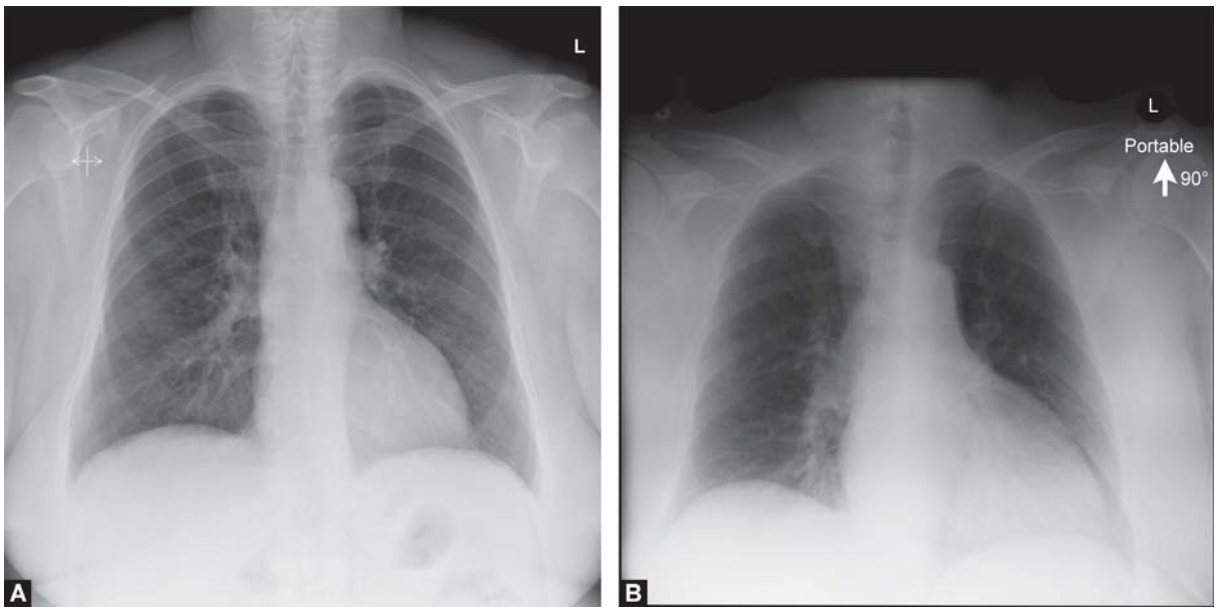
Plain film radiography of the chest offers valuable information about the cardiovascular system, and appropriately, should serve as the initial investigative test in patients suspected of having cardiovascular disease, especially those with presenting with chest pain. Furthermore, by analysis of cardiac morphology, pulmonary vasculature and the vascular pedicle, chest films can provide additional semi-quantitative information about heart function, pulmonary blood flow and circulating blood volume. As such, serial chest films ideally serve as a non-invasive, inexpensive modality to monitor the efficacy of treatment regimens for conditions, like heart failure, and provide useful surveillance of the cardiovascular system in post-surgical patients following coronary bypass or heart transplantation. This chapter will cover the salient features of a variety of those cardiovascular diseases and anomalies which are commonly encountered in adults.

CHEST FILM TECHNIQUE

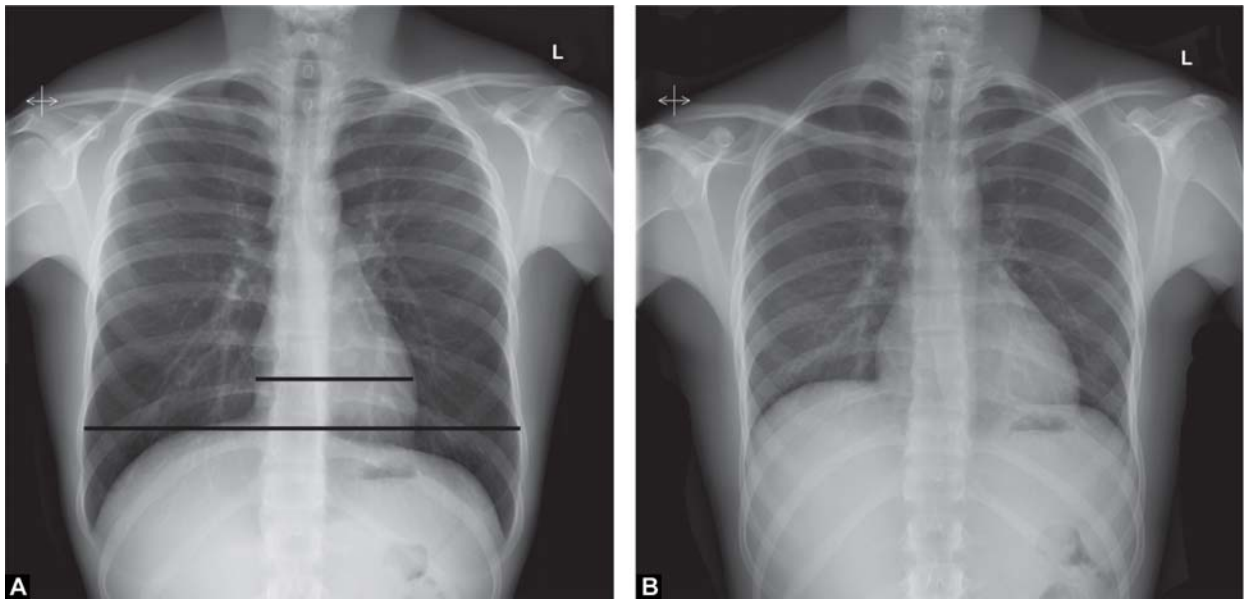
Radiographic assessment of the thoracic cardiovascular structures ideally requires the acquisition of two projections of the chest. This is primarily due to the oblique position of the heart within the chest. Frontal chest radiographs can be obtained either with the ventral chest closest to the film (PA projection) or reversed (AP film). Conventionally, frontal radiographs of the chest obtained within the department are usually obtained in the PA projection while all portable films use an AP technique. Selection between these two options however is not entirely academic as there are significant changes relating to heart size between these two exams. Since the heart is located ventrally within the chest cavity, the divergence of the X-ray beam which occurs with AP films results in an undesirable artifactual magnification of the cardiac silhouette (Figs 1A and B). Furthermore, portable AP films usually compound this problem in large part to associated recumbency and diminished lung volumes, which tend to further magnify the apparent size of the heart.

Qualitative assessment of cardiac enlargement can be quickly established radiographically by measuring the cardiothoracic ratio (CTR). This ratio, as measured on upright PA chest radiographs, refers to the ratio of the transverse diameter of the cardiac silhouette (measured horizontally) compared to the transverse chest diameter (as measured horizontally from inner margins of the ribs at the level of the right diaphragm). A normal CTR measured by this method should be 0.5 or smaller, provided there is good inspiratory effort. Decreases in lung volumes will produce an artificial increase in the systolic time ratio (STR), due the more horizontal axis of the heart along the left diaphragm (Figs 2A and B). Due to magnification and diminished lung volumes commonly encountered with AP chest films, the calculation of the STR is unreliable and should not be performed, especially on portable films.

Due to the oblique orientation of the heart within the chest, single frontal radiographs generally do not provide sufficient qualitative information about cardiac morphology, and as such complementary lateral films are desirable whenever possible. Normal anatomy of the heart on both frontal and lateral chest radiographs will be discussed later.



FIGURES 1A AND B: PA vs AP films: (A) PA film and (B) AP film on the same patient days apart. Note the significant increase in the size of the cardiac silhouette on the AP film due to magnification



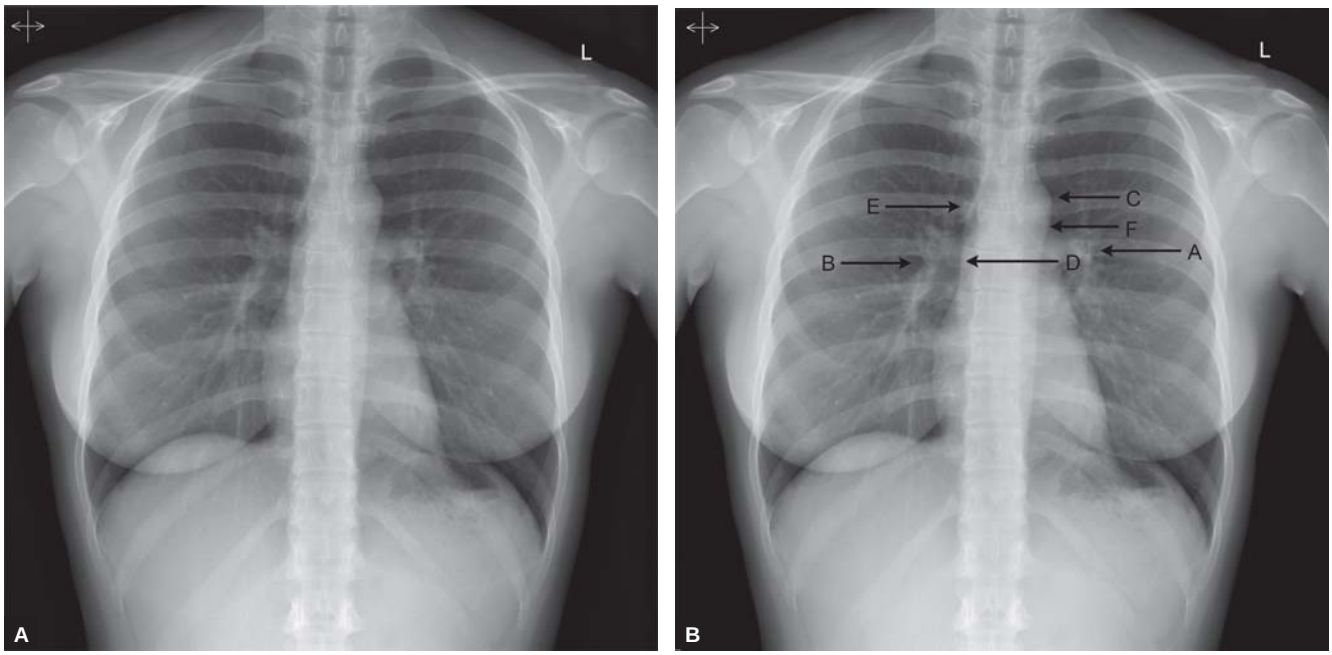
FIGURES 2A AND B: (A) Inspiratory vs (B) expiratory PA chest films. Horizontal lines reflect points of measurements for the cardio-thoracic ratio (TR). Note the apparent increase in the size of the heart with expiration (B)

OVERVIEW OF CARDIOMEDIASTINAL ANATOMY

Located centrally within the chest, the cardiomediastinal silhouette comprises the heart, the central large vessels (aorta, pulmonary artery, superior and inferior vena cava and azygos vein), the tracheobronchial, esophagus and the adipose tissue of the mediastinum (Figs 3A and B).

On either side of the central core structures are the hilar regions, which are composed of the central pulmonary arteries, mainstem bronchi, pulmonary veins and lymphatics. In general, the hila on chest films are largely composed of the pulmonary arterial shadows. The left hilum on the frontal radiographs is almost always higher in location than the right, reflecting the normal anatomical location of the left pulmonary artery as it courses superior to the left mainstem bronchus. This anatomical relationship is inverted on the right side, i.e. the right mainstem bronchus is hyparterial. These relationships are also substantiated on the lateral film as well.

The assessment of the pulmonary vasculature should be performed on review of every chest radiograph as changes either in the vessel size or border definition provides excellent physiologic information both about the volume status of the patient as well as the severity of congestive heart failure. Normally, the pulmonary arteries should be sharply defined and show a normal gravitationally dependent increase in lower lobe vascular conspicuity compared to the upper



FIGURES 3A AND B: (A) Normal PA chest film with (B) annonations. (Abbreviations: A: Left hilum; B: Right hilum; C: Aortic knob; D: Superior vena cava (SVC); E: Azygous vein; F: AP window)

lobes (Fig. 3A). This phenomenon, reflecting the increase in blood flow to the lower portions of the lungs can be demonstrated to good advantage by viewing an inverted PA chest film. With this maneuver, the observer will quickly appreciate the disparity of blood flow, i.e. vessel size and conspicuity between the upper and lower regions of the lungs. Furthermore, the observer should always evaluate the caliber of the pulmonary arteries. The normal caliber of normal pulmonary arteries should approximate the caliber of the adjacent bronchus. Determination of this arterial-bronchial ratio (A:B ratio) (normal = 1:1) is most easily performed evaluating the central-most vessels in the perihilar regions (Fig. 4). An increase in the size of the upper lobe vessels indicating recruitment can be seen in left to right shunt lesions, high intravascular volumes/pregnancy and left heart failure or left heart obstructive lesions.

The thoracic aorta is visible in several regions on chest radiographs. Normally the ascending portion of the thoracic aorta is best demonstrated on the lateral projection residing in the retrosternal space. The ascending aorta is not usually apparent on frontal chest radiographs but with enlargement, the ascending aortic shadow may become visible along the right edge of the mediastinal silhouette above the right hilum. Conspicuous dilatation of the ascending aorta is seen in systemic hypertension, aneurysm, or aortic stenosis (Figs 5 and 23A). The transverse portion of the thoracic aorta creates the aortic knob which is visible at the top left portion of the mediastinum above the left hilar shadow (Fig. 3B). On well-penetrated films, the descending aorta may be visible as a tubular opacity running inferiorly, parallel to the thoracic spine.

On the lateral radiograph, the thoracic aorta will be seen as an arch, extending superiorly from the cardiac silhouette, arching backward and subsequently inferiorly along the ventral aspects of mid and lower portions of the thoracic spine. The descending thoracic aorta is usually poorly visualized on the lateral film, unless atherosclerotic calcifications exist.

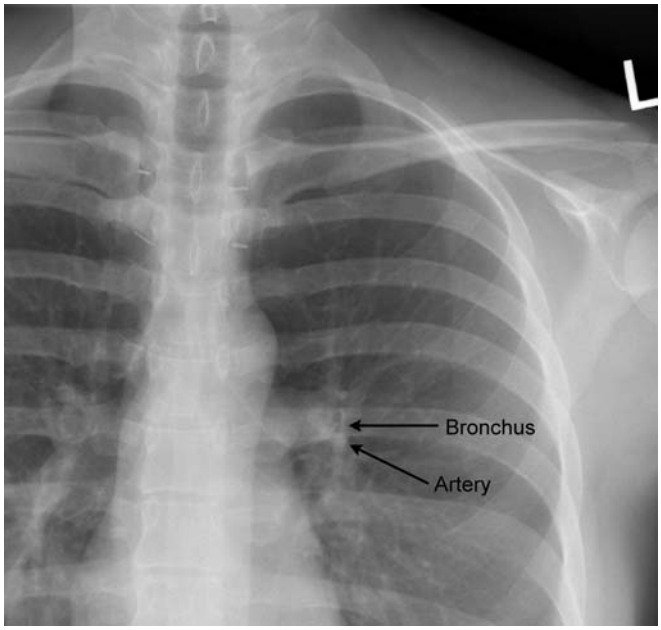


FIGURE 4: Normal arterial-bronchial relationship. Coned image from a PA chest film showing the normal 1:1 ratio of vessel size to adjacent bronchus (arterial-bronchus ratio). Also note the normal sharp definition of the arterial wall and thin bronchial wall

CARDIAC ANATOMY ON CHEST RADIOGRAPHS

On the frontal radiograph (Fig. 6), the heart is normally orientated slight to the left of midline with the inter-ventricular septum normally orientated 30 degrees left anterior oblique (LAO). This orientation results in superimpositioning of the right ventricle in front of the left ventricle. As such, the left heart border is composed entirely of the left ventricle. On the right side, the right atrium composes the right heart shadow (Fig. 3B). The shadow of the superior vena cava (SVC) comprises the vertical right paramedian shadow coursing

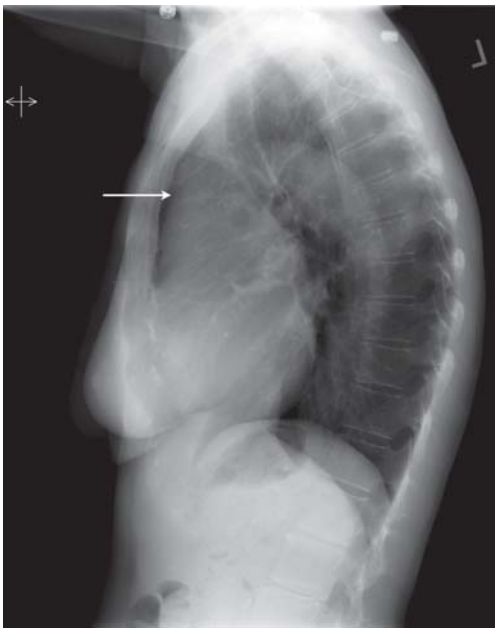


FIGURE 5: Patient with systemic hypertension. Lateral chest radiograph showing fusiform dilatation of the ascending thoracic aorta (arrow)

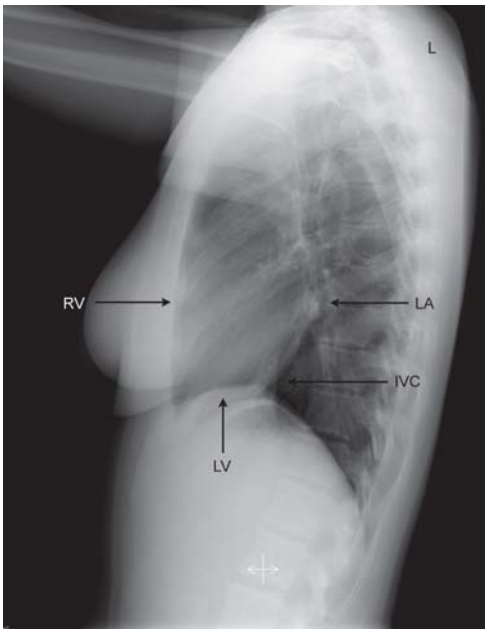


FIGURE 7: Normal cardiac anatomy on lateral radiograph. The right ventricle (RV) forms the ventral border of the cardiac silhouette while the inferoposterior border is composed of the left ventricle (LV). The left atrium (LA) composes the posterior-most border of the cardiac silhouette. The posterior border of the inferior vena cava (IVC) is also demonstrated to good advantage

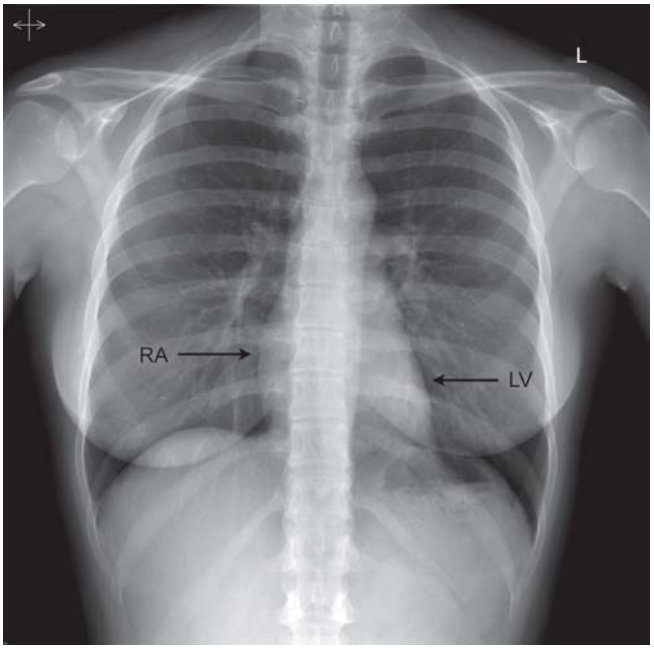


FIGURE 6: Normal PA chest film. The left ventricle (LV) forms the left heart border while the right heart border is composed of the lateral margin of the right atrium (RA)

inferiorly from the upper mediastinum to the right atrium. In the middle of the SVC, directly superior to the proximal right mainstem bronchus lies the azygous vein, which appears as a teardrop vascular shadow reflecting the anterior course of this vein as it empties into the SVC. The left atrium, which is the most posterior cardiac chamber, is not normally visualized on frontal chest films, unless it is enlarged. Normally, the left heart border in adults should be concave on frontal radiographs.

On frontal radiographs, the concept of the three cardiac mogul shadows comprising the left cardiomediastinal silhouette needs to addressed. The superior most mogul reflects the aortic knob. Inferiorly, the left hilum (pulmonary artery) comprises the second mogul. While not normally present, the third mogul arises when there is enlargement of the left atrial appendage. This enlargement produces a conspicuous convexity along the normally concave left heart border (Fig. 11A).

The aorticopulmonary window refers to the concave space which is located immediately inferior to the aortic knob and just above the left pulmonary artery. Filling in or convexity of this space usually reflects either adenopathy or a mediastinal mass (Fig. 3B).

On the lateral radiograph (Fig. 7), the cardiac silhouette occupies the retrosternal region with the apex directly inferiorly toward the xiphoid process. Anteriorly, the right ventricle creates the anterior cardiac border. The left atrium forms the superior portion of the posterior aspect of the cardiac silhouette, with the mainstem bronchi immediately superiorly. The left ventricle forms the lower portion of the posterior margin of the heart shadow, with the diaphragm immediately below it. With sufficiently good inspiration, the posterior border of the inferior vena cava (IVC) may be visualized on well positioned lateral films (Fig. 7).

CARDIAC CHAMBER ENLARGEMENT

LEFT VENTRICULAR ENLARGEMENT

Enlargement of the left ventricle will result in an enlargement of the cardiac silhouette, producing a bulbous left cardiac apex which is displaced down and out on the frontal radiograph (Fig. 8). On the lateral projection (Fig. 9), the left ventricular shadow will extend toward the thoracic spine away from the posterior border of the IVC. Normally, the posterior edge of the left ventricular shadow should reside within two centimeters of the posterior edge of the IVC at a point two centimeters above

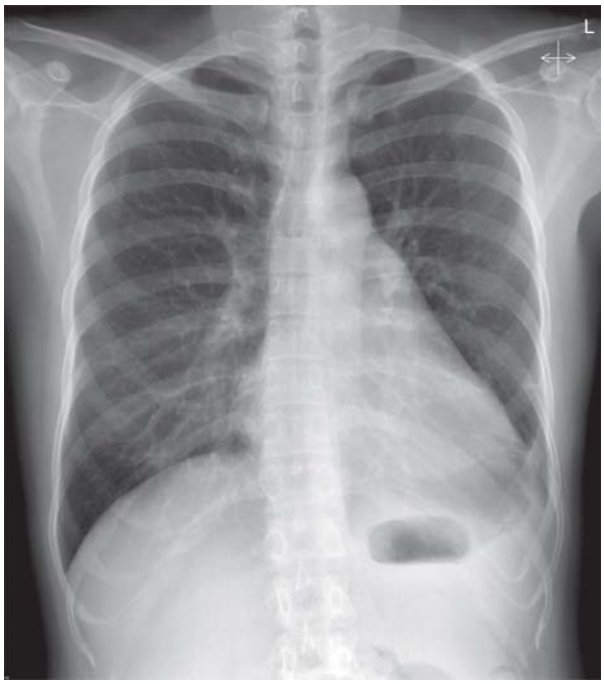


FIGURE 8: Left ventricular enlargement. PA chest film showing classic down and out configuration of the cardiac silhouette

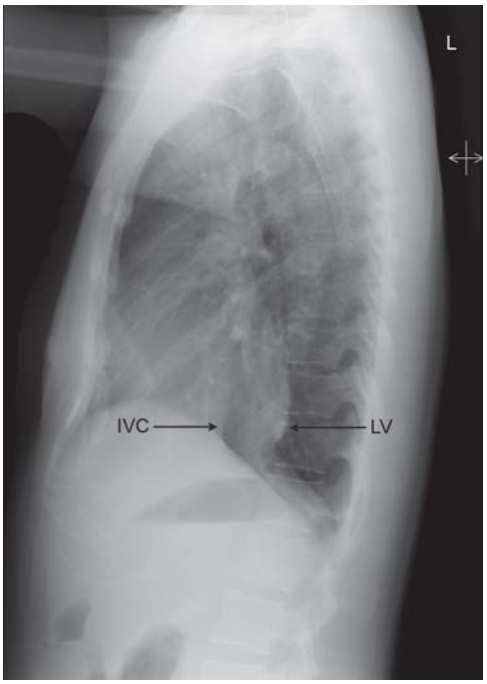


FIGURE 9: Left ventricular (LV) enlargement. Lateral film shows posterior displacement of the left ventricular shadow relative to the inferior vena cava (IVC) (arrows)

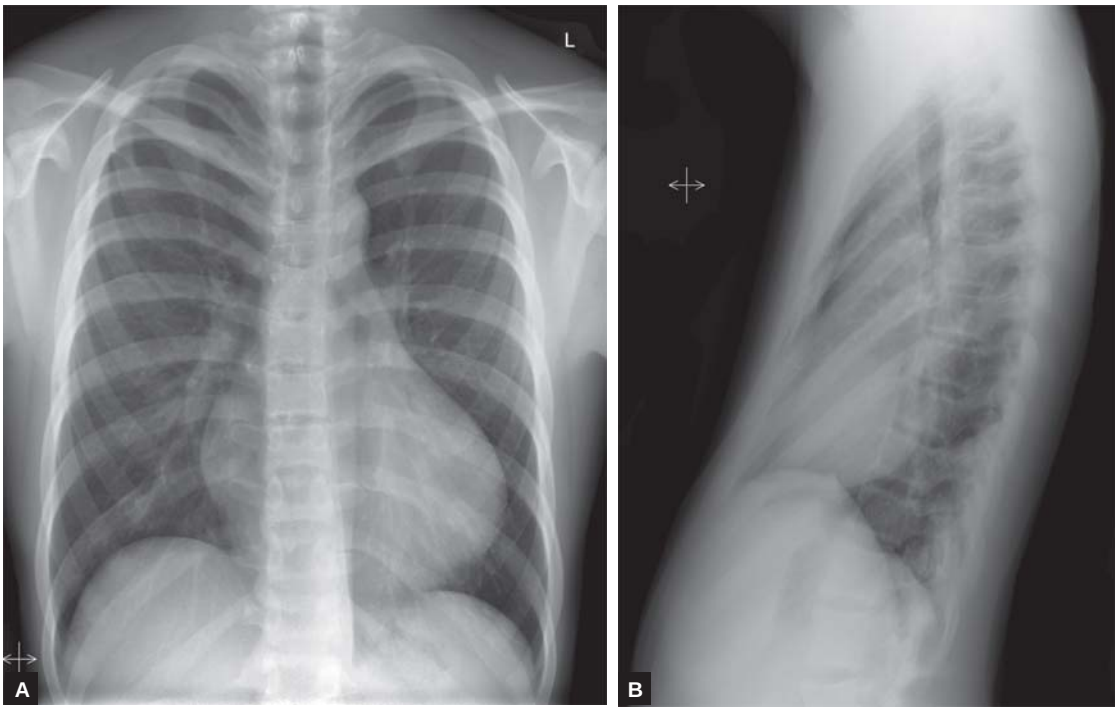
the diaphragm (Rigler's rule). With left ventricular hypertrophy, cardiac morphology is generally preserved with no apparent increase in the overall size or change in the configuration of the left ventricle.

RIGHT VENTRICULAR ENLARGEMENT

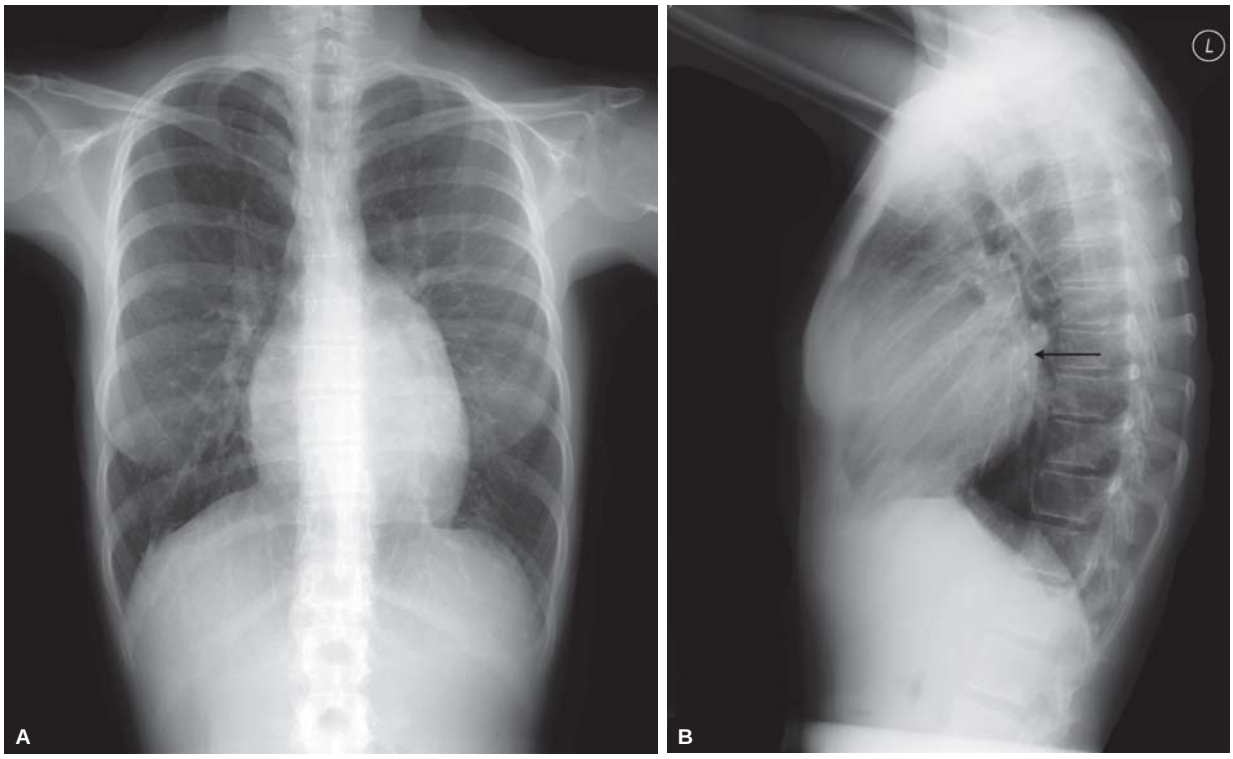
Right ventricular enlargement, although uncommon, is manifested by uplifting of the ventricular apex on frontal projections producing the "boot-shaped" heart or *coer en sabot* configuration. On the lateral film there should be corresponding encroachment toward the sternum with "filling in" the retrosternal clear space (Figs 10A and B).

LEFT ATRIAL ENLARGEMENT

Left atrial/appendage enlargement will result in the formation of the third mogul as described above (Figs 11A and B).



FIGURES 10A AND B: Right ventricular enlargement. PA and lateral films in patient with Tetralogy of Fallot. (A) The PA film shows the upturned ventricular shadow producing the "*coer en sabot*" or boot shaped heart. (B) The lateral film shows filling in of the retrosternal region by the enlarged right ventricle



FIGURES 11A AND B: Left atrial enlargement. (A) PA and (B) lateral chest films showing classic cardiac silhouette of left atrial dilatation. On the PA film, there is bulging of the left cardiac border (third mogul). On the lateral film, note the conspicuous posterior displacement of the left atrial shadow (arrow). Also see Figure 25

With progressive atrial enlargement the left atrial shadow may extend across midline to produce a second shadow overlapping upon the right atrium (double density sign) (Figs 25A and B).

Soft tissue fullness in the subcarinal region which reflects enlarged atrial volume can occasionally produce uplifting of the left mainstem bronchus. On the lateral radiography, the posterior heart border will appear protruberant (Fig. 25B).

RIGHT ATRIAL ENLARGEMENT

Right atriual enlargement often goes relatively unnoticed, but will result in lateral displacement of the right cardiac border on the frontal radiograph (Fig. 12). A sausage shaped density may become more evident as the atrial appendage enlarges.

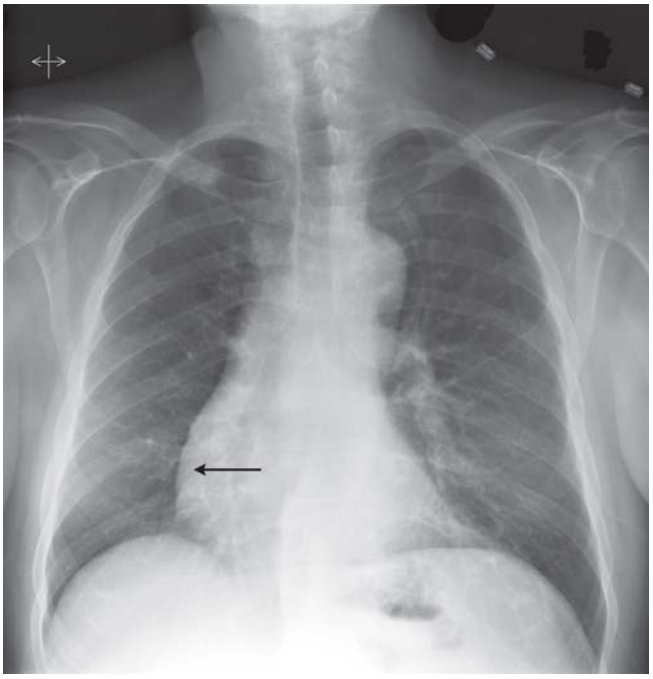
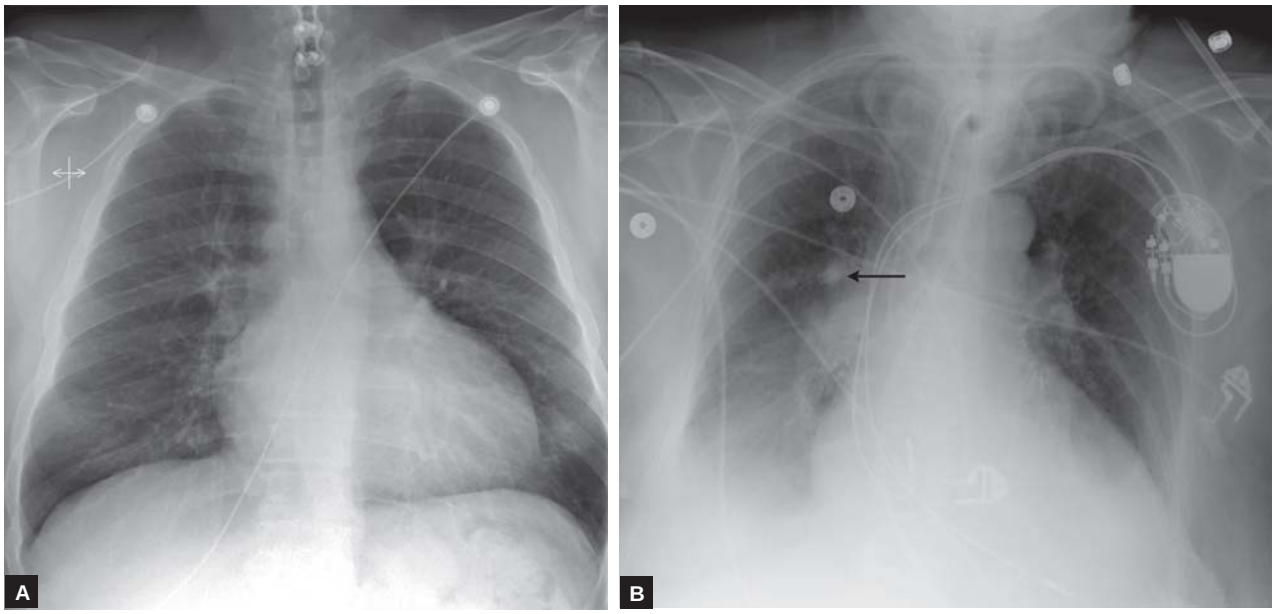


FIGURE 12: Right atrial enlargement. PA chest film showing lateral prominence of the right heart border (arrow) in patient with tricuspid insufficiency

RADIOGRAPHIC MANIFESTATIONS OF CONGESTIVE HEART FAILURE

Plain film radiography of the chest is an excellent modality to diagnose and measure the effectiveness of therapy in patients with congestive heart failure. In fact, it has been established that the characteristic stages of radiographic features of congestive heart failure on chest films correlate very well with hemodynamic measurements obtained with left atrial wedge pressures as determined with Swan Ganz catheterization.

The radiographic stages of congestive heart failure are well known, and relate to the physiologic changes and hemodynamic perturbations occurring along the capillary and venous regions of the pulmonary circulation. The physiologic factors that determine the quantity of extravascular fluid depend on several factors namely: intravascular hydrostatic pressure (promoting fluid escape from the intravascular space); plasma oncotic pressure and interstitial hydrostatic pressures (which acts to keep intravascular fluid within vessels) and interstitial oncotic forces (acting to pull fluid out of the intravascular spaces). Normally, these opposing forces result in a net positive fluid escape from



FIGURES 13A AND B: Cephalad redistribution of pulmonary blood flow in patient with mild left ventricular heart failure. (A) Note the increase in the size and conspicuity of the upper lobe vessels compared to normal. Also note the characteristic morphology of the heart reflecting left ventricular dilatation. (B) This figure shows the corresponding enlargement of the upper lobe arteries (arrow) with corresponding A:B ratio of 3:1. On both films, the vessel definition remains sharp

the intravascular spaces into the interstitum which is in turn returned to the central venous circulation via the lymphatics. In heart failure, as hydrostatic forces within the pulmonary arterial circulation increase, there are corresponding and predictable radiographic changes which reflect the increase of both increased pulmonary blood flow and eventual transudation of fluid out around the arterioles and capillaries into the perivascular interstitum and lymphatic spaces. The following discusses the characteristic radiographic manifestations of congestive heart failure as they correlate with capillary wedge pressures.

As was previously discussed, the normal pulmonary vascular pattern on upright chest radiographs exhibit the expected gravitational effects of increased blood flow to the lower lobes. Again, this can best be demonstrated by inverting the chest film upside down, which shows the conspicuous increase expected in the pulmonary vascular markings in the lower lobes compared to the upper lobes. It is also important to recognize that the pulmonary vessels should themselves be normally sharply defined throughout both lungs. Close inspection of the pulmonary arteries in the perihilar regions also reveal that the size of the pulmonary arteries closely approximate the caliber of the adjacent bronchus, both of which travel together in a common adventitial sheath. This relationship, known as the A:B ratio is essentially 1:1 (Fig. 4). In the earliest stages of cardiac decompensation where there is only a modest increase in left atrial wedge pressures above normal (16–18 mm Hg), chest radiographs will demonstrate an increase in the size of the pulmonary vessels in the upper lobes reflecting shunting of blood flow to the upper lobes (Fig. 13A). This recruitment phenomenon, known as cephalad redistribution, results in disruption of normal A:B ratio whereby the caliber of the vessel becomes larger than the adjacent bronchus (Fig. 13B).

Despite this redistribution, the pulmonary vessels should remain sharply defined as should the associated bronchus. This recruitment of upper lobes vessels is felt to reflect a physiologic attempt to improve gas O_2-CO_2 exchange, i.e. oxygenation.

In the second stage of congestive heart failure, corresponding to wedge pressures around 18 mm Hg, there is enough intravascular hydrostatic force at the venule side of the capillary to increase or drive fluid out into the interstitial spaces surrounding the artery and bronchus. When this occurs, the increase in interstitial fluid essential creates a partial masking or silhouetting of the vessels which is known as vascular congestion (Fig. 14).

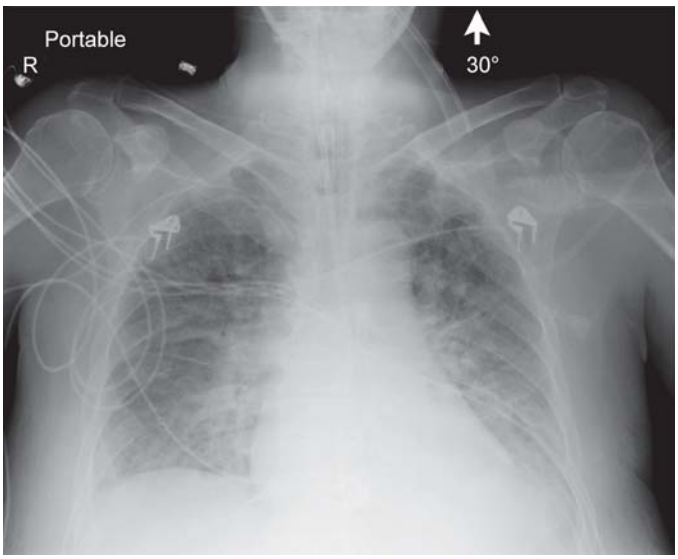


FIGURE 14: Pulmonary vascular congestion. AP radiograph of the chest showing indistinct margins of the pulmonary vasculature reflecting perivascular edema. Also note the fluid around the bronchi producing peribronchial cuffing

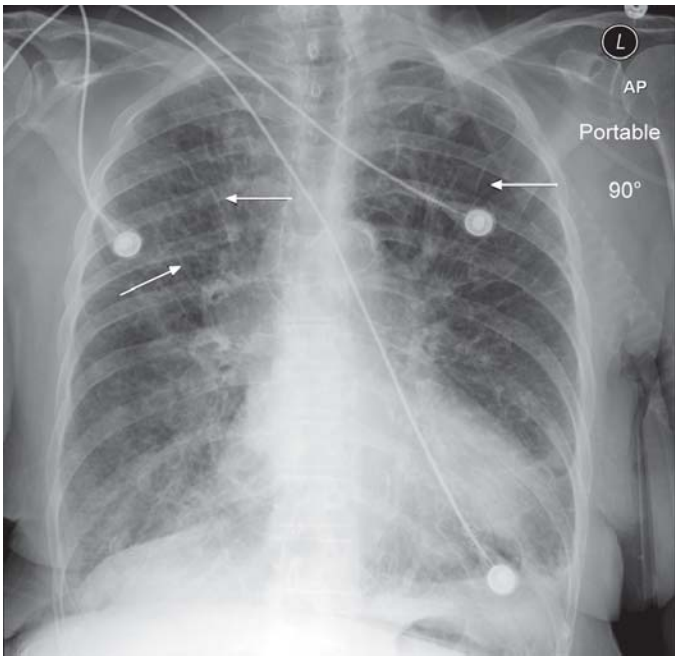


FIGURE 15: Interstitial edema. PA radiograph of patient in moderate congestive heart failure showing Kerley A (arrows) and parallel Kerley B lines in the lung bases reflecting interstitial edema

Similarly, the increase in interstitial fluid surrounding to the airways produces a blurring of central perihilar vessels, and with time, a collar of haze may develop resulting in bronchial cuffing. Both of these observations collectively indicate an increase in interstitial fluid. It should be pointed out that in itself, peribronchial cuffing can also occur with bronchial inflammation, so if observed alone, peribronchial cuffing is not specific for early heart failure.

With further increases in vascular hydrostatic pressures, and as progressively more fluid accumulates in the interstium of the lungs, fine linear shadows develop which are known as Kerley lines (Fig. 15). Radiographically, Kerley lines represent thickening (edema) of the intralobular septae that surround the secondary pulmonary lobule. Normally invisible on chest films, these septae histologically represent a part of the connective tissue supporting infrastructure of the lungs in which course the pulmonary veins and lymphatics. In congestive heart failure, the development of septal lines, which reflect both interstitial fluid and augmentation of lymphatic flow, become radiographically visible as either long linear shadows emanating out into the middle para-central regions of both lungs (Kerley A lines) (Fig. 15) or as parallel shorter subpleural lines (Kerley B lines) running perpendicular to the pleural surface (usually in the midle and lower lung zones regions). Kerley C lines, which are believed to represent summation of Kerley B lines, typically are found in the lower lung zone regions but are more central, slightly longer and much less common than B lines. When present, Kerley lines should be identified in both lungs and generally should be symmetric in distribution. Kerley lines develop with modest elevations of left atrial wedge pressures (20–22 mm Hg). One must also recognize that other etiologies capable of elevating the intravascular hydrostatic pressures will similarly produce interstitial edema separate from left heart failure, namely fluid overload, lymphatic blockage, left heart obstructive lesions (mitral stenosis and atrial myxoma) and pulmonary embolic disease. Renal failure and hypervolemia may also produce interstitial edema both through an increase in hydrostatic pressure and decreases in plasma oncotic pressures.

With further increases in intravascular hydrostatic pressures, typically corresponding following the development of interstitial edema, accumulation of fluid in the pleural spaces bilaterally (pleural effusions) may occur, and depending on the degree of intravascular hydrostatic elevation, range from small to moderate in size.

In cases of significant elevations of hydrostatic pressures, (wedge pressures greater than 25 mm Hg), after the interstitial space is saturated and no longer capable of accommodating additional fluid, migration of fluid occurs into the lower pressure environment of the alveoli and airways. Once this occurs, chest radiographs will exhibit the classic perihilar haze or batwing airspace changes of pulmonary edema. Again, radiographically this phenomenon should be bilateral, and characteristically symmetric in distribution. In cases of severe heart failure, the edema may become generalized resulting in uniformly opaque lung tissue (Fig. 16). In cases when there is an abrupt massive rapid elevation of intravascular hydrostatic pressures, the chest radiograph may progress directly into frank pulmonary edema without a significant or appreciable interstitial phase. Pleural effusions are common at this stage due to significant accumulations of edema within the subpleural regions of the lungs.

The concept of the vascular pedicle needs to be addressed when evaluating radiographs for heart failure as it provides ancillary information regarding the circulating blood volume. The vascular pedicle essentially refers to the conglomerate radiographic shadows encompassing both the venous and arterial circulation within the mediastinum. Since the contour of the right paramedian mediastinal shadow is largely composed of large compliant mediastinal veins, i.e. SVC and azygous vein, widening or narrowing of this border effectively conveys changes in intravascular volume. The vascular pedicle width is determined on frontal radiographs by drawing a line across the

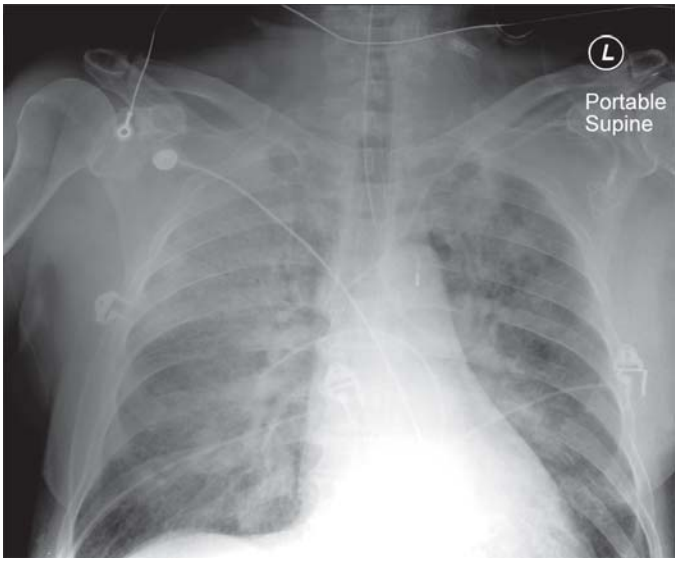


FIGURE 16: Pulmonary edema in patient with severe congestive heart failure due to acute myocardial infarction

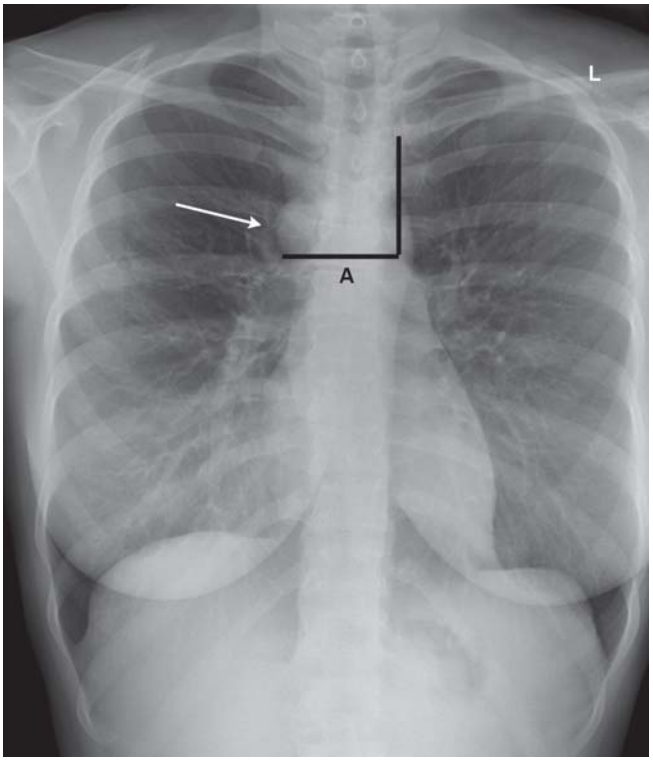


FIGURE 17: Vascular pedicle. The assessment of the vascular pedicle can easily be determined on PA chest radiographs by drawing a horizontal line from the junction of the SVC and right mainstem bronchus to a point drawn perpendicular from the left innominate artery. The horizontal line (A) represents the vascular pedicle which should be normally around 5 cm in length

mid portion of the mediastinum extending from where the right mainstem bronchus crosses the SVC, to a point intersecting a vertical line drawn the origin of the left brachiocephalic artery (Fig. 17). A normal vascular pedicle is around 5 cm. The actual measurement of the pedicle width is not as important as are *changes* in the width on serial radiographs. Widening of the vascular pedicle width between comparable radiographs (i.e. AP vs PA films) provides useful information indicating an increase in intravascular volume, and/or an increase in right atrial pressure. Similarly, decreases in the pedicle width are seen in patients with volume depletion, or those responding to diuretic therapy. In similar fashion, the width of the azygous vein (normal = 1 cm) as noted on frontal projections also provides clues as to changes in circulating blood volume, and right atrial pressures, similar to the vascular pedicle width. As such the serial changes or increases in both the vascular pedicle width and azygous venous diameter on radiographs provide diagnostic evidence of fluid balance (acute increase relating to hypervolemia, or elevated right heart pressures, i.e. right heart failure.

These observations hold important clues when evaluating radiographs in patients with heart failure. In patients with acute left heart decompensation (no predecedent heart disease) there is usually not a corresponding increase in the vascular pedicle width despite the presence of frank pulmonary edema. In contrast, those patients with chronic left heart failure, where there is usually an increase in intravascular volume due salt and water retention secondary to impaired renal perfusion. In patients with right heart decompensation, there is usually an increase in both the vascular pedicle width and azygous venous diameters without the corresponding pulmonary vascular changes of left heart failure. These changes reflect the increase in the volume of venous blood secondary to the failing right heart. In cases of acute biventricular failure, one should expect to see both the pulmonary manifestations of acute failure as well as concomitant widening of the pedicle and azygous venous diameter.

The interpretation of the radiographic changes characteristic of left sided heart failure can be further refined to assist in differentiating between acute and chronic left ventricular failure. In acute (rapid) heart failure, it is common not only to see a normal vascular pedicle width along with a normal cardiac silhouette despite the presence of frank pulmonary edema. In these cases, the normal or narrowed vascular pedicle reflects a diminished intravascular fluid balance due to the development of edema within the lungs. Additionally in cases of very rapid left ventricular decompensation (acute infarction), the distribution of edema within both lungs is often para-central (batwing edema), and may develop without any radiographic evidence of interstitial edema and peribroncial cuffing. Redistribution of pulmonary blood flow also is usually conspicuously absent in cases of rapid left heart failure. Pleural effusions generally are uncommon as well secondary to an absence of sup-pleural pulmonary edema. In cases of chronic left heart failure, cephalad redistribution is much more common, likely a physiologic response of regional impaired O_2-CO_2 exchange in the lower lobes due to microscopic edema along the capillary-alveolar interface as well as reflex vasoconstriction of the lower lobe pulmonary veins to augment left atrial stroke volume. The conspicuous absence of interstitial edema in patients with chronic compensated left ventricular dysfunction may also be explained by augmentation of pulmonary lymphatic drainage that develops over time to facilitate the removal of interstitial edema from the lungs.

CARDIAC CALCIFICATIONS

Evaluation of unusual of calcifications overlying the cardiac silhouette may provide important clues about specific disease processes which may not be clinically suspected. Most importantly, the identification of coronary calcium indicates severe, advance atherosclerosis, which in younger patients suggests possible abnormalities of blood lipid levels, i.e. hypercholesterolemia (Fig. 18). Due to the limitations of resolution of coronary calcium on chest radiographs, the identification of coronary calcium implies significant disease with an associated higher likelihood of significant stenosis, and portends even more significance when discovered in patients with acute chest pain syndromes. Linear myocardial calcifications may be encountered in patients with a history of prior myocardial infarction (Figs 19A and B), and if protuberant, may indicate associated formation of ventricular aneurysm (Figs 20A and B). Typically, the protuberant thin-walled calcified aneurysms at the apex of the left ventricle are true aneurysms, while those residing along the posterior aspect of the left ventricle are most commonly pseudoaneurysms.

Valvular calcifications when identified on chest films generally are associated with significant valvular stenosis.

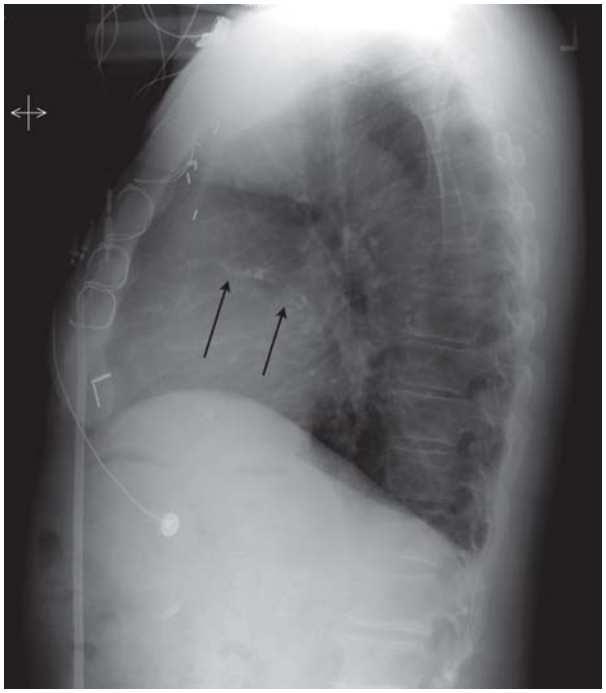


FIGURE 18: Calcification of the left anterior descending coronary artery (arrows)

Mitral annular calcifications are commonly demonstrated on radiographs occurring on 10% of adult patients, usually appearing as an incomplete ring of beaded appearing calcification (Figs 21A and B). Usually, mitral annular calcifications due to atherosclerosis in the elderly are incidental and of no clinical significance. Although there is little correlation with the extent of annular calcifications and likelihood of mitral valve disease, mitral annular calcifications are seen in 35–40% of patients with mitral stenosis. Generally, the more severe the annular calcification, the greater likelihood of associated mitral valve disease.

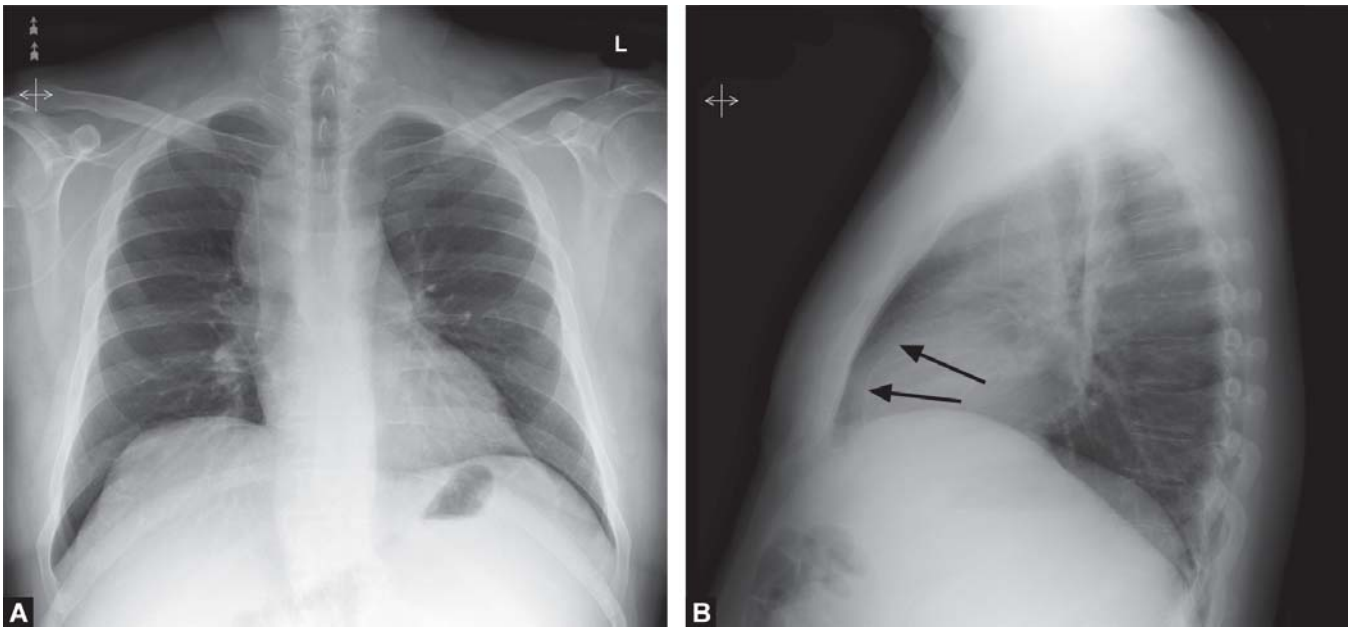
Pericardial calcifications (Figs 22A and B), usually stemming from either prior pericarditis or hemopericardium, may be associated with hemodynamic features of pericardial constriction, and as such may warrant further evaluation of cardiac function with echocardiography as well as ventricular compliance by assessment of diastolic filling. Conglomerate calcifications within the cardiac chamber can reflect either intracardiac thrombus, or rarely calcification within intracardiac tumors (fibroma, myxoma and teratoma).

ACQUIRED VALVULAR HEART DISEASE

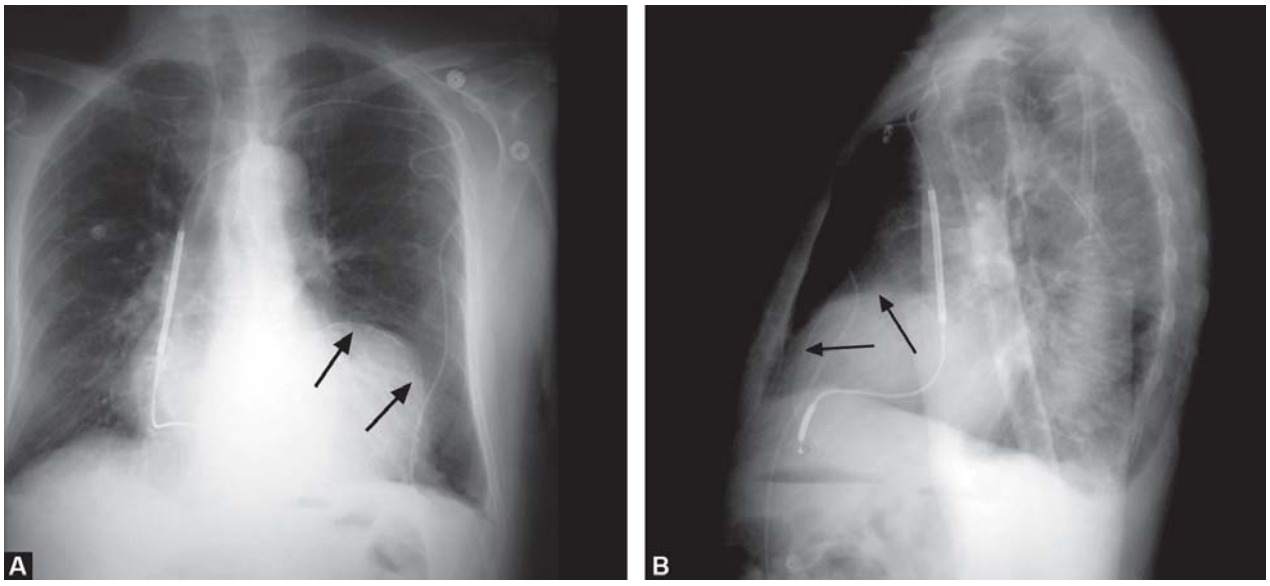
Aortic and mitral valve disorders are the most commonly encountered forms of valvular heart disease in adults and both have characteristic radiographic manifestations. Characteristically, most of these disorders stem from either congenital structural valvular abnormalities or rheumatic heart disease. Tricuspid and pulmonary valve disorders in adults are overall less common and less commonly are associated with cardiovascular changes on radiographs.

AORTIC STENOSIS

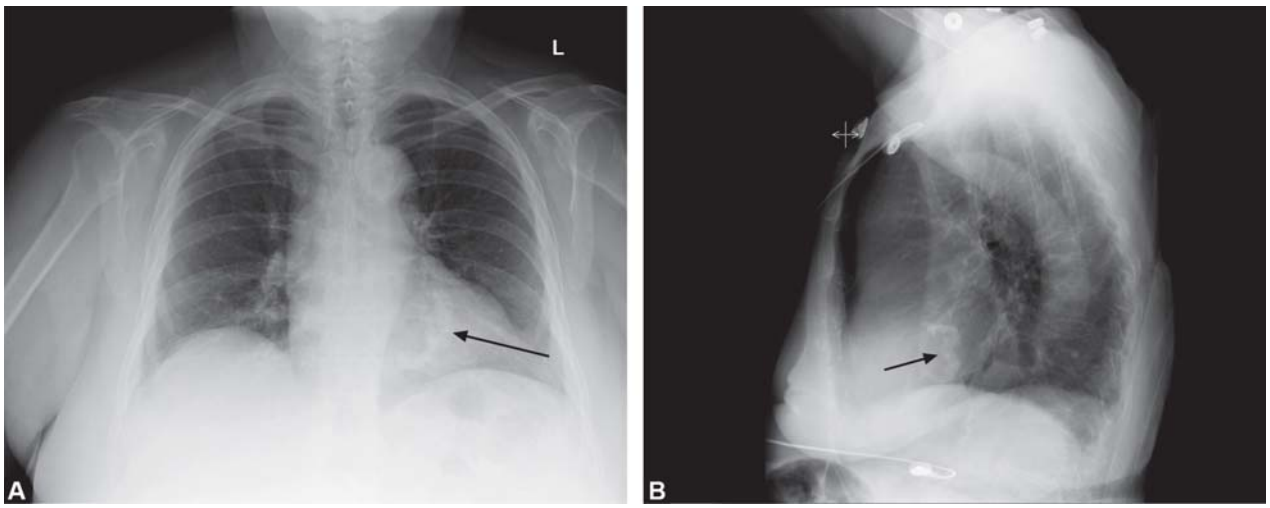
The most common form of congenital heart disease is the biscuspid aortic valve, with a prevalence of 1–2% in the general population. Responsible for most all cases of aortic stenosis in adults, the severity of the hemodynamic derangements across the aortic valve coincide with the degree of associated thickening and/or calcification of the aortic valve leaflets. Other causes of aortic stenosis which include degenerative aortic valve disease and rheumatic heart disease are likewise are associated with similar valvular changes, although the presence of valve calcium is less common in these entities. The typical radiographic feature of aortic stenosis which is related to the severity of stenosis is poststenotic dilatation of the ascending thoracic aorta due to the jet effect of blood exiting the stenotic valve (Figs 23A and B).



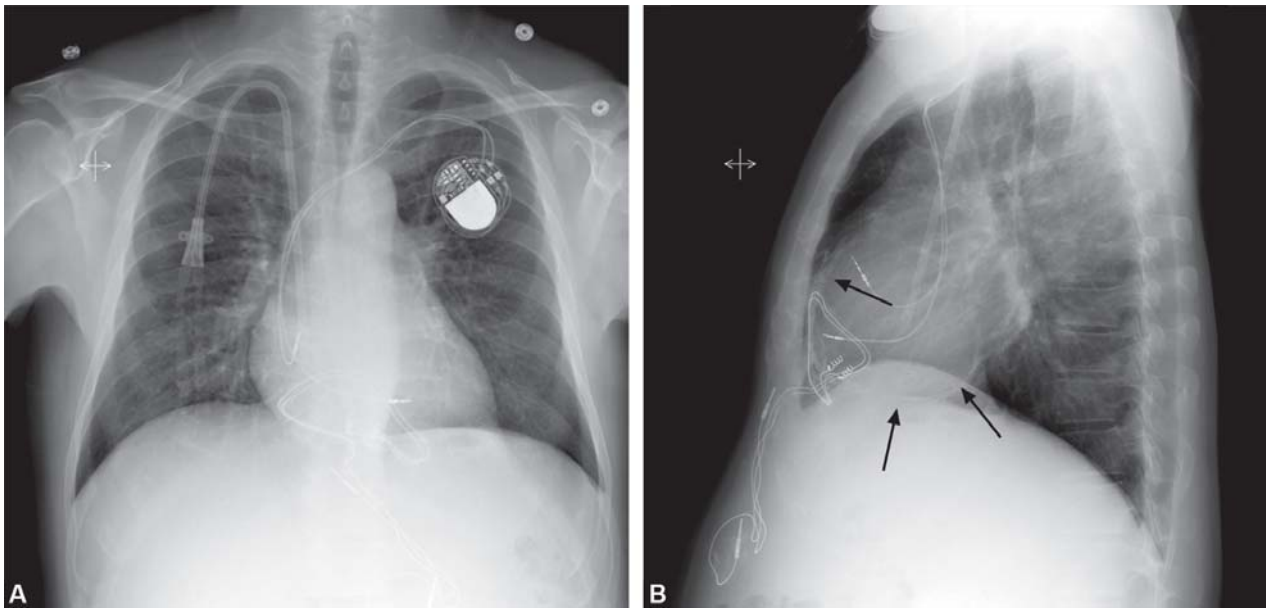
FIGURES 19A AND B: (A) Myocardial calcification in patient with prior myocardial infarction. (B) Note on the lateral projection a fine linear zone of calcification within the myocardium (arrows)



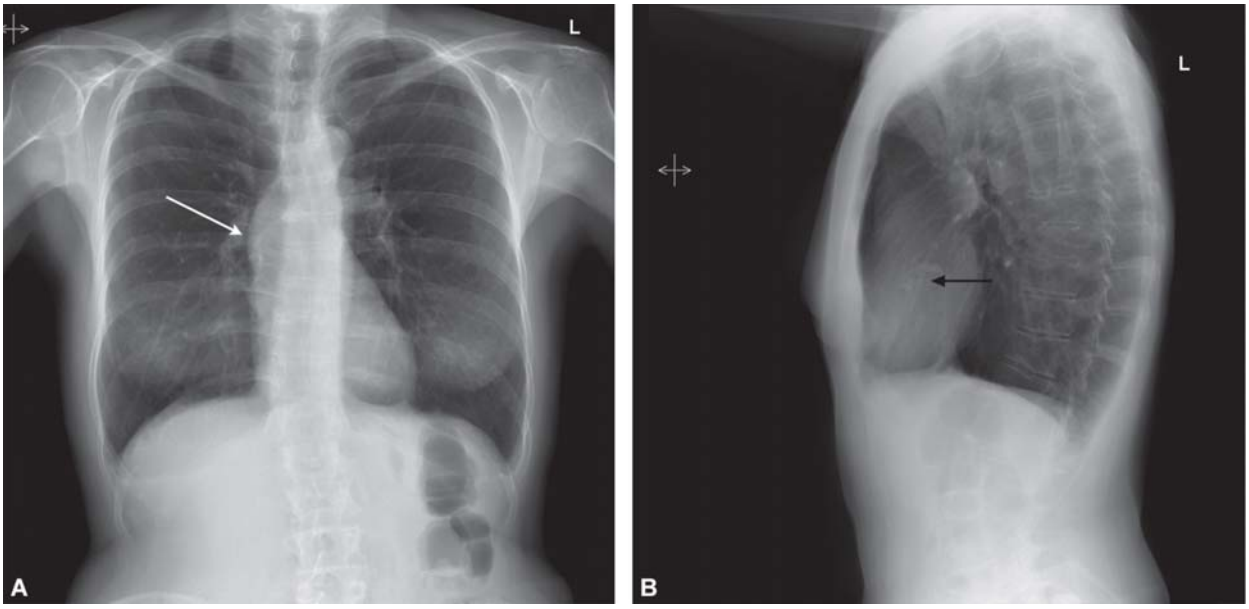
FIGURES 20A AND B: Left ventricular aneurysm. (A) PA and (B) lateral chest films showing linear calcification along the border of a large left ventricle aneurysm (arrows)



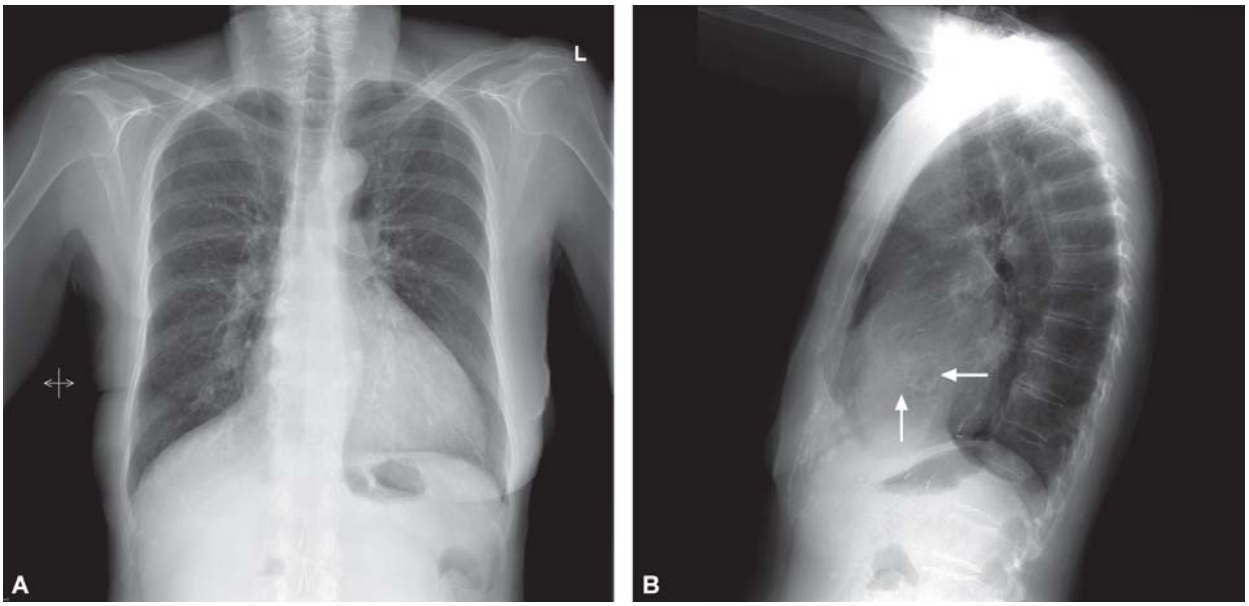
FIGURES 21A AND B: Mitral annular calcification. (A) PA and (B) lateral chest films showing the beaded calcium within the mitral valve annulus (arrows)



FIGURES 22A AND B: (A and B) Pericardial calcification. Lateral chest film shows heavy calcifications along the pericardial surface (arrows)



FIGURES 23A AND B: Aortic stenosis. (A) PA film shows dilatation of the ascending thoracic aorta (arrow) without associated left ventricular dilatation. (B) Lateral film shows calcification of the aortic valve (arrow)



FIGURES 24A AND B: Aortic stenosis. (A) PA film shows characteristic changes in the cardiac silhouette reflecting left ventricular dilatation (failure). (B) Lateral film showing calcifications involving the aortic valve apparatus (arrows)

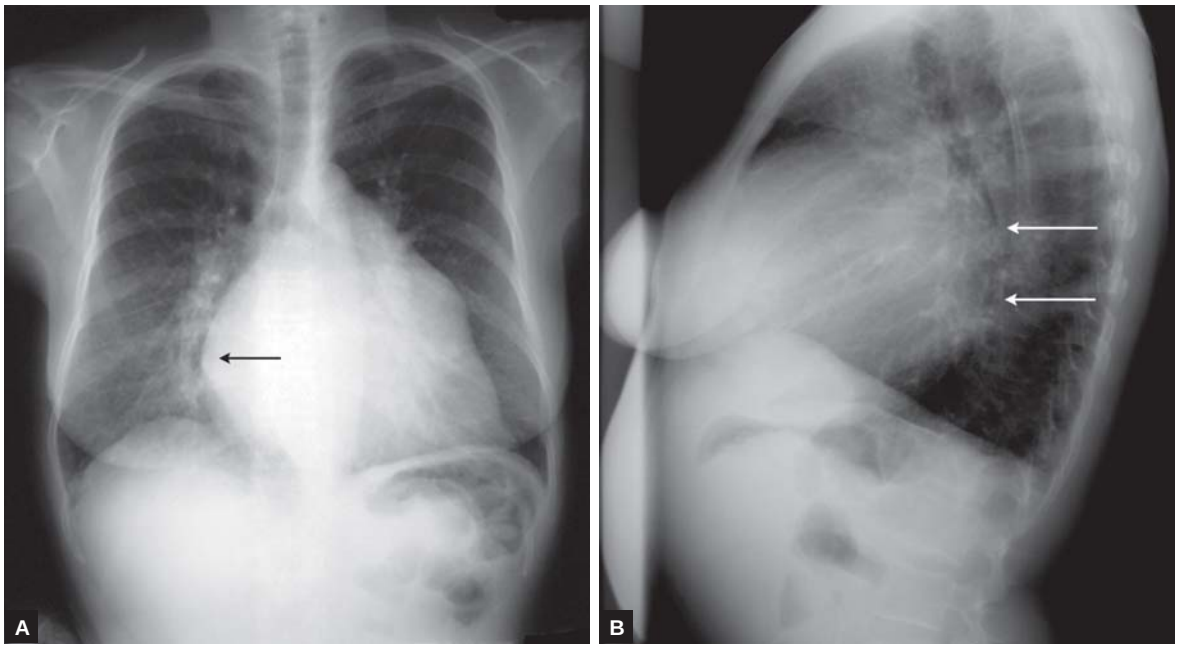
Usually the configuration of the heart appears normal. Not until left ventricular failure develops will there be radiographic changes in the heart shadow reflecting left ventricular enlargement which occurs late in the disease, if at all (Figs 24A and B). Left ventricular hypertrophy, in and by itself, is not associated with any morphologic changes of the cardiac silhouette on chest radiographs. When present, aortic valve calcifications, which are best identified on lateral radiographs, indicates significant valvular stenosis, and are most commonly seen in cases of biscuspid aortic stenosis (Figs 23A and B and 24A and B). The pulmonary vascular pattern in aortic stenosis is normal.

AORTIC INSUFFICIENCY

Aortic insufficiency in adults can be attributed to either aortic valve disease or disorders of the aortic root such as aneurysm or dissection. The radiographic manifestations of aortic insufficiency, like aortic stenosis, are related to both the severity and duration of the disease. Features of aortic insufficiency on chest films include both dilatation of the ascending thoracic aorta with associated left ventricular enlargement. Enlargement of the left atrium rarely occurs providing compentency of the mitral valve. In most cases the pulmonary circulation appears normal.

MITRAL STENOSIS

Most cases of mitral stenosis are a sequela of rheumatic fever. The radiographic manifestations of mitral stenosis coincide with the degree of the severity of the stenosis. Characteristically, radiographs will usually are diagnostic for this disease and demonstrate left atrial enlargement which can be marked in severe cases (Figs 25A and B). Severe stenosis at the mitral valve resulting in significant left heart obstruction may also



FIGURES 25A AND B: Mitral valve stenosis. (A) PA film shows radiographic findings of mitral valve stenosis including left atrial enlargement and pulmonary venous hypertension. The arrow points to the double density sign reflecting overlap of the left atrial shadow upon the right atrium. (B) The lateral film shows marked posterior bulging of the left atrial shadow (arrows)

produce radiographic changes of congestive heart failure as well as pulmonary arterial hypertension. Recurrent pulmonary edema in cases of long-standing mitral stenosis may result in deposition of hemosiderin with the lungs which radiographically appears as discrete punctate calcified pulmonary nodules, occasionally with associated areas of associated pulmonary fibrosis. Calcification of the mitral valve, annulus or the left atrium may also be detected on radiographs (Fig. 26).

MITRAL REGURGITATION

While associated with rheumatic heart disease, mitral valve insufficiency in adults is more commonly seen in mitral valve prolapse. Similar to mitral stenosis, chest films demonstrate marked left atrial enlargement with pulmonary venous hypertension. Frequently, there is a component of associated dilatation of the left ventricle as well, especially in long-standing cases. Occasionally in cases of severe mitral regurgitation, passive venous congestion with or without pulmonary edema may be encountered. Unilateral right upper lobe edema/hemorrhage secondary to the jet effect of regurgitant blood entering the right upper lobe pulmonary vein may also occasionally be encountered (Fig. 27). Patients, presenting with mitral insufficiency due to acute rupture of a papillary muscle, usually present with radiographic features of acute congestive heart failure without corresponding cardiomegaly.

PULMONARY VALVE STENOSIS

Pulmonary valve stenosis is generally a component of congenital heart disease and is an uncommon acquired valvular disorder in adult, resulting from fusion on the commissures. In any case, the typical radiographic feature of pulmonary stenosis is unilateral dilatation of the left pulmonary artery arising from the poststenotic jet effect of blood exiting the pulmonary valve (Fig. 28). Long standing cases may show associated enlargement of the right ventricular shadow.

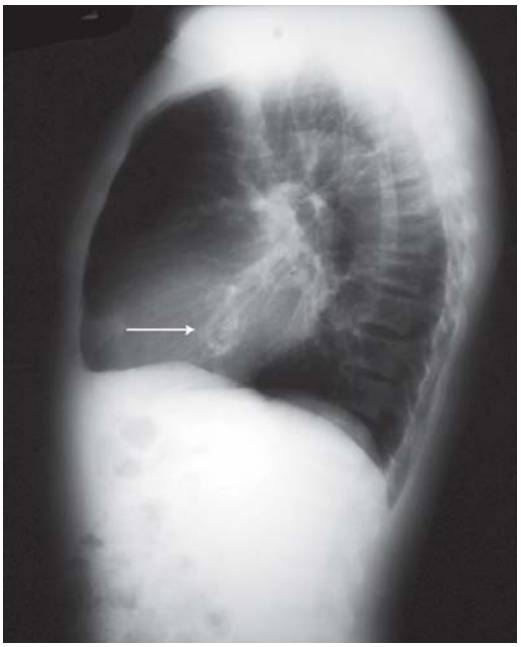


FIGURE 26: Mitral valve calcification. Lateral chest film showing extensive calcification of the mitral valve and annulus (arrow)

PULMONARY VALVE INSUFFICIENCY

Distinctly uncommon in adults, insufficiency of the pulmonary valve often is not associated with any specific morphologic changes of the cardiovascular structures on chest films other than occasional right heart enlargement.



FIGURE 27: Mitral valve insufficiency. PA chest film showing unilateral right upper lobe edema from severe mitral regurgitation in patient with acute papillary muscle rupture

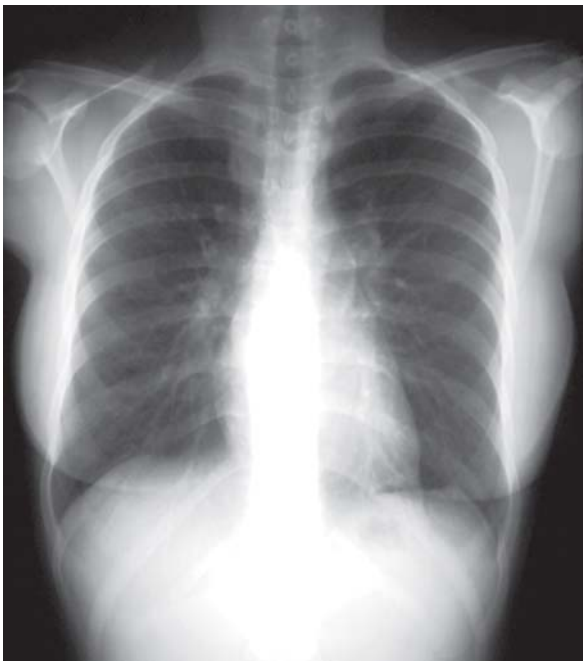


FIGURE 28: Pulmonary valve stenosis. PA film showing unilateral dilatation of the left pulmonary arterial trunk

TRICUSPID INSUFFICIENCY

In most cases of triscuspid insufficiency, there are no discernable radiographic changes suggestive of this disease. When severe, prominence of the right heart border reflecting right atrial enlargement occurs (Fig. 12). Associated widening of the vascular pedicle (especially SVC shadow) and dilatation of the azygous vein may also present indicating an increase in right atrial pressure.

PERICARDIAL DISORDERS

PERICARDIAL EFFUSION

It is important to realize that the heart shadow as demonstrated on plain films is composed of both the heart and the surrounding pericardial sac. As such, an apparent increase in the heart shadow may be due to either intrinsic cardiac chamber(s) dilatation or alternatively reflect accumulation of fluid in the pericardial space. While small pericardial effusions usually will go undetected by chest films, large amounts will alter the overall shape of the heart shadow resulting in a globular relatively featureless cardiac silhouette (aka water bottle configuration) (Fig. 29). The lateral film may show an opaque line (fat pad sign) along the ventral surface of the heart reflecting separation of visceral and parietal pericardial fat by the effusion. The absence of ancillary findings of congestive heart failure, such as pulmonary venous hypertension, may help differentiate a pericardial effusion from dilated cardiomyopathic heart (Fig. 30). A sudden or significant enlargement of the size of the

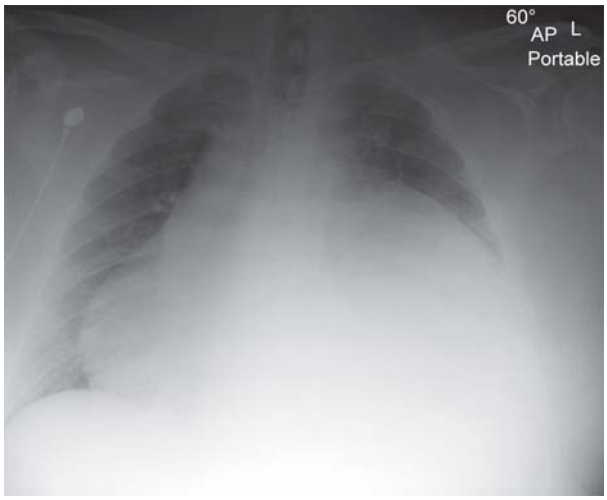


FIGURE 29: Pericardial effusion. PA chest films shows marked global enlargement (water bottle configuration) of the cardiac silhouette secondary to a large pericardial effusion

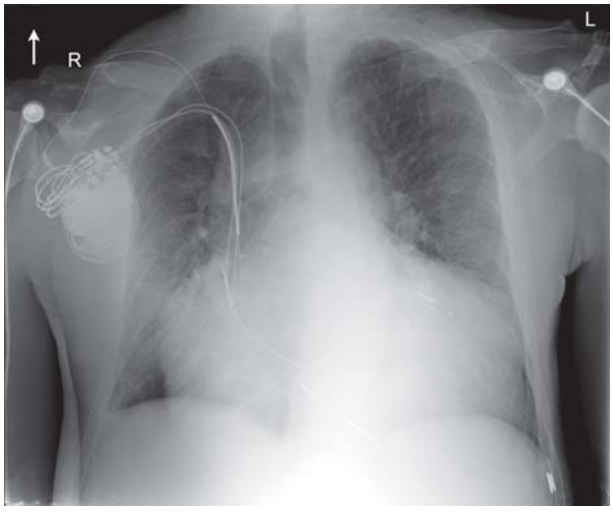
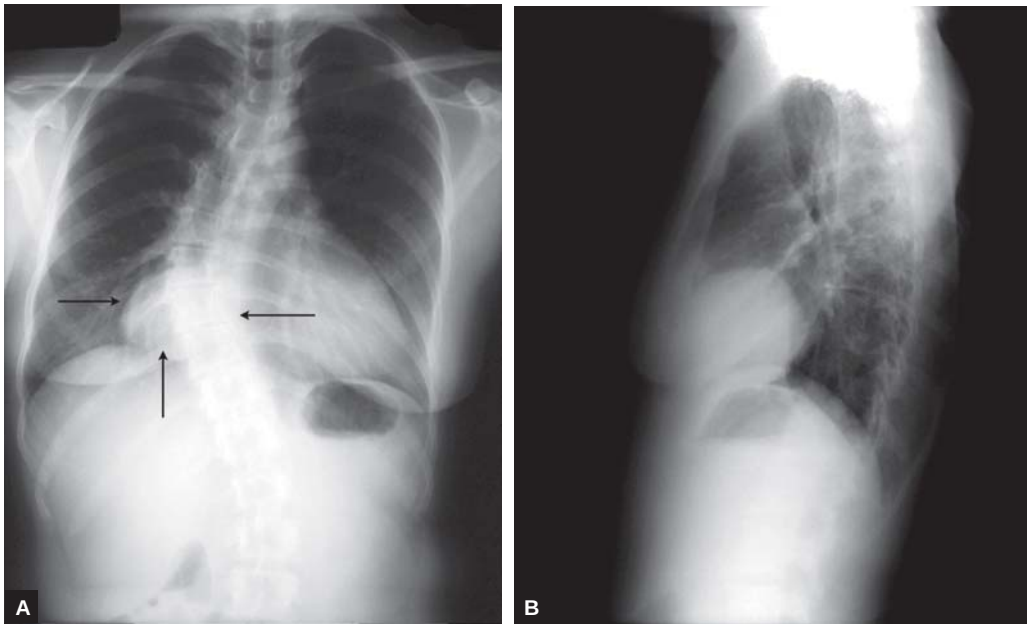


FIGURE 30: Dilated cardiomyopathy. PA chest radiograph showing global enlargement of the cardiac silhouette. Note the similar cardiac configuration to Figure 29



FIGURES 31A and B: Pericardial cyst. (A) PA and (B) lateral chest films showing sharply demarcated pericardial cyst residing in the right cardiophrenic angle (arrows)

heart shadow on serial chest films is an important radiographic observation that should suggest a pericardial effusion rather than intrinsic heart disease. Unfortunately, too many times patients' films have been erroneously interpreted as cardiomegaly (failing heart) only to discover on further evaluation that the heart was entirely normal but enveloped within a large pericardial effusion.

PERICARDIAL CYSTS

Pericardial cysts present radiographically as sharply demarcated mass-like opacities usually residing immediately adjacent to the heart, and are usually an incidental discovery in asymptomatic patients. Most commonly residing in the region of cardiophrenic angles, more so on the right side, these cysts are usually several centimeters in diameter (Figs 31A and B). Once discovered, computed tomography or magnetic resonance imaging scans can provide confirmation of the diagnosis by demonstrating the characteristic morphologic features of these cysts.

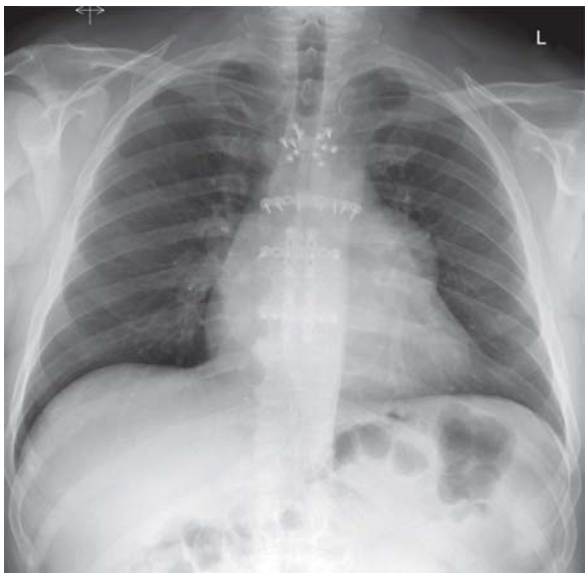


FIGURE 32: Absence of the pericardium. PA chest radiograph showing herniation of the left atrial appendage in patient who had recently undergone coronary bypass surgery. Note the focal bulge along the left heart border. Similar findings would be expected in congenital absence of the pericardium

CONGENITAL ABSENCE OF THE PERICARDIUM

Congenital defects of the pericardial sac, like pericardial cysts, are usually an incidental finding in either children or adults. The pericardial defect may be focal, partial or complete. Left-sided absence, the most common variety, occurs in 55% of the cases of congenital absence of the pericardium. Radiographically, these pericardial defects produce unusual changes in the shape of the cardiac silhouette, resulting in focal bulge-like contour changes reflecting herniation of cardiac structures such as the left atrial appendage (Fig. 32). Radiographic features of complete absence of the pericardium are leftward displacement of the cardiac silhouette without a corresponding shift of the mediastinum.

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Chapter 12

Electrocardiogram

Donald Brown

Chapter Outline

- Basis of Electrocardiography
- Component Parts of the Electrocardiogram
- Lead Systems Used to Record the Electrocardiogram
- Common Electrode Misplacements
  - Left Arm
  - Right Leg Electrode
- Other Lead Systems
  - A Systematic Way of Looking at the Interpretation of the Electrocardiogram
- Identification of Atrial Activity
- Characterization of QRS Complex
- ST-T Wave Abnormalities
- The "U" Wave
- The QT Interval
  - Abnormalities Suggesting Right or Left Atrial Enlargement, Dilatation or Hypertrophy

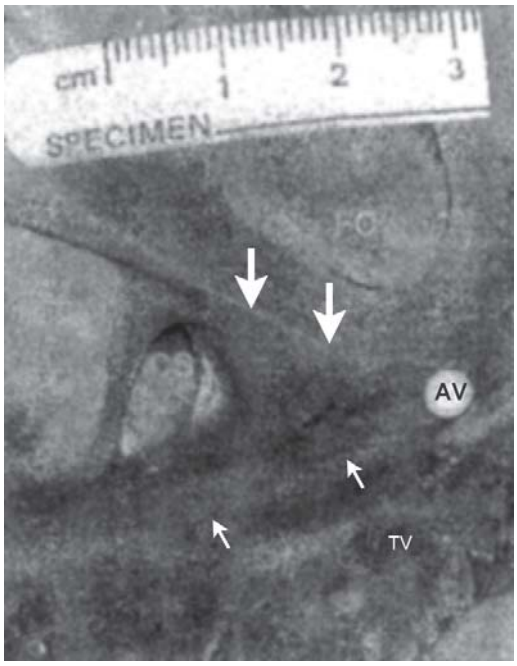
INTRODUCTION

The electrocardiogram remains one of the most valuable, most readily available and relatively least expensive laboratory tools. Its accurate interpretation is absolutely critical to patient care. While computer assisted interpretation of the 12 lead electrocardiogram is almost universally available, the computer based interpretation should never be assumed to be accurate. In addition rhythm strips off of monitors do not usually have computer based interpretation. Therefore, the clinician's ability to interpret accurately a 12 lead electrocardiogram and a rhythm strip is absolutely crucial to patient care.

BASIS OF ELECTROCARDIOGRAPHY

The electrocardiogram in its most basic sense represents the recording of electrical potentials from the heart projected on to the body surface and fed into a galvanometer set up as a voltmeter. The electrical potentials are produced by depolarization and repolarization of the atrial and ventricular myocardial cells of the heart. The basic principle is that as a set of cells depolarize the negative charge of the interior of the cell relative to the exterior is reversed as channels open to allow ions to flow out of the cell to produce an interior now more positively charged relative to the exterior. As this process moves longitudinally along a line of cells in a direction toward the exploring electrode of a voltmeter, an upright or positive deflection is produced. As a repolarizing wave moves in the same direction along the same longitudinal path, a negative deflection is inscribed by the voltmeter.

As is well appreciated, the heart's activation normally begins with the discharge of the sinoatrial node located in the right atrium beginning just below the superior vena cava. This discharge is of such a tiny magnitude that the electrocardiogram cannot record it. Nevertheless this leads to the depolarization of the atrial musculature from the high right atrium, over the right atrium and over to the left atrium creating what has been designated as a p wave. Under normal circumstances, this depolarizing wave then moves from the atrial chambers and passes on to the discrete conduction pathways connecting the atrium to the ventricular musculature, specifically through the atrioventricular (AV) node, then through the common or His bundle, and then out simultaneously through the right and left bundle branches to activate the ventricular musculature. The AV node is located at the base of the atrial septum on its right atrial side. Specifically it is located at the apex of "Koch's triangle". The apex of this triangle is formed by the annulus of the tricuspid valve's septal leaflet and Todaro's tendon, a structure that runs from the rostral portion of the coronary sinus downward to the central fibrous body ("cardiac skeleton") of the heart. The base of the triangle is the orifice of the coronary sinus (Fig. 1). The depolarization then proceeds through the AV bundle (common bundle or bundle of His) that penetrates the dense connective tissue of the central fibrous body and runs down along the right ventricular side of the membranous interventricular septum. The common bundle then bifurcates into the right and left bundles. The right bundle runs as a quite discrete bundle along a particularly prominent trabecular band known as the moderator band across to the base of the anterior papillary muscle of the right ventricle. The left bundle passes beneath the membranous part of the interventricular septum to reach the left side of the septum where it eventually divides into two broad bands. The anterior division is relatively more discrete and activates the anterior superior portion of the left ventricle. The much broader band is the posterior division that activates the posterior inferior portion of the left ventricle. All three bundles fan out as the Purkinje fibers of the interior of



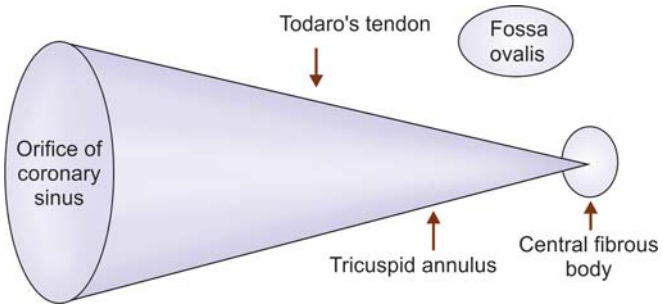


FIGURE 1: Illustration of Koch's triangle

the ventricles activating the ventricular musculature from the endocardial to epicardial surface.

The first portion of the ventricle to be activated is the ventricular septum. This begins via tiny fibers off of the left bundle spreading out as Purkinje fibers from about the midportion of the left side of the ventricular septum leading to depolarization of the septal musculature from its left ventricular side to its right ventricular side. Hence septal depolarization under normal circumstances accounts for a dominate portion of the initial portion of the depolarization of the ventricles recorded by the electrocardiogram and designated the QRS complex. Continued conduction in the right and left bundles is occurring simultaneously while this septal activation is occurring. The right and left bundles carry their impulse on to the interior of the free walls of the two ventricles as they spread out as cells identical to themselves known as Purkinje cells coating the endocardial surface of the two ventricles. This leads to depolarization of the entire ventricular muscles masses from endocardium to epicardium. Importantly these depolarizing waves spreads out in a spiral fashion that leads to excitation and thus contraction of the ventricular musculature from apex to base, thus wringing out the heart from apex to base toward the aortic and pulmonary valves.

The blood supply of the sinoatrial node and the portions of the conducting system noted above are important particularly from the standpoint of patients afflicted with ischemic heart disease and the electrocardiographic consequences of infarction. Estimates of the percentages of blood supply to portions of the conducting system vary from author to author and also vary according to the technique used, e.g. dissection, injection of the coronaries by various materials or by various modern imaging techniques. Percent estimates will also be affected by the numbers of heart examined, thus leading to variance based on sample size.

The supply to the sinoatrial node most commonly is from the right coronary artery, perhaps 60–70% of the time. Usually this arterial supply arises quite proximally from the right coronary artery, although occasionally distally. The supply is from the left coronary artery in about 10–30% of the cases. The artery supplying the sinoatrial node from the left coronary artery almost always arises from the proximal circumflex coronary artery, although it may rarely arises from the left main coronary artery or the quite distal circumflex artery. There appears to be a dual supply from both right and left coronary arteries about 5–10% of the time.

The blood supply to the AV node is almost always from an artery that arises at the U-turn of the artery that crosses the crux of the heart where the AV groove meets the proximal posterior interventricular groove. Relatively consistently the supply to this node is solely by the right coronary artery 80% of the time, solely from the circumflex artery in about 10% of the time and from both right coronary and left circumflex arterial sources about 10% of the time.

The His or common bundle most commonly has a dual blood supply from the AV nodal artery and a septal branch of the anterior descending coronary artery. The proximal portion of the right bundle may have a similar dual supply in perhaps 50% of the cases with most of the remainder of cases demonstrating supply only by the septal artery and in rare cases solely by the AV nodal artery. The portion of the right bundle along the moderator band appears to be supplied solely by a septal branch from the left anterior descending coronary artery. The supply to the proximal portion of the anterior half of the left bundle is similar to the right bundle in its blood supply, with about half of all individuals having a dual supply from the AV nodal artery and a septal branch of the left anterior descending, about half the individuals having a supply by just a septal branch only, and, uncommonly, an individual's supply by the AV nodal artery only. The posterior portion of the left bundle is supplied solely by the AV nodal artery about half the time with most of the remainder of the time by a dual supply from the AV nodal artery and a septal artery; occasionally the supply is solely by a septal artery.

Of importance to some of the nonischemic causes of conduction disturbances is the proximity of the His bundle and proximal bundles to the cardiac skeleton. This fibrous skeleton consists of the fibrous annuli of the four cardiac valves plus the membranous septum and the aortic intervalvular, right and left fibrous trigones. The dominant portion of the skeleton is the right fibrous trigone through which the His bundle passes. The left bundle as previously noted passes beneath the membranous septum.

COMPONENT PARTS OF THE ELECTROCARDIOGRAM

The depolarization of the atrial chambers produces waves called p waves. In a general any type of rhythm that involves depolarization of the atrial chambers could be called a p wave; however, certain waves typical of certain atrial rhythm disturbances have been given specific names such as flutter waves or fibrillatory waves. The repolarization of the atrial chambers is usually not evident on the surface ECG tracing. The summation of all the depolarizations of the ventricular chambers (a summation of phase 0 of all the action potentials of the ventricular myocardial cell depolarizations) is expressed as the QRS complex. By custom, a Q wave must be an initial deflection of a QRS complex and must be a negative or downward deflection. All upward or positive deflections are called R waves and negative deflections that are not the initial deflection of the QRS complex are called S waves. If there is more than one R or S wave in the complex, the second deflection is labeled R prime (R') or S prime (S'). Descriptively sometimes R or S waves may be represented by capital or lower case letters depending on the size of the deflection. The summation of the repolarization of the ventricular chambers (primarily the phase 3 of the action potentials of the ventricular myocardial cells) is represented on the ECG by the T wave. The deflection or direction of the T wave is generally in the same direction as the major direction of the QRS complex for most leads since the left ventricle, which by its mass dominates the formation of the QRS complex, depolarizes from the endocardium out to the epicardium but repolarizes from the epicardium inward to the endocardium. The T wave may be followed by a low voltage wave names the U wave. The origin of this wave remains in dispute.

LEAD SYSTEMS USED TO RECORD THE ELECTROCARDIOGRAM

As mentioned, the electrocardiogram is just the recording of cardiac electrical potentials from the body surface by a galvanometer set up as a voltmeter. The original system devised by Einthoven consists of the leads from the left arm, the right arm and left leg set up to compare the recordings from one extremity to a second extremity by feeding the recordings into the either side of the voltmeter. The three potential combinations have been designated as bipolar leads. As designed by Einthoven, lead I is the comparison of the left arm potentials versus the right arm potentials connected to the voltmeter so that an upright wave is recorded in lead I when the left arm's potential is positive relative to the right arm's electrical potential. Given the assumption that the Einthoven triangle for the three leads is an equilateral triangle, this means that lead I looks horizontally straight across from left to right (though the scalene triangle described by Burger and van Milaan more accurately depicts the geometry, Einthoven's triangle is so entrenched and so useful as to remain the conceptual framework for the limb lead system). Einthoven's second lead, lead II, consists of the comparison of the potentials on the left leg versus the right arm connected so that an upright deflection in lead II occurs when the left leg's potential is positive compared to the right arm's potential. Lead III is a comparison of the potentials from the left leg versus the left arm connected to the voltmeter so that this lead registers an upright deflection when the left leg's potential is positive relative to the left arm's potential. Thus the three leads create a triangle with three points of view separated by 60 degrees (Fig. 2). Kirchhoff's second law based on the conservation of energy states that the algebraic sum of the potentials around a closed path must be zero. This means that the electrical potential recorded in lead II is equal to the sum of the potentials recorded in leads I and III. This can perhaps be better visualized and understood by collapsing the three leads points of view so they intersect at a central points and thinking in terms of vector forces (Fig. 2). Viewed in this manner, all the vector forces in lead II are predicted by leads I and II.

Frank Wilson and his colleagues developed a system of recording electrical potentials from a single extremity compared to an "indifferent electrode" whose recorded potentials are minimal. The purpose was to record just the potentials from a given extremity representing each of the apices of Einthoven's triangle. They created the indifferent electrode by fusing the connections of each into a single central terminal. A 5,000 ohm resistor was placed between each extremity electrode and the fusion at the central terminal. The potentials from the exploring electrode from the right arm, left arm or left leg are compared by the voltmeter with this minimal potential from the central terminal lead. Electrocardiographic leads using this system are indicated by the letter V, hence VR, VL and VF. The connections to the voltmeter are such that an upright wave is recorded in VR when its potentials are positive. Emanuel Goldberger modified this V lead system as it pertains to the extremity leads in such a way as to increase the amplitude of the potentials recorded. Goldberger removed the resistors between the extremity connections and the central terminal. Goldberger further modified the "central terminal" by removing the connection of an extremity's electrode to the "central terminal" when that extremity's electrical potential was to be compared to the central terminal's minimal potential. This augmentation of the potential recorded from a given extremity is indicated by the "a" preceding the name of that lead, i.e. aVR, aVL and aVF (Fig. 2). Traditionally these augmented leads have been called the "augmented unipolar leads", a phrase from Goldberger's original paper in 1942. In truth, the term "unipolar" is improper in an electrical sense. Thus aVR is really the comparison of the electrical potential recorded from the right arm versus the averaged potentials recorded from the left leg and left arm. Thus aVR is right arm potential minus (i.e. versus) [left arm potential + left leg potential/2]. By the same reasoning as used to state that lead II's recording is predicted by the potentials recorded in leads I and III, lead aVR's recording is entirely described by "minus" the recording in aVL and "minus" the recording in aVF. From the standpoint of vectors for each lead, the potential recorded in any given lead is already described by any two leads equidistant from that leads point of view. For instance, lead aVF is completely described by the sum of lead II and lead III divided by 2.

The formulae usually presented then are as follows:

$$\text{II} = \text{I} + \text{III};$$
$$\text{aVF} = (\text{II} + \text{III})/2.$$

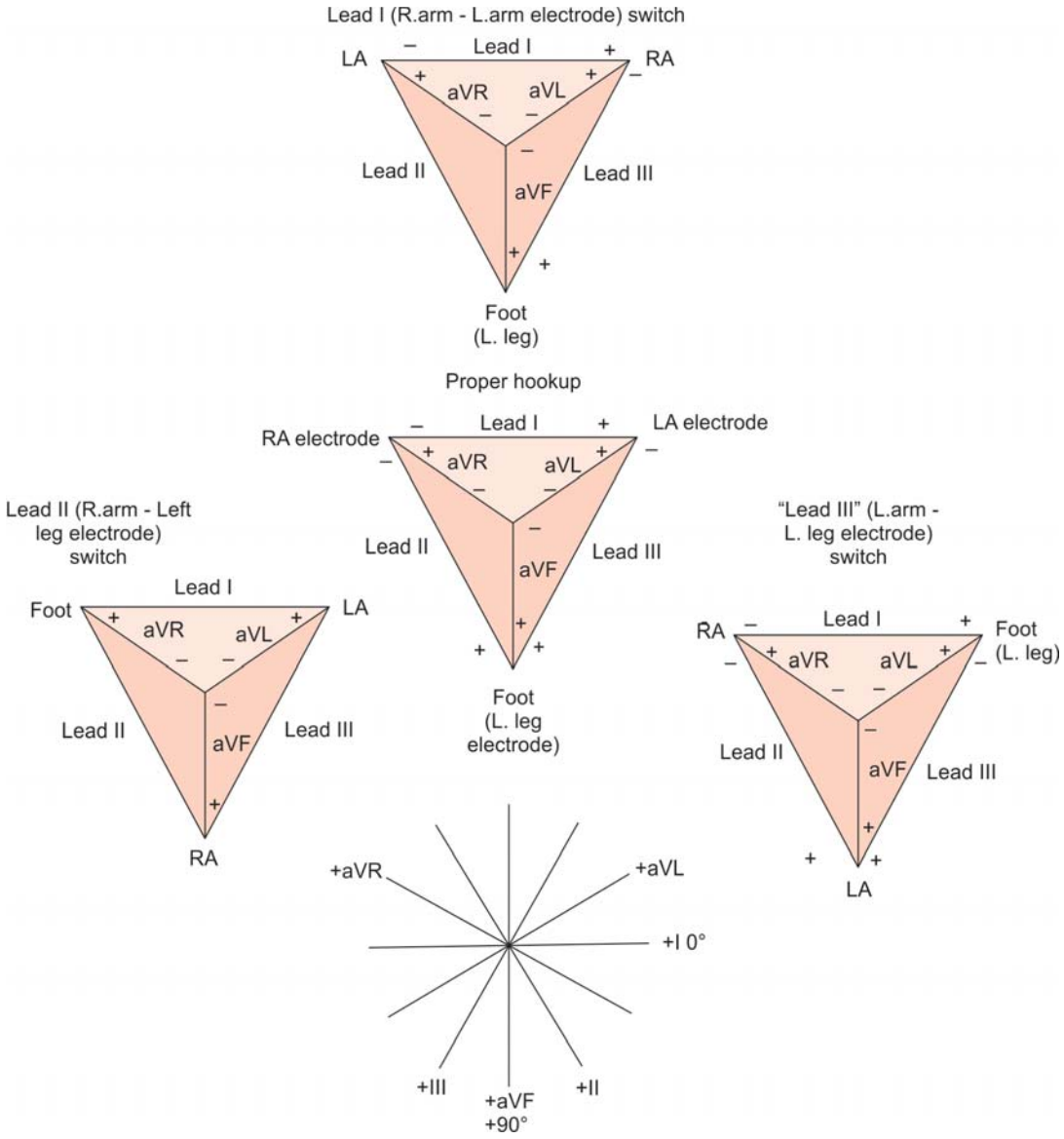


FIGURE 2: Leads orientation and vector forces

All other comparisons can be given by algebraic rearrangement of these two equations.

Later the precordial leads were developed using Wilson's central terminal versus the exploring electrode placed at various positions on the chest wall. For accuracy of electrocardiographic interpretations and especially in comparing serial recordings, the correct placement of the precordial leads is absolutely essential. Lead V1 must be placed in the 4th intercostal space just to the right of the sternal border; lead V2 in the 4th intercostal space just to the left of the sternal border; lead V4 at the left midclavicular line in the 5th intercostal space; lead V3 at the midpoint of a diagonal line connecting leads lead V2 and lead V4. Lead V5 is placed at the anterior axillary line at the anterior axillary line's intersection with a line extending out perpendicular to the rostral-caudal line of the body from the position of V4. Lead V6 is placed at the midaxillary line along the same line as V4 and V5. The midaxillary line is best defined in terms of lead placement as the mid or central plane of the thorax. There is a common misconception that V5 and V6 stay in the same interspace as V4. If the anterior axillary line is not well defined, lead V5 should be placed midway between V4 and V6.

COMMON ELECTRODE MISPLACEMENTS

An experienced interpreter of the electrocardiogram should be able to recognize artifact produced by improper placement of the electrocardiographic electrodes. A distinct discrepancy of a current electrocardiogram compared to a previous one in terms of P, QRS and T wave axes or precordial leads showing tall R waves in V1 declining progressively in V2 and V3 and then abruptly becoming larger again in V4 provide clues that electrodes have been misplaced. Specific examples will now be discussed.

Misplacements of the left arm, right arm or left leg electrodes onto the wrong extremity (as a visual reference see Figure 2). Viewing Einthoven's triangle with the six frontal plane (extremity leads) properly connected predicts what would happen to the QRS complex when improperly connected.

A common extremity electrode misplacement involves placement of the right arm electrode on the left arm and the left arm electrode on the right arm. In terms of Einthoven's triangle the configuration now looks as depicted in Figure 2 under lead I switch. Recalling that a lead's point of view is from the positive looking toward the negative, lead I's point of view has been switched from looking left toward right and now looks right toward left. Thus, what should be the proper inscription of lead I is inscribed upside down. Further inspection of the diagram reveals that the inscription labeled lead II, normally a comparison of the electrical potentials of the left leg versus the right arm now is inscribing a comparison of the potentials of the left leg versus the left arm and thus is inscribing lead III. Similarly the inscription labeled as lead III is actually an inscription of lead II. Similarly, aVR should be a comparison of the potential from the right arm versus the input from the modified central terminal lead. With this electrode switch that inscribed as aVR is actually a comparison of the potential from the left arm versus the central terminal lead or lead aVL. The inscription of lead aVF is not changed.

A visual clue that this electrode switch has occurred is that not only is the QRS upside down but the p wave in lead I is also inverted. An additional clue comes from the precordial leads V1–V6. When properly placed, leads V5–V6 should have the same left to right point of view. When lead I appears to be the inversion of V5–V6, consideration should be given to a left arm-right arm electrode switch (a "lead I switch"). When the heart's anatomical position is truly "switched from left to right" as occurs in situs inversus, the standard proper hookup of the electrocardiogram will look like a left arm-right arm electrode switch in the frontal plane and the precordial V1 through V6 leads will show a progressive decrement of the amplitude of the R wave rather than the progressive increment expected in the amplitude of the R wave. In a patient with situs inversus the interpretation of the recording of the electrocardiogram using the usual criteria for QRS, ST and T abnormalities in the various leads can be facilitated by intentionally placing the right arm electrode on the left arm and the left arm electrode on the right arm, and placing the precordial electrodes in the usual interspaces but starting with V1 at the left sternal border and moving rightward so that V6 is at the right anterior axillary line.

LEFT ARM

A less common but not rare electrode switch involves placing the left arm electrode on the left leg and the left leg electrode on the left arm, a so-called lead III switch (Fig. 2). To correct for this electrode switch, the inscription of lead I, normally a comparison of left arm versus right arm is actually an inscription that compares left leg to right arm and thus is actually inscribing lead II; similarly lead II is not inscribing the comparison of left leg to right arm but rather left arm to right arm or lead I. By similar analysis lead III will be inscribed upside down (inverted). Similarly lead aVL is actually inscribing lead aVF, lead aVF is inscribing aVL. Lead aVR is not altered since the right arm electrode is in the proper location.

A quite uncommon extremity electrode switch involves placement of the left leg electrode on the right arm and the right arm electrode on the left leg, a so-called lead II switch (Fig. 2). In this case, lead I is actually inscribing a comparison of left arm to left leg or the inversion of lead III; lead III is actually inscribing comparison of right arm to left arm or the inversion of what lead I should be and lead II is inscribing the comparison of right arm to left leg or the inversion of lead II. Lead aVR is now recording aVF, lead aVF is recording lead aVR, and lead aVL is properly recording lead aVL since the left arm electrode has not been moved.

From these descriptions, the electrocardiographer can appreciate what would happen to the main direction of the QRS forces in the frontal plane, called the mean QRS axis in the frontal plane, a concept to be further described subsequently. Normally the main direction of the QRS forces is about 60 degrees, i.e. forces pointing down and leftward. Visualize how a "lead I switch", the switch of the left arm and right arm electrodes, turns Einthoven's triangle by flipping it right to left along the axis of the point of view of lead aVF. Thus the mean QRS axis moves from about 60 degrees to about 150 degrees, i.e. now pointing down and rightward. A lead II switch or right arm-left leg electrode switch rotates the triangle around the axis of the point of view of lead aVR and thus flips a normal QRS axis upward and leftward. Such marked axis shifts help in recognizing these electrode switches compared to prior electrocardiograms. By recognizing around which augmented lead axis the rotation of the axis has occurred and realizing that this augmented lead axis will be perpendicular to the point of the lead that has been switched, e.g. lead aVL being perpendicular to lead II indicates a right arm-left leg electrode switch, i.e. a lead II switch. The lead III switch or left arm-left leg switch can be difficult to recognize since the rotation of the triangle is around the axis of lead aVR. This does not change the mean QRS since it is normally directed down and leftward and it will remain pointing down and to the left. Nevertheless noting that the prior electrocardiogram's lead III has been inverted in the present electrocardiogram will allow recognition. An extension of the above descriptors is the appreciation that the augmented "unipolar" lead that does not change in a frontal plane electrode switch compared to the prior electrocardiogram helps to identify the type of electrode switch. The augmented "unipolar" lead that does not change be the lead that is perpendicular to the line connecting the electrode switch, e.g. lead aVF point of view is perpendicular to the right arm-left arm (lead I) point of view in a right arm-left arm electrode switch.

RIGHT LEG ELECTRODE

This electrode acts as an electronic reference that serves to improve the rejection of unwanted noise. Misplacing the right leg electrode by switching it with the left leg electrode does not alter the electrocardiogram since the isopotential lines are identical for the two legs. However, misplacing it onto the arms, most commonly by switching it with the right arm electrode, completely distorts the electrocardiogram in such a way that no interpretation of the frontal plane leads can be done. This misplacement of the right leg electrode placed on the right arm and the right arm electrode placed on the right leg is most easily detected by noting that lead II is essentially a flat line with minimal QRS deflections. This is true because the "right arm electrode" placed on the right leg will feed into the "negative"

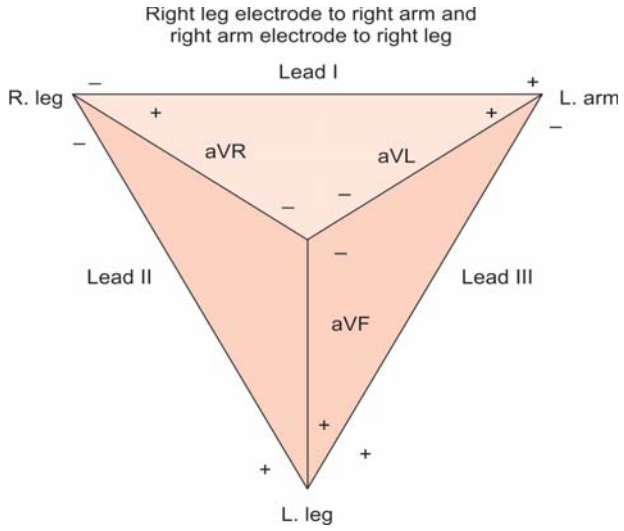


FIGURE 3: Leads inversion

side of the voltmeter an identical electrical potential to that fed into the positive side of the voltmeter from the electrode on the left leg when the machine is recording what "it" thinks is lead II. Thus the comparison between the two by the voltmeter renders a straight line. In addition lead I will be an exact inversion of lead III, and lead aVL and lead I will be identical (Fig. 3).

Under the bizarre circumstance that the right leg electrode is switched with the left arm electrode, lead III will be an essentially flat line with minimal QRS deflections.

Lead II now records Foot versus Foot and thus records a straight line.

The most bizarre of all the electrodes switches is when the right and left leg electrodes are moved to the right and left arms and the electrodes from the arms are moved to the legs. This produces a straight line in lead I.

A frequent technical error involving the precordial leads consists on switching V1 and V3 electrode placements creating a taller R in "V1" with a smaller R in V3 with then a suddenly taller R in V4.

Misplacements of the precordial leads an interspace to high often creates the impression of unusually small r waves or actual Q waves in the right precordial leads. Improper placement of leads V4, V5 and V6 often creates the impression that these leads are recording R waves that are still less than the S wave amplitudes in those leads.

OTHER LEAD SYSTEMS

For detection of p waves difficult to define on the surface electrocardiogram, bipolar esophageal lead systems that combine simultaneously recorded electrograms from an electrode positioned in the esophagus directly behind the left atrium and a surface lead, such as lead II, can be quite helpful. However, these systems are not routinely readily available. Routinely available is a "Lewis lead" for detection of sinus activity. To obtain a Lewis lead the right arm electrode is placed just to the right of the sternum in the second right intercostal space or just to the right of the manubrium and the left arm electrode is placed in the fourth or fifth intercostal space just to the right of the sternum.

A SYSTEMATIC WAY OF LOOKING AT THE INTERPRETATION OF THE ELECTROCARDIOGRAM

A Systematic Way of Looking at the Rhythm

For the purposes of this discussion, the suggestions to follow are principally for interpretation of the electrocardiogram of adults.

IDENTIFICATION OF ATRIAL ACTIVITY

Proceeding in a systematic fashion helps to prevent omissions and leads to better conclusions. It is recommended that analysis should start with identification of the atrial activity including its name, e.g. sinus activity, atrial flutter, etc. Following identification of the atrial activity, attention should go on to determining the numerical relationship to the dominant atrial activity and the dominant (most frequent) QRS complexes. Basically this amounts to a decision as to whether there is a 1:1 relationship with a fixed PR or RP interval, or the dominant atrial activity is more frequent (going faster) than the dominant QRSs or the dominant QRSs outnumber the dominant atrial waves. While proceeding through the identification of the atrial activity and the relation of the atrial activity to the dominant QRSs, certain diagnoses or impressions will have occurred that indicate that the atrial activity is not responsible for producing the dominant QRSs, e.g. AV dissociation. At that point and only then the reader should proceed to the determination of what is creating the QRS complexes, a decision based primarily on the QRS duration and the rate of the QRS complexes.

In identifying the name of the atrial activity, the first question should be is the atrial activity "sinus activity". This is based on the rate (for adults perhaps as low as 40 per minute and up to 180 when at rest and faced with high output stresses such as fever, infection, etc. and up to about 200 with maximal exercise). The maximal heart rate for the adult with exercise can be roughly estimated by subtracting the person's age from 220. If the activity fits within these ranges, then sinus activity is a potential diagnosis. The next criterion is the morphology of the p waves, especially in lead II. At the slower rates, the p of sinus activity should be upright or flat but not inverted in lead II and at faster rates definitely upright in lead II. The p morphology generally remains constant in appearance, although at the slower rates associated with sinus arrhythmia the p wave in lead II may be more upright when the p to p interval is shorter and more flat when the p to p interval is longer. The third criterion on the electrocardiogram is that the p intervals are reasonably regular. With high vagal tone producing slower rates such as in athletes the p to p interval may expand and shorten in synchrony with inspiration and exhalation, a normal variant called sinus arrhythmia. Finally, at the bedside, activity thought to be sinus should make sense with the clinical presentation. For instance, a rhythm disturbance to be discussed later, focal ectopic atrial tachycardia, may present with upright p waves in lead II and a quite regular rate of 140 BPM or more, thus simulating sinus

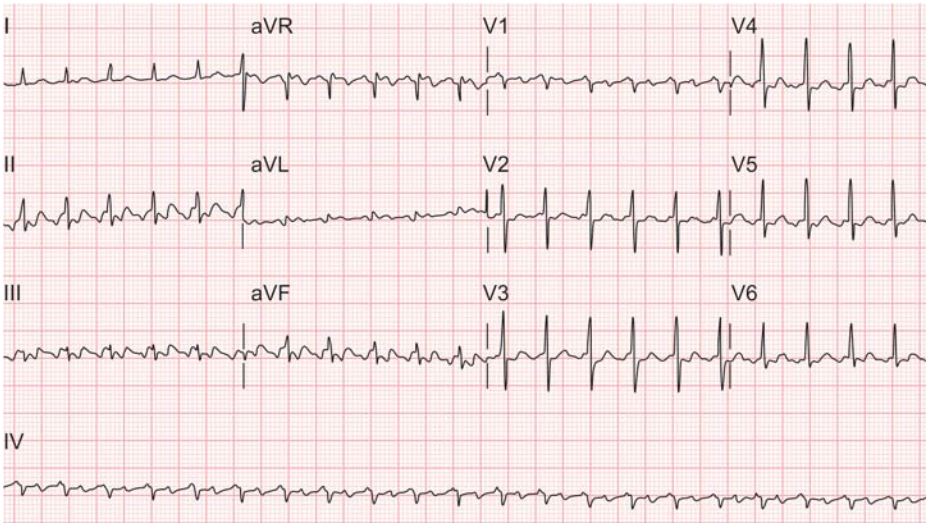


FIGURE 4: An example of atrial flutter with 2:1 conduction

tachycardia. One of the clues that the diagnosis probably is not sinus tachycardia but rather is a focal ectopic atrial tachycardia may be that the clinical situation does not seem to include any state, such as fever, volume depletion, etc., that would lead to a sinus tachycardia.

If the conclusion is that the atrial activity is not sinus, the observed atrial activity should be categorized into one of three groups: (1) "Organized": specifically that the atrial wave morphology in any given lead maintains a constant morphology and a constant atrial wave to atrial wave interval; (2) "Chaotic": specifically that the atrial morphology in any given lead is constantly varying in morphology and wave to wave interval or (3) The atrial activity cannot be found consistently.

If the conclusion is that the atrial activity is organized but not sinus, then the proper diagnosis can usually be based on the rate of the atrial waves and their morphology. Based on these considerations, usually the conclusion will be that the atrial activity represents atrial flutter (Fig. 4), an ectopic atrial tachycardia (re-entrant or focal ectopic) (Fig. 5) or retrograde p waves. For instance if the atrial rate is 220–360 inclusively and the atrial waves, especially in leads II, III and aVF, have the typical saw tooth or sine wave appearance, the diagnosis of atrial flutter is almost unequivocal. However, atrial flutter may present with slightly slower rates in the presence of antiarrhythmic drugs that slow conduction velocity in the atrial reentrant pathway. If the atrial rate is around 140 and up to a bit less than 220 and no flutter waves are discernible, then the diagnosis of one of the types of the ectopic supraventricular tachycardias (reentrant or focal ectopic) is appropriate. If there is a single p wave apparent as an inverted p waves in leads II and aVF immediately following each narrow QRS (duration of less than 120 msecs), then the diagnosis of a reentrant (usually AV nodal using) supraventricular tachycardia is secure. If the p waves, inverted in II or not, do not bear a fixed relation with one p following each QRS, then the diagnosis of a focal ectopic atrial tachycardia is appropriate. Since these p waves may be upright in lead II because they emanate from an ectopic focus near the sinus node, they will resemble sinus p waves. Due to the rapid rates of these p waves, these focal ectopic atrial tachycardia p waves often conduct with variable degrees of second degree AV block whereas most sinus tachycardias at these rates will conduct 1:1. The lack of expected response to physiologic interventions such as vagal maneuvers and the lack of the presence of any clinically apparent reason for a sinus tachycardia also help to distinguish these focal ectopic tachycardias from sinus tachycardia. The third general category for organized atrial waves is the retrograde p wave, i.e. an inverted p wave in leads II and aVF indicative of depolarization of the atria from caudal to rostral. These can be of two varieties: the passive retrograde p wave that is the result of activation from some source distal to the atrium, e.g. from the AV node, the junctional tissue or ventricular rhythms. The hallmark of the passive retrograde p wave is that the p wave is found right after the QRS and is locked onto the QRS by a fixed interval, usually about 260 msecs from the beginning of the QRS complex to the end of the retrograde p wave. The other type of retrograde p wave is the active retrograde p wave, i.e. the atrial wave is derived directly from the atrium but its point of origin is low in the atrium. It is distinguished from the passive retrograde p wave because it is never in a one to one relation with the QRS complexes and attached just after the QRS complex. Note should be made of the fact that passive retrograde p waves may certainly be observed as part of the reentrant supraventricular rhythms but that passive retrograde p waves may also be seen due to other rhythms such as junctional or ventricular rhythms including ventricular tachycardia. The distinction among these potential sources of passive retrograde p waves is usually apparent based on the width of the QRS complexes and their rate. Note should be made again that focal ectopic atrial tachycardias may demonstrate active retrograde p waves when the focal source is low in the atrium; however, if that focal source is near the sinus node, the p waves will be similar to sinus p waves and will not be retrograde in appearance.

If the atrial activity is not organized but instead is chaotic, i.e. constantly varying in morphology and wave to wave interval, the two most likely rhythms are atrial fibrillation and multifocal atrial tachycardia. The former, of course, is characterized by rapidly undulating atrial wavelets at 400 or more beats per minute, and the ventricular response to uncomplicated atrial

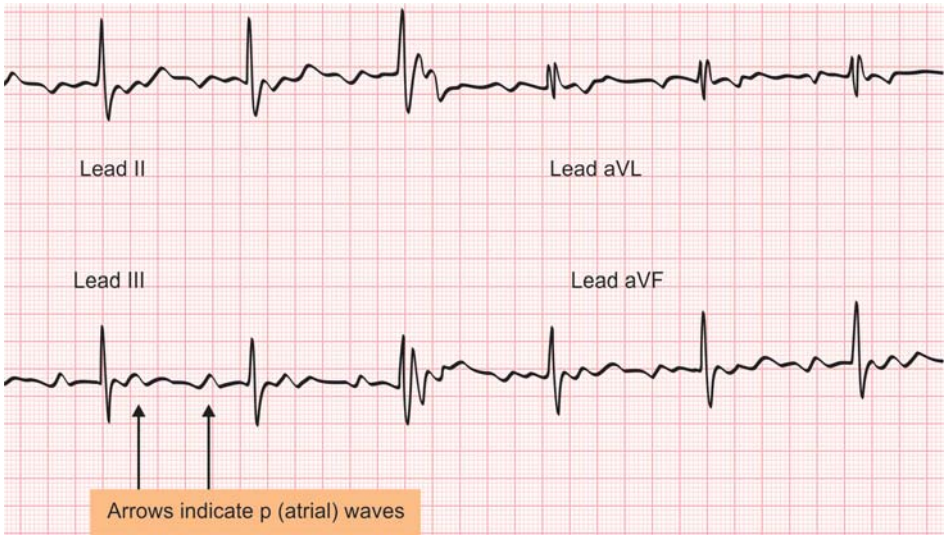


FIGURE 5: An example of focal ectopic atrial tachycardia with 2:1 atrio-ventricular block

fibrillation will manifest irregularly irregular R-to-R intervals. The ventricular response in those individuals with normal AV conduction pathways and on no rate controlling medications is usually about 130–180 beats per minute. A regular ventricular response in the presence of atrial fibrillation implies complete AV dissociation with a junctional escape rhythm or an accelerated junctional escape rhythm, the latter often reflecting digitalis toxicity. In contrast the atrial activity in multifocal atrial tachycardia consists of isolated p waves consistent with sinus activation plus three or more premature atrial complexes, each of different morphology, with an average heart rate of greater than 100 BPM. For the most part there will be one atrial wave per QRS, although an occasional premature atrial beat may not be conducted.

An atrial wave with consistent p wave morphology but an irregular p to p interval is retrograde activation of the atria from conduction from a source distal to the AV node, e.g. a ventricular tachycardia, but conducting retrograde back up through the AV node with a ventriculoatrial second degree block, e.g. with Mobitz I (Wenckebach) characteristics. However, this is a quite rare phenomenon and difficult to detect on the routing electrocardiogram. Theoretically junctional or ventricular rhythms could penetrate the AV node with 2 to 1 conduction ratios producing one retrograde p with a fixed R-P interval after every other QRS complex.

The third general observational possibility involving detection and characterization of the atrial activity is that the atrial activity either cannot be clearly found or is only detected for only one or two beats during the rhythm strip. Under these circumstances, characterizing the dominant QRS complexes into one of three general observational groups is helpful.

The first such group would be *regular* R-to-R intervals with "narrow" QRS complexes (arbitrarily defined by this author as being < 120 msecs wide). This breaks down into a slow variety and a fast variety. The slow variety would in general consist of a heart rate of 60 BPM or less with plenty of room between QRS complexes to allow for detection of atrial waves. If no such waves can be observed in any of the 12 leads, it is likely that this represents atrial asystole with the expected emergence of a junctional escape rhythm. The more common situation is the "fast" variety in which there is rapid QRS rates of about 100–220 BPM) The likely candidates explaining this finding include sinus tachycardia where the sinus p waves have become difficult to identify, atrial flutter with 2 to 1 AV conduction and "paroxysmal supraventricular tachycardia" (usually AV nodal using reentrant supraventricular tachycardia) (Fig. 6). In general a first approximation of the likely diagnosis or diagnoses is to note the exact rate of the tachycardia. If the rate is greater than 180 it would be quite unlikely to be sinus tachycardia in an adult who is not exercising and equally unlikely that it would be atrial flutter with 2 to 1 AV conduction, since it would be quite unusual for the atrial rate in atrial flutter to exceed 360. At rates significantly less than 140 BPM, the paroxysmal supraventricular tachycardia becomes much less likely. Of course, at rates of about 140–180, all three possibilities are reasonably likely just based on the heart rate. Given these latter two rate possibilities, reexamine the electrocardiograph (EKG) and look more closely for the p wave on the downstroke of the T wave right before the next QRS complex and to assess the patient clinically to see if there is a clinical reason evident that would account for a sinus tachycardia. Given that none is found, it becomes reasonably unlikely that the rhythm is sinus. The next possibility to consider and the possible rhythm most likely to be present in the postoperative state is atrial flutter with 2 to 1 AV conduction. Multiple different observations often need to be used to unmask atrial flutter with 2 to 1 AV conduction. The first is to ignore the QRS complexes in leads II, III and aVF, and in doing so try to appreciate the sine wave or saw tooth pattern in those leads. Scrutiny for a potential atrial wave in leads V1 and V2 should be carried out. Often with atrial flutter, one of the two flutter waves will be evident in those leads and often the wave resembles a sinus generated atrial wave. Note the PR interval in those leads. If the PR interval is not reasonably short as would be expected with a sinus tachycardia, there is a high probability that the wave is not a sinus p wave. In addition, take the measured PR interval in those leads and apply it to lead II. Does a potential atrial wave there as identified by the PR interval look like a sinus p wave? Finally

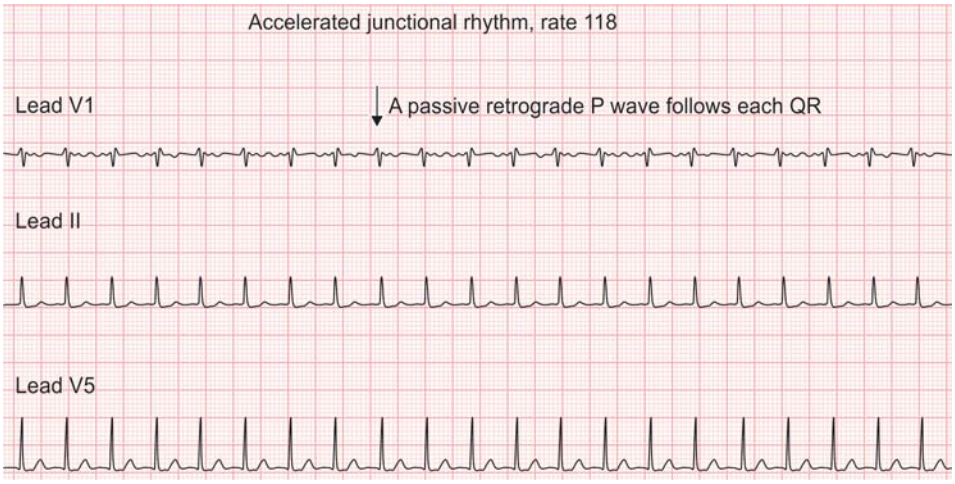


FIGURE 6: An example of atrio-ventricular reentratachycardia (AVNRT)

take the measured observed p to p interval or the measured R-to-R interval observed in lead V1 or V2 and cut that interval time in half, e.g. the measured interval will be about two large electrocardiogram boxes plus a couple of small electrocardiogram boxes. Simply reduce the caliper tip to tip distance to one big and one small EKG box. Place one tip of the caliper on the observed p wave in lead V1 or V2 and swing it forward and backward so that the second tip brings your visual attention to the second identical wave often merged to the beginning or end of the QRS complexes. In addition, using that same caliper distance, examine leads II, III and aVF to see if that will trace out a sine wave or saw tooth pattern. Failing to be able to dissect out flutter waves or identify definite sinus p waves leaves the paroxysmal supraventricular tachycardia as the likely diagnosis given that the ventricular rate is from about 140 up to about 220 BPM. Finally, at the bedside performing vagal maneuvers or giving intravenous adenosine may clarify the diagnosis substantially. Sinus activity should slow and then reaccelerate gradually; atrial flutter waves will continue unabated but the conduction numbers through the AV node should diminish substantially creating long R-to-R intervals and exposing obvious flutter waves; and, if done effectively, the reentrant supraventricular tachycardias should cease abruptly.

The next possibility under the "can't find the atrial activity section", is that the dominant QRS intervals are varying in an irregularly irregular way, i.e. a completely unpredictable and unpatterned R-to-R variation. A reasonable assumption under the circumstance when no atrial activity can be discerned is that the rhythm is "fine" (very low amplitude) atrial fibrillation.

The final observational set under "can't find the atrial activity" is that the above two steps did not lead to a reasonable diagnosis or, more commonly, that there are regular but wide (≥ 120 msec) regular QRSs. Under this circumstance, moving to the ventricular analysis to be described subsequently is useful in choosing whether the QRSs reflect a ventricular rhythm versus a rhythm that is not of ventricular origin and is not from an atrial source.

Given that an atrial activity has been identified, the next step is to identify in a general way what the numerical relationship is between the dominant atrial waves and the dominant QRSs. Simplistically, the first possibility is that the dominant atrial activity and the dominant QRSs exist in a one to one relationship. Thus one atrial wave would need to be observed for each dominant QRS complexes with either a fixed PR length or a fixed RP length. The fixation of the timing implies that that which occurs first gives rise to the following event. With a fixed PR, the atrial wave (most commonly a sinus p wave) proceeds antegrade to give rise to the QRS. In situations where the atrial wave is found at the end of the QRS complex or shortly thereafter in the ST segment with a fixed interval between the QRS and a p wave that is inverted in leads II and aVF, almost always this represents a passive retrograde activation of the atria from a source distal to the atrial chambers. This source can be a reentrant focus using the AV node, a junctional mechanism or a ventricular mechanism.

When the rate of the dominant atrial waves is consistently always greater than the dominant QRS rate, almost invariably this indicates a second or third degree AV block. This block could be pathological, i.e. given that at the atrial rate discerned, atrial waves would be expected to conduct one to one to the ventricles. On the other hand, this block could be physiologic in that the atrial rate is so rapid that it would not be likely to conduct one to one in the presence of healthy conducting pathways, e.g. atrial flutter conducting with a 2 to 1 conduction ratio. Regardless, the name of the type of block can be most easily and quickly discerned by first looking at the PR intervals, although not assuming that a p followed by a QRS necessarily indicates that the p gives rise to the QRS. If the PR interval does not vary, then describing the numerical relation between the number of p waves and the number of the dominant QRS complexes will produce an appropriate name for the block. If there are two waves for each QRS with a fixed PR, the appropriate name is 2 to 1 second degree AV block. If there is a fixed ratio of 3 or more p waves per QRS with a fixed PR, the appropriate name would be advanced second degree AV block. All others fitting the description of more dominant p waves than dominant QRS complexes but with a fixed PR can be appropriately diagnosed as Mobitz II second degree AV block. If the PR does vary, the two possibilities are Mobitz type I second degree AV block (essentially synonymous with Wenckebach second degree AV block) and third degree or complete AV block. Given that Mobitz I second degree AV block

intermittently manifests as a p wave that does not produce a QRS, the other hallmark of this type of block besides the varying PR interval is the intermittent production of a significantly longer R-to-R interval. On the other hand, with the third degree AV block junctional or ventricular escape rhythms should emerge and these rhythms are regular and do not demonstrate intermittent, patently obvious, R-to-R pauses. Thus if the PR varies and the R-to-R distinctly and obviously varies, the diagnosis is Mobitz type I or Wenckebach second degree AV block. If the R-to-R interval does not grossly vary, then the diagnosis becomes third degree (complete) AV block. There may be caliper detectable, subtle variations in the R-to-R interval with third degree AV block with a junctional escape rhythm since the junctional mechanism is under the influence of vagal tone, which is likely to vary under this circumstance with variable atrial filling of the ventricles as well as with inhalation and exhalation.

There is one final caveat relative to the appropriate diagnosis of third degree AV block when atrial rate exceeds ventricular rate. When electronic pacing of the ventricle is occurring in the now less common circumstance where there is no sequential atrial pacing, confirmation of the presence of third degree AV block should include inspection of the rhythm strip to be sure that no p waves occurring after the T wave of the preceding QRS are producing an early QRS complex, i.e. an atrial capture of the ventricle. If such capture is observed then the situation is not truly complete AV block.

The third possibility for the numerical relationship of the dominant atrial activity and the dominant ventricular activity is more frequent, more rapid dominant QRS complexes than dominant atrial waves. This usually constitutes another and different form of AV dissociation than third degree AV block. This usually represents interference AV dissociation created by a slowing of the sinus rate below the rate of normal physiologic escape pacemakers, usually junctional escape pacemakers, and/or development of a pathological ectopic tachycardia, from a source distal to the AV node, regardless if that is junctional or ventricular (Fig. 7). The explanation for the dissociation is that impulses are arriving at the top and the bottom of the AV node almost simultaneously, with conduction into the AV node antegrade and retrograde almost simultaneously. Thus there is collision of the impulses nearly head on or at least within the refractory periods caused by each one. The key point is that the AV dissociation here is not a matter of pathology in the AV conducting pathways. The AV pathway is the innocent bystander of the effect of inappropriately slow sinus activity and/or pathological ectopic focus distal to the AV node. Clinically the distinction is important. Under this circumstance attention should be directed to increasing the rate of sinus activity or suppressing the pathological ectopic focus and not trying to improve AV conduction.

There is one other potential circumstance when AV dissociation may occur. This is when there is a slow sinus arrhythmia whose rate gradually slows and gradually quickens to rates just above and below that of a junctional escape rhythm. Under this circumstance the atrial rate may not ever accelerate enough to place a p wave far enough ahead of the next QRS emanating from the junctional focus and thus is never able to capture the ventricle. This circumstance is called isorhythmic AV dissociation.

Having clarified the AV numerical relationship as best as possible, the next step is only necessary if some impression or diagnosis has come about in the preceding step that implies that the dominant atrial mechanism is not producing the dominant QRS complexes. In general the descriptors or diagnoses that would indicate this would be: (1) passive retrograde p waves (inverted p waves in II and aVF following the QRS with a fixed interval from onset of QRS to completion of the p wave); (2) AV dissociation (whether it be due to complete AV block or interference dissociation) and (3) the final step three under "can't find the atrial activity". Specifically this last situation means that the first two steps under "can't find the atrial activity" didn't work or there are regular wide QRSs without discernible atrial waves. Given the findings noted for steps 1, 2 and 3 as just stated, the QRS complexes are likely the result of a ventricular rhythm or a nonventricular rhythm that is not of atrial origin. The next step in sorting out the possibilities is to note if the dominant QRS complexes are unusually wide, specifically 120 msecs or greater. In making this determination, the measurement should take into account the inscription of the QRS in all 12 leads, using the widest inscription found for the dominant QRS. If the QRS is less than 120 msecs, it is quite likely that the rhythm producing the QRS complexes is not of ventricular origin. Thus the likely possibilities become a junctional escape rhythm recognized by its rate of about 60 BPM or less, an accelerated junctional rhythm recognized by its rate of greater than 70 BPM but less than 130 BPM (Fig. 6), or the paroxysmal (usually AV nodal using reentrant) supraventricular

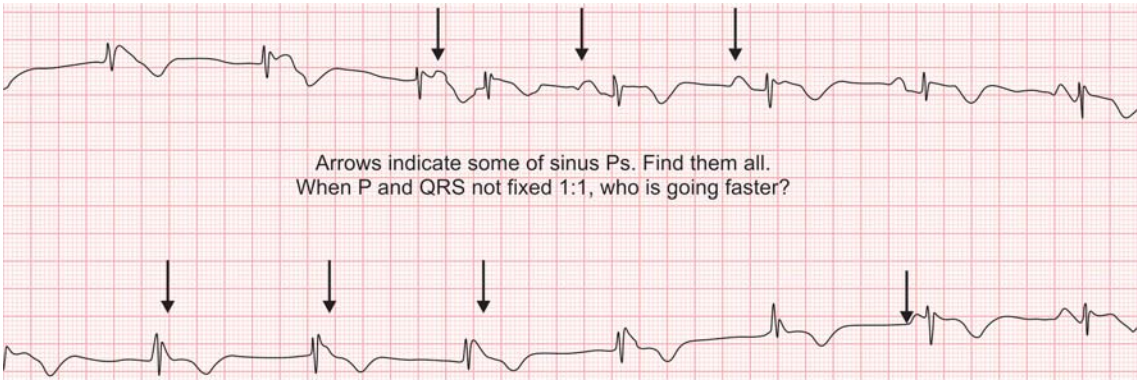


FIGURE 7: An example of sinus bradycardia with junctional escape rhythm creating interference atrio-ventricular dissociation

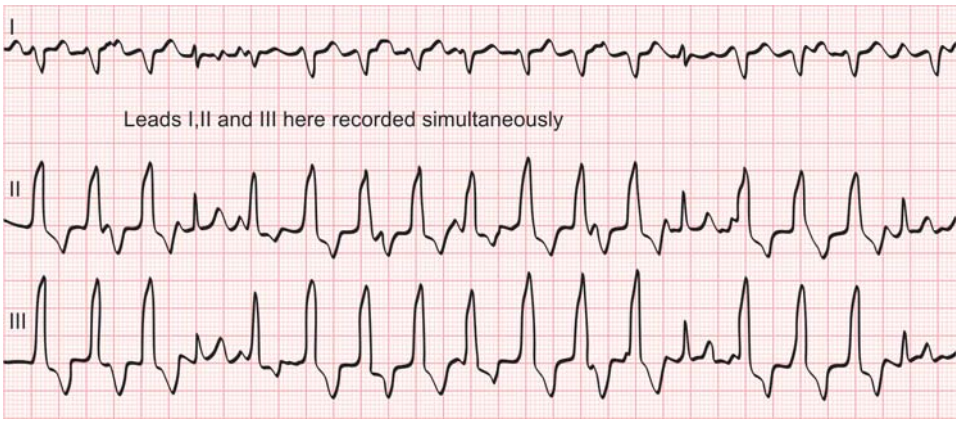


FIGURE 8: An example of accelerated idioventricular rhythm

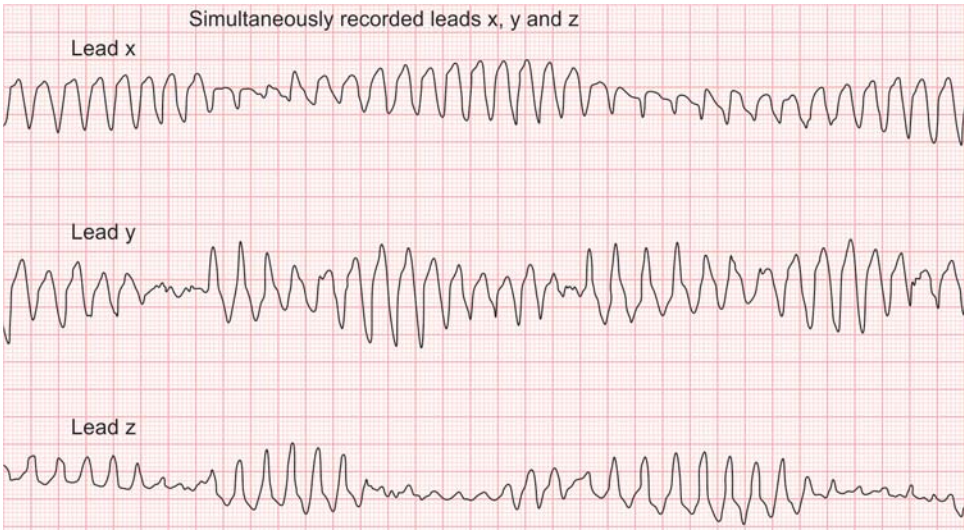


FIGURE 9: An example of torsades de pointes

tachycardia recognized by its rate of about 140 BPM or more. If the QRS duration is 120 msecs or greater, knowledge of the morphology of the QRS complexes prior to the onset of the rhythm disturbance can be critical. For instance, if the QRS prior to the onset of a pathological tachycardia happened to be a left bundle branch block and the patient then developed a paroxysmal supraventricular tachycardia, it would be likely that the QRS complexes under this circumstance would be identical to those prior to the tachycardia and thus would simulate a ventricular tachycardia. Therefore, if the QRS complexes after the onset of a rhythm disturbance are identical to those prior to its onset, the analysis should proceed as though the QRS complexes during the dysrhythmia are narrow and the diagnosis made on the basis of the rates given for the narrow QRS complexes discussed above. If the QRS complexes are wide and not identical to those prior to the onset of the rhythm disturbance, the correct diagnosis can usually be made by noting the QRS rate. If the rate is less than 40 BPM, the diagnosis is ventricular escape rhythm. If the rate is about 55–110, the diagnosis is accelerated idioventricular rhythm (Fig. 8). If the rate is above 120 BPM, the diagnosis is ventricular tachycardia. The rate in this circumstance is usually 140 or more. Ventricular tachycardias, especially those due to ischemic heart disease maintain the same QRS morphology in any given lead and are appropriately called monomorphic ventricular tachycardia. In contrast, some ventricular tachycardias display QRS morphologies that gradually change their shape as though the depolarization and repolarization of the ventricle was turning on a point. When associated with factors that prolong the QT interval, the ventricular tachycardia is called torsades de pointes (Fig. 9). When the ventricular tachycardia has this same appearance but has not been provoked by factors causing prolongation of the QT interval, the tachycardia is called polymorphous ventricular tachycardia.

There is one peculiar circumstance where a pathological tachycardia of supraventricular origin, such as paroxysmal supraventricular tachycardia, may conduct to the ventricles with a new bundle branch block morphology not present prior to the pathological tachycardia. This usually indicates the presence of a conduction phenomenon known as aberrancy. The phenomenon is created by the arrival of a premature supraventricular impulse at just the precise moment that the AV node and one of the bundle branches is beyond their absolute refractory periods but the opposite bundle is still within its refractory period. Thus the supraventricular impulse is conducted with a new bundle branch block morphology. The situation is made more likely to

occur if the premature supraventricular impulse occurs after a preceding R-to-R interval that is longer than usual. When only a single premature beat is involved it is relatively easy to discern a premature atrial contraction from a premature ventricular contraction by identifying the premature p wave in front of the premature QRS. However, when there is a sustained ectopic tachycardia, the situation is significantly more difficult in discriminating between supraventricular reentrant tachycardia conducted aberrantly and ventricular tachycardia. The actual rate of the tachycardia is of no value in the discrimination and the presence of various symptoms in reaction to the tachycardia is equally of no value. The finding of AV dissociation due to interference with sinus p waves beating completely independently from the regular QRS complexes is almost diagnostic that the tachycardia under this circumstance is ventricular tachycardia. Finding AV association with one passive retrograde p wave discernible following each wide QRS is of no value in the discrimination since almost all the paroxysmal supraventricular tachycardias and perhaps a third of the ventricular tachycardias will also demonstrates one QRS to one passive retrograde p wave relationship. Other more subtle points have been developed by Brugada and his coworkers and by other research groups. However, too much time spent trying to make this distinction following the onset of the dysrhythmia can have disastrous results for the patient presenting in an emergency situation. Discriminating between ventricular tachycardia on the basis of the heart rate itself or the presence versus the absence of symptoms and hypotension is completely unreliable. Quickly looking for a single p wave in front of the QRS complexes is reasonable. Taking an undue amount of time trying to discern if there are sinus p waves walking through the QRS complexes (i.e. defining that there is AV interference dissociation) will only use up precious time and, if found, will only confirm that the diagnosis is what was believed in the first place, namely ventricular tachycardia. A practical approach in the emergency situation is to assume that a rapid, quite regular, wide QRS tachycardia of rate 120, usually 140 or higher, is ventricular tachycardia until proven otherwise and not to waste too much time trying to prove otherwise.

Having completed the analysis to this point, the next step is to look for unexpected early QRS complexes and to look for unexpected long R-to-R pauses, given that the dominant QRS complexes have been otherwise characterized by regular R-to-R intervals. Except in the presence of interference AV dissociation, unexpected early QRS complexes would represent ectopic premature beats of atrial, junctional or ventricular origin. If the premature complex (whether identical to or different than the dominant QRS complexes in morphology) is preceded by a premature p wave, then it is reasonably to presume that the premature beat is an atrial premature beat, usually associated with a noncompensatory pause (the R-to-R interval encompassing the premature beat being less than the R-to-R interval preceding or following the premature beat). If the premature beat is distinctly different than the prior QRSs and does not have a premature p in front of it, then it is reasonable to presume that the beat is a ventricular premature beat, which will usually produce a fully compensatory pause (the R-to-R interval encompassing the premature beat being essentially twice the R-to-R interval preceding or following the premature beat). Junctional premature complexes tend not to be preceded by a premature p wave and tend to be identical to the morphology of the dominant QRSs and tend to be associated with a completely compensatory pause.

There is one circumstance when an unexpected early QRS does not represent a premature ectopic beat. The circumstance is the presence of interference AV dissociation. An early QRS complex with the dominant atrial activity in front of it terminating the AV interference dissociation will represent an atrial capture of the ventricle.

Attention should then turn to identifying any long R-to-R intervals (unexpected pauses) interrupting otherwise regular R-to-R intervals. Since the usual reason that a QRS complex is created is that an atrial impulse has traveled via the conduction pathways to activate the ventricles, the usual general reason that a QRS complex does not appear on time and thus creates a long R-to-R interval is that no atrial impulse arrived at the ventricles. This could occur if no on time atrial activity occurred, which would represent sinoatrial arrest or block. A second reason is that the dominant atrial activity, usually sinus, failed to conduct, thus the appearance of a Mobitz I or Mobitz II second degree AV block. The final possibility is that a premature atrial beat occurred so premature that it ran into the refractory period of some portion of the conducting network, usually the AV node. Thus, to define the reason for an unexpectedly long pause, observe what has occurred during the pause. An early p represents a nonconducted atrial premature beat; an on time p represents the appearance of Mobitz I or II second degree AV block and the absence of either a premature p or an on time p represents sinoatrial arrest or sinoatrial block. The distinction between SA arrest and block may be difficult, but if the p-to-p interval of the pause seems to represent a mathematical relationship to the preceding or following p-to-p intervals (e.g. twice the dominant p-to-p interval), then sinoatrial block may be more likely.

One final commentary is necessary with regard to rhythm analysis. This involves the presence of atrial and/or ventricular electronic pacing. Pacing spikes are vertical slashes occurring during the rhythm. What they are pacing is given by the wave that follows them, i.e. an atrial wave for atrial pacing, a QRS for ventricular pacing, or neither if the pacing fails to capture. Most commonly in the current era, pacing electrodes will be placed, usually transvenously, to stimulate the right atrium and one or both ventricles in sequential fashion. In the presence of chronic atrial fibrillation, an atrial pacing wire may not be placed. The electronics of the generator system will be adjusted so that the atrial or ventricular pacing will not occur if there is spontaneous atrial or ventricular activity respectively of a given rate, i.e. they are set in a demand mode. Inspection of the QRS complexes associated with transvenous pacing will usually indicate the pacing site. With ventricular pacing from the right ventricular apex, the site most commonly used the QRS complex in lead V1 will have a left bundle branch block appearance, i.e. mainly a negative deflection, and will have a left axis deviation. Under the unusual circumstance of pacing from near the outflow tract of the right ventricle, the QRS will have the same left bundle branch appearance but will have a normal axis. In the modern era, usually in patients with poor left ventricular systolic function and a wide QRS other than a right bundle branch block,

biventricular pacing of the right ventricle and of the left ventricle via the coronary sinus is often used. This produces a greater initial r wave in lead V1 than with the right ventricular pacing and a QRS axis that is either rightward or is in the northwest quadrant between 180 and minus 90 degrees.

CHARACTERIZATION OF QRS COMPLEX

Having characterized the rhythm fully, the next step is to characterize the QRS complexes as to whether they are normal or represent some deformity indicative of a bundle branch block, myocardial hypertrophy, myocardial infarction, etc. However, if the dominant QRS complexes represent a ventricular rhythm (ventricular escape, accelerated idioventricular rhythm or ventricular tachycardia), such an analysis is not reasonable since that QRS has already been deformed by the rhythm and the QRS diagnoses to follow cannot be made with accuracy. Given that the QRS complexes concerned do not represent a ventricular rhythm, e.g. a ventricular escape rhythm, then the clinician can reasonably proceed with the QRS analysis. Starting with the determination as to whether the QRS complexes are wider than normal (≥ 120 msecs) is important since several of the conditions producing this widening render further QRS diagnoses relatively difficult and inaccurate. Having determined that the QRSs in question are unusually wide, attention should shift to determine if the PR interval is unusually short, usually less than 120 msecs. Visually this may be best appreciated by looking for the PR segment (end of p to onset of QRS) where the QRS inscription is the widest in the 12 leads. The absence of any PR segment associated with the wide QRS complexes almost always indicates the diagnosis of the Wolff-Parkinson-White anomaly (preexcitation sydrome) due to the presence of an anomalous or accessory conducting pathway from atrium to ventricle (Fig. 10). In general, any further QRS diagnoses are very difficult to make. A practical approach under the circumstance is always to obtain a transthoracic echocardiogram to look for any further structural heart disease that might be associated with this anomaly. In fact, for all causes of an unusually wide QRS, obtaining a transthoracic echocardiogram would be quite justifiable.

If the QRS is wide, a very practical next step is to look in lead V1. The reason is that this will almost always allow the interpreter to determine if there is a right bundle branch block (Fig. 11). This conduction disturbance produces a delayed and prolonged depolarization of the right ventricle causing R waves to be found as the terminal portion of the QRS with these depolarizing forces directed anteriorly and rightward toward lead V1. It does not matter in this circumstance if the pattern is the traditional rSR' pattern or a qR pattern or even just a tall, although fractured R wave. All are indicative at this point in the analysis of a right bundle branch block. While the additional presence of left anterior hemiblock usually does not obscure the presence of this diagnostic R wave in V1, rarely the presence of left anterior hemiblock accompanying a wide QRS will obscure the characteristic pattern of an associated right bundle branch block in lead V1. The presence of the characteristic R in V1 can be demonstrated by placing the V1 lead in a higher intercostal space and also by recording right-sided chest leads.

If the diagnosis of right bundle branch block has been established, this implies that the conduction disturbance by itself has not distorted left ventricular depolarization. Therefore, having made the diagnosis of right bundle branch block, the interpreter can proceed on to the next two steps, specifically determination of the QRS axis and the search for pathological Q waves indicative of the presence of a myocardial infarction.

If inspection of the EKG does not confirm the presence of a right bundle branch block, but rather shows a tiny r-large S wave or a QS pattern in lead V1, left bundle branch block then needs consideration. Classic left bundle branch block is best confirmed by finding notching or fracturing in the middle of the QRS complex with a QRS duration of at least 120 msecs (Fig. 12). This notching is usually best seen in the leads with tall R waves, although it may be observed in those with deep S waves. Since a left bundle branch block implies a completely distorted activation of the left ventricle, attempting to make other diagnoses, such as left ventricular hypertrophy or myocardial infarction, cannot be done with a great deal of accuracy. Thus, further QRS analysis as given below is probably not of significant value. Pursuit of such further diagnoses is probably best done by utilization of echocardiography, perfusion scans

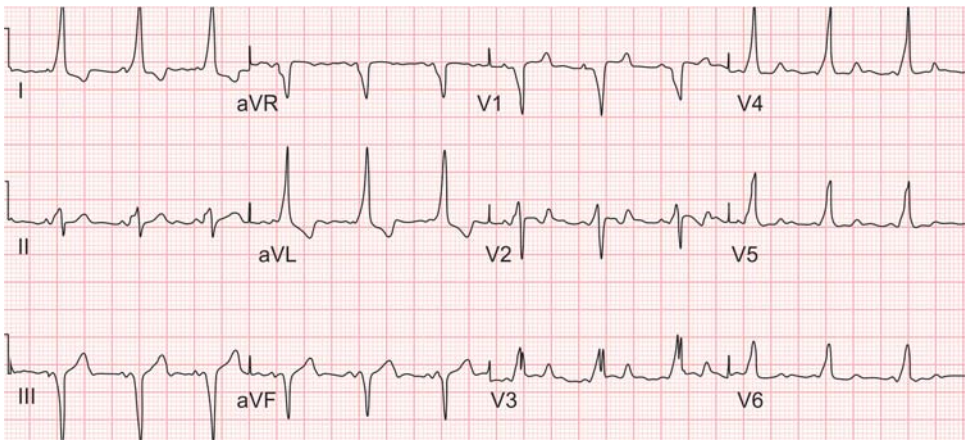


FIGURE 10: An example of accessory pathway

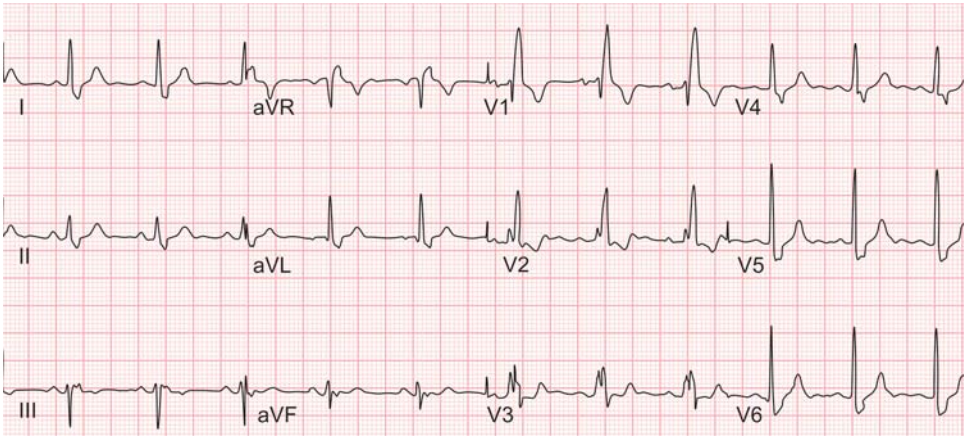


FIGURE 11: An example of right bundle branch block

and/or angiography. In addition, due to the complete distortion of left ventricular depolarization, marked ST and T wave abnormalities called secondary STT changes are to be expected in the presence of a left bundle branch block. However, these STT abnormalities are relatively predictable in any given EKG lead in that the ST and T waves should be directed in the opposite direction of the direction of the QRS complex in that lead. Finding ST and T waves and QRS complexes headed in the same direction usually indicates that some other process over and beyond the left bundle branch block is present, for instance some type of ischemia. However, it is well to remember that not finding such inappropriately directed ST and T does not mean that there is not some other process such as ischemia going on. The QRS axis, to be discussed next, is almost always either a normal axis or a left axis. While those with normal versus left axis differ generally in their clinical presentation, the axis itself does not seem to have relevance to the conduction disturbance itself. In very rare instances a left bundle branch block will demonstrate a right axis deviation.

If the wide QRS of 120 msecs or more is not due to Wolff-Parkinson-White anomaly, right bundle branch block or left bundle block, then the descriptive term of nonspecific intraventricular conduction defect is appropriate and the QRS analysis can proceed as outlined next.

If the analysis given above allows the interpreted to proceed on, attention should be directed to the mean QRS axis. The range of the normal mean frontal plane QRS axis is dependent on the age group of the individuals, shifting leftward with increasing age. For adults the normal axis is from about positive 90 degrees up and leftward to minus 30 degrees. In normal young people in their early teenage years it is not unusual to find an axis as far rightward as positive 120 degrees. In normal persons in their later teenage years and early twenties, an axis as rightward as 105 degrees is not surprising. Arbitrarily moderate left axis deviation is between minus 30 and minus 45 degrees and marked left axis deviation is from minus 45 to minus 90 degrees. When marked left axis deviation is present (i.e. an axis of minus 45 degrees to minus 90 degrees), a diagnosis of left anterior hemiblock is appropriate. Right axis deviation in adults has been divided into moderated right axis deviation when the axis is from plus 90 to plus 120 degrees and marked right axis deviation when the axis is between plus 120 and plus 180 degrees. When right axis deviation is present, three general considerations should come to mind: (1) right ventricular hypertrophy and/or emphysema; (2) high lateral myocardial infarction and (3) left posterior hemiblock. Often other electrocardiographic features and other clinical information will need to be assessed in order to choose among these three. If other

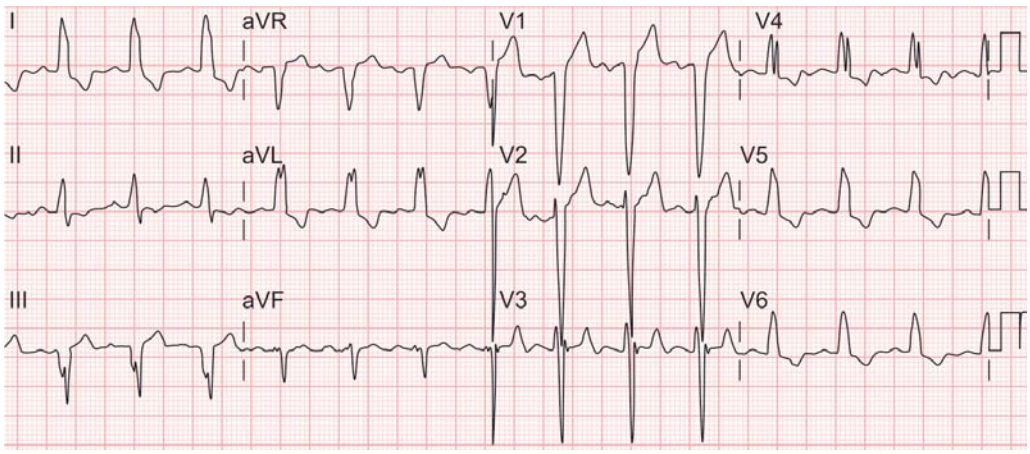


FIGURE 12: An example of left bundle branch block

electrocardiographic evidence of right ventricular hypertrophy, such as an unusually tall R or R prime wave is present in lead V1, then the diagnosis of right ventricular hypertrophy is the most likely correct choice. However, the absence of a prominent R wave in lead V1 does not mean that right ventricular hypertrophy is not the correct interpretation. The lack of a pathologically large Q wave in lead I speaks against the choice a "high lateral" infarct as the cause of the right axis deviation. However, the presence of such a Q wave merely allows infarction as a reasonable choice but still allows other possibilities such as right ventricular hypertrophy. Left posterior hemiblock is statistically the least common abnormality present. When left posterior hemiblock is present, often extreme right axis deviation is present. The presence of other conduction defects, such as right bundle branch block or Mobitz type II second degree AV block, would tend to favor left posterior hemiblock as the correct explanation of the right axis deviation.

Occasionally all of the leads in the frontal plane appear to be essentially isoelectric and then the term "indeterminate axis" is appropriate.

One final comment about the calculation of the mean QRS axis is necessary. Technically the determination of the axis by the electrocardiographer uses the area inscribed the Q, R and S waves. This is the manner in which the axis is determined by most computer-assisted electrocardiographic interpretations. This works well when the individual deflections in a given lead are of about the same width. However, in the presence of a right bundle branch block, it would be advisable to ignore the contribution of the wide terminal deflection to the QRS when estimating the axis, especially when trying to suggest the additional presence of left anterior or left posterior hemiblock.

Having dealt with the mean QRS axis, attention can then be given to the presence of Q waves indicative of the presence of a myocardial infarction. What constitutes a pathological Q wave indicative of the presence of a myocardial infarction, previously termed a "transmural" infarction and now defined simply as a Q wave infarction has been based on studies of autopsy series and patient records and expert consensus documents reflecting the combined expertise of such organizations as the American Heart Association, the American College of Cardiology and the European Society of Cardiology and the World Heart Federation. With no prior electrocardiogram with which to compare, the presence of a prior myocardial infarction has been defined as probably present if the Q waves meet certain standards of width and of depth. Currently, Q waves of equal to or greater than 0.3 s width and equal to or greater than 0.1 mV depth (1 mm depth on the usual electrocardiographic recording) when found in leads I or II or aVF or one of the precordial leads V2 through V6 correlate well with the diagnosis of myocardial infarction. Large Q waves in lead III or lead aVL or lead V1 unsupported by large Q waves in spatially adjacent leads (aVF or I or V2 respectively) have little or no diagnostic import. In addition smaller q waves in V2 of 0.02 s duration should be considered abnormal and suggestive of a prior myocardial infarction. As a practical matter, judgments based on q waves in lead aVF are traditionally problematic. Frequently, the q in this lead on one day may be quite unimpressive in width, and an electrocardiogram done shortly thereafter may show Q waves that appear to meet width criteria for infarction, and an electrocardiogram done subsequently may record QRS complexes in that lead some of which look quite nondiagnostic and some look quite diagnostic. In addition, there is variation from one interpreter to the next as to the width of the q wave.

These criteria discussed above should not discourage the diagnosis of a Q wave infarction when new but small q waves develop on serial electrocardiograms accompanied by associated evolving ST elevations and T wave changes.

The naming of the infarction as to site has been based upon the leads in which the Q waves developed. This may vary from author to author. Pathological Q waves in lead I might be termed a high lateral myocardial infarction. Pathological Q waves in aVF may be termed inferior (or diaphragmatic) wall myocardial infarction (Fig. 13). Pathological Q waves in lead II are usually accompanied by pathological Q waves in lead aVF as part of an inferior wall myocardial infarction, but, if not, might be referred to as an apical infarction. Pathological Q waves in V2 and/or V3 might be termed anterior, anteroseptal or septal myocardial infarcts. Discriminating as to whether the anterior wall or the septum or both are involved cannot be done with great accuracy. Pathological Q waves in leads V5 and/or V6 might be termed a lateral wall infarction. Pathological Q waves in lead V4 may be considered to be part of either anterior wall or lateral wall infarctions. As will be discussed, with normal QRS widths a tall R wave in lead V1 (indicative of a large Q

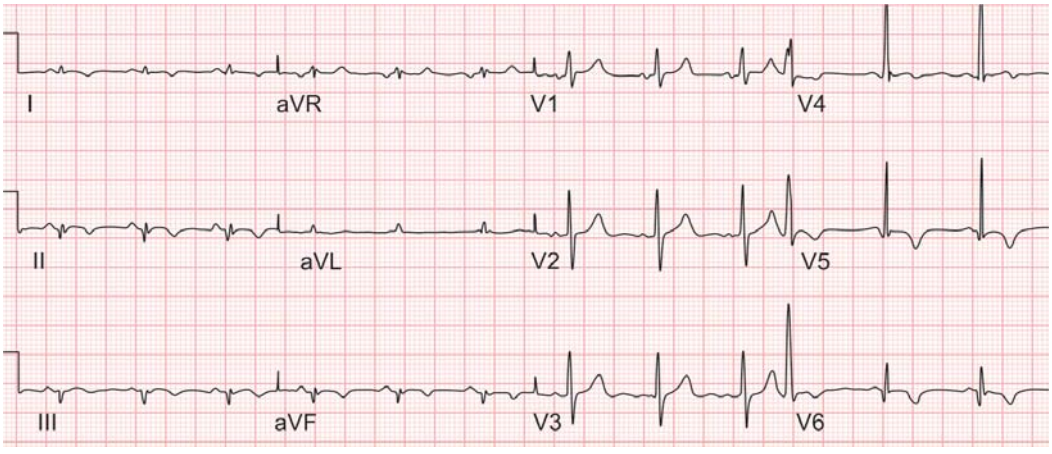


FIGURE 13: An example of inferior, posterior and lateral myocardial infarction

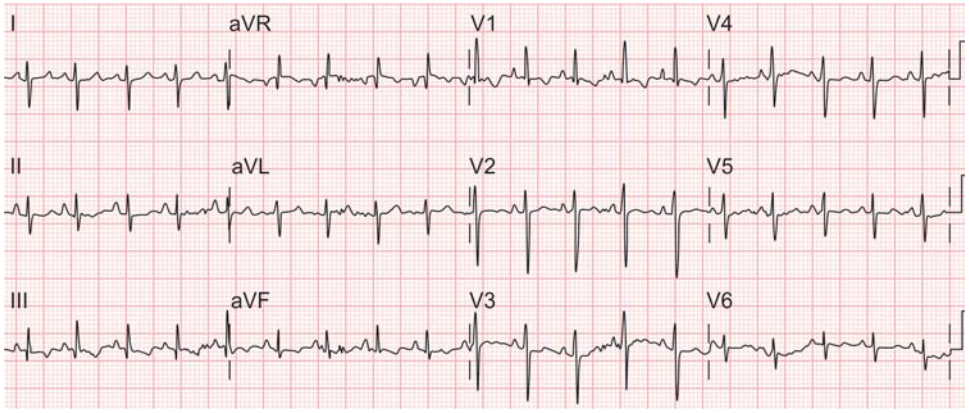


FIGURE 14: An example of right ventricular hypertrophy

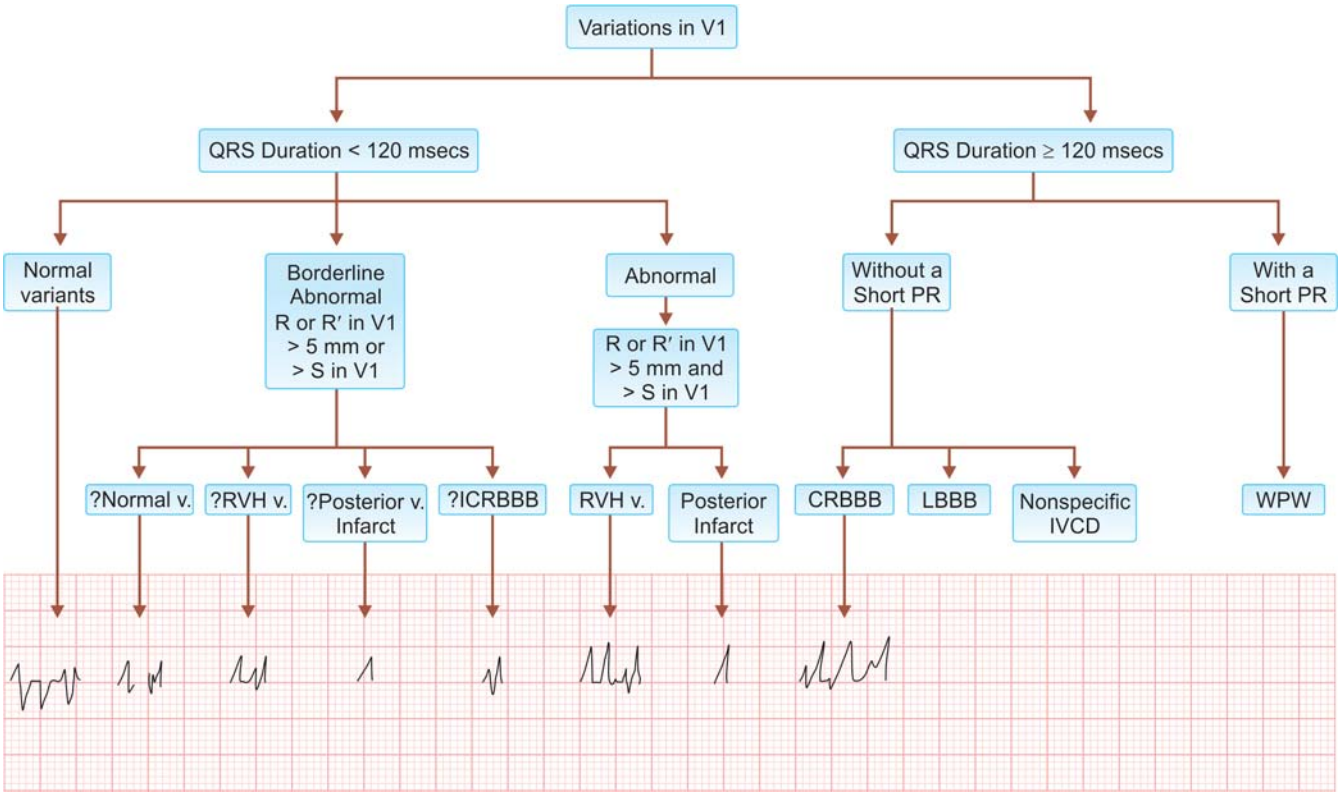
wave posteriorly) may represent a posterior wall myocardial infarction.

Having completed analysis for the presence of pathological Q waves, attention can turn to the relative amplitudes of the negative and positive QRS deflections in the precordial leads. This starts with an analysis of the relative amplitudes of R waves in lead V1. Given that a right bundle branch block will produce prominence of R waves in lead V1, it would be reasonable to stop further analysis of the electrocardiogram manifesting a right bundle branch block following the search for pathological Q waves and not proceed on to this section. Reasonable screening criteria for unusually prominent R waves in lead V1 would include an R or R prime that is greater than 0.5 mV (5 mm height) and also is greater than the amplitude of any negative deflection in lead V1. This would reflect unusually prominent anteriorly directed forces which could be explained by addition of electromotive forces anteriorly, i.e. right ventricular hypertrophy (Fig. 14) or destruction of equivalent forces posteriorly, i.e. a posterior myocardial infarction (in truth probably a posterolateral infarction). The choice between the two possibilities is based on accompanying electrocardiographic features. The presence of Q waves indicative of an inferior wall infarction or of a lateral wall infarction would lead to the diagnosis of posterior wall infarction (Fig. 13). The presence of right axis deviation (in the absence of a high lateral wall infarction) would lead to the diagnosis of right ventricular hypertrophy as the explanation of the prominent R or R prime in V1.

The above conclusions are based on the observations that the R or R prime in V1 is taller than 5 mm and bigger than any negative deflection in V1 and that the QRS is not abnormally wide. In discussing this possibility, it is useful to think of the variations in V1 from normal to definitely abnormal. The normal variants in lead V1 include the most common pattern of a small r followed by a deeper S wave. A QS pattern in V1 is a normal finding. A variation found in about 5% of the population is the rSr' pattern where neither r is bigger than 5 mm tall or bigger than the S wave in V1. As defined above, a distinctly abnormal pattern would be an R or R prime greater than 5 mm tall and bigger than any negative deflection. If the R or R prime is bigger than 5 mm tall or taller than the depth of any negative wave in V1 but not both the possibilities would be: (1) possibly still a normal variant; (2) right ventricular hypertrophy; (3) a posterior infarction and (4) a right bundle branch block that is not quite as wide as usual, an "incomplete" right bundle branch block (Flow chart 1). If right axis deviation is present, this would favor either incomplete right bundle branch block or right ventricular hypertrophy. If other evidence of conduction disturbance exists, e.g. Mobitz type 2 second degree AV block, then the former would be favored. If not, right ventricular hypertrophy would be favored. Volume overload leading to right ventricular hypertrophy more often presents with prominence of the R prime whereas pressure overload leading to right ventricular hypertrophy more commonly produces just a prominent R wave. Presence of infarction in a wall adjacent to the posterior wall favors posterior infarction. Since this is really the reciprocal of a large posterior Q wave, the pattern here will be that of a prominent initial R wave rather than a prominent R prime.

Observation then proceeds to assessment of unusually deep negative waves in the right precordial leads and unusually tall R waves in lateral leads. Using the voltages recorded in these leads has been used to suggest the presence of left ventricular hypertrophy (Fig. 15). The problem with the electrocardiographic diagnosis of left ventricular hypertrophy based solely on voltage criteria is that the sensitivity of such criteria using precordial leads is only about 50% and about 10–15% of normal people will be labeled as having left ventricular hypertrophy when they do not have it. Using voltage criteria from the limb leads, such as lead I or lead aVL, eliminates much of the inaccuracy related to people without left ventricular hypertrophy but only identifies about 15% of those who do have left ventricular hypertrophy. An additional problem with voltage criteria is normal young people tend to have larger negative deflections in the right precordial leads and taller R waves in the lateral precordial leads apparently related to their more slender chest walls and due to the fact that many of them have physiologic hypertrophy related to endurance training. The presence of the typical ST and T abnormality accompanying left ventricular hypertrophy (called by some a "strain pattern") and found in the tall R wave leads as so beautifully demonstrated by Romhilt and Estes only reduces the false positives but still leaves the sensitivity at about 50%. Finally, newer imaging modalities, such as magnetic resonance imaging, are now beginning to help sort out the relative values of various voltage criteria. For the time being, using a combined sum of the largest negative wave in

FLOW CHART 1: Variations in V1



(Abbreviations: +: Consider possible; RVH: Right ventricular hypertrophy; ICRBBB: Incomplete right bundle branch block; CRBBB: Complete right bundle branch block; LBBB: Left bundle branch block; IVCD: Intraventricular conduction defect; WPW: Wolff-Parkinson-White anomaly)

V1 or V2 plus the tallest R wave in V5 or V6 of more than 35 mm in an individual over 35 years of age as an electrocardiographic screening to suggest possible left ventricular hypertrophy would seem reasonable. Unless the voltages are extreme, perhaps the best interpretation might be to apply the term "possible left ventricular hypertrophy" and label the electrocardiogram as perhaps borderline abnormal. R waves of greater than 15 mm in lead I or in lead aVL of greater than 11 mm in the absence of moderate to marked left axis deviation might be more forcefully labeled as representing true left ventricular hypertrophy. For those electrocardiograms with high precordial voltages in those less than 35 years old, one should be cautious about being dogmatic about the diagnosis of left ventricular hypertrophy. Of course, the presence of the typical STT "strain pattern" should be respected as relatively quite diagnostic of the diagnosis of left ventricular hypertrophy, especially when accompanied by voltage criteria. Currently, the most readily available and reasonably accurate method to follow-up on the possibility of left ventricular hypertrophy is the transthoracic echocardiogram.

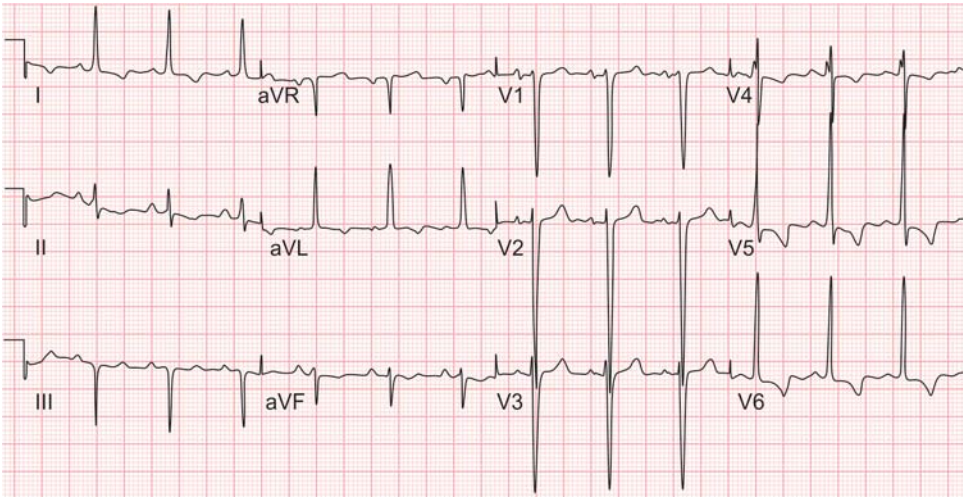


FIGURE 15: An example of left ventricular hypertrophy with secondary repolarization abnormality

Completion of the inspection of the precordial leads involves looking for "poor r wave progression" and/or "late precordial transition". These are purely descriptive terms and should not be viewed as necessarily reflecting any true pathology of the heart. Descriptively "poor r wave progression" is meant to mean that there is an unusually small initial r wave in lead V2 and/or that the r wave in V3 is not larger than the r wave in V2. Late precordial transition means that the transition across the precordial leads from right to left to the lead where the R wave has become larger than the S wave has not occurred by at least lead V5. Transition before that in the right precordial leads including lead V2 is usually a normal finding. Unfortunately these aberrations described may be produced by improper electrode placement such as placement of the right precordial leads an interspace too rostral or by improper placement of leads V5 or V6. Even without improper lead placement, the significance of these findings is not substantial. The interpreter might suggest the possibility of right ventricular hypertrophy and/or emphysema, the possibility of an anterior wall myocardial infarction, the possibility that the finding simply reflects conditions causing right or left axis deviation, or the possibility that the poor r progression might be due to left ventricular hypertrophy. In the absence of electrocardiographic or other clinical abnormalities, it would be more than reasonable to deemphasize this finding.

ST-T WAVE ABNORMALITIES

Having completed, the observation for QRS abnormalities, attention can be given to T wave abnormalities. In the adult with no prior electrocardiogram for comparison, the leads that are the most critical are the same leads as suggested for identification of pathological Q waves indicative of a myocardial infarction. Specifically this would exclude leads aVR, III, aVL and V1. Consistently in the adult the T waves in leads I and II should be upright and should be isoelectric or upright in lead aVF. In the precordial leads, T waves should be isoelectric or upright in lead V2 and always upright in leads V3 through V6. In the pediatric age group, inverted T waves extending further leftward than lead V2 are often present. By the teenage years and in some individuals in their early twenties, T wave inversion in V2 and sometimes V3 may represent normal variants. If prior electrocardiograms are available, then new T wave changes in any lead may have clinical relevance.

Having identified definite T wave abnormalities always requires clinical correlation without assuming that the changes represent serious cardiac abnormality. Certainly they could reflect a relatively benign condition such as hyperventilation. In some young people, T wave inversions have been observed following meals and are absent when the electrocardiogram is recorded in the fasting state. Such T changes following a meal revert to normal following the administration of oral potassium. They usually do not represent serious cardiac abnormality. Other conditions such as low serum potassium or the presence of a drug affecting cardiac ion channels may be responsible for T wave changes. Subarachnoid hemorrhage may produce profound and diffuse T wave abnormalities and in some cases produce changes of an acute evolving ST elevation myocardial infarction. Certainly T wave changes may also reflect serious myocardial abnormality from chronic or new ischemia to injury to non-Q wave myocardial infarction.

Perhaps the most difficult judgments have to do with ST segment deviations. In general observable ST depressions other than in lead aVR should be considered abnormalities. While many of these ST depressions are quite nonspecific, the ST segments manifesting as a straight line that is horizontal or downsloping in two spatially adjacent leads should suggest serious cardiac ischemia as a highly likely possibility. The greatest difficulty can be the discrimination between ST elevations that might represent a normal variant and those that represent acute transmural ischemic injury. Standards have been published that state that ST elevations with a J point elevation of equal to or greater than 0.2 mV (2 mm) in men and equal to or greater than 0.15 mV in women in leads V2-V3 and equal to or greater than 0.1 in any other two contiguous leads should be considered as indicative of acute myocardial ischemia in the absence of left bundle branch block or left ventricular hypertrophy. As opposed to these more focal ST elevations in leads "overlying" specific ventricular wall segments served by a specific coronary artery, more diffuse ST elevations have a different interpretation. Diffuse ST elevations may be defined as ST elevation in leads I, II, aVF and usually III plus leads V2 through V6. Usually lead aVL is not involved while lead V1 does not show significant ST elevation, although it may. The finding of this diffuse ST elevation should strongly suggest the presence of acute pericarditis (Fig. 16). The additional finding of PR depression can be a helpful confirmatory finding. Nevertheless, for both localized ST elevations and diffuse ST elevations, the overlap with ST elevations representing such normal variants as "early repolarization" is quite real. Prior electrocardiograms are most helpful in making this discrimination. In addition ST elevations that are greater with faster heart rates than those elevations recorded on prior electrocardiograms with slower heart rates favors epicardial injury from pericarditis over early repolarization.

Following the schema outline above with practice and experience should lead to rapid and reasonably accurate interpretations of electrocardiograms. Once the rhythm is determined, then, when appropriate, moving on to the QRS-ST-T analysis. A quick determination of QRS width and QRS axis leads to the implications and diagnoses described above. A sweep of the eye of leads I, II and aVF plus leads V2 through V6 for pathological Q waves, ST and T waves, plus looking at the precordial leads V1 through V6 for indications of right and left ventricular hypertrophy (plus observing leads I and aVL for voltages suggesting left ventricular hypertrophy) almost completes the process. As mentioned observing the precordial leads for the nebulous terms "poor r wave progression and/or late precordial transition" would be included as the eye sweeps across leads V2 through V6.

THE "U" WAVE

The U wave is a low amplitude wave of about 0.3 mV (0.3 mm) following the T wave. It is most likely to be observed in leads V2 and V3. Under normal circumstances, it most commonly observed at heart rates of 65 or less and uncommonly

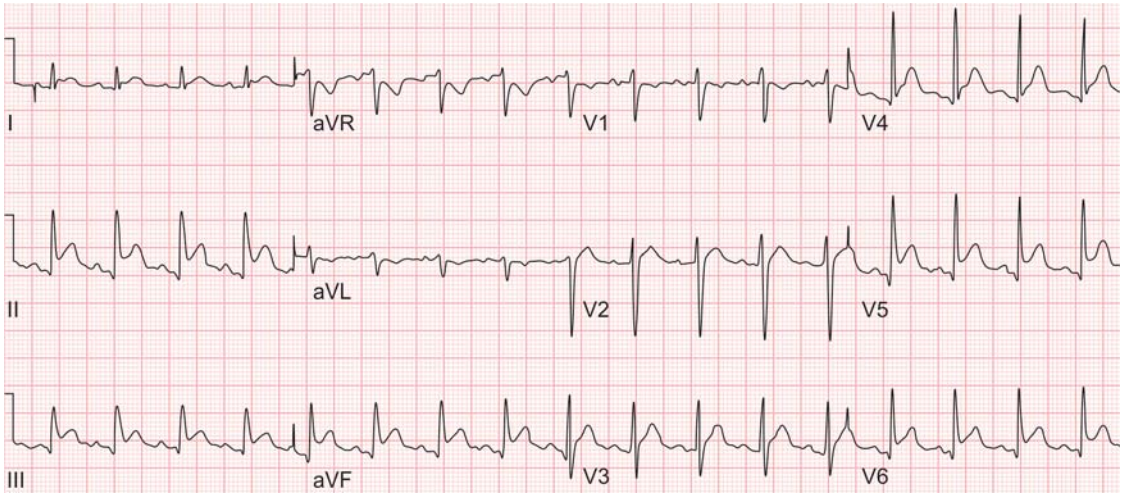


FIGURE 16: An example of acute pericarditis

with heart rates above. Under these circumstances, it is a normal finding. Its physiologic explanation is still debated. Exaggeration of the amplitude of the U wave may exist by itself without accompanying ST or T wave abnormality. More commonly exaggerated amplitude of the U wave may be associated with ST depression and/or diminished T wave amplitude. In some instances the u wave may fuse with the T wave. Under these circumstances, search for causative factors is critical, including hypokalemia as well as cardioactive and other medications that lead to a prolonged QT interval as well congenital varieties of the long QT syndrome.

THE QT INTERVAL

The QT interval is derived by the measurement from the onset of the QRS complex representing the onset of ventricular depolarization to the end of the T wave representing the latest indication of ventricular repolarization. There are major problems with defining the normal QT interval because of variations on a gender and age basis, because of difficulties in determining the end of the T wave, because of lack of consensus as the best way to correct for the normal variation in the QT interval based on heart rate, and because of unified opinion as to which lead or leads should be used to measure the QT interval. Further compounding the problem is potential fusion of the u wave with the T wave. Furthermore, the initial estimates of the normal QT interval were done using single channel machines with leads recorded sequentially. Most electrocardiograms today are done using digital automated machines recording all leads simultaneously. In the latter instance, the true initial onset of the QRS and the true completion of the T wave can be derived. Relative to correction of the QT interval for heart rate, the most commonly used method is the Bazett's formula in which the measured QT is divided by the square root of the R-to-R interval in seconds. For instance, a measured QT derived at a heart rate of 60 beats per minute would be the corrected the corrected QT interval or QTc. However, the validity of this correction especially at elevated heart rates is open to serious question. More recent population studies have used correction of the QT based on a linear or power function of the R-to-R interval. Attempting to define a QT interval when there is substantial variation in the R-to-R intervals as occurs with atrial fibrillation or when the defining the end of the T wave is unreliable is discouraged.

Current recommendations defining an abnormally prolonged adjusted QT interval are equal to or greater than 460 msecs in women and equal to or greater than 450 msecs in men. Current recommendation defines a short rate adjusted QT as equal to or less than 390 msecs. The FDA has recommended that rate corrected QT intervals should be subdivided into three severities when considering QT prolonging properties of drugs: greater than 450 msecs, greater than 480 msecs and greater than 500 msecs.

Adjustment of the QT interval in situations where the QRS duration is prolonged can be done by using the QT interval minus the QRS duration and applying established standards for this JT interval.

Finally, all QT prolongations generated by computer-assisted automated electrocardiographic machines should be confirmed by visual inspection by the interpreter.

ABNORMALITIES SUGGESTING RIGHT OR LEFT ATRIAL ENLARGEMENT, DILATATION OR HYPERTROPHY

Perhaps better terms would be right or left atrial abnormality. Tall p waves in lead II, e.g. 3 mm or greater in amplitude, might suggest right atrial abnormality related to emphysema or congenital heart disease. However, sinus tachycardia by itself may also cause this. Tall p waves in the right precordial leads reasonably correlate with right abnormality in congenital heart disease. Left atrial abnormality may manifest as broadened and double humped p waves in lead II and/or as a prominent terminal downward deflection of the p wave in lead V1. A similar finding may occur with sinus tachycardia. Since the validation of the right atrial and left atrial abnormalities with both pressure and volume changes in the respective chambers has been somewhat lacking, sparing and judicious use of these terms is to be recommended, and dogmatic use of these diagnoses in the absence of clinical correlates is to be avoided.

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Chapter 13

ECG Exercise Testing

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Chapter Outline

- Before the Test
  - Indications for Exercise Testing (Patient Selection)
  - Exercise Testing for Diagnosis
  - Exercise Testing for Prognosis
  - Exercise Testing Patients Presenting with Acute Coronary Syndromes
  - Exercise Testing Patients with Heart Failure
  - Exercise Testing Patients after Myocardial Infarction
  - Contraindications to Exercise Testing
- Methodology of Exercise Testing
  - Safety Precautions and Equipment
  - Pretest Preparations
  - Exercise Test Modalities
- During the Test
  - Physiology Review
  - Autonomic Control
  - Autonomic Modulation during Immediate Recovery from Exercise
  - Clinical Correlations
- After the Test
  - ECG Interpretation: Factors Determining Prognosis
  - Silent Ischemia
  - Exercise Induced Arrhythmias
  - Prognostic Utilization of Exercise Testing
- Screening
- Modified Summary for Guidelines

INTRODUCTION

Exercise testing is a noninvasive tool to evaluate the cardiovascular system's response to exercise under carefully controlled conditions. Exercise is the body's most common physiologic stress, and it places major demands on the cardiopulmonary system. Thus, exercise can be considered the most practical test of cardiac perfusion and function. The exercise test, alone and in combination with other noninvasive modalities, remains an important testing method due to its high yield of diagnostic, prognostic and functional information.

In short, the adaptations that occur during an exercise test allow the body to increase its metabolic rate to greater than 20 times that of rest, during which time cardiac output can increase as much as sixfold. The magnitude of these responses is dependent on a multitude of factors including age, gender, body size, type of exercise, fitness and the presence or absence of heart disease. The major central and peripheral changes that occur from rest to maximal exercise will be described in the proceeding pages of this chapter. The interpretation of the exercise test requires understanding exercise physiology and pathophysiology as well as expertise in electrocardiography. Certification for those who conduct the exams is extremely important because this technology has spread beyond the subspecialty of cardiology. For this reason, the American College of Physicians (ACP) and American College of Cardiology (ACC) and the American Heart Association (AHA) have published clinical competence guidelines for physicians performing exercise testing (www.acc.org/qualityandscience/clinical/statements.htm, www.cardiology.org)[1,2]

The exercise test plays a critical role in the diagnosis and management of heart disease patients because the equipment and personnel for performing it are readily available, the testing equipment is relatively inexpensive, it can be performed in the doctor's office, and it does not require injections or exposure to radiation. Furthermore, it can determine the degree of disability and impairment to quality of life as well as be the first step in rehabilitation and altering a major risk factor (physical inactivity).

BEFORE THE TEST

INDICATIONS FOR EXERCISE TESTING (PATIENT SELECTION)

The indications for an exercise test according to the guidelines are now presented and will be discussed later.

EXERCISE TESTING FOR DIAGNOSIS

The ACC/AHA guidelines for the diagnostic use of the standard exercise test have stated that it is appropriate for testing of adult male or female patients (including those with complete right bundle-branch block or with less than one millimeter of resting ST depression) with an *intermediate pretest probability* of

TABLE 1

Pretest probability of coronary artery disease by symptoms, gender and age

Age[a]	*Gender*	*Typical/angina*[b]	*Atypical/probable angina*	*Nonanginal chest pain*	*Asymptomatic*
30–39	Men	Intermediate	Intermediate	Low	Very low
	Women	Intermediate	Very low	Very low	Very low
40–49	Men	High	Intermediate	Intermediate	Low
	Women	Intermediate	Low	Very low	Very low
50–59	Men	High	Intermediate	Intermediate	Low
	Women	Intermediate	Intermediate	Low	Very low
60–69	Men	High	Intermediate	Intermediate	Low
	Women	High	Intermediate	Intermediate	Low

[a]There are no data for patients younger than 30 or older than 69, but it can be assumed that the prevalence of CAD is low for those less than 30 years of age and higher for those over 69 years of age.
[b]High = > 90%, intermediate = 10–90%, low = < 10%, very low = < 5%.

coronary artery disease (CAD) based on gender, age and symptoms (Table 1).

EXERCISE TESTING FOR PROGNOSIS

Indications for exercise testing to assess risk and prognosis in patients with symptoms or with a prior history of CAD:

Class I (Definitely Appropriate)

Conditions for which there is evidence and/or general agreement that the standard exercise test is useful and helpful to assess risk and prognosis in patients with symptoms or a prior history of CAD who:

- are undergoing initial evaluation with suspected or known CAD. Specific exceptions are noted below in Class IIb.
- have suspected or known CAD previously evaluated with significant change in clinical status.

Class IIb (May Be Appropriate)

Conditions for which there is conflicting evidence and/or a divergence of opinion that the standard exercise test is useful and helpful to assess risk and prognosis in patients with symptoms or a prior history of CAD but the usefulness/efficacy is less well established.

- Patients who demonstrate the following ECG abnormalities:
  - — Pre-excitation (Wolff-Parkinson-White) syndrome
  - — Electronically paced ventricular rhythm
  - — More than one millimeter of resting ST depression
  - — Complete left bundle branch block.
- Patients with a stable clinical course who undergo periodic monitoring to guide management.

EXERCISE TESTING PATIENTS PRESENTING WITH ACUTE CORONARY SYNDROMES

The CNR Cardiology Research group in Italy has reviewed the literature to evaluate whether evidence still supports the use of ECG as first-choice stress-testing modality for acute coronary syndromes (ACS).[3] They concluded that a large body of evidence still supports the use of the exercise ECG as the most cost-effective tool for prognostic purposes as well as for quality of life assessment following ACS. This is consistent with the ACC/AHA guidelines, which state that patients who are pain free, have either a normal or non-diagnostic ECG or one that is unchanged from previous tracings, and have a normal set of initial cardiac enzymes are appropriate candidates for further evaluation with exercise ECG stress testing. If the patient is low risk and does not experience any further ischemic discomfort has a low risk follow-up 12-lead ECG after 6–8 hours of observation, the patient may be considered for an early exercise test. Ideally, this test is performed before discharge and is supervised by an experienced physician. In the conservative arm of the Treat Angina with aggrastat and determine Cost of Therapy with an Invasive or Conservative Strategy—Thrombolysis In Myocardial Infarction (TACTICS-TIMI) 18 trial, patients with appropriate medical therapy could safely endure exercise or pharmacologic stress testing within 48–72 hours of admission, as only one death occurred following stress testing in 847 patients with unstable angina or non-ST elevation myocardial infarction (NSTEMI).[4] Alternatively, a patient can be discharged and return for the test as an outpatient within 3 days. A recent study randomizing patients with ACS and negative troponins to either stress echocardiography or symptom-limited ECG treadmill testing, however, suggested that the incorporation of the imaging modality resulted in better risk stratification. Furthermore, there was significant cost benefit as fewer patients were classified as intermediate risk which would elicit further testing.[5]

EXERCISE TESTING PATIENTS WITH HEART FAILURE

Traditionally, exercise tests were thought to only be a tool to diagnose coronary disease; however, it is now recognized to have major applications for assessing functional capabilities, therapeutic interventions, and estimating prognosis in heart failure. Numerous hemodynamic abnormalities underlie the reduced exercise capacity commonly observed in chronic heart failure, including:

- impaired heart rate responses;
- inability to distribute cardiac output normally;

- abnormal arterial vasodilatory capacity;
- abnormal cellular metabolism in skeletal muscle;
- higher than normal systemic vascular resistance;
- higher than normal pulmonary pressures;
- ventilatory abnormalities that increase the work of breathing and cause exertional dyspnea.[6]

Intervention with angiotensin-converting enzyme (ACE)-inhibition, β blockade, cardiac resynchronization therapy (CRT) or exercise training can improve many of these abnormalities. Over the last 20 years, exercise testing with ventilatory gas exchange responses has been shown to have a critical role in the risk paradigm in heart failure.

EXERCISE TESTING PATIENTS AFTER MYOCARDIAL INFARCTION

The benefits of performing an exercise test in post-MI patients are listed in Table 2. Evaluation of patients with exercise testing can expedite and optimize their discharge from the hospital. Patients' responses to exercise, their work capacity and limiting factors (pulmonary, cardiovascular, or mechanical) at the time of discharge can be assessed by the exercise test. An exercise test prior to discharge is helpful in providing patients with guidelines for exercise at home, reassuring them of their physical status, advising them to resume or increase their activity level, advising them on timing of return to work and in determining the risk of complications. Psychologically, it can improve the patient's self-confidence by making the patient less anxious about daily physical activities and help them to rehabilitate themselves, which is an unquantifiable benefit. The test has been helpful in reassuring spouses of post-MI patients of their physical capabilities as well.

Exercise testing is also an important tool in exercise training as part of comprehensive cardiac rehabilitation. It can be used to develop and modify an exercise prescription, assist in providing activity counseling and assess the patient's progress by comparing physiologic response at the initiation of the exercise training program to response after weeks or months of training.

TABLE 2

Benefits of exercise testing post-MI

Predischarge submaximal test
• Optimizing discharge • Altering medical therapy • Triaging for intensity of follow-up • First step in rehabilitation—assurance, encouragement • Reassuring spouse • Recognizing exercise-induced ischemia and dysrhythmias
Maximal test for return to normal activities
• Determining limitations • Prognostication • Reassuring employers • Determining level of disability • Triaging for invasive studies • Deciding on medications • Exercise prescription • Continued rehabilitation

TABLE 3

Contraindications to exercise testing

Absolute
• High-risk unstable angina • Uncontrolled cardiac arrhythmias causing symptoms or hemodynamic compromise • Symptomatic severe aortic stenosis • Uncontrolled symptomatic heart failure • Acute pulmonary embolus or pulmonary infarction • Acute myocarditis or pericarditis • Acute aortic dissection
Relative[a]
• Left main coronary stenosis • Moderate stenotic valvular heart disease • Electrolyte abnormalities • Severe arterial hypertension[b] • Tachyarrhythmias or bradyarrhythmias • Hypertrophic cardiomyopathy and other forms of outflow tract obstruction • Mental or physical impairment leading to inability to exercise adequately • High-degree atrioventricular block
[a]Relative contraindications can be superseded if the benefits of exercise outweigh the risks. [b]In the absence of definitive evidence, the committee suggested systolic blood pressure (SBP) of greater than 200 mm Hg and/or diastolic blood pressure of greater than 110 mm Hg. (*Source:* Gibbons, Balady, Bricker, et al.[9])

One consistent finding in the review of the post-MI exercise test literature that included a follow-up for cardiac end points, is that patients who achieved whatever criteria set forth for exercise testing were at lower risk than patients not tested. From meta-analyses of multiple studies, only an abnormal SBP response or a low exercise capacity were consistently associated with a poor outcome and were more predictive of adverse cardiac events after MI than measures of exercise-induced ischemia.[7,8]

CONTRAINDICATIONS TO EXERCISE TESTING

Table 3 lists some of the absolute and relative contraindications to exercise testing that must be considered prior to prescribing a test for a patient.

METHODOLOGY OF EXERCISE TESTING

Use of proper methodology is critical for patient safety and accurate results. Updated guidelines are available from the AHA/ACC that are based on a multitude of research studies over the last 20 years and have led to greater uniformity in methods.[9,10]

SAFETY PRECAUTIONS AND EQUIPMENT

The safety precautions outlined in the guidelines are very explicit with regard to the requirements for exercise testing. Perhaps due to an expanded knowledge concerning indications, contraindications and endpoints, maximal exercise testing appears safer today (< 1 untoward event per 10,000 tests) than it did two decades ago.

Besides emergency equipment, the safety and accuracy of the testing equipment must be considered. The treadmill should

have front and side rails to help subjects steady themselves and should be calibrated monthly. Although numerous clever devices have been developed to automate blood pressure measurement during exercise, none can be recommended except those that allow audible monitoring of the Korotkoff sounds with operator validation. The time-proven method of holding the subject's arm with a stethoscope placed over the brachial artery remains the most reliable.

PRETEST PREPARATIONS

When the test is scheduled, the patient should be instructed not to eat, drink or smoke at least 2 hours prior to the test and to come dressed for exercise, including proper footwear.

During the pretest evaluation, the patient's usual level of exercise activity should be established to help determine a baseline and an appropriate target workload for testing. The physician should also review the patient's medical history, considering any conditions that can increase the risk of testing. The Table 3 lists the absolute and relative contraindications to exercise testing. Testing patients with aortic stenosis should be done with great care because they can develop severe cardiovascular complications. *Thus, a physical examination—including assessment of systolic murmurs—should be performed before all exercise tests.* If a loud systolic murmur is heard and/or the carotid pulse exhibits a slow upstroke, an echocardiogram is recommended prior to testing.

Pretest standard 12-lead ECGs are necessary in both the supine and the standing positions. Good skin preparation is necessary for appropriate conductance to avoid artifacts and is especially important for elderly patients who have a higher skin resistance with tendency toward contact noise. The electrical perturbations and artifact caused by exercise can be minimized by appropriate electrode placement, keeping the arm electrodes off the chest and placing them on the shoulders, placing the ground (right leg) electrode on the back, outside of the cardiac field, placing the left leg electrodes below the umbilicus and recording the baseline ECG supine. The supine baseline ECG in this modified exercise limb-lead placement can serve as the reference resting ECG prior to the onset of exercise.

Hyperventilation should be avoided before testing. Subjects with or without disease can exhibit ST-segment changes with hyperventilation; thus, hyperventilation to identify false-positive responders is no longer considered useful. The next important methodological issue is when to terminate for safety reasons and these indications are summarized in the Table 4.

TABLE 4

Indications for terminating exercise testing

Absolute indications
• Moderate to severe angina • Increasing nervous system symptoms (e.g. ataxia, dizziness or near-syncope) • Signs of poor perfusion (cyanosis or pallor) • Technical difficulties in monitoring ECG or SBP • Subject's desire to stop • Sustained ventricular tachycardia • ST-segment elevation (≥ 1.0 mm) in leads without diagnostic Q waves (other than V_1 or aVR)
Relative indications
• Drop in SBP of ≥ 10 mm Hg from baseline blood pressure despite an increase in workload in the absence of other evidence of ischemia • ST or QRS changes such as excessive ST-segment depression (> 2 mm of horizontal or down-sloping ST-segment depression) or marked axis shift • Arrhythmias other than sustained ventricular tachycardia, including multifocal PVCs, triplets of PVCs, supraventricular tachycardia, heart block or bradyarrhythmias • Fatigue, shortness of breath, wheezing, leg cramps or claudication • Development of bundle branch block or intraventricular conduction delay that cannot be distinguished from ventricular tachycardia • Increasing chest pain • Hypertensive response[a]
(Abbreviation: PVCs: Premature ventricular contractions) [a]In the absence of definitive evidence, the committee suggests SBP of > 250 mm Hg and/or a diastolic blood pressure of > 115 mm Hg. (*Source:* Gibbons, Balady, Bricker, et al.[9])

EXERCISE TEST MODALITIES

Three types of exercise can be used to stress the cardiovascular system: (1) isometric; (2) dynamic or (3) a combination of the two. *Isometric exercise*, defined as constant muscular contraction without movement (such as handgrip), imposes a disproportionate pressure load on the left ventricle relative to the body's ability to supply oxygen. *Dynamic exercise* is defined as rhythmic muscular activity resulting in movement, and it initiates a more appropriate increase in cardiac output and oxygen exchange. This chapter considers only dynamic exercise testing, because a delivered workload can be calibrated accurately and the physiologic response measured easily. Isometric exercise is not recommended for routine exercise testing.

Bicycle Ergometer versus Treadmill

The bicycle ergometer usually costs less, takes up less space and makes less noise than a treadmill. Although bicycling is a dynamic exercise, most individuals perform more work on a treadmill because a greater muscle mass is involved, and most subjects are more familiar with walking than cycling. These factors create considerable variability in test results, which is reflected in most studies comparing exercise on an upright cycle ergometer versus a treadmill exercise. Specifically, while maximal heart rate values have been demonstrated to be roughly similar, maximal oxygen uptake has been shown to be up to 25% greater during treadmill exercise.

Exercise Protocols

The most common protocols, their stages and the predicted oxygen cost of each stage are illustrated in Figure 1. The exercise protocol should be progressive with even increments in speed and grade whenever possible. Smaller, even, and more frequent work increments are preferred over larger, uneven, and less frequent increases, because the former yield a more accurate estimation of exercise capacity. Recent guidelines suggest that protocols should be individualized for each subject such that test duration is approximately 8–12 minutes. Because ramp testing uses small and even increments, it permits a more

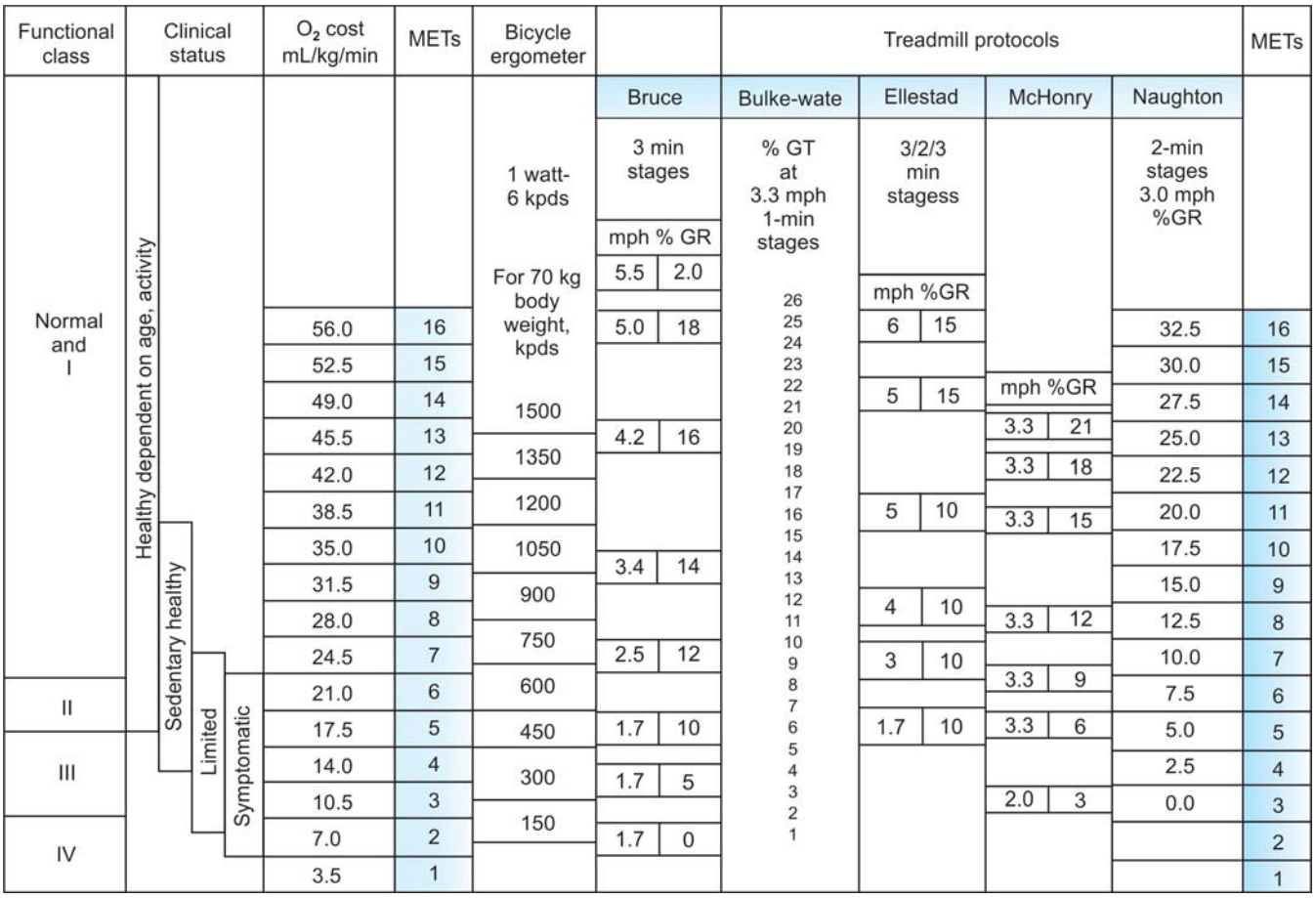


FIGURE 1: The most common protocols, their stages and the predicted oxygen cost of each stage (Abbreviations: GR: Grade; METs: Metabolic equivalents)

accurate estimation of exercise capacity and can be individualized to yield targeted test duration.

Add-Ons to the Exercise Test

Some of the newer add-ons or substitutes for the exercise test have the advantage of being able to localize ischemia as well as diagnose coronary disease when the baseline ECG negates ST analysis (more than one millimeter ST depression, left bundle-branch block, WPW). Stress echocardiograms, stress nuclear perfusion scans and cardiac MRIs also provide an estimation of ventricular function as well as tissue viability information. Non-exercise stress techniques also permit diagnostic assessment of patients unable to exercise. Although the newer technologies appear to have better diagnostic characteristics, this is not always the case. When used, diagnostic scores that incorporate other variables in addition to the ST-segment yield results similar to imaging procedures.

DURING THE TEST

PHYSIOLOGY REVIEW

This would be a good time to do a quick review of some of the basic principles of physiology that are pertinent to understanding the mechanisms behind the body's response to exercise. For brief overviews of the major central and peripheral adaptations that occur from rest to maximal exercise see Figures 2A and B.

Oxygen Consumption

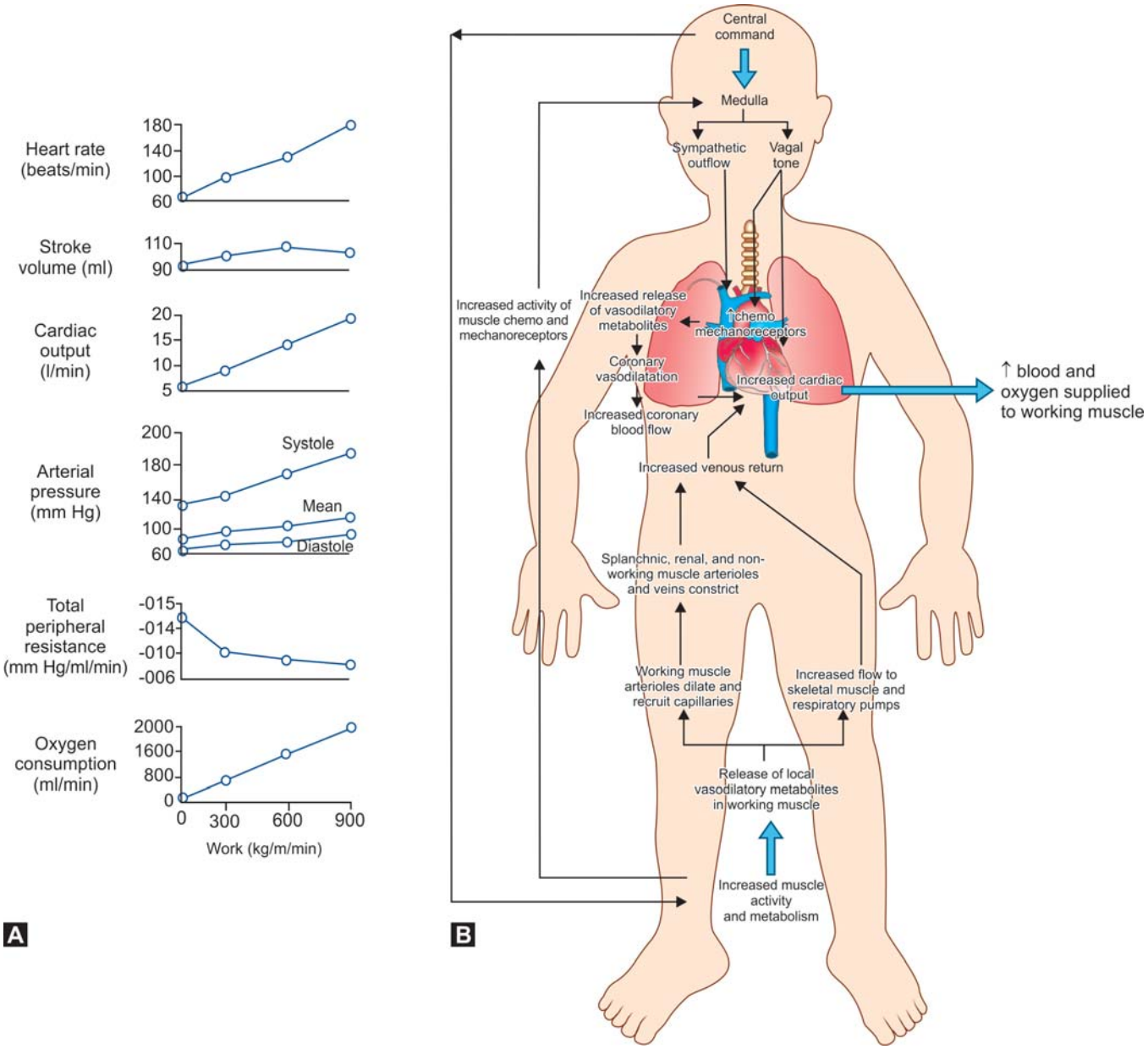
Two basic principles of exercise physiology are important to understand in regard to exercise testing. The first is a *physiologic* principle: total body oxygen uptake and myocardial oxygen uptake are distinct in their determinants and in the way they are measured or estimated (Table 5).

TABLE 5

Two basic principles of exercise physiology

Myocardial oxygen consumption	=	Heart rate × SBP (determinants include wall tension = left ventricular pressure × volume; contractility; and heart rate)
Ventilatory oxygen consumption (VO_2)	=	External work performed, or cardiac output[a] × A-VO_2 difference

(Abbreviations: A-VO_2: Arteriovenous oxygen difference; VO_2: Volume oxygen consumption; vol%: Volume percent).
[a]The arteriovenous O_2 difference is approximately 15–17 vol% at maximal exercise in most individuals; therefore, VO_{2max} generally reflects the extent to which cardiac output increases.



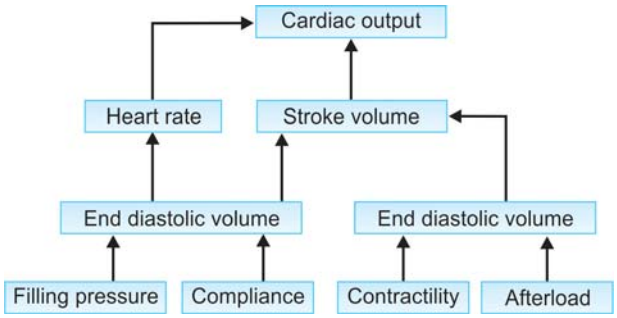
FIGURES 2A AND B: (A) Graphs of the hemodynamic responses to dynamic exercise. (B) Sequence of physiological responses to dynamic exercise (*Source*: Modified from Cardiovascular Physiology at a Glance, Blackwell Publishers, 2004)

Total body or ventilatory oxygen uptake [volume oxygen consumption (VO_2)] is the amount of oxygen extracted from inspired air (Flow charts 1 and 2). The determinants of VO_2 are cardiac output and the peripheral arteriovenous oxygen difference. Maximal arteriovenous difference is physiologically limited to roughly 15–17 ml/dL. Thus maximal arteriovenous difference behaves more or less as a constant, making maximal oxygen uptake an indirect estimate of maximal cardiac output.

Myocardial oxygen uptake is the amount of oxygen consumed by the heart muscle. The determinants of myocardial oxygen uptake include intramyocardial wall tension (left ventricular pressure and end-diastolic volume), contractility, and heart rate. It has been shown that myocardial oxygen uptake can be estimated by the product of heart rate and SBP, or double product. This information is valuable clinically because exercise-induced angina often occurs at the same myocardial oxygen demand (double product), and the higher the double product achieved, the better is myocardial perfusion and prognosis. When such is not the case, the influence of other factors should be suspected, such as a recent meal, abnormal ambient temperature or coronary artery spasm. Thus, it is not surprising that the double product during exercise testing has long been known to be a significant independent predictor of myocardial ischemia severity[11] and prognosis.[12,13]

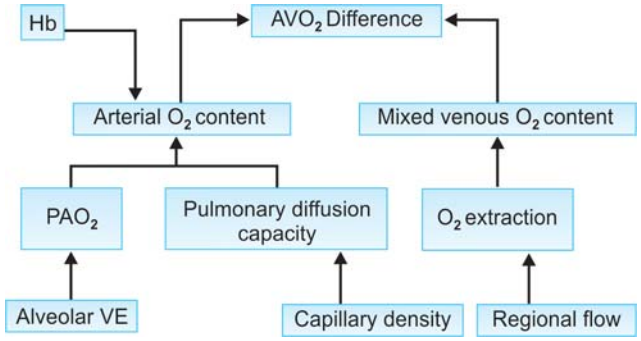
The second principle is one of *pathophysiology*: considerable interaction takes place between the exercise test manifestations of abnormalities in myocardial perfusion and function. The electrocardiographic response and angina are closely related to myocardial ischemia (usually secondary to CAD), whereas exercise capacity, SBP and heart rate responses to exercise can

FLOW CHART 1: Central determinants of maximal oxygen uptake



(*Source*: Myers J, Froelicher VF. Hemodynamic determinants of exercise capacity in chronic heart failure. Ann Intern Med. 1991;115:377-86)

FLOW CHART 2: Peripheral determinants of maximal oxygen uptake. The A-VO_2 difference is the difference between arterial and venous oxygen



(Abbreviations: A-VO_2: Arteriovenous oxygen difference; Hb: Hemoglobin; PAO_2: Partial pressure of alveolar oxygen; VE: Minute ventilation). (*Source*: Myers J, Froelicher VF. Hemodynamic determinants of exercise capacity in chronic heart failure. Ann Intern Med. 1991;115:377-86)

be determined by the presence of myocardial ischemia, myocardial dysfunction or responses in the periphery. Exercise-induced ischemia can cause cardiac dysfunction which results in exercise impairment and an abnormal SBP response.

Metabolic Equivalents Term (MET)

Since exercise testing fundamentally involves the measurement of work, there are several concepts regarding work that are important to understand. The common biologic measure of total body work is the oxygen uptake, which is usually expressed as a rate (making it a measure of power) in liters per minute. The MET is the term commonly used to express the oxygen requirement of work during an exercise test on a treadmill or cycle ergometer. One MET is equated with the resting metabolic rate (approximately 3.5 mL of O_2/kg/min), and a MET value achieved from an exercise test is a multiple of the resting metabolic rate, either measured directly (as oxygen uptake) or estimated from the maximal workload achieved using standardized equations.[14] Table 6 lists clinically meaningful METs for exercise, prognosis and maximal performance, and Figure 3 depicts exercise capacity and the relationship between age and METs.

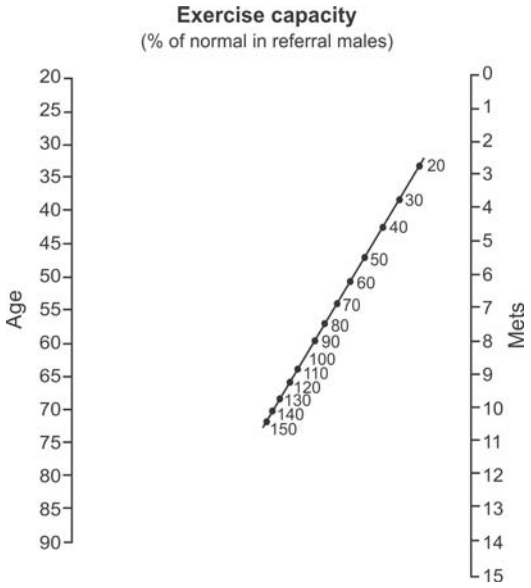


FIGURE 3: The exercise capacity nomogram, providing a relative estimate of normal for age, with 100% being as expected for age in a clinical population. (Abbreviation: METs: Metabolic equivalents)

TABLE 6

Clinically significant metabolic equivalents for maximum exercise

1 MET	Resting
2 METs	Level walking at 2 mph
4 METs	Level walking at 4 mph
< 5 METs	Poor prognosis; peak cost of basic activities of daily living
10 METs	Prognosis with medical therapy as good as coronary artery bypass surgery; unlikely to exhibit significant nuclear perfusion defect
13 METs	Excellent prognosis regardless of other exercise responses
18 METs	Elite endurance athletes
20 METs	World-class athletes

(Abbreviations: MET: metabolic equivalent, or a unit of sitting resting oxygen uptake; 1 MET: 3.5 mL/kg/min oxygen uptake; mph: Miles per hour)

Acute Cardiopulmonary Response to Exercise

The intact cardiovascular system responds to acute exercise with a series of adjustments that assure the following (Fig. 2):

- Active muscles receive blood supply according to their metabolic demands
- Heat generated by the muscles is dissipated
- Blood supply to the brain and heart are maintained

This response requires a major redistribution of cardiac output along with a number of local metabolic changes. The usual measure of the capacity of the body to deliver and use oxygen is the maximal oxygen consumption (VO_{2max}). Thus, the limits of the cardiopulmonary system are defined by VO_{2max}, which can be expressed by the Fick principle:

$$VO_{2max} = \text{maximal cardiac output} \times \text{maximal arteriovenous oxygen difference}$$

Cardiac output must closely match ventilation in the lung to deliver oxygen to the working muscle. The VO_{2max} is

determined by the maximal amount of ventilation [volume of expired gas (V_E)] moving into and out of the lung and by the fraction of this ventilation that is extracted by the tissues:

$$VO_2 = V_E \times (FiO_2 – FeO_2)$$

where V_E is minute ventilation, and FiO_2 and FeO_2 are the fractional concentration of oxygen in the inspired and expired air respectively. To measure VO_2 accurately, CO_2 in the expired air [carbon dioxide elimination (VCO_2)] must also be measured; the major purpose of VCO_2 in this equation is to correct for the difference in ventilation between inspired and expired air. The VCO_2 is also a valuable measurement clinically for chronic heart failure patients because the rate of increase in VCO_2 relative to the work rate or ventilation parallels the severity of heart failure and is a powerful prognostic marker.

The cardiopulmonary limits (VO_{2max}) are therefore defined by the following:

- A central component (cardiac output) describes the capacity of the heart to function as a pump.
- Peripheral factors (arteriovenous oxygen difference) describe the capacity of the lung to oxygenate the blood delivered to it as well as the capacity of the working muscle to extract this oxygen from the blood.

Central Factors

Heart rate: Sympathetic and parasympathetic nervous system influences are responsible for the cardiovascular system's first response to exercise, which is an increase in heart rate. Vagal withdrawal is responsible for the initial 10–30 beats per minute change, whereas the remainder is thought to be largely caused by increased sympathetic outflow. Of the two major components of cardiac output, heart rate and stroke volume, heart rate is responsible for most of the increase in cardiac output during exercise, particularly at higher levels. Heart rate increases linearly with workload and oxygen uptake.

The heart rate response to exercise is influenced by several factors including age, type of activity, body position, fitness, the presence of heart disease, medication use, blood volume and environment. Of these, the most important factor is age, as a significant decline in maximal heart rate occurs with increasing age. This attenuation is thought to be a result of intrinsic cardiac changes rather than neural influences. It should be noted that there is a great deal of variability around the regression line between maximal heart rate and age, thus, age-related maximal heart rate estimates are a relatively poor index of maximal effort. Since prediction of maximal heart rate is inaccurate, exercise should be symptom-limited and not targeted on achieving a certain heart rate. Therefore, diagnostic information can be obtained even if a certain target heart rate (i.e. 85% of age-predicted maximal heart rate) is not achieved. Interestingly, of all heart rate measurements during exercise and recovery, the heart rate increase at peak exercise in 1,959 patients referred for clinical treadmill testing was the most powerful predictor of cardiovascular prognosis after adjustments for potential confounders.[15] Maximal heart rate is unchanged or can be slightly reduced after a program of training whereas resting heart rate is frequently reduced after training as a result of enhanced parasympathetic tone.

Stroke volume: The product of stroke volume, which is the volume of blood ejected per heartbeat, and heart rate determines cardiac output. Stroke volume is equal to the difference between end-diastolic and end-systolic volume. Thus, a greater diastolic filling (preload) will increase stroke volume. Alternatively, factors that increase arterial blood pressure will resist ventricular outflow (afterload) and result in a reduced stroke volume. During exercise, stroke volume increases up to approximately 50–60% of maximal capacity, after which increases in cardiac output are caused by further increases in heart rate. The extent to which increases in stroke volume during exercise reflect an increase in end-diastolic volume or a decrease in end-systolic volume, or both, is not entirely clear but appears to depend on ventricular function, body position and intensity of exercise. In healthy subjects, after a period of exercise training, stroke volume increases at rest and during exercise. Although the mechanisms have been debated, evidence suggests that this adaptation is caused more by increases in preload, and possibly local adaptations that reduce peripheral vascular resistance, rather than by increases in myocardial contractility. The end-diastolic and end-systolic responses to acute exercise have varied greatly in the literature, but are certainly dependent on presence and type of disease, exercise intensity and exercise position (supine vs upright).

End-systolic volume: End-systolic volume depends on two factors: (1) contractility and (2) afterload.

Contractility describes the forcefulness of the heart's contraction. Increasing contractility reduces end-systolic volume, which results in a greater stroke volume and thus greater cardiac output. Contractility is commonly quantified by the ejection fraction, the percentage of blood ejected from the ventricle during systole (traditionally measured using echocardiographic, radionuclide or angiographic techniques).

Afterload is a measure of the force resisting the ejection of blood by the heart. Increased afterload (or aortic pressure, as is observed with chronic hypertension) results in a reduced ejection fraction and increased end-diastolic and end-systolic volumes. During dynamic exercise, the force resisting ejection in the periphery (total peripheral resistance) is reduced by vasodilation, owing to the effect of local metabolites on the skeletal muscle vasculature. Thus, despite even a fivefold increase in cardiac output among normal subjects during exercise, mean arterial pressure increases only moderately.

Peripheral Factors (Arteriovenous Oxygen Difference)

Oxygen extraction by the tissues during exercise reflects the difference between the oxygen content of the arteries (generally 18–20 ml O_2/100 ml at rest) and the oxygen content in the veins (generally 13–15 ml O_2/100 ml at rest, yielding a typical arteriovenous oxygen difference (A-VO_2) at rest of 4–6 ml O_2/100 ml, approximately 23% extraction). During exercise, this difference widens as the working tissues extract greater amounts of oxygen; venous oxygen content reaches very low levels and A-VO_2 can be as high as 16–18 ml O_2/100 ml with exhaustive exercise. Some oxygenated blood always returns to the heart; however, as smaller amounts of blood continue to flow through,

metabolically less active tissues do not fully extract oxygen. The A-VO_2 is generally considered to widen by a relatively *fixed* amount during exercise, and differences in VO_{2max} are predominantly explained by differences in cardiac output. Some patients with cardiovascular or pulmonary disease, however, exhibit reduced VO_{2max} values that can be attributed to a combination of both central and peripheral factors.

Determinants of arterial oxygen content: Arterial oxygen content is related to the partial pressure of arterial oxygen, which is determined in the lung by alveolar ventilation and pulmonary diffusion capacity, as well as hemoglobin content of the blood. In the absence of pulmonary disease, arterial oxygen content and saturation are usually normal throughout exercise. Patients with symptomatic pulmonary disease often neither ventilate the alveoli adequately nor diffuse oxygen from the lung into the bloodstream normally, resulting in a decrease in arterial oxygen saturation during exercise. Arterial hemoglobin content is also usually normal throughout exercise.

Determinants of venous oxygen content: Venous oxygen content reflects the capacity to extract oxygen from the blood as it flows through the muscle and capillary beds. Extraction is effected by the volume of regional flow through the muscle and capillary density. Muscle blood flow increases in proportion to increased oxygen requirement, which is determined by increased work rate. The increase in blood flow is brought about not only by the increase in cardiac output but also by a preferential redistribution of the cardiac output to the exercising muscle. Locally produced vasodilatory mechanisms along with possible neurogenic dilatation resulting from higher sympathetic activity reduce local vascular resistance and mediate the greater skeletal muscle blood flow. A marked increase in the number of open capillaries reduces diffusion distances, increases capillary blood volume and increases mean transit time, facilitating oxygen delivery to the muscle.

AUTONOMIC CONTROL

Neural Control Mechanisms

The neural control mechanisms responsible for the cardiovascular response to exercise occur through two processes that initiate and maintain this response:

1. *Central command*: Neural impulses, arising from the central nervous system, recruit motor units, excite medullary and spinal neuronal circuits and cause the cardiovascular changes during exercise.
2. *Muscle afferents*: Muscle contraction stimulates afferent endings within the skeletal muscle, which in turn, reflexively evoke the cardiovascular changes.

The latter mechanism called *exercise pressor reflex*, comprises all of the cardiovascular responses reflexively induced from contracting skeletal muscle that cause changes in the efferent sympathetic and parasympathetic outputs to the cardiovascular system. This is ultimately responsible for increases in arterial blood pressure, heart rate, myocardial contractility, cardiac output and blood flow distribution. A specific subset of muscle afferents serve as ergo-receptors activated by either mechanical or metabolic perturbations.

As the demand for cardiac output increases, parasympathetic activity becomes attenuated, while sympathetic activity increases. The sympathetic system releases norepinephrine directly through the sympathetic trunk to the sinus node and myocardium. In addition, norepinephrine and epinephrine from the adrenal medulla act to increase heart rate and increase myocardial contractility, as well as to shunt blood flow to working muscle. By mediating peripheral vasoconstriction in relatively inactive tissues (e.g. kidney and gut), the sympathetic system increases venous return, and vasodilatory metabolites maintain local increased flow to active skeletal muscle. Actively contracting skeletal muscle also increases preload by acting as a venous pump and stimulating sympathetic afferent fibers within the muscle itself.

Pharmacologic blockade studies have helped to elucidate the differential contributions of the two autonomic branches during exercise. Blockade of parasympathetic control with atropine reveals that most of the initial response to exercise, up to a heart rate of 100–120 beats per minute [i.e. a delta heart rate (HR) of 30–40 beats per minute (bpm)], is attributable to the withdrawal of tonic vagal activity. Vagal withdrawal induces a rapid increase in heart rate and cardiac output. Conversely, blockade of sympathetic control with propranolol reveals the importance of augmented sympathetic activity during moderate and heavy exercise. During light exercise, with work loads of 25–40% of VO_{2max} or while heart rate remains within 30 beats per minute over baseline, plasma norepinephrine levels do not significantly increase, confirming that the sympathetic nervous system is more important with higher levels of exercise.

AUTONOMIC MODULATION DURING IMMEDIATE RECOVERY FROM EXERCISE

Autonomic physiology during recovery from acute bouts of exercise involves reactivation of the parasympathetic system and deactivation of sympathetic activity. The decline of heart rate after cessation of exercise is the variable most commonly analyzed to assess the underlying mechanisms. A delay in heart rate recovery has been used as a marker of autonomic dysfunction and/or failure of the cardiovascular system to respond to the normal autonomic responses to exercise. This delay has been shown to be a powerful prognostic marker.[16,17] Time constants have been calculated by fitting heart rate decay data to a number of mathematical models, but the simple change in heart rate from peak exercise to minute 1 or 2 of recovery appears to distinguish and prognosticate survival as well. Early recovery after acute bouts of exercise appears to be dominated by parasympathetic reactivation, with sympathetic withdrawal becoming more important later in recovery. In a pharmacologic blockade study, Imai and his colleagues[18] computed HR recovery decay curves using beat-to-beat data and concluded that short-term and moderate-term HR recovery curves are vagally mediated, because HR decay 30 seconds and 2 minutes into recovery was prolonged with atropine and dual blockade; however, the HR decay for 2 minutes was more prolonged with dual blockade than with atropine alone, indicating that later recovery also depends on sympathetic modulation. Rather than declining, plasma norepinephrine concentrations during the first minute of recovery remain constant or even increase immediately after exercise.

The above principles explain the mechanisms of change during exercise, and now we will explain the clinical correlations that you may expect to see in the patient and how the parameters we follow for diagnostic and prognostic indicators change.

Hemodynamics

The increased demand for myocardial oxygen required by dynamic exercise is the key to the use of exercise testing as a diagnostic tool for CAD. Myocardial oxygen consumption cannot be directly measured in a practical manner, but its relative demand can be estimated from its determinants, such as heart rate, wall tension (left ventricular pressure and diastolic volume), contractility and cardiac work. Although all of these factors increase during exercise, increased heart rate is particularly important in patients who have obstructive CAD. An increase in heart rate results in a shortening of the diastolic filling period, the time during which coronary blood flow is the greatest. In normal coronary arteries, dilation occurs. In obstructed vessels, however, dilation is limited and flow can be decreased by the shortening of the diastolic filling period. This causes inadequate blood flow and therefore insufficient oxygen supply.

Hemodynamic data, including heart rate, blood pressure, and exercise capacity, are important features of the exercise test. Since it can objectively quantify exercise capacity, exercise testing is now commonly used for disability evaluation rather than reliance on functional classifications. No questionnaire or submaximal test can provide as reliable a result as a symptom-limited exercise test.

Heart Rate

Age-predicted maximal heart rate targets are relatively useless for clinical purposes, and they should not be used for exercise testing endpoints. It is surprising how much steeper the age-related decline in maximal heart rate is in clinically referred populations as compared with age-matched normal subjects or volunteers.

Exercise Capacity

When expressing exercise capacity as a relative percentage of what is deemed normal, careful consideration should be given to population characteristics. Exercise capacity is influenced by many factors other than age and gender, including health, activity level, body composition and the exercise mode and protocol used. Exercise capacity should not be reported in total time, rather as the oxygen uptake or MET equivalent of the workload achieved. This method permits the comparison of the results of many different exercise testing protocols. In a recent study of 974 patients who underwent quantitative exercise myocardial perfusion imaging, only 2 of 473 (0.4%) patients achieved greater than or equal to 10 METs demonstrated nuclear perfusion defects consistent with ischemia while 7.1% of patients who achieved fewer than 7 METs had nuclear defects consistent with ischemia.[19] Thus, myocardial perfusion imaging is of little value in patients with predicted exercise capacity greater than 10 METs and simple referral for ECG exercise testing will provide substantial cost-savings.

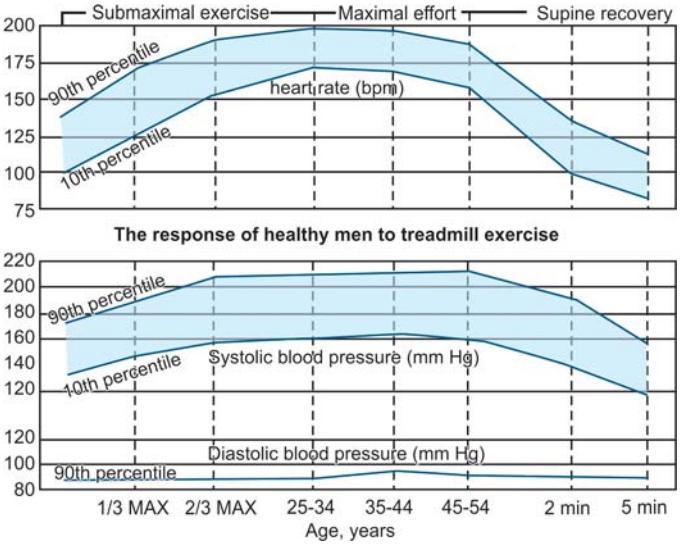


FIGURE 4: The results of a large number of normal individuals who underwent a progressive treadmill test show the response of heart rate and blood pressure according to age (Abbreviation: bpm: Beats per minute)

Blood pressure: The SBP should rise with increasing treadmill workload, whereas diastolic blood pressure usually remains approximately the same or drops (Fig. 4). Although exertional hypotension has been described in many different ways, it has been shown to predict severe angiographic CAD and is associated with a poor prognosis.[20] A drop in SBP below pre-exercise values is the most ominous criterion. A failure of SBP to adequately increase is particularly worrisome in patients who have sustained an MI, have valvular heart disease or have heart failure.

Possible complications: Most complications of the exercise stress test can be avoided by measuring blood pressure, monitoring the ECG, questioning the patient about symptoms and levels of fatigue and assessing appearance during the test. Subjects should be reminded not to grasp the front or side rails because this decreases the work performed and creates noise in the ECG. The subject can rest his or her hands on the rails for balance but should not hang on. Hanging on the rails results in an overestimation of exercise capacity.

As previously mentioned, target heart rates based on age should not be used because the relationship between maximal heart rate and age is poor, and a wide scatter exists around the many different recommended regression lines. Such heart-rate targets result in a submaximal test for some individuals, a maximal test for some, and an unrealistic goal for others. The absolute and relative indications for test termination are listed in Table 4. If none of these endpoints are met, the test should be symptom-limited. The Borg scales are an excellent means of quantifying an individual's effort. Subjects should be monitored for perceived effort level by using the 6–20 Borg scale at 2-minute intervals.

To ensure the safety of exercise testing, the following list of the most dangerous circumstances in the exercise testing laboratory should be recognized:

- When patients exhibit ST-segment elevation (without baseline diagnostic Q waves), this can be associated with

dangerous arrhythmias and infarction. The prevalence is approximately 1 in 1,000 clinical tests and usually occurs in V_2 or aVF rather than V_5.

- When a patient with an ischemic cardiomyopathy exhibits severe chest pain due to ischemia (angina pectoris), a cool-down walk is advisable.
- When a patient develops exertional hypotension accompanied by ischemia (angina or ST-segment depression) or when it occurs in a patient with a history of congestive heart failure (CHF), cardiomyopathy or recent myocardial infarction (MI), safety is a serious issue.
- When a patient with a history of sudden death or collapse during exercise develops premature ventricular depolarizations that become frequent, a cool-down walk is advisable.

Recovery after Exercise

If maximal sensitivity is to be achieved with an exercise test, patients should return to a supine as soon as possible during the post-exercise period (maximal wall stress). It is advisable to record approximately 10 seconds of ECG data while the patient is standing motionless but still at near-maximal heart rate and then have the patient lie down. Having the patient perform a cool-down walk after the test can delay or eliminate the appearance of ST-segment depression, while having patients lie down enhances ST-segment abnormalities in recovery.[21]

Monitoring should continue for at least 5 minutes after exercise or until changes stabilize. An abnormal response occurring only in the recovery period is neither unusual nor necessarily suggestive of a false-positive result. The recovery period, particularly the third minute is critical for ST analysis. Noise should not be a problem, and ST depression at that time has important implications regarding the presence and severity of CAD.[22,23]

A cool-down walk can be helpful in performing tests on patients with an established diagnosis undergoing testing for other than diagnostic reasons, as in testing athletes or patients with CHF, valvular heart disease or a recent MI.

Beta blockers: In our most recent study of the effects of β blockade and heart rate response, we found the sensitivity and predictive accuracy of standard ST criteria for exercise-induced ST-depression significantly decreased in male patients taking β blockers and not reaching an adequate heart rate. In those who fail to reach target heart rate and are not β blocked, sensitivity and predictive accuracy were maintained. The only way to maintain sensitivity with the standard exercise test in the β blocker group who failed to reach target heart rate was to use a treadmill score or 0.5-mm ST-depression as the criterion for abnormal.[24] Due to a greater potential for cardiac events with the cessation of β blockers, they should not be automatically stopped prior to testing. If a patient is to be tested off β blockers, they should not be stopped abruptly but tapered off gradually under physician guidance.

Women

The summary from the guidelines are clearly stated regarding testing women: concern about false-positive ST responses can be addressed by careful assessment of pretest probability and selective use of a stress imaging test before proceeding to angiography. The optimal strategy for circumventing false-positive test results for the diagnosis of coronary disease in women requires the use of scores. There is insufficient data to justify routine stress imaging tests as the initial test for women.

Variable	Circle response	Sum	
Maximal heart rate	Less than 100 bpm = 30		Men
	100 to 129 bpm = 24		
	130 to 159 bpm = 18		
	160 to 189 bpm = 12		
Exercise ST depression	190 to 200 bpm = 6		< 40 = Low probability
	1-2 mm = 15		
Age	>2 mm = 25		
	>55 yrs = 20		40-60 = Intermediate probability
Angina history	40 to 55 yrs = 12		
	Definite/typical = 5		
	Probable/atypical = 3		
	Non-cardiac pain =1		> 60 = High probability
Hypercholesterolemia?	Yes = 5		
Diabetes?	Yes = 5		
Exercise test induced angina?	Occurred = 3		
	Reason for stopping = 5		
	Total Score :		

FIGURE 5: Calculation of the simple score for angiographic coronary disease in men. Choose only one per group. (Abbreviation: bpm: Beats per minute)

Diagnostic Scores

Studies considering non-ECG data consistently demonstrate that the multivariable equations outperform simple ST diagnostic criteria. These equations generally provide a predictive accuracy of 80% (ROC area of 0.80). To obtain the best diagnostic characteristics with the exercise test, clinical and non-ECG test responses should be considered. We have validated simple scores for both men and women. Calculation of a *simple* exercise test score can be done using Figure 5[25] for men and Figure 6[26]

Variable	Circle response	Sum	
Maximal heart rate	Less than 100 bpm = 20		Women
	100 to 129 bpm = 16		
	130 to 159 bpm = 12		
	160 to 189 bpm = 8		
	190 to 220 bpm = 4		
Exercise ST depression	1-2 mm = 6		< 37 = Low probability
Age	> 2 mm =10		
	> 65 yrs = 25		
Angina history	50 to 65 yrs =15		37-57 = Intermediate probability
	Definite/typical = 10		
	Probable/atypical = 6		
	Non-cardiac pain = 2		
Hypercholesterolemia?	Yes = 10		> 57= High probability
Diabetes?	Yes = 10		
Exercise test induced angina?	Occurred = 9		
	Reason for stopping = 15		
Estrogen status	Positive = -5, Negative = 5		
	Total Score :		

FIGURE 6: Calculation of the simple score for angiographic coronary disease in women. Choose only one per group

for women. Diagnostic scores should be applied during every exercise test because they are easy to use and significantly improve the prediction of angiographic CAD.[27]

AFTER THE TEST

ECG INTERPRETATION: FACTORS DETERMINING PROGNOSIS

ST-Segment Analysis

ST-segment depression represents global subendocardial ischemia, with a direction determined largely by the placement of the heart in the chest. ST-depression does not localize coronary artery lesions. ST-depression in the inferior leads (II, AVF) is most often caused by the atrial repolarization wave, which begins in the PR segment and can often extend into the beginning of the ST-segment. Severe transmural ischemia, resulting in wall motion abnormalities, causes a shift of the vector in the direction of the wall motion abnormality. Preexisting areas of wall motion abnormality (i.e. scar), however, usually indicated by a Q wave are also capable of causing such shifts resulting in ST elevation without the presence of ischemia. While the resting ECG exhibits Q waves from an old MI, ST elevations are caused by ischemia, wall-motion abnormalities, or both, whereas accompanying ST-depression can be caused by a second area of ischemia or reciprocal changes. When the resting ECG is normal, however, ST elevation is a result of severe ischemia (spasm or a critical lesion), although accompanying ST-depression is reciprocal. Such ST elevation is uncommon, very arrhythmogenic, and it is localizing. Exercise-induced ST-depression loses its diagnostic power in patients with left bundle-branch block, Wolff-Parkinson-White (WPW) syndrome, electronic pacemakers, intraventricular conduction defects (IVCDs) with inverted T-waves and in patients with more than one millimeter of resting ST-depression. ST-segment changes isolated to the inferior leads are more likely to be false-positive responses unless profound (i.e. > 1 mm). The various patterns of ST segment changes are illustrated in Figure 7.

Precordial lead V_5 alone consistently outperforms the inferior leads or the combination of leads V_5 with II, because lead II has been shown to have a high false-positive rate.[28] Exercise-induced ST-segment depression in inferior limb leads is a poor marker for CAD in and of itself.[29] In patients without prior MI and normal resting electrocardiograms, ST-depression in precordial lead V_5 along with V_4 and V_6 are reliable markers for CAD, and the monitoring of inferior limb leads adds little additional diagnostic information. This said, however, elevation inferiorly should not be ignored.

Exercise-induced R-wave and S-wave amplitude changes are not associated with the changes in left ventricular volume, ejection fraction or ischemia. Many studies suggest that such changes do not have diagnostic value. ST-segment depression limited to the recovery period does not generally represent a "false-positive" response. Inclusion of analysis during this time period increases the diagnostic yield of the exercise test. Other criteria including down-sloping ST changes in recovery and prolongation of depression can improve test performance.

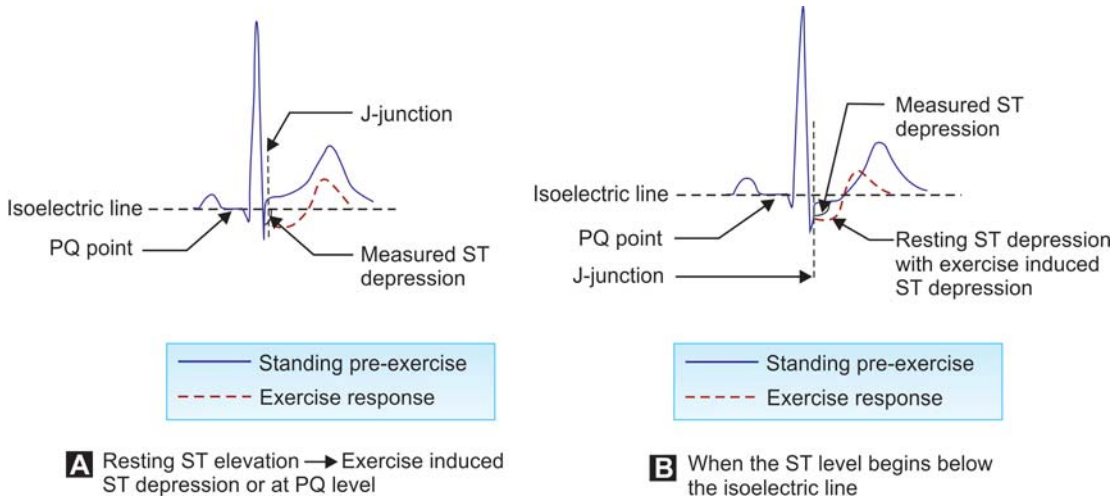
Computerized ST measurements should be used cautiously and require physician over-reading. Errors can be made both in the choice of isoelectric line and the beginning of the ST segment. Filtering and averaging can cause false ST depression due to distortion of the raw data.

SILENT ISCHEMIA

There is minimal evidence in the literature for exaggerated concern with silent ischemia. Patients with silent ischemia (painless ST-depression) usually have milder forms of coronary disease and consequently, a better prognosis. The evidence base for silent ischemia being more prevalent in diabetics is not as convincing as one would think given its widespread clinical acceptance. Many physicians feel that treadmill testing should be used for routine screening of diabetics but has yet to be adopted as it is not evidence based.[30]

EXERCISE INDUCED ARRHYTHMIAS

As with resting ventricular arrhythmias, exercise-induced ventricular arrhythmias have an independent association with



FIGURES 7A AND B: The various patterns of ST-segment shift. The standard criterion for abnormal is 1 mm of horizontal or downsloping ST-segment depression below the PR isoelectric line or 1 mm further depression if there is baseline depression

death in most patients with coronary disease and in asymptomatic individuals.[31] The risk can be more delayed (> 6 years) than that associated with ST-depression. Nonsustained ventricular tachycardia is uncommon during routine clinical treadmill testing but is usually well-tolerated if exhibited. In patients with a history of syncope, sudden death, physical examination with a large heart, murmurs, ECG showing prolonged QT, pre-excitation, Q waves and heart failure, then exercise-testing-induced ventricular arrhythmias are more worrisome. When healthy individuals exhibit premature ventricular contractions (PVCs) during testing, there is no need for immediate concern. However, in patients referred for exercise stress testing, frequent PVCs during recovery have been demonstrated to be associated with increased mortality during follow-up, while PVCs during exercise were related to heart rate increase with exercise.[32,33] Exercise-testing-induced supraventricular arrhythmias are relatively rare compared to ventricular arrhythmias and appear to be benign except for their association with the development of atrial fibrillation in the future.

PROGNOSTIC UTILIZATION OF EXERCISE TESTING

The two principal reasons for estimating prognosis are to:

- Provide accurate answers to patients' questions regarding the probable outcome of their illnesses
- Identify those patients in whom interventions might improve outcome and which measures to take to achieve such benefits.

Exercise capacity is the primary predictor of prognosis in all categories of patients. With each decrease in the MET value achieved there is a 10–20% increase in overall mortality.[34] Exercise capacity interacts with age such that even after accounting for age and gender, exercise capacity is a weaker predictor of death in elderly individuals than younger individuals undergoing exercise stress testing.[35] To further validate the continued use of exercise testing, a recent meta-analysis of 33 studies with over 100,000 healthy subjects undergoing exercise stress testing demonstrated the prognostic importance of exercise capacity and value in predicting the presence of CAD.[36]

Recent studies of prognosis have provided important information focused on endpoints specific to cardiovascular causes, such as death of cardiovascular etiology. In current society, this data is relatively easy to obtain from death certificates, whereas previously investigators had to follow the patients, contact their survivors, or review their medical records. While death certificates have their limitations, in general, they classify those with accidental, gastrointestinal (GI), pulmonary and cancer deaths so that those remaining are most likely to have died of cardiovascular causes. Although all-cause mortality is a more important endpoint for intervention studies, cardiovascular mortality is more appropriate for evaluating a cardiovascular test (i.e. the exercise test).

The mathematical models for determining prognosis are usually more complex than those used for identifying severe angiographic disease. Diagnostic testing can use multivariate discriminant function analysis to determine the probability of severe angiographic disease being present or not. Prognostic testing, however, must use survival analysis, which includes censoring for patients with uneven follow-up due to "lost to follow-up" or other cardiac events [i.e. coronary artery bypass surgery or percutaneous coronary intervention (PCI)] and must account for time-person units of exposure.

TABLE 7

Prognostic scores: the Duke Treadmill Score and the VA Treadmill Score

Duke score	=	METs – 5 × (mm E-I ST depression) – 4 × (TMAP index)
VA score	=	5 × (CHF/Dig) + mm E-I ST depression + change in SBP score – METs

(Abbreviations: CHF: Congestive heart failure; METs: Metabolic equivalents; SBP: Systolic blood pressure; TMAP: Treadmill angina pectoris).
TMAP score: 0 if no angina, 1 if angina occurred during test, 2 if angina was the reason for stopping.
Change in SBP score: from 0 for rise greater than 40 mm Hg to 5 for drop below rest.

There is ample data supporting the use of exercise testing as the first noninvasive step after the history, physical examination and resting ECG in the prognostic evaluation of CAD patients. It accomplishes both of the purposes of prognostic testing to provide information regarding the patient's status and to help make recommendations for optimal management. This assessment should always include calculation of a properly designed score such as the Duke Treadmill Score or the VA Treadmill Score (Table 7).

Recently, we have added to the Duke nomogram to improve its prognostic value (Fig. 8).[37,38]

Recent studies have considered other exercise test responses including heart rate recovery[39] and ectopy[40] and found both to have independent prognostic power in patients with heart failure. These exercise test responses have not yet been combined or compared to expired gas analysis results and could improve risk stratification. Interestingly, heart rate recovery has been shown to improve following exercise training in patients with heart failure.[41,42]

In summary, VO_{2max} or other related measures should not be used as the only prognostic markers in heart failure. The combination of cardiopulmonary exercise data and other clinical and hemodynamic responses in multivariate scores has been shown to more powerfully stratify risk.

SCREENING

Screening for asymptomatic CAD has become a topic of increased interest as some recent data suggest efficacy of the statins in reducing the risk of cardiac events even in asymptomatic individuals. Global risk factor equations, such as the Framingham score, should be the first step in screening asymptomatic individuals for preclinical coronary. These are available as nomograms that can easily applied by health care professionals, or be calculated as part of a computerized patient record. Several additional testing procedures that have promise for screening include the simple ankle-brachial index (particularly in the elderly), C-reactive protein and other emerging biomarkers, carotid ultrasound measurements of intimal medial



FIGURE 8: Age and double product (DP) adjusted Duke Treadmill Score (DTS) nomogram. Determination of average annual CV mortality adjusted for age and DP reserve proceeds as follows: at first, DTS will be obtained as described before; briefly, the marks for the observed amount of exercise-induced ST-segment deviation (1A) and degree of angina (1B) on their respective lines are connected with a straight edge. The point where this line intersects the ischemia-reading line (1C) is noted. Then, the mark for ischemia (2A) is connected with that for exercise duration in minutes or the equivalent in METs (2B). The point at which this line intersects the DTS line indicates the amount of DTS and the average annual CV mortality (2C). Subsequently, the point at which the drawing line from the marks for DTS (3A) to the corresponding value for age (3B) intersects age—DTS line indicates average annual CV mortality adjusted for age (3C). Finally, the point where the modified DTS line intersects the line drawn from the age—DTS line (4A) to the corresponding value for DP reserve/1,000 (4B) indicates average annual CV mortality adjusted for age and DP reserve (4C) (*Source:* Modified from Sadrzadeh Rafie AH, et al. Age and double product (SBP x heart rate) reserve-adjusted modification of the Duke Treadmill Score nomogram in men. Am J Cardiol. 2008;102:1407-12

thickness, and the resting ECG (particularly spatial QRS-T wave angle). Despite the promotional concept of atherosclerotic burden, electron-beam computed tomography (EBCT) has not been shown to have test characteristics superior to the standard exercise test.

Screening tests are controversial because they often generate a high rate of false positives, which can lead to unnecessary follow-up procedures and unquantifiable negative consequences like emotional repercussions. Ultimately, the overall cost-benefit to society is unclear.

This is further highlighted by the uncertainty of what to do with the information obtained from the screening test. In other words, it is unclear whether asymptomatic patients with silent ischemia detected on exercise treadmill testing have improved outcomes with revascularization compared with medical therapy. Given the findings of the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial in which patients with stable angina had similar major adverse cardiovascular events with either medical therapy or revascularization,[43] it seems unlikely that patients with silent ischemia demonstrated during exercise testing would benefit from revascularization unless they have left main or three-vessel CAD. However, the Asymptomatic Cardiac Ischemia Pilot (ACIP) study demonstrated that patients randomized to revascularization had significantly lower major adverse cardiovascular events at 2-year follow-up compared with those randomized to antianginal therapy.[44] Therefore, given these seemingly contradictory reports and the lack of clarity involving the data, it seems reasonable that patients with CAD risk factors should simply be initiated on aspirin, statin therapy and other medications with proven cardioprotective benefits rather than proceeding with CAD screening tests unless the findings will truly change management.

Several well-designed follow-up studies have improved our understanding of the application of exercise testing as a screening tool. The predictive value of the abnormal maximal exercise electrocardiogram ranges 5–46%. The first prospective studies of exercise testing in asymptomatic individuals included angina as a cardiac disease end point. As this is a soft or subjective endpoint, there was a bias for individuals with abnormal tests to subsequently report angina or to be diagnosed as having angina resulting in a high predictive value being reported for the test. When only hard end points (death or MI) were used, the results were less encouraging. The test could only identify one-third of the patients with hard events, and only 5% of the abnormal responders developed coronary heart disease over the follow-up period. Therefore, greater than 90% of the abnormal responders were false positives. Overall, the exercise test's characteristics as a screening test probably lie in between the results of studies using hard or soft endpoints because some of the subjects who develop chest pain really have angina and coronary disease. The sensitivity is probably between

30% and 50% (at a specificity of 90%), but the critical limitation is the predictive value (and risk ratio), which depends on the prevalence of disease (which is low in the asymptomatic population).

The iatrogenic problems resulting from screening (i.e. morbidity from subsequent procedures, employment and insurance issues) would make using a test with a high false-positive rate unreasonable. The recent US Preventive Services Task Force statement states that "false positive tests are common among asymptomatic adults, especially women, and can lead to unnecessary diagnostic testing, over treatment and labeling" (www.preventiveservices.ahrq.gov or www. guideline.gov).[45] In the majority of asymptomatic people, screening with any test or test add-on is more likely to yield false positives than true positives. This is the mathematical reality associated with all of the available tests.

If the exercise treadmill test is to be used to screen, it should be done in groups with a higher estimated prevalence of disease using the Framingham score or another predictive model. Additionally, a positive test result should not immediately lead to invasive testing. In most circumstances an add-on imaging modality (echo or nuclear) should be the first choice in evaluating asymptomatic individuals with an abnormal exercise test. The Detection of Ischemia in Asymptomatic Diabetics (DIAD) study highlights the challenges of screening an asymptomatic population.[30] The study randomized 1,123 subjects with type 2 diabetes mellitus and no symptoms of CAD to either undergo adenosine-stress radionuclide myocardial perfusion imaging or no screening. During the mean follow-up of 4.8 years, there was no difference in cardiovascular death or non-fatal MI between the two groups (2.7% vs 3%, p = 0.73). Interestingly, the primary medical prevention appropriately increased equally in both groups, suggesting that the results of screening did little to change medical management. While pharmacologic stress imaging has obvious differences from ECG exercise testing, this study highlights the potential pitfalls of screening asymptomatic patients, and how careful physician discretion should be applied to only screen asymptomatic high-risk patients such as sedentary diabetics with other risk factors prior to engaging in an exercise program (class IIa recommendation[9]).

Three recent studies lead to the logical conclusion that exercise testing should be part of the preventive health recommendations for screening healthy, asymptomatic individuals along with risk-factor assessment. The data from Norway (2,000 men, 26-year follow-up),[46] the Cooper Clinic (26,000 men, 8-year follow-up),[47] and Framingham (3,000 men, 18-year follow-up)[48] provide additional risk classification power and demonstrate incremental risk ratios for the synergistic combination of the standard exercise test and risk factors.

There are several other reasons why the exercise test should be promoted for screening. Most tests currently being promoted for screening do not have the documented favorable test characteristics of the exercise test. In addition, physical inactivity has reached epidemic proportions and what better way to make our patients conscious of their deconditioning than having them do an exercise test that can also "clear them" for exercise? Including the exercise test in the screening process sends a strong message to our patients that we consider their exercise status as important. Each 1 MET increase in exercise capacity equates with to a 10–25% improvement in survival in all populations studied[49] as well a 5% decline in health care costs.[50]

If screening could be performed in a logical way with test results helping to make decisions regarding therapies rather than leading to invasive interventions, insurance or occupational problems, then the recent results summarized above should be applied to preventive medicine policy. There may still be enough evidence, however, to consider recommending a routine exercise test every five years for men older than 40 and women older than 50 years of age, especially if one of the potential benefits is the adoption of an active lifestyle.[51]

CONCLUSION

The exercise test complements the medical history and the physical examination, and it remains the second most commonly performed cardiologic procedure next to the routine ECG. The addition of echocardiography or myocardial perfusion imaging does not negate the importance of the ECG or clinical and hemodynamic responses to exercise. The renewed efforts to control costs undoubtedly will support the role of the exercise test. Convincing evidence that treadmill scores enhance the diagnostic and prognostic power of the exercise test certainly has cost-efficacy implications.

Use of proper methodology is paramount for safety and obtaining accurate and comparable results. The use of specific criteria for exclusion and termination, interaction with the subject and appropriate emergency equipment is essential.

Table 8 lists important rules to follow for getting the most information from the standard exercise test.

TABLE 8

Exercise testing rules to maximize information obtained

• The exercise protocol should be progressive, with even increments in speed and grade whenever possible.
• The treadmill protocol should be adjusted to the patient, and one protocol is not appropriate for all patients; consider using a manual or automated ramp protocol.
• Report exercise capacity in METs, not minutes of exercise.
• Hyperventilation prior to testing is not indicated.
• ST-segment measurements should be made at ST0 (J-junction), and ST-segment depression should be considered abnormal only if horizontal or downsloping.
• Raw ECG waveforms should be considered first and then supplemented by computer-enhanced (filtered and averaged) waveforms when the raw data are acceptable.
• In testing for diagnostic purposes, patients should be placed supine as soon as possible after exercise, with a cool-down walk avoided.
• The 3-minutes recovery period is critical to include in analysis of the ST-segment response.
• Measurement of SBP during exercise is extremely important and exertional hypotension is ominous; manual blood pressure measurement techniques are preferred.
• Age-predicted heart rate targets are largely useless due to the wide scatter for any age; exercise tests should be symptom limited.
• A treadmill score should be calculated for every patient; use of multiple scores or a computerized consensus score should be considered as part of the treadmill report.
(Abbreviaition: METs: Metabolic equivalents).

The ACC/AHA guidelines for exercise testing clearly indicate the correct uses of exercise testing. Since the last guidelines, exercise testing has been extended as the first diagnostic test in women and in individuals with right bundle-branch block and resting ST-segment depression. The use of diagnostic scores and prognostic scores, such as the Duke Treadmill Score, increases the value of the exercise test. In fact, the use of scores results in test characteristics that approach the nuclear and echocardiographic add-ons to the exercise test.

MODIFIED SUMMARY OF GUIDELINES

AAA/AHA 2002 Guideline Update for Exercise Testing: Summary Article: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1997 Exercise Testing Guidelines) Circulation 2002;106:1883-92

Modified by Kanu Chatterjee

Class I: Conditions for which there is evidence and/or general agreement that a given procedure/therapy is useful and effective

Class II: Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of performing the procedure/therapy

Class IIa: Weight of evidence/opinion is in favor of usefulness/efficacy

Class IIb: Usefulness/efficacy is less well established by evidence/opinion

Class III: Conditions for which there is evidence and/or general agreement that a procedure/therapy is not useful/effective and in some cases may be harmful

Level A (highest): Derived from multiple randomized clinical trials

Level B (intermediate): Data are on the basis of a limited number of randomized trials, nonrandomized studies or observational registries

Level C (lowest): Primary basis for the recommendation was expert opinion

Exercise Testing Guideline Recommendation

Class I:

1. Patients undergoing initial evaluation with suspected or known CAD including patients with complete right bundle branch block or less that 1 mm ST depression (Level of Evidence B)
2. Patients with known or suspected CAD previously evaluated presenting with new or changing symptoms (Level of Evidence B)
3. Low-risk unstable angina patients (Level of Evidence B)
4. Intermediate-risk unstable angina patients 2-3 days after presentation and without evidence active ischemia or heart failure (Level of Evidence B)

Class IIa: Intermediate-risk unstable angina patients with negative cardiac markers and without significant change in ECG (Level of Evidence B)

Class IIb:

1. Patients with ECG abnormalities of pre-excitation, electronically paced ventricular rhythm, 1 mm or more resting ST depression, patients with LBBB or QRS duration of > 120 ms.
2. Patients with a stable clinical course who undergo periodic monitoring to guide treatment (Level of Evidence B)

Class III:

1. Patients with severe comorbidity likely to limit the expectancy and/or candidacy for revascularization
2. High-risk unstable angina patients (Level of Evidence C)

Patients With Acute Coronary Syndrome

Class I:

1. Submaximal exercise at about 4 to 6 days before discharge for assessment of prognosis, activity prescription or for evaluation of medical therapy
2. Symptom limited exercise test about 14 to 21 days after discharge for assessment of prognosis, activity prescription, or evaluation medical therapy if predischarge exercise test has not been done.
3. Symptom limited exercise test at 3 to 6 weeks after discharge to assess prognosis, activity prescription or evaluation of medical therapy if early exercise test was submaximal

Class IIa: After discharge for activity counseling and/or exercise training as part of cardiac rehabilitation in patients who have undergone reavascularization

Class IIb:

1. In patients with ECG abnormalities of LBBB, pre-excitation syndrome, left ventricular hypertrophy, digoxin therapy, greater than 1 mm resting ST depression electronically paced ventricular rhythm
2. Periodic monitoring in patients who continue to participate in exercise training or cardiac rehabilitation

Class III:

1. Severe comorbidity likely to limit life expectancy and/or candidacy for revascularization.
2. To evaluate patients with acute myocardial infarction with uncompensated heart failure, cardiac arrythmia or noncardiac conditions that limit the ability to exercise (Level of Evidence C)
3. Predischarge exercise test in patients who had already cardiac catheterization (Level of Evidence C)

Asymptomatic Diabetic Patients

Class IIa: Evaluation of asymptomatic patients with diabetes who plan to do vigorous exercise
(Level of Evidence C)

Class IIb:

1. Evaluation of patients with multiple risk factors as guide to risk-reduction therapy
2. Evaluation of asymptomatic men older than 45 years or women older than 55 years who plan to do vigorous exercise or who are involved in an occupation in which exercise impairment may impact public safety or who are at high risk for CAD

Class III: Routine screening of asymptomatic men or women.

Patients with Valvular Heart Disease

Class I: In patients with chronic aortic regurgitation for assessment of symptoms and functional capacity in whom it is difficult assess symptoms

Class IIa:

1. In patients with chronic aortic regurgitation for evaluation of symptoms and functional capacity before participation in athletic activity
2. In patients with chronic aortic regurgitation for assessment of prognosis before aortic valve replacement in asymptomatic or minimally symptomatic patients with left ventricular dysfunction

Class IIb: Evaluation of patients with valvular heart disease (see guidelines in valvular heart disease)

Class III: For diagnosis of CAD in patients with moderate to severe valvular heart disease or with LBBB, electronically paced rhythm, pre-excitation syndrome or greater than 1 mm ST depression in the rest ECG.

Patients with Rhythm Disorders

Class I:

1. For identification of appropriate settings in patients with rate-adaptive pacemakers
2. For evaluation of congenital complete heart block in patients considering increased physical activity or participation in competitive sports (Level of Evidence C)

Class IIa:

1. Evaluation of patients with known or suspected exercise-induced arrhythmias
2. Evaluation medical, surgical or ablation therapy in patients with exercise-induced arrhythmias (including atrial fibrillation)

Class IIb:

1. Investigation of isolated ventricular ectopic beats in middle aged patients without other evidence of CAD
2. For investigation of prolonged first degree atrioventricular block or type I second degree Wenckebach, left bundle-branch block, right bundle-branch block or isolated ectopic beats in young persons considering participation in competitive sports (Level of Evidence C).

Class III: Routine investigations of isolated ectopic beats in young patients.

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Chapter 14

The Left Ventricle

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Chapter Outline

- Systolic Function
  - Left Ventricular Ejection Fraction
  - Components of Ejection Fraction
- Contrast-enhanced Echocardiography
- Other Echo-derived Indices of LV Systolic Function
- Strain-derived Indices
- Recognizing the Etiology of Cardiac Dysfunction
- Dilated Cardiomyopathy
  - Echocardiographic Findings
  - Ischemic Cardiomyopathy
- Hypertrophic Cardiomyopathy
  - Primary Hypertrophic Cardiomyopathy
  - Echocardiographic Features
  - Secondary Hypertrophic Cardiomyopathy
  - Echocardiographic Features
- Restrictive Cardiomyopathy
  - Diabetes Mellitus
  - Amyloid Infiltrative Cardiomyopathy
  - Endomyocardial Fibrosis
- Left Ventricular Noncompaction
- Visual Qualitative Indicators of Systolic Dysfunction
  - Left Ventricular Mass
- Diastolic Function
  - Technical Aspects of Recording and Measurement of Diastolic Parameters
  - Types of Diastolic Dysfunction
  - Evaluation of Left Ventricular Filling Pressures
  - Formulae that Attempt to Provide Quantitation of LV Filling Pressure

INTRODUCTION

Echocardiography is the most commonly used clinical diagnostic tool for the evaluation of left ventricular (LV) systolic and diastolic function. In addition to measuring LV ejection fraction (EF), echocardiography provides clinically useful information about various aspects of LV structure and function. For instance, the anatomy of the LV may be altered in several pathologically significant ways and can be accurately measured and expressed by measuring cross-sectional segments of the LV from sets of echocardiographic images. The LV may dilate in diastole and remains so in systole and this enlargement may change both its global shape and regional geometry. There may be hypertrophy of the LV walls in several distinct patterns (some are uniform and some are not), each of which has its own implications. The systolic function of the LV may be normal (or not) while its filling or diastolic function is greatly impaired. Thrombi and tumors may form within the walls or cavity and the interstitium of the myocardium may become glycosylated, infiltrated with fibrous tissue, infused with protein deposits or invaded with tumor cells. Most, if not all, of these processes are recognized by echocardiography, their severity quantified, their rate of progression documented and their recovery appreciated. Finally, impressions of LV function gained by quantitation are verified by observing the beating heart in real time as images are being acquired or at anytime thereafter on archived digital loops. Echocardiography, after all, is the only imaging modality that permits continuous acquisition and visualization of highly resolved real time images.

SYSTOLIC FUNCTION

The reliable, precise, cost effective and expeditious characterization of regional and global systolic LV function is best accomplished by echocardiography. Quantitative expressions of global LV function may be obtained directly by calculation of left ventricular ejection fraction (LVEF) from its components, end systolic volume (ESV) and end diastolic volume (EDV), by determination of rate of pressure rise in the left ventricle from spectral Doppler flow signals, by low velocity tissue Doppler signals from annular and myocardial motion and by determination of global strain and strain rate using either tissue Doppler or speckle tracking. An initial impression of LV systolic function may be accomplished by visual evaluation of LV contraction. The standard views from the apical and parasternal windows are sufficient for this purpose. One usually starts with parasternal long and short axis views of the LV. From the apical window, the LV should be examined in standard 4-chamber, 2-chamber and long axis views. The LV may also be evaluated from the subcostal window in both short and long axis views.

LEFT VENTRICULAR EJECTION FRACTION

The most commonly applied measure of the global LV systolic function in the clinical setting is the EF of the left ventricle (LVEF), or the fraction of the LV diastolic volume ejected with each contraction. It is determined as:

$$LVEF = (EDV - ESV)/EDV \times 100\%$$

where EDV is end diastolic volume and ESV is end systolic volume.

However, because EF is highly sensitive to loading conditions and varies widely, it is a rough estimate of myocardial contractile state. Moreover, despite its clinical importance, and despite recommendations from the American Society of Echocardiography (ASE) of 20 years' standing[1,2] to the opposite, EF is still frequently estimated visually from real time two-dimensional (2D) images and not *measured* quantitatively.

There are a number of reasons for the universality of LVEF: it expresses the complex motion of a three-dimensional (3D) structure with a simple number; it is easy to measure or estimate; it is interchangeable when determined by different methods; it parallels LV contractility; its prognostic significance and clinical utility for treatment stratification are considered established.

These advantages notwithstanding, EF has significant limitations, and these should be considered in each clinical setting. Besides LV contractility, LVEF, as with most other indices, depends on the loading conditions under which the ventricle operates. These conditions include the *preload* (filling pressure and EDV) and *afterload or wall stress* (blood pressure, chamber volume, wall mass and aortic valve resistance). For example, in valvular insufficiency, the EDV or preload of the left ventricle may increase; as a result, LVEF may appear depressed despite normal LV contractility. Conversely, in mitral regurgitation, the low resistance pathway offered by back flow into the low pressure left atrium may mask diminished contractility by augmenting EF. In hypertrophy, wall stress (the ultimate expression of afterload) is reduced and a normal value may mask an inherent deficiency in contractility. The nature of indices of contractility necessitates consideration of other data to characterize LV function. For example, ESV is frequently used as an index of LV contractility that is *relatively* load independent. Finally, small changes in EDV (either through measurement variability or minimal preload fluctuations) may raise or lower EF without there having been any clinically meaningful change in systolic function.

The universal practice of "eyeball" estimation of EF and the few studies that support its accuracy among experienced observers notwithstanding, other studies and our own cumulative experience[3] show they are inferior to calculated LVEF; we recommend *routine* quantitation unreservedly. This recommendation has been reinforced by improvements in imaging that have resulted from engineering improvements such as harmonic imaging, contrast-enhanced border detection and improved electronic focusing and beam formation. It is expected that with refinements in the emerging technique of 3D imaging, the accuracy of the component measurements of EF will improve to the point where they will be automated.

We therefore recommend calculation of LV volumes in all patients both for their own inherent value and as the sole means of calculating EF. There are several reasons for this recommendation:

- When performed properly from technically adequate images, quantitatively acquired volume and EF are more accurate than the visual estimation and the gap in accuracy continues to widen with improvement of imaging techniques.
- Quantitation provides additional valuable informations—LV volume and mass—which are superior in outcome prediction to linear dimensions.[4,5]
- Continuous feedback to the echocardiographer allows maintenance of skill in visual estimation of LV global function; the ability of the physician to perform accurate visual estimation further increases the reliability of calculations, allowing the reader to identify those studies, in which calculations were performed poorly, and repeat or correct those measurements. In the final analysis, visual estimation, however skillful the observer, is less reliable than quantification by a skilled sonographer.[3]

There are multiple methods for the calculation of LV volumes from the 2D echocardiographic images. Most of these formulae are based on certain geometric assumptions regarding the shape of the LV. Consequently, these formulae are less reliable when the shape of LV is distorted. The authors have not discussed most of these methods.

The method of disk summation, or modified Simpson's rule, is the only biplane algorithm without geometric assumptions and is the standard method for LV volume calculations.[1,2] In this method, the left ventricle is modeled as stacked disks or coins (usually 20), and the volume of each disk is calculated from its orthogonal diameters. The sum of the volumes of each of these disks represents chamber volume. Once the endocardial border is traced or planimetered manually in two orthogonal imaging planes of equal length (usually, the apical 2- and 4-chamber views), software bundled with contemporary echocardiography instruments automatically performs these calculations. These measurements are from tracings obtained at end diastole and end systole.

Figure 1 demonstrates two orthogonal views of the LV for volume calculations by the method of disk summation. The endocardial border should be traced covering the inner contour; papillary muscles are excluded from measurements. Care must be taken to avoid mistaking trabeculations for the endocardium along the lateral free wall, especially in the apical half of the ventricle. Trabeculations mimic the endocardial border when sonographers foreshorten the image to improve resolution of the lateral wall. A clue that this error has been committed is observing that the myocardial tracing creates an inner apical border where the underlying myocardium appears to be thicker than the base rather than its usual thinner dimension. Proper imaging and tracing of the lateral endocardium is best learned by using left sided contrast to improve endocardial border detection. Normal values of the end diastolic volume and index of the left ventricle are provided in the Table 1.

Accurate measurements of the LV volumes require that:

- Imaging plane transects the true apex of the left ventricle. 3D echocardiography facilitates avoidance of foreshortening the left ventricle; however, with 2D echocardiography this mistake can be avoided by maximizing the image of the cavity and by using pulmonary crossing left sided

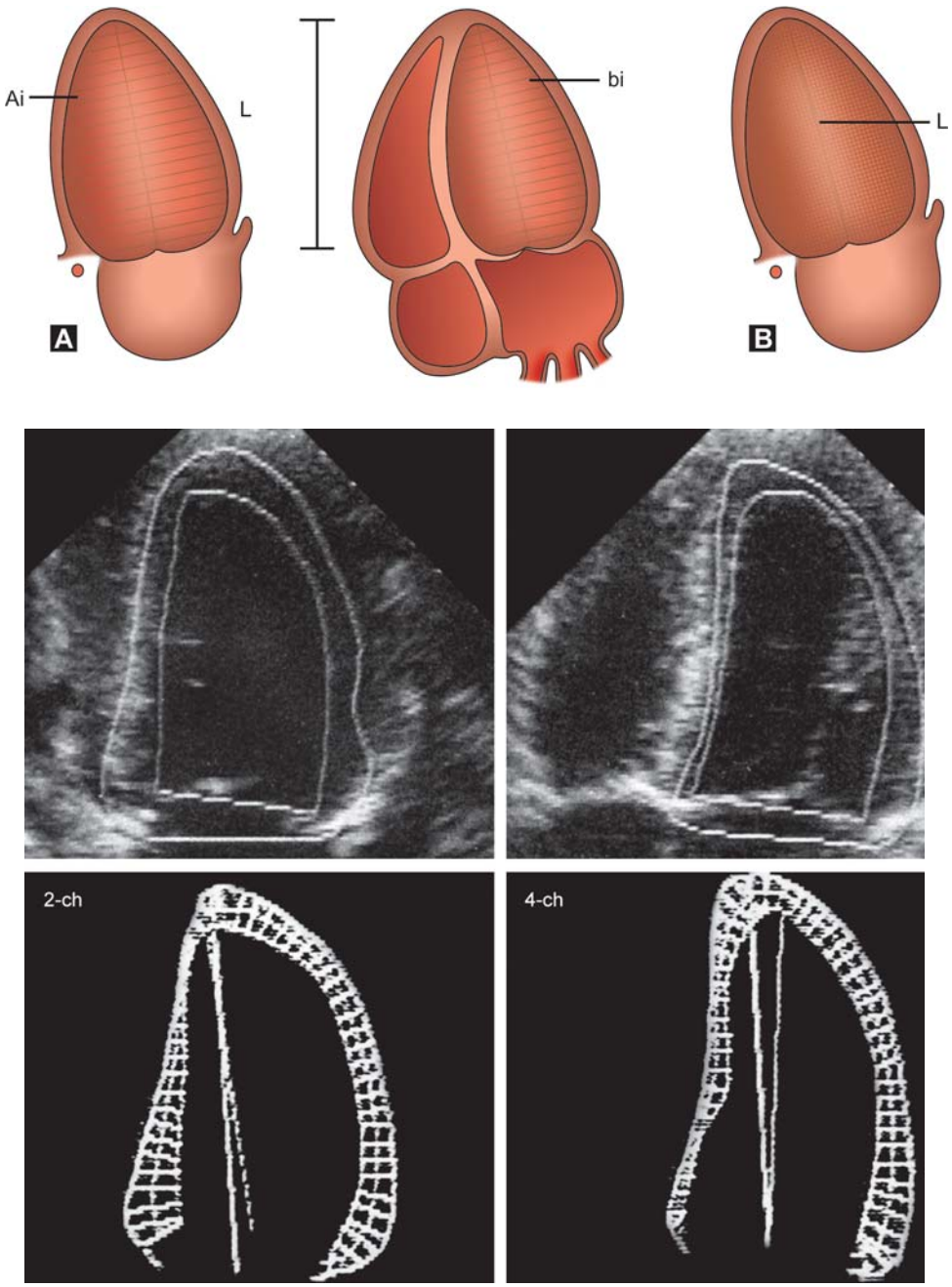


FIGURE 1: (A and B) Diagrammatically shows paired two and four chamber views (orthogonal planes) that have been divided into slices for analysis by the biplane method of discs. A single plane view (two chamber view on B) is a usable but less accurate alternative to biplane volume analysis.

Computer processing of the left ventricular images. (Above) Superimposition of systolic and diastolic left ventricular contours in 2- and 4-chamber views. (Below) Diastolic and systolic contours are combined for quantitative analysis of regional left ventricular function. In this case, the center of the left ventricle, rather than the long axis, was combined for systolic and diastolic images. Automatic methods for evaluation of regional left ventricular function should be used with caution, as their reliability has not been sufficiently documented. In the example above, the left ventricular mass has been calculated using the formula for truncated ellipsoid, and left ventricular ejection fraction was calculated both by the method of disk summation and by the area-length formula in each of the views. Left ventricular mass turned out to be elevated at 220 gm. Values for left ventricular ejection fraction were markedly different for different views (61% for 2-chamber and 46% for 4-chamber). These differences are explained by the hypokinesis of the interventricular septum. The more exact method of disk summation provides left ventricular ejection fraction of 55%. End diastolic volume of the left ventricle is increased at 147 mL; however, the body surface area is 1.93 m^2, and the end diastolic volume index of the left ventricle (76 mL/m^2) is within normal[9]

contrast in poor images to enhance endocardial borders. To image the apex, the transducer should be initially placed just posterior to the apical impulse location and moved gradually anteriorly until maximized full length images are obtained.

- Record images during suspended respiration.
- Exclude papillary muscles and trabeculations from the tracings.
- Doppler echocardiography adds to the information provided by 2D imaging. Accuracy of Doppler methods in the

TABLE 1

Normal left ventricular end-diastolic volume and index in adults

	End diastolic volume (ml)	*End diastolic volume index (ml/m²)*
Method of disks in orthogonal planes:		
Males	111 ± 22 (62–170)	55 ± 10 (36–82)
Females	80 ± 12 (55–101)	

Note: Average values and standard deviations are listed. Limits of normal are provided in brackets.

determination of the stroke volume has been demonstrated, and may be used for quality control of LV volume measurements. In the absence of significant mitral or aortic regurgitation, stroke volume obtained by volume calculations may be compared with the Doppler stroke volume, and in case of significant discrepancy, calculations ought to be repeated.

Linear Measurements in the Assessment of LV Function

Linear dimensions (so-called m-mode) should be performed under 2D guidance, and only if the beam can be directed perpendicular to the transected LV walls and cavity long axis. Linear dimensions are not routinely performed in our laboratory but relegated to a confirmatory role; as discussed above, the authors prefer to use 2D volumetric and Doppler quantitative flow data instead because they have demonstrated superiority in predicting outcomes and because they are interchangeable with MRI and CT derived volume data. The use of linear dimensions may lead to two types of errors: the first is from the incorrect positioning of the ultrasound beam (Fig. 2) that may be corrected by meticulous use of 2D echo guidance. The second is that linear dimensions sample only a limited area near the LV base; assumptions regarding the geometric shape and symmetry of the left ventricle must be made to derive indices of global LV function. In patients with CAD and segmental wall motion abnormalities, these assumptions cannot be made. Consequently, linear measurements are not representative of global function and are thus misleading. Single dimensional derivations of LVEF are only reliable in patients with completely symmetric LV function in a LV having a ratio of its long axis twice that of the short.

Despite our reservations regarding the use of linear dimensions, the authors are mindful of the widespread use of these measurements and provide herein a table with normal linear measurements (Tables 2A and B). Figure 3 demonstrates the nomogram, used for body surface area (BSA) calculations; these are needed for calculation of indexes of both volumetric and linear measurements. Although some laboratories recommend correcting linear and volumetric measurements by height or body mass index (BMI), our research has shown no advantage (or particular disadvantage) of any method over that of correcting measurements by BSA.[6] The authors therefore continue to recommend the universally used BSA correction for normalization of echocardiographic data.

Diameters of the left ventricular outflow tract (LVOT) and of aortic root are also measured more correctly from the 2D images.

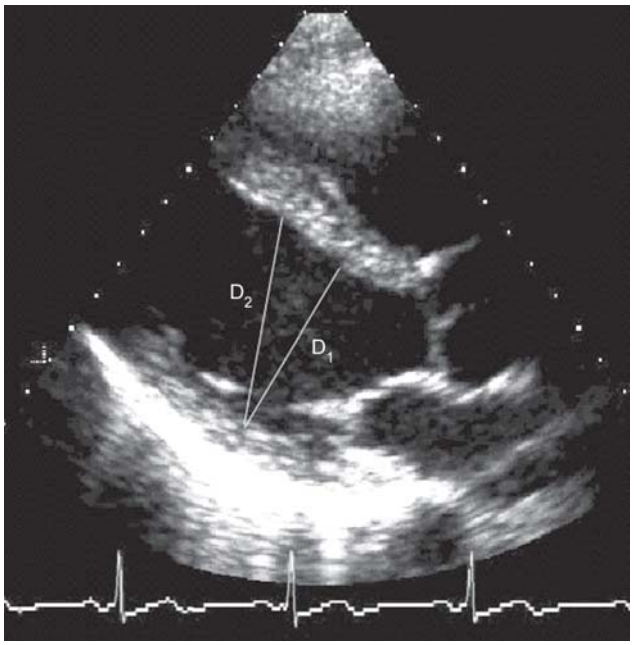


FIGURE 2: Anterior-posterior dimension of the left ventricle is easier to determine from the 2D images, than from the m-mode. M-mode measurements frequently lead to exaggeration of the true size, due to oblique direction of the ultrasound beam that results from either an angulated (sigmoid) septum of a low interspace. End systolic dimension of the left ventricle here by 2D examination (D1) is 46 mm and by unguided m-mode (D2) is 55 mm. The complexity of the "endoarchitecture" of the endocardial surface is another source of error that arises from using discrete loci as line anchors

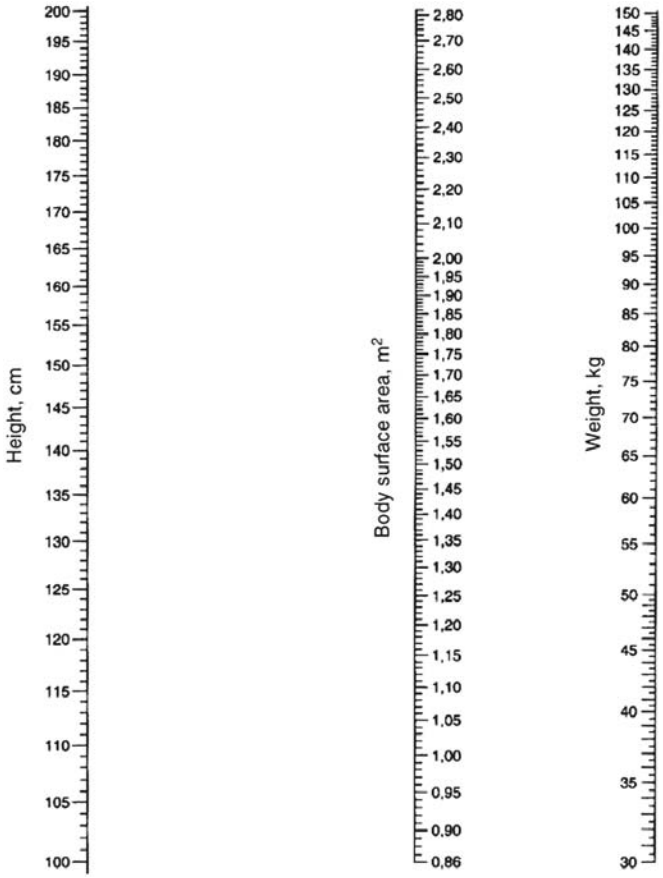


FIGURE 3: Nomogram for determination of the body surface area in adults. A straight line should connect patient's weight and height; its intersection with the middle scale will indicate the body surface area

TABLE 2A

Normal dimensions of left heart in normal adults

• Short axis left ventricle, diastole (end diastolic dimension of the left ventricle)	3.5–6.0 cm (2.3 ± 3.1 cm/m^2)
• Short axis left ventricle, systole (end systolic dimension of the left ventricle)	2.1–4.0 cm (1.4 ± 2.1 cm/m^2)
• Long axis of the left ventricle, diastole	6.3–10.3 cm (4.1 ± 5.7 cm/m^2)
• Long axis of the left ventricle, systole	4.6–8.4 cm
• Thickness of the interventricular septum and posterior wall of left ventricle	0.6–1.1 cm
• Anterior-posterior dimension of the left atrium	2.3–3.5 cm (1.6–2.4 cm/m^2)
• Medial-lateral dimension of the left atrium (from apical 4-chamber view)	2.5–4.5 cm (1.6–2.4 cm/m^2)
• Superior-inferior dimension of the left atrium (from apical 4-chamber view)	3.4–6.1 cm (2.3–3.5 cm/m^2)

Note: The indexes of dimension (normalized to BSA) are provided in brackets.

TABLE 2B

Normal dimensions of cardiac chambers and major vessels in adults

• Diameter of aortic annulus	1.4–1.6 cm (1.3 ± 0.1 cm/m^2, up to 1.6 cm/m^2)
• Diameter of aortic root (at the aortic cusps)	2.2–3.6 cm (1.7 ± 0.2 cm/m^2, up to 2.1 cm/m^2)
• Diameter of ascending aorta	2.1–3.4 cm (1.5 ± 0.2 cm/m^2)
• Diameter of aortic arch	2.0–3.6 cm
• Short axis left ventricle, diastole (end diastolic dimension of the left ventricle)	3.5–6.0 cm (2.3 ± 3.1 cm/m^2)
• Short axis left ventricle, systole (end systolic dimension of the left ventricle)	2.1–4.0 cm (1.4 ± 2.1 cm/m^2)
• Long axis of the left ventricle, diastole	6.3–10.3 cm (4.1 ± 5.7 cm/m^2)
• Long axis of the left ventricle, systole	4.6–8.4 cm
• Thickness of the interventricular septum and posterior wall of left ventricle	0.6–1.1 cm
• Anterior-posterior dimension of the left atrium	2.3–4.5 cm (1.6–2.4 cm/m^2)
• Medial-lateral dimension of the left atrium (from apical 4-chamber view)	2.5–4.5 cm (1.6–2.4 cm/m^2)
• Superior-inferior dimension of the left atrium (from apical 4-chamber view)	3.4–6.1 cm (2.3–3.5 cm/m^2)
• Thickness of the anterior wall of the right ventricle	0.2–0.5 cm (0.2 ± 0.05 cm/m^2)
• Anterior-posterior dimension of the outflow tract of the right ventricle	2.2–4.4 cm (1.0–2.8 cm/m^2)
• End diastolic dimension of the right ventricle (long axis)	5.5–9.5 cm (3.8–5.3 cm/m^2)
• End systolic dimension of the right ventricle (long axis)	4.2–8.1 cm
• Diameter of the annulus of the pulmonary valve	1.0–2.2 cm
• Diameter of the main pulmonary artery	0.9–2.9 cm
• Diameter of the inferior vena cava (at insertion into the right atrium)	1.2–2.3 cm

Note: The indexes of dimension (normalized to BSA) are provided in brackets.

The derived functional indices from single dimensional measurements include: fractional shortening of the left ventricle, E-point to septal separation (EPSS) and the amplitude of the aortic root motion.

Fractional shortening is a single dimensional analog of LVEF and is the ratio of the difference of the diastolic and systolic short axis diameters of the left ventricle to the diastolic short axis diameter [left ventricular end-diastolic dimension (LVEDD)-left ventricular end-systolic dimension (LVESD)/ LVEDD]. Normal fractional shortening is 30% or more.

E-point to septal separation is the distance between the tip of the anterior mitral leaflet at the time of its widest opening in the early diastole and the most posterior systolic excursion of the interventricular septum. Normally this distance is less than 7 mm.[7] With decreasing global LV contractility, the size of the chamber at end systole and its residual volume increase; concurrently, with decline of the cardiac output, the mitral valve open orifice has to accommodate smaller stroke volume, with resultant decrease of the amplitude of its opening. As LV contractility declines, the EPSS continues to increase. In their current practice, the authors use EPSS to divide patients into those with EFs above or below 45%.

Amplitude of the aortic root motion[8] has mostly qualitative significance. It is roughly proportionate to the stroke volume. Aortic root motion is determined by the filling of the left atrium relative to its smallest volume. Normally, aortic root moves anteriorly in systole by more than 10 mm.

COMPONENTS OF EJECTION FRACTION

End Systolic Volume

Left ventricular end systolic volume indexed (ESVI) to BSA is a simple yet powerful stand-alone marker of ventricular remodeling[9] that can and should be measured routinely in the clinical practice of echocardiography. It is the opinion of the authors that, among all other measures of systolic function, this single parameter is the most informative and load independent. From clinical experience and outcomes research,[10] the authors recommend first considering ESVI when judging systolic function. An example of a common situation where ESVI is particularly helpful include a borderline or low normal EF (i.e. between 50% and 60%); in this setting, only a minimally increased ESVI indicates that systolic function may be reduced to a degree sufficient to adversely influence major outcomes.[4]

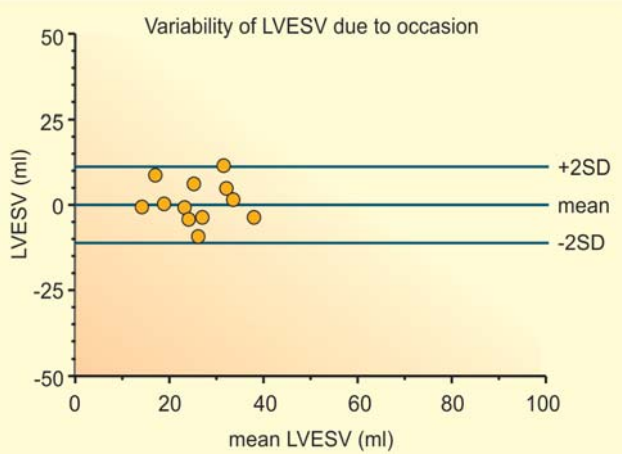


FIGURE 4: Variability of LVESV due to occasion

Figure 1 demonstrates manual digitization of the orthogonal apical 2- and 4-chamber views. From these planimetric images, frozen at end diastole and end systole, systolic and diastolic volumes are computed by an algorithm that models the LV cavity as a stack of coins (formally called the method of disks and often incorrectly called modified Simpson's rule). By summation of the volume of each coin in the stack, a close approximation of volume is achieved. This disk summation method is more commonly but incorrectly referred to as Simpson's rule. Although single plane measurements from either 2-chamber or 4-chamber view suffice in some settings, biplane measurements are the method of choice and recommended by the ASE. A technical note for the physician or sonographer about the proper and simplest method for choosing precise frames that represents the largest cavity (end diastole) and the smallest (end systole). The authors have found that the most logical and most reproducible marker of these events is the position of the mitral valve. The digital frame preceding the initial opening motion of the mitral valve identifies end systole while the initial moment of coaptation after the A wave, end diastole. Tantamount to frame selection is the selection of tomographic views that avoid foreshortening and that display at least 75% of the endocardium. Similarly critical, tracing the endocardium and not the epicardium will foster accuracy. Automated tracing (always with manual adjustment of tracking) and 3D volume sets promise to speed the quantitative process—if not automate it and provide stronger reproducibility. ESV is more reproducible than EDV because the endocardium is most visible during this phase of the cardiac cycle.

When properly measured, ESV is the most reproducible volumetric parameter of systolic function. Figure 4 shows a Bland Altman plot of the variability from examining the same hemodynamically stable subject on two occasions. Variability also arises from using different sonographers and different readers. These sources of variability were explored in a study from authors' laboratory.[11,12]

Invasively determined LV end systolic volume has been shown to be an important determinant of survival after myocardial infarction[9] (Fig. 5).

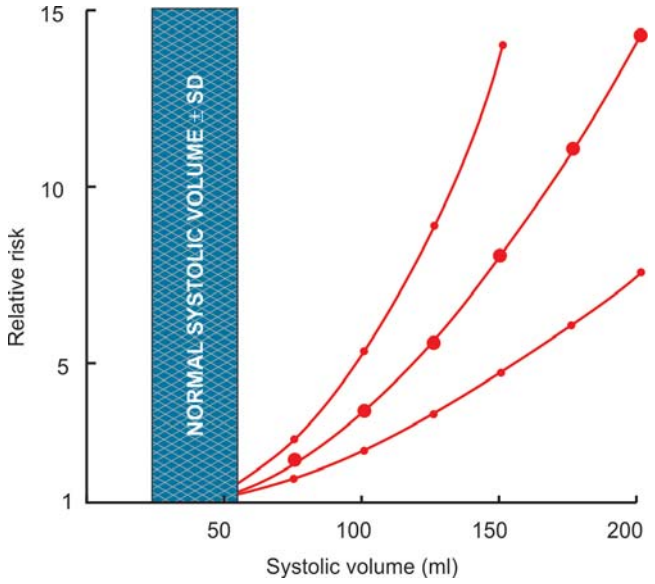


FIGURE 5: Left ventricular end systolic volume as the major determinant of survival after recovery from myocardial infarction[9]

Physiologic Basis of Left Ventricular End Systolic Volume

Physiologically, ESV is a direct window on a key property of the heart, elastance. Elastance is defined as the quality of recoiling without disruption on removal of pressure, or an expression of the measure of the ability to do so in terms of unit of volume change per unit of pressure change and is the reciprocal of compliance. Figure 6 (courtesy of Dr. Sanjiv J. Shah of Northwestern University) shows the location of ESV at the intersection of the lines defining arterial and end systolic elastance at fixed contractility and varying loading conditions.

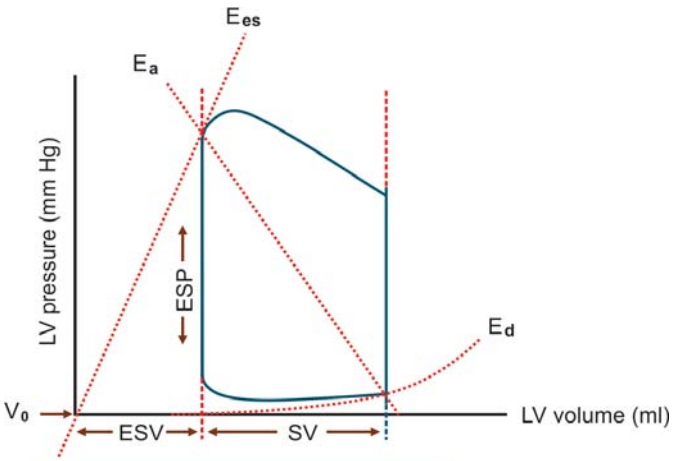


FIGURE 6: Pressure volume loop

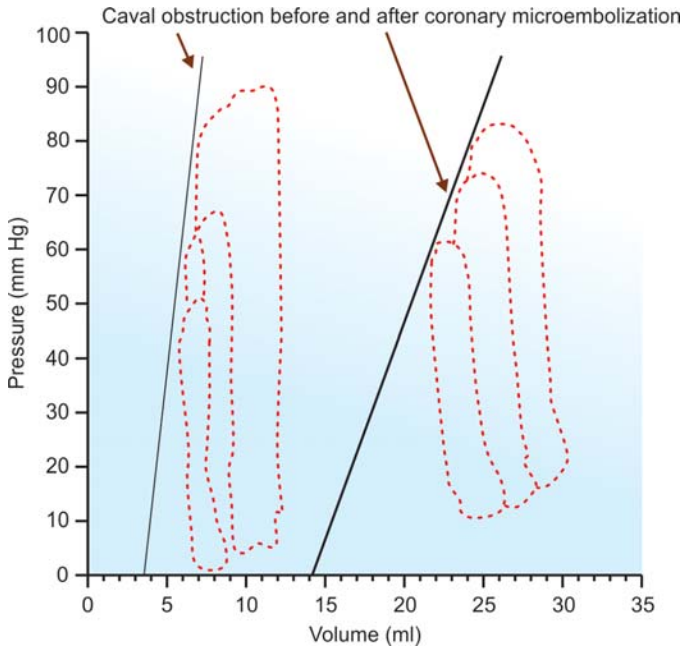


FIGURE 7: Caval obstruction before and after coronary microembolization[13]

In physiologic experiments, embolization of the myocardium increases the ESV and decreases the elastance slope. This effect can be seen when the response of the normal myocardium to changes in loading conditions (degrees of caval obstruction) to that of post-embolic myocardium[13] (Fig. 7).

Left Ventricular End Systolic Volume and Clinical Outcomes

A decrease in ESV with angiotensin converting enzyme inhibitor therapy has been associated with a reduction in cardiac events in patients with moderately decreased LV systolic function. Using LV contrast ventriculography, end systolic volume has been shown to be an important predictor of both postoperative ventricular function and survival after coronary artery bypass grafting in patients with decreased LV function.[9] The aforementioned studies have consistently shown that large increases in ESV predict adverse cardiovascular outcomes in participants with LV systolic dysfunction. In aortic regurgitation, a 10-year outcome study[10] (Mayo) has shown that ESV is a powerful predictor of outcome whereas systolic dimension is not predictive. The degree of elevation in ESVI has also been shown to most closely reflect BNP elevation in mitral regurgitation.[14]

Normal values for ESVI are given in Table 3. It points out that there is disagreement with where the abnormal range begins. Orginally, values as high as 33 mL/m^2 were considered within normal limits. However, in patients with coronary disease, values higher than 25 mL/m^2 are associated with sharply increased adverse outcomes. At the time of this writing, the upper range of normal for other subgroups such as patients with varying degrees of valve disease and young athletes have yet to be established. Note that MRI data from the Framingham normal cohort have smaller values for the lower and upper limits of normal than authors' data at UCSF and the ASE recommended value. Authors' outcomes research in coronary disease strongly suggests that at least in older individuals with that condition, the Framingham data is more likely to be correct.

In developing outcome data for ESV, the authors examined the association of ESVI with hospitalization for heart failure (HF) and mortality in a prospective cohort study of ambulatory patients with CHD.[4] The authors divided the study population into quartiles of ESVI and used a Cox proportional-hazards analysis to compare events among quartiles. The authors adjusted for potential confounders, including known cardiovascular risk factors, medication use and echocardiographic variables. Of 989 participants, 110 (11%) were hospitalized for HF during 3.6 ± 1.1 years of follow-up. Among participants in the highest ESVI quartile (> 25 mL/m^2), 67 of 248 (27%) developed HF, compared with 8 of 248 (3%) among those in the lowest quartile. The association of ESVI with HF hospitalization persisted after adjustment for potential confounders (HR 4.6, 95% CI 1.3–16.2; p = 0.02). When compared to other echocardiographic measures of LV remodeling using area under ROC curve analysis, ESVI was a superior predictor of hospitalization for HF. In this prospective cohort study of ambulatory patients with CHD, LV ESVI greater than 25 mL/m^2 was independently associated with a 4.6 fold increased rate of HF hospitalization (Fig. 8). Our findings suggest that even small increases in ESVI independently predict increased HF in patients with CHD.

Figure 9 demonstrates the incremental predictive value of ESV on combined end point of HF or mortality. Here systolic

TABLE 3

Normal values for end systolic volume index for men and women from three sources

	Men				*Women*			
LVESV/BSA	*Reference range*	*Mild Incr.*	*Moderate Incr.*	*Severe Incr.*	*Reference range*	*Mild Incr.*	*Moderate Incr.*	*Severe Incr.*
ASE 2005	12-30	31-36	37-42	> 42	12-30	31-36	37-42	> 43
F'ham MRI	Mean 15-24 (.9UCB)	24-31*	32-41	> 42	18-31 (.9UCB)	32-45	46-59	> 60
UCSF	Mean 18-32 (.9UCB)	33-47*	47-61	> 61	18-30 (.9UCB)	31-43	44-56	> 57

*mild, moderate, severe defined in increments of +2SD
(*Source:* American Society of Echocardiography 2005[2] recommendations, Framingham normal cohort by MRI[15] and University of California San Francisco (UCSF) published normal values.[16-18] Note that the abnormal range for MRI begins above 24 ml/m^2 (circled column). Authors' outcome data discussed above is in agreement with a lower estimate of where the abnormal range begins.

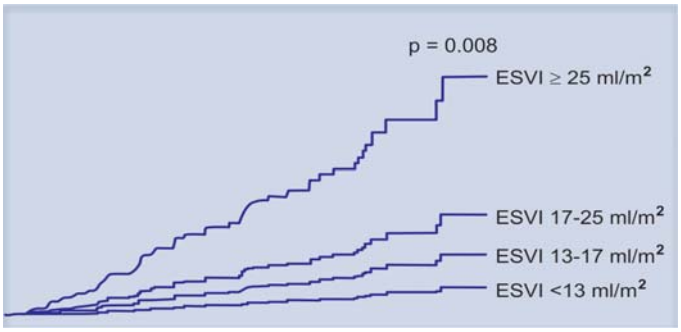


FIGURE 8: Cumulative risk of heart failure by quartile of end systolic volume index

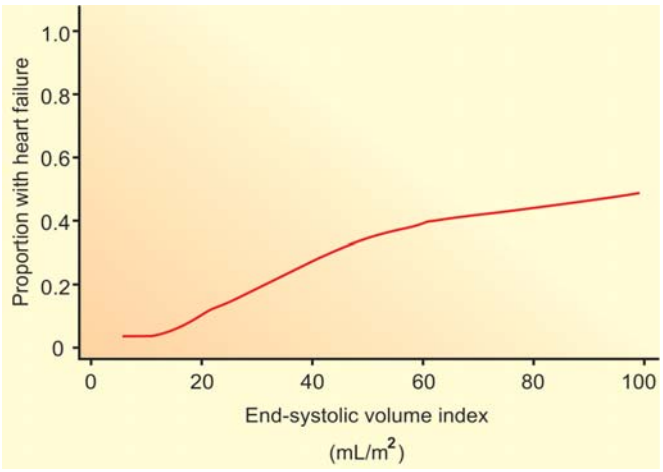


FIGURE 10: Lowess plot of the proportion of patients hospitalized with heart failure during follow-up according to baseline left ventricular end systolic volume index (Lowess = smooth locally-weighted scatterplot)

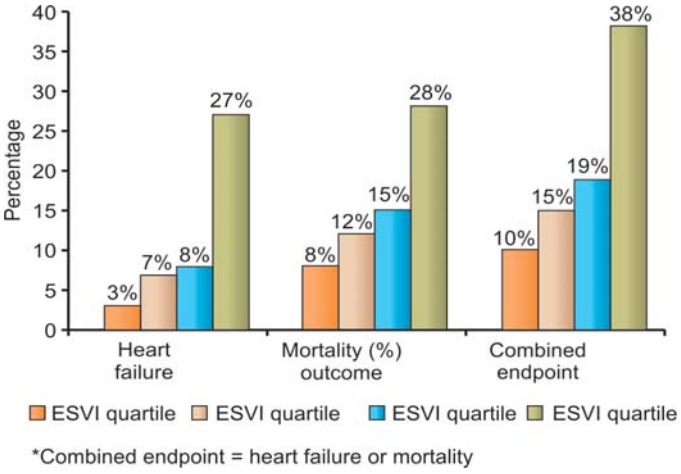


FIGURE 9: Percentage of participants with adverse cardiovascular outcomes by end systolic volume index (EVSI) quartile[4]

volumes are grouped by quartiles. Note that any increase of ESVI is associated with an increase in adverse outcomes.

Figure 10 is a Lowess plot of the magnitude of ESV and its association with the proportion of patients with stable coronary disease who develop HF in 5 years of follow-up. Note that even in the upper normal range (as defined by previous series) there is an increased risk of HF that continues to rise throughout the range of values.

Figure 8 shows that the cumulative risk of HF increases even within the normal range and that it rises sharply above 25 mL/m^2. The finding that ESVs that seemed only minimally elevated carried such strong predictive value for risk supports our contention that ESVI is among the most powerful parameters of outcome in cardiology.

Figure 11 compares the receiver operator curves for predicting CHF hospitalization of single end systolic linear dimension (so-called m-mode) with ESVI. Since the majority of laboratories continue to cling to linear dimensions as their central LV measurements, these data offer compelling reasons for abandoning this practice in favor of volumetric measurements. Hazard ratio plot for risk of hospitalization for heart failure associated with an ESVI greater than or equal to 25 mL/m^2 in specified subgroups described in Figure 12.

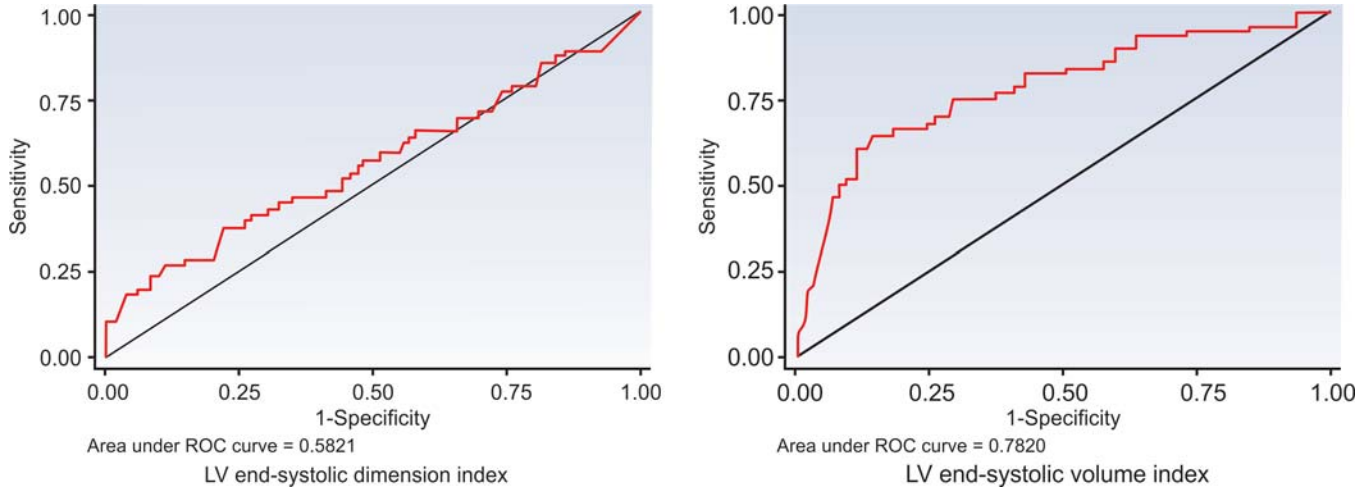
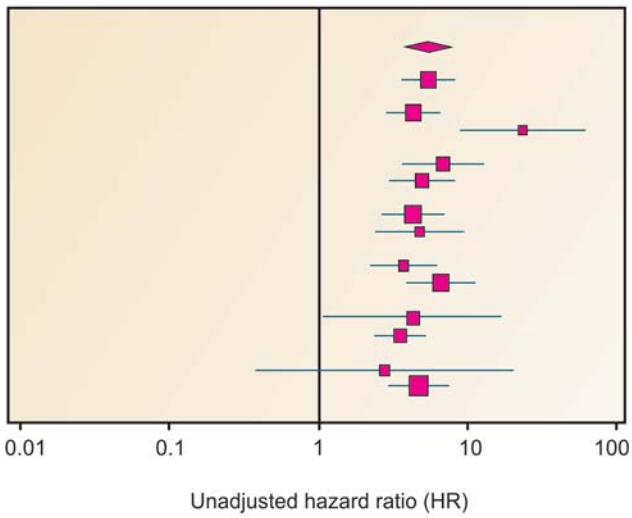


FIGURE 11: Receiver-operating characteristic curves for left ventricular end systolic dimension index and end-systolic volume index as predictors of hospitalization for heart failure ($p < 0.0001$)



	N	HR (95% CI)
Overall	989	5.6 (3.8-8.2)
Age < 65 years	413	5.7 (2.6-12.3)
Age ≥ 65 years	576	5.4 (3.5-8.4)
Male	804	4.4 (2.9-6.6)
Female	184	23.4 (8.8-62)
No history of MI	452	6.8 (3.6-12.8)
History of MI	530	5.0 (3.0-8.2)
No history of HF	809	4.3 (2.6-7.1)
History of HF	174	4.8 (2.4-9.6)
CrCl < 60 ml/min	227	3.7 (2.2-6.3)
CrCl ≥ 60 ml/min	706	6.6 (3.9-11.3)
NT-proBNP < 173 pg/ml	477	4.3 (1.1-16.8)
Nt-ProBNP ≥ 173 pg/ml	476	3.5 (2.4-5.3)
EF < 50%	112	2.8 (0.4-20.5)
EF ≥ 50%	876	4.6 (2.9-7.4)

FIGURE 12: Hazard ratio plot for risk of hospitalization for heart failure associated with an ESVI ≥ 25 mL/m^2 in specified subgroups

End Diastolic Volume

End diastole is the moment in the cardiac cycle when the left ventricle completes filling and reaches its largest volume. A healthy heart has the property of increasing diastolic volume in response to a spectrum of preloads without altering its elliptical shape and with only small increases in filling pressure. In cardiomyopathic states, the left ventricle remodels so that as volume increases it assumes a more spherical shape and filling pressure rises sharply with small increments in volume. In normality, ESV changes are small so that changes in stroke volume are mainly mediated by increases in EDV. Due to relative preload dependence, EDV changes and degrees of enlargement are less reliable indicators of myocardial contractility. Table 4 presents normal values for end diastolic volume index (EDVI) from three sources: ASE recommended values, Framingham MRI data and UCSF data. In unpublished data, the authors have found that adverse outcomes in an older coronary disease population begin to appear when left ventricle end diastolic volume index (LVEDVI) reaches 64 mL/m^2. Thus values as high as 80 mL/m^2 may be too liberal and based on the inclusion of younger persons with slow heart rates. Older normal subjects tend to have smaller hearts than their younger counterparts and thus dilation may be considered to begin at a small volume.

CONTRAST-ENHANCED ECHOCARDIOGRAPHY

Suboptimal endocardial border definition limits the accurate measurement of LV volumes by echocardiography. In the authors' experience, unenhanced 2D echocardiography underestimates LV volumes by 30–40% and LVEF by 3–6%. In addition, up to 11% of unenhanced scans are deemed uninterpretable for the assessment of LV function. Endocardial border definition is particularly challenging in the setting of obesity, chronic lung disease, ventilator support and chest wall deformities. Contrast echocardiography, by increasing the mismatch between the acoustic impedence of blood and that of myocardium enhances the discrimination between myocardial tissue and the blood pool and improves the accuracy of echocardiography to quantitate LV volumes. These advantages are particularly apparent in large spherical hearts in which the lateral and anterior walls are situated in the portion of the image with the poorest resolution. In the authors' experience, sonographers are likely to foreshorten the image of a spherically dilated ventricle in order to image the lateral wall and confuse

TABLE 4

Normal values for end diastolic volume index from three sources

		Men			*Women*			
LVEDV/BSA	*Reference range*	*Mild Incr.*	*Moderate Incr.*	*Severe Incr.*	*Reference range*	*Mild Incr.*	*Moderate Incr.*	*Severe Incr.*
ASE 2005	35-75	76-86	87-96	> 97	35-75	76-86	87-96	> 97
F'ham MRI	Mean 58-80 (.9UCB)	81-103*	104-126	> 127	50-66 (.9UCB)	67-83	84-100	> 101
UCSF	Mean 58-80 (.9UCB)	81-103*	104-126	> 127	53-66 (.9UCB)	67-80	80-93	> 94

*mild, moderate, severe defined in increments of +2SD

trabeculations along the lateral wall with the true endocardium. These technical problems may underestimate ventricular volume by as much as 100 cc in the largest hearts imaged without contrast. The LV cavity is effectively opacified by the intravenous administration of engineered microbubbles that consist of a gas contained by an outer shell. Recent studies indicate that contrast-enhanced 2D echocardiography has excellent correlation with radionuclide, magnetic resonance and computed tomographic measurements of LV volumes and LVEF, with improved interobserver agreement and physician interpretation confidence. The 2008 ASE consensus statement recommends the use of contrast agents in difficult-to-image patients with reduced image quality, where greater than or equal to 2 contiguous segments are not seen on unenhanced images and in patients requiring accurate quantification of LVEF regardless of image quality, with the intention of increasing the confidence of the interpreting physician in assessing LV volumes and systolic function.[19,20]

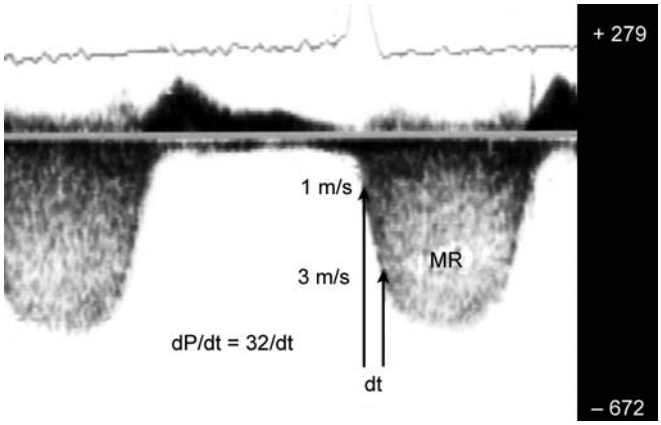


FIGURE 13: Calculation of dP/dt of the left ventricle, CW Doppler of mitral regurgitation (MR). Interval between velocities of mitral regurgitation of 1 and 3 m/sec here is 40 m/sec. Pressure difference is 32 mm Hg: according to Bernoulli equation $dP = 4(V_1^2 – V_2^2) = 4(3^2 – 1^2) = 32$. Thus dP/dt = 32/0.04 = 800 mm Hg/sec (normal > 1300)[23]

OTHER ECHO-DERIVED INDICES OF LV SYSTOLIC FUNCTION

Left ventricular stroke volume is routinely calculated by multiplication of the velocity-time integral (VTI) of the pulsed wave Doppler flow signal from the LVOT, by the cross-sectional area of the LVOT calculated from its radius [Area = pi × (radius)^2]. VTI of forward blood flow is the length of the column of blood in centimeter, passing through the LVOT during systole. Multiplication of this value by the cross-sectional area, through which this column is moving, provides an expression of stroke volume. The product of stroke volume and heart rate is cardiac output in l/min. Since the size of the LVOT is usually a function of BSA,[21,22] in our practice, the authors prefer to use VTI and minute distance (VTI × heart rate) as analogs of stroke volume. Normal VTI from LVOT pulsed wave Doppler is between 18 cm and 23 cm and normal minute distance between10 m/min and 20 m/min.

Another index of global LV systolic function is the velocity of pressure increase in the left ventricle at the initial part of ejection period (dP/dt).[23] Echocardiographic calculation of dP/dt is possible only in the presence of a complete mitral regurgitation continuous wave Doppler envelope during its initial acceleration (Fig. 13). Measurement of the time required for the mitral regurgitant jet to increase its velocity from 1 m/sec to 3 m/sec is obtained. Assuming that the left atrial pressure remains constant, pressure change in the left ventricle between velocities of 1 m/sec and 3 m/sec by modified Bernoulli equation is 32 mm Hg. This value is divided by the time, measured from the acceleration of the mitral regurgitant envelope, to accelerate from 1 m/sec to 3 m/sec to yield dP/dt, which normally is above 1,350 mm Hg/sec.

STRAIN-DERIVED INDICES

In mechanics, strain is the change in the metric properties of a *continuous* body in the displacement from an initial placement to a final placement in response to a *stress* field induced by applied *forces*. In echocardiography parlance, strain is defined as myocardial deformation relative to its baseline dimension due to a stress.[24,25] The rate of deformation over time is termed strain rate. Both strain and strain rates can be measured using tissue pulsed Doppler and speckle tracking. The former technique uses gated tissue Doppler to compare the myocardial motion of two points, usually 1 cm apart, along a single beam of interrogation; this method is angle dependent. The newer strain measurement technique that uses the gray scale speckle pattern of myocardial images is angle-independent. Strain and strain rate can be used to evaluate both regional and global LV systolic and diastolic function. Moreover, these deformation indices can quantify myocardial function in various planes, including longitudinal, circumferential and radial. These measures may be useful in determining early systolic dysfunction (regional and global) in the setting of normal EF. In a study comparing patients with hypertrophic cardiomyopathy (HCM) and a normal control group, both with normal LVEF, Richand and colleagues found that the patients with HCM had significantly reduced longitudinal, transverse, radial and circumferential strain as assessed by speckle tracking.[26] In another recent study, Ng and colleagues used speckle tracking to demonstrate impaired LV systolic and diastolic longitudinal strain and strain rate in patients with type 2 diabetes mellitus.[27] Interestingly, both circumferential and radial function was preserved in these patients. In addition to the utility of the amplitudes of systolic strain and strain rates, differences in time to peak systolic strain and strain rate among myocardial segments have been used extensively to quantitate electro-mechanical dyssynchrony, a potentially significant predictor of clinical outcomes in HF and response to cardiac resynchronization therapy.[28] In summary, strain and strain rate, especially, as quantified by speckle tracking, are emerging approaches to a more quantifiable understanding of myocardial systolic and diastolic function.

RECOGNIZING THE ETIOLOGY OF CARDIAC DYSFUNCTION

According to the report of the World Health Organization/International Society and Federation of Cardiology Task Force on the definition and classification of cardiomyopathies,[29] there are five major types of cardiomyopathy (i.e. diseases of the

myocardium associated with cardiac dysfunction) that can be appreciated by echocardiography. These conditions can affect either ventricle, but are most often recognized when they involve the left chamber.

1. Dilated cardiomyopathy arising as primary myocardial disease of unknown etiology or as disorders of ischemic, toxic, familial or infective origin.
2. Hypertrophic cardiomyopathy, arising as a primary condition or secondary process to conditions such as aortic stenosis or hypertension.
3. Restrictive or infiltrative cardiomyopathies such as cardiac amyloidosis.
4. Arrhythmogenic right ventricular dysplasia or cardiomyopathy (not discussed here).
5. Unclassified cardiomyopathy including endomyocardial fibroelastosis and ventricular noncompaction.

DILATED CARDIOMYOPATHY

Dilated cardiomyopathy is readily identified by echocardiography when it is fully developed but is more difficult to detect in its early stages. Without clinical history, patient examination and other diagnostic test results, echocardiography alone is often unable to establish the cause of myocardial disease.

ECHOCARDIOGRAPHIC FINDINGS

The most distinctive 2D echocardiographic findings in a dilated cardiomyopathy are LV spherical dilatation, normal or reduced wall thickness, poor systolic wall thickening and/or reduced inward endocardial systolic motion. All of the systolic indices are reduced, including fractional shortening, fractional area change and EF. Four-chamber cardiac enlargement is often present. On m-mode echocardiography, additional features related to systolic dysfunction are increased separation of the mitral leaflet E-point from the septum,[7] poor mitral valve opening, poor aortic valve opening[30] and early closure from a reduced stroke volume, and poor systolic aortic root motion.[8] In patients with dilated cardiomyopathy, the LVEDVI often exceeds 100 mL/m^2 (upper normal is approximately 75 mL/m^2). The EF, derived from the ESV and EDV determinations can, at times, fall below 20%, but is usually between 20% and 40% (normal > 55%). Despite the reduced EF, cardiac output calculations (stroke volume times heart rate) are frequently normal. There are two reasons for this finding. First, patients with cardiomyopathy frequently have elevated heart rates. Second, since the stroke volume is equal to the product of the LVEDV and EF, the effect of a low EF can be counter balanced by an elevation in EDV. As an example, a patient with an EDV of 300 mL, an EF of 30% and a heart rate of 100 beats per minute has a cardiac output of 9 l/min. In patients with ischemic cardiomyopathy who have global dysfunction with segmental evidence of infarction, an ESVI of 45 mL/m^2 identifies patients with a poor outcome.[9]

ISCHEMIC CARDIOMYOPATHY

Ischemic cardiomyopathy is a common cause of HF that can be difficult to differentiate from idiopathic or primary dilated cardiomyopathy. In both ischemic and primary forms, LV wall motion abnormalities and the intensity of scarring can be segmentally variable or heterogeneous. In most patients, ischemic cardiomyopathy is associated with regional remodeling, which is characterized by local segments that have their own radius of curvature. Ischemic cardiomyopathy also tends to have areas of endocardial brightening or scarring that occurs in the areas where infarctions are most common: the inferior base and the apex.

Patients with ischemic cardiomyopathy tend to have calcification of the aortic annulus, aortic valve, sinotubular junction, mitral annulus, papillary muscle and proximal coronaries. They may also have visible plaque in the aortic arch and abdominal aorta.

HYPERTROPHIC CARDIOMYOPATHY

Hypertrophic cardiomyopathy is characterized by increased LV mass, which is quantitated by determining the mean wall thickness and the volume of the cavity. When these findings are present without apparent etiology, it is considered to be a primary HCM that is likely to be genetic in origin. HCM is considered secondary when due to an identifiable disorder such as hypertension or aortic stenosis. The hypertrophy is often asymmetric in primary HCM, and symmetric in secondary disease.

PRIMARY HYPERTROPHIC CARDIOMYOPATHY

Primary HCM characteristically shows asymmetric septal hypertrophy (ASH); the increased wall thickness is localized or most intense in the basal septum. ASH is recognized by a septal to posterior wall ratio of 1.3 to 1; high-risk ASH is recognized by a ratio of 3 to 1. The patterns of distribution of this hypertrophic state are not well understood because they follow an unpredictable pattern. A puzzling aspect of this condition is that the patterns of involvement differ among affected family members.[31] In an unusual variant of ASH, the apex is the site of the most intensive hypertrophy.[32]

In our experience, apical hypertrophy is more difficult to identify by echocardiography because the apical myocardium is more difficult to image. When this condition is suspected (e.g. by finding deeply inverted precordial T waves on ECG), it is helpful to use an echocardiographic contrast agent to confirm the diagnosis.

ECHOCARDIOGRAPHIC FEATURES

The echocardiogram with Doppler is the most reliable means for diagnosing HCM, particularly when the condition is fully developed and outflow tract obstruction accompanies ASH. Since the outflow obstruction portends a poorer prognosis, identifying the presence of obstruction is critical. However, when the obstruction is dynamic, i.e. provocable but mild or absent at rest, the task of the echocardiographic laboratory is more difficult. Use of Doppler techniques, particularly continuous wave, is mandatory. This modality is typically used to measure the systolic flow velocity in the LVOT and mid cavity at rest and during provocative maneuvers (normal 0.9 m/sec). Doppler in this setting will also enable the recognition of dynamic mitral regurgitation that often appears in concert with outflow tract obstruction.

The echocardiographic diagnosis of HCM is based upon the finding of a hypertrophied, nondilated left ventricle and maximal wall thickness greater than or equal to15 mm that is not associated with systemic hypertension.

Fully developed HCM consists of the following features:

- Asymmetric septal hypertrophy
- Systolic anterior motion (SAM) of the mitral valve
- Crowding of the mitral apparatus by the LVOT
- Partial mid systolic closure or notching of the aortic valve
- Calcification of the mitral annulus frequently accompanies HCM, and, in some patients, this finding is the only clue to the potential for dynamic outflow tract obstruction
- Mitral regurgitation often accompanies obstruction and may be difficult to distinguish from one another
- Left atrial enlargement
- Diastolic dysfunction as manifested to delayed relaxation pattern occurring at an earlier age

SECONDARY HYPERTROPHIC CARDIOMYOPATHY

Secondary left ventricular hypertrophy (LVH) is most commonly encountered as a complication of hypertension or aortic stenosis. The presence of LVH in hypertensive subjects increases the likelihood of cardiovascular morbidity and mortality.

ECHOCARDIOGRAPHIC FEATURES

Echocardiography is the procedure of choice for identifying secondary HCM since the sensitivity of the different ECG criteria may be as low as 7–35% with mild LVH and only 10–50% with moderate to severe disease. Historically, echocardiographic criteria for the diagnosis of LVH were largely based on m-mode echocardiography and included a LV mass index greater than or equal to 134 g/m^2 in men and greater than or equal to 110 g/m^2 BSA in women.

Most of the echocardiographic studies of LVH have relied on m-mode echocardiography. However m-mode echocardiography may not be ideally suited for this task due to a relatively low yield in older patients, suboptimal reproducibility, possible erroneous results in distorted ventricles, and use of a geometric algorithm that tends to overestimate mass. 2D echocardiography increases the precision and produces estimates of LV mass that more closely approximate values derived from pathology, MRI and CT.

The most commonly used 2D methods for measure LV mass are area-length and truncated ellipse. Both methods have been previously validated and endorsed by the ASE.[1,2] The most recent ASE published guidelines for diagnosis of LVH included criteria for mild, moderate and severe LVH for men as 103–116, 117–130 and greater than 130 g/m^2, and for women as 89–100, 101–112 and greater than 112 g/m^2 respectively. Based on our outcome data,[33] the authors consider LV mass index greater than 95 g/m^2 indicative of mass in the abnormal range.

RESTRICTIVE CARDIOMYOPATHY

Restrictive cardiomyopathies are more difficult to diagnose with echocardiography than dilated or hypertrophic cardiomyopathies, and may be challenging to distinguish from constrictive pericarditis. Echocardiography, including Doppler interrogation, is the most effective noninvasive means for the recognition of this group of conditions. Restrictive cardiomyopathy is characterized by a low or normal diastolic volume, normal or only mildly reduced LVEF, atrial enlargement, normal pericardium and abnormal diastolic function. Diastolic dysfunction is frequently restrictive, with an elevated peak mitral inflow velocity, rapid early mitral inflow deceleration and reduced Doppler tissue imaging (DTI) early annular velocity.

DIABETES MELLITUS

Perhaps the most common restrictive cardiomyopathy is the small, stiff heart of diabetes arising from glycosylation of the myocardium, in which diastolic dysfunction is the predominant functional abnormality.[34] In the majority of diabetics, this condition is clinically unapparent. Quantitation of LV function reveals a normal EF and LV volumes that are lower than expected. Due to this form of diastolic dysfunction, diabetics with critical coronary artery stenosis and normal LV systolic function are highly prone to rapid onset of pulmonary congestion (flash pulmonary edema) in association with angina or acute myocardial infarction.

AMYLOID INFILTRATIVE CARDIOMYOPATHY[35]

Amyloid heart disease is an uncommon disorder that can occur as a part of systemic primary (AL) or secondary (AA) amyloidosis or as an isolated cardiac condition in patients with senile amyloidosis.[36] The last condition is more common in blacks apparently due to a higher frequency of a predisposing variant in the transthyretin gene. When the amyloid precursor protein is produced by the liver, liver transplantation may halt the process. The prognosis is poor, especially in those who exhibit restrictive diastolic filling patterns by Doppler. Diastolic dysfunction is the most common, earliest and most important echocardiographic abnormality in cardiac amyloidosis. Echocardiography in patients with overt cardiac amyloidosis frequently demonstrates symmetric LV wall thickening, typically involving the interventricular septum, small ventricular chambers, thickening of the atrial septum, pericardial effusion and dilated atria. Increased right ventricular wall thickness, when present, may be associated with right ventricular diastolic dysfunction, which can be demonstrated by Doppler examination. Disproportionate right ventricular enlargement may also occur.

Another common echocardiographic finding in cardiac amyloidosis is a granular, “sparkling” appearance of the myocardium, resulting from the presence of amyloid and collagen nodules in the heart. This finding alone is relatively nonspecific but the combination of these refractile echoes and atrial septum thickening are highly suggestive of cardiac amyloid.

Apparent preservation or exaggeration of contractile function in a subgroup of patients with amyloid cardiomyopathy is explained by very low wall stress, which is the ultimate expression of afterload and is greatly reduced by the combination of thickened walls, very small cavity and low generated systolic pressure (arterial hypotension). When contractile

function is preserved, amyloid cardiomyopathy can be mistaken for HCM and diagnosis can be delayed.

ENDOMYOCARDIAL FIBROSIS

Endomyocardial fibrosis (now designated by WHO as "unclassified cardiomyopathy") is a cause of restrictive cardiomyopathy in North Africa and South America. The condition is associated with eosinophilia in about 50% of those afflicted, and is also known as Loeffler's or Davies disease when encountered in North Africa.

The recognition of endomyocardial fibrosis[37,38] depends on a high level of clinical suspicion and characteristic echocardiographic appearance. There are mass-like apical lesions in the left ventricle resulting from a thrombotic fibrocalcific process. These lesions are associated with restriction of LV and right ventricular filling due to obliteration of one or both cardiac apices. In addition to the unique appearance of the apices, the atria are strikingly enlarged, and mitral and tricuspid regurgitation are often present. As the condition progresses, more and more of the LV cavity is obliterated, leading to a progressively restrictive physiology.

LEFT VENTRICULAR NONCOMPACTION

Left ventricular noncompaction,[39] also called LV hypertrabeculation or spongy myocardium, is an uncommon cause of dilated cardiomyopathy that results from intrauterine arrest of compaction of the loose interwoven meshwork that makes up the fetal myocardial primordium. This disorder should be suspected when unexpectedly heavy LV trabeculation is noted, particularly toward the lateral apex. Noncompaction has recently been reassigned to the "unclassified" category of cardiomyopathy, which also includes endomyocardial fibrosis, fibroelastosis, systolic dysfunction with minimal dilatation and mitochondrial diseases.

VISUAL QUALITATIVE INDICATORS OF SYSTOLIC DYSFUNCTION

Earlier in this chapter the authors discussed their recommendations concerning the visual estimation of EF. Foremost among these was that visual estimation be used as confirmatory evidence of quantitation rather than for primary evaluation. The authors believe that among the more useful qualitative findings associated with all stages of systolic dysfunction are *sphericity*[40] and *descent of the cardiac base*.[41]

The shape of the healthy left ventricle is elliptical and the ratio of its long axis to its short axis is approximately 2:1. In decompensated states, particularly those with volume overload, its shape becomes spherical with the ratio of the axes approaching unity (1:1). Although this ratio has been correlated with EF,[41] the concept of sphericity is most useful when appreciated visually (Fig. 14).

The descent of the cardiac base is the normal movement of the mitral annular plane toward the fixed location of the LV apex. This movement represents the longitudinal function of the LV that in three dimensions is seen to be a twisting, wringing or torsion of the myocardium around the cavity. This movement is most easily appreciated in the apical long axis 2- and 4-chamber views and to a lesser extent in the precordial long axis. Despite seemingly normal inward motion of the endocardium, blunting of basal descent should be treated as an early sign of myocardial dysfunction.

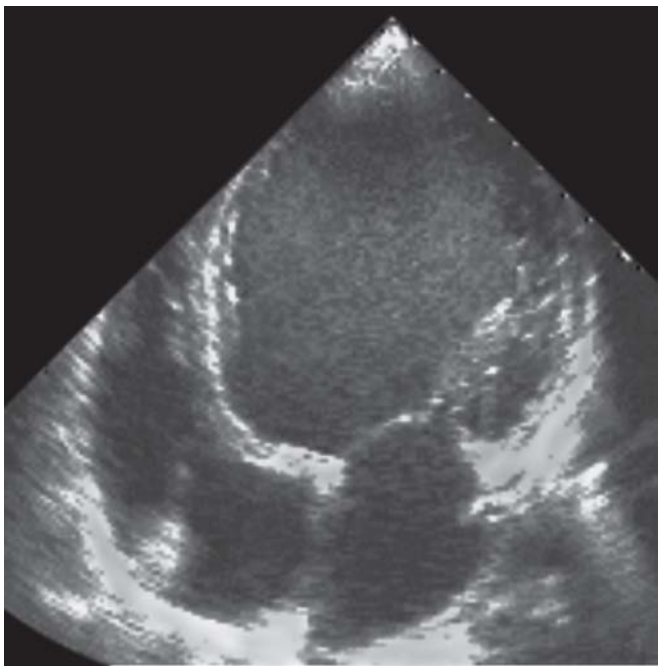


FIGURE 14: Four-chamber view of peripartum cardiomyopathy in a 25-year-old woman. Note the marked spherical remodeling of the LV such that the long and short axis dimensions approach a ratio of 1:1. Compare the shape with the LV shown in Figure 15. Note that the RV is relatively normal

LEFT VENTRICULAR MASS

Left ventricular hypertrophy is universal as an early compensatory change in LV disease and is commonly encountered in patients with ischemic heart disease, congestive HF and advanced age. Concentric LVH, in which LV mass is increased with preserved size and function, may occur in response to chronically increased afterload. Eccentric LVH is seen with ventricular remodeling and chamber enlargement in response to acute or progressive decline in systolic function and typically accompanies a dilated cardiomyopathy. Concentric remodeling is seen as an early stage of LVH[42] and is manifested by increased wall thickness but normal LV mass. All stages of hypertrophy have been associated with adverse outcomes, including sudden death and HF.[43]

The wall thickness of the LV has long been an informative m-mode echocardiographic measurement. Taken by itself, the linear thickness of the septum or of the posterior wall, or both, has been used as an index of LVH (> 1.1 cm). The ratio of posterior wall thickness to septal thickness is used as an index of asymmetric hypertrophy (> 1.3:1). As in the case of LV cavitary dimension, many laboratories use the simple linear measurement of wall thickness to assess LV mass indirectly and some extrapolate LV mass indirectly by an algorithm that extrapolates wall thickness from linear dimensions of opposing walls and subtended cavity. With the disappearance of stand-alone m-mode echocardiographs and the availability of 2D instruments, the use of wall thickness as an index of

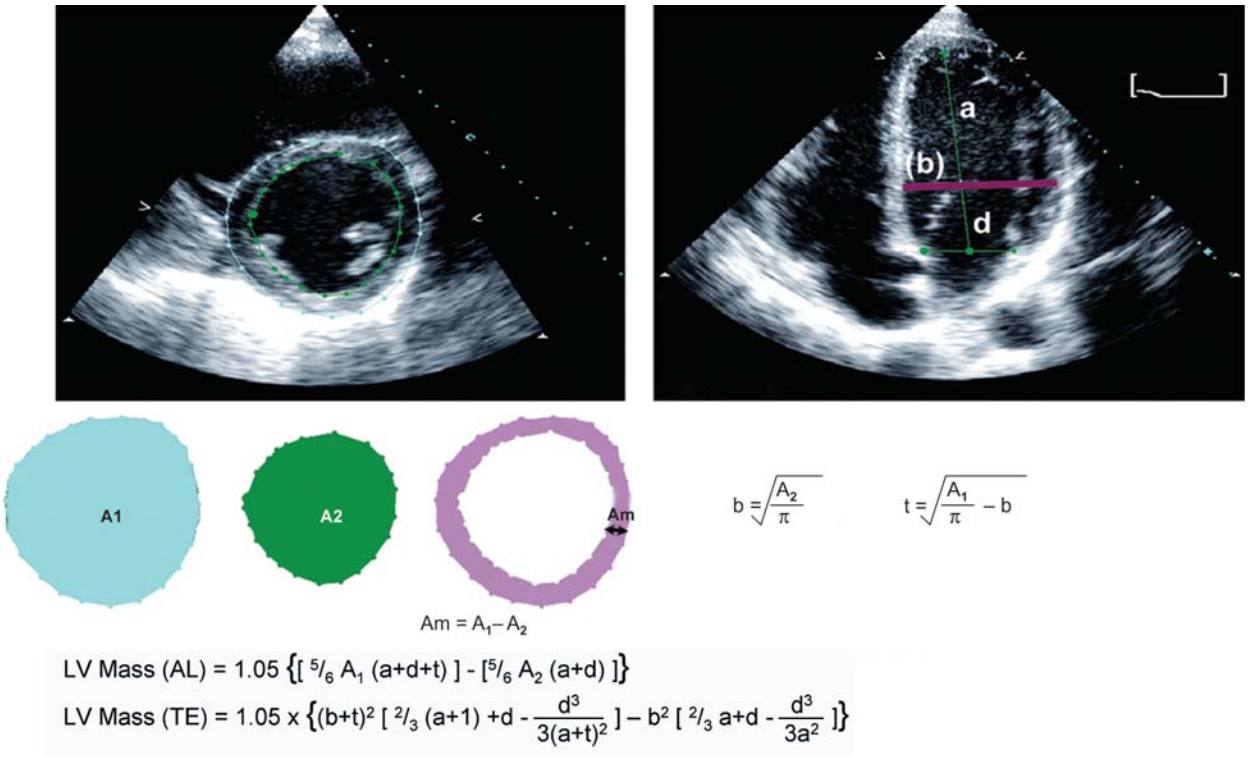


FIGURE 15: Truncated ellipsoid and area length methods of 2D LV mass measurement.[44] The mean wall thickeness is estimated by tracing the epicardial and endocardial areas at the papillary muscle tip level of the short axis LV view. The areas are treated as circles and their mutual radii subtracted to yield an expression of mean wall thickness. This method decreases the potential error of relying on two isolated measurements of wall thickness by averaging many points. As a rule, if the epicardial (outer area) is less than 40 cm^2, the mass is usually normal

hypertrophy has been questioned. The central point of this issue is that wall thickness is being used as an indirect expression of LV mass or weight. If, for example, the weight of the left ventricle is normal, but the preload or filling volume is greatly reduced, the wall will appear to be thickened in diastole. Similarly, if the cavity is dilated the wall will appear to be thin, in spite of normal or even increased mass. For these reasons the authors prefer to measure LV mass as an expression of LVH. There are a number of methods that have been proposed to measure LV mass from m-mode echocardiography. Unfortunately, they suffer the same theoretical limitation as the cube method of estimating LV volume from the minor axis dimension. This limitation is imposed in this case by the inability to extrapolate the volume of the myocardium from a linear dimension. This limitation is most keenly felt in attempting to deal with asymmetric hearts. Working with more uniform hearts and in large populations where individual variations become unimportant, a number of studies have used m-mode methods and have given us valuable insight into the implications of ventricular hypertrophy, and sensitivity and specificity of electrocardiographic criteria for hypertrophy in the hypertensive population.[45]

Based on their own outcomes research, the authors feel that LV mass should be measured directly from 2D images. The ASE recommended method for estimating LV mass is illustrated in Figure 15. See figure legend for details of methods.

Values of two dimensionally calculated mass are given in Table 5.

Note that the ASE values recommended in the 2005 standards document are larger than those from the Framingham MRI and UCSF 2D echocardiography studies. In coronary disease, the authors have found that increased adverse outcomes

TABLE 5

Normal values for LV mass from three sources

		Men			*Women*			
LVMass g/BSA	*Reference range*	*Mild Incr.*	*Moderate Incr.*	*Severe Incr.*	*Reference range*	*Mild Incr.*	*Moderate Incr.*	*Severe Incr.*
ASE 2005	50-102	103-116	117-130	> 131	44-88	89-100	101-112	> 113
F'ham MRI	Mean 78-95 (.95UCB)	96-113*	114-131	> 132	61-75 (.95UCB)	76-90	91-105	> 106
UCSF	Mean 71-95 (.9UCB)	96-120*	121-135	> 136	62-89 (.95UCB)	90-117	118-135	> 136

*mild, moderate, severe defined in increments of +2SD

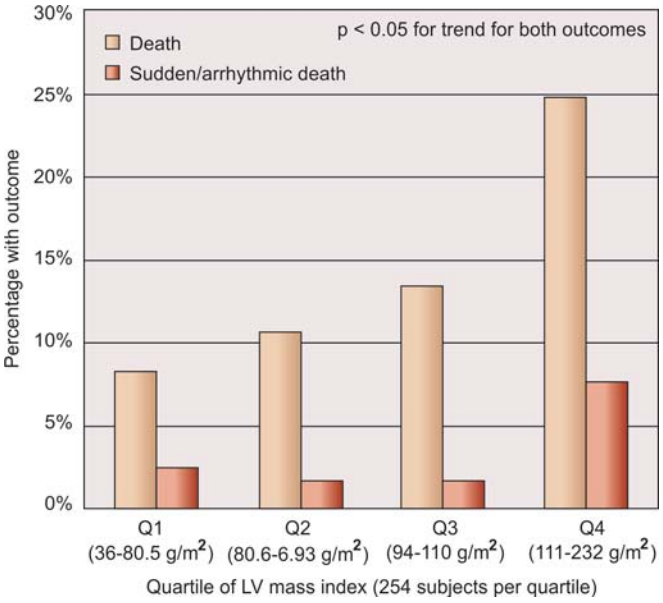


FIGURE 16: Rates of all-cause mortality and sudden death through the end of follow-up, stratified by quartile of left ventricular mass index

in males begin when LV mass exceeds 90 g/m^2 and in females 85 g/m^2.

In the Heart and Soul study, the authors have found that increased LV mass predicts adverse outcomes such as sudden death and HF.[33] In developing an index to predict HF hospitalization, the authors found that mass was the most powerful predictor of subsequent events.[46]

Relationship of death and sudden death to quartile of LV mass in a population of 1,000 patients with coronary heart disease follows for 5 years (Fig. 16).

DIASTOLIC FUNCTION

Echocardiography allows detailed investigation and integration of the complex array of flow related events that occur during LV filling. Whereas systolic function or the process of ejection is known as *inotropy*, diastolic function or the process of filling is termed *lusitropy*. As befits its complexity, multiple measurements and indices have been created to study "diastolic function" and many of these are now standard components of routine echocardiographic examinations. There are several reasons for emphasizing diastolic function:

1. At least one-third of patients with congestive HF have normal or minimally reduced LV systolic function[47] and, among these, congestive HF is mainly a consequence of diastolic dysfunction. In patients with clinical HF and normal systolic function, echocardiographic diastolic parameters confirm the presence and severity of diastolic dysfunction, and guide the type and intensity of treatment and follow-up.
2. Importantly, diastolic parameters are noninvasive surrogates of LV filling pressures in situations of both normal and abnormal LV systolic function. Lowering filling pressures is a goal of treatment and can be confirmed by documenting improvement in echocardiographic indices. Whether diastolic dysfunction is improved or merely masked by lowering filling pressure is a question that is neither easy to answer nor to fathom.

Diastolic function of the left ventricle is determined by interaction of an active, energy-consuming process of myocardial relaxation, defining the early phases of diastole—isovolumic relaxation and early filling—and by mechanical (elastic) properties of the myocardium, which influence all of diastole. Mechanical properties of the myocardium are described as elasticity (change of length per unit of force), compliance (change of ventricular volume per unit of pressure) and stiffness, which is the inverse of compliance. The filling portion of pressure-volume loops (Figs 17A and B) graphically illustrate the unique characteristics of specific abnormalities of diastolic function.

Echocardiographic analysis of the diastolic function of the left ventricle is based on multiple parameters, including pulsed wave Doppler of the transmitral flow, flow patterns in the pulmonary veins, flow propagation velocity by color m-mode of the LV inflow tract and tissue Doppler studies of motion of the LV base in diastole. In addition, left atrial volume provides a measure of the chronicity of abnormal LV filling conditions. Each of these parameters is determined by multiple physiologic processes, and when taken together, they permit a reasonable understanding of the diastolic state of the left ventricle.

TECHNICAL ASPECTS OF RECORDING AND MEASUREMENT OF DIASTOLIC PARAMETERS

Transmitral Flow

The measurement of transmitral flow velocities by the pulse wave Doppler is the starting point and central component of the classification of LV diastolic function by Doppler echocardiography (Figs 18A to D). However, it is important to understand that the recorded transmitral flow velocities are a result of complex interaction of the "pull" by the left ventricle (active suction which occurs in the early diastole) and the "push" from left atrial passive and active pressure. The pattern on the Doppler signal of transmitral flow created by cyclical rising and falling of transmitral velocity is highly sensitive to and influenced by relatively minor shifts in LV relaxation rate, as well as changes in left atrial pressure due to preload, force of contraction and left atrial compliance. Stand-alone recordings of transmitral flow do not usually provide sufficient information for conclusions about diastolic function and must be supplemented by other information.

Transmitral flow for analysis of intervals, velocities and patterns is recorded with the pulse wave sample volume placed in the inflow tract of the left ventricle at the level of the tips of opened mitral valve leaflets. Routine measurements obtained from transmitral flow recordings include maximal velocities of early and late diastolic LV filling (E and A), and deceleration time of the early LV filling (DT). Atrial fibrillation, mitral stenosis, prosthetic valves, severe aortic insufficiency, A-V block or rapid heart rate (above 90–100/min) leading to the fusion of E and A waves limit the use of transmitral flow for the classification of LV diastolic function.

The 2009 ASE recommendations for measurement of diastolic function list the following measurements to be made

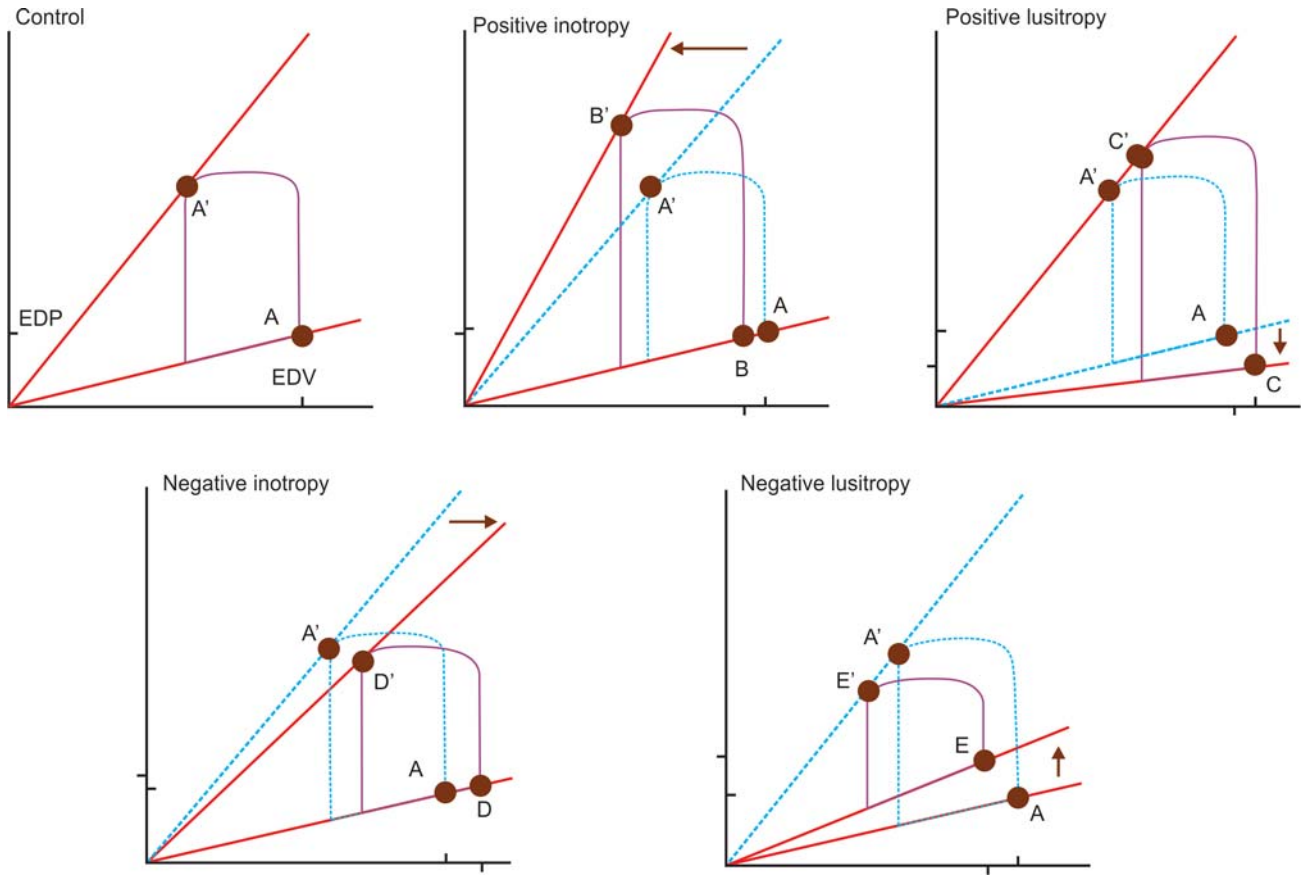


FIGURE 17A: Pressure-volume loops illustrating the result of pure changes in either inotropy (left) or lusitropy (right)[48]

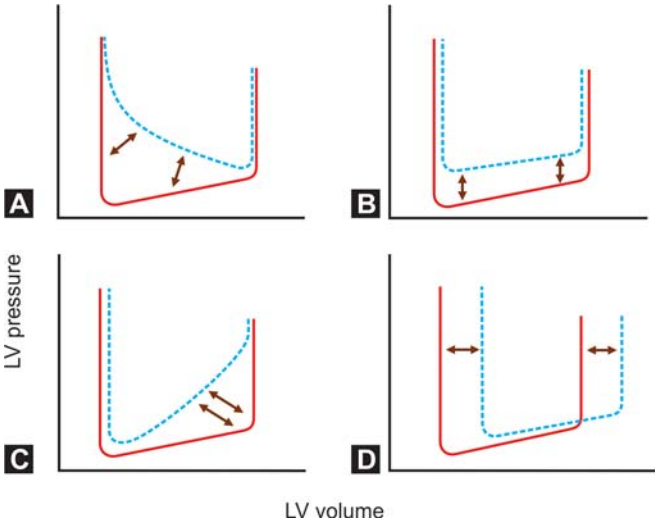


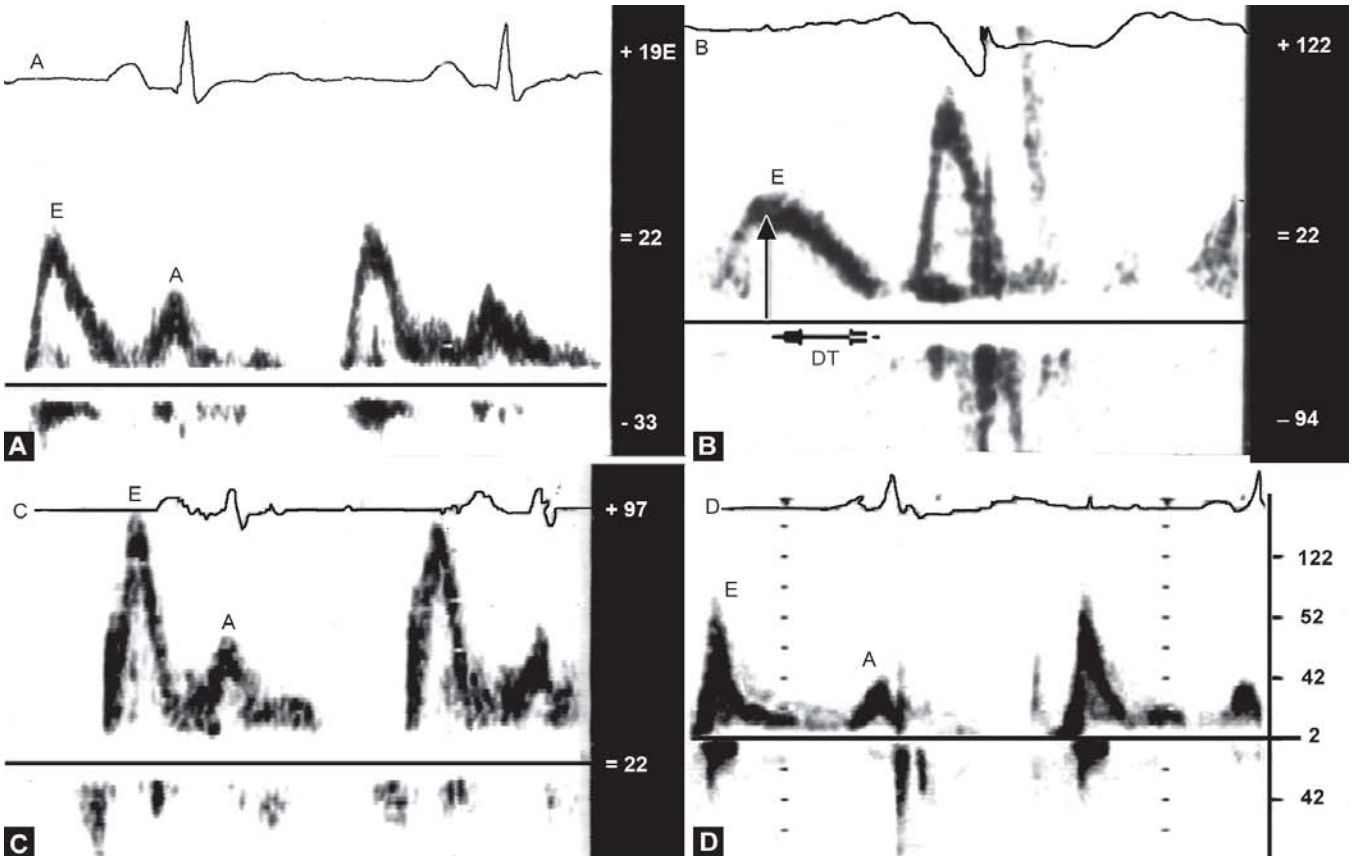
FIGURE 17B: Volume-pressure loops in abnormalities of diastolic function of the left ventricle, caused by different pathologic processes. Only lower parts of the loops, reflecting diastolic function, are shown. The uninterrupted line demonstrates normal diastolic function. (A) Abnormal relaxation of the left ventricle. (B) Restricted filling of the left ventricle in constrictive pericarditis or cardiac tamponade. (C) Decreased compliance of the left ventricle, commonly seen in left ventricular hypertrophy, cardiac amyloidosis, endomyocardial fibrosis or myocardial ischemia. (D) Increased filling pressure of the left ventricle (i.e. in volume overload of the left ventricle). (*Source:* Zile MR. Diastolic dysfunction: detection, consequences, and treatment: II diagnosis and treatment of diastolic function. Mod Concepts Cardiovasc Dis. 1990;59:1-6, Copyright 1990 American Heart Association)

from the mitral inflow signal: isovolumic relaxation time (IVRT), E/A ratio, DT (deceleration time or time required for deceleration of peak early diastolic inflow to baseline), A duration. Normal ranges are given in Table 6.[49]

Measurement of the IVRT, the time interval between cessation of flow in LVOT and the onset of flow in LV inflow tract is obtained from a continuous or pulse wave recording, with the sample volume in a position intermediate between those used for recording of the LV inflow and outflow (Fig. 19). If mitral inflow is used for flow quantitation, the sample volume is placed in the annulus so that its cross-sectional area can be measured from annular diameter and used for calculating volumetric flow.

Propagation Velocity of the Early Diastolic Flow in the Left Ventricle

Normal diastolic filling, enhanced by forceful suction by the left ventricle, produces rapid flow propagation; Figure 20 demonstrates color Doppler recording of normal diastolic filling with simultaneous unidirectional flow rapidly reaching uniform maximum velocity from the starting point of the pulmonary veins and continuing in an unbroken line into the apex of the left ventricle. Because the column of inflow blood accelerates to its maximum so rapidly, the authors believe that the initial acceleration occurs simultaneously in all parts (i.e. from base to apex) of the end systolic blood pool and is an expression of coordinated global active relaxation rather than the migration



FIGURES 18A TO D: PW Doppler recording of transmitral flow patterns commonly encountered. Types of transmitral flow are shown: normal (A) delayed relaxation with dominant left ventricular filling in atrial systole (B), pseudonormal (C) and restrictive (D)

of a bolus of blood from the pulmonary veins to apex. Measurement of the propagation velocity (Vp) of early diastolic flow in the left ventricle uses color m-mode (Fig. 21). For proper measurement, the Nyquist limit is decreased to achieve aliasing in the early diastolic flow. Propagation velocity is the rate at which the wave front of the fastest red cells appear to migrate from base to apex and is represented by the slope of the border between normal and aliased spectrum of the flow signal. Normal values for Vp are greater than 55 cm/sec (45 cm/sec in the elderly). Since Vp is a relatively preload (LA pressure) independent index of LV relaxation, it may be used in the differentiation of normal from pseudonormal mitral flow pattern.

Limitations of Vp include loss of reliability in small ventricular chambers and poor reproducibility due to the

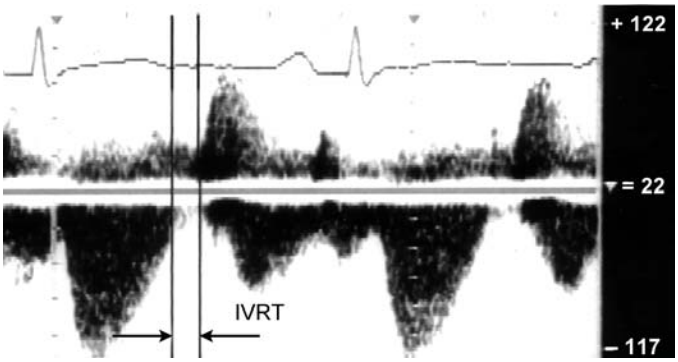


FIGURE 19: Measurement of isovolumic relaxation time is done from a position, intermediate between those used for recording of left ventricular inflow and outflow; both aortic and mitral flow are seen in this tracing; IVRT is the time interval between cessation of aortic flow and onset of mitral flow

TABLE 6

Normal values for Doppler-derived diastolic measurements

	Age group (y)			
Measurement	*16-20*	*21-40*	*41-60*	*>60*
IVRT (ms)	50 ± 9 (32-68)	67 ± 8 (51-83)	74 ± 7 (60-88)	87 ± 7 (73-101)
E/A ratio	1.88 ± 0.45 (0.98-2.78)	1.53 ± 0.40 (0.73-2.33)	1.28 ± 0.25 (0.78-1.78)	0.96 ± 0.18 (0.6-1.32)
DT (ms)	142 ± 19 (104-180)	166 ± 14 (138-194)	181 ± 19 (143-219)	200 + 29 (142-258)
A duration (ms)	113 ± (79-147)	127 ± 13 (101-153)	133 ± 13 (107-159)	138 ± 19 (100-176)

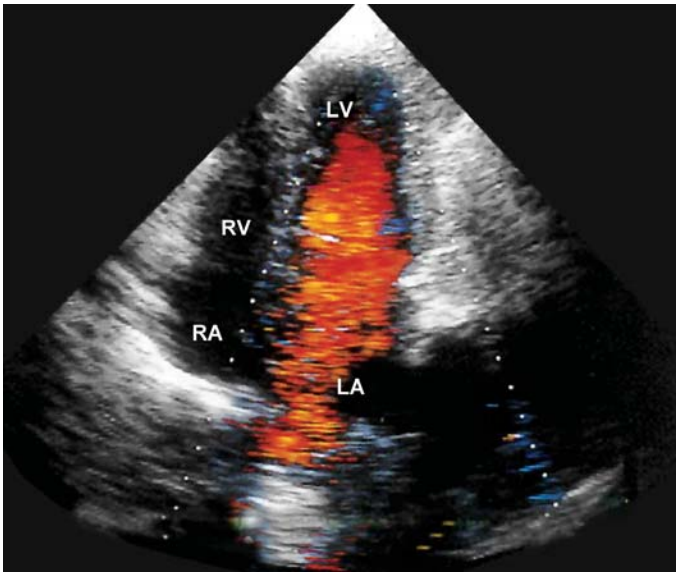


FIGURE 20: Color Doppler study of early diastolic filling of the left ventricle from apical 4-chamber view. Unidirectional flow is seen from pulmonary veins into the left atrium and deep into left ventricle, almost all the way to the apex. (Abbreviations: LA: Left atrium; LV: Left ventricle; RA: Right atrium; RV: Right ventricle)

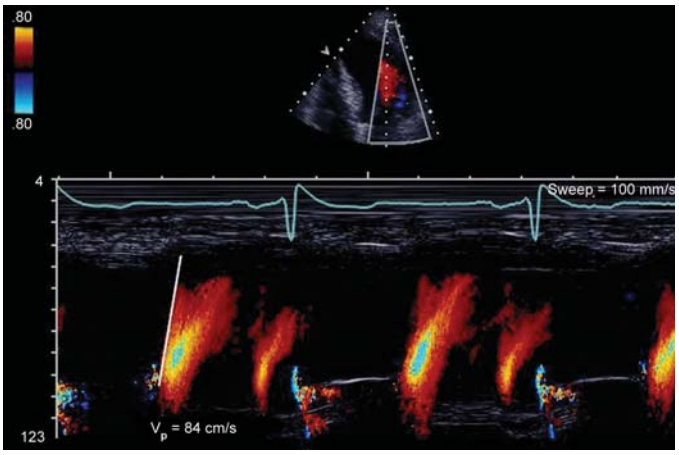


FIGURE 21: Color m-mode study of transmitral flow from apical window: propagation velocity (Vp) of early diastolic left ventricular filling is determined as the slope of aliased flow in the early filling spectrum. Normal Vp exceeds 55 cm/sec, in elderly—45 cm/sec

frequently curvilinear shape of early diastolic flow slope, which can make measurement of Vp somewhat arbitrary.

Pulmonary Venous Flow

The recording of pulsed wave Doppler signal from the pulmonary venous flow is an integral part of each echocardiographic study. Transthoracic echocardiography allows accurate recording of blood flow in pulmonary veins in nearly 90% of patients. Examples of flow signals recorded in pulmonary veins are shown in Figure 22 and diagrammatically in Figure 23. Systolic flow from the veins into the left atrium consists of two components, the first generated by suction from left atrial relaxation (SE) and the second by suction provided by the piston-like descent of the base of the heart toward apex while the mitral valve is closed (SL).[50] Diastolic flow is influenced by left atrial and ventricular filling pressures, and is concurrent with the E wave of transmitral flow. The impetus for early pulmonary vein flow (directly from vein to ventricle) is provided simultaneously by both atrial preload and by active ventricular relaxation. The former provides a push while the latter provides suction into the ventricle. At slow heart rates, the interval between the early rapid flow into the ventricle and the reverse flow retrograde into the pulmonary vein is called the conduit phase. During this phase, flow is slower but continues antegrade. Although both VTIs and peak velocities of the systolic and diastolic components of pulmonary venous flow are measured, the literature correlating pulmonary vein flow with LV filling pressure is based on comparing the integral of the systolic component with the diastolic forward component.[51] Normally the VTI of systolic flow is at least 60% of the total forward flow.

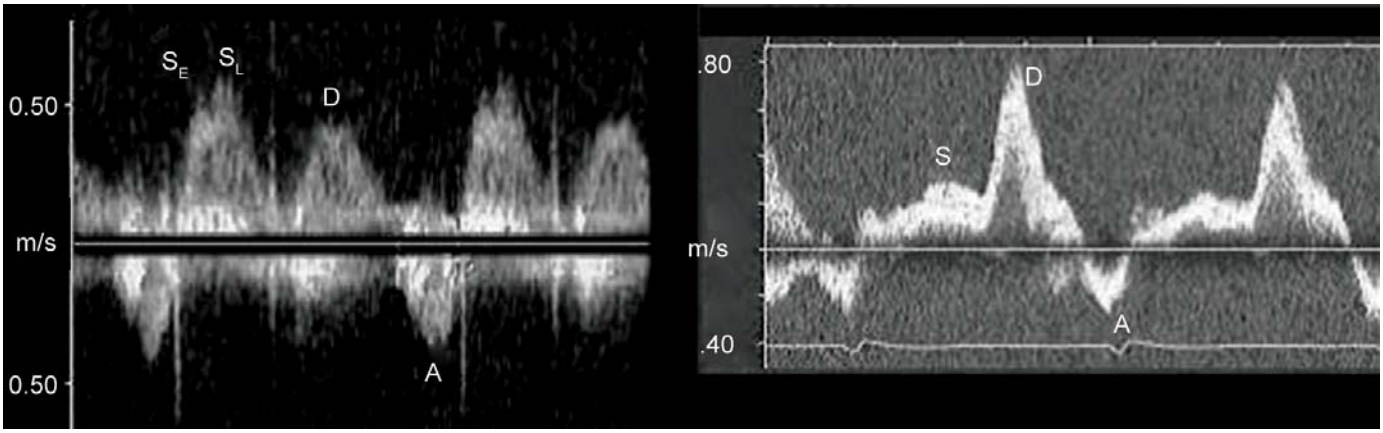


FIGURE 22: Recording of the PW Doppler of pulmonary venous flow from apical 4-chamber view (left) and TEE (right). Two antegrade waves are seen—systolic (S) and diastolic (D)—and a small retrograde wave during atrial systole (A). Sometimes (as in this case in transthoracic study) two systolic antegrade waves are present—early (SE) and late (SL). SE is considered to result from left atrial relaxation, SL—from the movement of the base of the left ventricle toward apex. Diastolic wave D corresponds to early diastolic filling of the left ventricle, although it starts approximately 50 msec later. In rapid heart rates, systolic and diastolic waves merge. Thus antegrade flow in pulmonary veins may be monophasic, biphasic or triphasic. It is important to note that dominance of systolic or diastolic flow should be determined from velocity-time integrals, and not from maximal flow velocities

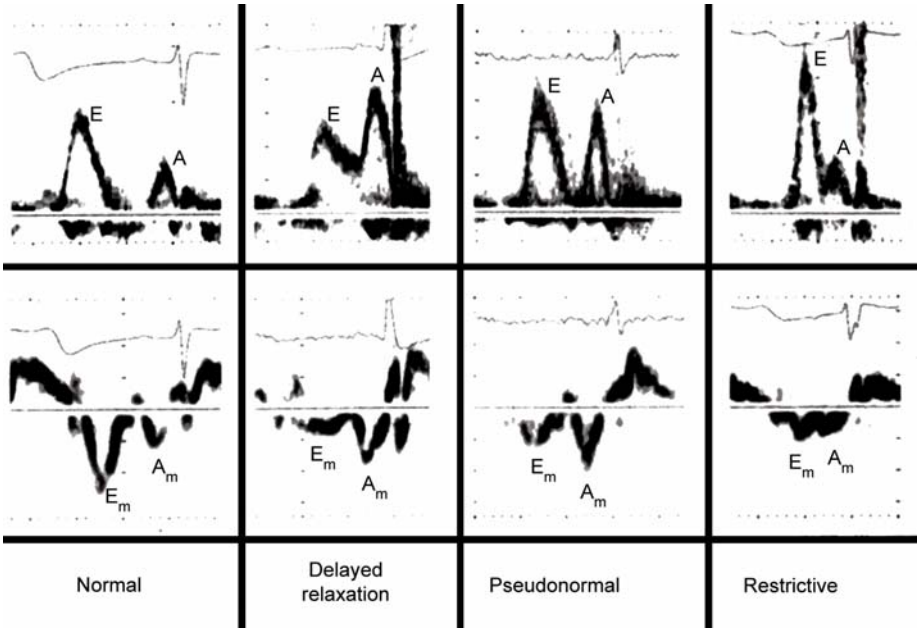


FIGURE 23: The mitral inflow at rest in the subgroups of diastolic dysfunction

In healthy subjects greater than 30 years old, systolic flow usually is dominant (as is true for all central veins). When the patient is younger than 30 and/or when the heart rate is slow, systolic flow remains robust but peak velocity of diastolic flow may be slightly higher. In hypovolemia, diastolic flow in pulmonary veins decreases and may disappear, while systolic component increases. In atrial fibrillation most of the flow in pulmonary veins occurs in diastole, and systolic flow appears blunted. Some research suggests that systolic dominance may be maintained in hypertrophic cardiomyopathies despite elevated LVEDP.[52] In this study and in the ASE guidelines on diastolic function, pulmonary vein measurements are limited to peak systolic and diastolic velocities despite direct experimental hemodynamic data that supports the use of the VTI ratio of systolic and diastolic components and not peak velocity.[50,53] For this reason and for others, the authors remain unconvinced that the recognition of normal LV filling pressure by systolic dominance is vitiated in hypertrophy; the authors have noted that, in unstable conditions where LVEDP is rising from low levels to elevated, the change in pulmonary vein in flow pattern from systolic to diastolic dominant may lag behind the hemodynamics. On the other hand, in the OR, the pulmonary vein Doppler pattern tracks hemodyamic changes accurately.[53]

It should also be noted that with appearance of atrial fibrilation, systolic components of PV flow either become attenuated without necessarily connoting elevated filling pressure. Failure to recognize atrial fibrillation may lead to a false assumption that filling pressure is elevated.

Additional attention should be directed to measurement of duration of the wave of atrial systolic reversal of pulmonary flow (A in Figure 22). With left atrial contraction, blood can move either antegrade into the left ventricle, or flow retrograde into the pulmonary veins. Comparison of flow duration from atrial contraction retrograde from the left atrium into the pulmonary veins (atrial systolic reversal) with antegrade flow into the left ventricle (A wave of transmitral flow) allows another expression of end diastolic LV pressure. Increase of end diastolic pressure in the left ventricle causes longer duration of retrograde flow into the pulmonary veins during atrial contraction than duration of forward transmitral flow. Normally, the duration of atrial reversal should not exceed the forward A wave of transmitral flow by more than 30 msec.[54]

The deceleration of the diastolic component of pulmonary vein inflow is also a useful index of diastolic dysfunction.[55] When the deceleration time of this wave form is less than 150 msec, elevated LV filling pressure is suspected. The validity of this measurement is retained in atrial fibrilation.

Doppler Tissue Imaging of Mitral Annular Motion in Diastole

Recording of mitral annular diastolic ascent (reflective of timing and amount of filling volume) and systolic descent (reflective of quantity and timing of LV emptying) (Fig. 24 lower panel) is accomplished from the apical acoustic window by imaging the 4-chamber view and placing the pulse wave Doppler sample volume on the lateral mitral annulus (preferred) or the intersection of the interventricular septum and the medial annulus (second choice). Filters are set to allow only very low frequencies (< 20 cm/s) to eliminate high-velocity blood flow signals and allow only the slower motion of the annulus to form the signal. Annular motion is proportional to the quantity of blood flow that leaves and enters the ventricle and provides a vehicle to compare with cavitary Doppler flow signals that represent velocity of blood but not its amount. Three main waives can be identified on the Doppler tracing of mitral annular motion (as conventionally displayed): (1) a positive wave reflects systolic motion of the annulus toward the apex (Sm); (2) two negative diastolic waves resulting from motion of the annulus away from apex in early diastole (Em) and (3) with atrial systole (Am). Normally, Em is of greater amplitude than Am.

Tissue Doppler early diastolic velocity mitral annular motion (e'), when combined with mitral inflow peak diastolic

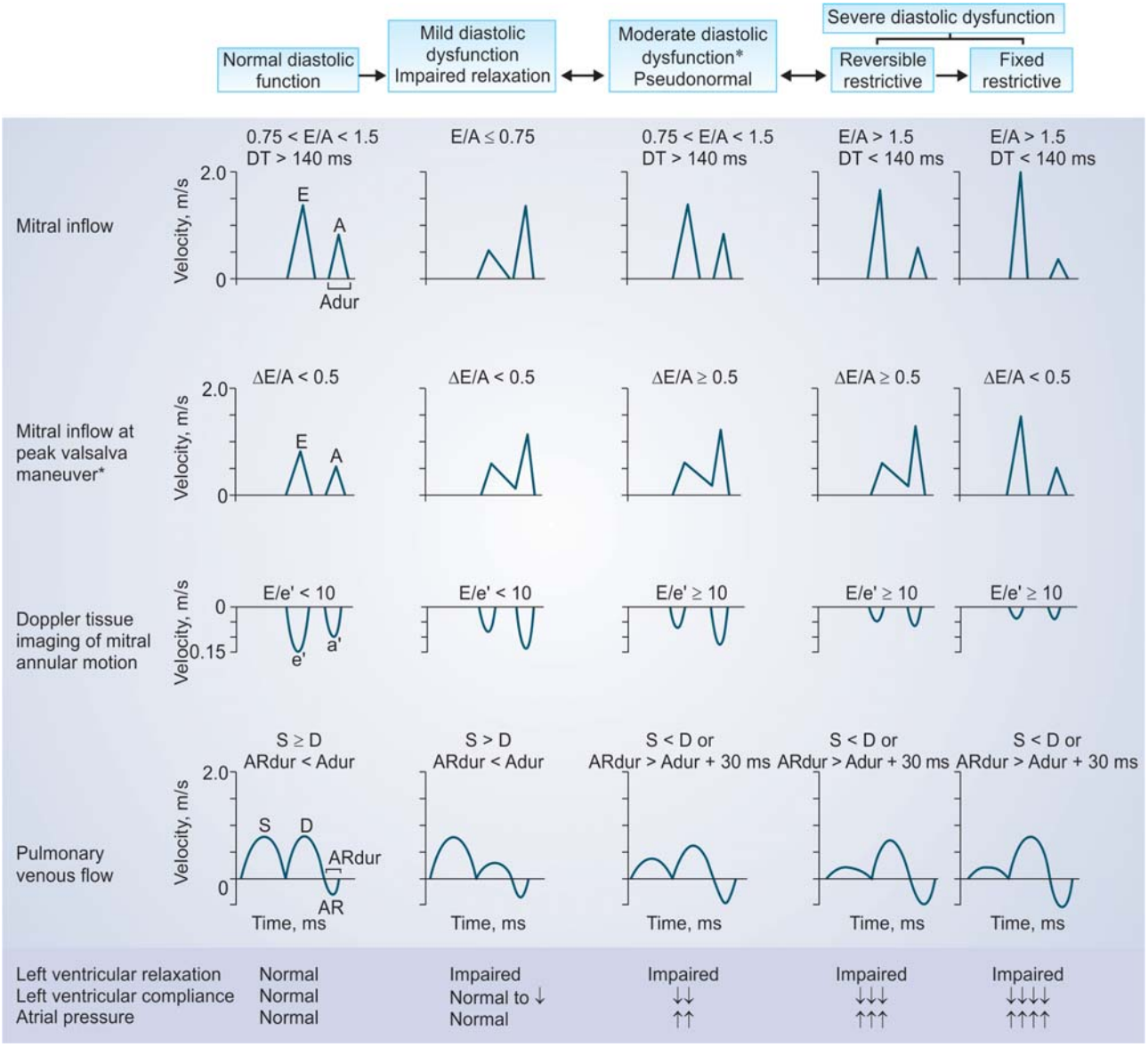


FIGURE 24: Types of transmitral flow (upper row) and corresponding types of tissue Doppler interrogation of the mitral annular motion (lower row). Sample volume is placed on the interventricular septal part of the mitral annulus from the apical 4-chamber view. Tissue Doppler recording allows discrimination of normal and pseudonormal flow. (Abbreviations: A: Transmitral flow during atrial systole; Am: Mitral annular motion during atrial systole; E: Early diastolic transmitral flow; Em: Early diastolic motion of the mitral annulus[56])

velocity (E) as a ratio (E/é), provides an independent measure of LV diastolic performance and can reliably differentiate normal from patterns that arise from elevated filling pressure. In practice, |E/é ratios that are less than 8 or more than 16 have a high sensitivity for normal and elevated filling pressure respectively and can help to avoid misinterpretation of pseudonormal Doppler flow pattern from one that is normal (Fig. 23). However, this method, like most others, has drawbacks. Principally, the E/e' ratio presents a rather wide gray area between the ratios of 8 and 16 where there is poor correlation between this ratio and filling pressure.[52]

Left Atrial Volume and Index

Left atrial volume can be considered tantamount to "the hemoglobin A1c of LV diastolic function", because it seems to reflect the historic average of the filling pressure of the left ventricle; it should be viewed as an important part of the complete evaluation of LV diastolic function. The left atrial volume index (left atrial volume indexed to BSA) predicts risk of cardiac death in patients after myocardial infarction. In addition, in ambulatory patients with stable coronary artery disease, left atrial volume index predicted both HF and death. Left atrial function may also be calculated so as to differentiate from abnormal those atria that are considered enlarged but have become so as a result of elevated stroke volume rather than diastolic dysfunction. It is also a useful in measuring the degree of dysfunction and noting recovery. The formula is:

LA fractional change × LVOT VTI/LAESVI = LAFI

Where fractional change is = LA end systolic volume – LA end diastolic volume/LA end systolic volume; LAESVI is LA end

systolic volume corrected for BSA and LVOT VTI is the VTI of the systolic flow signal obtained from the LVOT.[57]

TYPES OF DIASTOLIC DYSFUNCTION

Abnormalities of diastolic function exist along a continuum, which, based on echocardiographic parameters, may be categorized into four relatively distinct types: (1) impaired relaxation of the left ventricle (type 1 diastolic dysfunction); (2) pseudonormal filling (type 2 diastolic dysfunction); (3) restrictive filling (type 3 diastolic dysfunction) that is reversible with Valsalva maneuver and (4) type 4 diastolic dysfunction-restrictive pattern that is irreversible with Valsalva maneuver. Figure 24 diagrammatically shows the mitral inflow at rest and its response to Valsalva in the subgroups of diastolic dysfunction. Pulmonary vein and DTI patterns are also depicted for each of the subgroups.

Impaired Relaxation of the Left Ventricle

The initial stage of LV diastolic dysfunction is manifest by impaired or slowed relaxation of the left ventricle (type 1 diastolic dysfunction). It is characterized by slowing of the energy-consuming process governing ventricular relaxation; the filling pressures usually remain normal, with brief elevation at the end of diastole at the time of atrial contraction. Because the elevation of the presystolic a wave at end diastole is brief, the mean diastolic pressure remains low. However, when tachycardia intervenes, diastole shortens and the contribution of the A wave to mean diastolic pressure increases; in many patients, exercise intolerance results. Furthermore, patients with type 1 dysfunction may be intolerant to atrial fibrillation because the loss of atrial contraction causes left atrial pressure to rise in compensation for the loss of 60% of filling volume by active transport and refilling atrium with an equal amount through the suction of active relaxation.[49] Delayed relaxation can be recognized by examination of mitral inflow where the ratio of the E and A waves is less than1, IVRT is prolonged and deceleration time (pre-A wave deceleration of inflow) (DT) lengthened. Pulmonary venous flow demonstrates pronounced systolic dominance associated with augmented atrial relaxation and decreased VTI of the diastolic wave, and slowed propagation velocity (Vp). The Em velocity on the tissue Doppler recording of mitral annular motion is also reduced. This filling pattern is consistent with essentially normal mean LV and LA diastolic pressures and does not impart a worsened prognosis in coronary disease.

Pseudonormal Filling

The next stage, stage 2, in the decline in diastolic function that follows impaired LV diastolic function (stage 1) is associated with elevation of the LV and left atrial diastolic pressure. Although LV relaxation remains slowed, higher left atrial pressure leads to an increase in early transmitral filling (E wave) velocity and impaired LV compliance leads to rapid termination of filling when ventricular capacity is prematurely achieved. The abrupt termination of filling shortens the deceleration time toward normal. The increase in left atrial pressure also causes mitral valve to open sooner with consequent shortening of the IVRT. The elevation of LV filling pressures is a direct consequence of decreased chamber compliance which sees the pressure in the left ventricle rise more rapidly during filling. These changes "pseudonormalize" transmitral flow, and make it difficult to distinguish from normal. However, with the Valsalva maneuver, preload decreases, left atrial pressure drops and the "pseudonormal" pattern may temporarily revert back to the pattern of impaired LV relaxation (stage 1).

Other features of the pseudonormal filling pattern include loss of or decrease in the degree of systolic dominance of pulmonary flow; the proportion or systolic fraction of PV inflow to the atria during systole falls below the normal value of 60% of the total of systole plus diastole. Atrial flow reversal in the pulmonary veins is prolonged relative to the duration of mitral A wave inflow.[54]

Color m-mode of inflow velocity reveals slowed acceleration of the propagation velocity. Em velocity on the tissue Doppler recording of mitral annular motion is markedly decreased, and becomes confirmatory evidence that differentiates pseudonormal from normal transmitral flow pattern.

Pseudonormal filling pattern is consistent with elevated LV and left atrial pressures and imparts a worsened prognosis in patients with CHF or CAD.[47]

Restrictive Filling (Grades 3 and 4 Diastolic Dysfunction)

Further increase in LV filling pressure results in worsening effective LV compliance. During diastolic filling, pressure in the left ventricle rises exponentially, and exceeds left atrial pressure very early in diastole. Consequently, most of the diastolic filling occurs early, contribution of late filling is minimal, E to A ratio becomes more than 2:1, deceleration time shortens to less than 140 msec and IVRT shortens further.

By the time of mitral valve closure at the end of diastole, the left atrium does not empty completely. Due to this, the systolic wave of pulmonary venous flow becomes severely blunted and most of pulmonary venous flow occurs in diastole. Moreover, left atrial systolic reversal is prolonged and increased in amplitude. Also, color m-mode reveals further slowing of the propagation velocity and Em velocity on the tissue Doppler recording of mitral annular motion is also markedly decreased. Restrictive LV filling is a poor prognostic sign in various disease states, including patients with low LVEF and in patients with infiltrative cardiomyopathies. Patients who continue to exhibit restrictive filling pattern despite Valsalva (stage 4) or following aggressive medical treatment are at especially high risk.

EVALUATION OF LEFT VENTRICULAR FILLING PRESSURES

The ultimate significance of diastolic parameters is due to their ability to noninvasively evaluate LV filling pressure (Fig. 25). Identification of the diastolic filling pattern provides an approximate understanding of the level of LV filling pressure. Typically, delayed relaxation pattern is associated with normal filling pressures, pseudonormal pattern with mild to moderate elevation of pressures and restrictive pattern with markedly elevated filling pressures. In addition, deceleration time of early diastolic filling may be an accurate indicator of LV filling

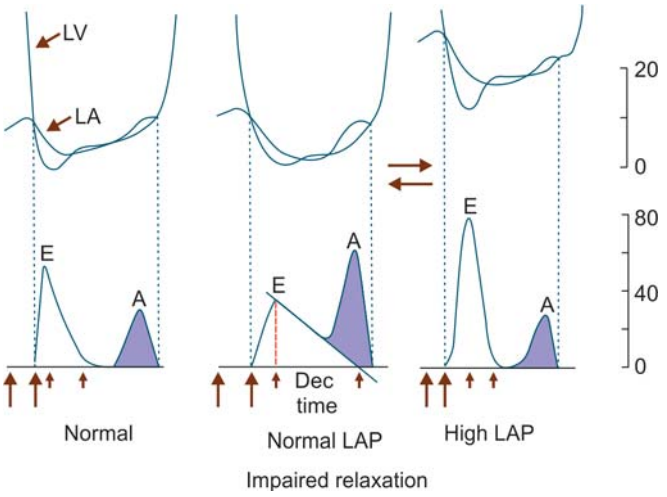


FIGURE 25: Diagrammatic relationship between filling pressure and mitral inflow pattern[49]

pressure in patients with low LVEF, in whom a deceleration time less than 150 msec nearly always indicates mean left atrial pressure above 25 mm Hg.[58]

However patterns of mitral inflow as predictors of filling pressure are vulnerable to confounding. Heart rate, preload, afterload, contractility, valvular regurgitation and the position of the sample volume may influence transmitral flow independently of diastolic function. In certain diseases, mitral inflow pattern has been found unreliable by some investigators: in patients with hypertrophic obstructive cardiomyopathy or severe LVH, transmitral pattern frequently remains consistent with delayed relaxation despite elevated filling pressures (Figs 26A and B). Even in these patients, however, serial studies will reveal changes within these patterns as filling pressure changes.

FORMULAE THAT ATTEMPT TO PROVIDE QUANTITATION OF LV FILLING PRESSURE

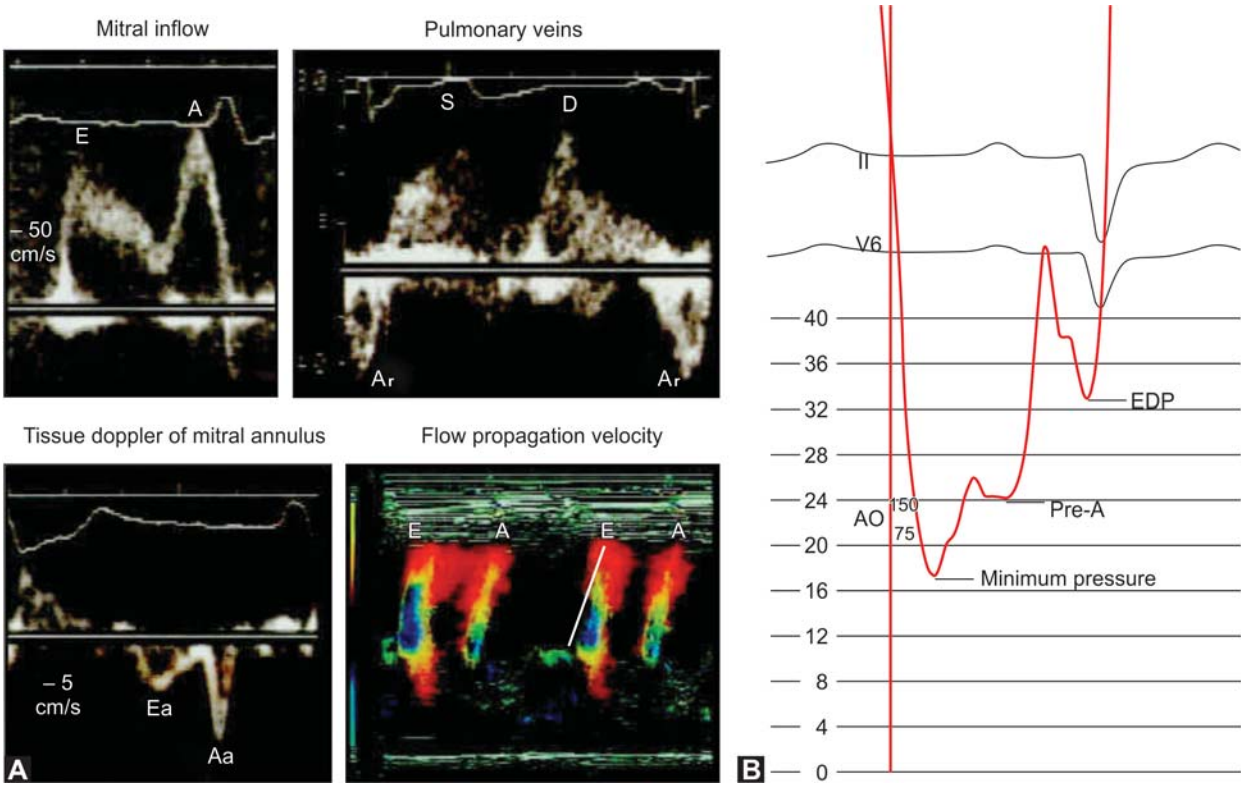
More quantitative estimations of LV filling pressure may be calculated from Doppler-derived parameters. The following methods illustrate attempts at more precise determination of LV filling pressures:

1. Systolic fraction of the pulmonary venous flow is a simple and reliable way of identifying patients with elevated left atrial pressures. Separate measurement of systolic and diastolic wave VTIs allows calculation of the systolic fraction of pulmonary venous flow:

   Systolic fraction = SVTI/(SVTI + DVTI) × 100%

   where SVTI is velocity-time integral of systolic, and DVTI is velocity-time integral of diastolic pulmonary venous flow. Normal systolic fraction of pulmonary venous flow exceeds 55%. Investigation conducted by Kuecherer and colleagues[53] demonstrated a correlation of systolic fraction with mean pressure in the left atrium, and diastolic pressure in the left ventricle. The following formula allows noninvasive calculation of this pressure:

   Pressure in the left atrium (mm Hg) =
   35–0.39 [systolic fraction (%)]



FIGURES 26A AND B: (A) Transmitral velocities, PV velocities, mitral annular velocities by TD and flow propagation velocity in an HCM patient. Time lines represent 200 ms. Notice that E velocity is (almost equal to) 1 m/s and lower than A velocity. DT = 400 ms. Systolic (S) PV flow is almost equal to the diastolic (D) flow. Ea = 6 cm/s, flow propagation velocity = 37 cm/s. (B) LV diastolic pressures from the same patient. LVEDP = 33 mm Hg, preA pressure = 24 mm Hg and minimal pressure = 17 mm Hg. EDP indicates LVEDP; Pre-A indicates preA[59]

In practice, it is sufficient to calculate systolic fraction; if it is less than 40%, end diastolic pressure in the left ventricle is likely to be above18 mm Hg, and frequently coincides with either pseudonormal or restrictive types of LV filling.

2. Tissue Doppler evaluation of mitral annular motion in early diastole (E') provides a relatively preload in dependent measure of LV relaxation. Since the E wave of transmitral filling is determined by an interaction of left atrial pressure and LV relaxation, the ratio of E/E', which corrects E for the volume of inflow (ascent of the base) that resulted in the E' velocity; E/E' relates well to mean left atrial pressure or pulmonary capillary wedge pressure (PCWP).

   Nagueh and colleagues (JACC 1997;30(6):1527-33) showed that the following formula allows noninvasive estimation of PCWP:

   $$PCWP\ (mm\ Hg) = 1.24\ [E/Ea] + 1.9$$

   Subsequently E/Em index was demonstrated to retain its utility in patients with sinus tachycardia and fused E and A waves, and in patients with atrial fibrillation. Moreover, it seems valid in both low and normal LVEF.

   E/Em greater than or equal to 15, where Em is measured in the septal part of annulus, is specific for elevated LVEDP, whereas E/E' less than or equal to 8 is specific for normal to low filling pressures.[60] The method has a problematic weakness in that the values between an E/e' 8 and 15 correlated poorly with LVEDP and weaker correlation in HCM.[52]

3. Propagation velocity of early diastolic filling also correlates with LV relaxation, and is relatively independent of left atrial pressure. The propagation of flow into the LV is due to a complex interaction of events but in health it occurs very rapidly (see above discussion). Garcia and colleagues[61] established this correlation, and suggested the following formula:

   $$PCWP\ (mm\ Hg) = 5.27 \times (E/Vp) + 4.6$$

CONCLUSION

Left ventricular systolic and diastolic parameters can be comprehensively measured by echocardiography/Doppler and provide a wealth of information about ejection and filling functions and have strong prognostic significance. However they are best utilized when interpreted together in an expertly performed comprehensive echocardiographic study in the light of the pertinent clinical questions and context.

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Chapter 15

Ventricular Function—Assessment and Clinical Application

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Chapter Outline

- Determinants of Left Ventricular Performance
  - — Preload
  - — Afterload
  - — Ventricular-arterial Coupling
  - — Contractile State
  - — Measures of Maximum Rate of Pressure Development
  - — Velocity of Contractile Element
- Left Ventricular Pump Function
  - — Ventricular Function Curve
  - — Ejection Fraction
  - — Techniques for Assessment of Left Ventricular Ejection Fraction
  - — Pressure-volume Relations
- Heart Rate
- Diastolic Function
  - — Techniques of Measurement of Diastolic Function
  - — Cardiac Magnetic Resonance Imaging
- Left Ventricular Functional Assessment during Stress
- Right Ventricular Function

INTRODUCTION

Assessment of ventricular mechanical function is essential in clinical cardiology not only for understanding of the pathophysiologic mechanisms of various cardiovascular disorders but also for appropriate management of the dysfunctions and for assessment of prognosis.

The ability to shorten and develop force is the fundamental functional characteristic of cardiac muscle. The performance of the cardiac muscle is influenced by the change in initial muscle length (Frank-Starling mechanism) and in contractility. The determinants of performance of cardiac muscle are initial muscle length (preload), the load against which the muscle shortens (afterload), the contractile state and heart rate.

The same principles and the determinants regulate the performance of the intact ventricles.

Since left ventricle delivers cardiac output to maintain organ perfusion and systemic arterial pressure, more studies have been done to assess left ventricular (LV) function. However right ventricle also plays an important role to maintain appropriate pulmonary blood flow, adequate LV filling and systemic output.

In this chapter, assessments of both right and left ventricular function and clinical implications have been discussed.

DETERMINANTS OF LEFT VENTRICULAR PERFORMANCE

The major determinants of LV performance are preload, afterload, contractile state and heart rate.

PRELOAD

In the isolated muscle the initial muscle length before shortening represents preload. In the intact heart, ventricular wall stress before ejection is regarded as its preload.[1] Wall stress in clinical practice is calculated as follows:

$$\text{Wall stress} = \frac{\text{Ventricular pressure} \times \text{Radius of curvature (volume)}}{2 \times \text{Wall thickness}}$$

It is apparent that wall stress is increased with an increase in intraventricular pressure and ventricular volume and a decrease in wall thickness. In the intact heart preload is represented by the end-diastolic wall stress. The calculation of wall stress is difficult in clinical practice. Frequently ventricular end-diastolic volume or end-diastolic pressure is used to represent its preload. It should be appreciated that LV diastolic pressure can be used as filling pressure only when pressures opposing distention of the ventricles during filling is normal. The transmural pressure is also used as the filling pressure and is calculated as follows:

Transmural pressure = LV diastolic pressure – pericardial and mediastinal pressure. It is apparent that in presence of normal pericardial and mediastinal pressures, LV diastolic pressure can be used as its preload. When intrapericardial pressure is increased as in cardiac tamponade, LV diastolic pressure cannot be used to represent its transmural and filling pressures.

The LV end-diastolic volume can be determined by contrast ventriculography during cardiac catheterization. However, in clinical practice, it is assessed noninvasively by

echocardiography, radionuclide angiography, contrast computerized tomography or cardiac magnetic resonance (CMR) imaging. Transthoracic echocardiography is the most frequently employed noninvasive imaging modality to determine LV end-diastolic volume. In the critical care units, it is difficult to use transthoracic echocardiography to measure LV end-diastolic volume frequently. With the advent of balloon floatation catheters, pulmonary capillary wedge pressure (balloon occluded pressure) is frequently used to represent LV end-diastolic pressure and preload.[2] It should be appreciated that pulmonary capillary wedge pressure represents LV end-diastolic pressure only in the absence of mitral valve obstruction.

In patients with normal LV function and in the absence of obstruction to flow between pulmonary artery and left ventricle, pulmonary artery end-diastolic or pulmonary capillary wedge pressures maintain a constant relationship to left atrial and LV diastolic pressure. At end-diastole, pulmonary capillary wedge, left atrial and LV diastolic pressures are equal.[3-6]

The LV diastolic and pulmonary capillary wedge pressures correlates well with LV end-diastolic volume in presence of normal LV compliance.[7,8] When LV compliance is decreased, there is a poor correlation between LV end-diastolic volume and end-diastolic pressure.[7,8]

AFTERLOAD

In the isolated heart muscle, the afterload is defined as the additional load that the muscle faced as it develops force and attempt to shorten. In the intact heart, wall stress during LV isovolumic systole and ejection phases represents its afterload. It should be appreciated that LV wall stress constantly changes during systolic phases as the volume, pressure and wall thickness change. Although peak systolic wall stress can be used to represent LV afterload, it appears that some more integrated measure of overall wall stress during systole is more appropriate and desirable.

The measurement of changing systolic wall stress is thus difficult in clinical practice and the alternative measures of afterload are frequently used. Aortic instantaneous impedance is another index of LV afterload, which is less dependent on preload. Aortic impedance comprises of pulsatile reactive component and a static resistive (mean) component of the vascular loads. The dominant component of the impedance is systemic vascular resistance. However, the compliance of the aorta and the larger arteries and the branching characteristics of the arterial system which generates reflected waves contribute substantially to aortic input impedance, also difficult to measure in routine clinical practice.[9-12] Aortic input impedance can be estimated from LV pressure-volume loop. The end-systolic pressure/stroke volume (Pes/SV) ratio which is termed effective arterial elastance (Ea) has been used as an estimate of aortic impedance.[13]

Aortic pressure can be used as LV afterload as the left ventricle has to eject its stroke volume against aortic systolic pressure. Another measure of LV afterload is systemic vascular resistance which is calculated as follows:

$$\text{Systemic vascular resistance} = \frac{\text{Mean arterial pressure (mm Hg)} - \text{Mean right atrial pressure(mm Hg)}}{\text{Cardiac output (l/min)}}$$

In patients with systemic hypertension, systemic vascular resistance is increased primarily due to increased arterial pressure. In patients with systolic heart failure, however, systemic vascular resistance may increase even without hypertension primarily due to peripheral arterial vasoconstriction. It should be appreciated that these indices are only indirect measures of afterload and the true afterload is LV wall stress.

VENTRICULAR-ARTERIAL COUPLING

The matching of systolic force generated by the heart to the vascular load during each ejection is termed "ventricular-arterial coupling". The interactions of these two components influence several hemodynamic functions such as cardiac output, arterial pressure, ejection fraction, and mechanical work and efficiency. Left ventricular-arterial coupling also influences LV systolic and diastolic function. Changes in arterial stiffening is associated with changes in LV end-systolic chamber stiffness.[14,15] Increased arterial stiffening increases LV end-systolic stress which can occur irrespective of LV hypertrophy.[14,15] Ventricular-arterial coupling also influences the adaptation of the cardiovascular system in response to stress such as exercise.

Ventricular-arterial coupling is often determined from LV pressure-volume loops. The pressure-volume loops are constructed by relating ventricular pressure and volume throughout the cardiac cycle (Fig. 1). Several loops can be constructed during transient reduction of preload, for example by venacaval inflow obstruction by balloon catheter. The end-systolic pressure volume relation (ESPVR) and its slope are determined. The ventricular-arterial coupling is expressed as the ratio of the Ea/ESPVR slope. The optimal ventricular arterial performance is observed when the ratio is 1.0 or close to 1.0.[16,17]

CONTRACTILE STATE

In the isolated cardiac myocyte, the contractile state refers to the rate of actin myosin interaction with fixed preload and afterload. In the intact heart it is difficult to measure contractility and various indices have been proposed; however, none of these indices have been proven to be entirely satisfactory. In clinical practice it is easier to measure indices of pump function which appears to have a greater clinical applicability.

MEASURES OF MAXIMUM RATE OF PRESSURE DEVELOPMENT

The maximum rate of force development (dF/dt) has been documented as a useful index of cardiac muscle contractility. With a constant preload, dF/dt reflects a reliable measurement of contractility.

Extrapolation of this concept to measure contractile state of the left ventricle, the maximum rate of pressure development (dP/dt) has been used.[18] It should be appreciated that there are a number of limitations for the use of dP/dt to assess contractile state of left ventricle. The maximal dP/dt is influenced by changes in LV end-diastolic pressure and the level of the arterial pressure at the time of the opening of the aortic valve. The maximal dP/dt is also influenced by the heart rate.

However, the maximal dP/dt can be used as an index of contractility if the heart rate, LV end-diastolic pressure and aortic pressure remain unchanged.

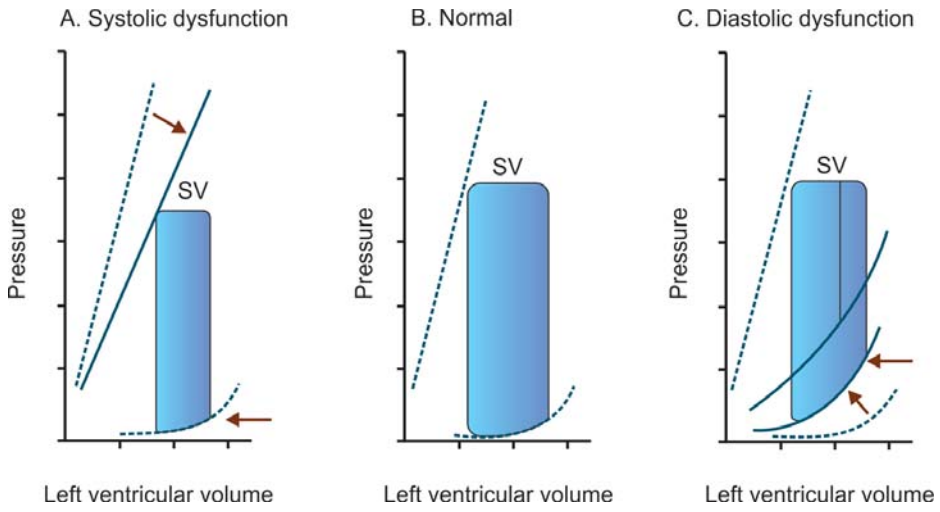


FIGURE 1: Left ventricular pressure-volume relation. Diastolic filling starts with the opening of the mitral valve. At the end of diastole the mitral valve closes and the isovolumic systole begins. During this phase there is an increase in left ventricular pressure without any change in volume. At the end of isovolumic systole, the aortic valve opens and left ventricle ejects its stroke volume into aorta. At the end of ejection the aortic valve closes and the isovolumic relaxation phase begins. During this phase, left ventricular pressure falls without any change in its volume. At the end of isovolumic relaxation phase, the mitral valve opens and the cardiac cycle is repeated. At the end of ejection, the end-systolic pressure terminates on the isovolumic pressure line. With increased contractility, the end-systolic pressure-volume line shifts to the left and upward. With decreased contractile function it shifts downward and to the right. In diastolic heart failure the diastolic pressure-volume curve shifts upward and to the left. This is associated with an increase in left ventricular diastolic pressure and patients may experience of symptoms of pulmonary venous congestion. With a further upward and leftward shift of the diastolic pressure-volume curve, there is also restriction of ventricular filling which is associated with decreased stroke volume

The LV dP/dt is usually measured invasively in the cardiac catheterization laboratory during diagnostic or interventional cardiac catheterization; however, it can be measured non-invasively by echocardiography.[19] Echocardiographic and Doppler studies were performed simultaneously with cardiac catheterization. The maximal LV dP/dt was determined both invasively and noninvasively. In this study, 30 patients undergoing clinically indicated LV catheterization were investigated. Between invasive and noninvasive techniques there was a statistically significant correlation between the measured maximal dP/dt. The noninvasively determined maximal dP/dt was found to be independent of preload and afterload and correlated well to the changes in contractility. The mitral regurgitant velocity spectrum can be used to measure LV maximal dP/dt and the relaxation time constant.[20] In 12 patients with mitral regurgitation, the Doppler mitral regurgitant velocity spectrum was recorded concurrently with LV pressure pulse with the use of micromanometer catheter. The correlation coefficient between the catheter derived and the Doppler derived maximal dP/dt was excellent (r = 0.91). There was also an excellent correlation between the catheter derived and the Doppler derived relaxation time constant (r = 0.93).

Doppler myocardial imaging has been employed to assess LV contractile reserve during dobutamine infusion.[21] In this study, 25 patients with non-ischemic dilated cardiomyopathy with left ventricular ejection fraction (LVEF) of less than 30% were investigated. The peak systolic velocity was measured in the basal segment of the septum and the inferior wall, and LVEF was measured concurrently. The peak systolic velocity and LVEF increased during dobutamine infusion. There was a significant and linear correlation between the changes in peak systolic velocity and ejection fraction. The results of this study suggest that Doppler myocardial imaging can be used to assess LV contractile reserve.

It has been suggested that the isovolumic acceleration measured by tissue Doppler echocardiography can be used to assess LV global contractile function and it appears not to be influenced by changes in preload.[22]

Systolic time intervals, such as pre-ejection period (PEP) and left ventricular ejection time (LVET) and the ratio of PEP/LVET, have been used to assess LV contractile function. Systolic time intervals can be measured by echocardiographic techniques. In a multicenter study, LVEF, maximal dP/dt, LV stroke volume, PEP, LVET and PEP/LVET ratio were measured prospectively in 134 consecutive patients with systolic heart failure and 43 normal control subjects by pulsed Doppler echocardiography.[21] The PEP/LVET ratio increased with increased LVEF and there was a significant positive correlation. Using the receiver operating curve analyses, for PEP/LVET ratio, the area under the curve was 0.91 which allowed detection of LVEF of less than 35% with a specificity of 84% and sensitivity of 87%. Thus, measurement of systolic time intervals may be useful for assessment of LV contractile function. It should be appreciated however that PEP is influenced by developed pressure. In patients with severe heart failure, the developed pressure may be very low, causing disproportionate changes in PEP, LVET and the PEP/LVET ratio.[23] Furthermore, in the most echocardiographic laboratories, this index of contractile function with measurement of systolic intervals is not routinely measured.

VELOCITY OF CONTRACTILE ELEMENT

In the isolated myocyte or papillary muscle studies, velocity of the contractile element reflects a reliable index of contractility.

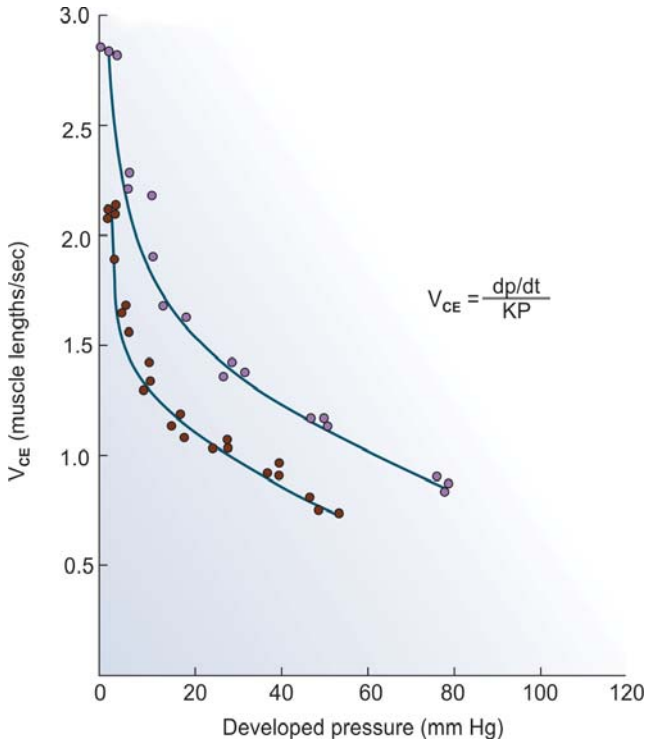


FIGURE 2: Calculated pressure-velocity relation (VCE) in relation to developed pressure and before or after coronary artery bypass surgery demonstrating an upward and rightward shift after coronary artery bypass surgery indicating improved contractile function

In the intact human left ventricle, overall mean contractile element velocity (VCE) can be measured from the simultaneously recorded LV pressure pulse and its first derivative (dP/dt) using the formula VCE = dP/dt/KP (where P is the developed pressure and K is the series elastic constant). It should be appreciated that the measurement of VCE in the intact beating human heart is not precise. Usually the VCE at 5 mm Hg developed pressure is used to measure as an approximation of maximal velocity of contraction. Myocardial ischemia is a potent cause of depressed contractile function. Relief of ischemia following coronary artery bypass graft surgery is associated with a right and upward shift of the pressure velocity curves (Fig. 2).[24] These findings suggest that it is feasible to measure LV contractile function in the cardiac catheterization laboratory applying the three-element mechanical model used in the isolated papillary muscles.[25,26] Other indices of contractility have been developed from the measurements of rate of rise of LV pressure and the developed pressure.[27] It has been suggested that (dP/dt)/P at different levels of developed pressure can be used to assess LV contractility.[27] It should be appreciated that for measurements of these contractile indices, in the intact heart, high-fidelity micromanometer tip catheters should be used.

In the intact heart, LV contractility can be measured by determining the maximum rate of flow velocity (acceleration) in the ascending aorta.[28]

Aortic flow during systole is LV stroke volume which is influenced by changes in preload and afterload. Any index of contractility dependent on measurement of stroke volume is also influenced by changes in preload and afterload. In the modern echocardiographic laboratories, Doppler echocardiography can be employed to measure aortic flow. Transthoracic echocardiography and simultaneous measurement of blood pressure allows normalization of aortic flow for preload and afterload.

The LV ejection rate normalized for end-diastolic volume (EDV) can be used to assess LV contractile state.[29,30] The LVEF is calculated from the ratio of LV total stroke volume (TSV) and EDV. To calculate normalized ejection rate, LVEF is divided by left ventricular end-diastolic volume (LVEDV). Normalized ejection rate is best calculated from a volume-time curve. The normalized ejection rate is decreased in patients with systolic heart failure compared to normal subjects. The ejection rate can be measured invasively by contrast ventriculography or noninvasively such as radionuclide ventriculography.

LEFT VENTRICULAR PUMP FUNCTION

VENTRICULAR FUNCTION CURVE

The construction of ventricular function curve provides useful information about ventricular performance. In clinical practice, stroke volume or stroke work (vertical axis) is plotted against a measure of preload such as EDV or end-diastolic pressure (horizontal axis) (Fig. 3). In the critical care units, pulmonary capillary wedge pressure (pulmonary artery occluded pressure) is frequently used as LV preload. When LV volume or pressure is increased, as during volume expansion therapy, the stroke volume increases by the Frank-Starling mechanism. When right ventricular function is assessed, right atrial pressure is used as its preload. The optimal LV filling pressure is usually 15–20 mm Hg.[31] The optimal filling pressure of the right ventricle is 3–8 mm Hg. As discussed earlier right atrial or pulmonary capillary wedge pressures can be used as their filling pressures only in presence of normal pericardial and mediastinal pressures.

The ventricular function curve shifts upward and to the left with the improvement of ventricular function, and downward and to the right, when it is depressed. In many clinical situations there is a disparity between changes in right and left ventricular function. For example, in patients with acute or chronic isolated

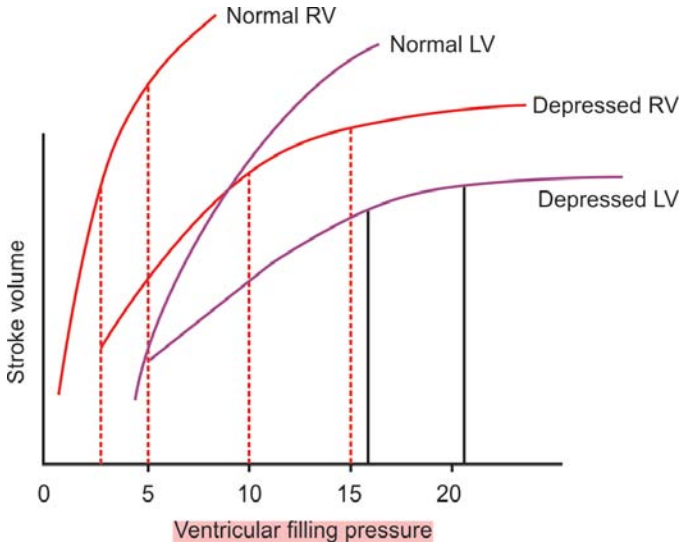


FIGURE 3: Ventricular function curves constructed relating stroke volume (vertical axis) to the ventricular filling pressures (horizontal axis) (Abbreviations: RV: Right ventricle; LV: Left ventricle)

right ventricular failure (right ventricular myocardial infarction or pre-capillary pulmonary hypertension), right ventricular filling pressure is elevated and right ventricular function curve shifts downward and to the right; however, LF filling pressure and function curve remain unchanged. In contrast, in patients with isolated acute or chronic LV failure (LV myocardial infarction or dilated cardiomyopathy), LV filling pressure is elevated and its function curve shifts downward and to the right.[32] When the changes in the right and left ventricular functions are not parallel, treatments to improve right or left ventricular function may be associated with worsening function of the contralateral ventricle. For example, in patients with depressed LV function with normal right ventricular function, volume loading to correct hypotension may precipitate pulmonary edema. In presence of depressed LV function with a flat LV function curve, the pulmonary capillary wedge pressure is already elevated and during volume loading, there is an excessive increase in pulmonary capillary wedge pressure which induces pulmonary edema. It should also be appreciated that in presence of very depressed LV systolic function the magnitude of increase in stroke volume is relatively small with an increase in end-diastolic volume during volume loading therapy compared to when LV systolic function is preserved. For example, in patients with systolic heart failure, when LV end-diastolic volume is increased by timed atrial contraction, stroke volume increases only slightly compared to the patients with normal ejection fraction, when there is a substantial increase in stroke volume with a similar increase in EDV.[33]

EJECTION FRACTION

In clinical practice, ejection fraction is most commonly used index to assess LV pump function. As discussed earlier, ejection fraction is the ratio of left ventricular total stroke volume (LVSV) and end-diastolic volume (EDV) and it can be measured by various invasive and noninvasive methods. The normal ejection fraction has not been clearly defined and it varies with age, gender and the loading conditions. For clinical purposes, 55% ejection fraction is used to distinguish between diastolic and systolic heart failure. In many clinical studies, an ejection fraction of 45% has been used to separate between heart failure with preserved and reduced ejection fraction.

It should be appreciated that ejection fraction is load dependent. Thus, at the time of measurement of ejection fraction, the loading conditions should be considered. For example, if the blood pressure is high, the ejection fraction will be lower when the blood pressure is reduced.

The LV stroke volume may remain normal not only at rest but also during exercise even when the ejection fraction is markedly reduced. This is accomplished by a markedly increased LVEDV.

TECHNIQUES FOR ASSESSMENT OF LEFT VENTRICULAR EJECTION FRACTION

Echocardiography

Two-dimensional (2D) echocardiography is the most frequently used technique for measurement of LVEF. The visual assessment of LVEF has poor reproducibility. Also, there is a wide variation in the reproducibility of the quantitative measurements of LV global and regional function.[34] In ten healthy subjects, two experienced echocardiographers performed 20 complete echo-Doppler studies. The inter-observer reproducibility was better in the measurements of systolic M-mode annulus excursion than other traditional and newer indices of LV systolic and diastolic function. The quantitative measurements by 2D transthoracic echocardiography using biplane methods can introduce errors in estimation of ejection fraction due to underestimation of LVEVD.[35] To reduce the errors, echocardiography with the use of ultrasound contrast agents have been introduced.[36,37] The use of contrast agent allows a clearer delineation of the LV endocardium. Measurements of LV volumes and ejection fraction by 2D transthoracic echocardiography with contrast agents have a better agreement with other imaging modalities such as CMR imaging and radionuclide ventriculography.[38] Myocardial contrast echocardiography has been used to assess hibernating myocardium and has been compared to single photon emission computed tomography (SPECT).[39] In a preliminary study of 39 patients with ischemic heart disease, myocardial contrast echocardiography was found to be superior in predicting the recovery of LV function. It should be appreciated that the use of ultrasound contrast agents are contra indicated in patients with intra-cardiac shunts.

Three-dimensional real time echocardiography (3DE) with or without the use of ultrasound contrast agents are being increasingly used to measure LV volumes and ejection fraction. The determination of LV volumes by 3DE does not require any geometric assumption. The determinations of LV volumes by 3DE have a low intra- and inter-observer variability and good agreements with other imaging modalities, such as CMR, have been observed.[40] Three-dimensional speckle tracking echocardiographic technique has been used to assess regional LV function.[41] In 32 subjects with or without LV dysfunction, 3DE and 2DE speckle tracking echocardiography was performed concurrently. In this study, 3DE speckle tracking was superior to 2DE speckle tracking echocardiography to measure regional wall motion indices (please see the chapter "Three Dimensional Echocardiography").

Cardiac Computed Tomography

Cardiac computed tomography (CCT) can be used for measurement of LV volumes and ejection fraction. Most frequently multislice multiphase CCT with the use of contrast agent is employed to assess LV volumes and ejection fraction. The measurement of LV volumes by CCT does not require geometric assumption. There is also a good agreement between CCT, CMR, echocardiography and contrast ventriculography for the measurements of LV volumes and ejection fraction.[42]

Assessment of LV volumes and ejection fraction with 320-row multidetector computed tomography has been performed and compared to 2D echocardiographic imaging.[43] In this study, the 320-row multidetector CCT and 2D echocardiography were performed in 114 patients concurrently. There was an excellent correlation between the two imaging techniques. Thus, an accurate assessment of LV function is feasible with a single cardiac cycle 320-row multidetector CCT.

The contrast CCT can be used to assess right ventricular volumes and function. It can also be used for the diagnosis of coronary artery anomalies and to assess the severity of coronary artery obstruction.

It should be appreciated that CCT is associated with radiation exposure and, when contrast agent is used, it can induce contrast nephropathy (please see the chapter "Cardiac Computed Tomography").

Nuclear Scintigraphy

A number of radionuclide scintigraphic techniques can be employed for the measurement of ventricular volumes and ejection fraction.

The gated equilibrium radionuclide angiography and first-pass radionuclide angiography can be used for assessment of both right and left ventricular volumes and ejection fraction. These nuclear scintigraphic techniques do not require geometric assumptions.[44,45]

In clinical practice, however, LV volumes and ejection fraction are determined more frequently, during gated SPECT and positron emission tomography (PET) usually used for detection of presence and the severity of myocardial ischemia and viability.[46] The PET appears to have advantages over SPECT due to better spatial and temporal resolution. The gated blood-pool SPECT has been compared to CMR in assessing LV volumes and ejection fraction.[47] In this study, 55 consecutive patients were investigated. The correlation coefficients between these two techniques in measuring LV end-diastolic and end-systolic volumes were r = 96 and 92 respectively. For determination of LVEF it was 0.84.[47] It should be appreciated that nuclear imaging techniques are associated with radiation exposure.

Cardiac Magnetic Resonance Imaging

The CMR imaging can be used to measure LV volumes and ejection fraction. The measurement of LVEF by CMR has several advantages. It is not associated with radiation exposure. It has also high temporal and spatial resolution. The measurement of LV volume by CMR does not depend on geometric assumptions. The CMR is used as the reference technique for measurement of ventricular volumes and ejection fraction[48] (please see the chapter "Magnetic Resonance Imaging").

Left ventricular volumes and ejection fraction measured by CMR were compared to those measured by monoplane cine ventriculography and unenhanced echocardiography.[48a]

There were good agreements between these three techniques are discussed in Table 1.

TABLE 1

LV volumes and EF determined by the different imaging techniques

	Cine	*Echo*	*MRI*
EDV (ml)	184.78 ± 69.77	159.90 ± 54.00	177.10 ± 73.50
ESV (ml)	53.53 ± 50.62	71.97 ± 44.74	73.82 ± 54.93
EF (%)	73.28 ± 17.22	57.49 ± 12.41	61.43 ± 14.34

(Source: Published with permission from Reference 48a)

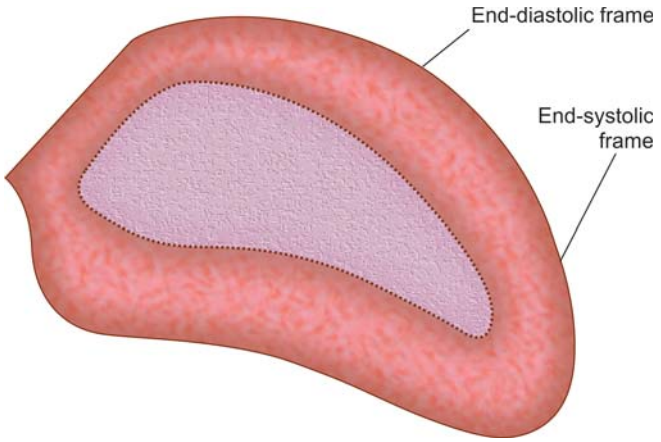


FIGURE 4: Schematic illustration of contrast ventriculography to determine left ventricular ejection fraction. The EDV is determined by outlining the end-diastolic frame. The end-systolic volume is determined by outlining the end-systolic frame

Contrast Ventriculography

Contrast ventriculography is usually performed during cardiac catheterization. The injection of contrast agent into the cavity of left ventricle allows measurement of LV volumes and ejection fraction. Most frequently biplane methods are used. The LV cineangiograms are obtained at a high speed (30–60 frames/sec). The endocardial edge detection and calculation of LV volumes and ejection fraction are done by automated computerized techniques (Fig. 4).

PRESSURE-VOLUME RELATIONS

The pressure-volume relation is one of the precise methods for the assessment of LV systolic and diastolic functions in the intact heart as illustrated in the Figure 1. During diastole with the opening of the mitral valve, LV filling begins. Most of the ventricular filling occurs during the early rapid filling phase. During atrial contraction, there is further ventricular filling. At the end of diastole, the isovolumic phase of ventricular systole begins and during this phase the LV pressure rises without any change in its volume. Following opening of the aortic valve, the ejection phase starts. Initially the ejection is rapid and then it is slower till the aortic valve closes. Following closure of the aortic valve, the isovolumic relaxation phase begins. During this phase LV pressure declines without any change in its volume till the mitral valve opens and the rapid filling phase begins. The pressure-volume loop is counterclockwise. The area inside the pressure-volume loop represents LV stroke work. Stroke work is calculated by the formula:

Stroke work = Stroke volume × (Mean LV systolic ejection pressure – Mean LV diastolic pressure)

In clinical practice, mean arterial pressure is used instead of mean LV systolic ejection pressure, and mean pulmonary capillary wedge pressure is used to represent mean LV diastolic pressure, for calculation of stroke work. The stroke work index is calculated by dividing the stroke work by the body surface area to normalize for the size of the patients. In critical care units, LV function is assessed by relating stroke work index to the pulmonary capillary wedge pressure.

The construction of the pressure-volume loops allows a more precise load independent measurement of LV contractile function. When a number of pressure-volume loops are constructed by increasing or decreasing LV volumes the endpoint of systolic contraction of each loop tends to fall on the same line which is termed the isovolumic pressure line. In the intact heart, the endpoint of systolic contraction is recognized by the crossing point of dicrotic notch pressure and end-systolic volume. The isovolumic pressure line does not appear to be influenced by changes in afterload or preload.[49] With changes in contractile state however there is shifts of the isovolumic pressure-volume line; with increased contractility the isovolumic pressure line shifts upward and to the left and with decreased contractility, it shifts downward and to the right. It should be appreciated that there are a few limitations in using the isovolumic pressure-volume line as a totally load independent index of contractility. The isovolumic pressure-volume line may shift upward and to the left without any changes in intrinsic contractility, when the LV systolic pressure is higher than normal as in patients with hypertension or aortic stenosis. In these patients, end-systolic volumes may also be lower than normal; thus the end-systolic pressure/volume ratio is increased as occurs when the contractility is increased. In patients with relatively lower end-systolic pressures as following use of vasodilators or in patients with severe chronic aortic regurgitation, the isovolumic pressure-volume line may shift downward and to the right as when intrinsic contractility is decreased. In these clinical circumstances, the end-systolic pressure/volume ratio may also decrease without any change in intrinsic contractility. In presence of significant mitral regurgitation, there is no isovolumic systole and thus the isovolumic pressure-volume index cannot be used to assess contractility. However, despite these limitations, the uses of pressure-volume loops remain an important method of determining LV contractility. In some studies, peak systolic pressure/end-systolic volume ratio has been used to assess contractility and appears that it is practical and can be determined noninvasively.[50] The peak systolic pressure can be measured by measuring cuff blood pressure, and end-systolic volume can be measured by noninvasive imaging techniques such as transthoracic echocardiography.

HEART RATE

Heart rate is a major determinant for cardiac performance. Cardiac output is the product of the heart rate and stroke volume, and the higher the heart rate, higher is the cardiac output. However, an excessive increase in heart rate may compromise ventricular filling and decrease stroke volume. It should also be appreciated that left ventricle is perfused during diastole. Thus a marked increase in heart rate is associated with decreased LV perfusion time. Heart rate is also a major determinant of myocardial oxygen demand, and faster heart rate increases myocardial oxygen demand.[51] Impaired LV perfusion and a concomitant increase in myocardial oxygen demand may induce myocardial ischemia and decrease contractile function.

Normally an increase in heart rate is associated with an increased force of contraction.[51] This phenomenon is defined as a positive force-frequency relation. Noninvasive techniques, such as tissue Doppler imaging, have been used to assess changes in contractility with changes in heart rate.[52] Myocardial acceleration during isovolumic systole was used to measure contractility. The LV maximal dP/dt was also measured by micromanometer catheter. In this study, there was a positive correlation between heart rate and myocardial acceleration during isovolumic systole and maximal dP/dt. As heart rate increased, both indices of contractility increased. In other studies using maximal dP/dt as a measure of contractility, the positive force-frequency relation has been demonstrated.[53]

Effects of changes in heart rate have been investigated in failing and non-failing explanted human hearts.[54] In the non-failing hearts, contractility increased with increased heart rates. In the failing hearts, however, increasing heart rate was associated with a decrease in force of contraction which is termed inverse force-frequency relation. The alterations of the force frequency relation in failing heart are more pronounced in patients with more severe heart failure.[54a] In the study by Schmidt et al., myocardium from explanted human heart of patients with end stage systolic heart failure (NYHA IV) (ejection fraction 24 ± 2%), patients with mitral valve disease with mild to moderately severe heart failure (NYHA II-III), (ejection fraction 55.9 ± 2.9%) and normal non-failing heart from donor hearts were studied. There were 22 patients in NYHA IV group; 10 patients in the NYHA II-III group and 5 patients in the non-failing group. Myocardial biopsy specimens in patients with mitral valve disease were obtained during mitral valve replacements surgery. Myocardial force generation during increasing frequency of stimulation was markedly reduced in NYHA IV patients compared to control. It was mildly reduced in the myocardium of patients NYHA II-III heart failure (Table 2). There was also downregulation of the beta-adreno-receptors in the myocardium of the failing hearts. It has been reported in patients with non-ischemic or ischemic dilated cardiomyopathy, that during increased heart rate left ventricular maximal dP/dt declines and it has been thought to be due to myocardial beta-adrenergic dysfunction.[54b] Altered handling of intracellular calcium has been demonstrated as the potential mechanism of the inverse force-frequency relation in human dilated cardiomyopathy.[55] In patients with severe systolic heart failure, a reduction in heart rate may be associated with an increase in force development and contractile state. This might be a contributory mechanism for the beneficial effect of beta blocker therapy in patients with systolic heart failure.

In patients with diastolic heart failure the force-frequency relation remains normal but the relaxation-frequency relation

TABLE 2

Force-frequency relation in human left ventricular papillary muscle strips from non-failing heart (12 preparations), NYHA II-III (18 preparations) and NYHA IV (39 preparations) are summarized

Frequency (HZ)	*Non-failing (FOC mN)*	*NYHA II-III (FOC mN)*	*NYHA IV (FOC mN)*
0.5	1.7 ± 0.2	2.3 ± 0.1	2.4 ± 0.2
1.5	2.7 ± 0.3	2.6 ± 0.1	2.0 ± 0.1
3	3.0 ± 0.2	2.0 ± 0.1	1.4 ± 0.1

(Abbreviation: FOC: Force of contraction). (*Source:* Modified from Reference. 54a and published with permission from Schmidt U et al. AM J Cardiol. 1994;74:1066-8)

is impaired.[55a,55b] The time constant of left ventricular relaxation (minimal negative dP/dt) is decreased.

DIASTOLIC FUNCTION

Diastolic function is an important determinant of hemodynamic abnormalities of heart failure. Diastolic function can be assessed from studies of the pressure-volume relations during diastole (Fig. 1). The diastolic pressure-volume curve is exponential which indicates that, when the patient is on the flat portion of the curve, there is less change in pressure with a given change in volume. When the patient is on the steep portion of curve, there is much greater increase in pressure for the same change in volume.

The LV compliance or distensibility is altered in many pathologic conditions. Decreased compliance (increased stiffness) is associated with an upward and leftward shift of the diastolic pressure-volume relation. For a given increase in diastolic volume, there is a disproportionate increase in LV diastolic pressure. There is a passive increase in left atrial and pulmonary venous pressure which may precipitate pulmonary edema. If ventricular filling is also compromised due to a marked upward shift of the diastolic pressure-volume relation, stroke volume decreases and cardiac output may also decline. Along with increase in pulmonary venous pressure, pulmonary artery pressure increases which may cause right heart failure due to increased right ventricular afterload.

Increased diastolic stiffness may be caused by LV hypertrophy. In patients with hypertension, there is not only increase in LV mass but also in myocyte thickness. There is also myocardial fibrosis. Increased fibrosis occurs not only in hypertensive hearts but also in the hearts of patients with diastolic and systolic heart failure. Diastolic dysfunction contributes to the hemodynamic abnormalities in both systolic and diastolic heart failure. Decreased LV diastolic compliance may occur both acutely and chronically.

An acute increase in LV afterload causes an upward and leftward shift of the diastolic pressure-volume curve.[56] Acute changes in the diastolic pressure-volume relation can also occur in patients with ischemia during angina.[57]

Pericardial constraining effect also decreases LV compliance. In patients with acute right ventricular infarction, right ventricular dilatation is associated with increased intrapericardial pressure as the pericardium cannot stretch acutely. The pericardial constraining effect impairs ventricular filling and cardiac output declines. During acute volume expansion, pericardial constraining effect causes upward and leftward shift of the LV diastolic pressure-volume curve.[58] In constrictive pericarditis also, pericardial constraining effect shifts diastolic pressure-volume curve upward and produces similar hemodynamic abnormalities. It should be appreciated that increased myocardial stiffness is a major mechanism of diastolic dysfunction independent of pericardial constraining effect.

The interaction between the intracardiac chambers also alters diastolic function.[59] In patients with pre-capillary pulmonary hypertension and enlarged right atrium and right ventricle, inter-atrial and inter-ventricular septum shift toward the left atrium and left ventricle and left atrial and LV volumes are decreased with a concomitant increase in their diastolic pressures. In patients with severe LV systolic heart failure with markedly enlarged left ventricle, right ventricular volume decreases due to the rightward shift of the inter-ventricular septum with consequent decrease in right ventricular compliance.

In certain clinical conditions LV diastolic compliance is increased. The diastolic pressure-volume curve shifts to the right as in patients with chronic aortic regurgitation and primary mitral regurgitation. In these conditions, even with a substantial increase in LV diastolic volume there is very little increase in diastolic pressure and these patients remain asymptomatic even during exercise.

TECHNIQUES OF MEASUREMENT OF DIASTOLIC FUNCTION

Conventionally assessment of LV compliance by measurements of LV pressure-volume relation has been performed by invasive techniques during cardiac catheterization. During cardiac catheterization it is also possible to determine the negative dP/dt and the time constant of the LV pressure decay (tau). With decreased compliance the values of negative dP/dt and tau are decreased. The LV diastolic function however can be assessed by noninvasive techniques.[60]

Echocardiography

Echo-Doppler methods are most frequently employed to assess LV diastolic function. Determination of isovolumic relaxation time provides insight about diastolic functional properties. In patients with impaired LV relaxation, the isovolumic relaxation time is prolonged. It should be appreciated that the isovolumic relaxation time is influenced by changes in preload.

The mitral inflow patterns are frequently employed to assess LV diastolic function by Doppler echocardiography. The early filling of left ventricle is termed "E" wave and filling during atrial systole is termed "A" wave. When LV compliance is decreased, the "E/A" ratio is decreased. Tissue Doppler mitral annular motion appears to be a more load independent index of diastolic function.[61] The mitral valve moves away from the apex in early diastole resulting in 'e' wave. During late diastole during atrial contraction there is an 'a' wave. When there is significant diastolic dysfunction, the 'E/e' ratio increases. The pulmonary vein flow patterns, the propagation velocity of the wave front of LV filling and other echocardiographic indices can be used to assess LV diastolic function (please see the chapter "Transthoracic Echocardiography").

Nuclear Scintigraphy

Radionuclide ventriculography and gated SPECT can be used to measure indices of diastolic function. The time-count curves or time-volume curves are constructed and time to peak filling rate and peak filling rates are calculated. Diastolic dysfunction is associated with increased time to peak filling and decreased peak filling[62,63] (please see the chapter "Nuclear Imaging").

Cardiac Magnetic Resonance Imaging

Similar to nuclear scintigraphy CMR can be used to construct LV time-volume curve and filling rate can be measured to assess

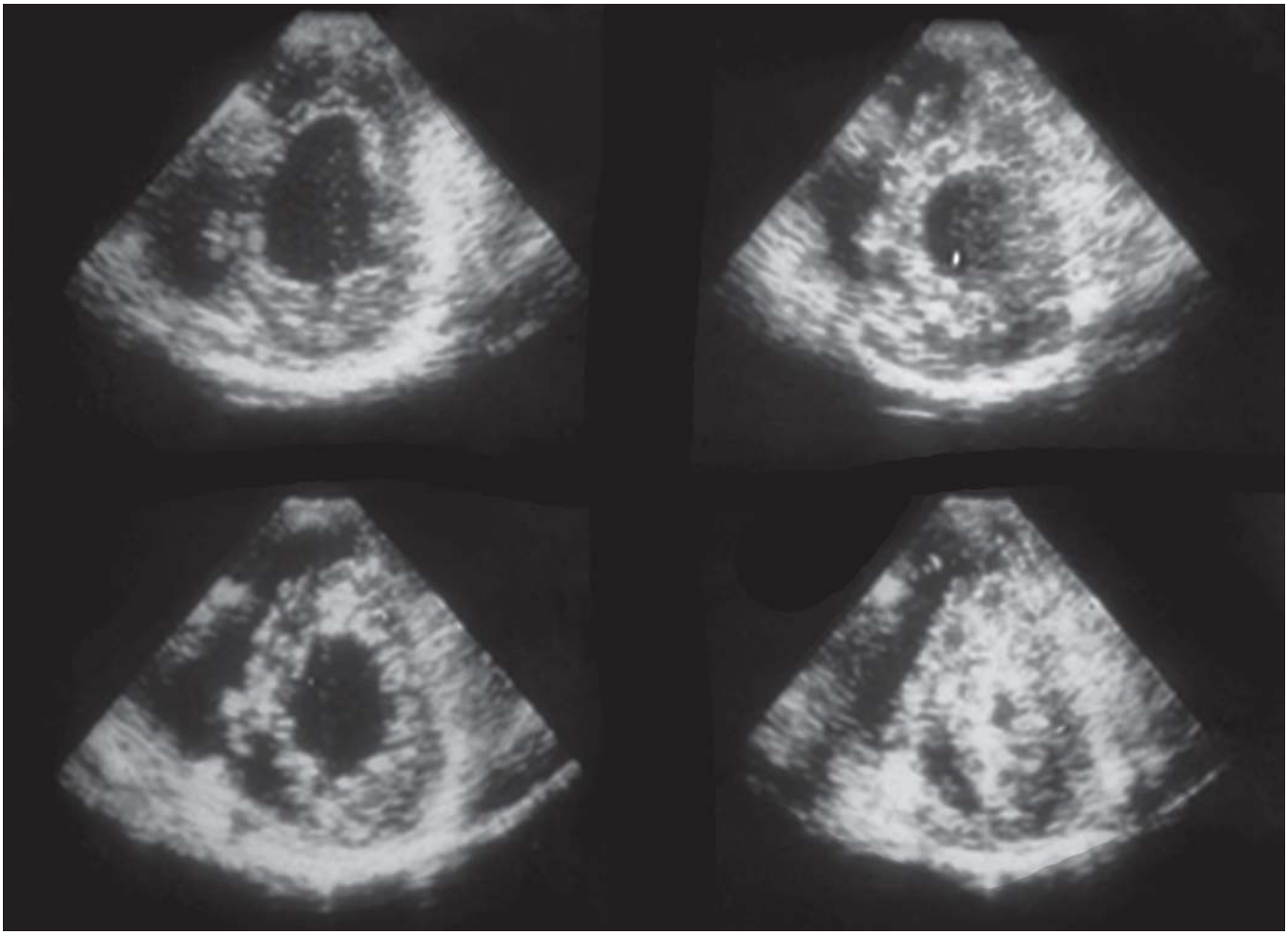


FIGURE 5: The transthoracic echocardiographic images in the short-axis view during exercise. During exercise left ventricular volumes decrease and calculated ejection fraction increases

diastolic function.[64,65] The CMR can also be used to measure diastolic flow across the mitral valve and pulmonary veins flow (please see the chapter "Cardiac Magnetic Resonance").

LEFT VENTRICULAR FUNCTIONAL ASSESSMENT DURING STRESS

Assessment of LV function during stress is useful to determine patient's functional capacity and LV reserve.[66] In clinical practice, noninvasive tests, such as treadmill exercise test with or without nuclear imaging, and exercise or dobutamine stress echocardiography (Fig. 5), are most commonly used. During stress tests the severity of symptoms and the level of exercise that induces symptoms are observed.

RIGHT VENTRICULAR FUNCTION

The right ventricle has complex geometry and anatomic features which are different from that of left ventricle. Normally it is a thin-walled structure and the thickness of the free wall of the right ventricle is less than 4 mm. It has a pyramidal shape and has three anatomic areas: (1) the inflow region formed by the tricuspid valve apparatus; (2) the trabeculated apical and the free wall and (3) the outflow region.[67] During right ventricular systole, the tricuspid valve annular descent is followed by contraction of apical, free wall and outflow tract segments. In the absence of tricuspid or mitral valve regurgitation and intracardiac shunts, right and left ventricular stroke volume is the same. Normally right ventricular afterload is lower than that of left ventricle primarily due to lower pulmonary artery pressure and pulmonary vascular resistance compared to systemic arterial pressure and systemic vascular resistance. Due to lower afterload, right ventricle can eject the same stroke volume as that of left ventricle but at a lower level of work.[67-69]

Right ventricular function can be assessed by both invasive and noninvasive techniques. In the critical care units, right ventricular function curve is constructed by correlating right ventricular stroke work to right ventricular filling pressure. Right ventricular filling pressure is determined by measuring right atrial pressure. Determination of right ventricular stroke work requires measurement of pulmonary artery pressure, pulmonary capillary wedge pressure and stroke volume. With the use of balloon floatation catheters, the determinants of the right ventricular stroke work can be estimated in the critical care units at the bedside. The right ventricular stroke work is calculated by the formula:

$$\frac{\text{Mean pulmonary artery pressure} - \text{Mean pulmonary capillary wedge pressure}}{\text{Right ventricular stroke volume}}$$

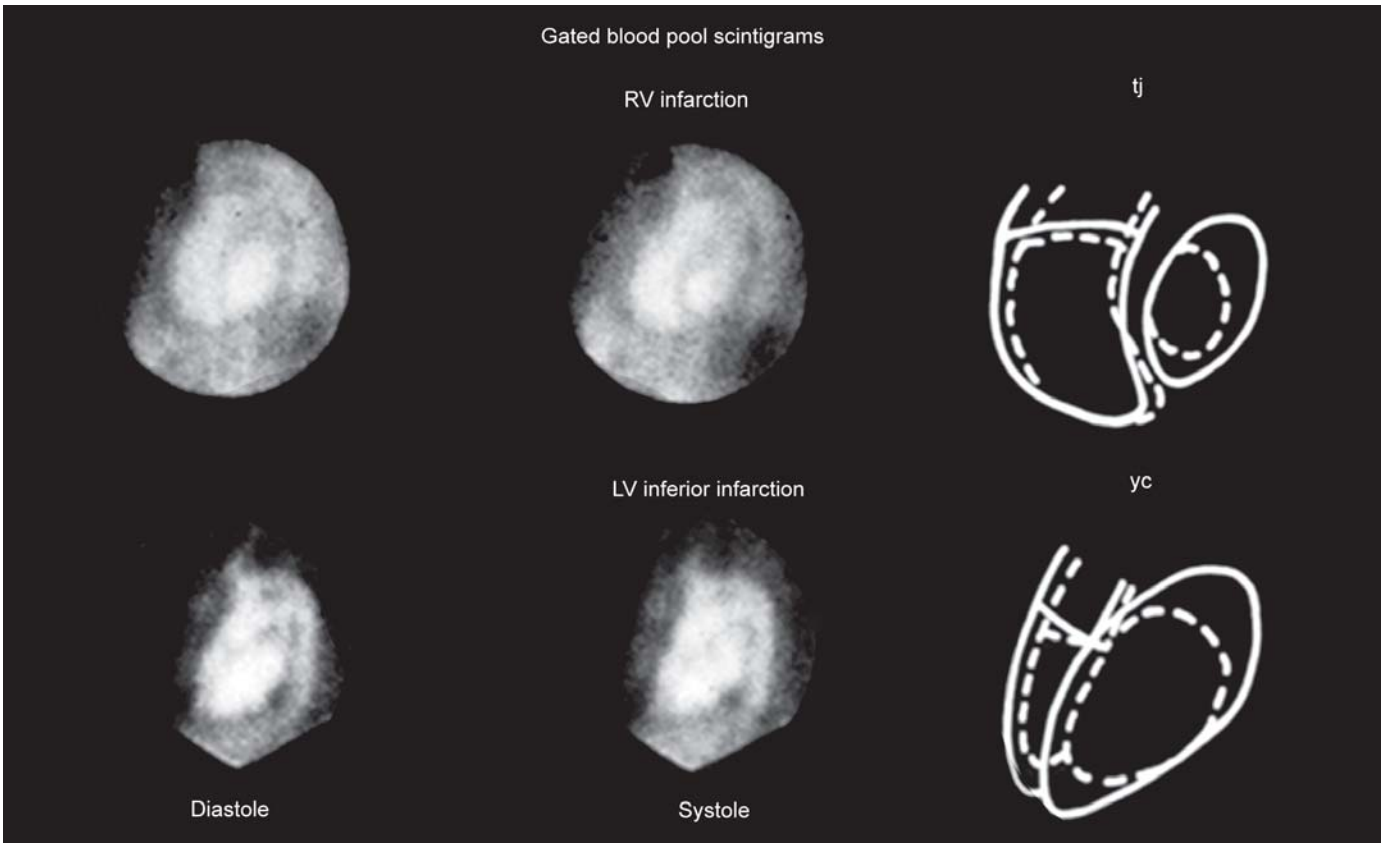


FIGURE 6: Gated blood pool scintigraphy in a patient with right ventricular infarction showing increased right ventricular end-diastolic and end-systolic volumes. Left ventricular volumes remain normal. In a patient with inferior wall myocardial infarction without right ventricular involvement, right and left ventricular volumes remain normal

With the improvement of right ventricular function the right ventricular function curve shifts upward and to the left. With the deterioration of right ventricular function, right ventricular stroke work declines even with an increase in right ventricular filling pressure (Fig. 3).

Right ventricular function can also be assessed by a number of noninvasive techniques. Different radionuclide techniques can be employed to evaluate right ventricular volumes and ejection fraction.[68,69]

Radionuclide ventriculography has been employed to assess right ventricular volumes and ejection fraction. The first pass, equilibrium and gated blood-pool SPECT can be used to estimate right ventricular volumes and ejection fraction. For example, in patients with acute right ventricular myocardial infarction, right ventricle is dilated and its ejection fraction is decreased (Fig. 6). In patients with inferior myocardial infarction, without involvement of the right ventricle, right ventricle is not dilated and its ejection fraction remains normal.

The equilibrium or first pass radionuclide ventriculography has been employed to assess right ventricular function.[70] The SPECT/PET techniques may also be used for determination of right ventricular volumes and ejection fraction.[71]

In clinical practice, echocardiography is most frequently used imaging technique to evaluate right ventricular function.[72] Two-dimensional transthoracic echocardiography allows qualitative assessment of right ventricular volumes and function. It is also useful for the diagnosis of the etiology of right ventricular dysfunction. For example, in patients with right ventricular failure due to severe precapillary pulmonary hypertension right ventricle is dilated and right ventricular ejection fraction is reduced (Fig. 7). Doppler-echocardiography can be used concurrently to measure the severity of pulmonary hypertension.

Two-dimensional and Doppler-echocardiography can also be used for quantitative assessment of right ventricular volumes and ejection fraction. Measurement of right ventricular functional area and tricuspid annular plane systolic excursion provides a quantitative measure of right ventricular systolic function.[73] The measurement of right ventricular myocardial performance index by Doppler-echocardiography is also used for quantitative assessment of right ventricular systolic function.[74]

Right ventricular function can also be assessed non-invasively by measuring right ventricular myocardial acceleration during isovolumic systole, using tissue Doppler imaging.[75] Three-dimensional echocardiography is being increasingly employed for quantitative assessment of right ventricular volumes and function. Right ventricular volumes and ejection fraction measured by three-dimensional echocardiography correlate well with the values determined by CMR imaging.[76] In a study of 25 patients with postoperative severe pulmonary regurgitation, three-dimensional echocardiography and CMR imaging were performed. There was a significant positive correlation in right ventricular volumes and ejection fraction determined by the two techniques.[77]

The multidetector CCT has been used for assessment of right ventricular volumes and function. However, cardiac magnetic resonance (CMR) imaging is currently employed for accurate

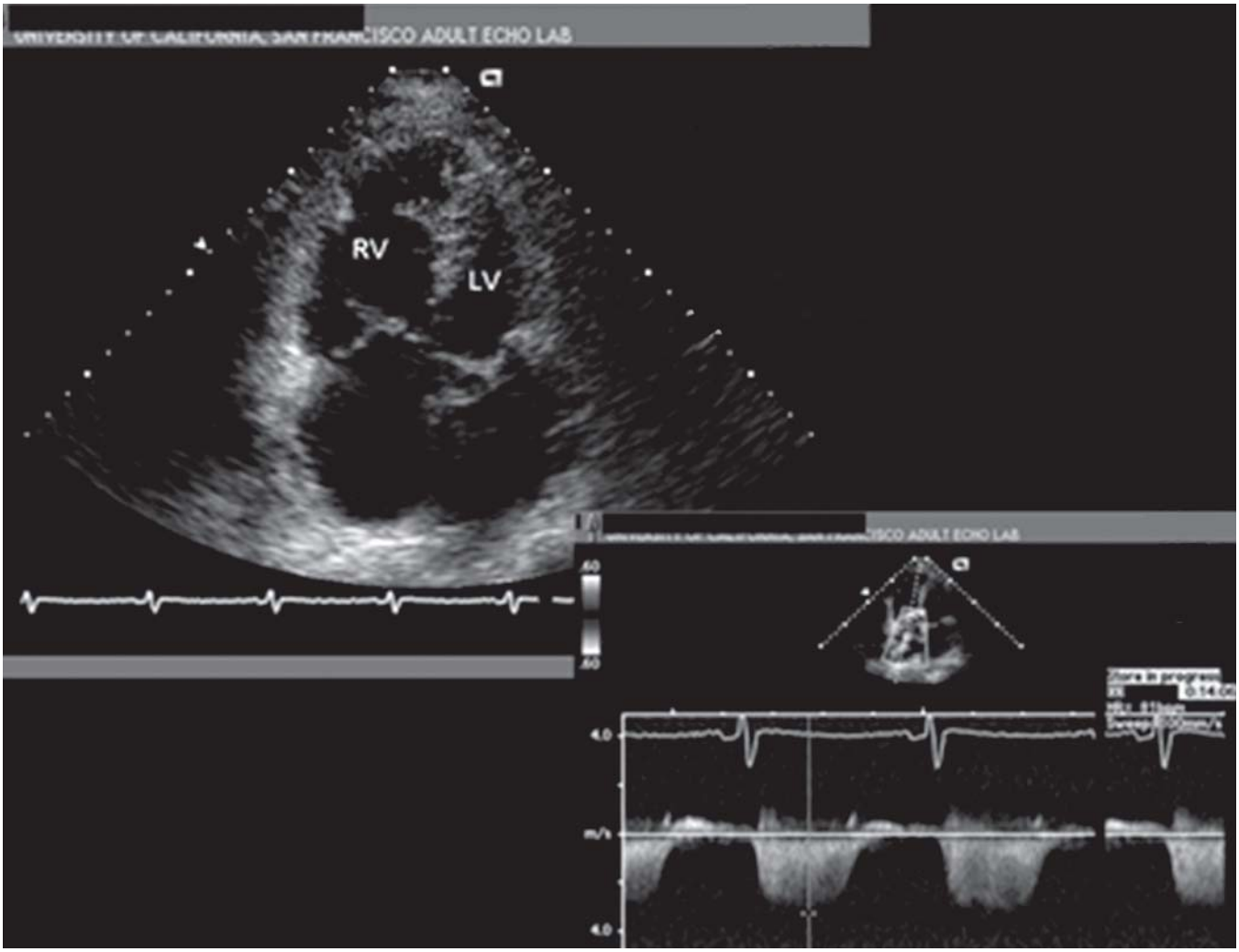


FIGURE 7: Transthoracic two-dimensional echocardiography in a patient with precapillary pulmonary hypertension is illustrated. Right ventricular volume is increased with a shift of the interventricular septum toward the left ventricle. Doppler echocardiographic studies reveal pulmonary arterial hypertension

quantitative assessment of right ventricular volumes and ejection fraction. The three imaging techniques—CMR imaging, multidetector CCT and three-dimensional echocardiography—were compared, and CMR imaging yielded the most accurate values for right ventricular volumes and ejection fraction.[78]

CONCLUSION

Assessment of left and right ventricular function is essential for understanding of the pathophysiologic mechanisms of various cardiac disorders. In clinical studies, LVEF is routinely employed to distinguish between systolic and diastolic heart failure. Assessment of left and right ventricular functions is also used to assess response to therapy. In critical care units, hemodynamic measurements of left and right ventricular functions are useful of selection of therapies and response to therapy.

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Chapter 16

Transthoracic Echocardiography

Byron F Vandenberg, Richard E Kerber

Chapter Outline

- Chamber Quantitation
- Doppler Echo
- Diastolic Function
- Pulmonary Hypertension
- Pericardial Disease
- Valvular Heart Disease
  - Aortic Stenosis
  - Aortic Regurgitation
  - Mitral Stenosis
  - Mitral Regurgitation
  - Tricuspid Stenosis
  - Tricuspid Regurgitation
  - Pulmonic Stenosis
  - Pulmonic Regurgitation
- Infective Endocarditis
- Intracardiac Masses
- Contrast Echocardiography
- Cardiac Resynchronization Therapy

INTRODUCTION

Echocardiography is the examination of the heart using reflected sound waves. The early clinically applied technology was m-mode (i.e. motion-based mode). This provided a one dimensional view of the heart with motion recorded at a high frame rate of 1,000–2,000 frames per second. A variety of two-dimensional (2D) methods have become available for cross-sectional display of cardiac structures, but at a lower frame rate of 30–100 frames per second. Doppler techniques provide the recording of intracardiac blood flow, and with color Doppler, the Doppler signal is displayed as 2D imaging using color to denote the direction and character of flow.

Echocardiography is widely recognized as an appropriate imaging modality in evaluating patients with a variety of symptoms and signs of heart disease (Table 1). These indications include the assessment of chamber quantitation, left ventricular (LV) systolic and diastolic function, pulmonary hypertension, pericardial disease, valvular heart disease, intracardiac masses and congenital heart disease.[1]

CHAMBER QUANTITATION

Left ventricular linear dimensions are important measurements in the management of patients with heart disease, especially in patients with volume overload due to valvular heart disease.[2] LV internal dimensions at end-diastole (LVIDd) and at end-systole (LVIDs) are usually made from parasternal long axis images at the level of the minor axis (i.e. perpendicular to the long axis of the left ventricle), at the level of the mitral leaflet tips or chords with measurements obtained at the tissue-blood interface (Fig. 1). The normal reference range for LV end diastolic diameter varies with gender: women, less than or equal to 5.3 cm [≤ 3.2 cm/m^2 when indexed for body surface area (BSA)] and men, less than or equal to 5.9 cm (≤ 3.1 cm/m^2 when indexed for BSA).[3]

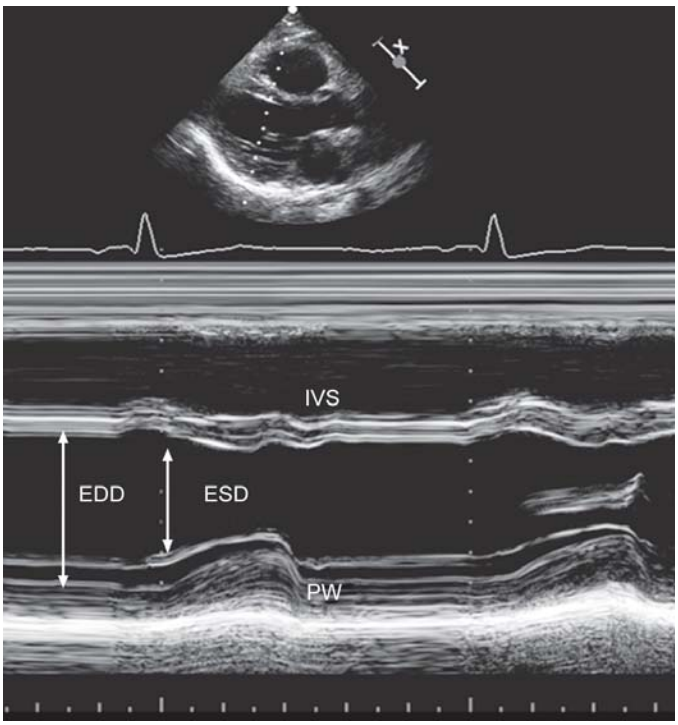


FIGURE 1: Measurement of left ventricular end diastolic dimensions (EDD) and end systolic dimensions (ESD) from m-mode of the LV using the parasternal long axis view (inset) for landmark identification. (Abbreviations: IVS: Interventricular septum; PW: Posterior wall)

The development of LV hypertrophy (Figs 2A and B) predicts increased risk of stroke, systolic heart failure and mortality; however, reduction in LV mass corresponds with improved outcomes.[4,5] Wall thickness is measured at end

TABLE 1

Appropriate indications for echocardiography

Symptoms:
- Dyspnea
- Chest pain with suspected myocardial ischemia in patients with nondiagnostic laboratory markers and ECG and in whom a resting echocardiogram can be performed during pain
- Lightheadedness or syncope
- TIA or cerebrovascular event

Prior testing that is concerning for heart disease (e.g. abnormal chest X-ray or electrocardiogram, elevated BNP)

Native valve disease:
- Murmur
- Suspected mitral valve prolapse
- Initial evaluation of known or suspected native valve stenosis or regurgitation
- Routine (yearly) re-evaluation of asymptomatic patient with severe native valvular stenosis or regurgitation
- Re-evaluation of patient with native valve stenosis or regurgitation with a change in clinical status

Prosthetic valve:
- Initial evaluation of prosthetic valve for establishment of baseline after placement
- Re-evaluation due to suspected dysfunction or thrombosis or a change in clinical status

Infective endocarditis:
- Initial evaluation of suspected infective endocarditis with positive blood culture or new murmur
- Re-evaluation of infective endocarditis in patients with virulent organism, severe hemodynamic lesion, aortic involvement, persistent bacteremia, a change in clinical status or symptomatic deterioration.

Known or suspected adult congenital heart disease

Sustained or nonsustained ventricular tachycardia

Evaluation of intracardiac and extracardiac structures and chambers
- Cardiovascular source of embolus
- Evaluation for cardiac mass due to suspected tumor or thrombus
- Evaluation of pericardial conditions such as effusion, constrictive pericarditis and tamponade

Known or suspected Marfan disease for evaluation of proximal aortic root and/or mitral valve

Heart failure:
- Initial evaluation of known or suspected heart failure (systolic or diastolic)
- Re-evaluation to guide therapy in a patient with a change in clinical status

Pacing device evaluation:
- Evaluation for dyssynchrony in patient being considered for cardiac resynchronization therapy
- Known implanted pacing device with symptoms possibly due to suboptimal pacing device settings to re-evaluate for dyssynchrony and/or revision of pacing device setting

Hypertrophic cardiomyopathy:
- Initial evaluation of known or suspected hypertrophic cardiomyopathy
- Re-evaluation of known hypertrophic cardiomyopathy in a patient with a change in clinical status to guide or evaluate therapy

Cardiomyopathy:
- Evaluation of suspected restrictive, infiltrative or genetic cardiomyopathy
- Screening for structure and function in first-degree relatives of patients with inherited cardiomyopathy

Cardiotoxic agents:
- Baseline and serial re-evaluation in patients undergoing therapy with cardiotoxic agents

Myocardial infarction:
- Initial evaluation of LV function after acute MI
- Re-evaluation of LV function following MI during recovery when results will guide therapy
- Evaluation of suspected complication of myocardial ischemia/infarction such as acute mitral regurgitation, ventricular septal defect, heart failure, thrombus and RV involvement

Pulmonary:
- Respiratory failure with suspected cardiac etiology
- Known or suspected pulmonary embolism to guide therapy (i.e. thrombectomy and thrombolytics)
- Evaluation of known or suspected pulmonary hypertension including evaluation of RV function and estimated pulmonary artery pressure

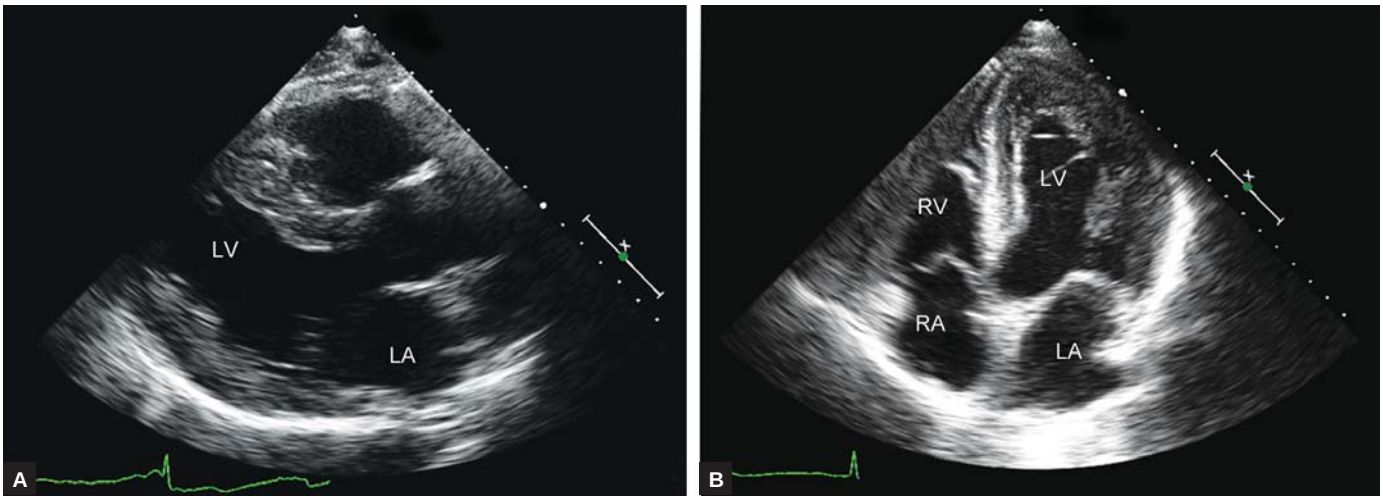
Hemodynamic instability of uncertain or suspected cardiac etiology

(*Source:* Reference 1)

diastole with normal thickness less than or equal to 0.9 cm.[3] Formulas are available for the calculation of LV mass. The American Society of Echocardiography (ASE) recommended formula for estimation of LV mass from LV linear dimensions is:

$$\text{LV mass} = 0.8 \times \{1.04\ [(\text{LVIDd} + \text{PWTd} + \text{SWTd})^3 - (\text{LVIDd})^3]\} + 0.6\ \text{gm}$$

where PWTd and SWTd are posterior wall thickness and septal wall thicknesses at end diastole respectively. The normal



FIGURES 2A AND B: Increased LV wall thickness consistent with LV hypertrophy due to hypertension. (A) Parasternal long axis view. (B) Apical 4-chamber view. (Abbreviations: LV: Left ventricle; LA: Left atrium; RV: Right ventricle; RA: Right atrium)

reference range varies with gender: men, 88–224 gm and women, 67–162 gm. LV mass can also be calculated from measurement of myocardial area at the mid-papillary muscle level 2D echo with long axis linear dimensions.[3]

Left ventricular ejection fraction (LVEF) predicts mortality and is proportional to survival (i.e. the lower the LVEF, the lower the individual patient's survival). In addition, LVEF guides therapeutic decision-making, helping to identify patients for drug therapy initiation (e.g. angiotensin converting enzyme inhibitors and beta-blockers in patients with LVEF $\leq$ 40%) and for implantation of internal cardiac defibrillators.[4] Left ventricular ejection fraction is calculated from the end diastolic volume (EDV) and end systolic volume (ESV) from the formula: EF = (EDV – ESV)/EDV. The normal LVEF is greater than or equal to 55%.[3] Left ventricular ejection fraction is frequently visually estimated but it can be estimated using quantitative methods. LV volume assessment is commonly obtained from 2D measurement using the biplane method of disks (also known as the modified Simpson's rule). Total volume is calculated as the sum of the volumes of a stack of elliptical disks (Fig. 3). If two orthogonal planes are not available, a single plane can be used, assuming the each disk has the area of a circle. When

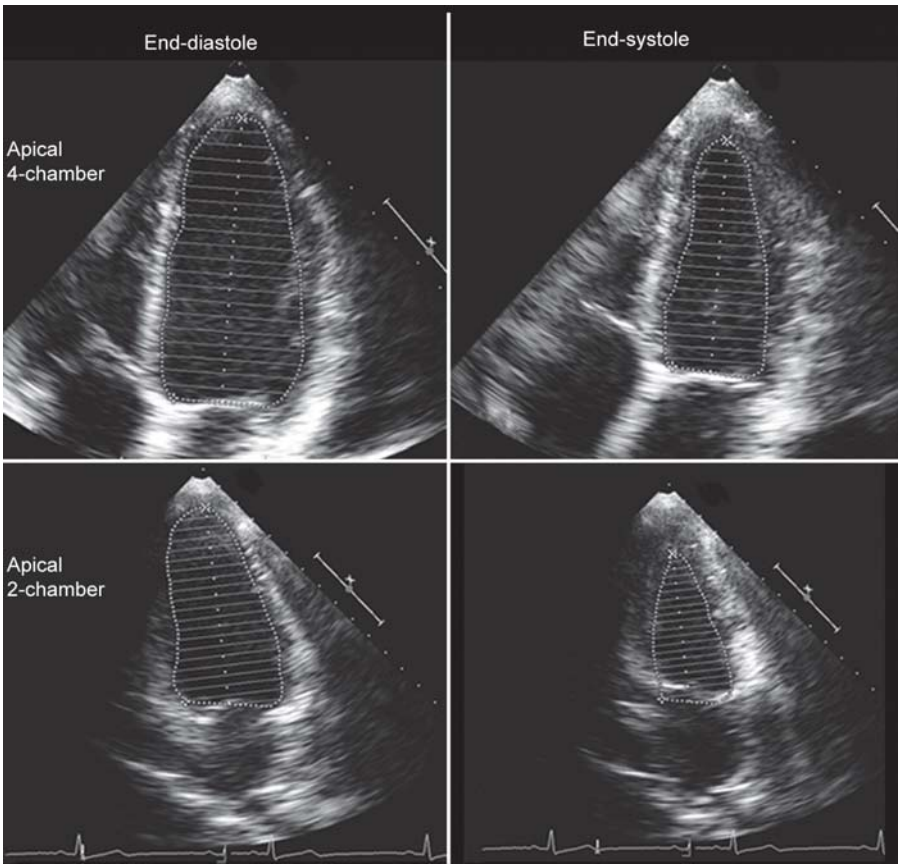


FIGURE 3: Two-dimensional measurements for LV volume calculation using the biplane method of disks in apical 4-chamber and 2-chamber views at end-diastole and end-systole

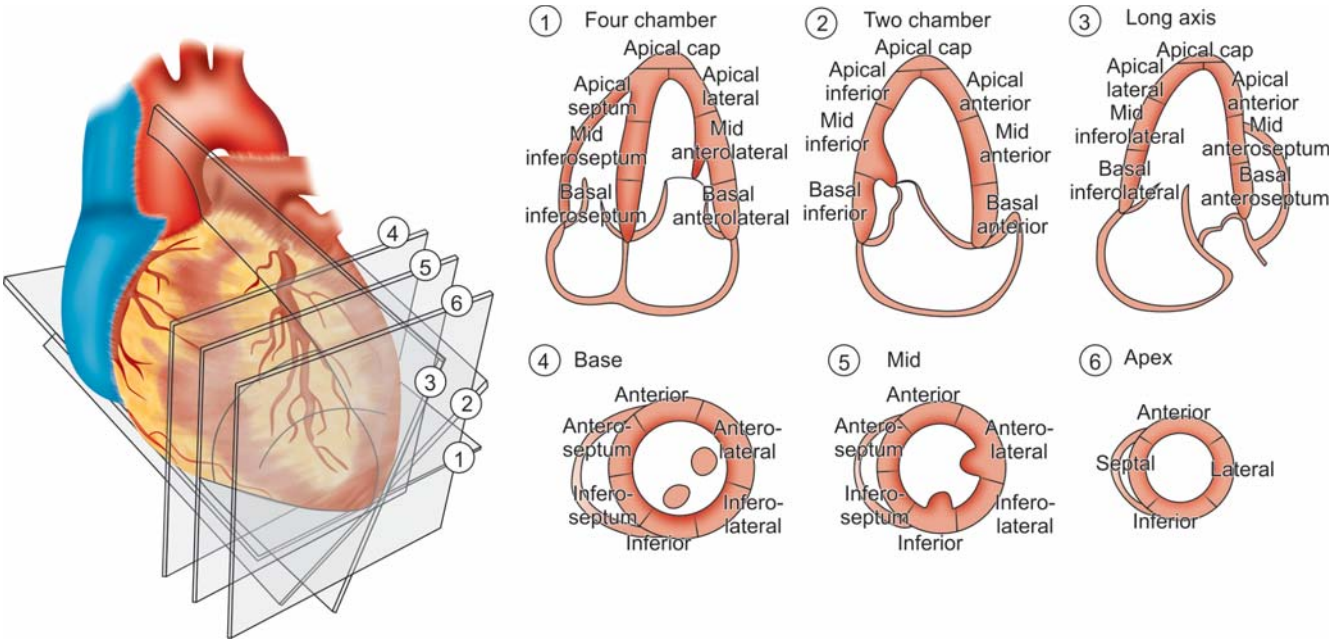


FIGURE 4: Seventeen segment model of left ventricular regional wall analysis based on apical and parasternal short axis views. (*Source:* Modified from Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's guidelines and standards committee and the chamber quantification writing group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echo. 2005:18:1440-63, with permission)

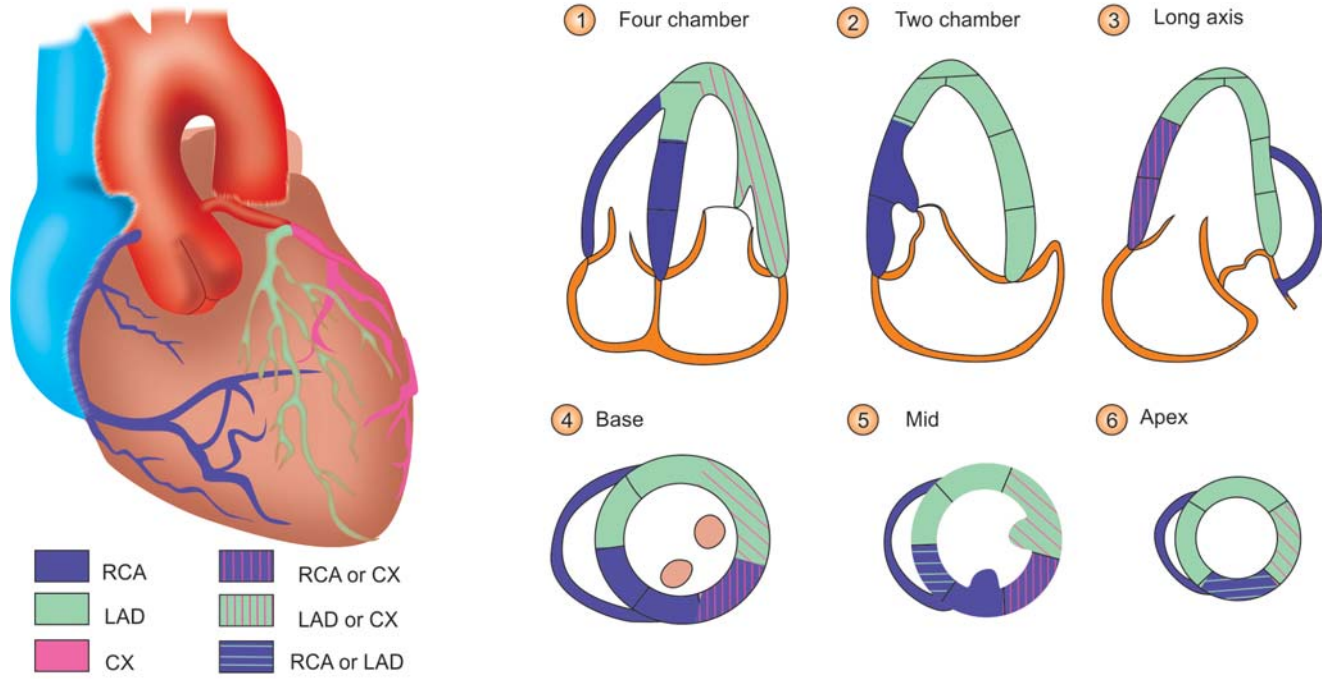


FIGURE 5: Identification of coronary artery perfusion beds by two-dimensional echocardiography. (Abbreviations: RCA: Right coronary artery; LAD: Left anterior descending artery; CX: Circumflex coronary artery). (*Source:* Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's guidelines and standards committee and the chamber quantification writing group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echo. 2005:18:1440-63, with permission)

endocardial definition is not adequate for tracing, area-length methods using the major length and a short axis LV cross-sectional area have been validated as alternative methods for volume estimation. The upper limit of normal for the LV end diastolic volume varies with gender: women, less than or equal to 104 ml ($\leq$ 75 ml/m^2 when indexed for BSA) and men, less than or equal to 155 ml ($\leq$ 75 ml/m^2 when indexed for BSA).[3]

Regional wall motion of the left ventricle can be assessed with 2D echocardiography. A standard model of analysis involves dividing the left ventricle into 17 segments (Fig. 4). The identification of segments is useful for the identification of coronary perfusion territories (Fig. 5). In the presence of a functionally significant stenosis, segmental wall motion (usually assessed as endocardial excursion and/or myocardial thickening)

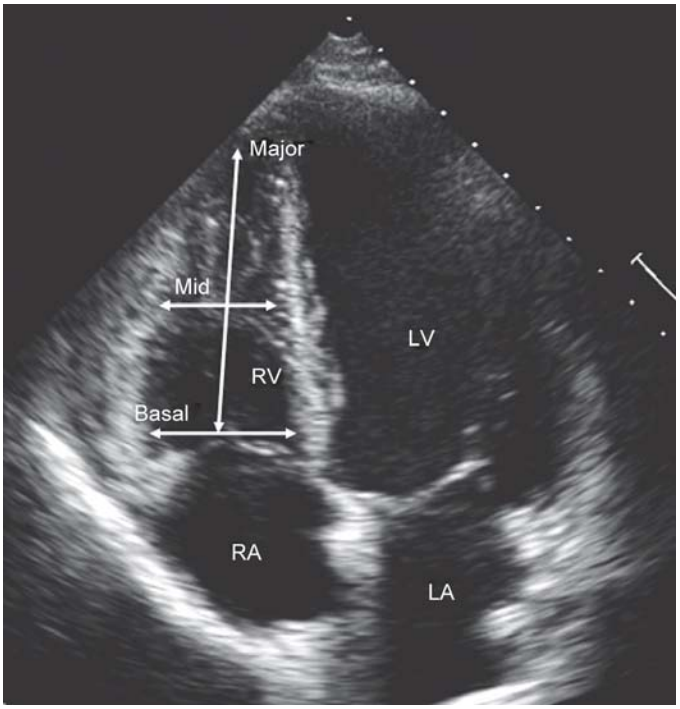


FIGURE 6: Right ventricular diameters measured in apical 4-chamber view. (Basal) Minor diameter measured at the base of the RV. (Mid) Minor diameter measured at mid level of RV. (Major) Major length diameter measured from RV apex to RV base. (Abbreviations: RV: Right ventricle; LV: Left ventricle; RA: Right atrium)

may become abnormal at rest in the presence of supply ischemia, or under stress conditions that provoke demand ischemia. Regional wall motion can be quantitated [e.g. normal or hyperkinesis = 1, hypokinesis (i.e. decreased motion) = 2, akinesis (i.e. no motion) = 3, dyskinesis (i.e. paradoxical motion = 4 and aneurysmal = 5] and an index derived as the sum of the scores divided by the number of segments scored.[3]

Right ventricular (RV) size is influenced by afterload and pressure changes as well as diseases such as myocardial infarction and RV dysplasia. In the apical 4-chamber view, the RV area or midcavity diameter should be smaller that the LV, otherwise RV dilation is present. Right ventricular (RV) diameter is measure at end diastole and dilation is present with basal minor diameter greater than 4.2 cm, mid level diameter greater than 3.5 cm or major length greater than 8.6 cm (Fig. 6). The RV is composed of three distinct portions: the smooth muscular inflow (i.e. the body), the outflow region and the trabecular apical region. Volumetric quantitation of RV function is challenging due to many geometric assumptions. A simple method of quantitating RV systolic function involves measurements of area at end diastole and end systole and calculating the fractional area change with abnormal less than 35% (Figs 7A to C). Right ventricular (RV) wall thickness greater than 5 mm indicates RV hypertrophy.[6]

Left atrial (LA) enlargement as determined by echocardiography is a predictor of cardiovascular outcomes.[7] Left artrial (LA) size is measured at ventricular end systole, when the LA chamber is at its largest dimension. The standard measurement previously used in clinical practice was the m-mode or 2D anteroposterior (AP) linear dimension obtained from the parasternal long axis view. However, LA volume provides a more accurate measure of LA size since expansion of the LA may occur in directions other than the AP dimension. LA volumes are usually calculated using either an area length or method of disks model (Fig. 8). The normal LA volume indexed for BSA is 22 ± 6 ml/m^2.[3]

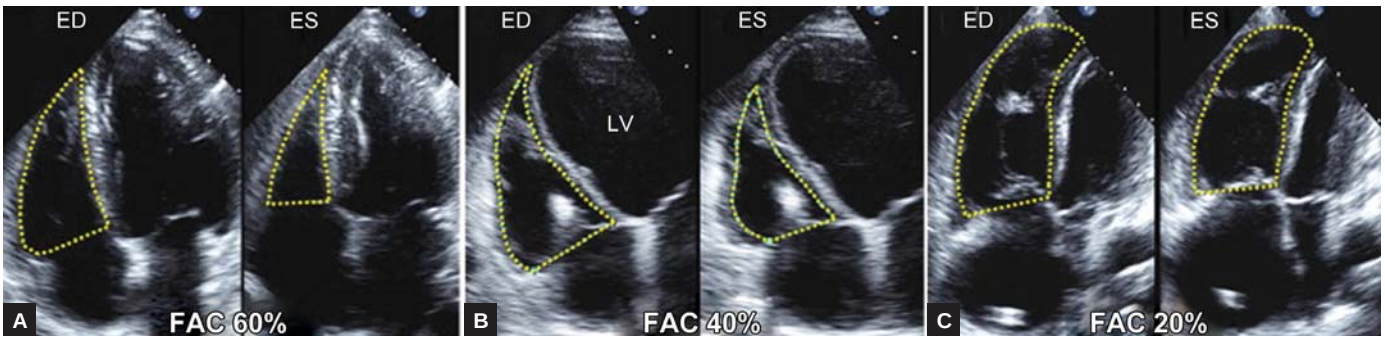
Right atrial (RA) enlargement has adverse prognostic implications in patients with pulmonary hypertension and is discussed later in this chapter. Compared to the LA, there is less data available on quantitation of the RA. However, RA enlargement is considered to be a minor dimension greater than 4.4 cm or a major dimension greater than 5.3 cm.[6]

DOPPLER ECHO

When ultrasound is reflected from moving red blood cells, there is a change in ultrasound frequency (ΔF), which is related to velocity (V) according to the equation:

$$\Delta F = (V \times 2F_o \times \cos \theta)/c$$

where F_o is the transducer frequency, θ is the angle between the direction of flow and insonifying beam and c is the speed of sound in tissue (i.e. 1,540 m/sec). When solving the Doppler equation, an angle between flow and beam of 0 or 180° (i.e. cosine θ = 1.0) is assumed for cardiac applications.[8] However, as the angle increases beyond 20°, the change in frequency is



FIGURES 7A TO C: Examples of right ventricular fractional area change (FAC). Percentage FAC = 100 × (end diastolic area – end systolic area)/end diastolic area. The endocardial border is traced in apical 4-chamber views from the tricuspid annulus along the free wall to the apex, then back to the annulus, along the interventricular septum at end diastole (ED) and end systole (ES). Trabeculation, tricuspid leaflets and chords are included in the chamber. (A) Normal subject, FAC 60%. (B) Moderately dilated right ventricle (RV), FAC 40% and a markedly dilated left ventricle (LV). (C) Dilated RV, FAC 20% and the LV is foreshortened as a result of optimizing the view for the right ventricular chamber. (*Source:* Rudski LG, Lai WW, Afilalo J, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography. J Am Soc Echocardiogr. 2010;23:685-713)

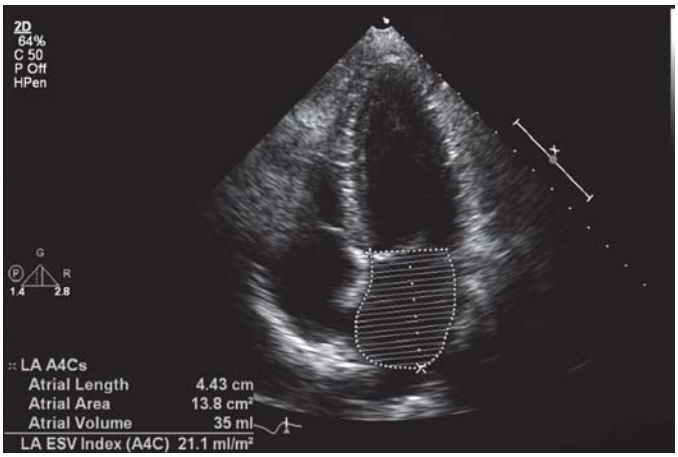


FIGURE 8: Measurement of the end systolic left atrial (LA) volume from the apical 4-chamber view using the method of disks

underestimated. Thus beam orientation is important for accurate measurements.

There are three modalities: (1) pulsed wave; (2) continuous wave and (3) color Doppler. Pulsed wave Doppler measures flow velocity within a specific site (i.e. range gate) but is limited in the measurement of high velocities. Continuous wave Doppler can record high velocities but cannot localize the site of origin of the velocity. Color Doppler estimates flow velocities within regions of interest with the 2D image. Color Doppler provides a rapid assessment of flow with a spatial and directional (color-coded) display of velocities on a 2D echo (Figs 9A and B). Pulsed and continuous wave Doppler provide quantitation of flow velocity and pressure gradient. Using the modified Bernoulli equation (i.e. pressure gradient = $4v^2$), velocity can be converted to pressure gradient and this permits estimation of hemodynamic variables such as valve stenosis and pulmonary hypertension severity. Flow is derived as the product of the cross-sectional area (CSA) of an orifice [e.g. the LV outflow tract (LVOT)] and the average velocity of the blood cells passing through the orifice. The calculation of flow can be used to estimate the CSA of the aortic valve (AV) using the continuity equation (Fig. 10) and is discussed in the section on valvular heart disease.[8]

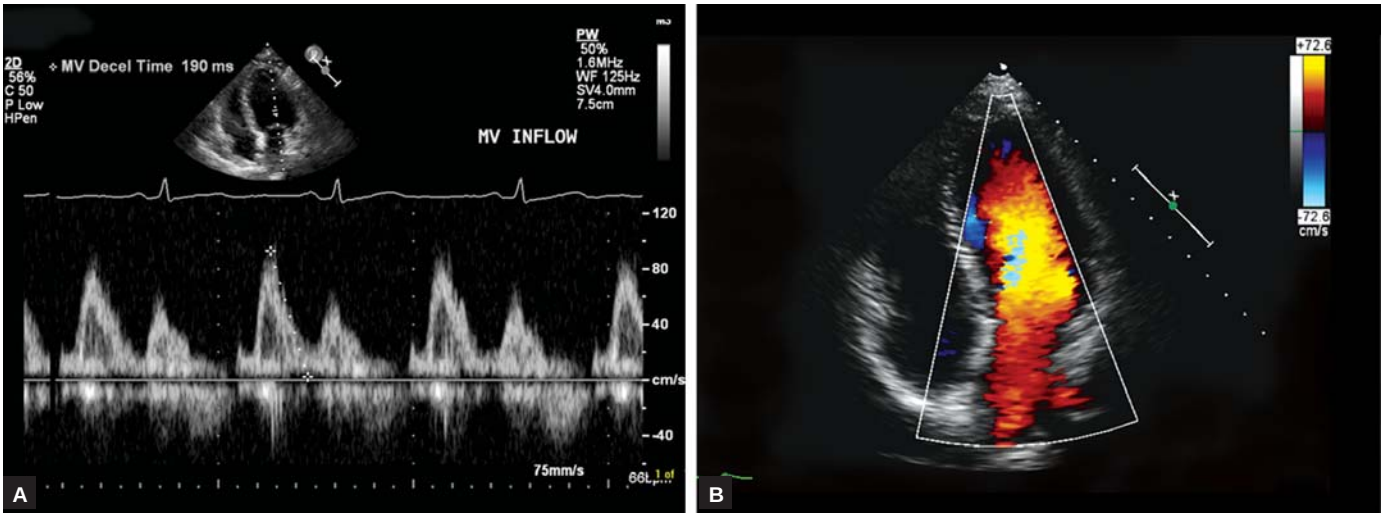
DIASTOLIC FUNCTION

Approximately one half of patients with a new diagnosis of heart failure have normal or near normal LV systolic function and these patients frequently have abnormalities of diastolic function. Morphologic abnormalities include LV hypertrophy. Wall thickness and LV mass can be assessed as described above and with increased filling pressures, LA volume increases which can also be assessed with 2D echocardiography.[9]

Doppler measurement of mitral inflow velocities, pulmonary vein velocities and LV myocardial tissue velocities are used to provide additional assessment of LV diastolic dysfunction (Figs 11A to C). These are obtained from the apical 4-chamber view which allows proper alignment of the Doppler beam. The major mitral inflow velocity parameters are: peak early filling (E) and late diastolic filling (A) velocities, the E/A ratio and deceleration time (DT) of early filling velocity. In addition, the isovolumic relaxation period can be determined by placing continuous wave Doppler beam in the LVOT to simultaneously display the end of aortic ejection and the onset of mitral inflow.[9]

The mitral E velocity primarily reflects the LA-LV pressure gradient during early diastole and is affected by preload and alterations in LV relaxation. The mitral A velocity reflects the LA-LV pressure gradient during late diastole, which is affected by LV compliance and LA contractile function. The DT of the E wave is influenced by LV relaxation, LV diastolic pressures after mitral valve opening and LV compliance (Fig. 12).[9]

The four mitral inflow patterns are: (1) normal (i.e. the mitral E velocity is dominant); (2) impaired LV relaxation (i.e. the mitral A velocity is dominant); (3) restrictive filling (i.e. elevated mitral E velocity with shortened DT) and (4) pseudonormal (i.e. normal mitral E velocity dominance) (Figs 13 and 14). A pseudonormal pattern is caused by a mild to moderate increase in LA pressure (and therefore an increase in the LA-LV gradient), in the setting of delayed myocardial relaxation and



FIGURES 9A AND B: Comparison of pulsed wave and color Doppler imaging. (A) Pulsed Doppler with sample volume placed in mitral inflow to measure velocities in this location for diastolic function assessment. (B) Color Doppler of diastolic inflow into left ventricle (LV) demonstrates spatial display of filling the LV. This display does not allow quantitation of velocities

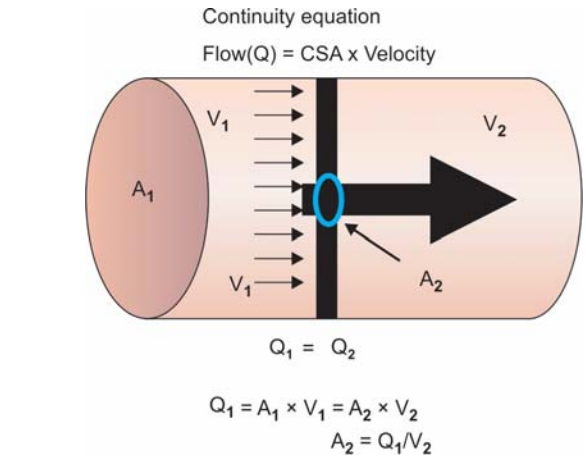
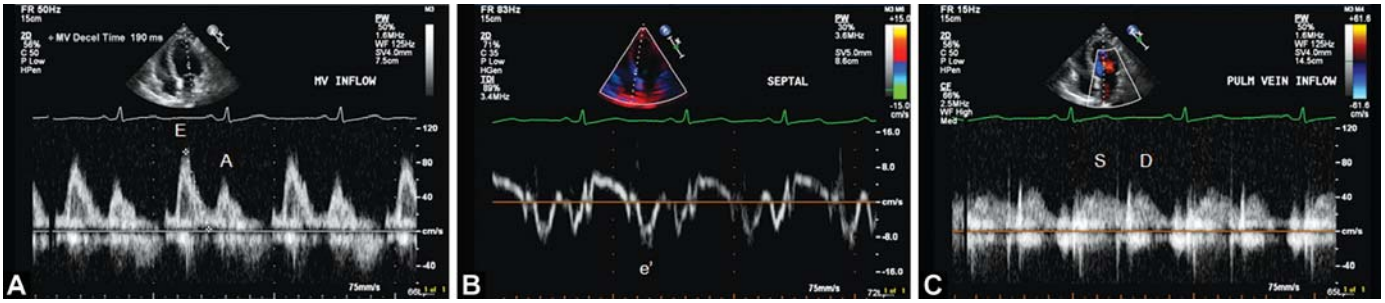


FIGURE 10: Diagrammatic representation of the continuity equation. When laminar flow encounters a small discrete stenosis, it must accelerate rapidly to pass through small orifice. Flow proximal to stenosis is same as flow passing through stenosis. Because flow equals velocity times cross-sectional area of stenotic orifice can be derived if velocity through orifice and flow is known (*Source:* Modified from Quinones MA, Otto CM, Stoddard M, et al. Recommendations for quantification of Doppler echocardiography: a report from the Doppler Quantification Task Force of the Nomenclature and Standards Committee of the American Society of Echocardiography. J Am Soc Echocardiogr. 2002;15:167-84, with permission)

the mitral inflow velocity pattern therefore appears normal. Additional Doppler measurements of pulmonary venous flow and myocardial velocities may be helpful to distinguish a normal pattern from a pseudonormal one.[9] For example, as LV relaxation is delayed, the LV myocardial velocity (e') is reduced.[10,11]

Impaired LV relaxation may occur with advancing age and LV hypertrophy. As the LV diastolic pressure increases, the LA-LV pressure gradient decreases and the contribution of atrial filling increases.[10] A restrictive filling pattern is seen in restrictive cardiomyopathies, such as amyloidosis, and is related to rapid early filling. Typically there is blunting of the normal respiratory variation in early filling velocity with restrictive physiology. Patients with a restrictive pattern and dilated cardiomyopathy have increased risk for poor prognosis.[12]

A Doppler beam placed into a pulmonary vein will provide a recording of the systolic (S) and diastolic (D) velocities. The S velocity is influenced by changes in LA pressure, contraction and relaxation. The D velocity is influenced by changes in LV filling and compliance. With an increase in LA pressure, the S velocity is expected to decrease and the D velocity increases (similar to the E velocity increase on mitral inflow Doppler). However, with increasing age, the S/D ratio will also increase as LV relaxation becomes impaired (Table 2).



FIGURES 11A TO C: Diastolic function assessment with Doppler echocardiography. (A) Mitral inflow Doppler velocity profiles of early (E) and late atrial (A) filling. (B) Septal wall tissue Doppler imaging for assessment of e'. (C) Pulmonary vein Doppler velocity profiles for measurement of systolic (S) and diastolic (D) velocities

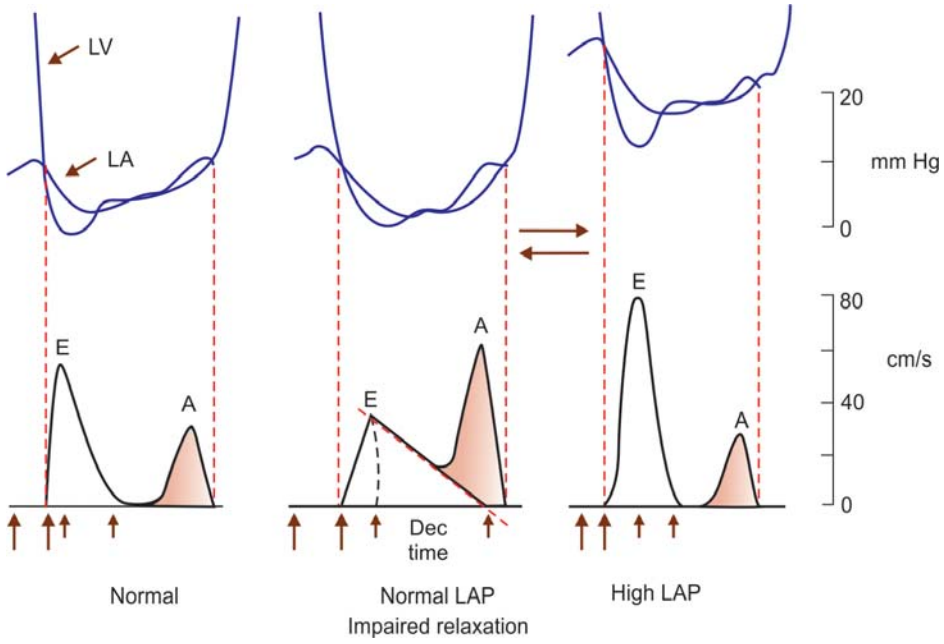


FIGURE 12: Schematic diagram of the changes in mitral inflow in response to the transmitral pressure gradient. (*Source:* Modified from Nagueh SF, Appleton CP, Gillebert TC, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. J Am Soc Echocardiogr. 2009;22:107-33, with permission)

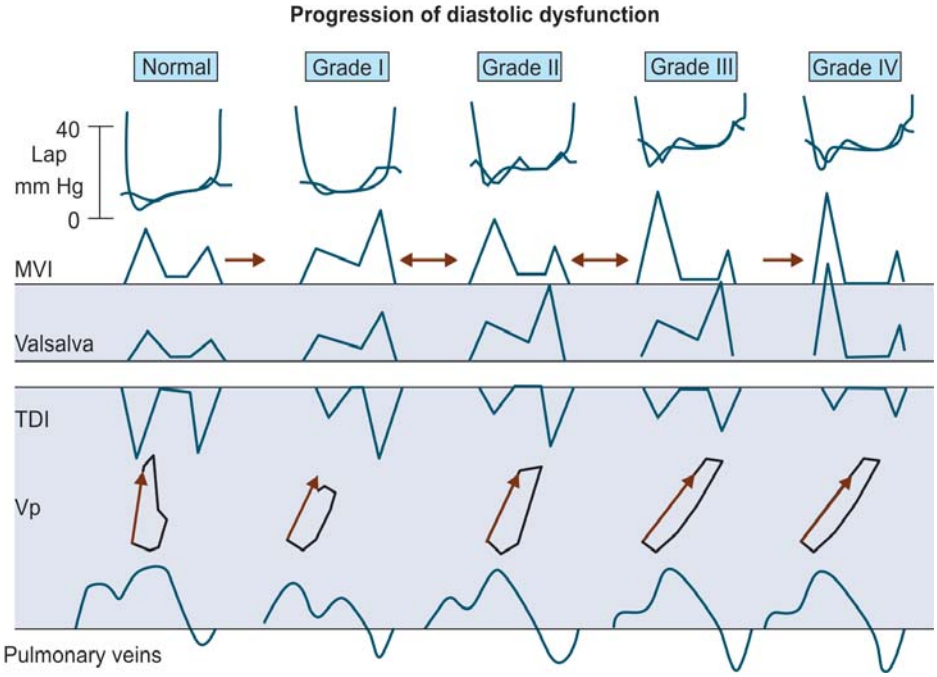


FIGURE 13: The progression of left ventricular diastolic dysfunction can be readily assessed using a combination of Doppler echocardiographic variables. Each successive grade represents a worsening state of diastolic dysfunction: Grade I—impaired relaxation; Grade II—pseudonormalization; Grade III/IV—restrictive. (Abbreviations: MVI: Mitral valve inflow; TDI: Tissue Doppler imaging; Valsalva: Response of mitral valve inflow to Valsalva maneuver; Vp: Mitral inflow propagation velocity). (*Source:* Modified from Ommen SR, Nishimura RA. A clinical approach to the assessment of left ventricular diastolic function by Doppler echocardiography: update 2003. *Heart.* 2003;89:iii18-23, with permission)

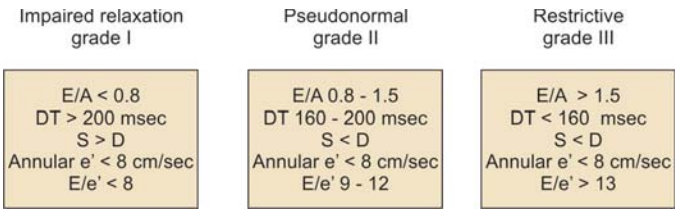


FIGURE 14: Grading diastolic dysfunction: integrating measurements from mitral inflow velocity, pulmonary vein and myocardial tissue velocities (Abbreviations: E/A: Mitral E/A velocity ratio; DT: Deceleration time of the mitral early filling velocity; S, D: Pulmonary vein systolic (S) and diastolic (D) velocities; Annular e': Tissue Doppler derived myocardial velocity averaged from septal and lateral tissue Doppler velocities). (*Source:* Modified from Nagueh SF, Appleton CP, Gillebert TC, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. J Am Soc Echocardiogr. 2009;22:107-33, with permission)

TABLE 2

Age related changes in Doppler indices of diastolic function

	Age		
	21–40 yr	*41–60 yr*	*> 60 yr*
E/A ratio	1.5 ± 0.4	1.3 ± 0.2	1.0 ± 0.2
DT (msec)	166 ± 14	181 ± 19	200 ± 29
PV S/D ratio	1.0 ± 0.3	1.2 ± 0.2	1.4 ± 0.5
Septal e' (cm/s)	16 ± 3	12 ± 2	10 ± 2
Lateral e' (cm/s)	20 ± 3	16 ± 2	13 ± 3

(*Source:* Reference 9)

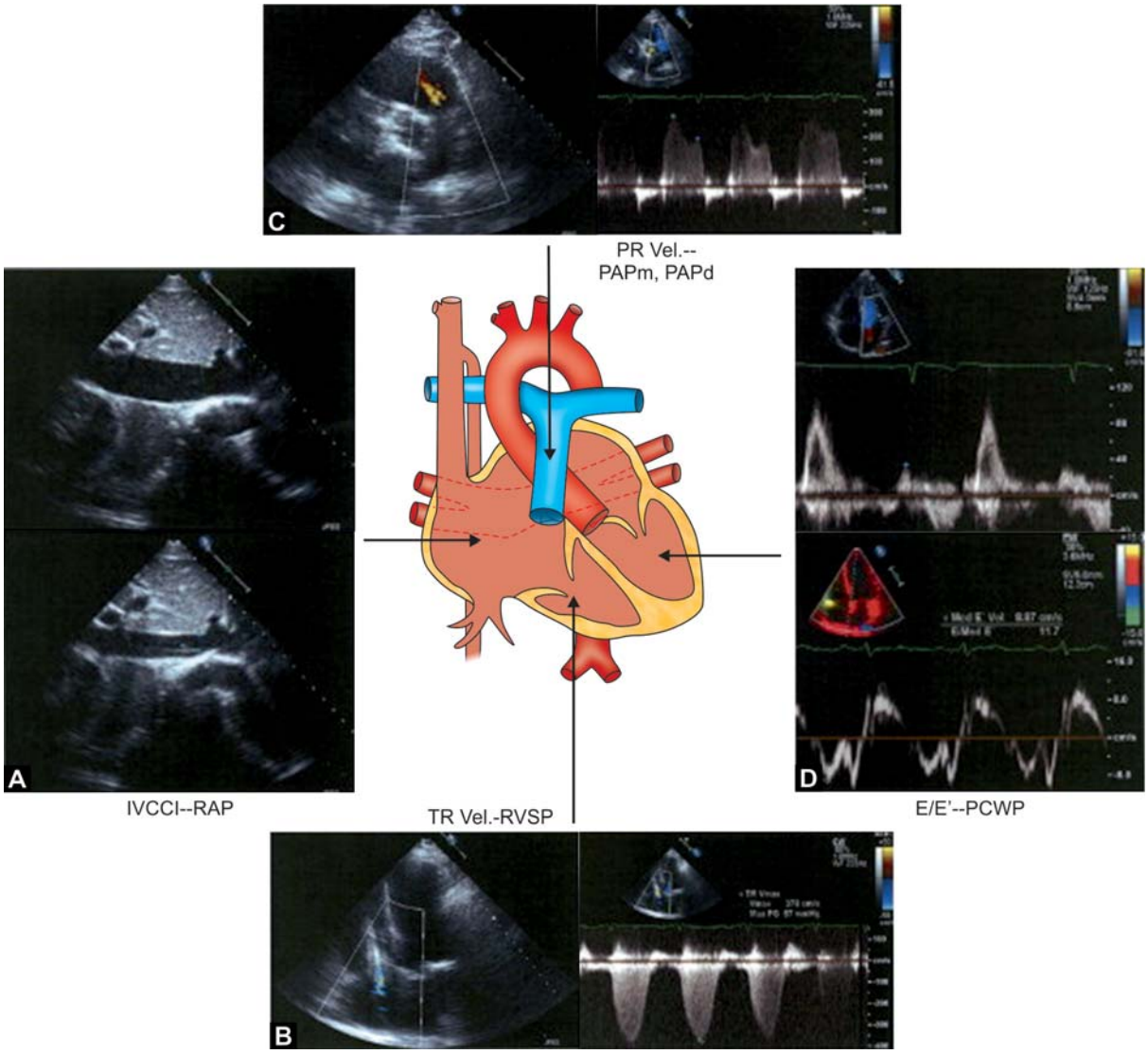
Pulsed Doppler measurement of myocardial velocities provides an additional method for assessing LV diastolic filling. The primary measurement is the early diastolic (e') velocity, which is influenced by LV relaxation, preload, systolic pressure and LV minimal pressure. Tissue Doppler signals are acquired at the septal and lateral sides of the mitral annulus and the e' velocities are averaged for the calculation of the E/e' ratio, a measure of LV filling pressure.[9] With impaired LV relaxation, the e' velocity is reduced. A ratio greater than 15 is associated with increased LV filling pressure and a ratio less than 8 is associated with normal LV filling pressure. A value between 8 and 15 is indeterminate for predicting LV filling pressure.[13] As is the case with mitral and pulmonary vein Doppler measurements, the normal value for e' velocity changes with age.[9]

PULMONARY HYPERTENSION

Pulmonary arterial (PA) hypertension results from restricted flow through the PA circulation, increased pulmonary vascular resistance and ultimately in right heart failure. Pulmonary arterial hypertension is defined as mean PA pressure greater than 25 mm Hg at rest, PA wedge pressure less than 15 mm Hg and pulmonary vascular resistance greater than 3 Wood Units. Pulmonary hypertension can also result from disorders associated with elevated LV filling pressures such as LV dysfunction (either systolic or diastolic) and valvular heart disease.[14]

Transthoracic echocardiography (TTE) may identify conditions that predispose to PH or suggest a specific disease entity (Table 3).[14] A complete 2D and Doppler echo study can provide an estimate of RV systolic pressure or cardiac sequelae of PH (Figs 15A to D). Right ventricular (RV) systolic pressure greater than 40 mm Hg generally warrants further evaluation in the patient with unexplained dyspnea. Other findings of PH are RA or RV enlargement or interventricular septal flattening (Figs 16A and B). The presence of any degree of pericardial effusion, RA enlargement and RV enlargement or dysfunction is predictor of poor prognosis.

When tricuspid regurgitation is present, the application of the modified Bernoulli equation to the peak tricuspid regurgitation velocity provides a close estimate of the peak pressure gradient between RV and RA. Then, RV systolic pressure can be derived by adding an estimate of mean RA pressure to the



FIGURES 15A TO D: Illustration of "Echo Right Heart Catheterization". (A) Inferior vena caval (IVC) size and degree of collapse yields an estimate of right atrial pressure (RAP). (B) The tricuspid regurgitant velocity (TR Vel) is used to estimate the systolic right ventricle—right atrium gradient (and the pulmonary artery systolic pressure, in the absence of pulmonic stenosis). (C) The maximal pulmonic valve regurgitant velocity is used to estimate the mean pulmonary artery pressure (PAPm). The end diastolic pulmonic regurgitant velocity is used to estimate diastolic pulmonary artery pressure (PAPd). (D) The early mitral inflow (E wave)/early diastolic mitral valve annular motion (E' wave) ratio is used to assess pulmonary capillary wedge pressure (PCWP). (Abbreviations: E/E': Ratio of early diastolic mitral inflow velocity to early diastolic velocity of the mitral valve annulus; IVCCI: Inferior vena cava collapsibility index; PR Vel: Pulmonic valve regurgitant velocity; RVSP: Right ventricular systolic pressure). (*Source:* Kirkpatrick JN, Vannan MA, Narula J, et al. Echocardiography in heart failure: application, utility, and new horizons. J Am Coll Cardiol. 2007;50:381-96)

peak RV-RA gradient.[6,15] In the absence of pulmonic stenosis, the peak RV pressure is equivalent to the PA systolic pressure.[8]

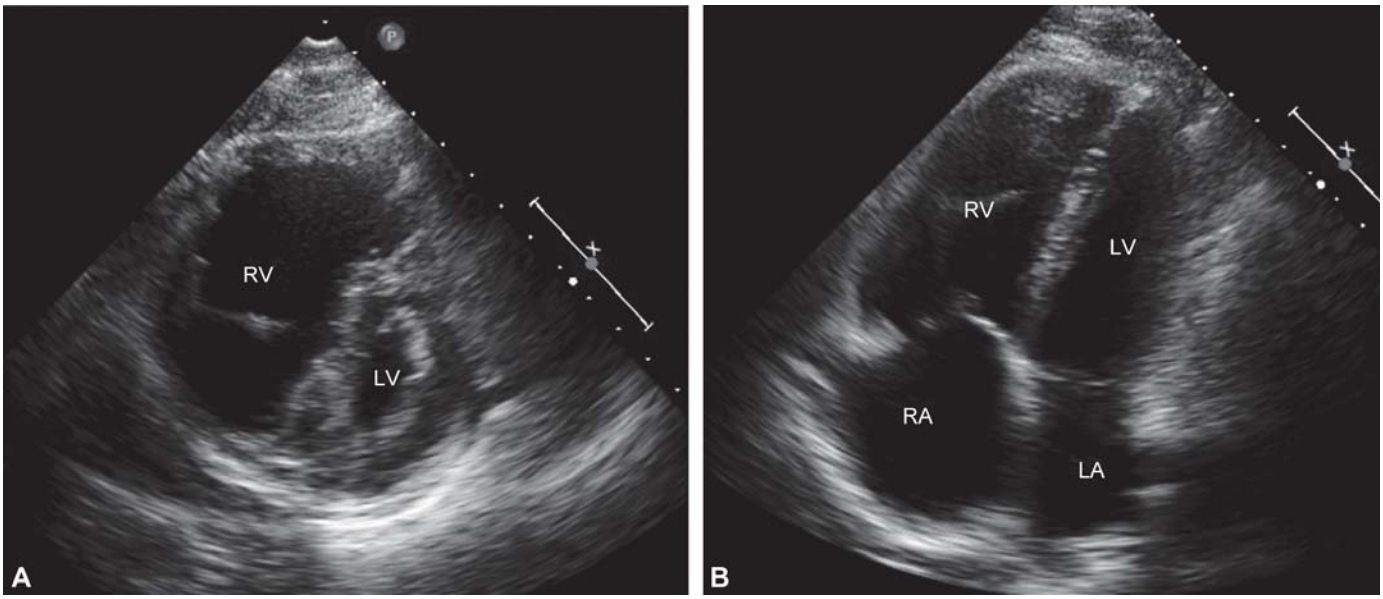
The RA pressure can be estimated by the inferior vena cava appearance. A normal RA pressure of 0–5 mm Hg is predicted by an inferior vena cava diameter of less than 2.1 cm with collapse greater than 50% with a sniff. An elevated RA pressure of 10–20 mm Hg is suggested by inferior vena cava diameter greater than 2.1 cm with collapse less than 50% with a sniff.[6]

PERICARDIAL DISEASE

Echocardiography can be useful in detecting a variety of conditions that affect the pericardium including: (1) effusion; (2) tamponade; (3) constriction; (4) partial or complete absence of the pericardium and (5) pericardial cysts or tumors.[16]

Pericardial effusion is recognized as an echo-free space between the visceral and the parietal pericardium surrounding the heart. Small effusions are generally limited to the posterior atrioventricular groove. As the effusion increases, fluid extends laterally and with large effusion, fluid surrounds the heart.[16]

When the ability of the pericardium to stretch is exceeded by fluid accumulation, pericardial sac pressure increases and may exceed intracardiac pressures during the cycle, resulting in tamponade physiology. The signs of tamponade include RA wall inversion and diastolic compression of the RV free wall. Plethora of the inferior vena cava is a useful indicator of elevated RA pressure. Tamponade produces reciprocal respiration-related changes in diastolic filling of the LV and the RV, and exaggerated respiratory changes in mitral and tricuspid inflow velocities can be demonstrated by pulsed Doppler (Figs 17A and B).[16,17]



FIGURES 16A AND B: Echocardiographic features of pulmonary hypertension. (A) Parasternal short axis view. (B) Apical 4-chamber view. Common echocardiographic findings in pulmonary hypertension include: right atrial enlargement; right ventricular enlargement; abnormal contour of the interventricular septum and underfilled left heart chambers. (Abbreviations: LA: Left atrium; LV: Left ventricle; RA: Right atrium; RV: Right ventricle)

TABLE 3

Causes of pulmonary hypertension identified by echocardiography

Conditions that predispose to pulmonary hypertension:

- Congenital or acquired valvular disease (mitral regurgitation, mitral stenosis, aortic stenosis and prosthetic valve dysfunction)
- Left ventricular systolic dysfunction
- Impaired left ventricular diastolic function (hypertensive heart disease, hypertrophic cardiomyopathy, Fabry's disease and infiltrative cardiomyopathy)
- Other obstructive lesions (coarctation, supravalvular aortic stenosis, subaortic membrane and cor triatriatum)
- Congenital disease with shunt (atrial septal defect, ventricular septal defect, coronary fistula, patent ductus arteriosus and anomalous pulmonary venous return)
- Pulmonary embolus (thrombus in inferior vena cava, right-sided cardiac chamber or pulmonary artery; tricuspid or pulmonic valve vegetation)
- Pulmonary vein thrombosis/stenosis

Findings that suggest specific disease entity:

- Left-sided valve changes (systemic lupus erythematosus and anorexigen use)
- Intra-pulmonary shunts (hereditary hemorrhagic telangiectasia)
- Pericardial effusion (idiopathic pulmonary artery hypertension, systemic lupus erythematosus and systemic sclerosis)

(*Source:* Reference 14)

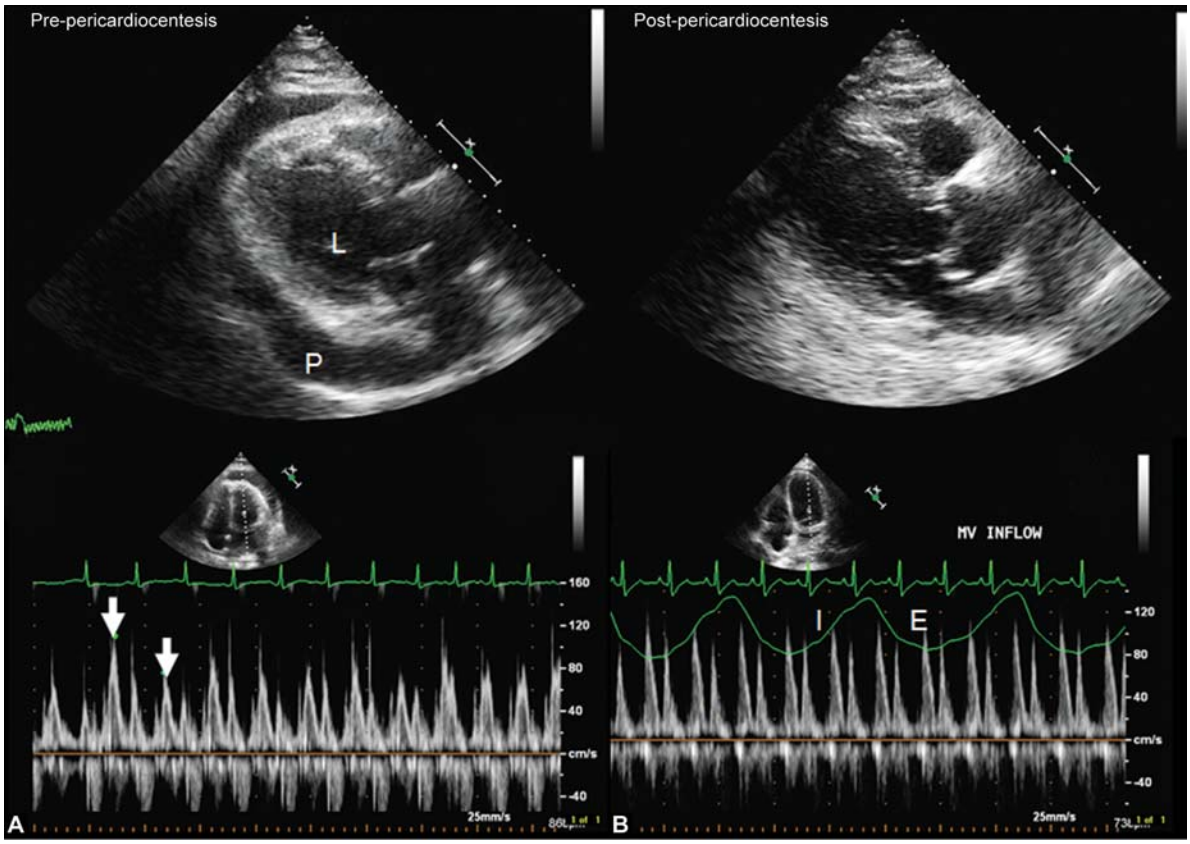
Constrictive pericarditis is characterized by impaired diastolic cardiac filling and elevated ventricular filling pressures due to a rigid pericardium with fusion of the visceral and parietal layers. While increased pericardial thickness may be visualized with TTE, sensitivity and correlation with pathologic measurement are suboptimal.[18] Constrictive pericarditis is usually associated with elevated and equal pressures in all four cardiac chambers. At the onset of diastole, the rate of ventricular filling is increased but is rapidly halted by pericardial constraint.[16] The abrupt early diastolic filling may be seen on the 2D echocardiogram as a septal "bounce". Mitral inflow as assessed by Doppler echocardiography demonstrates an increased early diastolic filling velocity and shortened DT (i.e. < 160 msec).[16,18] Increased filling of one ventricle occurs at the expense of the other and this results in a respiratory shift in the position of the interventricular septum (Fig. 18) and exaggeration of normal respiratory changes in mitral and tricuspid flow (Figs 19A to E).[19] In constrictive pericarditis, tricuspid flow increases greater than 25% and mitral flow decreases greater than 25% with inspiration.[16,18]

Constriction can be distinguished from restrictive cardiomyopathy since marked respiratory changes in intracardiac velocities are not present with the latter (Fig. 20, Table 4).[19] Hepatic vein Doppler profiles differ between the two disorders as well. In patients with constriction, during expiration there is a decrease in RV filling resulting in a decrease in tricuspid valve velocity and an augmentation of diastolic flow reversal in the hepatic vein. Patients with restrictive cardiomyopathy exhibit diastolic flow reversal in inspiration.[18,19] Analysis of mitral annular velocities can also help in the differentiation. Patients with restrictive cardiomyopathy have impaired myocardial relaxation, leading to reductions in myocardial velocity. On the other hand, with constriction, annular vertical velocity is usually preserved. Furthermore, the septal myocardial velocity is usually increased due to preserved LV longitudinal expansion compensating for limited lateral and AP expansion.[8]

VALVULAR HEART DISEASE

AORTIC STENOSIS

The most common cause of aortic stenosis in adults is calcification of a normal trileaflet or a congenital bicuspid



FIGURES 17A AND B: (A) Large pericardial effusion (PE) demonstrated on 2D echo and with respiratory variation > 25% of early filling velocity on mitral inflow Doppler (arrows) consistent with cardiac tamponade. (B) After pericardiocentesis, there is resolution of pericardial effusion and respiratory variation of early filling velocity. (Abbreviations: I: Inspiration; E: Expiration)

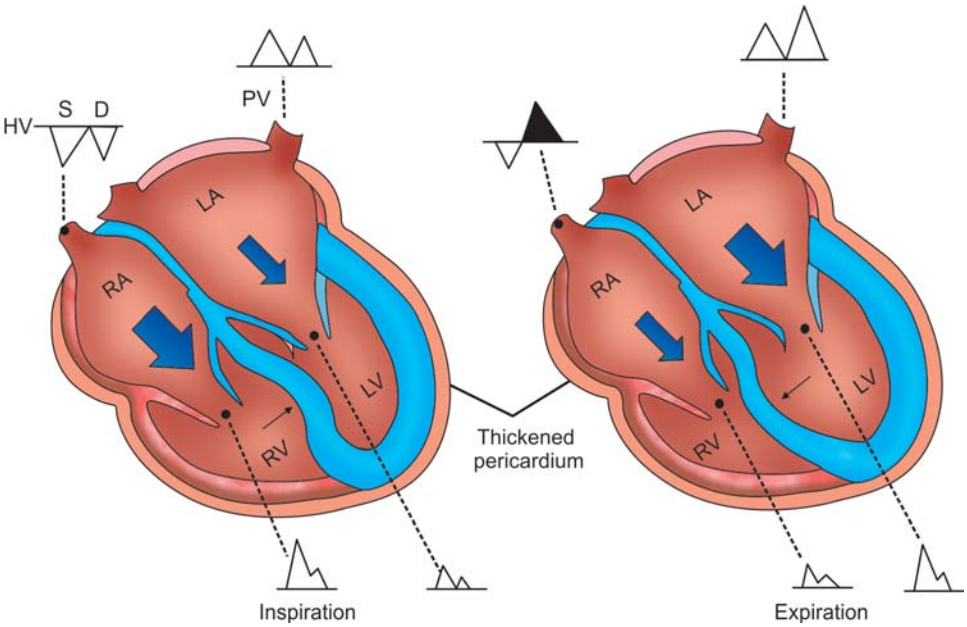
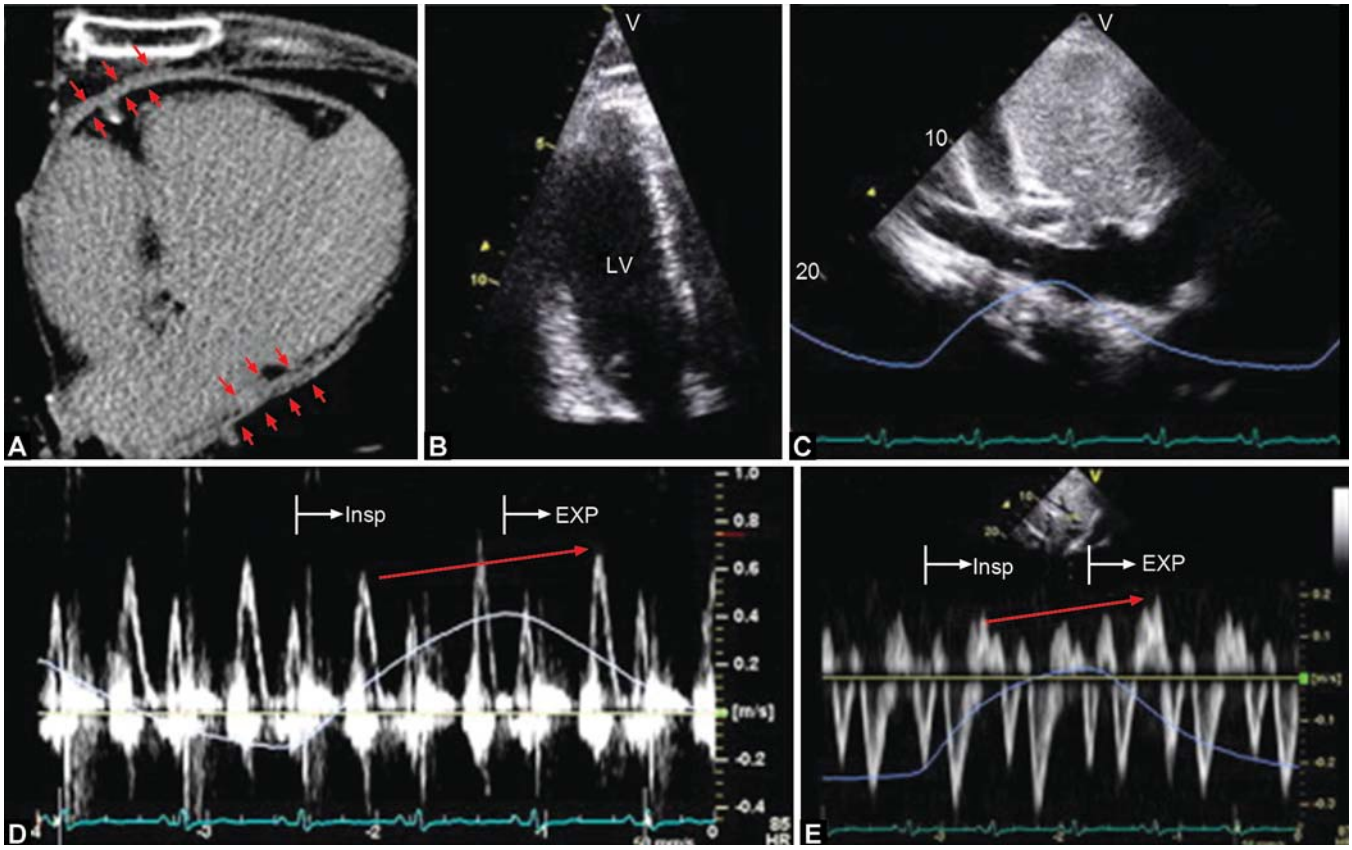


FIGURE 18: Schematic of respiratory variation in transvalvular and central venous flow velocities in constrictive pericarditis. With inspiration, the driving pressure gradient from the pulmonary capillaries to the left cardiac chambers decreases, resulting in a decrease in mitral inflow and diastolic pulmonary venous (PV) flow velocity. The decreased left ventricular filling results in ventricular septal shift to the left (small arrow), allowing augmented flow to the right-sided chambers shown as increased tricuspid inflow and diastolic hepatic venous (HV) flow velocity because the cardiac volume is relatively fixed as a result of the thickened shell of pericardium. The opposite changes occur during expiration. (Abbreviations: LA: Left atrium; LV: Left ventricle; RA: Right atrium; RV: Right ventricle; D: Diastole; S: Systole). (*Source:* Modified from Oh JK, Hatle LK, Seward JB, et al. Diagnostic role of Doppler echocardiography in constrictive pericarditis. J Am Coll Cardiol. 1994;23:154-62, with permission)



FIGURES 19A TO E: Findings in patients with constrictive pericarditis (CP). (A) Computed tomography in a patient with CP shows the extent of pericardial thickening (red arrows). Apical 4-chamber view of the left ventricle (LV) (B) and dilated inferior vena cava (C) with increased respiratory variations in transmitral early diastolic flow (D) and hepatic venous Doppler flow (E) are shown for the same patient with CP (red arrows in D and E indicate respiratory-dependent change in Doppler flow). (Abbreviations: Exp: Expiration; Insp: Inspiration). (*Source:* Dal-Bianco JP, Sengupta PP, Mookadam F, et al. Role of echocardiography in the diagnosis of constrictive pericarditis. J Am Soc Echocardiogr. 2009;22:24-33)

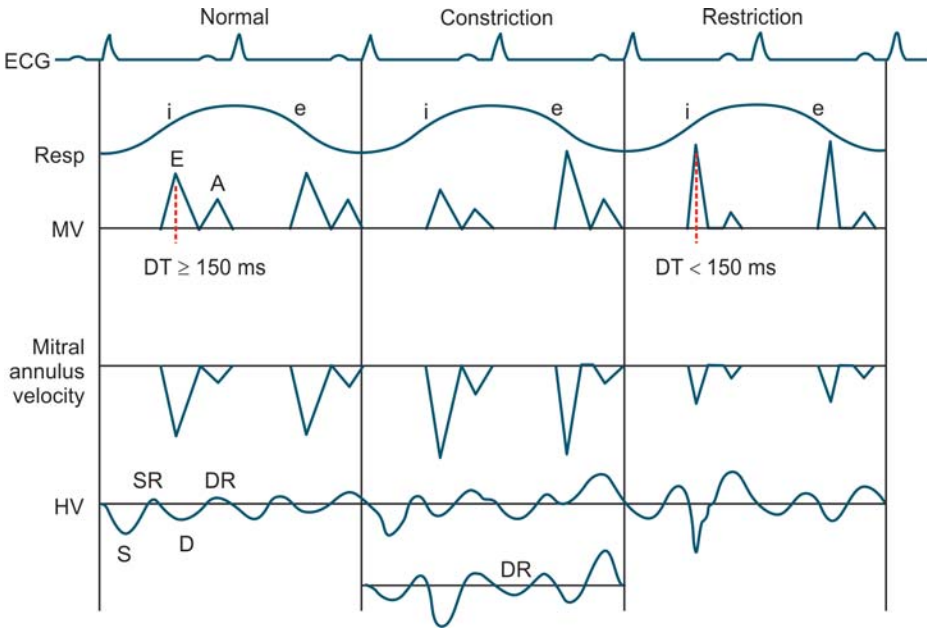


FIGURE 20: Schematic diagram of Doppler echocardiographic features in constrictive pericarditis versus restrictive cardiomyopathy. Schematic illustration of Doppler velocities from mitral inflow (MV), mitral annulus velocity and hepatic vein (HV). Electrocardiographic (ECG) and respirometer (Resp) recordings indicating inspiration (i) and expiration (e) are also shown. (Abbreviations: A: Atrial filling; D: Diastolic flow; DR: Diastolic flow reversal; DT: Deceleration time; E: Early diastolic filling; S: Systolic flow; SR: systolic flow reversal) (*Source:* Modified from Oh JK, Hatle LK, Seward JB, et al. Diagnostic role of Doppler echocardiography in constrictive pericarditis. J Am Coll Cardiol. 1994;23:154-62, with permission)

TABLE 4

Differentiation of constrictive pericarditis from restrictive cardiomyopathy

	Constriction	*Restriction*
Septal motion	*Respiratory shift ("septal bounce")*	*Normal*
Mitral E/A ratio	> 1.5	> 1.5
Mitral DT (msec)	< 160	< 160
Mitral inflow respiratory variation	Usually present	Absent
Hepatic vein Doppler	Expiratory diastolic flow reversal	Inspiratory diastolic flow reversal
Mitral septal annulus e'	> 7 cm/sec	< 7 cm/sec
Mitral lateral annulus e'	Lower than septal e'	Higher than septal e'

(*Source:* Reference 9)

valve.[2] Anatomic evaluation of the AV with 2D echo is based on a combination of short and long axis images to identify the number of leaflets, and to describe leaflet mobility, thickness and calcification. Unfortunately, the accuracy of direct planimetry of the valve area is limited by artifacts from calcification. Doppler echocardiography allows the determination of the level of obstruction and the quantitation of the pressure gradient (Table 5). The primary hemodynamic parameters for the clinical evaluation of aortic stenosis severity are jet velocity, mean transaortic gradient and valve area by the continuity equation.[20]

Jet velocity is measured across the narrowed AV using continuous wave Doppler ultrasound. Multiple acoustic windows are interrogated and the highest velocity is used. The pressure gradient (ΔP) between the left ventricle and the aorta in systole is calculated from the velocity (v) using the modified Bernoulli equation (i.e. $\Delta P = 4v^2$). The mean gradient is determined by averaging the instantaneous gradients over the ejection period. The modified Bernoulli equation assumes that the LV outflow velocity is negligible but if the proximal velocity is more than 1.5 m/sec, it should be included in the equation (i.e. $\Delta P = 4 (v^2_{max} - v^2_{proximal})$.[20]

Calculation of the stenotic orifice area or valve area is helpful when flow rates are very low or very high since the velocity

TABLE 5

Classification of aortic stenosis severity

	Mild	*Moderate*	*Severe*
Aortic jet velocity (m/s)	2.6–2.9	3.0–4.0	> 4.0
Mean gradient (mm Hg)	< 20 < 30*	20–40 30–50*	> 40 > 50*
Aortic valve area (cm^2)	> 1.5	1.0–1.5	< 1.0
Indexed aortic valve area (cm^2/m^2)	> 0.85	0.60–0.85	< 0.6
Doppler velocity ratio	> 0.50	0.25–0.50	< 0.25

*European Society of Cardiology Guidelines
(*Source:* Reference 20)

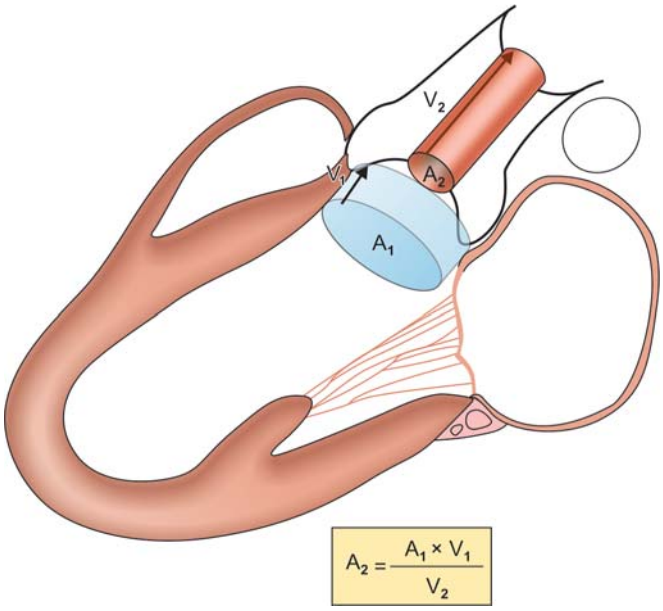


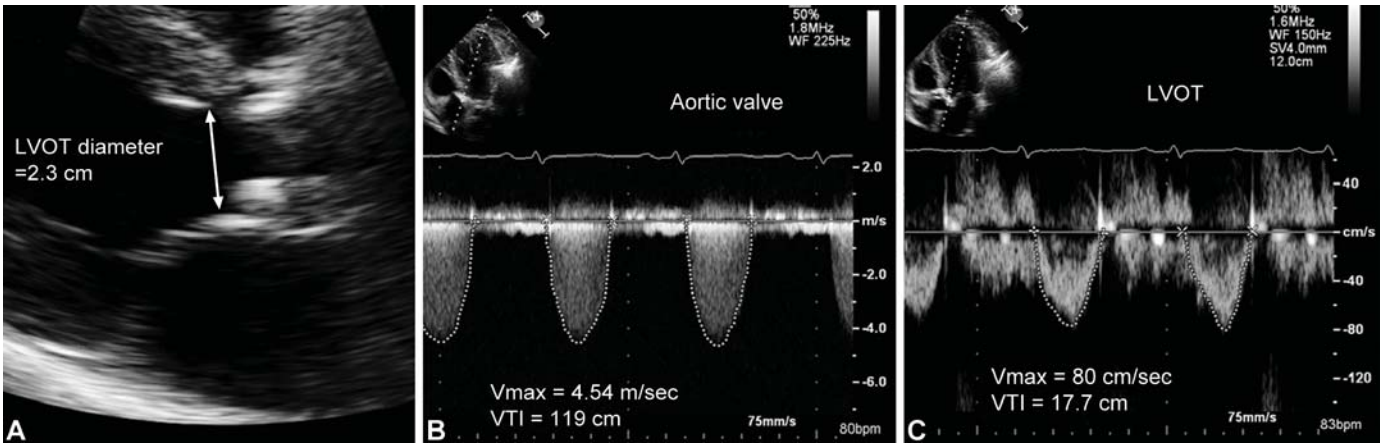
FIGURE 21: Schematic diagram of continuity equation. Since the stroke volume in the LV outflow tract (A_1 V_1) is the same as the stroke volume at the aortic valve (A_2 V_2), A_2 (the aortic valve area) can be solved if A_1, V_1 and V_2 are known. (*Source:* Modified from Baumgartner H, Hung J, Bermejo J, et al. Echocardiographic assessment of valve stenosis: EAE/ASE recommendations for clinical practice. J Am Soc Echocardiogr. 2009;22:1-23, with permission)

and pressure gradient are flow-dependent. According to the continuity equation, the stroke volume (SV) across the AV is equal to the SV in the LVOT. Since SV = CSA × flow velocity over the ejection period [or the velocity-time integral (VTI)], according to the continuity equation, $CSA_{AV} \times VTI_{AV} = CSA_{LVOT} \times VTI_{CSA}$. Solving for CSA_{AV}, the AV area = $(CSA_{LVOT} \times VTI_{CSA}) \div VTI_{AV}$ (Figs 21 and 22A to C, Video 1).[20,21]

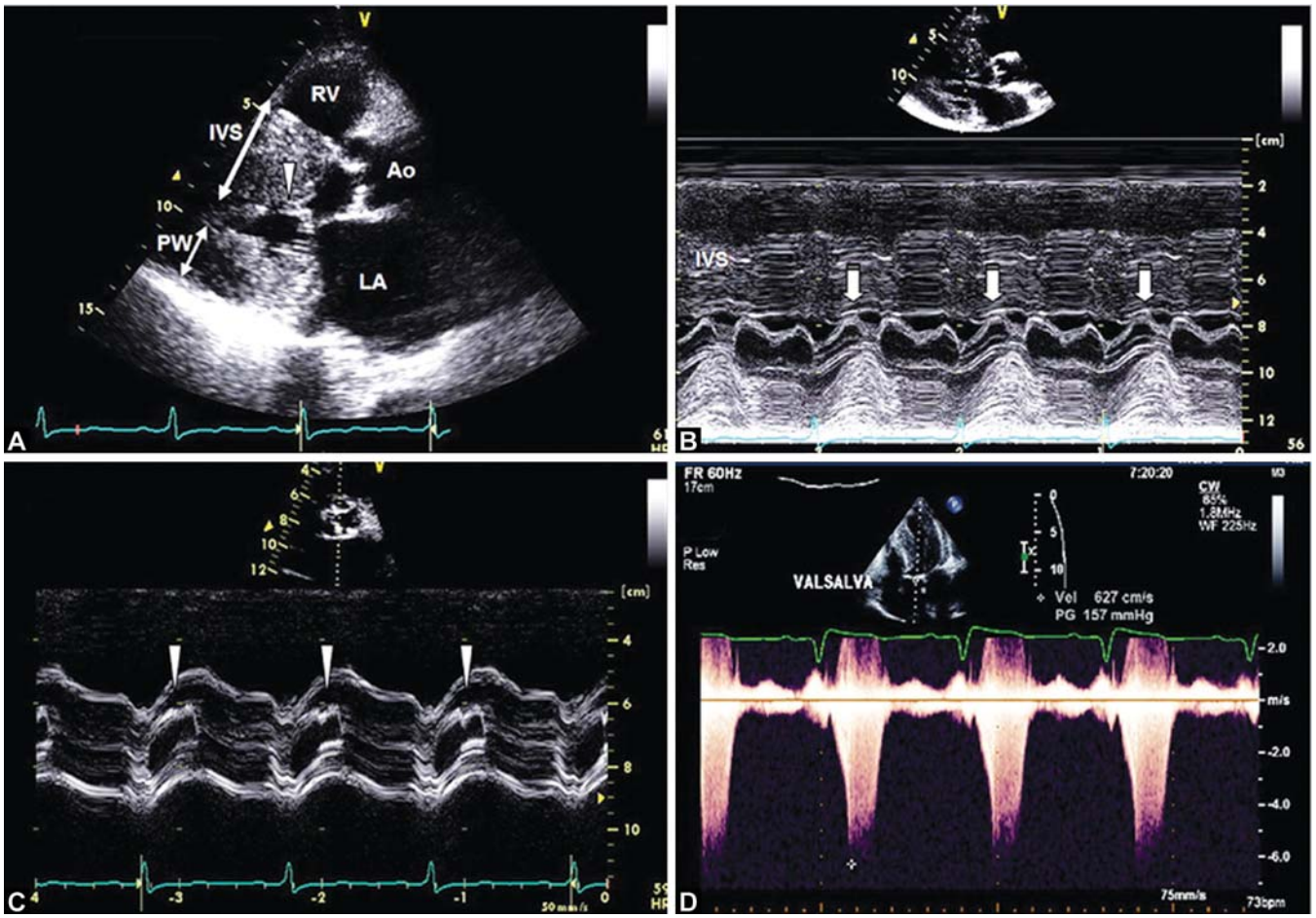
The CSA measurement may introduce error in the area calculation if images are not optimal for the LVOT diameter measurement. However, the Doppler velocity ratio (i.e. $V_{LVOT} \div V_{AV}$) provides an alternative assessment of valve stenosis severity if the CSA cannot be accurately determined. Severe stenosis is present when the ratio is less than or equal to 0.25.[19]

When low LV systolic function accompanies severe aortic stenosis, the transvalvular velocity and gradient may be low due to the low-flow state. Low-flow, low-gradient aortic stenosis generally refers to the presence of: (1) valve area less than 1.0 cm^2; (2) LVEF less than 40% and (3) mean pressure gradient less than 30–40 mm Hg. In cases when the stenosis severity is ambiguous, assessment of changes in gradient and area with increasing flow associated with dobutamine infusion may be helpful. An increase in valve area to a final valve area greater than 1.0 cm^2 suggests that the stenosis is not severe.[20]

Obstruction to LV ejection can occur at several levels: subaortic (LVOT), aortic (valvular) and supravalvular. Hypertrophic cardiomyopathy is characterized by inappropriate hypertrophy, interstitial fibrosis, myocardial disarray and impaired LV performance (Figs 23A to D). Asymmetric LV hypertrophy typically involves the septum, but almost any myocardial segment can be involved. Systolic anterior motion of the anterior mitral leaflet with or without a pressure gradient across the LVOT is related to the hydrodynamic



FIGURES 22A TO C: Calculation of the aortic valve area with the continuity equation includes: (A) an estimate of the left ventricular (LV) outflow tract area calculated from the diameter; (B) the velocity time integral (VTI) obtained across the valve and (C) the VTI in the LV outflow tract. Valve area was calculated as 0.62 cm^2 consistent with severe aortic stenosis



FIGURES 23A TO D: Characteristic echocardiographic features of obstructive hypertrophic cardiomyopathy: (A) parasternal long axis view depicting severe asymmetric septal hypertrophy and systolic anterior mitral valve motion (arrowhead); (B) m-mode across the mitral leaflets depicting prominent systolic anterior motion (thick arrows) of the anterior mitral leaflet; (C) m-mode tracing across the aortic valve demonstrating partial closure of aortic leaflets (arrowheads) and (D) accentuation of late-peaking dynamic left ventricular outflow tract obstruction after the Valsalva maneuver. (Abbreviations: Ao: Aorta; IVS: Interventricular septum; LA: Left atrium; PW: Posterior wall). (*Source:* Afonso LC, Bernel J, Bax JJ, et al. Echocardiography in hypertrophic cardiomyopathy: the role of conventional and emerging technologies. JACC Cardiovasc Imaging. 2008;1:787-800)

forces on the leaflet. The shape of the velocity profile may assist in identifying the level of obstruction as well as the severity. A dynamic LVOT obstruction in patients with hypertrophic cardiomyopathy shows a characteristic late-peaking velocity curve. A resting LVOT obstruction greater than 30 mm Hg is a strong predictor of death and progression to heart failure. In symptomatic patients with a resting gradient less than 30 mm Hg, obstruction may be provoked by amyl nitrite inhalation or the Valsalva maneuver. LV systolic function is typically normal, but diastolic

TABLE 6

Classification of aortic regurgitation severity

	Mild	*Moderate*	*Severe*
Jet width/LVOT width (%) - Color Doppler	< 25	25–64	≥ 65
Jet cross-sectional area/LVOT cross-sectional area (%) - Color Doppler	< 5	5–59	≥ 60
Vena contracta width (cm) - Color Doppler	< 0.3	0.3–0.6	> 0.6
Effective regurgitant orifice area (cm^2) - Color Doppler	< 0.10	0.10–0.29	≥ 0.30
Jet deceleration rate [Pressure half-time (msec)] - Continuous wave Doppler	> 500	500–200	< 200
Diastolic flow reversal in descending aorta - Pulsed wave Doppler	Early diastolic reversal	Intermediate	Prominent holodiastolic reversal

(*Source:* Reference 23)

dysfunction is common and characterized by Doppler echocardiography as impaired relaxation.[22]

AORTIC REGURGITATION

Chronic aortic regurgitation is a condition of combined volume and pressure overload. While the LV may compensate for the increased load, eventually depressed contractility may occur, sometimes while the patient remains asymptomatic. LV dysfunction is initially reversible with recovery after valve replacement but eventually this recovery may not be achievable. Thus echocardiography is useful not only in the assessment of aortic regurgitation etiology and severity but also for LV size and function.[2]

Color Doppler evaluation of aortic regurgitation includes the measurement of the regurgitant jet size, the vena contracta through the orifice, and the flow convergence toward the regurgitant orifice area[23] (Table 6). The proximal regurgitant jet width or CSA is measured in the LVOT, within 1 cm of the valve, usually from the parasternal view and then compared to the 2D echocardiographic measurement of LV outflow diameter or CSA. The vena contracta is measured as the width of diastolic flow at the AV. The flow convergence or proximal isovelocity surface area (PISA) method is discussed in detail in the section on mitral regurgitation (MR) since there is relatively less experience with the method in aortic regurgitation compared to MR.[23]

Continuous and pulsed wave Doppler methods for quantitation of aortic regurgitation are based on velocity measurements from systolic and diastolic velocity profiles. The rate of deceleration of the diastolic regurgitant jet (i.e. deceleration slope) reflects the equalization of pressures between the aorta and the left ventricle. As aortic regurgitation severity increases, the deceleration slope increases. In severe aortic regurgitation, the deceleration pressure half-time (i.e. the time required to decrease the diastolic pressure gradient between the aorta and the LV by one half) is under 200 msec. Reversal of aortic flow in the descending aorta suggests at least moderate regurgitation (Fig. 24, Video 2).[23]

Quantitation of forward and total SV can be determined flow by pulsed Doppler methods. In addition, total SV can be determined from quantitation of LV volumes by 2D echocardiography. However, these methods are for the most part limited to research.[23]

Transesophageal echocardiography (TEE) provides an alternative to evaluation of aortic regurgitation and is described in chapter "Transesophageal Echocardiography".

MITRAL STENOSIS

The principle cause of mitral stenosis is rheumatic heart disease and despite a decrease in the prevalence of rheumatic fever, mitral stenosis remains a significant problem, particularly due to immigration from developing countries. The evaluation of mitral stenosis with echocardiography is directed at determining severity of stenosis and suitability for balloon valvuloplasty.[24]

Direct measurement of the valve area is possible by tracing the valve orifice area from the parasternal short axis view (Figs 25A to D). However careful attention to gain settings is needed since excessive setting may lead to underestimation of area. In addition, scanning should be performed from the apex to base of the LV to assure that the area is measured at the level of the leaflet tips (i.e. the smallest measurable orifice).[20,24]

The estimation of the diastolic pressure gradient across the mitral valve in mitral stenosis uses the modified Bernoulli equation ($\Delta P = 4v^2$). For accurate measurement, the Doppler ultrasound beam must be oriented parallel to flow, so the apical 4-chamber view is preferred for imaging. Doppler ultrasound provides an alternative method to direct planimetry for assessing valve area. The decline in velocity of diastolic transmitral blood flow is inversely proportional to valve area according to the formula:

$$\text{Mitral valve area} = 220/T_{1/2}$$

where $T_{1/2}$ is the time (in msec) between the maximum mitral gradient in early diastole and the point at which the gradient is half the maximum initial value. $T_{1/2}$ can be measured directly from the velocity profile as the time from maximum velocity to the velocity corresponding to maximum velocity $\div \sqrt{2}$. In the valve area equation, 220 is an empirically derived constant (Fig. 26, Videos 3 and 4).[20]

Recommendations for classification of mitral stenosis severity (Table 7) are based on Doppler assessment of the mitral

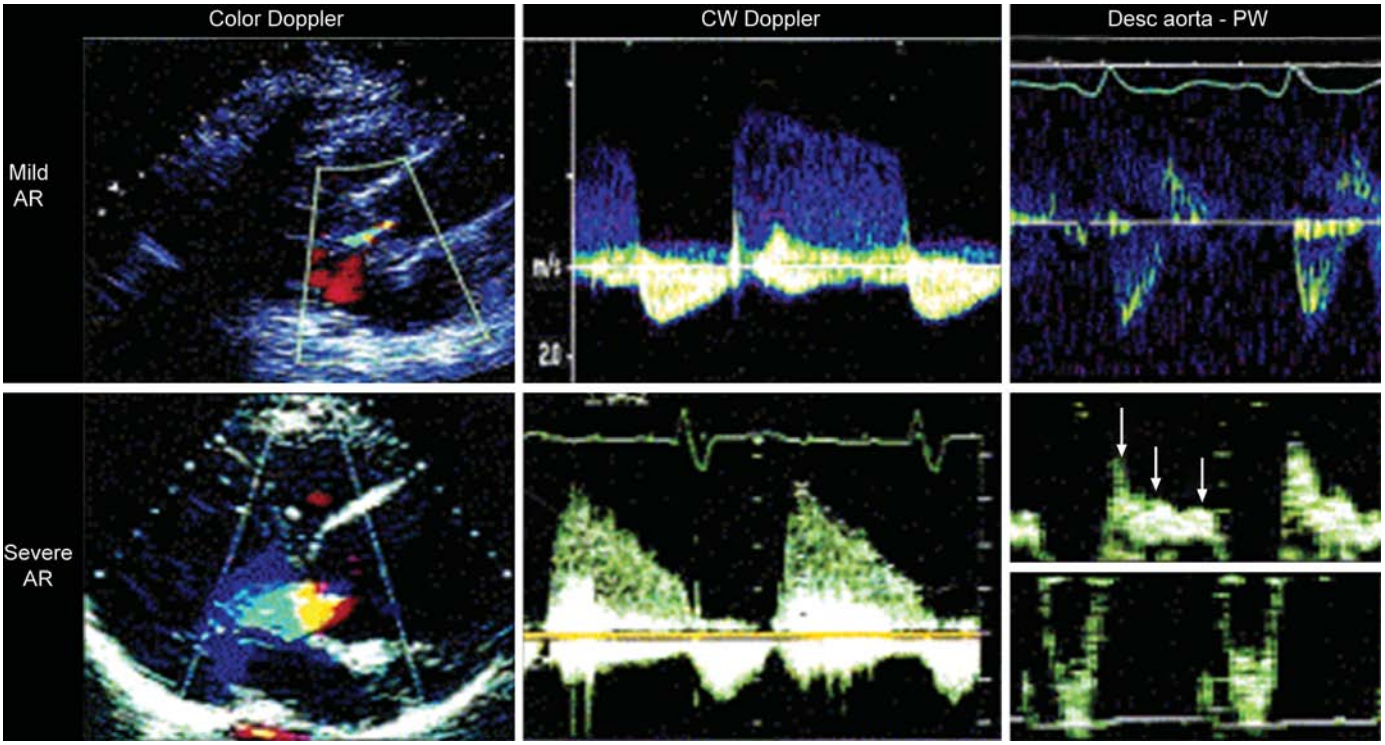
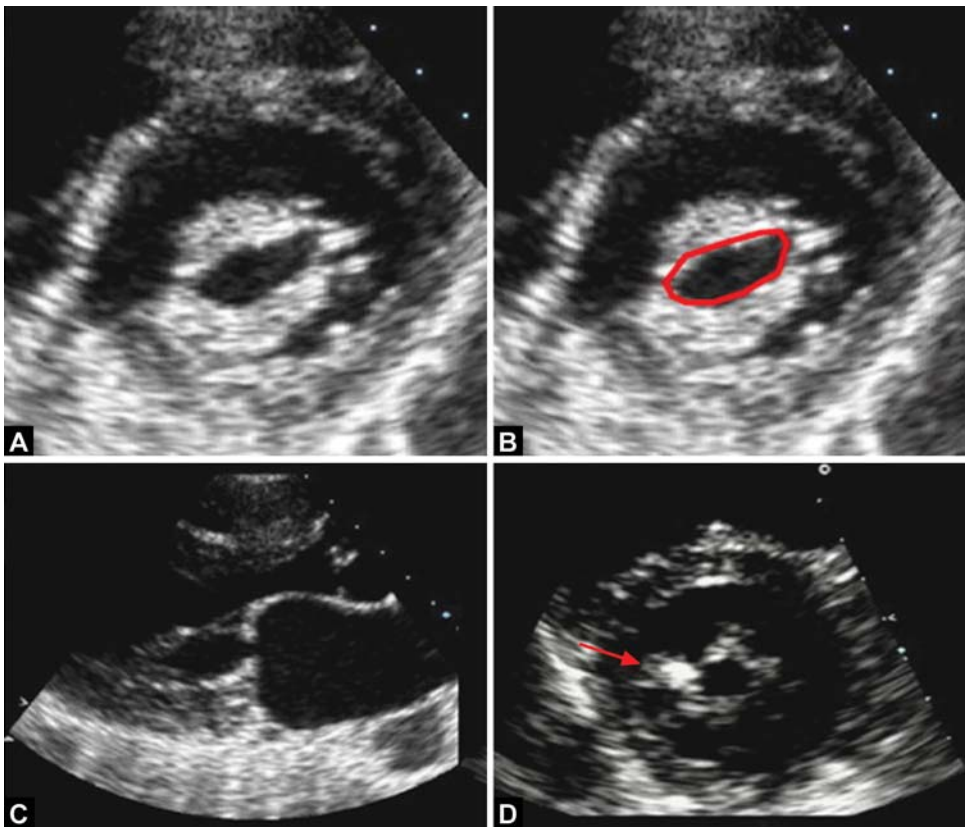


FIGURE 24: Color Doppler and continuous wave (CW) Doppler recordings of the regurgitant jet as well as pulsed wave (PW) Doppler recording of flow in the descending thoracic aorta in examples of mild and severe aortic regurgitation (AR). Compared to mild AR, severe AR has a larger jet width in the left ventricular outflow, a steep deceleration rate of the AR velocity by CW Doppler and a holo-diastolic flow reversal in the descending (desc) aorta (arrows). (*Source:* Zoghbi WA, Enriguez-Sarano M, Foster E, et al. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. J Am Soc Echocardiogr. 2003;16:777-802)



FIGURES 25A TO D: Examples of abnormal mitral valve anatomy. (A) Thickened valve leaflets without calcification. (B) Planimetry of mitral valve area in parasternal short axis view. (C) Rheumatic mitral valve in parasternal long axis view demonstrating "doming" of the anterior leaflet and failure of the mitral commissures to separate (i.e. commissural fusion). (D) Calcification localized at the level of the medial commissures (small red arrow). (*Source:* Messika-Zeitoun D, Lung B, Brochet E, et al. Evaluation of mitral stenosis in 2008. Arch Cardiovasc Dis. 2008;101:653-63)

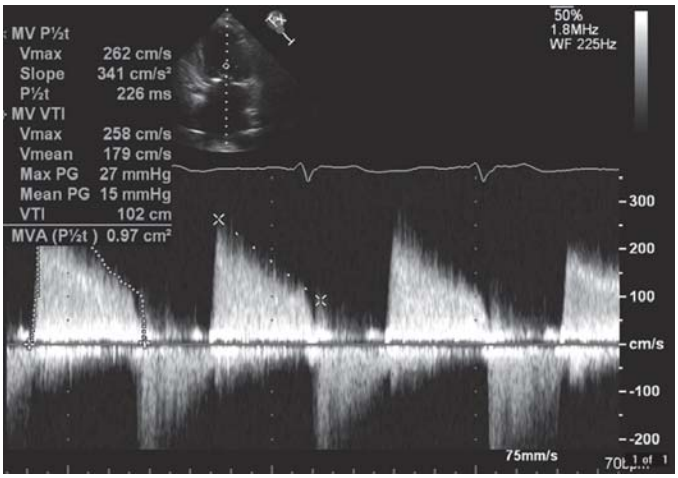


FIGURE 26: Continuous wave Doppler demonstrating severe mitral stenosis. The pressure half-time ($P_{1/2}t$) is 226 ms, predicting a valve area of 0.97 cm^2

TABLE 7

Classification of mitral stenosis severity

	Mild	*Moderate*	*Severe*
Valve area (cm^2)	> 1.5	1.0–1.5	< 1.0
Mean gradient (mm Hg)	< 5	5–10	> 10
Pulmonary artery systolic pressure (mm Hg)	< 30	30–50	> 50

(*Source:* Reference 20)

stenosis as well as secondary findings of pulmonary hypertension severity.

Percutaneous mitral balloon valvulotomy is effective treatment for patients with symptomatic moderate or severe mitral stenosis and favorable valve morphology, in the absence of LA thrombus or moderate to severe MR. Patients with valvular calcification, thickened fibrotic leaflets with decreased mobility and subvalvular fusion have a higher incidence of acute complications and a higher rate of recurrent stenosis on follow-up.[2]

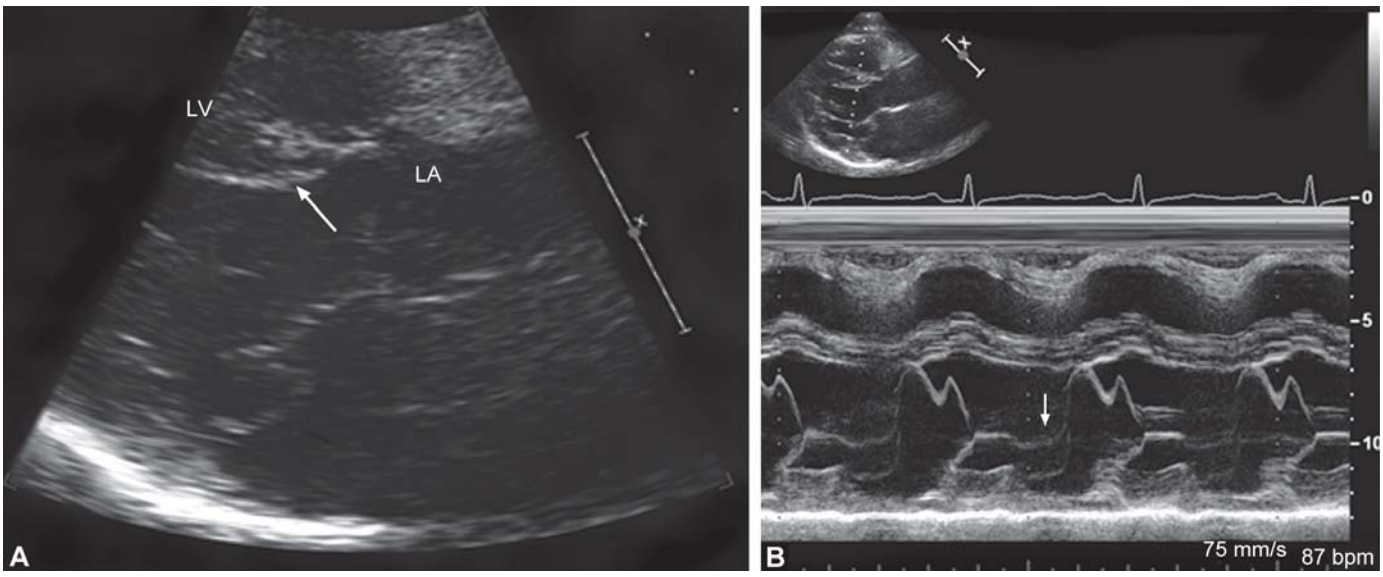
MITRAL REGURGITATION

An initial comprehensive TTE in a patient with suspected MR provides a baseline assessment left-sided chamber size and LVEF. In addition, TTE provides an approximation of MR severity, anatomic information regarding mechanism and PA pressure. Changes from baseline values are useful in guiding the timing of mitral valve surgery.[2]

The echocardiographic exam of the mitral valve begins with a 2D echo evaluation since the etiology of regurgitation may be visualized. Examples include underlying mitral valve prolapse[25] (Figs 27A and B, Video 5) and annular dilatation due to LV enlargement. The natural history of mitral valve prolapse is variable and the most frequent predictor of cardiovascular mortality is MR severity.[2] With chronic MR, enlargement of the LA and LV are common. Pulsed wave, continuous wave and color Doppler evaluation complement 2D echocardiography in the evaluation of MR (Table 8).[23]

Color flow Doppler evaluation includes visualization of the origin of the regurgitant jet and its width (i.e. the vena contracta), as well as spatial orientation in the left atrium. Visualization of the regurgitant jet area in the receiving chamber can provide screening for the presence and direction of the regurgitant jet as well as a semiquantitative assessment of severity. Jet area measurements are influenced by technical factors such as transducer frequency, gain settings, output power and Nyquist limit [i.e. aliasing velocity (Va)]. Planimetry of the jet area in the LA provides a quantitative parameter for assessing MR, but the jet area may underestimate severity if regurgitation is eccentric (Figs 28A to C, Videos 6 and 7).[23]

The vena contracta is the narrowest portion of a jet that occurs at or just downstream from the orifice and represents a



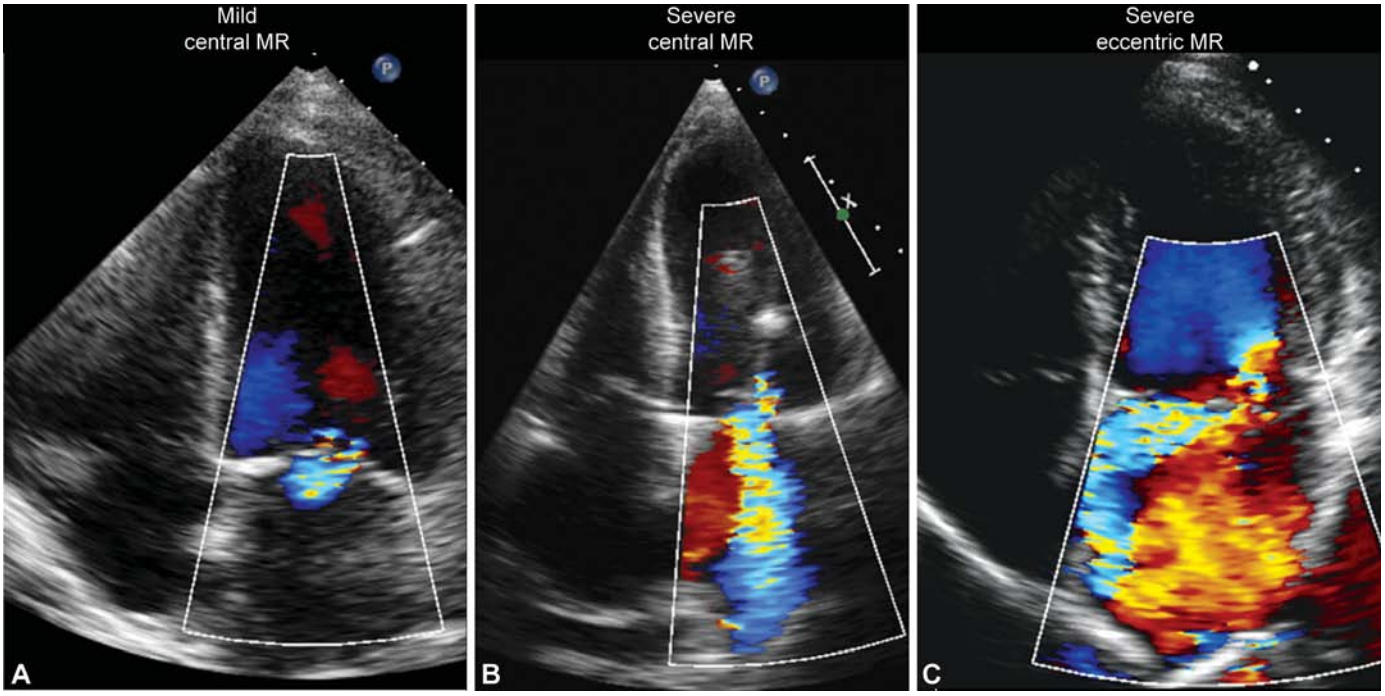
FIGURES 27A AND B: Parasternal long axis view 2D (A) and m-mode (B) echocardiograms demonstrating prolapse of the mitral valve posterior leaflet (arrow). (Abbreviations: LA: Left atrium; LV: Left ventricle)

TABLE 8

Classification of mitral regurgitation severity

	Mild	*Moderate*	*Severe*
Jet area - Color Doppler	< 4 cm^2 or < 20% of LA area	Variable	> 10 cm^2 or > 40% of LA area
Vena contracta width (cm) - Color Doppler	< 0.3	0.3–0.69	≥ 0.7
EROA (cm^2) - Color Doppler	< 0.20	0.20–0.39	≥ 0.40
Mitral inflow - Pulsed Doppler	A wave dominant	Variable	E wave dominant (usually ≥ 1.2 m/sec)
Mitral jet contour - Continuous wave	Parabolic	Usually parabolic	Early peaking
Mitral jet density - Continuous wave	Incomplete or faint	Dense	Dense
Pulmonary vein flow	Systolic dominance	Systolic blunting	Systolic flow reversal

(*Source:* Reference 23)



FIGURES 28A TO C: Examples of color flow recordings of different mitral regurgitation (MR) lesions from the apical window. (A) The case of mild regurgitation has a small regurgitant jet area, in contrast to that of severe central MR (B), which shows a larger regurgitant jet area. (C) Example with severe eccentric MR has a jet area impinging on the wall of the left atrium

measure of the effective regurgitant orifice area. The size of the vena contracta is independent of flow rate and driving force.[23]

Flow convergence into the regurgitant orifice area is a useful indicator of regurgitation severity. The PISA or flow convergence method is derived from the principle that blood velocity increases at a regurgitant orifice area as hemispheric shells of increasing velocity and decreasing surface area. The Va is determined by setting the Nyquist limit to visualize the hemisphere. The flow rate through the orifice area is the product of the hemisphere surface area (2 πr^2) and Va. The effective regurgitant orifice area is then calculated using the flow rate and the peak regurgitant velocity (i.e. effective regurgitant orifice area = flow rate/peak regurgitant velocity) (Fig. 29)[23,26]

Continuous wave Doppler signal of the regurgitant jet measures maximum velocity which does not provide quantitation of jet severity. However, the contour of the profile and its density are useful. Pulsed Doppler evaluation of the mitral inflow velocity at the mitral leaflet tips provides measurement of the early and late filling velocities. As regurgitation severity increases there is loss of relative contribution of atrial filling and an increase in early filling. Pulmonary vein flow into the LA demonstrates a progressive decrease in systolic velocity with increasing severity of MR, and reversal of flow in the presence of severe MR (Figs 30A and B).[23]

Estimates of regurgitant volume and fraction are possible with pulsed Doppler assessment of volumetric flow and 2D echocardiographic measurement of LV volumes for SV; however, these parameters have limited general clinical application due to the time constraints of these measurements.

Transesophageal echocardiography (TEE) provides improved visualization of the mitral valve and quantitation of regurgitation and is discussed in chapter "Transesophageal Echocardiography".

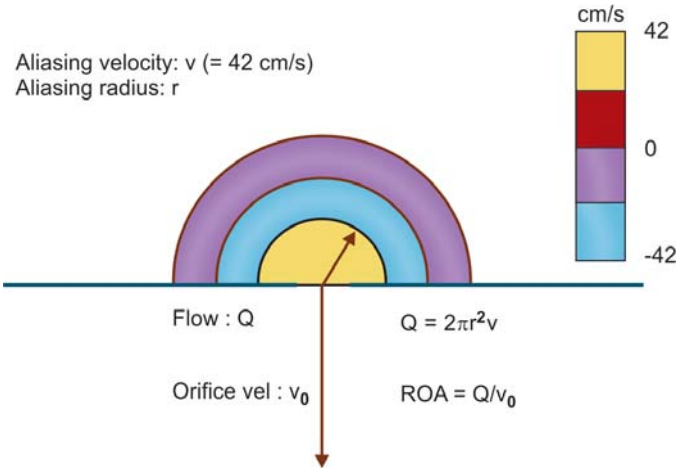
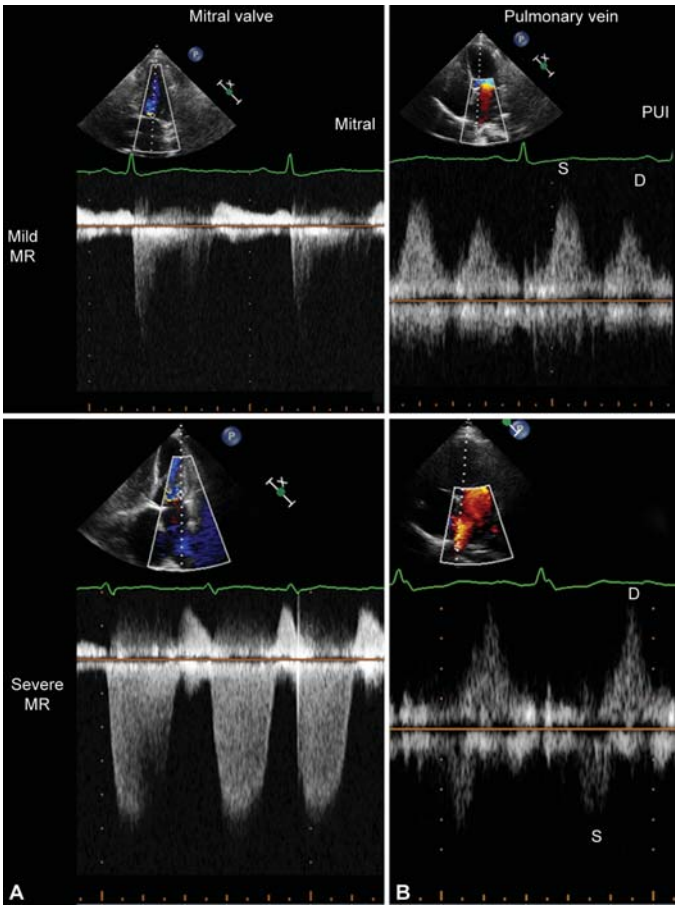


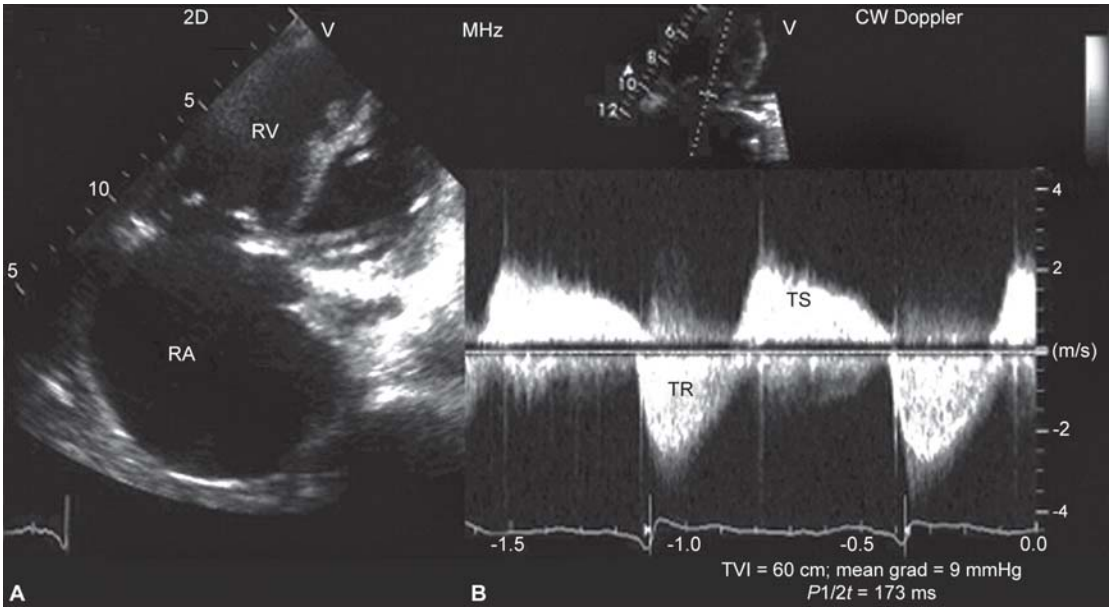
FIGURE 29: The proximal convergence method. By using the aliasing velocity of the color Doppler display, it is possible to measure the radius to an isovelocity shell as blood converges on the regurgitant orifice. Assuming a hemispheric shape to the shell, flow rate is given as $Q = 2\pi r^2 v$. Dividing this flow rate by the maximal velocity through the orifice (given by continuous wave Doppler) yields an estimation for the regurgitant orifice area (ROA). (*Source:* Modified from Thomas JD. Doppler echocardiographic assessment of valvar regurgitation. Heart. 2002;88:651-7, with permission)

TRICUSPID STENOSIS

Isolated tricuspid stenosis is uncommon and the same principles as for mitral stenosis apply. However, an empiric constant of 190 has been proposed and the mean gradient in significant tricuspid stenosis is lower than for mitral stenosis. Hemodynamically significant stenosis is defined as: a mean pressure gradient greater than 5 mm Hg, and $T_{1/2}$ greater than 190 msec (corresponding to a valve area less than 1.0 cm^2 and assuming an empiric constant of 190). Additional supportive findings on 2D echocardiography include enlargement of the RA and dilatation of the inferior vena cava (Figs 31A and B).[20]



FIGURES 30A AND B: Mitral valve continuous wave Doppler and pulmonary vein flow pulsed Doppler recordings in mild and severe mitral regurgitation (MR). In mild MR (A), continuous wave Doppler has a soft density with a parabolic, rounded contour of the regurgitant velocity whereas in severe MR (B), the jet is dense with a triangular, early peaking of the velocity. Pulmonary vein flow is normal in mild MR with predominance of systolic flow (S). In contrast, with severe MR systolic flow reversal may occur. (Abbreviation: D: Diastolic flow velocity)



FIGURES 31A AND B: (A) 2D echocardiographic image of a stenotic tricuspid valve obtained in a modified apical 4-chamber view during diastole. Note the thickening and diastolic doming of the valve and the marked enlargement of the right atrium (RA). (B) Continuous wave (CW) Doppler recording through the tricuspid valve. Note the elevated peak diastolic velocity of 2 m/s and the systolic tricuspid regurgitation (TR) recording. The diastolic time-velocity integral (TVI), mean gradient (Grad) and pressure half-time ($T_{1/2}$) values are listed. (*Source:* Baumgartner H, Hung J, Bermejo J, et al. Echocardiographic assessment of valve stenosis: EAE/ASE recommendations for clinical practice. J Am Soc Echocardiogr. 2009;22:1-23)

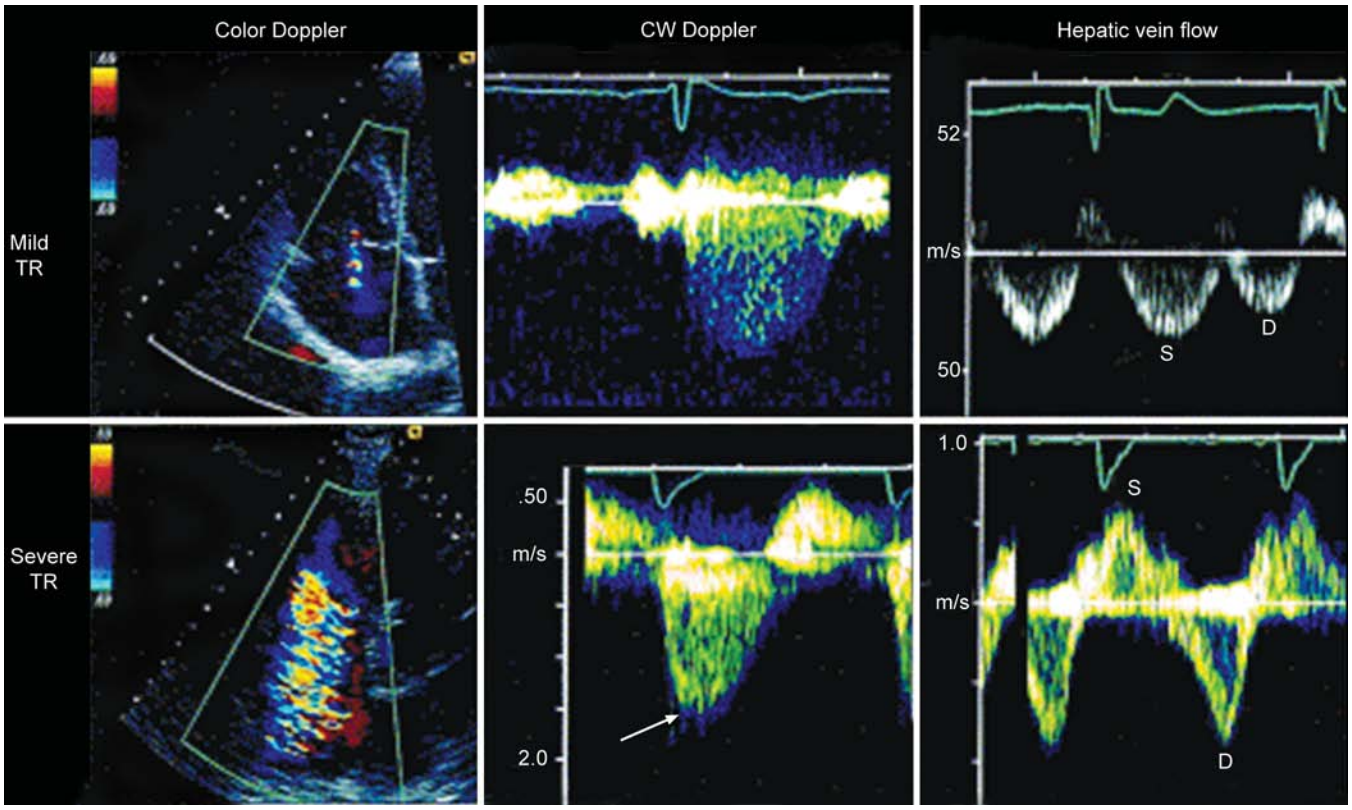


FIGURE 32: Examples of jet recordings by color Doppler, continuous wave (CW) Doppler, and hepatic vein flow by pulsed Doppler in mild and severe tricuspid regurgitation (TR). The case of mild TR shows a small central color jet with minimal flow convergence in contrast to the severe TR with a very large flow convergence and jet area in the right atrium. CW Doppler recording shows a parabolic spectral display in mild TR whereas in severe TR, early peaking and triangular shape of the velocity is seen (arrow). Hepatic vein flow pattern in mild TR is normal whereas in severe TR, hepatic venous flow reversal in systole (S) is seen. (Abbreviation: D: Diastolic hepatic venous flow). (*Source:* Zoghbi WA, Enriguez-Sarano M, Foster E, et al. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. J Am Soc Echocardiogr. 2003;16(7):777-802)

TABLE 9

Classification of tricuspid regurgitation severity

	Mild	*Moderate*	*Severe*
Jet area (cm^2) - Color Doppler	< 5	5–10	> 10
Vena contracta width (cm) - Color Doppler		< 0.7	> 0.7
PISA radius (cm) - Color Doppler	≤ 0.5	0.6–0.9	> 0.9
Tricuspid jet density - Continuous wave Doppler	Faint	Dense	Dense
Tricuspid jet contour - Continuous wave Doppler	Parabolic	Variable	Early peaking
Hepatic vein flow - Pulsed wave Doppler	Systolic dominance	Systolic blunting	Systolic flow reversal

(*Source:* Reference 23)

TRICUSPID REGURGITATION

Similar to MR, tricuspid regurgitation is assessed by integrating information on right-sided chamber size, septal motion and Doppler parameters (Fig. 32, Table 9). Significant tricuspid regurgitation is often associated with RA and RV enlargement and in the presence of significant volume overload of the RV, there may be paradoxical septal motion. Right atrial (RA) pressure estimation can be appreciated by the size and respiratory variation of the inferior vena cava.[23]

Color Doppler methods for assessing severity include measuring jet area, the vena contracta and the effective regurgitant orifice area using methods described above for MR. Continuous wave Doppler methods are also similar to those described for MR and include signal intensity and the contour of the velocity curve. Pulsed Doppler can measure the RV filling velocities and with severe tricuspid regurgitation, early filling velocities are elevated and can be greater than 1.0 m/sec. The hepatic vein velocity profile, in similar fashion to the pulmonary vein velocity profile in significant MR, demonstrates blunting of the normally dominant systolic wave with increasing regurgitation systolic flow reversal with severe regurgitation.[23]

PULMONIC STENOSIS

Isolated pulmonic stenosis is usually congenital in origin. In addition to valvular lesions, congenital subvalvular and supravalvular location of stenosis are possible and may be difficult to differentiate from valvular stenosis. The severity of stenosis is determined by the pressure gradient as calculated from the modified Bernoulli equation. The grading of severity based on peak pressure gradient is: mild [< 36 mm Hg (corresponding to peak velocity < 3 m/sec)]; moderate [36–64 mm Hg (or a peak velocity of 3–4 m/sec)] and severe [> 64 mm Hg (or a peak velocity of > 4 m/sec)].[20] Evaluation of the valve's

anatomy with 2D echo may provide additional information. For example, a domed shape of the leaflets suggests stenosis due to fusion of the leaflets.[2] In addition, RV hypertrophy and enlargement as well as RA enlargement may be present if there is significant pressure overload of these chambers.[20]

PULMONIC REGURGITATION

Mild pulmonic regurgitation may be present in normal subjects; however, significant regurgitation suggests the presence of underlying structural heart disease. In the adult, acquired pulmonic regurgitation is most often seen in patients with PH and related to dilation of the PA and/or RV, but is rarely severe. Pulmonic regurgitation of severe nature is usually observed in patients with anatomic abnormalities of the pulmonic valve or after valvotomy.[23]

Color Doppler flow mapping is the most widely used method for detection and regurgitation. The jet or vena contracta widths are common measurements in the assessment of regurgitation severity.[8] As severity of regurgitation increases, continuous wave Doppler demonstrates a rapid deceleration of diastolic flow as diastolic pressure in PA and RV equalize.[23]

INFECTIVE ENDOCARDITIS

Echocardiography is central to the diagnosis and management of patients with infective endocarditis. Transesophageal echocardiography (TTE) is an appropriate test for the detection of valvular vegetation, with or without positive blood cultures for the diagnosis of infective endocarditis (Fig. 33), although TEE is considered more sensitive than TTE in detecting vegetations. In addition, TTE can characterize the hemodynamic severity of valvular lesions and potential complications of endocarditis (e.g. abscess, valve perforation, shunt). Transesophageal echocardiography is also recommended for reassessment of high-risk patients (e.g. those with a virulent organism, clinical deterioration, persistent or recurrent fever, new murmur or persistent bacteremia).[2]

Echocardiographic evidence of endocardial involvement is considered the major criteria for the diagnosis of infective endocarditis according to the modified von Reyn criteria. Positive echocardiographic evidence of infective endocarditis is defined as an "oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation; or abscess; or new partial dehiscence of prosthetic valve; or new valvular regurgitation".[27] Transesophageal echocardiography has a sensitivity of 60–65% and specificity of 94–96% in the detection of vegetations. In contrast, improved sensitivity of 85–98% is reported for TEE. False negative TTE studies are more frequent with small vegetations, presence of prosthetic material or technically deficient studies.[28]

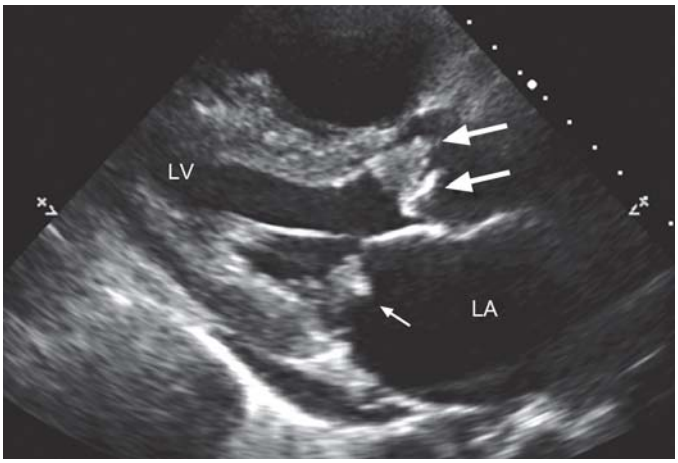


FIGURE 33: Parasternal long axis view of transthoracic echo showing large vegetations on the aortic valve (large arrows) and on the mitral valve (small arrow). (Abbreviations: LA: Left atrium; LV: Left ventricle)

Current recommendations for the use of TEE in patients with endocarditis include: (1) symptomatic patients with infective endocarditis if TTE is nondiagnostic (to assess hemodynamic severity of a valve lesion); (2) patients with valvular heart disease and positive blood culture if TTE is nondiagnostic; (3) patients with possible complications of infective endocarditis and (4) patients with suspected prosthetic valve endocarditis.[2] The role of TEE in the evaluation of endocarditis is discussed further in chapter "Transesophageal Echocardiography".

Echocardiographic features that suggest potential need for surgical intervention include: perivalvular extension with abscess formation, valve perforation, acute valve regurgitation and increasing vegetation size despite appropriate antibiotic therapy.[27,29] A vegetation size greater than 10 mm is associated with increased embolic risk and this risk appears higher in patients with mitral valve endocarditis.[2]

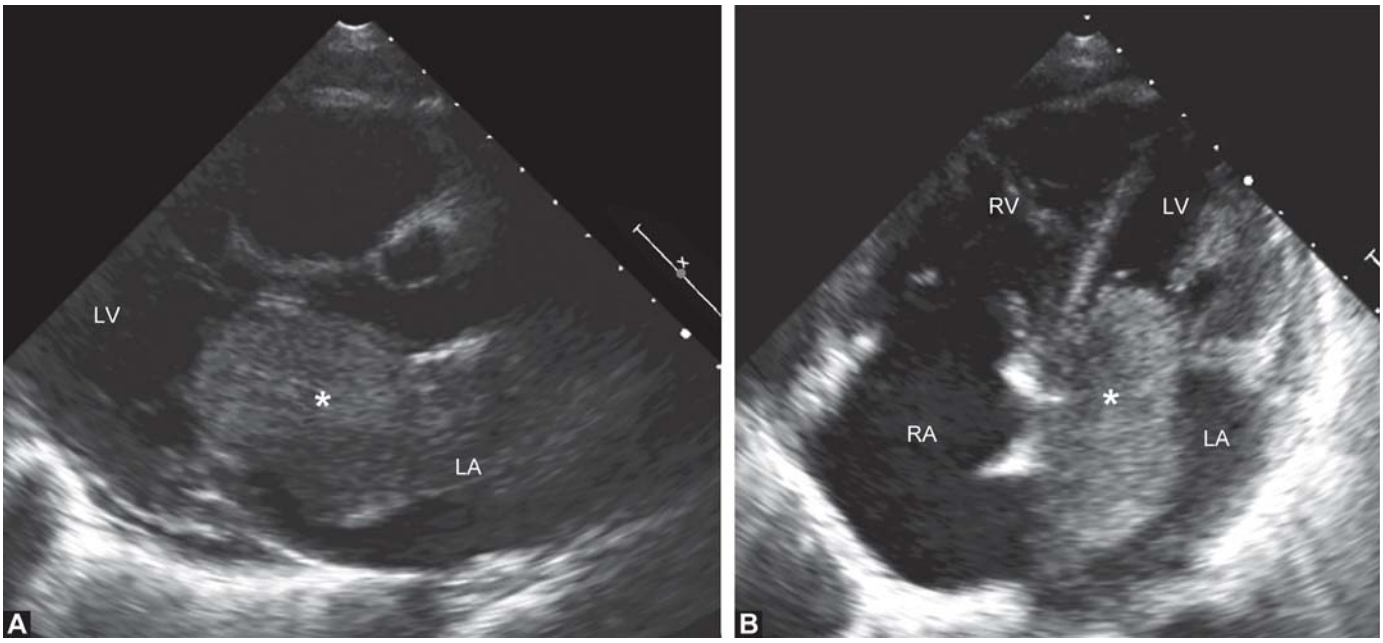
INTRACARDIAC MASSES

Abnormal intracardiac masses are typically echodensities that represent thrombus or tumor. However, there are normal variants that can be confused with mass lesions. For example, prominent papillary muscles, dense mitral annular calcification, a prominent moderator band in the RV, a prominent Chiari network in the RA and lipomatous hypertrophy of the interatrial septum can mimic abnormal pathology.[30]

Primary tumors are uncommon and about 75% are benign, usually representing myxoma in the adult and rhabdomyoma in children under 15 years. About 75–90% of myxomas are found in the LA, pedunculated and attached to the interatrial septum, in or adjacent to the fossa ovalis (Figs 34A and B). The remainder occurs in the RA, or infrequently in the ventricles. About one-fourth of primary cardiac tumors are malignant and the majority are sarcomas. Angiosarcoma is the most common sarcoma and has a propensity to occur on the right side of the heart, especially in the RA. Rhabdomyosarcoma can occur in any cardiac chamber, grow rapidly and have usually invaded the pericardium by the time of diagnosis. Leiomyosarcomas are very rare and are usually found in the LA.[30,31]

Metastatic tumors are up to 40 times more common than primary tumors, and are typically encountered in patients with widespread systemic tumor dissemination. Metastatic tumors are most commonly lung, breast, ovarian, kidney, leukemia, lymphoma and esophageal. However malignant melanoma appears to have a preference for metastasizing to the heart, with metastases occurring in up to 50% of patients.[30,32] Metastases to the pericardium are more common than to the myocardium.[30]

In patients presenting with unexplained stroke, attention is usually directed at identifying clinically inapparent sources of



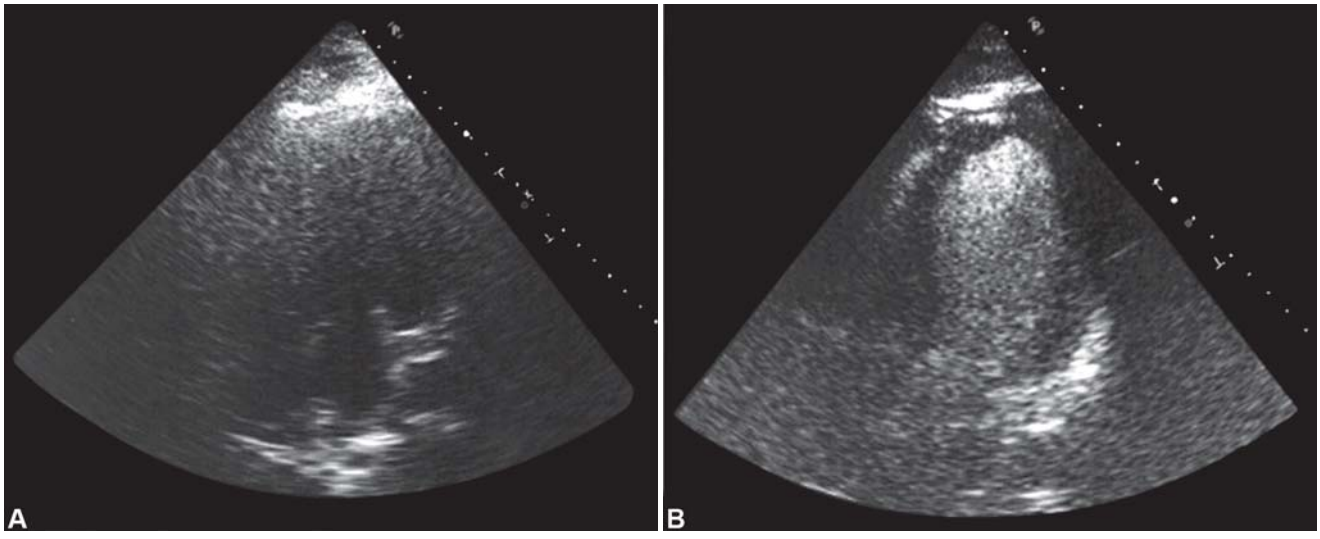
FIGURES 34A AND B: Transthoracic parasternal long axis (A) and apical 4-chamber (B) views demonstrating left atrial myxoma (asterisk). (Abbreviations: LV: Left ventricle; RV: Right ventricle; LA: Left atrium; RA: Right atrium)

embolism. Transesophageal echocardiography can usually exclude some of the high-risk abnormalities (e.g. LV akinesis/dyskinesis, dilated cardiomyopathy, LV thrombus and mitral stenosis). However, TEE is superior to TTE in the detection of LA thrombus, complex thoracic aorta atheromas, valve vegetations, interatrial septal aneurysm and small tumors.[33]

CONTRAST ECHOCARDIOGRAPHY

Echo contrast agents used in contrast echocardiography include agitated saline for the assessment of right-to-left intracardiac shunts and manufactured microbubbles with shell composition of lipid, human albumin or phospholipid and gas (e.g. air, perfluoropropane, sulfur hexafluoride, etc.). The manufactured microbubbles are very small (i.e. < 5 μ in diameter), able to traverse the pulmonary circulation and then opacify the left heart chambers.[34]

In the presence of a patent foramen ovale, there may be only intermittent right-to-left shunting of the microbubbles produced by IV injection of agitated saline since the flap of the patent foramen ovale may be functionally closed during part of the respiratory cycle, when LA pressure exceeds RA pressure. A cough or Valsalva maneuver release may be needed to provoke a transient increase in RA pressure relative to LA pressure and allow the flap of the foramen to open and allow microbubble passage from the RA to the LA. However late appearance (i.e. more than three cycles after appearance in the RA) of microbubbles into the LA may be related to transpulmonary passage of the microbubbles. When a right-to-left shunt is seen by saline contrast, the distinction between a patent foramen ovale and an atrial septal defect can be made by assessing the size of the RA and the RV, which are usually enlarged due to an atrial septal defect, but normal when a



FIGURES 35A AND B: Contrast opacification of the left ventricular cavity. (A) Apical 4-chamber views with poor endocardial definition. (B) The same view with improved endocardial definition after echocardiographic contrast administration. (*Source:* Echocardiography in heart failure: application, utility, and new horizons. J Am Coll Cardiol. 2007;50:381-96r)

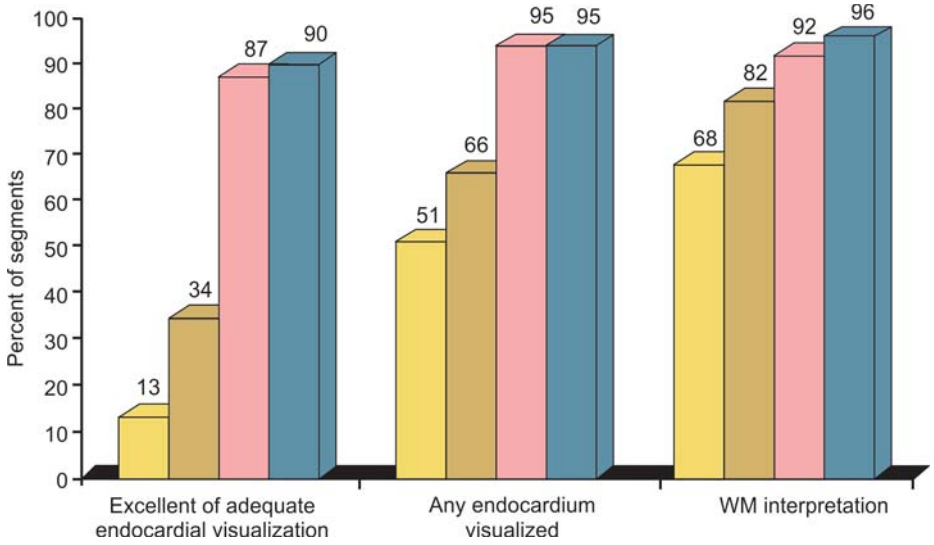
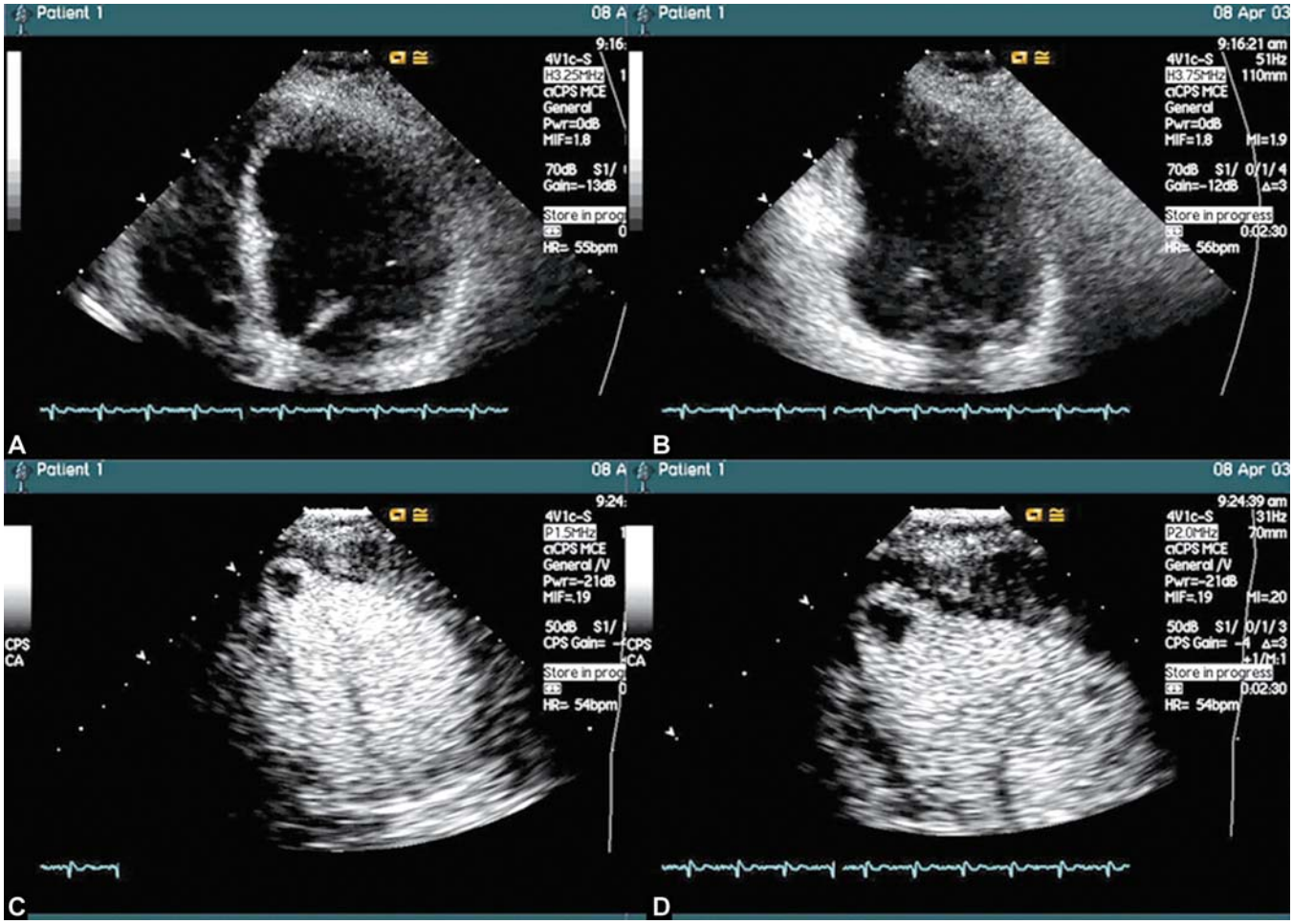


FIGURE 36: Percent of segments visualized and interpreted for wall motion (WM) using fundamental imaging (open bars), harmonics (dotted bars) and contrast echo (slashed bars) with harmonics from the transthoracic approach and with TEE (filled bars). (*Source:* Modified from Yong Y, Wu D, Fernandes V, et al. Diagnostic accuracy and cost-effectiveness of contrast echocardiography on evaluation of cardiac function in technically very difficult patients in the intensive care unit. Am J Cardiol. 2002;89:711-8, with permission)



FIGURES 37A TO D: Apical 4- and 2-chamber views in a patient post stroke (A and B). With contrast, an apical thrombus is visualized as a contrast defect in the cavity (C) 2-chamber view, (D) Zoomed apex). (*Source:* Kirkpatrick JN, Vannan MA, Narula J, et al. Echocardiography in heart failure: application, utility, and new horizons. J Am Coll Cardiol. 2007;50:381-96)

patent foramen ovale is present. Contrast echo is also useful in the detection of a residual shunt after device closure of an atrial septal defect.[35]

Manufactured contrast agents may be useful in improving the accuracy and reproducibility of the assessment of LV structure and function at rest and during stress. Suboptimal echocardiograms can be converted to diagnostic examinations in 75–90% of patients due to improved endocardial definition (Figs 35A and B). This is especially helpful in patients who are obese, have lung disease or are on ventilators (Fig. 36).[36-38]

Echocardiographic contrast agents may be particularly useful in improving the visualization of the apex. In addition, apical thrombi may be difficult to visualize in non-contrast images due to the uncertainty of proper beam orientation and

potential shortening of the major length of the left ventricle due to poor endocardial definition of the apex (Figs 37A to D).

Patients with pulmonary hypertension or unstable cardiopulmonary conditions should be monitored for 30 minutes after contrast agents administration. In addition, these products should not be administered to patients with right-to-left, bidirectional or transient right-to-left cardiac shunts; hypersensitivity to perfluorocarbon; or hypersensitivity to blood, blood products or albumin (which applies to those agents with an albumin shell).[36]

Finally, there is experimental work in the assessment of myocardial perfusion using contrast agents. The initial studies demonstrated definition of risk area during acute coronary occlusion and progressed to evaluation of the success of tissue reperfusion and residual infarct size. More recent studies have shown the ability of myocardial contrast echocardiography to detect coronary stenosis during stress. However the application of myocardial contrast echocardiography as a clinical tool awaits approval of the contrast agents for this indication.[34]

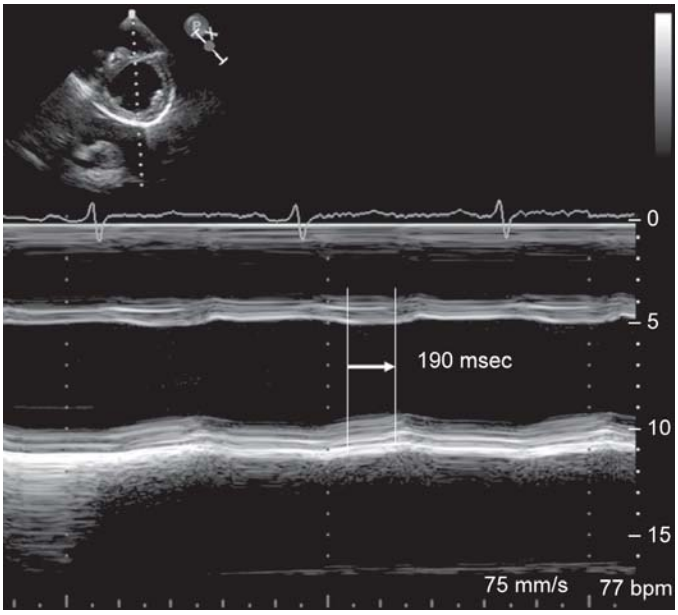


FIGURE 38: M-mode echocardiogram at midventricular level of left ventricle (LV) demonstrating septal to posterior wall delay of 190 msec, consistent with significant dyssynchrony

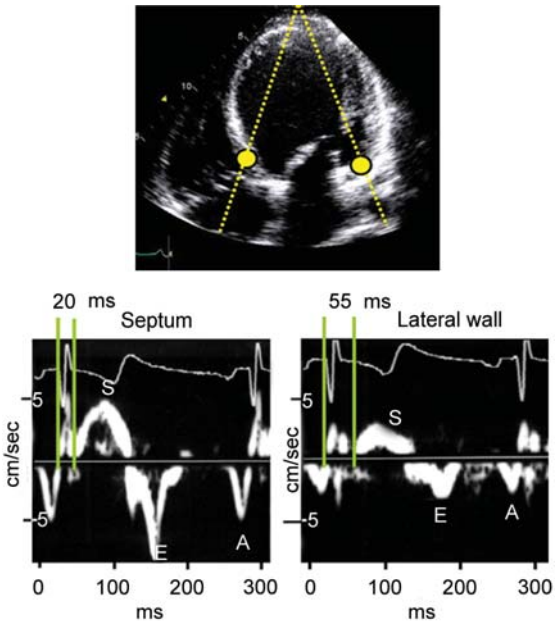


FIGURE 39: Pulsed tissue Doppler demonstrating dyssynchrony with delayed time to onset of systolic velocity in lateral wall, as compared with septum in a patient with left bundle branch block before resynchronization therapy. (Abbreviations: S: Systolic velocity; E: Early filling velocity; A: Atrial filling velocity). (*Source:* Gorcsan J 3rd, Abraham T, Agler DA, et al. Echocardiography for cardiac resynchronization therapy: recommendations for performance and reporting—a report from the American Society of Echocardiography dyssynchrony writing group. J Am Soc Echocardiogr. 2008;21:191-213)

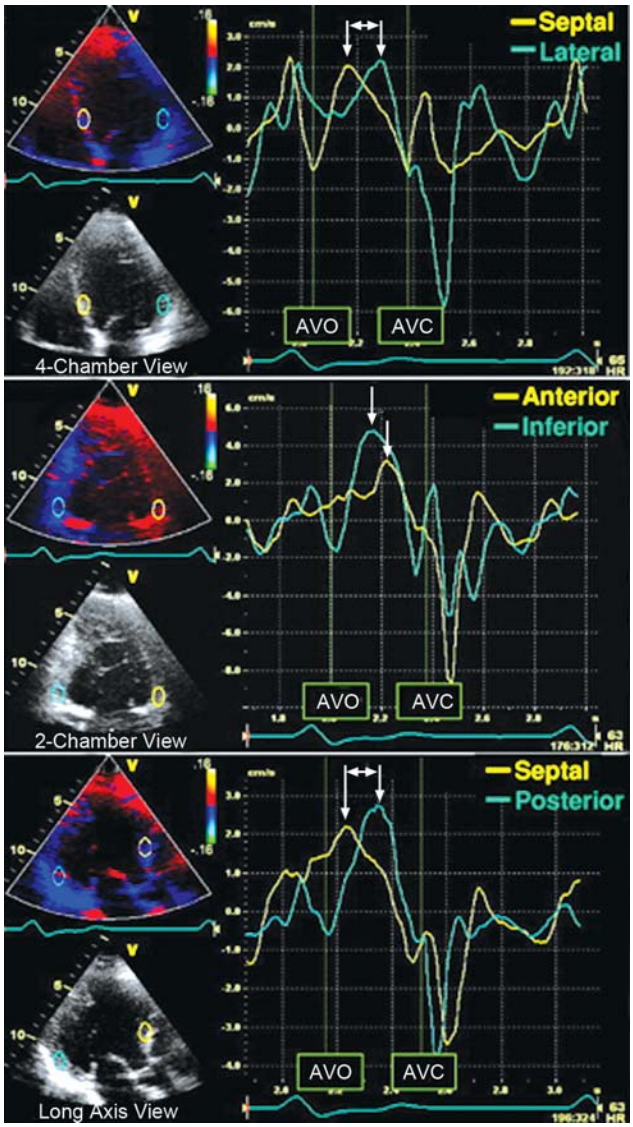
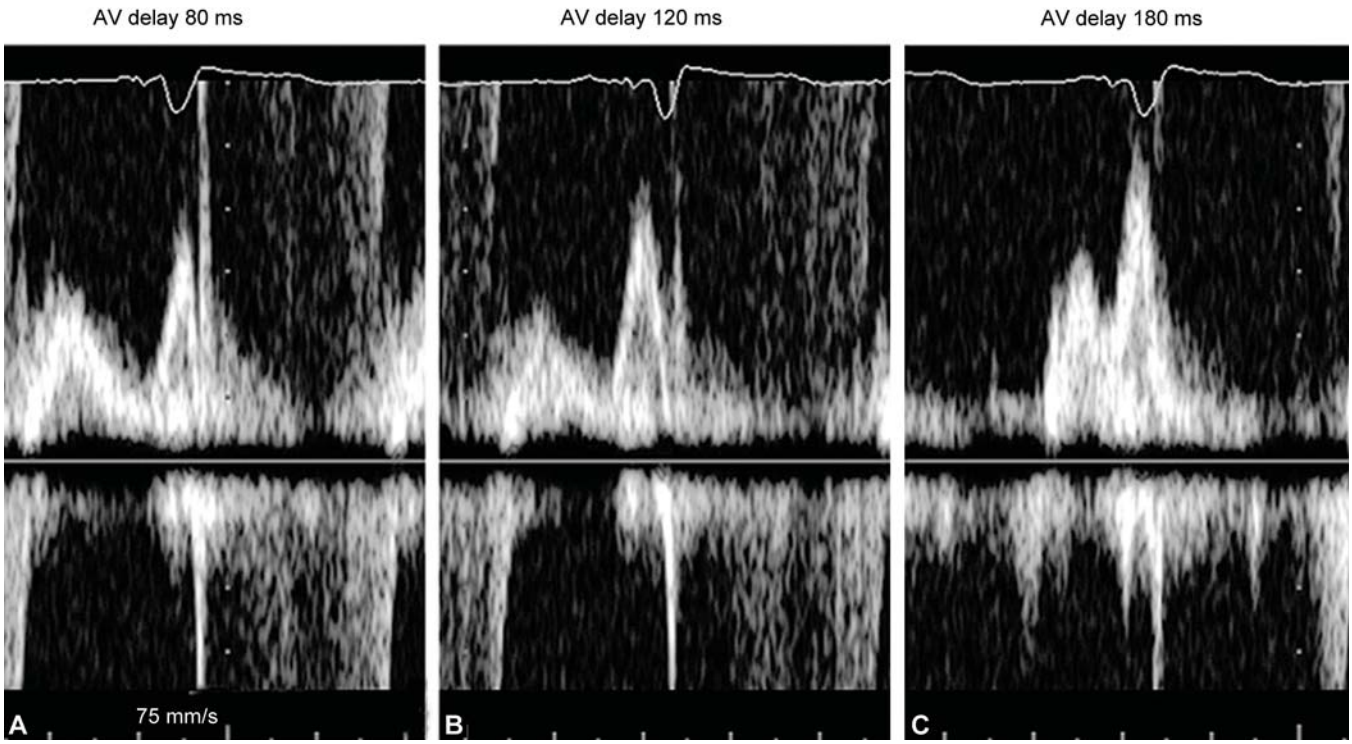


FIGURE 40: Color-coded tissue Doppler study from three standard apical views of a patient who responded to resynchronization therapy. Time-velocity curves from representative basal or mid levels are shown. Maximum opposing wall delay was seen in apical long axis view of 140 milliseconds between septum and posterior wall, consistent with significant dyssynchrony (≥ 65 milliseconds). (Abbreviations: AVO: Aortic valve opening; AVC: Aortic valve closure). (*Source:* Gorcsan J 3rd, Abraham T, Agler DA, et al. Echocardiography for cardiac resynchronization therapy: recommendations for performance and reporting—a report from the American Society of Echocardiography dyssynchrony writing group. J Am Soc Echocardiogr. 2008;21:191-213)



FIGURES 41A TO C: The iterative method for atrioventricular optimization. (C) The sequence starts at a long atrioventricular (AV) delay (180 ms, shorter than intrinsic PR interval to ensure capture) and then shortening by 20 ms increments, until (A) A wave truncation appears (80 ms). Then atrioventricular delay is lengthened by 10 ms increments until A wave truncation disappears and maximum E and A wave separation is provided (B). (*Source:* Abraham T, Kass D, Tonti G, et al. Imaging cardiac resynchronization therapy. JACC Cardiovasc Imaging. 2009;2:486-97)

CARDIAC RESYNCHRONIZATION THERAPY

Echocardiography has been used to improve patient selection for chronic resynchronization therapy (CRT), also referred to as biventricular pacing, and to optimize device settings after implantation. Current recommendations for CRT include New York Heart Association functional class III or IV, widened QRS interval greater than or equal to 120 msec and LVEF less than or equal to 35%.[39]

Unfortunately, approximately 25–35% of patients undergoing CRT do not have an appropriate response. While a number of explanations have been proposed for the suboptimal response, the absence of dyssynchrony (i.e. regions of early and late contraction within the left ventricle) is a likely factor and can potentially be identified by echocardiography. A number of measurements have been proposed and evaluated, but there is no parameter that would justify withholding CRT therapy. Rather, a dyssynchrony study may be of potential benefit when evaluating patients with borderline QRS duration, borderline ejection fraction or ambiguous clinical history for NYHA functional class.[39]

M-mode echo provides excellent temporal resolution due to a sampling rate 1,000/sec. A delay from septal wall peak inward motion to posterior wall peak inward motion of greater than or equal to 130 msec has been proposed as a marker of dyssynchrony (Fig. 38). However follow-up studies have found the reproducibility of this technique to be suboptimal and the method should be used only to supplement other methods. The parameter may be difficult to obtain due to inaccuracy in determining the maximal septal deflection in patients with ischemic cardiomyopathy.[39,40]

Tissue Doppler imaging (TDI) measures the velocity of myocardium in relationship to the cardiac cycle and parameters such as peak systolic velocity, time to onset of systolic velocity and time to peak systolic velocity can be measured. With pulsed wave TDI, only one region can be interrogated at a time which increases procedure time and precludes simultaneous comparison of segments (Fig. 39). Color-coded TDI acquires velocity data from the entire sector and allows multiple simultaneous interrogations (Fig. 40).[40]

The majority of studies have used color-coded tissue Doppler to assess LV dyssynchrony and predict outcomes. The delay between segmental motion is measured and delay greater than 65 msec is predictive of clinic response to CRT. Speckle tracking is a more recent advance in assessing dyssynchrony. Tracking at the midventricular short axis level measures radial strain and a difference greater than or equal to 130 msec in peak strain between anterior septal and posterior wall has been used to identify responders.[39,40]

Since the ventricles are paced with CRT, the AV delay is programmed. The optimal AV delay is the time that allows completion of the atrial contribution to diastolic filling. This can be determined by optimizing the pulsed Doppler mitral inflow velocity: the E and A waves should be separated and the A wave termination should occur before the QRS onset (Figs 41A to C).[41] In addition, optimization of interventricular delay (i.e. V-V delay) is possible. V-V optimization is generally performed by changing the V-V sequence, starting with the LV being activated before the RV and then stepwise lengthening or shortening the V-V interval by 20 msec intervals.[39]

Video 1 Aortic regurgitation, severe parasternal long axis
Video 2 Aortic stenosis (parasternal long axis and parasternal short axis)
Video 3 Mitral regurgitation parasternal long axis
Video 4 Severe mitral regurgitation apical 4 chamber
Vidoe 5 Mitral stenosis (parasternal long axis and parasternal short axis)
Video 6 Mitral stenosis apical 4 chamber
Video 7 Mitral valve prolapse parasternal long axis

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Chapter 17

Stress Echocardiography

Ellen El Gordon, Richard E Kerber

Chapter Outline

- Using Stress Echocardiography in Clinical Decisions
  - — Pathophysiology Involved in Stress Echo
  - — Stress Echocardiography and the Diagnosis of Coronary Artery Disease
  - — Stress Echocardiography and Estimating Risk or Prognosis in Coronary Artery Disease
  - — Stress Echocardiography and Myocardial Viability
  - — Stress Echocardiography and the Assessment of Hemodynamics of Valvular Disease
- The Future of Stress Echocardiography

A. INTRODUCTION

Coronary artery disease (CAD) has been the number one killer in Western society since the turn of the century. Identifying those at risk and preventing the sequelae of ischemic disease is thus a major goal of current day practice. Stress echocardiography (SE) has been used in this regard for over a quarter of a century. This chapter has explored the clinical uses of SE. Given the rapid escalation in use,[1,2] and the associated costs associated with SE, it is necessary for both cardiologists and non-cardiologists alike to have an in-depth understanding of all clinical uses.

Over three-fourth of a century ago, Tennant and Wiggers (1935)[3] occluded a coronary artery and demonstrated the resulting wall motion abnormality. The stage was set for measurement of the functional significance of a coronary stenosis but it would take 40 more years before the resulting wall motion abnormality could be seen by ultrasound.

In 1975, Kerber et al.[4] reported the characteristic of echo detectable wall motion abnormality following an experimental decrease in coronary blood flow.

In 1986, advances in computer technology allowed for ultrasound visualization of a functional myocardial blood flow mismatch. The resulting echo images, however, were viewed little more than a "complement" to standard electrocardiogram (EKG) exercise testing.[5]

Today, SE is far more than a complement to exercise testing. Indications for stress testing have expanded far beyond the initial role in diagnosing ischemic disease. Exercise and pharmacologic stress protocols have been developed to estimate prognosis and evaluate the hemodynamic effects of valvular heart disease.

In this chapter, the authors have focused on the clinical uses of echocardiographic stress testing. Sections have been organized by clinical questions. In the first section, the authors have reviewed the pathophysiology involved in SE imaging. This is followed by a review of the role of SE in diagnosing ischemic disease. Subsequent sections have focused on assessing prognosis in ischemic disease, and assessing myocardial viability. The final section has briefly listed the use of SE in other disease states. Within each section imaging protocols for the specific procedures have been provided, and pros and cons of the various SE modalities have been reviewed. Finally, speculation about what the future holds of SE imaging has been discussed.

B. USING STRESS ECHOCARDIOGRAPHY IN CLINICAL DECISIONS

1. PATHOPHYSIOLOGY INVOLVED IN STRESS ECHO

The major uses of SE have been in (1) diagnosing and (2) estimating risk in patients with suspected or known ischemic disease. An understanding of several factors involved in the disease pathophysiology and in the pathophysiology of the various forms of stress testing is critical to the appropriate use of SE. In order to establish a diagnosis of ischemic disease, SE must show a functional mismatch between myocardial oxygen supply and demand. The "gold standard", however, is not a functional test, but rather an anatomic measurement of coronary stenosis. In addition, the decrease in blood flow necessary to produce ischemia and, hence, a wall motion abnormality has been variably defined in the literature. Both 50% and 70% stenoses of a major epicardial artery (as defined by coronary angiography) have been used to derive sensitivity or specificity of SE. These distinctions are important in understanding the limitations of SE and have resulted in some variation in the reported test characteristics.

The increase in myocardial oxygen demand achieved by stress testing can occur by various mechanisms. Three general modalities are commonly used: (1) an exercise stress which produces a dynamic increase in myocardial oxygen demand;

(2) a pharmacologic stress (dobutamine) which increases in myocardial oxygen demand and (3) a vasodilator stress which produces a coronary "steal".

Exercise stress increases myocardial demand by increase in both chronotropy and inotropy. Due to the important prognostic implications associated with exercise tolerance, use of exercise as a stressor is almost always preferred.

In the United States, dobutamine is the predominant pharmacologic agent used to increase myocardial oxygen demand. It acts by both an increase in inotropy followed by an increase in chronotropy, both of which can be easily confirmed during the stress test. Atropine, added at the end of the protocol if heart rate (HR) response is inadequate, works via anticholinergic effects.

Dipyridamole (and adenosine) has been used more commonly in Europe in SE. The drug works as a vasodilator by setting up a coronary artery steal. An advantage of vasodilators includes the extremely short half-life of these drugs. Disadvantages include the lack of a physiologic endpoint (i.e. wall motion abnormality) as study conclusion is often based on completion of dipyridamole protocol.

2. STRESS ECHOCARDIOGRAPHY AND THE DIAGNOSIS OF CORONARY ARTERY DISEASE

a. Exercise Stress Echo (ESE)

(1) Assessment prior to an exercise stress echo: All stress testing begins with a review of the indication(s) for the stress test in particular, and contraindications for stress testing in general (Table 1).

Indications for SE have been outlined by several groups with the most recent being the appropriateness criteria endorsed by the major cardiac societies.[6] In the area of diagnosis of ischemic disease, the most common appropriate indications include the following: (1) diagnosis of chest pain syndromes in patients with intermediate probability of disease; (2) diagnosis of chest pain syndrome in patients with abnormal baseline EKG and (3) diagnosis in patients with prior equivocal stress testing. A more complete listing of appropriate indications can be found in Table 2. For a more detailed review of all SE indications (congestive heart failure, arrhythmias etc.), the reader is referred to the referenced article.

Inappropriate indications generally include patients in low-risk categories but can include both symptomatic and asymptomatic populations. Inappropriate conditions include: (1) use of SE in *symptomatic* patient with a low pretest probability of disease with an interpretable EKG and the ability to exercise and (2) use in *asymptomatic* patients with low or intermediate probability of CAD with an interpretable EKG.[6]

The recent literature suggests that there is room for improvement in the appropriate use of SE testing.[7] Using the 2008 appropriateness criteria, McCully et al. reviewed 298 consecutive stress echocardiograms and classified them as appropriate, inappropriate, uncertain or not classifiable. Of the 298, 54% were classified as appropriate, 8% as uncertain, 19% were not classifiable and 19% were inappropriate. The largest number of appropriate studies was in use of SE for diagnosis in symptomatic patients (94% appropriate). In contrast, the largest number of inappropriate studies involved use of SE in asymptomatic individuals (72% inappropriate and 26% uncertain).

TABLE 1

Checklist for patient assessment prior to exercise stress echocardiography

- Appropriate clinical indications (Table 2)
- No contraindications to exercise (Table 3)
- Ability to exercise—DASI score (Table 4)
  - Exercise limitations
  - Musculoskeletal limitations
- Clinical symptom review
  - Pretest probability (Table 5)
  - Pretest score (Morise) (Table 6)
- Baseline EKG review
  - Normal
  - Baseline abnormalities
- Current medications
  - Beta blocker (held for 48 Hrs)
  - Diltiazem or Verapamil
  - Long acting nitrates
  - Digoxin

Contraindications to exercise stress echocardiography (ESE) are similar to those outlined for exercise testing in general. They are listed in Table 3.[8-11]

If there are no absolute or relative contraindications to testing, assessing the patient's ability to exercise should be the next clinical question. Use of the Duke activity status index (DASI) can be helpful in this regard. Initially developed in 1989 by Hlatky et al.,[12] it has recently been validated in women.[13,14] DASI consists of 12 questions about daily activity. The patient is instructed to circle all activities that they can do with "no difficulty". Answers such as "I don't do this" or "I can do this with some difficulty" do not count in the final assessment (Table 4). Positive answers are summed using the scores listed in the far right column under metabolic equivalent (MET) value. The total sum has been correlated with MET level achieved on the Bruce protocol and is, therefore, helpful in choosing the appropriate test protocol. Finally musculoskeletal limitations that may influence the patient's ability to exercise should be reviewed by asking what typically limits exercise.

If it is established that the patient can exercise, an exercise protocol is almost always recommended due to the added information gained about prognosis. If the patient cannot exercise or if exercise is limited, then a pharmacologic stress protocol should be considered.

Regardless of the type of study to be used, clinical symptoms should then be reviewed in order to assess pretest risk. Traditional definitions of angina outlined by the coronary artery surgery study (CASS) registry and later validated by Diamond et al. can provide a good start for estimating pretest probability. Definitions are shown in Table 5.

An additional scoring system published by Morise is shown in Table 6. This pretest score has been validated in both men and women and can also be used to assess pretest probability.[15-18]

TABLE 2

Selected appropriate indications for stress testing—detection of CAD in chest pain syndromes, CHF or abnormal testing[6]

Indication	*Evaluation of chest pain syndrome or anginal equivalent*	*Appropriateness score (1–9)*
1.	• Low pre-test probability of CAD • ECG interpretable and able to exerccise	1 (3)
2.	• Low pre-test probability of CAD • ECG uninterpretable or unable to exercise	A (7)
3.	• Intermediate pre-test probability of CAD • ECG interpretable and able to exercise	A (7)
4.	• Intermediate pre-test probability of CAD • ECG uninterpretable or unable to exercise	A (9)
5.	• High pre-test probability of CAD • Regardless of ECG interpretability and ability to exercise	A (7)
6.	• Prior stress ECG test is uninterpretable or equivocal	A (8)
Acute Chest Pain		
7.	• Intermediate pre-test probability of CAD • ECG no dynamic ST changes and serial cardiac enzyme negative	A (8)
8.	• High pre-test probability of CAD • ECG-ST elevation	I (1)
New-Onset/Diagnosed Heart Failure with Chest Pain Syndrome or Anginal Equivalent		
9.	• Intermediate pre-test probability • Normal LV systolic function	A (8)
10.	• LV systolic function	U (5)

(*Source:* Douglas PS, Khandheria B, Stainback RF, et al. ACCF/ASE/ACEP/AHA/ASNC/SCAI/SCCT/SCMR 2008 appropriateness criteria for stress echocardiography. J Am Coll Cardiol. 2008;51:1127-47)

TABLE 3

Contraindications to exercise testing

- Acute myocardial infarction, recent
- Unstable angina (not stabilized by medical therapy or recent pain at rest)
- Uncontrolled heart failure
- Uncontrolled symptomatic arrhythmias
- Symptomatic severe aortic stenosis
- Acute pulmonary embolus or pulmonary infarction
- Deep vein thrombosis
- Acute myocarditis or pericarditis
- Acute aortic dissection (or recent aortic surgery)
- Uncontrolled hypertension (> 220/120 mm Hg)
- Significant left main coronary stenosis
- Significant electrolyte abnormalities (particularly hyper or hypokalemia)
- Severe hypertrophic cardiomyopathy
- High-degree atrioventricular block
- Inability to exercise adequately due to physical or mental limitation

(*Source:* References 9–11)

Both of these measures provide an estimate of the pretest probability, necessary for correctly interpreting any exercise result.

The next clinical decision will be based on the patient's EKG. A normal EKG with no ST segment abnormalities in a low-risk patient would not require the use of or added expense of imaging testing and is in keeping with current guidelines.[6] However with any baseline ST segment abnormality, a stress imaging protocol using imaging should be considered.

The final clinical decision to be made before starting an exercise test is to review the medication list for medications which may interfere with testing or with test interpretation. Concomitant use of beta blockers may result in an inability to achieve 85% of maximum predicted HR, and as a result, has been reported to lower the sensitivity of testing. Therefore, if beta blockers can be discontinued safely prior to testing, then it is recommended that they be discontinued for approximately 4–5 half lives or 48 hours prior to testing. Similarly, other drugs which slow HR response (diltiazem and verapamil) or alter the ischemic response (nitrates) should be reviewed and discontinued if clinically appropriate. If the question is not diagnostic in nature but rather one of adequacy of treatment, then beta blockers may be continued in certain clinical circumstances. Use of digoxin, a known cause of baseline ST changes on EKG, is also another appropriate indication for the addition of imaging to exercise testing.[6]

(2) Choosing an exercise protocol: The choice of the type of exercise is often made by what is available at one's own institution. In the United States, exercise treadmill is the most common form of stress exercise. Outside of the United States, exercise using a bicycle ergometer is performed more frequently. There are advantages and disadvantages to both. Exercise treadmill has the advantage in that walking is familiar to all, whereas patients may not be as familiar with use of a bike. From an SE standpoint, however, imaging must be performed after

TABLE 4

The Duke Activity Status Index (in METs)[12,14]

Can you.....		*Score only for answers: "Yes, with No difficulty"*	*MET value*
1.	Take care of yourself, that is, eating, dressing, bathing, and using the toilet?		0.8
2.	Walk indoors, such as around your house?		0.5
3.	Walk a block or two on level ground?		0.8
4.	Climb a flight of stairs or walk up a hill?		1.6
5.	Run a short distance?		2.3
6.	Do light work around the house like dusting or washing dishes?		0.8
7.	Do moderate work around the house like vacuuming, sweeping floors, carrying in groceries?		1.0
8.	Do heavy work around the house like scrubbing floors, or lifting or moving heavy furniture?		2.3
9.	Do yard work like raking leaves, weeding or pushing a power mower?		1.3
10.	Have sexual relations?		1.5
11.	Participate in moderate recreational activities, like golf, bowling dancing, doubles tennis, or throwing baseball or football?		1.7
12.	Participate in strenuous sports like swimming, singles tennis, football, basketball or skiing?		2.1
			Total score:

(*Source:* Shaw LJ, Olson MB, Kip K, et al. The value of estimated functional capacity in estimating outcome: results from the NHBLI-sponsored Women's Ischemia Syndrome Evaluation (WISE) Study. J Am Coll Cardiol. 2006;47:S36-43)

TABLE 5

Pretest probability of coronary artery disease (defined as >70% stenosis) in men and women according to chest pain description and age

Age (yrs)	*Non-anginal*		*Atypical angina*		*Typical angina*	
	Men	*Women*	*Men*	*Women*	*Men*	*Women*
30–39	5	1	22	4	70	26
40–49	14	3	46	13	87	55
50–59	22	8	59	32	92	79
60–69	28	19	67	54	94	91
Overall	21	5	70	40	90	62

(*Source:* Adapted overall data from Reference 111 and Age data from Reference 112)

TABLE 6

Pretest score[16]

Variable		*Choose response*	*Sum*
Age	Men / Women		
	< 40 / < 50	3	
	40–54 / 50–64	6	
	≥ 55 / ≥ 65	9	
Estrogen status		Positive	= – 3
Women only		Negative	= +3
Angina history		Typical	= 5
Diamond method		Atypical	= 3
		Non-anginal	= 1
Diabetes?		2	
Hyperlipidemia?		1	
Hypertension		1	
Smoking? (Any)		1	
Family Hx CAD? 1°		1	
Obesity? BMI > 27		1	
		Total score:	

(Abbreviation: BMI: Body mass index). (*Source:* Morise AP, Olson MB, Merz CN, et al. Validation of the accuracy of pretest and exercise test scores in women with a low prevalence of coronary disease: the NHLBI-sponsored Women's Ischemia Syndrome Evaluation (WISE) study. Am Heart J. 2004;147:1085–92)

the completion of treadmill exercise and carries the risk that ischemic wall motion abnormalities will have resolved before imaging can be completed. In contrast, imaging is performed continuously during bicycle exercise, although image degradation due to motion artifact can be troublesome. It is therefore, not surprising that there is a lower sensitivity for SE performed with treadmill versus bike ergometry.[19-21] Most recently, Peteiro et al. have reported success with imaging during peak treadmill exercise. While technically more difficult, the technique appears promising with potentially higher sensitivities.[22]

The most common protocol used in exercise treadmill testing is the Bruce protocol. This protocol has the advantage of widespread use and literature validation. However, the large MET increase between stages is not optimal for all patients. For example, patients with musculoskeletal disorders may do better with a protocol such as the Naughton, with a 1 MET workload increase between each stage. This compares with the 4.7, 7 and 10 MET levels attained at the end of Bruce stages I, II and III respectively. Often a modification to the Bruce protocol is used which involves starting exercise at a lower level. The workload at the end of the two additional stages is equal to 2.9

and 3.7 METs, for Stages 0 and 1/2 respectively. Finally, if an exercise prescription for rehabilitation is to be given based on the stress testing results, a protocol, such as the Naughton or Balke-Ware, is recommended.[8,9]

Overall, complication rates are low with ESE. Marwick has estimated a rate of approximately 3:1,000 serious complications.[23] The risk of death or myocardial infarction (MI) with exercise testing has been reported to occur in approximately 1/2,500 patients.[8,9] Earlier data involving exercise testing alone suggested a serious complication rate (MI, serious arrhythmia or death) of approximately 1/10,000.[24]

(3) Conducting the exercise stress echo: A detailed account of the technique required to conduct treadmill exercise testing is beyond the scope of this chapter. The reader is referred to the references provided on exercise testing[8,9] and to the chapter on Treadmill Exercise Testing (see Chapter 13). Comments about the protocol will be limited to the additional considerations associated with echo imaging.

Baseline echo images should be reviewed prior to the start of exercise. Secondary harmonic imaging should always be used. Images should be checked to ensure that they are centered within the chamber and not foreshortened. Segments within all coronary distributions should be visualized prior to starting exercise. If two or more segments cannot be visualized, then use of a contrast agent should be considered.[25] Given the US food and drug administration (FDA) black box warning associated with the use of contrast agents, use of perflutren contrast agents cannot be used in many situations. Originally, the FDA issued a black box warning which restricted the use of perflutrens and required that all patients be monitored for 30 minutes following use (Table 7). Recently, however, Kusnetzky et al. reported a retrospective review of all deaths that occurred with 24 hours of an echo study.[26] No statistically significant difference was found in death rates between patients who received a contrast agent versus those who did not. Patients who did receive the contrast agent were found to have an increased number of comorbidities. The FDA black box warning has subsequently been revised and is shown in Table 7.

In the majority of cases, a symptom limited exercise study is recommended unless a study endpoint is reached. Exercise endpoints have been outlined by the ACC and AHA in guidelines published in 2002.[8,9] Exercise endpoints are listed in Table 8.

TABLE 7

FDA black box warning reuse of an ultrasound contrast agents

A. Original black box warning:
- Unstable angina
- Acute heart attacks
- Unstable cardiopulmonary disease

ECG monitoring of all patients for 30 minutes after completion of the study.

B. Revised Black Box Warning:
- Known or suspected right-to-left, bidirectional or transient right-to-left cardiac shunts
- Hypersensitivity to perflutren

ECG monitoring in only patients with pulmonary hypertension or unstable cardiopulmonary conditions

Do not administer definity by intra-arterial injection

(Abbreviation: FDA: US food and drug administration)

TABLE 8

Endpoints for stress echocardiography

- Achievement of target heart rate
- Symptom limitation
- Protocol completion (i.e. maximal dobutamine or dipyridamole dose)
- Significant wall motion abnormality (see text)
- Ischemic EKG response (i.e. $\geq$ 2 mm ST depression or ST elevation > 1 mm in non-Q wave lead)
- Severe ischemic symptoms (i.e. chest discomfort or exertional dyspnea)
- Severe hypertension (systolic BP > 220 mm Hg or diastolic BP > 120 mm Hg)
- Hypotension or fall in BP > 20 mm Hg with exercise
- Arrhythmias (SVT, VT, heart block, BBB)
- CNS symptoms

(*Source:* Reference 8)

(4) Interpretation of exercise stress echo: Final interpretation of the ESE should consider all components of the study: symptoms, EKG changes, blood pressure (BP) response, echo imaging and exercise tolerance. Reports should contain all of the information that is standard in exercise treadmill studies. This would include information about limiting symptoms, BP response to exercise, EKG changes with exercise, HR achieved and percentage of maximum predicted HR, rate pressure product and exercise tolerance as a percent of predicted.

The most widely used method of echo interpretation is visual. Function in each myocardial segment is evaluated at rest and then compared at peak exercise. Contraction in each segment is graded as normal or hyperdynamic, hypokinetic, akinetic or dyskinetic. Both the timing of wall motion and thickening should be considered as ischemia results in both delayed contraction and relaxation (Videos 1 to 4). A wall motion scoring system can be used in a semiquantitative way to report the findings. The overall ventricular cavity size in systole should also be reviewed. Lack of a decrease in cavity size (or failure to develop hyperdynamic function) would be indicative of significant CAD.[27] For a review of the recommended left ventricular (LV) segments see chapter "Transthoracic Echocardiography", Figure 4, ASE 16 or 17 segment model.

Final interpretation of the stress echocardiogram should include a review of factors known to reduce the sensitivity of exercise stress echocardiograms: inadequate HR response (< 85%), concomitant antianginal treatment, poor image quality and delayed imaging post exercise. To avoid problems with the latter, HR for both maximal exercise and image acquisition should be reviewed.[23] Finally, mild CAD, particularly involving the left circumflex distribution can result in falsely negative studies. In contrast, false positive studies can be seen with pre-existing disease, in particular baseline abnormal septal motion (commonly seen following cardiothoracic surgery or in LBBB) or with a hypertensive response to stress. Overinterpretation has been documented. Interobserver agreement is lowest for isolated basal inferior wall motion abnormalities and highest for basal anterior wall segments.[28]

(1) Assessing the patient prior to pharmacologic stress testing: Similar to the ESE, pharmacologic SE starts with a review of the indication(s) for the stress test and contraindications for stress agent to be used (Table 9). As with ESE, the reader is referred to the appropriateness criteria for SE for a review of the indications.[6] Appropriate indications for use of dobutamine stress echocardiography (DSE) for diagnosis are similar to those listed for use of ESE (Table 1).

Contraindications to DSE differ considerably from ESE. Contraindications for both dobutamine use and atropine use should be reviewed.[28-30] A detailed list can be found in Table 10. Because beta blockers are potent inhibitors of the increase in HR and contractility seen with dobutamine and may be frequently needed to reverse ischemic signs or symptoms, contraindications to their use should also be considered. In our laboratory, we use an intravenous dose of the beta blocker, esmolol, to immediately slow the HR response and decrease contractility in the setting of any significant ischemic response.

Contraindications for dipyridamole stress echocardiography (DiSE) include severe conduction disease or advanced asthma. Vasodilator stress should be avoided in these patients, particularly given the other options for testing.

Similar to ESE, clinical symptoms are next reviewed to assess pretest risk (Table 5). As DSE is being performed in higher risk patients, it is incumbent that clinical stability of the patient be confirmed prior to initiating the study. Baseline EKGs should be reviewed and compared with previous tracings whenever possible. When performed in the setting of acute chest pain, serial cardiac enzymes should also be documented to be normal before proceeding with the test.

The final clinical decision before starting a DSE is a review of the medications. Not only should medications that slow the HR response be considered, but review should include medications which interact with either dobutamine or atropine. Beta blockers are routinely stopped 48 hours (4–5 half lives) before the study if the question is one of diagnosis. If dipyridamole stress is being considered, all xanthine containing medications should be stopped for 72 hours or caffeine containing substances should be stopped 24 hours prior to testing.

TABLE 9

Checklist for patient assessment prior to pharmacologic stress testing/echocardiography

- Appropriate clinical indications (Table 2)
- No Contraindications to:
  - Dobutamine:
    - Contraindications (Table 10)
    - Precautions due to known side effects of dobutamine (Table 10)
    - Other considerations (Table 10)
  - Atropine:
    - Contraindications (Table 10)
    - Precautions due to known side effects of atropine (Table 10)
    - Beta blockers (if needed to reverse ischemic response)
    - Dipyridamole
- Clinical symptoms:
  - Pretest probability (Table 4)
  - Clinically stable
- Baseline EKG
  - Baseline abnormalities
  - Previous EKG available for comparison
- Current medication use:
  - Beta blocker held?
  - Diltiazem or verapamil held? (particularly if high dose)
  - Xanthine containing medications or caffeine (if using dipyridamole)

TABLE 10

Contraindications and precautions with use of dobutamine and atropine[28-30]

Contraindications to dobutamine:
- Symptomatic severe aortic stenosis
- Acute aortic dissection
- Recent or unstable coronary syndrome
- Obstructive hypertrophic cardiomyopathy
- Hypersensitivity

Conditions which may worsen due to dobutamine side effects:
- Uncontrolled atrial fibrillation or PSVT
- Uncontrolled hypertension
- Known ventricular arrhythmias

Precautions with other conditions:
- Electrolyte abnormalities (particularly hypokalemia)
- Intraventricular thrombus
- Arterial aneurysms
- High degree AV block
- Significant asthma and high risk patients (higher need for use of beta blockers as reversal agent)

Contraindications to atropine:
- Narrow angle glaucoma
- Obstructive GI disease
- Myasthenia gravis
- Hypersensitivity to atropine or anticholinergics
- Significant BPH or obstructive uropathy

Conditions which may worsen because of atropine side effects:
- Uncontrolled atrial fibrillation or PSVT
- Uncontrolled hypertension
- Known ventricular arrhythmias

(2) Pharmacologic stress echo protocols:

(i) Dobutamine stress protocol: In early studies, dobutamine protocols started with 5 mcg/kg per minute and increased every 3 minutes to a maximum dose of 40 mcg/kg per minute.[5,10,20,30] If the maximum HR was less than 85% of the target HR, atropine was then added in 0.5 mg doses up to a dose of 1–2 mg. Today, protocols have routinely become more aggressive. They begin at 10 µg/kg per minute and now increase to a maximum dose of 50 mcg/kg per minute.[31] Atropine is added at the doses listed above. Use of atropine at the end of the protocol also allows additional time for dobutamine to reach steady state. If there is a vagal response to dobutamine with manifest bradycardia and relative hypotension, atropine may be added prior to the end of the dobutamine protocol. This is not uncommonly seen at dobutamine doses of 40 mcg/kg per minute or greater. In settings where atropine will not be used or is contraindicated, an additional 3 minutes may be added to protocol to ensure that dobutamine reaches steady state.

(ii) Dipyridamole stress protocol: Dipyridamole continues to be widely used in Europe.[32,33] Protocols vary but generally can be divided into two types. The first standard, longer protocol consists of dipyridamole intravenously at a total dose of 0.84 mg/kg over 10 minutes. The initial infusion rate is

0.56 mg/kg for 4 minutes, followed by a 4 minute period of no infusion. A second infusion follows at a lower dose of 0.28 mg/kg. If no endpoint is reached, atropine can be added in doses of 0.25 mg up to a maximal dose of 1 mg. The second, shorter protocol consists of dipyridamole infusion at the 0.84 mg/kg over 6 minutes.

With the use of either protocol, aminophylline 240 mg IV should be readily available for immediate use with any adverse events and is often routinely infused at the end of the protocol (120 mg in 1 minute up to a total of 240 mg in 2 minutes).

Other protocols have been described in the literature include infusion of adenosine, use of atrial pacing[34] and hand grip exercise.[35] These protocols are less commonly used in the routine clinical setting. The reader is referred to the listed references for additional details.

(3) Complications of pharmacologic stress echo:

(i) Dobutamine: As familiarity with use of dobutamine has grown, sicker patients are now being referred for DSE testing. Given the increase in dosing and increased severity of illness, concern has been raised about the safety of the DSE. Geleijnse et al. have recently reviewed the complications associated with DSE testing.[31] In their review of over 55,000 patients in 26 studies, they report a complication rate of potentially life-threatening complications of approximately 1/475 cases. Marwick reports a serious complication rate of 3:1,000.[23] A list of the complications and incidence reported by Geleijnse is provided in Table 11.

An additional complication of dobutamine infusion reported by Pellikka et al. is that of left ventricular outflow tract (LVOT) obstruction with associated hypotension.[36] Pellikka described an average increase in velocity of 2.3 m/sec (21 mm Hg gradient) at peak dose. Peak dose velocities ranged from 2 m/sec to 5 m/sec. The associated change in BP ranged from a drop of 15 mm Hg to an increase of 4 mm Hg. In our experience, this complication is most often seen in patients with small LV cavities, hyperdynamic LV function at baseline or significant left ventricular hypertrophy (LVH) at baseline. In this setting, we routinely measure the LVOT Doppler at baseline and intermittently throughout the procedure. This complication can be rapidly reversed by saline infusion and reversal of the effects of dobutamine with beta blocker.

TABLE 11

Complications associated with use of dobutamine and atropine

Complication	*Incidence (%)*
Mortality	< 0.01
Cardiac rupture	< 0.01
Myocardial infarction incidence	0.02
Cardiovascular accident	< 0.01
Cardiac asystole	< 0.01
Sustained ventricular tachycardia	0.15
Premature atrial complexes	7.9
Supraventricular tachycardia	1.3
A fib	0.9
AV block	0.23
Coronary spasm	0.14
Hypotension	1.7
Hypertension	1.3
Atropine intoxication	0.03
Dobutamine extravasation	one in two cases
Dobutamine hypersensitivity	1 patient

(ii) Dipyridamole: Varga et al. have recently reported complications associated with the use of dipyridamole as a stress agent in over 24,000 cases. Serious, life-threatening complications were reported in 19 patients for an event rate of 1 in 1,294 cases. This compared to dobutamine event rate of 1 in 557 and exercise event rate of 1 in 6,574 cases. There was 1 reported death following dipyridamole stress testing. The authors concluded that exercise was the safest testing modality with dipyridamole stress second. However they noted that selection bias could account for the latter. As outlined, most complications due to dipyridamole can be rapidly reversed with the use of IV aminophylline. For a more complete review, the reader is referred to the listed reference.[37]

(4) Conducting the pharmacologic stress test: As with ESE, baseline echo images should be reviewed prior to the start of the DSE. Secondary harmonic imaging should always be used.[38] Images should be checked to ensure that they are centered within the chamber and not foreshortened. An off-center baseline image may result in a "smaller" LV cavity. When compared to peak stress imaging, this may result in the false conclusion that there was no hypercontractile response.

Segments within all coronary distributions should be visualized prior to starting dobutamine infusion. If two or more segments cannot be visualized, then use of a contrast agent should be considered.[25] Contraindications to the use of contrast agents and a more extensive discussion of their use has been previously outlined and can be found in Table 7.[26]

Throughout the DSE, the patient is monitored by 12 lead EKG. Blood pressure (BP) is checked at the end of every stage (every 3 minutes) and as clinically indicated. Echo imaging may be screened for all stages but is recorded at low dose (20 mcg/kg per minute) and at peak dose. Recovery images are also recorded at the end of the protocol when the HR was returned to baseline and clinical symptoms have resolved. Today's SE software allows additional image acquisition at anytime during the study. For example, we routinely record additional echo images with any ischemic symptoms or EKG changes.

During infusion of dobutamine, a flow sheet listing the dobutamine dose, use of atropine, patient's symptoms, HR response and BP response is recommended. Unlike ESE, the DSE protocol may be terminated due to imaging endpoints. This would include the development of a new wall motion abnormality or worsening of a baseline abnormality.

(5) Interpretating the pharmacologic stress echo: The most widely used method of echo imaging interpretation is visual. Like ESE, function in each myocardial segment is evaluated at baseline, and then compared at peak dobutamine or dipyridamole dose (Videos 5 to 8). With use of dobutamine, however, comparison with low dose must be considered. An ischemic biphasic response may occur in which an increase in contractility is seen at low dose, followed by no further change

or a decrease at peak dose. As with ESE, contraction in each segment is graded as normal or hyperdynamic, hypokinetic, akinetic or dyskinetic. Both the timing of wall motion and thickening are evaluated. A wall motion scoring system, such as the ASE 16 segment model or the 17 segment model, can be used in a semiquantitative way to report the findings. (see chapter 16 "Transthoracic Echocardiography" Figure 39) The overall change in ventricular cavity size in systole should also be reviewed. A progressive decrease in chamber size reflecting the progressive increase in contractility is expected. A lack of a decrease in cavity size in systole would be indicative of severe CAD.

The definition of an abnormal DSE has varied in the literature. In many studies, either a stress-induced wall motion abnormality or a fixed wall motion abnormality has been used as the definition of an ischemic response. In other studies, only stress-induced wall motion abnormalities are felt to represent ischemia. In studies which included patients with prior MIs (and presumably an increase in resting wall motion abnormalities), sensitivities are generally reported higher with lower specificities. This has resulted in considerable variation in the reported test characteristics. Sensitivities have ranged from 54% to 96% and specificities have ranged from 62% to 93%.[39]

In a meta-analysis summarizing 45 studies which included patients with prior MI and 17 studies which excluded prior MI, Geleijnse et al. have reported the test characteristics for DSE (Table 12). The factor found to have the largest effect on test characteristics was the inclusion or exclusion of baseline wall motion abnormalities. Defining cases with resting wall motion abnormalities as positive raised sensitivity. Specificity, however, was lower when referral bias was present.[39] Test characteristics for DiSE are similar and can be found in Table 13.

The inclusion of patients with resting wall motion abnormalities likely affects study validity in multiple ways. By including patients with previous MI, spectrum bias and inclusion of sicker patients may falsely increase study sensitivity, just as including resting wall motion abnormality in the definitions of abnormal would be expected to increase sensitivity. Other factors which have been reported to affect sensitivity and specificity include referral bias (Table 14). The varying definition of the gold standard between 50% and 70% stenosis should theoretically affect test characteristics but was not found to be a significant factor in Geleijnse's review.[39] The authors theorized that few patients actually had stenoses between 50% and 70% as the reason for this finding. Surprisingly, neither use of beta blockers nor use of atropine was found to affect outcome. Addition of atropine has been reported by others to affect test characteristics.[40]

In addition to interpretation of imaging results, a complete SE report, should include information about symptoms, BP response to dobutamine, EKG changes or arrhythmias noted during infusion or in recovery, HR achieved in beats per minute and as a percentage of the maximum predicted HR and rate pressure product.

Final interpretation of the pharmacologic stress echocardiogram (dobutamine or dipyridamole) should include a review of factors known to reduce the sensitivity of stress echocardiograms: inadequate HR response (< 85%), concomitant antianginal treatment, poor image quality. Finally, mild CAD, particularly involving the left circumflex distribution can result in falsely negative studies. In contrast, false positive studies can be seen with pre-existing disease, in particular baseline abnormal septal motion (commonly seen following cardiothoracic surgery or in LBBB) or with a hypertensive response

TABLE 12

Summary of test characteristics for DSE: (A) Test characteristics for studies without resting wall motion abnormalities; (B) Test characteristics for studies with resting wall motion abnormalities; (C) Sensitivities for studies which allowed calculation of single versus multivessel disease

A. Studies without resting wall motion abnormalities (17 studies)	
Sensitivity (weighted mean)	*Specificity (weighted mean)*
74% LR(+) 2.84	85% LR (–) 0.35
B. Studies with resting wall motion abnormality (45 studies)	
Sensitivity (weighted mean)	*Specificity (weighted mean)*
83% LR (+) 4.37	81% LR (–) 0.21
C. Studies which allowed calculation of sensitivity for single vs multivessel disease (n–48)	
Degree of CAD	*Sensitivity (%)*
Overall Single vessel CAD Multivessel CAD	81 73 88
(*Source:* Reference 39)	

TABLE 13

Summary of test characteristics for dipyridamole stress echocardiography[33]

Overall sensitivity (%)	*Sensitivity (single vessel CAD) (%)*	*Sensitivity (mutivessel CAD) (%)*	*Specificity (%)*
87	81	90	90

TABLE 14

Factors which alter test characteristics of stress echocardiography[39]

Factors associated with increased sensitivity of stress echocardiography
- Clinical spectrum of coronary disease in study population
- Inclusion of resting wall motion abnormality in definition of abnormal response

Factors associated with decreased specificity of stress echocardiography
- Referral bias

to stress. As with ESE, interpretation has varied the most with wall motion changes involving the basal inferior wall.[28]

In summary, diagnosis of ischemic disease can be assessed with either exercise or pharmacologic SE. The choice of the testing modality should be based on the ability of the patient to exercise, the presence or absence of baseline EKG abnormalities, and the experience of the echocardiography lab. A compilation of studies which directly compare the various echo modalities can be found in the consensus statement by the European Association of Echocardiography.[33] When used in patients with appropriate indications, both study types have been shown to identify patients at risk of ischemic disease with a high degree of accuracy.[28]

3. STRESS ECHOCARDIOGRAPHY AND ESTIMATING RISK OR PROGNOSIS IN CORONARY ARTERY DISEASE

a. Assessing Prognosis—Introduction

Stress echocardiography has been used to answer questions about diagnosis and can also be used to estimate ischemic risk and prognosis. For example, SE has been used to predict severity and risk of coronary disease, and assess risk of mortality. This section will first review caveats regarding the design of studies about prognosis, and will be followed by a review of the use of ESE and pharmacologic SE in assessing prognosis of ischemic disease. A summary of prognostic implications of SE in special populations will be provided.

(1) Caveats for the busy clinician regarding studies about prognosis: In a perfect world, testing for ischemic disease would identify those patients who not only have obstructive CAD but also those who have an unstable plaque (diagnosis). Prognostic studies would then tell us which unstable plaque is likely to rupture or cause thrombosis (prognosis). The reader is reminded that, because stress testing is often correlated with an anatomic diagnosis (coronary angiography), SE is best used in the setting of obstructive disease. Our ability to predict the future ischemic events that often result from non-flow limiting atherosclerotic plaque is, therefore, limited.

Study design represents another limitation of prognostic studies. Study populations are rarely randomized to various workups with measurements of patient outcome, although the need for such studies has recently been outlined.[41-43] In the worst case, studies are designed based on retrospective reviews of cases and controls with their inherent selection bias. In better studies, non-randomized cohorts of consecutive patients are followed prospectively. The study population should consist of a well-defined population who are at a similar point in the course of disease.[44] Due to this, prognostic studies are, therefore, highly dependent on the make-up of the selected patient population and have a high potential for both selection bias and referral filter bias.

The definition of outcome is another important factor in determining quality of a prognostic study. Due to the expense of conducting long-term studies, investigators often use a combination of events (composite outcome) as their primary endpoint. This can result in a decrease in time of study design but can introduce significant problems in clinical application.

By definition, a composite endpoint represents a combination of multiple endpoints. Montori et al. have developed three questions designed to help interpret composite endpoints:[45]

1. "Are the component outcomes of similar importance to patients?"
2. "Did the more and less important outcomes occur with similar frequency?"
3. "Are the component outcomes likely to have similar relative risk reductions (RRRs)?"

To illustrate further assume that a statistically significant decrease in a composite endpoint of angina and cardiac death is reported. This may not mean that a significant decrease in both events has occurred. By applying Montori's questions, an appropriate interpretation can be made. For example, in answering the first question, it becomes obvious that the importance of angina and cardiac death may differ. The second question reveals that the outcomes will likely occur at differing frequencies. Finally, by quickly looking at the RRR and confidence intervals for the individual events, a final interpretation can be made. In the example provided, it is conceivable that a statistically significant composite outcome could be based predominantly on the change in frequency of angina.

b. Exercise Stress Echo (ESE) and Prognosis in Coronary Artery Disease

(1) Prognostic variables in ESE: Exercise SE has been used to assess prognosis in ischemic disease for many years. The advantages of ESE include the additional clinical information found from the exercise portion of the study. In reviewing ESE studies and prognosis, both exercise, imaging and combination variables have been shown to be helpful in predicting prognosis and will be subsequently reviewed. ESE variables which have been used to predict prognosis are listed in Table 15.

TABLE 15
Exercise stress echocardiography—summary of prognostic variables

Variable	*Poor prognostic indicators*
Summary	*Effort-induced or limiting angina*
EKG	• ST segment depression or elevation • Arrhythmias
Hemodynamics—BP	• No rise in BP with exercise • Fall in BP with exercise
Hemodynamics—HR	< 85% of maximum predicted heart rate
Echo imaging	• New or worsening regional wall motion abnormality • Lack of decrease in LV systolic dimension with exercise
Workload	• < 5 METs in women • < 7 METs in men
Combination variables	• Duke treadmill score (≤ 11 points) • Exercise score (men > 60; women > 57)

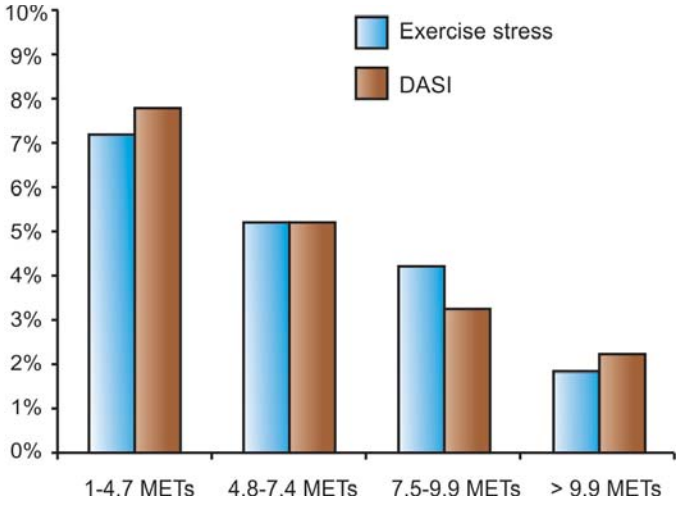


FIGURE 1: Mortality and exercise capacity in the WISE study.[14] Annual mortality is predicted by exercise treadmill stage (blue bars) or estimated exercise capacity using the Duke activity status index (DASI) (brown bars) (*Source:* Shaw LJ, Olson MB, Kip K, et al. The value of estimated functional capacity in estimating outcome: results from the NHBLI-sponsored Women's Ischemia Syndrome Evaluation (WISE) Study. J Am Coll Cardiol. 2006;47:S36-43)

(i) Exercise variables: Despite years of technical progress, one of the most powerful predictors of outcomes remains exercise tolerance. Arruda-Olson et al. confirmed this with exercise echo in 2002.[46] The authors followed 5,798 consecutive patients who had an exercise echo for known or suspected CAD for an average of 3.5 years. Outcomes were defined as non-cardiac death and nonfatal MI. Of all of the exercise EKG predictors, workload was the only one predicted by multivariate analysis. Other authors have reported similar findings.[47] Additional predictive variables have included a fall (or lack of rise) in systolic BP with exercise which has also correlated with a poorer prognosis.[48] Exercise-induced angina was originally found to predict a poorer prognosis[49] but has been shown to be less predictive when exercise tolerance is included.[48-50]

The importance of exercise tolerance as a predictor of mortality is not new as it has been shown to be important in non-imaging stress testing. In the WISE study, exercise tolerance in women, whether measured by treadmill stage or estimated by DASI score, correlated inversely with mortality and was shown to be one of the strongest predictors of mortality (Fig. 1).

Nomograms for predicted exercise capacity have been published for both men and women. Myers et al. followed 6,213 men with cardiovascular risk factors who had undergone exercise testing. They found that exercise tolerance was the most powerful predictor of death. For every 1 MET increase in exercise tolerance, there was a 12% decrease in mortality.[51] Gulati et al. found that the risk of death in women with exercise tolerance less than 85% of that predicted for age was twice that of women whose exercise tolerance was greater than 85% of predicted. This was found in both symptomatic and asymptomatic women.[52]

Achievement of greater than 85% of maximal predicted HR has been a standard component of exercise testing. Failure to achieve this threshold has reported as a poor prognostic indicator

TABLE 16

Duke treadmill score[59]

Duke Treadmill Score:
- low risk: ≥ +5 points,
- intermediate risk: –10 to +4 points,
- high risk: ≤ –11 points (9).

Duke Treadmill Score Equation:
Duration of exercise in minutes – (5 × the maximal ST segment deviation during or after exercise, in millimeters) – (4 × the treadmill angina index)

even after adjustment for echo indicators of myocardial ischemia.[53]

(ii) Imaging variables: Echo imaging abnormalities have been found to be highly predictive and have been reported to add incremental value to the exercise variables. Abnormal responses have variably been defined by the following ways:
- New or worsening regional wall motion abnormality
- No decrease in LV end systolic size with exercise
- Abnormal resting LV wall motion.

The most commonly agreed upon definitions include the first two. The reader is again cautioned as inclusion of resting LV wall motion abnormalities as part of the abnormal response can have significant effects on reported sensitivity and specificity. Numerous authors have reported that the severity and extent of wall motion abnormalities was predictive of cardiac death and major adverse cardiac events (MACEs), most often defined as cardiac death, nonfatal MI and unstable angina.[22,46,54-56]

(iii) Combining clinical variables: Adding clinical information to the data obtained from an ESE has been reported to show further increases in predictive accuracy. In 2001, Marwick et al. reported that the use of the Duke treadmill score added to the prognostic ability of ESE, particularly when applied to intermediate risk patients.[57] Previously shown to improve clinical prediction in men, the Duke treadmill score[12] has recently been validated in women.[13,58] The scoring system outlined in Table 16. Duke treadmill score can be quickly calculated following any exercise test using the Bruce protocol.

Morise et al. have also combined clinical factors with ESE results and published an exercise score for both men (Table 17A) and women (Table 17B). In patients undergoing exercise testing for suspicion of CAD, clinical factors and ESE results are scored as outlined. The total exercise score correlates with probability of outcome and has shown an improved prediction of all-cause mortality when compared with the Duke treadmill score.[16]

Both scores can be used to complement ESE interpretation as they provide a way to incorporate clinical factors which have been shown to independently predict risk in ESE studies.

(2) ESE in ischemic disease: Exercise SE has been used in many populations. Most commonly it has been used to assess chest pain in patients with known or suspected CAD. Because the interpretation of any study is highly dependent on the extent and severity of ischemic disease in the study population, studies will be reviewed according to clinical presentation. This section will review early prognostic studies, followed by a review of

TABLE 17A

Exercise score—men[16]

Variable	*Choose response*		*Sum*
Maximal heart rate	Less than 100 bpm	= 30	
	100 to 129 bpm	= 24	
	130 to 159 bpm	= 18	
	160 to 189 bpm	= 12	
	190 to 220 bpm	= 6	
Exercise ST depression	1–2 mm	= 15	
	> 2 mm	= 25	
Age	> 55 years	= 20	
	40 to 55 years	= 12	
Angina history	Definite/typical	= 5	
	Probable/atypical	= 3	
	Non-cardiac pain	= 1	
Hypercholesterolemia?	Yes	= 5	
Diabetes?	Yes	= 5	
Exercise test induced angina	Occurred	= 3	
	Reason for stopping	= 5	
	Total Score:		

(*Source:* Morise AP, Olson MB, Merz CN, et al. Validation of the accuracy of pretest and exercise test scores in women with a low prevalence of coronary disease: the NHLBI-sponsored Women's Ischemia Syndrome Evaluation (WISE) study. Am Heart J. 2004;147: 1085-92)

TABLE 17B

Exercise score—women[18]

Variable	*Choose response*		*Sum*
Maximal heart rate	Less than 100 bpm	= 20	
	100 to 129 bpm	= 16	
	130 to 159 bpm	= 12	
	160 to 189 bpm	= 8	
	190 to 220 bpm	= 4	
Exercise ST depression	1–2 mm	= 6	
	> 2 mm	= 10	
Age	> 65 years	= 25	
	50 to 65 years	= 15	
Angina history	Definite/typical	= 10	
	Probable/atypical	= 6	
	Non-cardiac pain	= 2	
Smoking?	Yes	= 10	
Diabetes?	Yes	= 10	
Exercise test induced angina	Occurred	= 9	
	Reason for stopping	= 15	
Estrogen status	Positive = –5, Negative	= 5	

(*Source:* Morise AP, Olson MB, Merz CN, et al. Validation of the accuracy of pretest and exercise test scores in women with a low prevalence of coronary disease: the NHLBI-sponsored Women's Ischemia Syndrome Evaluation (WISE) study. Am Heart J. 2004;147:1085-92)

studies in patients with chest pain, with known CAD and in patients undergoing coronary interventions.

(i) Early studies of ESE and prognosis: Early studies confirmed the increased prognostic ability of ESE over exercise treadmill testing.[60] In 1998, McCully et al.[47] reviewed the outcome of 1,325 patients who had a normal exercise echocardiogram. Regardless of pretest risk, patients with negative ESE were shown to be free of cardiac death, MI or revascularization over the ensuing year. At 1 year, 2 years and 3 years, event-free survival was reported as 99.2%, 97.8% and 97.4% respectively. Predictors of increased risk included low exercise tolerance, angina during exercise, echocardiographic LVH and increased age. In their meta-analysis, Metz et al.[61] confirmed the low event rate following a normal ESE. They reported 98.4% of those with a negative ESE to be free of cardiac death and MI over 33 months follow-up.

(ii) Patients presenting with atypical chest pain or as outpatients: Exercise stress echocardiography studies in patients with suspected ischemic symptoms are limited, as most include patients with known underlying CAD. Colon et al. reported an early retrospective analysis of patients presenting with atypical chest pain without known disease. The event-free survival at 30 months was found to be 93% when patients had a normal stress EKG and 97% following a normal stress echocardiogram. In contrast, an abnormal stress echocardiogram predicted an event-free rate of major cardiac events of only 74% when wall motion abnormalities were noted.[55]

Leischik et al. studied 3,329 outpatients with ESE. Patients were followed for 5 years for the occurrence of cardiac death, MI and revascularization. Patients with abnormal SE had a 61.9% event rate compared with a 6.3% event rate in patients who had negative stress echocardiographies.[56]

In order to evaluate the additive role of echo imaging, Bouzas-Mosquera et al. reported 4.5 years f/u on 4,004 pts (29% with history of CAD) who underwent ESE and had no chest pain or EKG changes with exercise.[54] Patients were stratified by development of an ischemic response, defined as development of new of worsening wall motion abnormality. In patients with ischemic response, death and MACE occurred at a rate of 12.1% and 10.1% respectively. In comparison, event rates in patients with no ischemic response were 6.4% and 4.2% respectively. The authors argued that ESE imaging provides prognostic information above that obtained by a normal exercise stress test.

In 2007, Metz et al. published a meta-analysis in which the prognostic value of a normal exercise echocardiogram was evaluated in patients with suspected CAD. The primary outcome was defined as MI and cardiac death. A normal ESE conferred a 98.4% negative event rate over 33 months or an annualized rate of 0.54% per year for primary events.[61]

Most recently, researchers have begun to evaluate the outcomes in patients with "false positive" SE, where patients, with an abnormal SE (exercise or dobutamine stress), are found to have less than 50% coronary artery stenosis by angiogram.

To answer this question, From et al. reported a retrospective analysis of 1,477 patients who had both a SE and a coronary angiogram within 30 days (patients represented a subset of 7,352 with abnormal stress echocardiographies). All had previously undergone coronary angiography within 30 days. Around 67.5% were found to have obstructive CAD defined as greater than or equal to 50% stenosis and 32.5% were categorized as "false positives" given the absence of significant coronary stenosis. Analysis of a subset with "markedly positive" stress echocardiographies (defined as an abnormal left ventricular end systolic size response to stress and > 5 segments abnormal at peak stress) and less than 50% stenosis by coronary angiogram revealed 140 deaths during 2.4 years follow-up. The death rate of this subgroup was reported to be similar to the death rate of those with significant coronary stenosis.

In an editorial response, Labovitz reviews the limitations of the study but argues for the prognostic power of an abnormal stress echocardiogram.[62] Regardless of whether or not the mechanism for the poor outcome is due to vasomotor changes, endothelial dysfunction, small vessel disease or microvascular abnormalities, one is reminded that the culprit is the unstable plaque, which is not always obstructive. Clearly additional studies are needed to more fully understand the meaning of a "false positive" SE. In the interim, the literature includes increasing support for medical treatment of this population and aggressive risk factor modification.[62,63]

(iii) Patients with known or suspected CAD: A negative ESE also confers an excellent prognosis on patients with known CAD. In 2001, Marwick et al. reported 10 years follow-up following SE in over 5,000 patients with known or suspected ischemic disease. During the study period, 649 deaths were reported. In this setting, a normal ESE predicted an overall mortality rate of 1% per year.[57]

Similarly, in a study of over 3,000 outpatients who were undergoing evaluation for chest pain, patients with known CAD and a negative SE were reported to have cardiac death rates of less than 1% during the subsequent year.[56]

An abnormal ESE confers a significantly higher risk of death and MI. Patients who developed a new or worsening wall motion abnormality with ESE had a 5-year mortality rate of 12.1% and 5-year MACE rates of 10.1%.[54] Peteiro looked at peak and post-exercise imaging and also reported high rates for patients with abnormal wall motion score indexing (5-year mortality rate 15.3% at peak exercise, and 14% post exercise).[22]

Once again, the importance of exercise tolerance is found to be an important clinical predictor. In patients with suspected or known CAD who had an abnormal ESE and good exercise tolerance (women > 5 METs and men > 7 METs), McCully et al. reported a low event rate for cardiac death and nonfatal MI per person year of follow-up (1.6% for patients with a decrease in LV systolic size with exercise; 1.2% for patients without regional wall motion abnormalities).[64] However, in patients with an abnormal ESE and poor exercise tolerance, the event rate increased (4.4% risk per person year of follow-up).[65]

Finally, ESE is predictive in various age groups, including the elderly. In 2001, Arruda et al. reported the results of ESE in 2,632 patients over the age of 65 years. Fifty-six percent of the population were male and 44% female. All underwent clinically indicated ESE testing and were followed for an average of 2.9 ± 1.7 years. Thirty-six percent had baseline wall motion abnormalities. Both clinical exercise and echo variables were recorded. An exercise-induced wall motion abnormality was seen in 1,082, or 41% of the population. Follow-up revealed 68 cardiac deaths and 89 fatal MIs. Multivariate analysis revealed that predictors of cardiac death included workload achieved and exercise EF. When exercise EF was excluded, the regional wall motion score was highly predictive. The presence of angina during testing or ST segment changes did not add to the predictor. An increase in or lack of decrease in exercise left ventricular end systolic volume (LVESV) correlated with an increase in cardiac events.

In summary, a negative ESE in patients with good exercise tolerance appears to confer a good prognosis regardless of the presence or absence of CAD, whereas a positive ESE appears to carry a poorer prognosis regardless of the presence or absence of obstructive CAD. Good exercise tolerance may provide additional risk stratification in those with abnormal studies.

(iv) Prognosis following ESE—patients undergoing percutaneous coronary intervention (PCI): Another major use of ESE has been in the evaluation of patients undergoing PCI. Identifying an ischemic region has been shown to help plan coronary interventions, particularly in patients with known underlying disease. Consequently, current guidelines recognize PCI in patients with class I or II angina and a "moderate to severe degree of ischemia on noninvasive testing" as a class IIa indication (level of evidence B) and PCI in patients "no evidence of myocardial injury or ischemia on objective testing" as a class III indication.[66]

It would, therefore, be assumed that ESE would play a large role in the planning of coronary interventions. However recent medicare data suggests that noninvasive testing is rarely used in this setting. Less than 50% of patients undergoing PCI had any type of noninvasive testing prior to PCI.[67] Whether or not this practice will change given the current emphasis of optimal utilization of resources remains to be seen.[68]

(3) ESE in special populations: Exercise stress echocardiography has been successfully studied in many populations. It has been shown to be predictive in women,[46,52,58,69-75] patients with hypertension or LVH,[76] diabetics,[77,78] patients with atrial fibrillation[79] and patients with ESRD.[80] Detailed review of all of these studies is beyond to scope of this chapter. The reader is referred to references provided in the reference section. ESE, however, is not routinely recommended for use in patients with LBBB. Guidelines suggest use of pharmacologic stress[81] in this setting.

In summary, a normal ESE with good exercise tolerance appears to correlate with a good prognosis regardless of the presence or absence of known CAD (not necessarily angiographically negative). Use of a clinical prediction score appears to improve clinical assessment. Exercise tolerance and LVESV response to exercise (or wall motion score, if LVESV response not analyzed) are powerful predictors of hard cardiac endpoints.

In contrast, an abnormal ESE appears to predict a poorer prognosis. In the presence of underlying obstructive CAD, the event rates are significant. However, even in the presence of underlying nonobstructive CAD, events rates are significantly higher, particularly when studies are markedly abnormal.

c. Dobutamine Stress Echo (DSE) and Prognosis in Coronary Artery Disease

Like ESE, many articles have been published regarding the use of DSE in predicting risk and prognosis. Like ESE, imaging variables have been shown to be highly predictive. This section is, therefore, reviewed the general prognostic factors associated with DSE, evaluate prognostic implications of both normal and abnormal DSE in ischemic disease, and finally review the use of DSE in predicting preoperative risk.

Unlike ESE, DSE has the disadvantage of not providing the additional prognostic value associated with exercise variables. While this will vary considerably with the severity

of disease in the study of population, the reader is reminded that, in general, prognosis is poorer in patients who cannot exercise.

This was well-illustrated by Shaw et al. when they studied 5-year mortality in 4,234 women and 6,898 men who had undergone either ESE or DSE.[75] Women with no ischemia on DSE had a similar risk adjusted 5-year mortality as women with either 2 or 3 vessel ischemia on ESE (95% and 95% respectively). This finding was also seen in men with no ischemia on DSE compared with men with 2 or 3 vessel ischemic response on ESE (5-year mortality was 92% and 94% respectively).

(1) Prognostic variables in DSE: One of the earliest DSE studies by Chuah et al. followed 860 patients with known or suspected CAD for 52 months.[82] In this population they found that multivariate predictors of cardiac events included a history of congestive heart failure, an abnormal LVESV response to stress, and the number of abnormal segments at peak stress. A new wall motion abnormality was also found to be a powerful predictor in studies by Poldermans[83] and Elhendy.[84] Poldermans' study included patients with resting wall motion abnormalities while Elhendy's study included only patients with normal baseline LV systolic function. In the former study, 5-year probability of an abnormal cardiac outcome (cardiac death, MI or revascularization) following a normal DSE was 14%. In the latter, only an ischemic wall motion abnormality was predictive of hard cardiac endpoints.

(2) Dobutamine stress echo and prognosis in ischemic disease: In evaluating patients with ischemic disease, Marwick et al. reported a low risk of death following a normal DSE.[85] In this study, he evaluated 3,156 patients who had undergone DSE (1,073 of whom had coronary angiography). These patients were then followed for 9 years. A normal DSE was associated with a total mortality of 8% per year and a cardiac mortality of 1% per year. Similar outcomes were reported by Sozzi (2% mortality in first 2 years, 2.4% in years 4 and 5)[86] and Yao (0.9% per year event rate).[87] In one of the larger studies, Chaowalit reported a 95% survival at 1 year.[88] In this study, 3,014 patients were studied following a normal DSE. Cardiac event-free rates were 98% at 1 year, 93% at 5 years and 89% at 10 years.

In contrast, both mortality and cardiac event rates increase in the setting of an abnormal DSE. Whereas a negative DSE resulted in 1.1% annual rate, an ischemic response increased the event rate fivefold (5% annual event rate)[84] in patients with normal resting LV systolic function.

In reviewing DSE in men and women, Shaw et al. reported risk adjusted 5-year survival rates of 95% in women with no ischemia and 86% in patients with ischemia consistent with multivessel disease. Men with no ischemic response on DSE had a 92% survival at 5 years compared to 84% survival in the setting of an ischemic response.[75] There was no statistically significant difference between men and women who had a nonischemic response. There was, however, felt to be a significant difference in survival between men and women who exhibited an ischemic response. This was attributed to a greater extent of ischemic disease in men.

Recently, From et al. retrospectively analyzed markedly abnormal stress tests in patients who were found to have nonobstructive coronary disease.[89] An about 1,477 consecutive patients who had both an abnormal SE and coronary angiography were analyzed. Around 67.5% were found to be true positives, whereas 32.5% were considered false positives (coronary stenosis < 50% by angiography). In this latter population, 605 patients were felt to have a markedly abnormal response, defined as greater than 5 segments abnormal at peak stress or an abnormal LV in systolic size response to stress. After 2.4 years of follow-up the investigators found no difference in death rates between those with obstructive disease and those with nonobstructive disease. In other words, the outcome of patients with markedly abnormal "false positive" studies was similar to that seen in patients with obstructive coronary disease.

In summary, prognosis following a normal DSE is generally good whereas prognosis following a markedly abnormal DSE is not good, irrespective of the presence or absence of underlying obstructive disease.

(3) Dobutamine stress echo and prognosis in special settings: Like ESE, DSE has been used in special settings. These include risk assessment prior to and following PCI, and risk prediction prior to noncardiac surgery. Special populations have also been studied using DSE and include women, diabetics, patients with peripheral vascular disease and patients found to have LVOT gradients.

Stress testing has been studied prior to and following PCI. In patients with stable CAD, stress testing has been recommended as a gateway to invasive procedures. Updated guidelines recommend use of PCI in patients with stable angina who meet the following conditions:[66]

Percutaneous coronary intervention (PCI) is reasonable in patients with asymptomatic ischemia or CCS class I or II angina and with 1 or more lesions in 1 or 2 coronary arteries suitable for PCI with a high likelihood of success and a low risk of morbidity and mortality. The vessels to be dilated must subtend a moderate to large area of viable myocardium or be associated with a moderate to severe degree of ischemia on noninvasive testing (level of evidence B).

As indicated, stress testing would be expected to help define the severity and degree of ischemia and therefore justify the need for invasive procedures, particularly given the problems with visual estimates of coronary lesions, the risks of dual antiplatelet therapy, and the lack of a decrease of stroke, MI or death in patients with stable symptoms.[90] Early studies found SE testing prior to PCI did just this and described testing as a clinically useful, cost effective strategy in patients with stable angina[91] and in women with suspected CAD.[92]

As previously noted, recent medicare data suggests that stress testing is not frequently used prior to the planning of PCI in patients with stable angina.[67] In a randomized trial, Sharples et al. reported that in 20–25% of cases, the results of the stress test resulted in a change in management plan (i.e. patients were not referred for angiography).[93] This data, in combination with the results of the recent COURAGE trial,[94] suggests that stress testing may be an underused modality in patients with stable angina.

Yao et al. recently confirmed the value of SE in predicting cardiac events in a retrospective analysis of 3,121 consecutive patients. They found SE to be an effective gatekeeper and that an abnormal SE positively influenced the need for revascularization.[95]

Cortigiani et al. have studied the use of exercise, dipyridamole and dobutamine stress tests in 1,063 patients following PCI.[96] Ischemia during stress was associated with higher 5-year mortality and a higher instance of heart cardiac endpoints.

A large literature has also addressed the use of SE in evaluating perioperative risk. Guidelines currently recommend use of stress testing in patients with active cardiac symptoms, and in patients with significant risk factors and a low functional capacity (< 4 METs) prior to undergoing either vascular surgery or intermediate risk surgery (for detailed list of the recommendations, the reader is referred to the reference by Fleisher et al.[97]). DSE has been shown in several studies to add to the predictive ability of clinical data.[98,99] Labib et al. found that a negative DSE predicted a similar perioperative event rate in patients regardless of whether or not they achieved their maximum predicted HR with stress. In the authors' hands, the presence of a resting wall motion abnormality predicted increased risk even in the absence of provacable ischemia.

As previously described, SE has been found studied in both women and men and found to be equally predictive of ischemia.[75,100]

In a study of 2,349 patients with diabetes followed for an average of 5.4 years, SE variables added to the clinical and resting echo prediction model.[101] Significant predictors of mortality derived from SE testing included failure to achieve target HR and percentage of ischemic segments.

Similarly, when DSE was studied in patients with peripheral arterial disease, Chaowalit et al. found that both the failure to achieve 85% maximum predicted HR in response to dobutamine and the ischemic response seen with imaging was predictive of mortality and morbidity.[102]

Left ventricular outflow tract obstruction is a finding not commonly seen with SE. In order to evaluate its prognostic significance, Dawn et al.[103] studied 237 patients with LVOT documented by continuous wave Doppler. They then followed a subset with no DSE provocable ischemia for 31 months. The presence of dobutamine-induced or resting LVOT obstruction predicted an increased incidence of chest pain and syncope or near syncope.

Finally, Sicari et al. reviewed the implications of concomitant antianginal treatment in the setting of DSE testing. Antianginal therapy was defined as use of nitrates, calcium channel blockers or beta blockers. The best overall survival was found in untreated patients who had a negative DSE. In contrast, the worst overall survival was found in treated patients with abnormal stress testing response. Survival rates at 2.6 years were 95% versus 81% respectively.[104] There was no statistically significant difference between treated patients with a negative test (88% survival) and untreated patients with a positive test (84% survival).

(4) Dipyridamole stress echo (DiSE) and prognosis in coronary artery disease: As previously noted, DiSE is used more frequently in Europe. Studies using this modality have confirmed its use in assessing prognosis in patients with CAD. As with DSE, a negative DiSE confers a good prognosis. As with dobutamine, dipyridamole has been tested to be useful in ambulatory patients,[105] in planning PCI[96] and in perioperative risk assessment.[106]

In summary, the major predictor of mortality following a pharmacologic SE is extent of ischemic response. In general, prognosis following a normal study is generally good. This contrasts significantly with the outcomes in patients who exhibit an ischemic response.

4. STRESS ECHO AND MYOCARDIAL VIABILITY

In addition to use in diagnosis and prognosis of ischemic disease, SE has also been used to determine myocardial viability. In patients with resting wall motion abnormalities, viable myocardium is felt to be present when an increase in contractility or increase in endocardial motion can be demonstrated in response to stress. Given that revascularization may benefit up to 50% of patients with chronic "hibernating" myocardial (myocardium that is chronically ischemic and, therefore, dysfunctional), determination of viability may have a significant impact on management decisions.[107-109]

Due to the need to assess serial response to an increase in stress, DSE is the preferred testing modality and has been reported to be the most specific test.[109] The assessment prior to the start of the procedure is similar to that described under diagnostic testing. The protocol, however, varies slightly and is much less aggressive. Dobutamine infusion starts at 5 µg/kg per minute for 3 minutes and increases to 10 µg/kg per minute for an additional 3 minutes. In patients with critical coronary disease, some have advocated starting at an even lower dose—2.5 µg/kg per minute. The endpoints include the following: (1) a lack of increase in baseline contractility suggesting myocardial necrosis; (2) an increase in myocardial contractility suggesting myocardial stunning or hibernation or (3) a biphasic response in which an increase in contractility is seen at the lower dose but regional wall motion worsens at the higher dose as ischemia is induced.

In order to assess the prognosis of patients following revascularization, Rizzello et al. performed dobutamine viability studies in 128 consecutive patients with ischemic cardiomyopathy prior to revascularization.[110] The best multivariate predictors of cardiac death included the presence of multivessel disease, the wall motion score index at low dose dobutamine, and echo evidence of an increase in contractility (or viability) in greater than or equal to 25% of the dysfunctional segments. Patients with viable myocardium were found to have a good prognosis following revascularization. This compared with a much poorer outcome in patients with viable myocardium who were treated medically.[111]

Schinkel et al. have recently reported a comparison of dobutamine echo with Thallium-201, and with technetium-99m scintigraphy.[108] Dobutamine viability studies compared favorably with other modalities and were found to have the highest specificity.[108] A recent review by the European Association of Echocardiography also recommended low dose dobutamine as the best test for viability.[33] For additional details regarding comparisons of the various testing modalities, the reader is referred to references provided in the reference section.

5. STRESS ECHO AND THE ASSESSMENT OF HEMODYNAMICS OF VALVULAR DISEASE

Because both cardiac structure and valvular hemodynamics can be assessed, SE is increasingly being used to assess valvular

heart disease. The most common uses of SE have included assessment of patients with valvular stenosis. ACC/AHA guidelines support use of SE in the assessment of asymptomatic patients with severe aortic stenosis (AS) (class IIb), patients with AS and LV dysfunction, and in patients with mitral stenosis who are either asymptomatic with severe mitral stenosis, or who are symptomatic with mild to moderate mitral stenosis at rest (class I recommendation, level of evidence C). The role of SE in patients with mitral regurgitation or aortic regurgitation is less clear. For a detailed review, the reader is referred to the listed references[112] provided in the reference section and to the textbook chapters on the Specific Valves.

C. THE FUTURE OF STRESS ECHO

In summary, SE has been proven to be vital resource in evaluation of CAD. Future advances with a focus on 3-dimensional SE, tissue Doppler and contrast perfusion scoring will likely further enhance its usefulness. Given the lack of radiation exposure and cost effectiveness,[113] it will likely to be used for many years to come. Future studies of comparative effectiveness research will likely help to refine its use as a diagnostic and prognostic tool in cardiovascular disease.[9]

VIDEO LEGENDS

Video 1 Abnormal exercise stress (parasternal long axis view)

Video 2 Abnormal exercise stress (parasternal short axis view)

Video 3 Abnormal exercise stress (apical 4 chamber view)

Video 4 Abnormal exercise stress (apical 2 chamber view)

Video 5 Normal dobutamine stress (parasternal long axis view)

Video 6 Normal dobutamine stress (parasternal short axis view)

Video 7 Normal dobutamine stress (apical 4 chamber view)

Video 8 Normal dobutamine stress (apical 2 chamber view).

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Chapter 18

Transesophageal Echocardiography

Seyed M Hashemi, Paul Lindower, Richard E Kerber

Chapter Outline

- History
- Guidelines
- Performance
- Safety
- Views
- Major Clinical Applications
  - Source of Embolism
  - Atrial Fibrillation
  - Endocarditis
- Structural Valve Assessment
- Acute Aortic Dissection
- Procedural Adjunct or Intraoperative TEE

INTRODUCTION

Over the past few decades, transesophageal echocardiography (TEE) has become a commonly performed imaging modality that is complementary to transthoracic echocardiography (TTE).[1-3] It is widely available, portable, provides real time imaging, and may be performed in a variety of clinical settings. These settings range from the ambulatory echocardiography laboratory to the cardiac catheterization laboratory as well as the intensive care unit. The use of the esophagus as an acoustic window has permitted the use of higher frequency transducers than those used in TTE studies. This results in improved spatial resolution allowing for visualization of small structures such as small vegetations and thrombi. In addition, the esophagus provides a unique window to posterior cardiac structures that are not well seen from the chest surface. These structures include the left atrial appendage, the interatrial septum, the mitral valve and the thoracic aorta.

HISTORY

Doppler TEE was initially reported by Side and Gosling in 1971 who performed continuous wave Doppler velocity measurements in the thoracic aorta using a dual element transducer mounted on a standard gastroscope.[4] In 1976, Frazin and his colleagues performed m-mode TEE imaging with a crystal mounted on a modified endoscopic probe (Fig. 1).[5] Hisanaga and his colleagues then reported the first two-dimensional (2D) TEE imaging in 1977 using a single rotating element enclosed in an inflatable oil bag to ensure contact with the esophageal wall.[6] More recently, TEE technology has significantly evolved and it currently permits all major echocardiographic capabilities. These include multiplane 2D imaging, color Doppler, pulse wave Doppler, continuous wave Doppler as well as three-dimensional (3D) volume acquisitions.

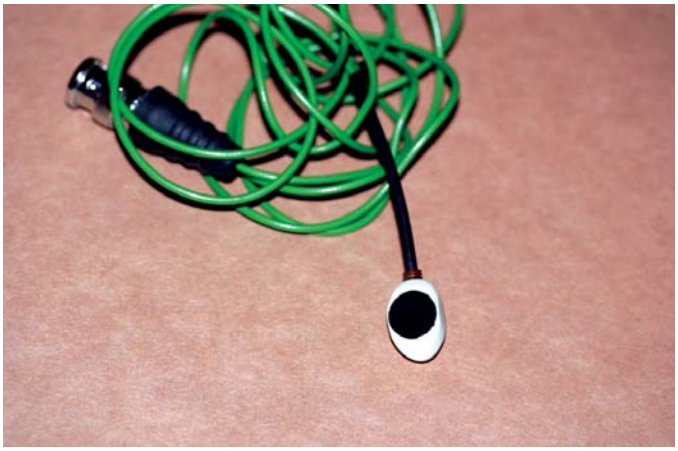


FIGURE 1: Frazin m-mode transesophageal echocardiography probe

GUIDELINES

Transesophageal echocardiography is a minimally invasive procedure that is being increasingly performed by cardiologists as well as anesthesiologists, surgeons and intensive care specialists. Guidelines for TEE competence have been published by the American College of Cardiology and American Heart Association.[7] Training requirements endorse attainment of at least Level 2 experience in TTE as well as the performance of 25 esophageal intubations with a TEE probe and further performance of approximately 50 TEE studies under the supervision of an experienced (Level 3 trained) echocardiographer.

PERFORMANCE

Transesophageal echocardiography should be performed in a laboratory equipped with appropriate tools as well as trained personnel. In addition to the ultrasound machine and multiplane

imaging probe, the laboratory must possess the necessary sanitizing equipment to disinfect the TEE probes and transducers. Since performing TEE requires conscious sedation, it necessitates the assistance of a nurse or another qualified assistant who monitors the patient's vital signs, arterial saturation and level of consciousness throughout the procedure. The patient's airway is also monitored with suctioning of oral secretions as necessary to reduce the risk of aspiration. Prior to esophageal intubation, a careful history is obtained from the patient to exclude significant laryngeal or gastroesophageal pathology. If necessary, the assistance of an anesthesiologist or gastroenterologist may be obtained to facilitate the intubation part of the procedure. The patient is kept fasting for at least 6 hours, and peripheral IV access is obtained to provide moderate conscious sedation with low doses of an IV benzodiazepine and a narcotic. The oropharynx is anesthetized by asking the patient to gargle and swallow a lidocaine solution. Additionally, topical benzocaine spray may be utilized if there is a significant residual gag reflex. Since topical benzocaine products carry risk of methemoglobinemia, we do not recommend using benzocaine spray routinely or as the first choice. The patient is then placed in the left lateral decubitus position with the neck flexed. The TEE probe is positioned in the posterior oropharynx. The esophagus is then intubated as the patient initiates a swallow.

SAFETY

The procedural risks of TEE are relatively small but may include: transient throat pain, laryngospasm, aspiration, hypoxemia, hypotension, dysrhythmia, bleeding, esophageal rupture or even death. In a large European multicenter study analyzing 10,419 TEE examinations, premature termination was necessary in 90 procedures (0.88%).[8] Most of these were due to patient intolerance to the probe. There were also 18 patients who had pulmonary, cardiac, bleeding related or other complications. One of the bleeding related complications resulted in a death (0.01%). In general, bleeding complications are rare and usually mild in the face of therapeutic levels of anticoagulation. The risk of bacteremia with TEE is very low and most operators do not routinely treat with prophylactic antibiotics. Methemoglobinemia is a potentially life-threatening complication of topical benzocaine use. It is suspected clinically in the presence of cyanosis with normal arterial oxygen saturation and may be treated with methylene blue and supportive measures. Contraindications to TEE include esophageal stricture, diverticulum, tumor and recent esophageal or gastric surgery. Relative contraindications include prior mediastinal irradiation, esophageal varices and coagulopathy. Patients should always be questioned about a history of dysphagia, esophageal varices and/or liver disease before attempting intubation.

VIEWS

Using a multiplane transesophageal echoscope, standard echocardiographic views of the heart may be obtained.[9] The American Society of Echocardiography (ASE) recommends twenty cross-sectional views composing a comprehensive TEE examination (Figs 2A to T). The probe is initially advanced into the proximal esophagus, and images are taken from four general positions: (1) the basal esophagus; (2) mid esophagus or 4-chamber view; (3) transgastric and (4) aortic positions. In addition, the plane of the scan may be rotated through an arc of 180°. At 0°, the plane of interrogation is horizontal or transverse to the heart. More vertical orientation of the crystal provides longitudinal sectioning of the heart. The probe may also be manipulated anteriorly or posteriorly by flexing or extending the probe respectively in the coronal plane.

MAJOR CLINICAL APPLICATIONS

SOURCE OF EMBOLISM

According to the 2011 ASE appropriateness criteria, TEE evaluation for cardiovascular source of embolic event in a stroke patient with no identified non-cardiac source is considered highly appropriate (score 7/9). Up to 15–20% of ischemic strokes may be on the basis of an intracardiac source.[10] Transesophageal echocardiography (TEE) has been found to be superior to TTE in detecting cardiac sources of embolism[11,12] and may also be a more cost effective approach in their detection.[13] The yield of TEE is higher in patients with clinical cardiac disease including atrial fibrillation, rheumatic mitral stenosis, prosthetic valves, atherosclerosis, left ventricular aneurysm and infective endocarditis.[14] Potential cardiac sources of embolism may be categorized as: (1) masses (thrombus, atherosclerotic plaque, vegetation or tumor); (2) passageways for paradoxic embolization (patent foramen ovale and atrial septal aneurysm) and (3) propensity for thrombus formation (left atrial spontaneous echo contrast, mitral annular calcification).

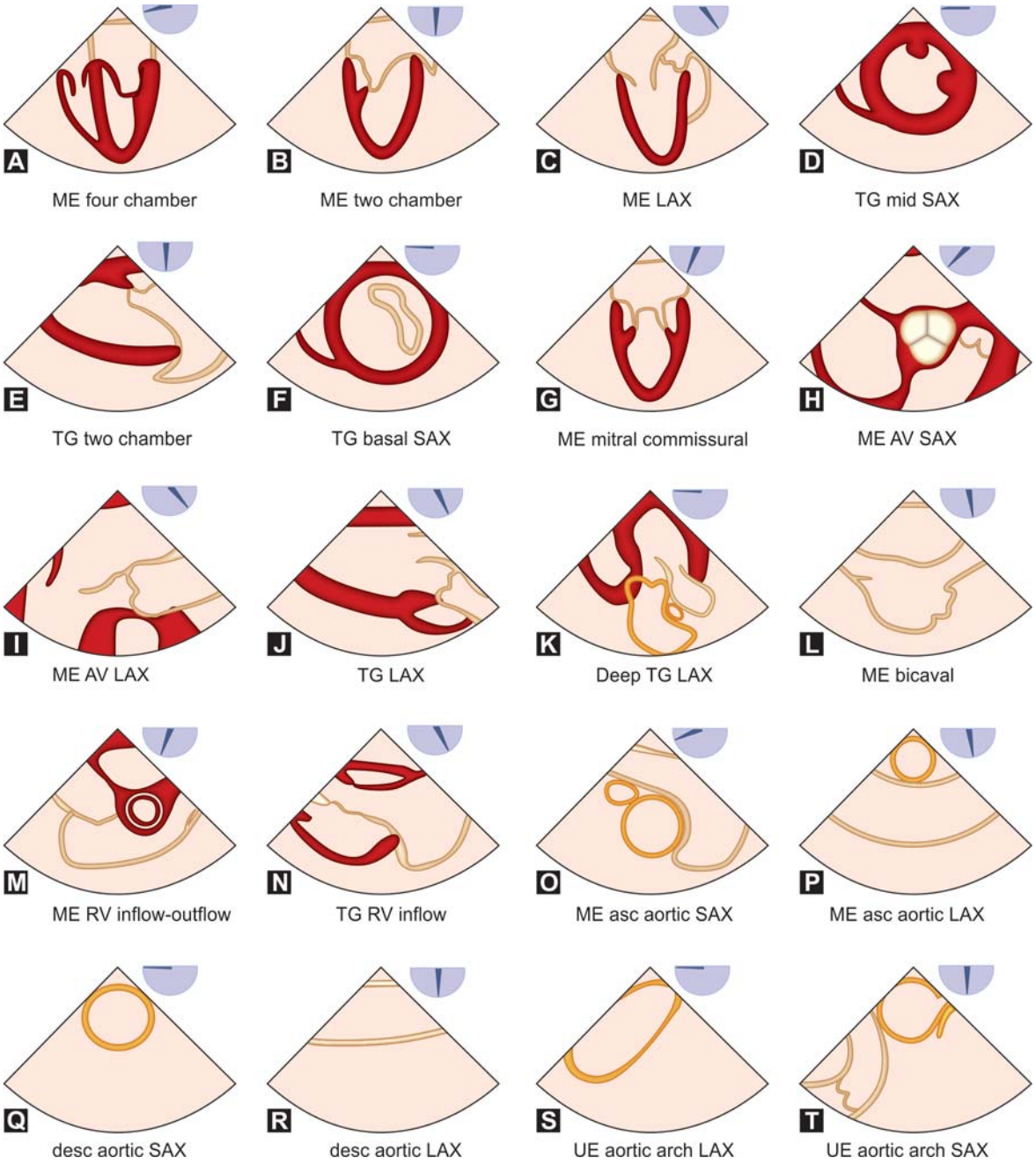
Masses

Left atrial thrombus is commonly associated with atrial fibrillation and rheumatic mitral stenosis. It may be seen in up to 27% of patients with chronic atrial fibrillation (Fig. 3).[15] It is only present in 1% of patients in sinus rhythm and no mitral valve disease or left atrial dysfunction.[16] Left ventricular thrombus occurs in approximately 5% of patients with acute myocardial infarction, particularly when the infarct is anterior in location.[17] It is also seen in about 4% of patients with dilated cardiomyopathy. These same cardiomyopathy patients also have an even greater risk of developing left atrial thrombus.[18] Prosthetic valves may develop thrombus, especially mechanical valves in the atrioventricular position, in the setting of subtherapeutic anticoagulation.[19] Thrombi may display high-risk characteristics for embolization which include large size, protruding appearance, high mobility and central echolucency.

Aortic atherosclerotic plaques are associated with hypertension and are more common in elderly patients. Plaques may be categorized as simple or complex with the latter being more prone to thromboembolization. Features of complex atheromas include a wall thickness greater than 4 mm, ulceration, mobility, pedunculation and echolucency (Fig. 4).[20]

Vegetative lesions are readily identified in patients with clinical features of infective endocarditis (Fig. 5). Vegetation size greater than 1 cm, vegetation mobility and mitral location are all risk factors for systemic embolization.[21] Additionally, TEE permits visualization of perivalvular abscess in patients with infective endocarditis (Fig. 6).

Primary cardiac tumors commonly include myxomas and papillary fibroelastomas. Myxomas are usually benign tumors



FIGURES 2A TO T: Twenty cross-sectional views composing the recommended comprehensive TEE examination. Approximate multiplane angle is indicated by the icon adjacent to each view. (Abbreviations: ME: Mid esophageal; LAX: Long axis; TG: Transgastric; SAX: Short axis; AV: Aortic valve; RV: Right ventricle; Asc: Ascending; Desc: Descending; UE: Upper esophageal). (*Source:* Reproduced with permission from Shanewise JS et al. ASE/SCA guidelines for performing a comprehensive intraoperative multiplane TEE. J Am Soc Echocardiogr. 1999;12:884-900)

found in the left atrium attached to the interatrial septum in the region of the fossa ovale (Fig. 7). They may present with embolization greater than 50% of the time.[22] Papillary fibroelastomas generally are pedunculated and commonly located on the aortic or mitral valve, although they are also found on the endocardial surface.[23]

Passageways for Paradoxic Embolization

Interatrial septal abnormalities are associated with thromboembolic events. These include atrial septal defect as well as patent foramen ovale with or without an atrial septal aneurysm.[24] Patients with an interatrial shunt may have intermittent right-to-left shunting particularly if there is a transient increase in right-sided pressure as occurs with coughing or performing a Valsalva maneuver. In this setting, venous thrombi may potentially enter the systemic circulation resulting in paradoxical embolism. Right-to-left shunting may be demonstrated by the administration of intravenous agitated saline contrast. Approximately 25% of normal hearts are found to have a patent foramen ovale at the time of autopsy.[25] A patent foramen ovale

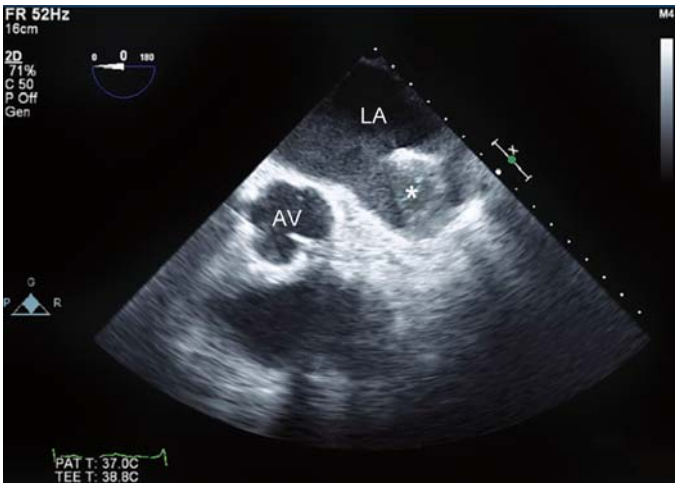


FIGURE 3: Transesophageal echocardiography (TEE) showing a left atrial appendage thrombus (depicted by the asterisk) in a patient with chronic atrial fibrillation. Note the presence of smoke in the left atrium. (Abbreviations: LA: Left atrium; AV: Aortic vlave)

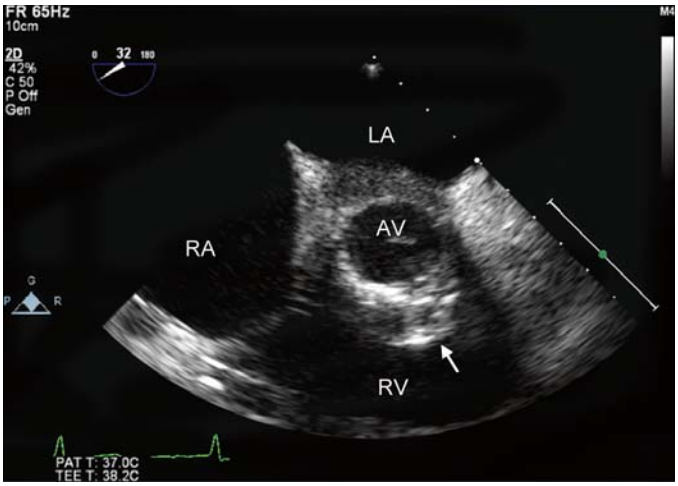


FIGURE 6: Short axis view through aortic valve demonstrating a bioprosthetic aortic valve with an aortic root abscess (arrow). (Abbreviations: LA: Left atrium; RA: Right atrium; RV: Right ventricle; AV: Aortic valve)

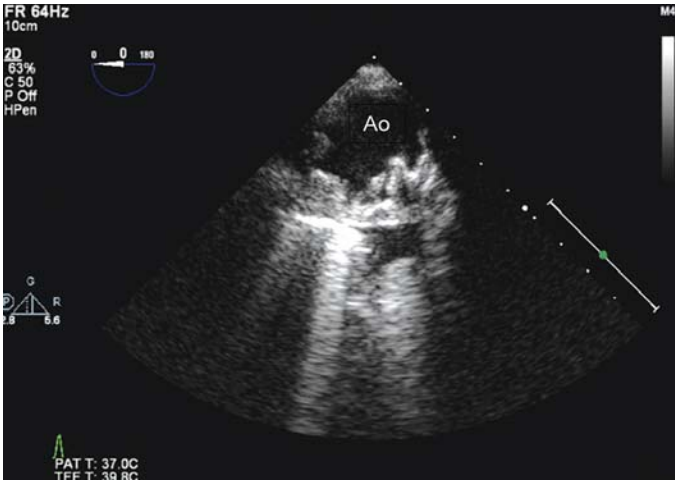


FIGURE 4: Transesophageal echocardiography (TEE) showing an example of atheroma in the descending aorta. Note the complex appearance of the atheroma with echodense and echolucent areas. (Abbreviation: Ao: Aorta)

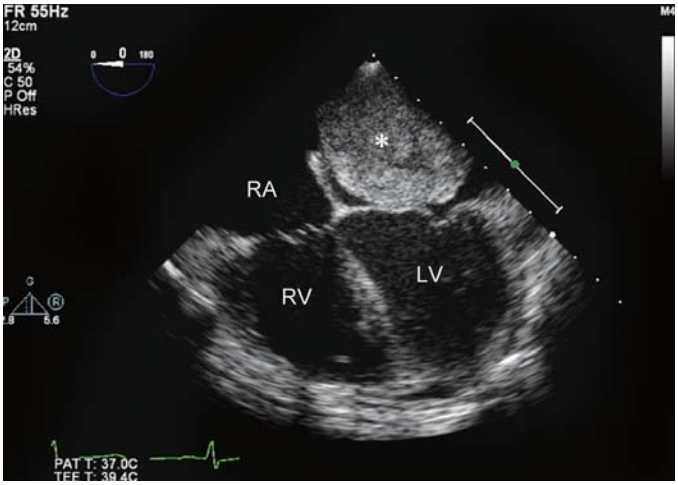


FIGURE 7: An example of a myxoma (depicted by the asterisk) in the left atrium. Myxomas vary in size and sometimes may occupy most of the left atrium. In this case, the tumor impedes the blood flow to the left ventricle during diastole which may lead to hemodynamic instability. (Abbreviations: RA: Right atrium; RV: Right ventricle; LV: Left ventricle)

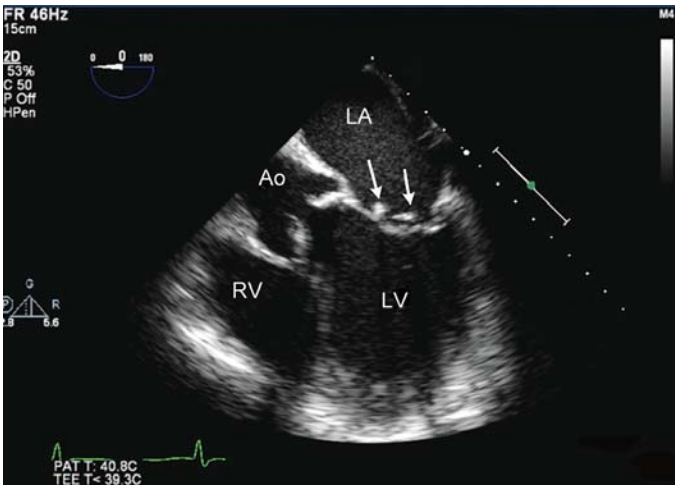


FIGURE 5: An example of vegetations (indicated by the arrows) involving the mitral valve in a patient with infective endocarditis. (Abbreviations: LA: Left atrium; Ao: Aorta; RV: Right ventricle; LV: Left ventricle)

alone is not associated with an increased risk of recurrent stroke or death in patients with a cryptogenic stroke. An atrial septal aneurysm is a congenital variant with redundant, mobile, interatrial septal tissue in the region of the fossa with a base measuring 15 mm and an excursion of at least 10 mm during the cardiorespiratory cycle.[26] Atrial septal aneurysms are associated with patent foramen ovale (Fig. 8). There is conflicting data as to whether the combination of a patent foramen ovale and an atrial septal aneurysm confers additional risk for recurrent stroke or death among patients with a cryptogenic stroke.[24,27]

Propensity for Thrombus Formation

Spontaneous echo contrast or smoke-like echoes are strongly associated with left atrial thrombi. This occurs in the setting of erythrocyte aggregation in low shear rate conditions and is



FIGURE 8: Interatrial septal aneurysm (denoted by the arrow) is often associated with a patent foramen ovale demonstrated by a positive bubble study in this patient. (Abbreviations: LA: Left atrium; RA: Right atrium)

mediated by plasma proteins such as fibrinogen.[28,29] These proteins reduce electrostatic forces on the surface of red blood cells which are usually repulsive, thus promoting rouleaux formation. Mitral annular calcification is commonly associated with the elderly, left atrial enlargement and atrial fibrillation. It is unclear whether this may also act as a nidus for thrombus formation.[30]

Transesophageal echocardiography is warranted when the history and physical examination is suggestive of a cardiac source of embolism and the treatment plan would be modified based upon its results.

ATRIAL FIBRILLATION

Atrial fibrillation is associated with a 4–6 fold increased risk of thromboembolism presumably from left atrial appendage thrombi.[31] Thrombi in the left atrial appendage have been demonstrated in up to 14% of patients with new onset atrial fibrillation and up to 27% of those in chronic atrial fibrillation (Fig. 3).[15] The conversion of atrial fibrillation to sinus rhythm involves a small risk of thromboembolism from blood clots that may form in the left atrial appendage during or shortly after sinus rhythm restoration. A conventional approach to cardioversion involves providing anticoagulation for at least 3 weeks before the procedure and continuing anticoagulation therapy for an additional 4 weeks afterward. With the advent of TEE, the left atrial appendage can be assessed for the presence of thrombus. This is the basis of a TEE guided strategy for cardioversion. If a thrombus is not detected, cardioversion may be expedited and performed immediately after TEE. If a thrombus is detected, anticoagulation may be intensified and then the TEE should be repeated before further cardioversion attempts are made. The ACUTE trial was a large, multicenter randomized study that compared the performance of a TEE guided strategy with a conventional strategy in patients with new onset atrial fibrillation.[31] Its major finding was that the TEE guided strategy afforded a shorter period of anticoagulation with a shorter time to cardioversion and fewer bleeding events when compared to the conventional strategy. There were no differences in embolization rate, death, maintenance of sinus rhythm or functional status between the two groups. It was felt by the authors that patients best suited for the TEE guided strategy are those who are hospitalized with new onset atrial fibrillation, or who have subtherapeutic or undetermined anticoagulation status, or who may be at a higher-risk for bleeding or thromboembolism.

ENDOCARDITIS

Transesophageal echocardiography has greatly facilitated the diagnosis of endocarditis. It permits improved detection of small vegetations and the identification of coexisting paravalvular abnormalities. Although the procedure is minimally invasive and entails added expense, it has been shown to have higher sensitivity and specificity than TTE and is also better able to assess complications of endocarditis than TTE.[32] These complications include abscess formation, valve perforation, fistulous communication or valvular regurgitation. The modified Duke criteria for endocarditis include four major criteria on the basis of echocardiography findings.[33] These are the presence of an oscillating mass (vegetation), abscess, partial dehiscence of a prosthetic valve and new valvular regurgitation. Vegetation characteristics by echocardiography may also indicate embolic potential. Larger vegetations are greater than 1 cm, increased mobility and mitral valve involvement are associated with increased embolic risk.[21] This risk of embolization is reduced with the duration of antibiotic therapy.[34] Right-sided valve lesions are not necessarily better demonstrated by TEE as they are in the far field of view; except in the transgastric position where the tricuspid valve is optimally imaged. In addition, prosthetic valve endocarditis may be confounded by impaired visualization of the valves from shadowing and reverberations associated with the prosthetic material. However, in the case of mitral valve prosthesis, the TEE probe is positioned behind the prosthetic valve and assessment is not confounded by these issues.[35] A negative TEE study in a patient with an intermediate likelihood of endocarditis effectively rules out endocarditis. A repeat TEE study would be warranted in high likelihood patients in approximately 7–10 days; however, as smaller vegetations may not be initially detected.[36]

STRUCTURAL VALVE ASSESSMENT

Transesophageal echocardiography is an ideal technique for visualization of the mitral valve apparatus owing to the proximity of the TEE probe to the left atrium. Mitral valve prolapse (Fig. 9, Videos 1 and 2) and flail mitral valve (Fig. 10, Video 3) are readily assessed by TEE. Another use of TEE is to identify the mechanism and severity of mitral valve regurgitation (Figs 11 and 12, Video 4). In patients with mitral stenosis in whom a high quality transthoracic echo can be obtained, TEE may not necessarily provide additional information. However TEE is capable of demonstrating high-resolution images of mitral stenosis (Fig. 13, Video 5).

Transesophageal echocardiography allows for highly accurate diagnosis of structural valvular abnormalities in aortic positions. Higher image resolution produces sharper images of aortic valve cusps and clear visualization of bicuspid aortic valve (Fig. 14, Video 8). Transesophageal echocardiography is also a

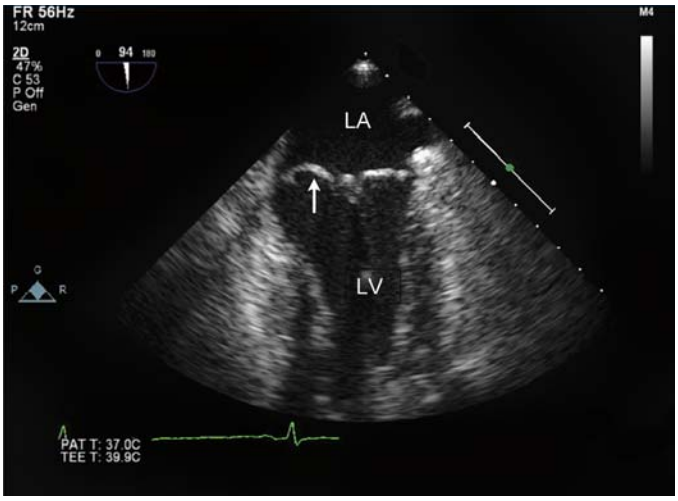


FIGURE 9: A 2-chamber view shows prolapse of the mitral valve posterior leaflet (arrow). (Abbreviations: LA: Left atrium; LV: Left ventricle)

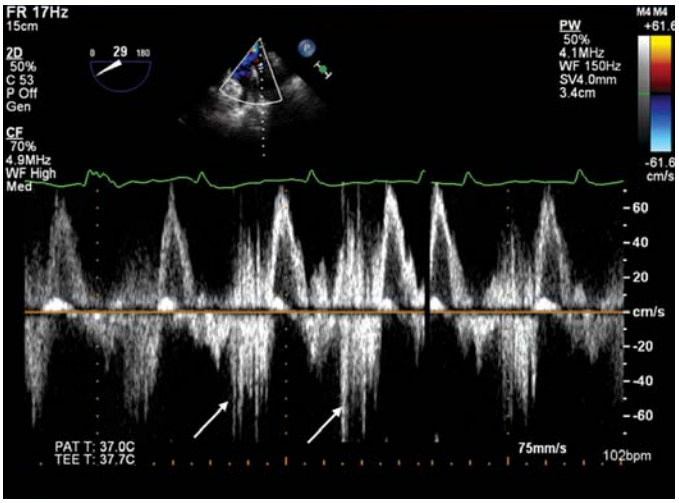


FIGURE 12: Pulmonary vein pulse Doppler imaging recorded from transesophageal echocardiography (TEE) in a patient with mitral regurgitation. Note the systolic flow reversal through the pulmonary vein indicating severe mitral regurgitation

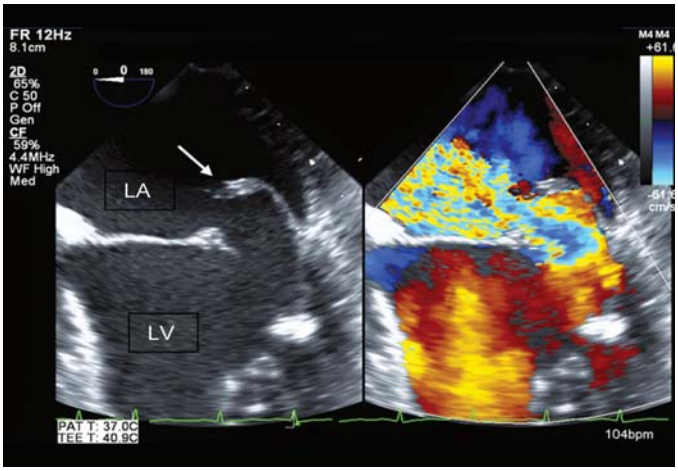


FIGURE 10: Close-up view of mitral valve showing flail posterior leaflet (arrow). The right-sided image demonstrates a regurgitant jet directed anteriorly. (Abbreviations: LA: Left atrium; LV: Left ventricle)

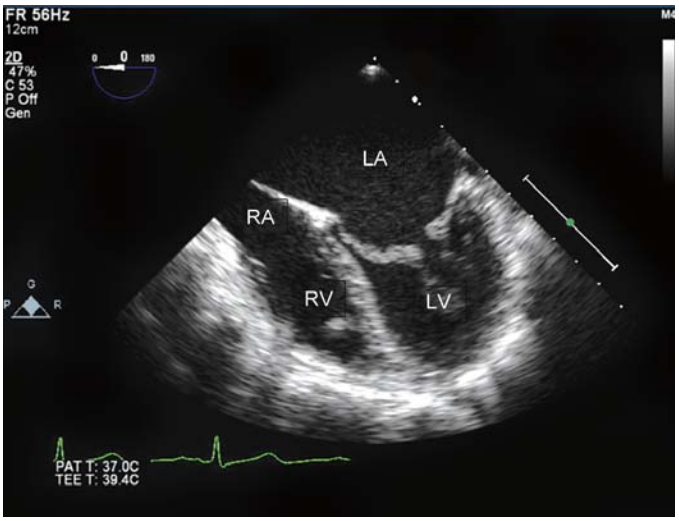


FIGURE 13: A 4-chamber view transesophageal echocardiography (TEE) showing rheumatic mitral stenosis. Note the thickened mitral valve leaflets with restricted mobility. (Abbreviations: LA: Left atrium; RA: Right atrium; RV: Right ventricle; LV: Left ventricle)

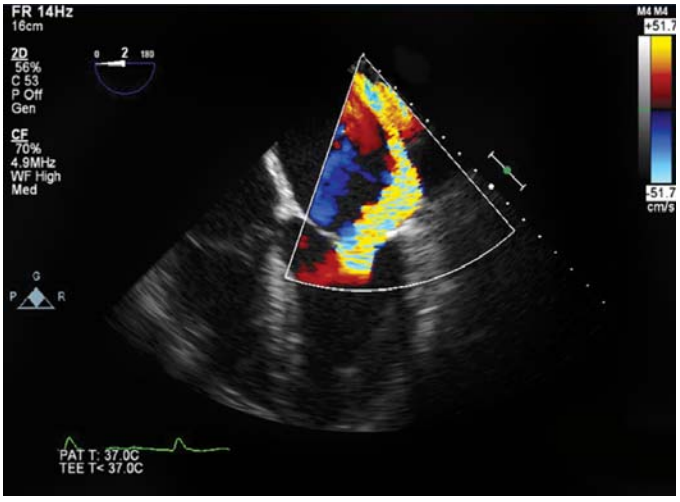


FIGURE 11: A 4-chamber view showing mitral regurgitation. Note the eccentric posteriorly directed MR jet indicating anterior MV pathology

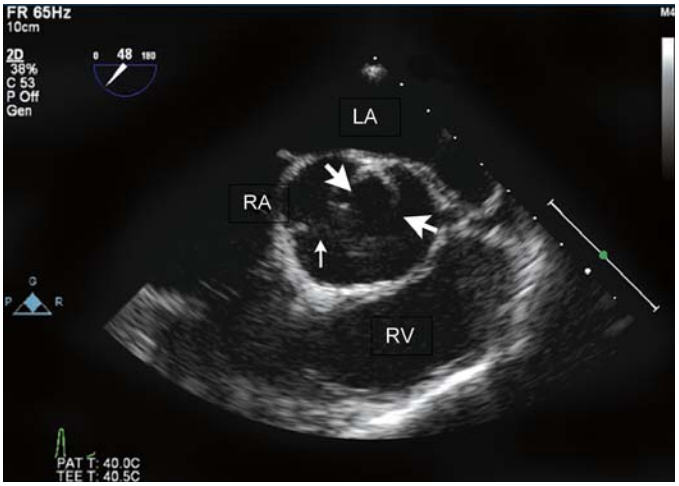


FIGURE 14: A short axis view of TEE through aortic valve showing an example of bicuspid aortic valve (thick arrows indicate the two leaflets and the thin arrow points to the raphe). (Abbreviations: LA: Left atrium; RA: Right atrium; RV: Right ventricle)

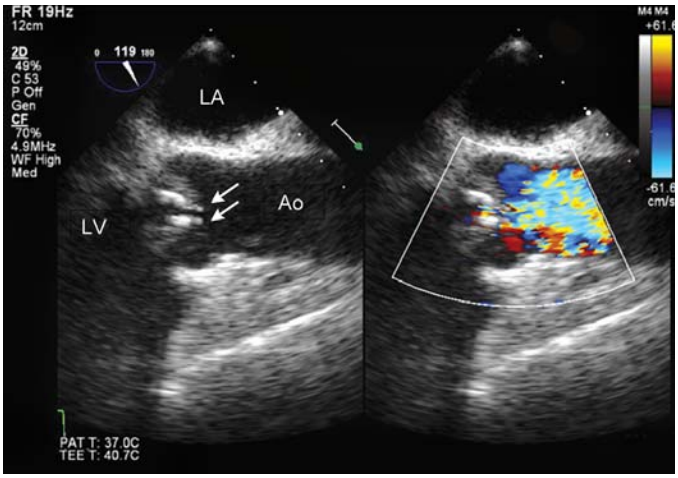


FIGURE 15: A long axis view transesophageal echocardiography (TEE) through the aortic valve from a patient with aortic stenosis. Note the severely restricted aortic valve leaflet mobility (arrows) causing turbulent flow (depicted by color Doppler on the right sided image). (Abbreviations: LA: Left atrium; LV: Left ventricle; Ao: Aorta)

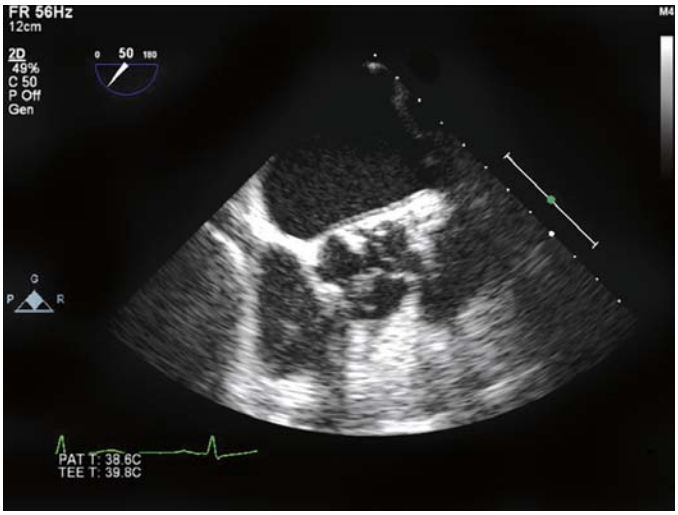


FIGURE 16: A short axis view of aortic valve in a patient with aortic stenosis showing restricted aortic valve leaflet mobility

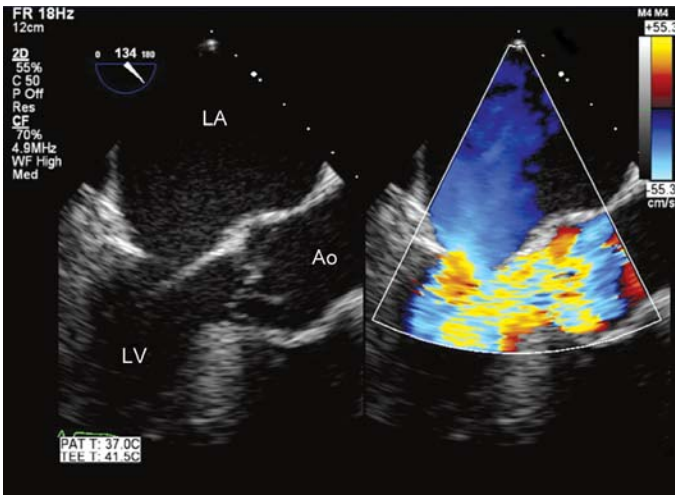


FIGURE 17: A 3-chamber view transesophageal echocardiography (TEE) showing long axis of the aortic valve with severe aortic insufficiency. (Abbreviations: LA: Left atrium; LV: Left ventricle; Ao: Aorta)

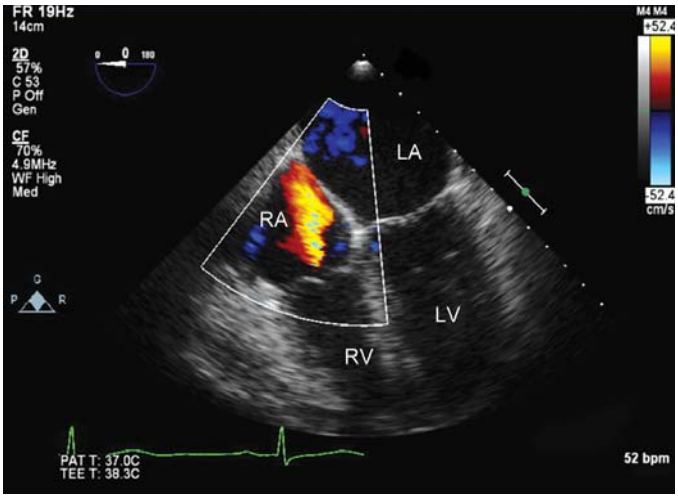


FIGURE 18: A 4-chamber view TEE showing tricuspid regurgitation. (Abbreviations: LA: Left atrium; RA: Right atrium; RV: Right ventricle; LV: Left ventricle)

valuable tool for assessment of aortic stenosis (Figs 15 and 16, Videos 6 and 7) and aortic regurgitation (Fig. 17, Video 8).

The valvular structures on the right side of the heart being positioned anteriorly (in the far field of view from the TEE probe) are less conducive to assessment by TEE. However the tricuspid valve in most cases can be assessed fairly accurately in transgastric view (Video 9). Four-chamber view is suitable for diagnosis of tricuspid regurgitation (Fig. 18, Video 10). Pulmonary valvular abnormalities are relatively rare and not necessarily easier evaluated by transesophageal echocardiography.

Prosthetic valves present several limitations to echocardiographic techniques due to artifacts that are created from shadowing and reverberation of ultrasound by the non-biologic material in the valve. Transthoracic Doppler echocardiography provides very reliable hemodynamic information regarding prosthetic valve function. Assessment of prosthetic mitral valve function by TTE, however, is difficult due to its posterior location. TEE is indicated when there is a high clinical suspicion of valvular dysfunction, there are difficulties surrounding poor acoustic transthoracic windows, or there is concern regarding prosthetic mitral valve function. Transesophageal echocardiography offers significant advantages over TTE, although the combination of both studies allows for a complete assessment of prosthetic valve function. All mechanical prosthetic valves demonstrate a small amount of transvalvular regurgitation due to the closure volume of the prosthesis with movement of the occluder disk.[37] In some prosthetic valves, gaps between the valve posts or holes in the valve disk result in small amounts of prosthetic valve regurgitation. This normal regurgitation varies depending on the type of prosthesis and must be distinguished from pathologic regurgitation. Paravalvular regurgitation is always pathologic and bioprosthetic valves generally display only trace or no regurgitation. An increased transvalvular pressure gradient compared with baseline or established normal values will be observed in patients with an obstructed prosthetic valve. The etiology of obstruction includes: pannus ingrowth, thrombus or vegetation. The most common etiology of prosthetic valve obstruction is thrombus formation. This may be further suggested in the setting of a short duration of symptoms,

subtherapeutic anticoagulation, and demonstration of a soft, mobile echodensity attached to the valve occluder.[38] Thrombolytic therapy may be an effective alternative to surgery in such patients although it is associated with modest morbidity and mortality.[39]

ACUTE AORTIC DISSECTION

Transesophageal echocardiography has significant advantages over magnetic resonance imaging (MRI) or computed tomography (CT) in the assessment of acute aortic dissection.[40] It may be rapidly performed at the bedside of patients who are unstable for transport to MRI or CT suites. It may also be performed in the operating room as patients are being prepared for surgery. The characteristic finding in patients with an aortic dissection is the identification of an intimal flap (Figs 19 and 20). Furthermore, the location and extent of the flap as well as entry and exit points may be well delineated by TEE. Additional pertinent findings on TEE would include the aortic diameter, presence of thrombus in the false lumen, presence of a pericardial effusion, presence of aortic regurgitation, or involvement of branch vessels or coronary arteries. An aortic intramural hematoma is characterized by thickening of the aortic wall greater than 7 mm and may be either crescentic or circular in nature with evidence of an intramural accumulation of blood.[41] A penetrating atherosclerotic ulcer may be identified as an ulcer-like projection into an aortic intramural hematoma, usually in the descending aorta.[42] These entities may coexist with an aortic dissection and they are managed in a similar fashion. Acute aortic dissection patients with proximal involvement of the aorta are considered for emergent surgery. Patients with isolated distal aortic involvement are initially managed medically, but may require surgery if propagation, leak or ischemic complications develop. The sensitivity of TEE to detect aortic dissection is approximately 98%. The specificity is somewhat lower at 95% due to false positive findings in the ascending aorta.[40] Reverberation artifacts may be differentiated from dissection by using m-mode echocardiography.[43] The upper portion of the ascending aorta and arch is difficult to visualize due to the interposition of the air-filled trachea between the esophagus and the aorta.

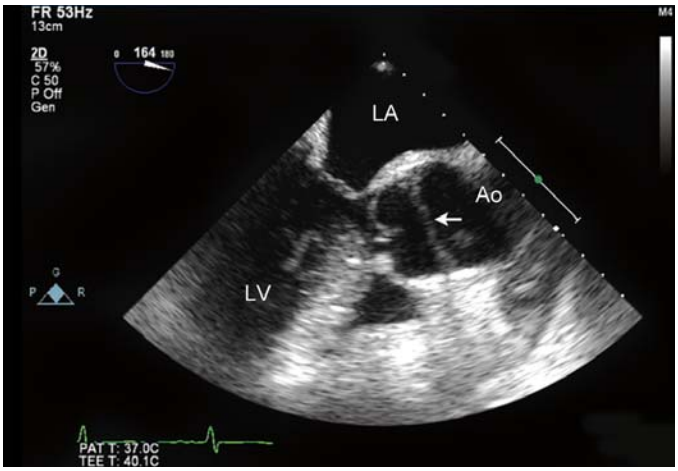


FIGURE 19: A 3-chamber view transesophageal echocardiography (TEE) demonstrating type A aortic dissection. The arrow denotes the dissection flap. (Abbreviations: LA: Left atrium; Ao: Aorta; LV: Left ventricle)



FIGURE 20: Longitudinal view of the descending aorta demonstrating type B aortic dissection. The arrow indicates the dissection flap

PROCEDURAL ADJUNCT OR INTRAOPERATIVE TEE

Transesophageal echocardiography is commonly used as an adjunct to fluoroscopic imaging during interventional procedures in the cardiac catheterization laboratory. In patients with significant right-to-left shunting, percutaneous closure of an atrial septal defect or patent foramen ovale is an attractive alternative to open surgical repair. Transesophageal echocardiography offers the advantage of real time imaging of the interatrial septum as well as the surrounding structures, the closure device and catheters.[44] The atrial septal defect size may be measured by TEE for selection of the appropriate closure device (Fig. 21). The position and deployment of the device is also guided by TEE. Further, the adequacy of closure of the defect and the detection of potential complications may be determined with TEE. Transesophageal echocardiography is also used to guide many aspects of mitral balloon valvuloplasty.[45] It may be used for patient selection, guidance of transseptal puncture, exclusion of left atrial appendage thrombus, and wire and balloon positioning. It is also used to assess for potential complications of the procedure including atrial septal defect,

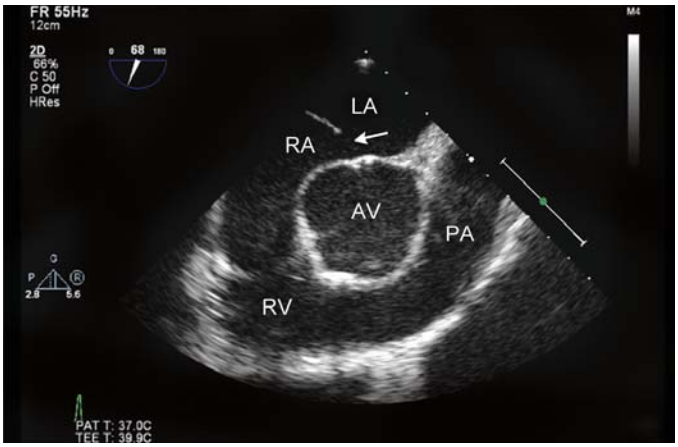


FIGURE 21: Short axis view through aortic valve demonstrating a defect in interatrial septum (depicted by the arrow) which represents an example of secundum atrial septal defect. (Abbreviations: LA: Left atrium; RA: Right atrium; RV: Right ventricle; PA: Pulmonary artery; AV: Aortic valve)

worsening mitral regurgitation or cardiac tamponade and may shorten procedural and fluoroscopic times.[46] Intraoperative TEE is increasingly performed for the evaluation of the mitral valve during surgical repair. A comprehensive examination of the mitral valve can accurately guide the surgeon.[47] Assessment of leaflet length, thickness, mobility and calcification is obtained. Leaflet motion may be characterized as excessive, restrictive or normal, and specific scallop involvement can be identified. In addition, annular dimension and calcification, left ventricular function, and the degree and direction of regurgitant jets are all noted. The anatomy most conducive to surgical repair is isolated posterior mitral leaflet prolapse. This is approached with quadrangular resection and placement of an annuloplasty ring.

CONCLUSION

Transesophageal echocardiography provides significant complementary information to TTE. Although semi-invasive in nature, it is generally safe when performed by appropriately trained operators. It may be rapidly performed at the bedside of critically ill patients. In some clinical applications, it is superior to TTE such as the detection of left atrial appendage thrombus, vegetations, aortic dissection and prosthetic mitral valve function. Transesophageal echocardiography will likely continue to expand in its application with future technologic advancements including 3D echocardiography which is discussed in a separate chapter "Real Time Three-Dimensional Echocardiography".

VIDEO LEGENDS

Videos 1 and 2	Mitral valve prolapse
Video 3	Flial mitral valve
Video 4	Mitral valve regurgitation
Video 5	Mitral stenosis
Videos 6 and 7	Aortic stenosis
Video 8	Aortic regurgitation
Video 9	Tricuspid valve
Video 10	Tricuspid regurgitation.

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Chapter 19

Real Time Three-dimensional Echocardiography

Manjula V Burri, Richard E Kerber

Chapter Outline

- Technique
- Clinical Applications
  - Determination of Left Ventricular Volumes and Function
  - Determination of Regional Wall Motion and Dyssynchrony
  - Applications to Stress Imaging
  - Myocardial Contrast Imaging and Quantification of Perfusion
  - Determination of Left Ventricular Mass
  - Assessment of Right Ventricular Volumes and Function
  - Assessment of Left and Right Atria
  - Assessment of Valvular Disorders
  - Miscellaneous Conditions
  - Guidance of Percutaneous Procedures
- Future Directions
- Limitations

INTRODUCTION

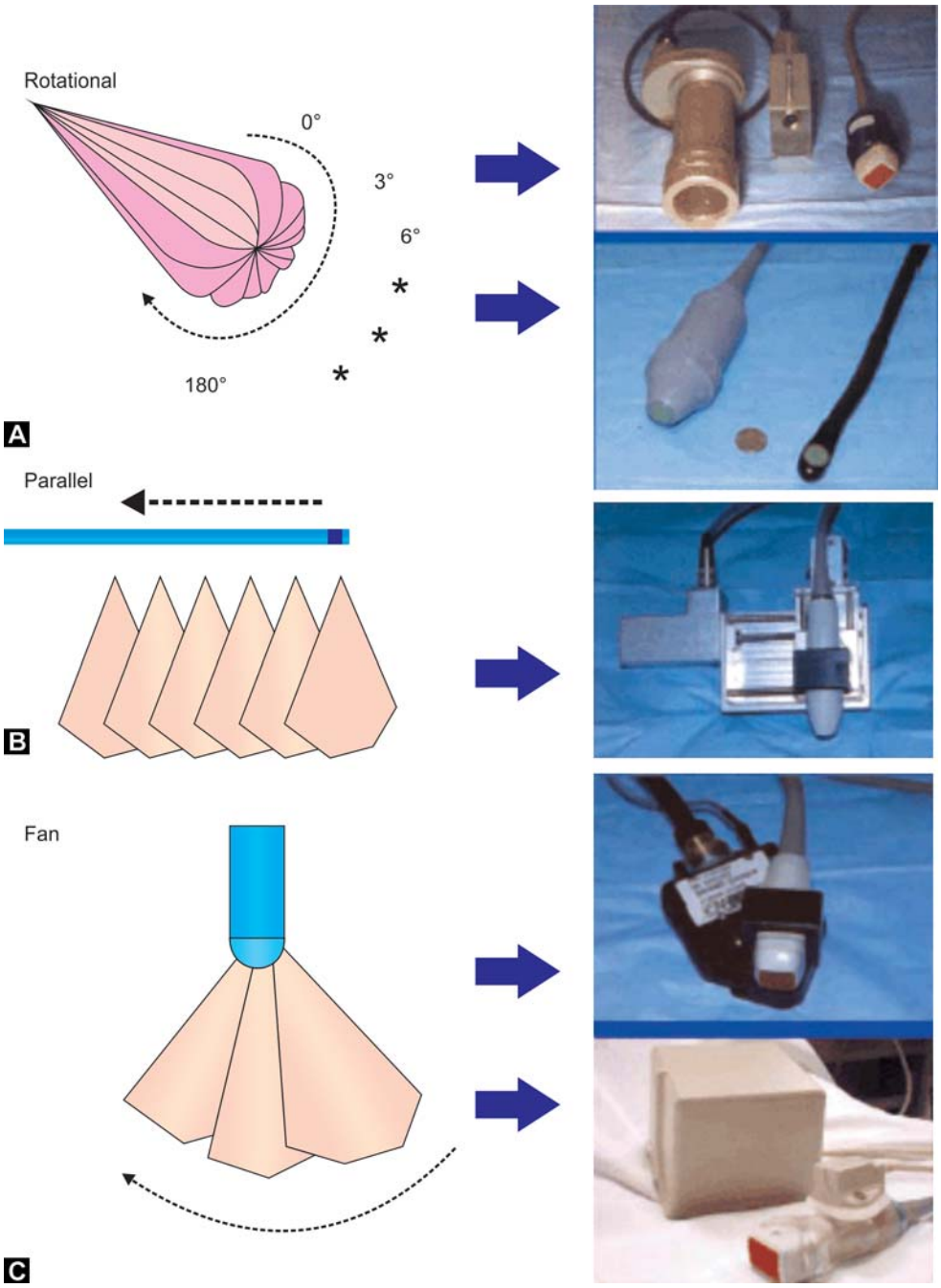
The heart is a three-dimensional structure with complex asymmetric anatomy and sophisticated functional mechanisms. Two-dimensional echocardiography (2DE) is a thin slice sector imaging technique that requires mental reconstruction and geometrical assumptions, and any slight error in image plane positioning will cause substantial errors in both qualitative and quantitative interpretation. This created the need and niche for three-dimensional echocardiography (3DE), the most preliminary of which was performed by Dekker and his colleagues in 1974.[1] They used a long mechanical arm to locate the position of the transducer in space, and allow alignment of multiple 2D images to generate a 3D image. Regrettably, they found the images to be primitive and the equipment to be impractical for clinical use. Subsequently, Raab and his colleagues[2] developed an electromagnetic locator that ultimately led to free-hand scanning, but this relatively advanced technique of those times was not put to much clinical use due to the complexity of equipment and time needed.

Drastically changing clinical practice, in the early 1990s transesophageal 3DE (3D TEE) was introduced; this used a special transesophageal transducer that allowed moving a phased-array transducer element parallel within the esophagus. The movement of this transducer was controlled by a stepper motor gated to the patient's Electrocardiograph (EKG) and respiratory cycle, monitored on a separate machine. One of the first 3D reconstructions using a multiplane TEE acquisition was performed by Nanda in 1992.[3] Subsequently, a mechanical device was used to advance a standard 2DE transducer over a region of interest and applied transthoracic 3DE (3D TTE) acquisition methods. Researchers then evaluated several different acquisition devices like parallel scan device, fan-like scan motion and rotational acquisition devices (Figs 1A to C) and digital reconstruction of spatially recorded images.[4] Mostly, rotational type devices achieved the greatest popularity, with others rarely used. Of note, all such techniques required laborious offline reconstruction to render 3D volumes, to permit further analysis and hence were not readily embraced.

The revolutionary technique of real time three-dimensional echocardiography (RT3DE) was originally developed by von Ram at Duke University during the last decade of the 20th century.[5] However, due to the limitations posed by lack of high speed computer processing and memory, true real time 3D imaging was impractical. Instead, multiple 2D slices derived from 3D imaging were available online but 3D volume rendering was possible only offline at a separate workstation.

Live or real time 3DE, that is in practice now, made all the above forms of reconstructive 3DE obsolete. This was made possible by enhanced computer processing speed and memory, and the invention of a micro-beamformer. The micro-beamformer has capabilities to fully sample more than 3,000 elements in a 10,000 channel dense matrix array transducer and generate a pyramidal burst of ultrasound. Initially limited to transthoracic capabilities, RT3DE is now also available in the transesophageal mode of image acquisition.

The newer generation RT3DE transducers available, depending on the vendor and model, are varyingly capable of providing instantaneous, dense, EKG gated, stitched 3D volumes with and without color Doppler within a single breath hold, or non-stitched sparse images even within a single heart beat. The latter increases the speed of acquisition, eliminates not only the need for inconvenient breath holding but also the stitch artifacts associated with the former. In addition, most new transducers have 2D, M-mode, biplane imaging, color and spectral Doppler; and harmonic generation capabilities. The footprint of the most



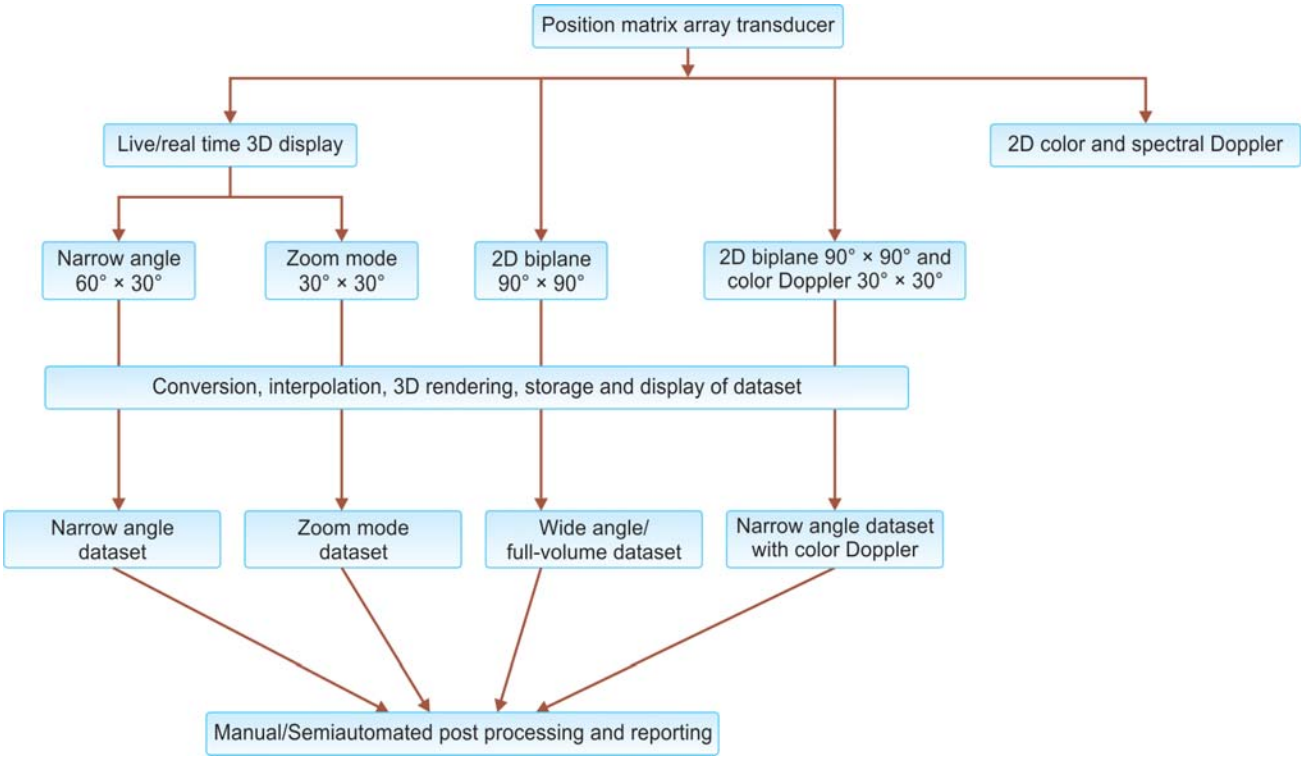
FIGURES 1A TO C: (A) Rotational methods of data collection used commercially available probes attached to an external device that mechanically rotated the probe (A, top) at defined angle increments or (A, bottom) internally electronically driven imaging planes using a transthoracic or transesophageal probe; (B) Parallel acquisition mode using a motorized device is illustrated; (C) Fanlike acquisition using a probe attached to either a motor-driven device (C, top) or a magnetic sensor (C, bottom). (*Source:* Modified from Sugeng L, Weinert L, Thiele K, et al. Real time three-dimensional echocardiography using a novel matrix array transducer. Echocardiography. 2003;20:623-35)

recent probes is small enough to image even pediatric patients. They also conveniently display, after volume rendering, 2–3 orthogonal 2D imaging planes if chosen besides several transverse planes. The full volume datasets or the real time images can be further processed as described below to extract more information. The authors focus on this latest RT3DE technique in this chapter for all practical purposes unless specified.

TECHNIQUE

Obtaining the best quality 2DE images is of paramount importance to acquiring interpretable 3D datasets. The Flow chart 1 shows the general overview, capabilities and commonly used pathways of RT3DE. The 3D capable matrix array transducer should be positioned to obtain the 2D view desired, the echocardiographic, color and time gain and compression should be

FLOW CHART 1: The general overview, capabilities and commonly used pathways of live/real time three-dimensional echocardiography

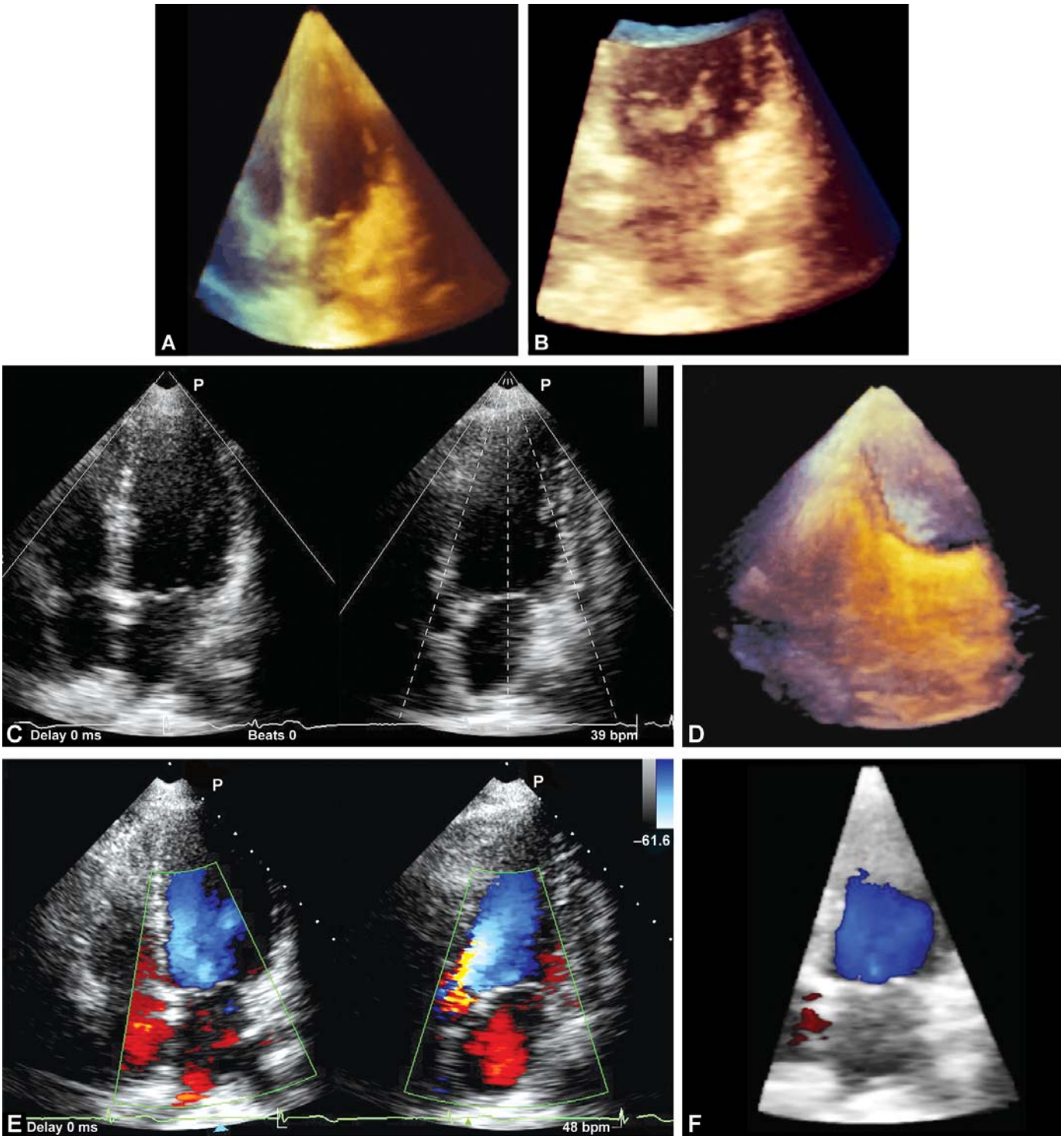


optimized to maximize the quality, and the depth should be decreased to the least required to increase the frame rate and temporal resolution of the 3D dataset to be acquired. Then, one can choose among various available modes of imaging, to display or acquire the 3D pyramidal datasets needed. Narrow angle real time 3D imaging (Fig. 2A, Video 1A) is commonly used for guiding interventional or electrophysiological procedures or to acquire a narrow angle pyramidal dataset in a single heartbeat to examine smaller structures of the heart, such as the valves, that are expected to fit within the 60° x 30° sector. The Zoom mode (Fig. 2B) can also be used for similar purposes but is popularly used to acquire and assess even smaller structures such as small vegetations or mass lesions. Biplane imaging (Fig. 2C) is the most commonly used standard modality to acquire a full volume dataset (Fig. 2D, Video 1B, wide angle, 90° × 90°) usually over 4 cardiac cycles, especially useful for chamber quantitation purposes. Biplane imaging with color Doppler (Fig. 2E) is used to acquire a pyramidal dataset with color (Fig. 2F), usually over 7 cardiac cycles, to commonly assess valvular or paravalvular regurgitation, atrial and ventricular septal defects and fistulae. This wide-angle mode requires ECG gating and is ideally performed during a single breath hold while the patient is lying still, as the full volume or color Doppler dataset is compiled by stitching 4 or 7 narrower pyramidal subvolumes obtained over 4 or 7 consecutive heartbeats respectively.

Most of the 3,000 element dense matrix array transducers used for RT3DE imaging have a bigger foot print than their 2DE counterparts, making it a difficult task to scan thin or pediatric patients with small windows. The rate of sampling of the 3DE system is less due to the magnitude of information it has to process. The decreased frame rate of the dataset leads to decreased temporal resolution compared to a 2D study. The line density which determines the spatial resolution of the image is directly proportional to the number of the subvolumes used to render the full volume 3D dataset and is inversely proportional to the sector width when it is altered. Hence, the more the number of subvolumes acquired, the narrower the sector width of each subvolume and higher the spatial resolution. One caveat is the ability of the patient to remain still without breathing for the entire duration of acquisition, limiting the process to 4–7 cardiac cycles. The Zoom mode has the highest number of individual images obtained within a narrow sector width over a single cardiac cycle and has the best spatial resolution. Various modes of RT3DE acquisition and their salient features are shown in Table 1.

In simple terms, the diagnostic value and the esthetic quality of RT3DE volume, rendering or displaying in addition to the above mentioned, depend on one or more of the following factors:

- The quality of the 2D images—the 2D image obtained with the 3D transducer must be optimized for gain, depth, sector width and focus. Too low a gain can not only fails to visualize certain structures with low echo density but also introduces artifacts in the cavities of the chambers that could be mistaken for thrombi or masses. Too high a gain may mask small structures of clinical significance. Effort should be made to make the gain uniform along the entire depth of the image. An uncompensated high gain in an area resulting in increased density of that structure could be erroneously interpreted as increased thickness or calcification. The depth and sector width should be decreased to the minimum needed if possible to increase the line density and the frame rate of the image.



FIGURES 2A TO F: Various modalities of imaging with a 3D phased matrix array transducer: (A) Narrow angle real time imaging (Video 1A); (B) Zoom mode real time imaging; (C) Biplane imaging without color, real time imaging used to acquire full volume datasets; (D) Wide angle or full volume acquisition (Video 1B); (E) Biplane imaging with color Doppler, real time imaging used to acquire color Doppler datasets; (F) the color Doppler acquisition

- A regular non-rapid heart rate—as the images acquired within a limited number of cardiac cycles are stitched on top of another, it is essential for them to be in synchrony with respect to the cardiac cycle or the subvolumes within the dataset would appear disjointed in time. However, if the heart rate is irregular or if the EKG signal is not detectable, 3D volume datasets can still be obtained by switching the EKG trigger mode to the user-defined time trigger mode, accepting the imperfect nature of same.
- The ability of the patient to lay still and hold his or her breath—as the subvolumes acquired over 4–7 cardiac cycles are stitched in time to obtain the volumetric dataset, any amount of movement or breathing will introduce artifacts

TABLE 1

Common modes of imaging: features and applications

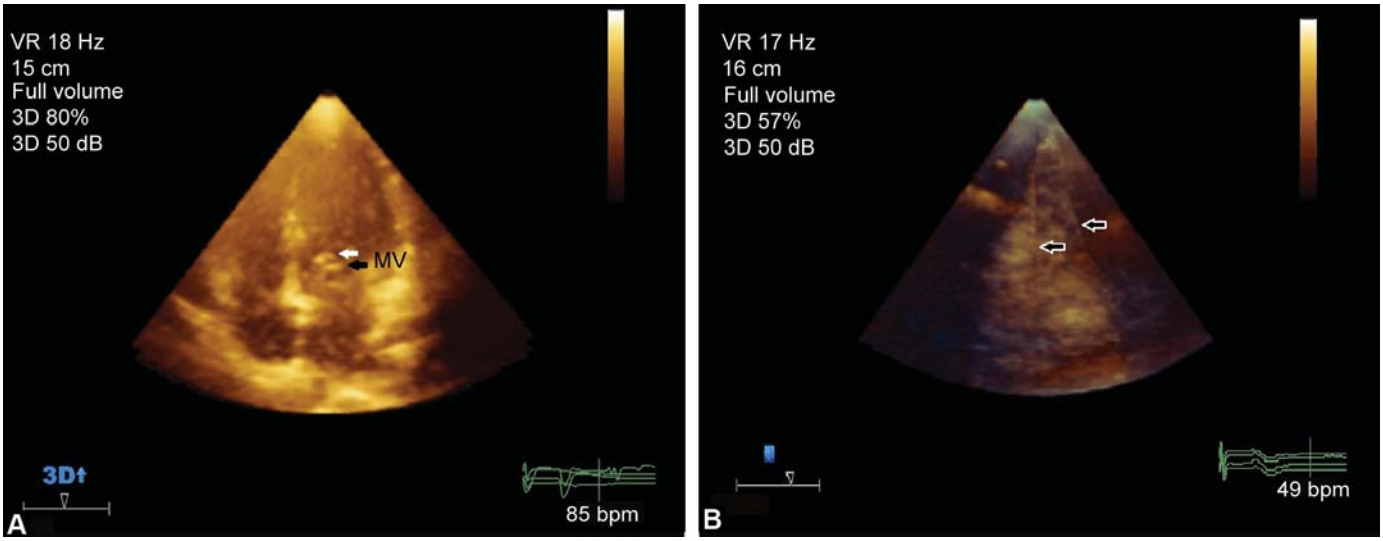
	Wide angle/full volume acquisition	*Color Doppler acquisition*	*Real time display/ acquisition*	*Zoom mode display/ acquisition*
Real time	No	No	Yes	Yes
Time taken to acquire	4–7 cardiac cycles for dense acquisition 1 cardiac cycle for sparse acquisition	4–14 cardiac cycles	1 cardiac cycle	Usually 1, can be up to 6 cardiac cycles if the sector is wide
Temporal resolution	Good (40–50 Hz)	Low (up to 20 Hz)	Moderate (20–30 Hz)	Lowest (up to 10 Hz)
Spatial resolution	Moderate (good for dense acquisitions with multiple subvolumes)	Moderate	Moderate	High
Applications	Volumetric analysis of various chambers, LV dyssynchrony, ASD, VSD, thrombi, tumors, pericardial pathology, mitral and tricuspid valve pathology, congenital heart disease	Valvular/paravalvular regurgitation, ASD, VSD, abscess, fistulae	Guidance of interventional and electrophysiologic procedures	Valvular pathology, vegetations, LAA

(Abbreviations: ASD: Atrial septal defects; VSD: Ventricular septal defects; LAA: Left atrial appendage; LV: Left ventricular)

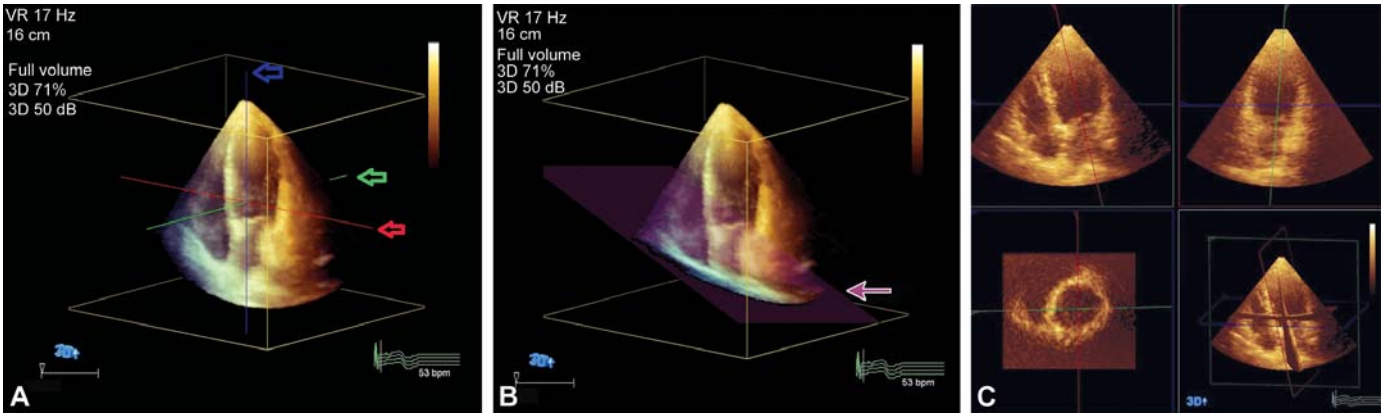
along the axis perpendicular to the axis of imaging (Figs 3A and B, Videos 2A and B) leading to a dataset that appears disjointed in space.

Using the latest generation 3D transducers that have a true real time volume rendering capabilities, patients with arrhythmias and those who cannot hold their breath for more than a few seconds should still be optimally imaged. Right and left ventricular contrast agents have been used with success similar to 2DE.

A good quality pyramidal 3D dataset thus acquired is stored usually after digital compression into smaller files for archiving purposes. The dataset may be retrieved from storage and cropped or cropped online to make visible the cardiac structures of interest and define their intricate anatomic relationships or function. Cropping can be performed in any of the three predetermined cropping planes (x, the green; y, the blue and z, the red) either individually or simultaneously, or in any single slice plane that is manually adjustable (purple) as shown in Figure 4A. Manually adjustable planar cropping may be repeated any number of times, one after another in different planes if needed (Fig. 4B). Alternatively, the 2D images derived from this dataset can be displayed in 3 or more user adjustable planes (Fig. 4C) by using commercially available software in addition to performing volumetric chamber analyses as described below.



FIGURES 3A AND B: Common artifacts during full volume acquisition in three-dimensional echocardiography: (A) the mitral valve (MV) appears double; part of it that belongs to one subvolume (black arrow) is lagging behind in time compared to the part of it from another subvolume (white arrow) due to a PVC or irregular heart rhythm causing a temporal stitch artifact (Video 2A); (B) respiratory motion causing stitch artifacts (arrows) in space, seen perpendicular to the axis of imaging between the subvolumes (Video 2B)



FIGURES 4A TO C: (A) Crop box display of a full volume dataset displaying three orthogonal axes (red, green and blue arrows) for convenient cropping; (B) Crop plane display showing a user adjustable cropping plane (purple arrow); (C) 2D display in three orthogonal user adjustable planes from a full volume 3D dataset

Some preliminary cropping of the datasets online is recommended to ensure their adequacy prior to ending the examination for post-processing. The reporting of findings should include two descriptors, the axis of imaging used to acquire the dataset and the viewing perspective in relation to the cropping plane as shown in Figures 5A to E.[6] The reader should note that the nomenclature of the axes refers to the heart as an organ and not the body of the person. There will be times when this classic nomenclature may not be applicable, especially when user defined adjustable potentially oblique plane or planes of cropping are used, in which case the pathology should be described as best possible using well known intra-cardiac structures as reference or vantage points.

Endocardial segmentation of full volume datasets of the ventricles using various commercialized software may be performed to render wire frame, surface and quantitative data display. Segmentation is a technique used to extract anatomic information from the volumetric data using either difference in texture of the image that is dynamically changing or by level setting. Shape and time information have also been incorporated in some of these models. Dimensions, volumes, ejection fraction (EF), time to peak contraction or time to minimal volume can be synthesized from the volume rendering (Figs 6A and B, Videos 3A and B). Wire frame and surface rendering can be color coded to show time to peak contraction which identifies the dyssynchronous myocardium. Epicardial segmentation is more challenging due to lack of significant contrast between myocardium and the background, compared to that between the endocardium and the blood pool.

Some of the commercial systems provide epicardial and endocardial speckle or wall motion tracking methods (Fig. 7) allowing estimation of myocardial deformation which facilitates determination of velocity, volumes; transmural or radial, longitudinal and circumferential global and regional strain or strain rate; twist and torsion.

The color Doppler datasets may be cropped to obtain regurgitant orifice area (ROA) which in combination with spectral Doppler derived velocity time integral (VTI) can aid in calculation of regurgitant volume using the formula ROA × VTI.

TABLE 2

A complete 3D echocardiographic protocol

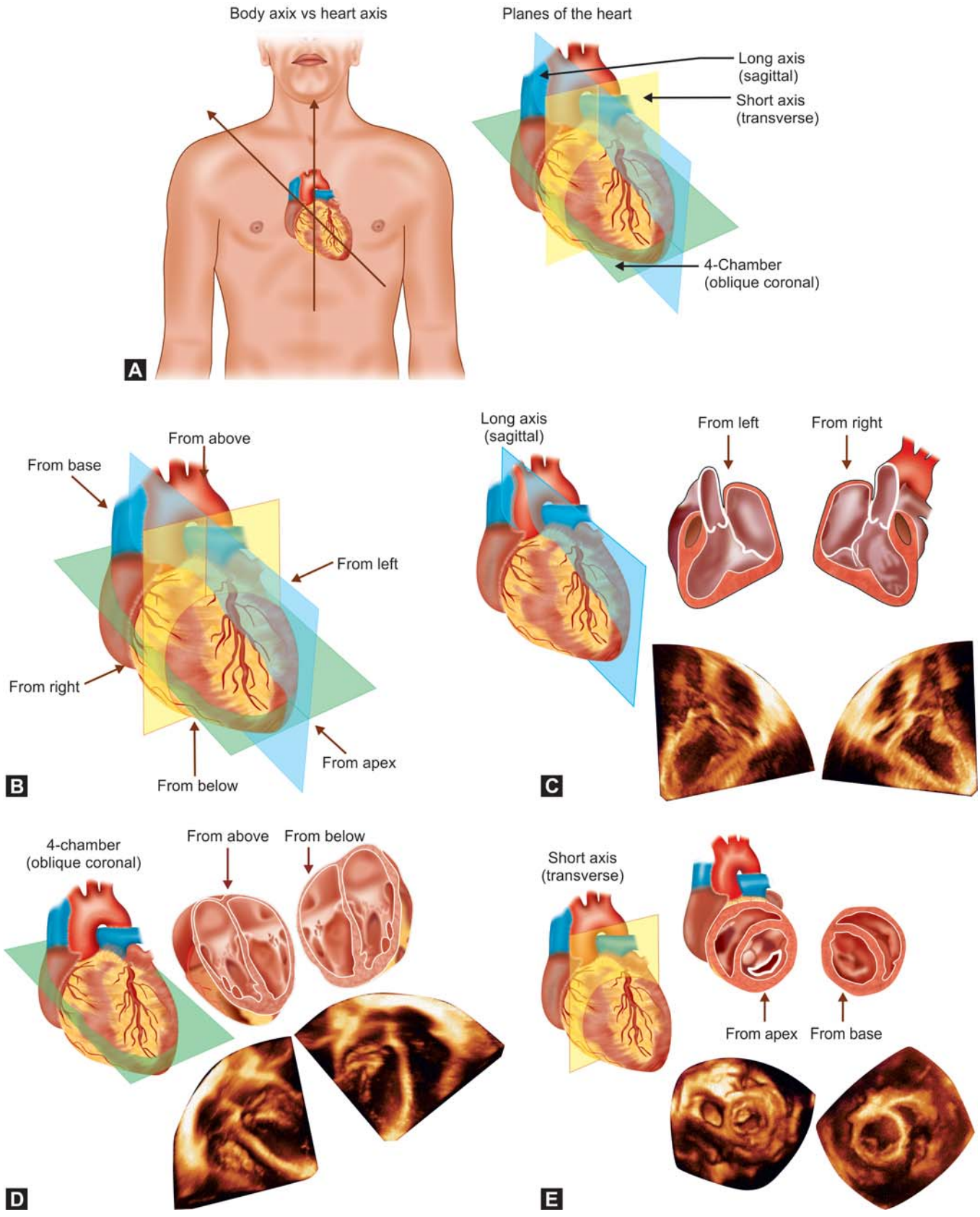
• Wide-angle acquisition, parasternal long-axis window: 3D color interrogation of the aortic and mitral valves; 3D color interrogation of the tricuspid and pulmonic valves
• Wide-angle acquisition, apical 4-chamber window: 3D color interrogation of the mitral, aortic and tricuspid valves
• Wide-angle acquisition, subcostal window: 3D color interrogation of the atrial and ventricular septa
• Wide-angle acquisition, suprasternal notch: 3D color interrogation of the descending aorta
(*Source:* Hung J, Lang R, Flachskampf F, et al. 3D echocardiography: a review of the current status and future directions. J Am Soc Echocardiogr. 2007;20:213-33)

The views needed to perform an RT3DE are dependent on the indication of the study. The American Society of Echocardiography position paper on 3DE, published in 2007 tabulates a protocol for complete study as shown in Table 2.[7] Frequently, RT3DE is added to a 2D study when the findings of the 2D study call for more information regarding a particular clinical issue; the authors encourage customizing the views to answer the question.

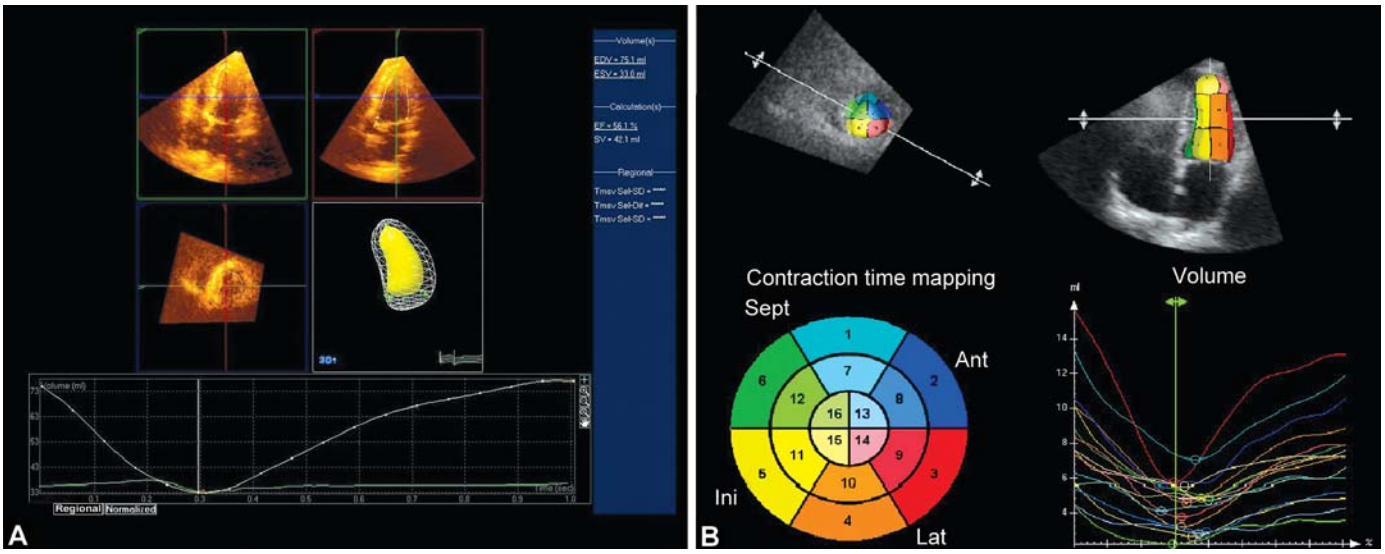
CLINICAL APPLICATIONS

DETERMINATION OF LEFT VENTRICULAR VOLUMES AND FUNCTION

Determination of left ventricular (LV) global and regional function and EF is crucial to decision-making in several clinical situations in the management of an adult cardiac patient and hence is the most common indication for echocardiography; as it is a versatile, real time and noninvasive technique with no risk. This assessment is commonly accomplished by a very subjective "eye-balling" method based on 2DE; a challenging technique for the inexperienced eyes. The other commonly used methods for EF quantification not only require accurate image plane positioning to avoid foreshortening but also make several geometric assumptions. The geometric assumptions are fraught



FIGURES 5A TO E: (A) The long axis of the heart is at an angle to the body axis. The planes of the heart are in reference to the heart itself and not the body axis; (B) The heart may be described using two descriptive terms, the plane and the viewing perspective; (C) Sagittal (long axis or longitudinal) section—viewed from left side or right side; (D) Oblique coronal (frontal) section—viewed from above and below; (E) Transverse (short axis) section—viewed from base or apex. (*Source:* Reproduced with permission from Nanda, et al[6])



FIGURES 6A AND B: (A) Semiautomated quantification of global and regional (Video 3A). (B) Left ventricular function showing the user adjustable contours and time volume curves (Video 3B)



FIGURE 7: Three-dimensional wall motion tracking (WMT) of a left ventricle with normal ejection fraction and without segment dysfunction (*Source:* Modified from Pérez de Isla L, Balcones DV, Fernández-Golfín C, et al. Three-dimensional-wall motion tracking: a new and faster tool for myocardial strain assessment: comparison with two-dimensional-wall motion tracking. J Am Soc Echocardiogr. 2009;22:325-30)

with inaccuracies especially in diseased hearts. Hence, EF determination based on 2DE has significant interobserver and intraobserver variability.[8,9]

Contrary to this, RT3DE analysis of LV volumes and function (Figs 6A and B) is based on user adjustable direct endocardial surface detection by segmentation techniques for every single frame of the cardiac cycle, and therefore obviates the need for geometric assumptions. This method is also not hampered by foreshortened views or oblique plane positioning. The volumes obtained by RT3DE are more reproducible than 2DE,[10] accurate compared to cardiac magnetic resonance imaging (CMR)[11,12] or quantitative gated single-photon emission computed tomography (SPECT)[13] and can be performed rapidly online or offline using commercially available software.

Several studies have reported that the LV volumes derived from RT3DE were significantly underestimated.[14-21] However, a recent multicenter study validated RT3DE determined LV volumes compared to *magnetic resonance imaging* (MRI), although with a small underestimation bias (end diastolic volume, EDV and end systolic volume, ESV were 26% and 29% lower by RT3DE in one study) which could be easily remedied by including the trabeculae in the endocardial border tracing.[14] RT3DE has also been shown to be accurate in assessing LV volumes in aneurysmal and remodeled ventricles following myocardial infarction (MI)[13,16,22] and is of value if sequential volumes are used to guide management.[12] In addition, the use of contrast to enhance LV endocardial border detection has been shown to help quantify both global and regional LV

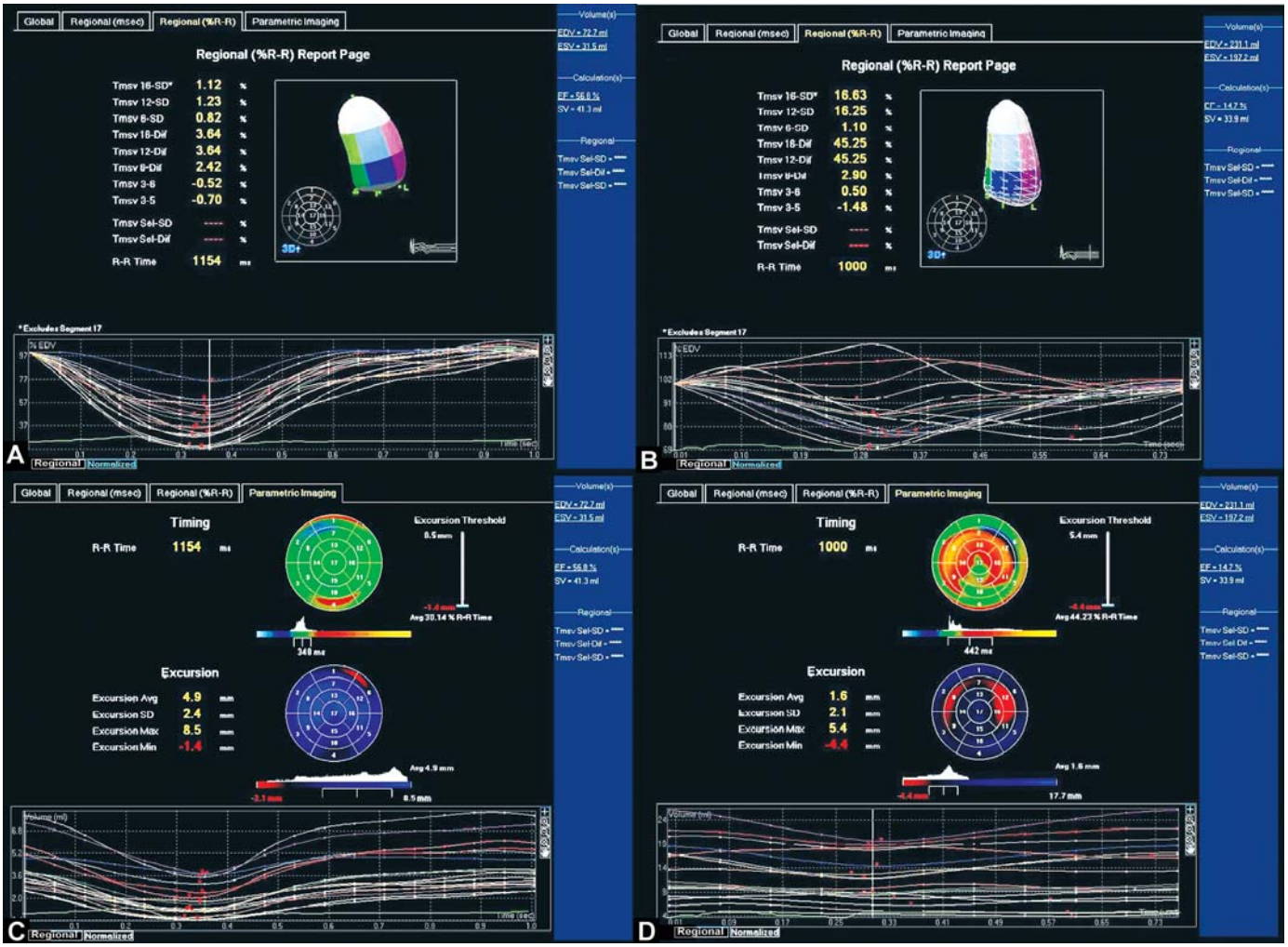
function in patients with poor acoustic windows.[20,23] However, acquisition of contrast images has been recommended by selective dual triggering at end-systole and end-diastole instead of during continuous imaging. This is to avoid microbubble destruction by continuous imaging which could then lead to under-opacification of the chambers and thereby underestimation of volumes.[24] The fusion imaging combining the 3DE images from various cardiac cycles has been shown to be of value in enhancing the image quality, aiding endocardial border detection and procuring complete datasets.[25]

DETERMINATION OF REGIONAL WALL MOTION AND DYSSYNCHRONY

Assessment of regional wall motion is crucial in evaluation of a patient with chest pain, ischemic heart disease or systolic dysfunction. Visual assessment for identification of regional wall motion abnormalities results in high-interobserver variability. As the RT3DE volumetric data comprises the information of all the segments in entirety, quantitative analysis of regional volumes and function by semi-automated segmentation techniques is feasible. The various segments are color coded and displayed either as a surface rendering or as a parametric map as shown in Figure 8A and Video 4A.

Segmental volumes and regional function based on time volume curves can be obtained in a quantitative manner (Fig. 8B, Video 4B).

RT3DE can also obtain information on time from R wave on ECG to regional endocardial contraction and hence, can identify differences in time to peak regional contraction and thus identify dyssynchrony. Color coded parametric maps, including deformation front mapping based on time to peak regional deformation can also be obtained. A 3D LV systolic dyssynchrony index (SDI), standard deviation of time to minimal regional volume, peak contraction or ejection expressed as a percentage of cardiac cycle, has been popularly used as an index of LV dyssynchrony (Figs 8C and D).[26] This has been validated against gated myocardial perfusion single photon emission computed tomography with phase analysis, with good correlation.[26] We lack large randomized controlled trials to show the usefulness of LVSDI in predicting favorable LV remodeling to cardiac resynchronization therapy (CRT) at this time.



FIGURES 8A TO D: Semiautomated quantitation of regional left ventricular (LV) volumes, function and dyssynchrony. Color-coded display of the16 LV segments depicted in the cast display and as a graph between time and regional volumes in a normal (A) (Video 4A) and a heart failure (B) (Video 4B) patient. Also depicted is the standard deviation of time to minimal systolic volume (Tmsv) of the 16 LV segments expressed as a percentage of R-R interval (systolic dyssynchrony index or SDI) is elevated in the heart failure patient. Parametric imaging showing uniform excursion in the normal patient (C), which is disturbed in the patient with heart failure (D) as cued by the color coding on the Bull's eye display of the LV segments

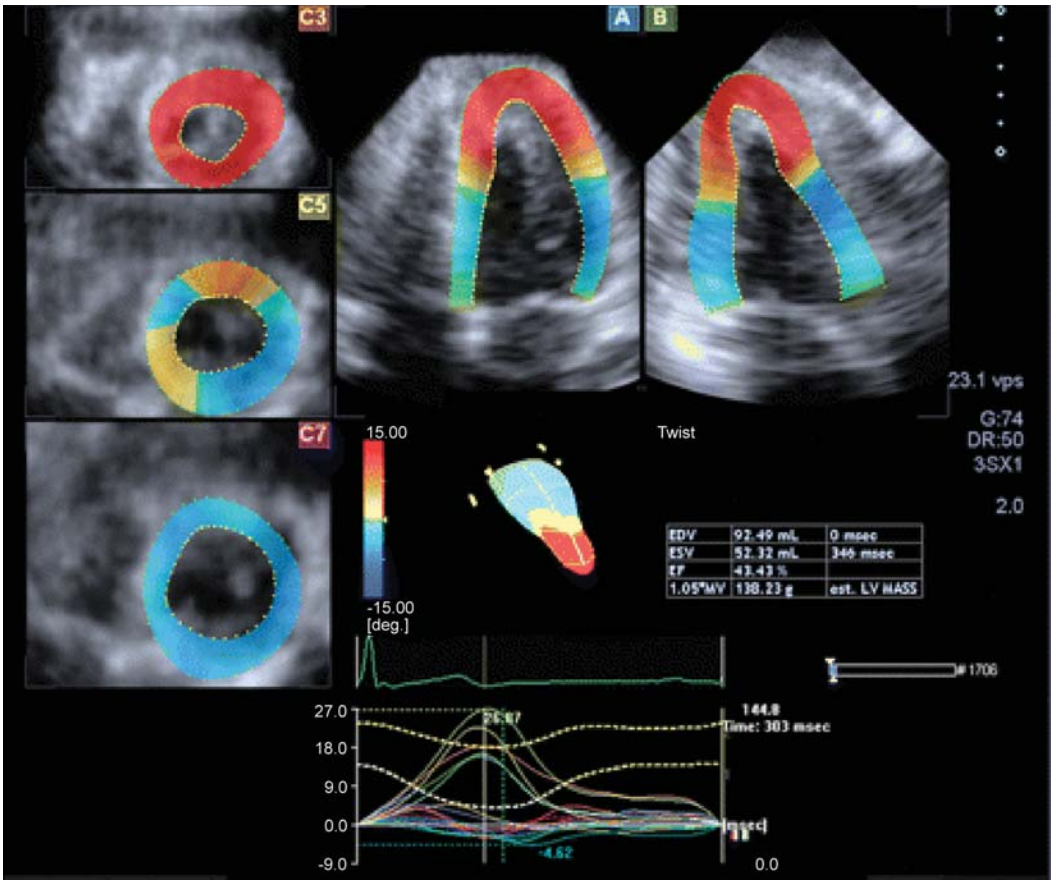


FIGURE 9: Global left ventricular twist values detected by three-dimensional speckle-tracking echocardiography and also shown in color overlays superimposed on the gray-scale images and color-coded three-dimensional cast (*Source:* Modified from Andrade, et al[39])

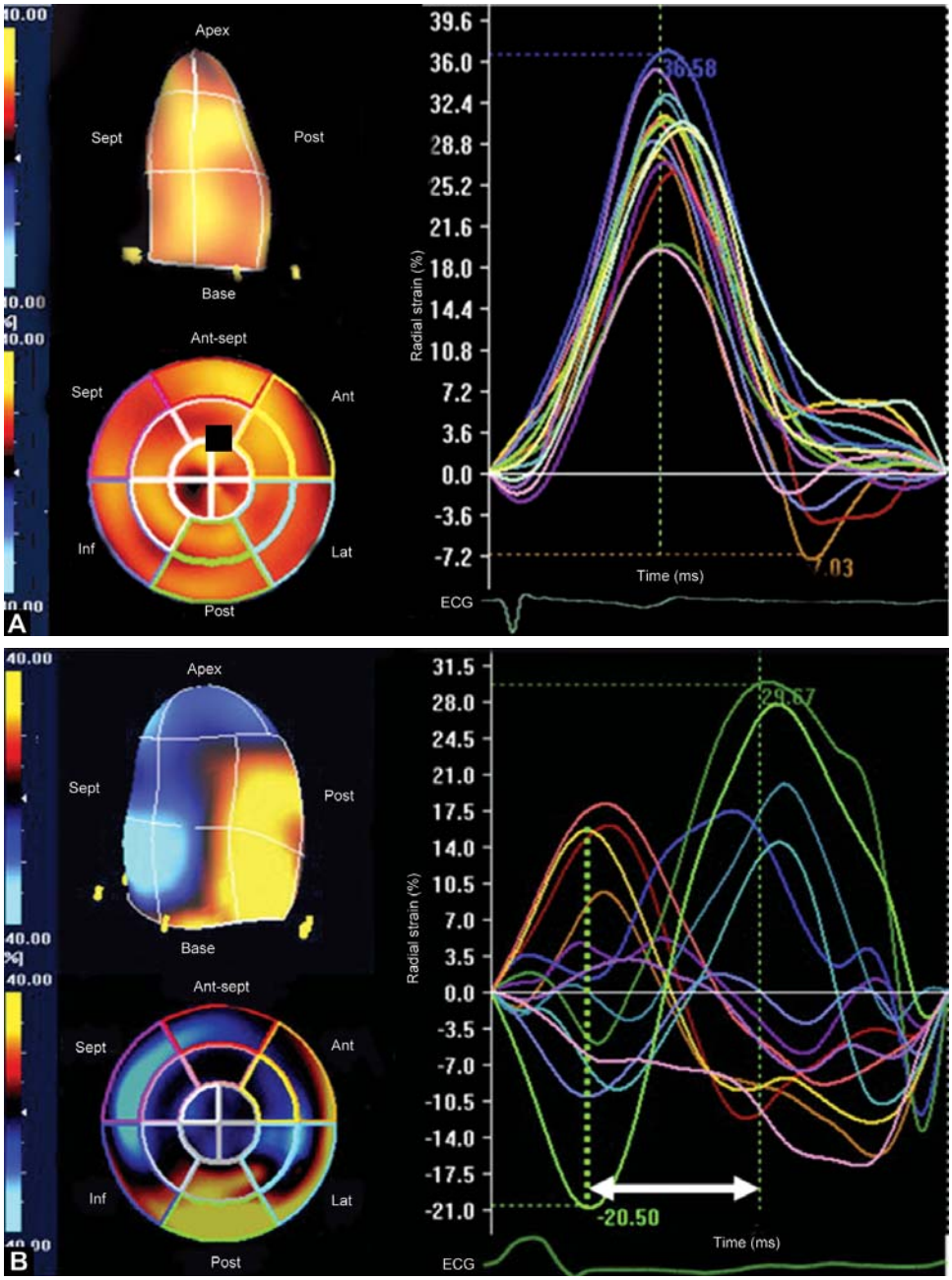
However, RT3DE is potentially superior to conventional tissue Doppler imaging (TDI) for dyssynchrony assessment, as the latter strictly evaluates the longitudinal or radial endomyocardial velocity or strain while RT3DE derives the regional function from segmental volumes which encompass overall endomyocardial contraction.[27,28] Reports of single center small observational studies studying the utility of LVSDI over TDI show that the presence of dyssynchrony by LVSDI correlated with favorable LV remodeling, regardless of the QRS duration. One study proposed a cut-off of 6.4% for SDI with a sensitivity of 88% and a specificity of 85% to predict response to CRT.[29-31] Further work is needed to determine the prognostic value of 3D echocardiography in potential CRT candidates, especially as its 4D applications and segmentations undergo technical improvements. The use of RT3DE in the electrophysiology laboratory can aid in accurate lead placement at the site of latest mechanical activation.

Strain imaging has the advantage of differentiating actual active deformation of normal myocardium from traction or translational motion of the scar tissue. 2D Speckle Tracking Echocardiography (2DSTE) has been favored to obtain angle independent measures of multidirectional myocardial strain in contrast to TDI which is dependent on the insonation angle of the ultrasound beam. However, the out of plane motion of speckles results in noise and suboptimal tracking. In addition due to the geometric assumptions needed, the LV volumes were underestimated by 2DSTE. RT3DE has been synergized with speckle tracking to take advantage of the utility of each modality. This allows insonation angle independent extraction of global and segmental parameters such as displacement and strain in longitudinal, radial and circumferential axes (Fig. 7).[32] This could either be displayed as numerical values on an excel spread sheet from the onset of the cardiac cycle, or as a graphical depiction over time, for all the frames of a cineloop. Color coded parametric mapping of any of these parameters provides a quick visual cue to the identification of the abnormal segment(s). In addition, regional and global volumes, function, rotation, twist (Fig. 9) and torsion can also be quantified using this technique. The decrease in the magnitude of displacement, contraction or strain and the temporal dispersion of the peak value of any of these parameters can give an indication of segmental LV dysfunction or dyssynchrony respectively (Figs 10A and B).

The clinical applications of such complex and time consuming techniques, which require advanced expertise in the field, are yet to be defined in a convincing fashion, although there are some promising preliminary reports of potential utility.[33-38] Based on the above techniques, one can also assess diastolic function from the diastolic velocity, displacement and strain.

APPLICATIONS TO STRESS IMAGING

The time window available to acquire peak stress images is brief. Conventional 2DE can only visualize a limited number of segments at a time. Hence, 2DE is very much dependent on the skill of the sonographer to acquire standard views in a rapid manner before heart rate recovery following peak



FIGURES 10A AND B: (A) Color-coded 3-D LV display (top left) and bull's-eye plot image (bottom left) and corresponding time-to-strain curves from 16 LV sites (right) from a normal control subject, demonstrating synchronous time-to-peak-strain curves represented by homogenous coloring at end-systole. (B) Color-coded 3-D LV display (top left) and bull's-eye plot image (bottom left) and corresponding time-to-strain curves from 16 LV sites (right) from a patient with HF and left bundle branch block, demonstrating dyssynchronous time-to-peak-strain curves represented by heterogeneous coloring at end-systole, with early peak strain in septal segments and delayed peak strain in posterior lateral segments (arrow). (Abbreviations: Ant: Anterior; Ant-sept: Anterior-septum; HF: Heart failure; Inf: inferior; Lat: Lateral; LV: Left ventricle; Post: Posterior; Sept: septal). (*Source:* Modified from Tanaka, et al[33])

exercise or dobutamine infusion. Imaging at lower heart rates decreases the sensitivity of the test and hence makes it essentially nondiagnostic. The ability to acquire a full volume dataset containing all the 17 segments of the LV within a few seconds or even within one heartbeat, using RT3DE makes this an interesting area of its application. Thus acquired dataset can be cropped in any plane desired, to obtain standard comparable views for rest and stress phases, to allow accurate interpretation. It has been shown that RT3DE decreases the study time, improves its sensitivity and diagnostic value compared to 2DE. There was also a trend toward increased sensitivity in 3DE group where coronary angiograms were available for correlation in one study.[39,40] The two limitations with the 3D technique are suboptimal spatial and temporal resolution. While the former can be overcome by using a contrast agent, the latter is of particular concern especially with higher heart rates at peak stress. This can cause undersampling of cardiac phases leading to potential misinterpretation from the available frames.

The 3D full volume dataset can also be fed into 4D analysis software for further segmentation and analysis of regional ventricular function over time as described above at rest and stress. Speckle tracking may be performed on the 3D datasets to obtain 3D strain, strain rate, twist and torsion during rest and stress phases of the study. Stress induced diastolic dysfunction can be assessed from the diastolic velocity, displacement and strain parameters.

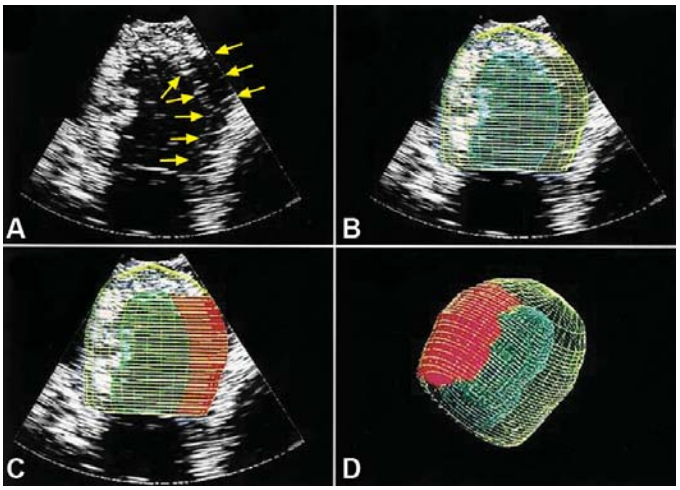
Multimodality stress imaging combining RT3DE and SPECT has been shown to be more accurate than any one of them, when angiography was used as the gold standard.[41]

MYOCARDIAL CONTRAST IMAGING AND QUANTIFICATION OF PERFUSION

Quantification of myocardium at risk, dependent on the presence or absence of collaterals in the distribution of a stenotic epicardial artery is of prognostic significance. The development of gas filled microbubbles that reflect ultrasound beam as they pass through the coronary circulation led to the potential application of echocardiography in identifying the ischemic myocardium at risk. However, 2DE is limited due to the number of views required to image all the LV segments. In some applications it requires repeated injections of contrast to obtain comprehensive information. Quantification of myocardium at risk was difficult, requiring mental 3D reconstruction based on 2D images, obtained at times in off-axis planes. RT3DE through its volume rendering capabilities can encompass the entire LV in 1 or 2 datasets and hence does not need repeat contrast administration. Several animal studies have indicated the feasibility, rapidity and accuracy of RT3DE in quantification of myocardial perfusion (Figs 11A to D)[42-45], while it remains in its infancy for clinical use at this time.[46,47]

DETERMINATION OF LEFT VENTRICULAR MASS

It has been established that left ventricular hypertrophy (LVH) or increased LV mass is an independent marker of cardiovascular disease and is of tremendous prognostic importance. Cardiologists follow LV mass to assess response to pharmacologic therapy in various cardiac conditions such as hypertension and other treatable causes of hypertrophic cardiomyopathy. M-mode and 2DE methods of determination of LV mass are fraught with limitations, similar to volume determination, due to inability to align the cursor perpendicular to the ventricular axis with the former, geometric assumptions and foreshortening associated with the latter. RT3DE by semiautomated tracking of endocardium and epicardium, directly quantifies LV myocardial volume (epicardial volume-endocardial volume), which then is multiplied by the myocardial tissue density (1.05 gm/ml) to derive the LV mass. LV mass derived from RT3DE has been validated by cardiac MRI and is more accurate than other echocardiographic methods with good reproducibility.[48]



FIGURES 11A TO D: Representative example of methodology used to quantitatively assess mass of underperfused myocardium from RT3D images in sheep with acute occlusion of circumflex coronary artery: (A) tomographic view derived from volumetric image showing area of myocardium devoid of contrast opacification (arrows); (B) three-dimensional rendering of left ventricular (LV) endocardial (in green) and epicardial (in yellow) surfaces generated by computer, based on operator's tracing. Area between both surfaces corresponds to myocardial volume, which is used to calculate myocardial mass; (C) rendering of LV region without contrast opacification generated by computer, based on operator's tracing of corresponding endocardial surface. Red area represents volume used to calculate mass of underperfused myocardium; (D) after tracing is completed, volumetric image can be freely rotated to examine three-dimensional appearance of LV endocardial and epicardial surfaces and underperfused myocardium. (*Source:* Modified from Camarano, et al[42])

ASSESSMENT OF RIGHT VENTRICULAR VOLUMES AND FUNCTION

The right ventricle (RV) is a complex structure with no standard geometric shape and hence 2DE, requiring geometric assumptions, is at a disadvantage in estimating the RV volumes and function. Currently MRI remains the gold standard, as both the area-length and the disc summation methods introduce a significant underestimation bias and hence are not recommended for clinical use.[49]

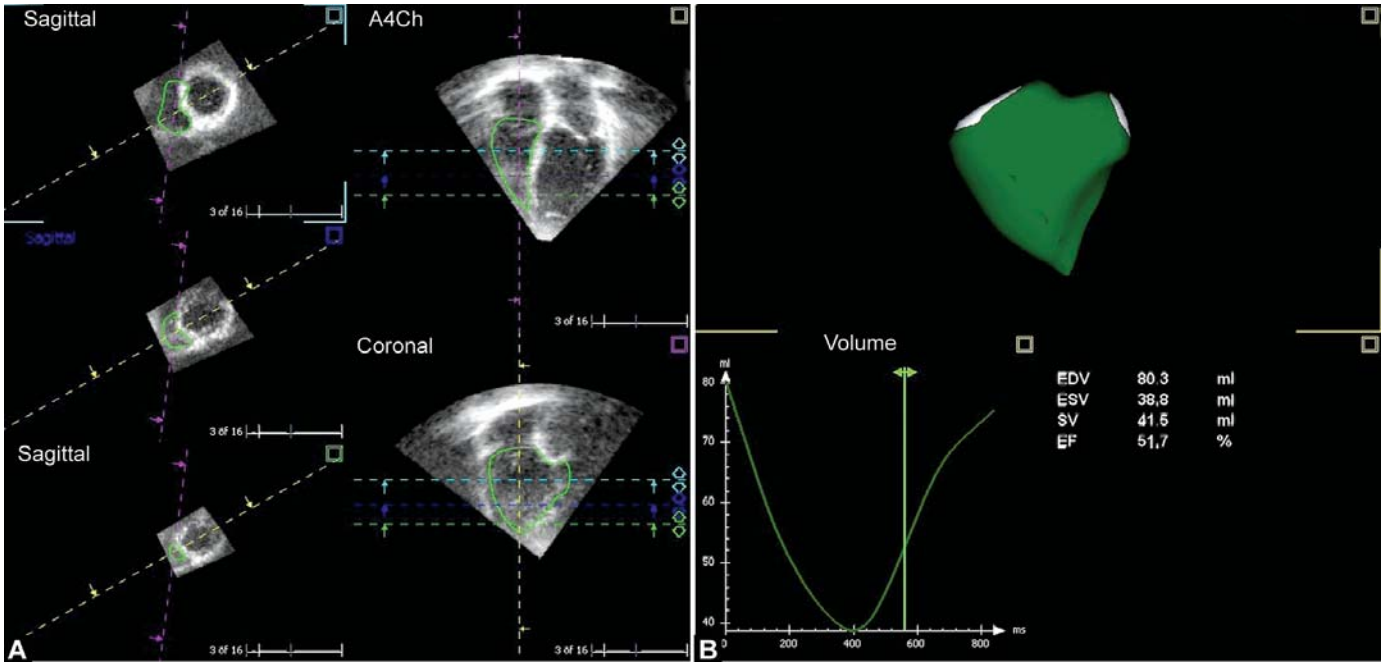
As with any chamber, the acquisition of an accurate 3D full volume dataset is dependent on the adequacy of the acoustic window and the experience and skill of the sonographer. A modified apical 4-chamber view to maximize visualization of RV with further anterior angulation to capture the RVOT or subcostal transducer locations has been commonly used. Contrast administration may be necessitated for endocardial delineation.

RT3DE by directly measuring RV volumes without the need for geometrical assumptions can reliably quantify RV size, stroke volumes and EF. The RV full volume dataset encompasses the RV 3D including the RV outflow tract. The commercially available 4D RV analysis software allows for semiautomated detection of the RV endocardial borders in axial, sagittal and coronal planes during various phases of the cardiac cycle (Figs 12A and B, Videos 15A and B). This method has been validated by several in-vitro and in-vivo models either by direct methods in the lab or the operating suite; or with radionuclide ventriculography and CMR. RT3DE analysis of RV was determined to be fast, feasible, accurate and reproducible not only in in-vitro models but also in normals and in a variety of disease states such as RV infarction, congenital heart disease and pulmonary arterial hypertension.[50-57]

RT3DE does seem to hold promise as a less expensive alternative to CMR in providing reliable estimation of RV volumes and EF in patients with adequate acoustic windows. Recently, there has been much interest in utility of RT3DE in the assessment of advanced pulmonary hypertension treatment effects. This is being addressed in an ongoing prospective study.[58]

ASSESSMENT OF LEFT AND RIGHT ATRIA

Left atrial enlargement is generally considered a marker for adverse clinical outcomes in conditions such as atrial fibrillation, MI, stroke, heart failure, hypertrophic obstructive cardiomyopathy, aortic and mitral valvular disease. Whether reversing this remodeling improves clinical outcomes remains



FIGURES 12A AND B: (A) Semiautomated right ventricular (RV) endocardial tracing in axial, sagittal and coronal planes of a full volume dataset acquired from the RV directed apical 4-chamber view (Video 15A). (B) 3D cast representation of the RV inclusive of outflow tract, based on above tracings obtained over various phases of the cardiac cycle providing RV volume and ejection fraction (Video 15B)

to be demonstrated. Assessment of left atrial volume is best accomplished by 3D imaging as the enlargement can happen asymmetrically in anteroposterior, transverse or superoinferior dimensions and geometric assumptions required by 2D techniques will be flawed. RT3DE has not only been shown to be feasible, more accurate and reproducible compared to 2DE but also been validated against CMR (Fig. 13). In addition to obtaining the volumes at the maximal and minimal atrial expansion, the pre-A (atrial contraction) volume can also be obtained. Indices of left atrial contractile and reservoir function, such as passive atrial emptying fraction, active atrial emptying fraction and atrial expansion index, can be calculated from the above.[59-64]

A common indication for TEE is to scrutinize the left atrial appendage (LAA) for thrombus or to ascertain the LAA orifice area for accurate sizing of the occluder device placement. RT3D TEE is instrumental in providing elaborate views of the LAA including *en face* views of the orifice and cross sectional views of the appendage at multiple levels that is just not feasible by 2DTEE. The sizing of LAA orifice area by RT3D TEE has been validated against 64 slice CT with narrow limits of agreement compared to 2DTEE (Figs 14A and B).[65] RT3D TTE also seems to be of diagnostic importance in patients with excellent acoustic views and may obviate the need for TEE to exclude an LAA thrombus especially as the spatial resolution of this technique gets enhanced in the future.[66]

There is limited experience with right atrial volume assessment by RT3DE.[67] RT3D TEE, due to high imaging quality also enables visualization of complex anatomic structures of the right atrium that might be of importance to the electrophysiologist.[68] Right atrial vegetations or thrombi potentially associated with pacemaker wires can be clearly visualized by RT3D TEE.

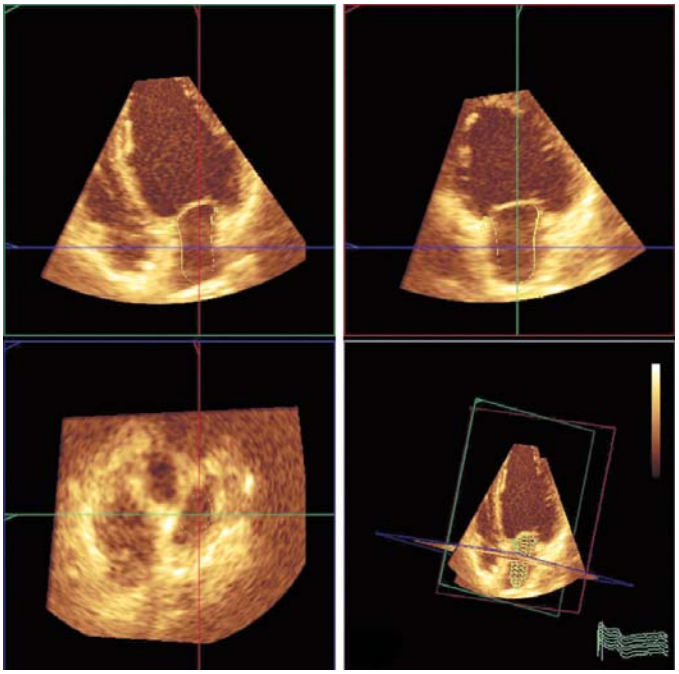
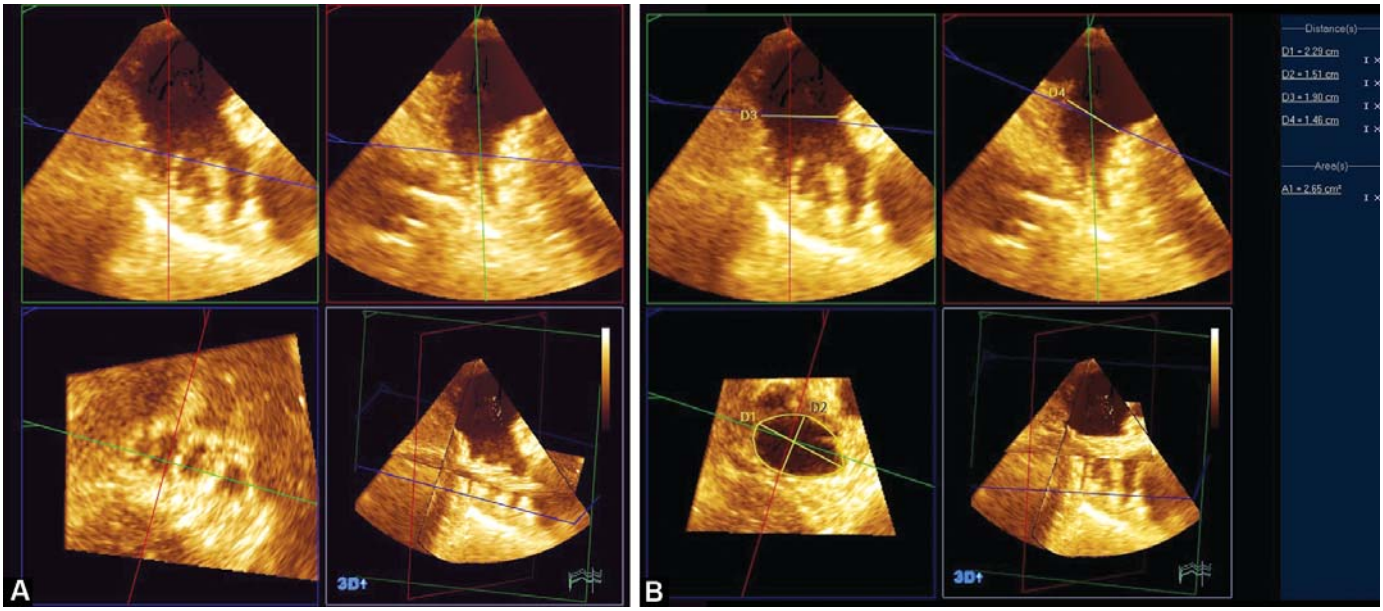


FIGURE 13: RT3DE for the assessment of left atrial volumes. Automatic border detection can be applied to the apical 4-chamber and 2-chamber view (upper panels) for quantification of left atrial volumes. (*Source:* Modified from Tops KF, Schalij MJ, Bax JJ, et al. Imaging and atrial fibrillation: the role of multimodality imaging in patient evaluation and management of atrial fibrillation. Eur Heart J. 2010;31:542-51.)

ASSESSMENT OF VALVULAR DISORDERS

Mitral Valve

The mitral valve is a complex structure and RT3D epicardial, transthoracic or TEE is instrumental in providing volume



FIGURES 14A AND B: (A) RT3D TEE of the left atrial appendage (LAA) cropping down into the appendage reveals pectinate muscles traversing the LAA from wall to wall. (B) The cropping needed to size the LAA occluder device and the position of its placement is shown by lines D^{1-4}

rendered images of the mitral valve, thus enabling the demonstration and quantification of the complex saddle shape of the mitral annulus, the commissural length, the coaptation area, the surface area of the leaflets and the scallops, the billowing height in MV prolapse, the aorto-mitral angle (the angle between the mitral valve plane at the highest saddle point and the aortic valve plane), the tenting volumes and the tethering distance to the papillary muscle using commercially available software.[69,70] Figure 15 illustrates several of these measurements.

RT3DE provides important insights into the pathophysiology of functional and ischemic mitral regurgitation which results from distortion of the spatial relationships between the LV and the mitral valve apparatus.[71-74] There is displacement of the papillary muscle along with tethering of the leaflets in ischemic mitral regurgitation.[74] Evolving new approaches for treatment of ischemic mitral regurgitation are based on the above mentioned information aiming at the chordal or papillary muscle level.[75,76] In contrast, the decrease in mitral valve coaptation surface area, possibly due to apical displacement of the coaptation or increase in tenting volume due to annular dilation, is thought to be the underlying mechanism of mitral regurgitation in dilated cardiomyopathy (DCM). The RT3DE derived coaptation index, the index of the difference in 3D tenting surface area at the onset of mitral valve closure and at maximal closure over that at the onset of mitral valve closure" this represents the proportion of the valve surface that engages in coaptation. This has been proposed as a quantitative measure of the extent of leaflet coaptation, which is shown to be significantly smaller in DCM patients compared to normals.[77] This could be used to follow these patients after optimal medical management to determine if there is favorable remodeling with improvement in mitral regurgitation.

RT3DE has been used to characterize the mitral valve (Figs 16A to D and 17) and its pathologies such as prolapse or flail,[78] native and prosthetic valve endocarditis,[79,80] and congenital abnormalities.[81,82] The identification and quantification of the prolapsed or flail segment is more accurate by RT3DE (Figs 18A to D) compared to 2DTTE and TEE.[69,83,84] The parasternal window acquisition has been shown to be superior in visualization of the posterior mitral leaflet[85] among the 3D transthoracic methods. Mitral valve repair is preferable to replacement for degenerative mitral regurgitation as it is more likely to preserve LV function and obviates the need for long-term anticoagulation and eliminates the risk of prosthetic valve complications. The success of the mitral valve repair depends upon proper understanding of anatomy under physiological conditions of a beating heart. 3D TEE assessment of native and prosthetic mitral valves (Figs 19A and B) has been validated against surgical pathology with 96% agreement in 87 patients.[86] The ability to maneuver the images to obtain the surgeon's view (Fig. 17) increases the surgeon's confidence in the diagnosis and helps with surgical planning. The degree of mitral regurgitation can be determined by RT3DE with more confidence compared to other methods and has been validated against velocity encoded CMR.[84,87,88] The regurgitant volume calculated by RT3DE is more accurate than that determined by 2DE and strongly correlated with that assessed by CMR with no significant bias, especially in the presence of an asymmetric regurgitant orifice.[88] The RT3DE derived ROA of the mitral valve is irregular (Figs 20A to D) and correlates with the recommended 2DE derived cut-offs for effective ROA for grading of mitral regurgitation severity, except in those with small orifices.[89] RT3DE is being used increasingly to assess the adequacy of surgical mitral valve repair and variably to guide percutaneous edge to edge mitral valve repair in a beating heart. For all the aforementioned causes, this would also be a good tool to follow patients with native or prosthetic mitral valve conditions either before or after percutaneous and surgical procedures.[90,91]

2D planimetry and Doppler methods (pressure half time, proximal isovelocity surface area) have several limitations in assessment of mitral stenosis. RT3DE allows identification of

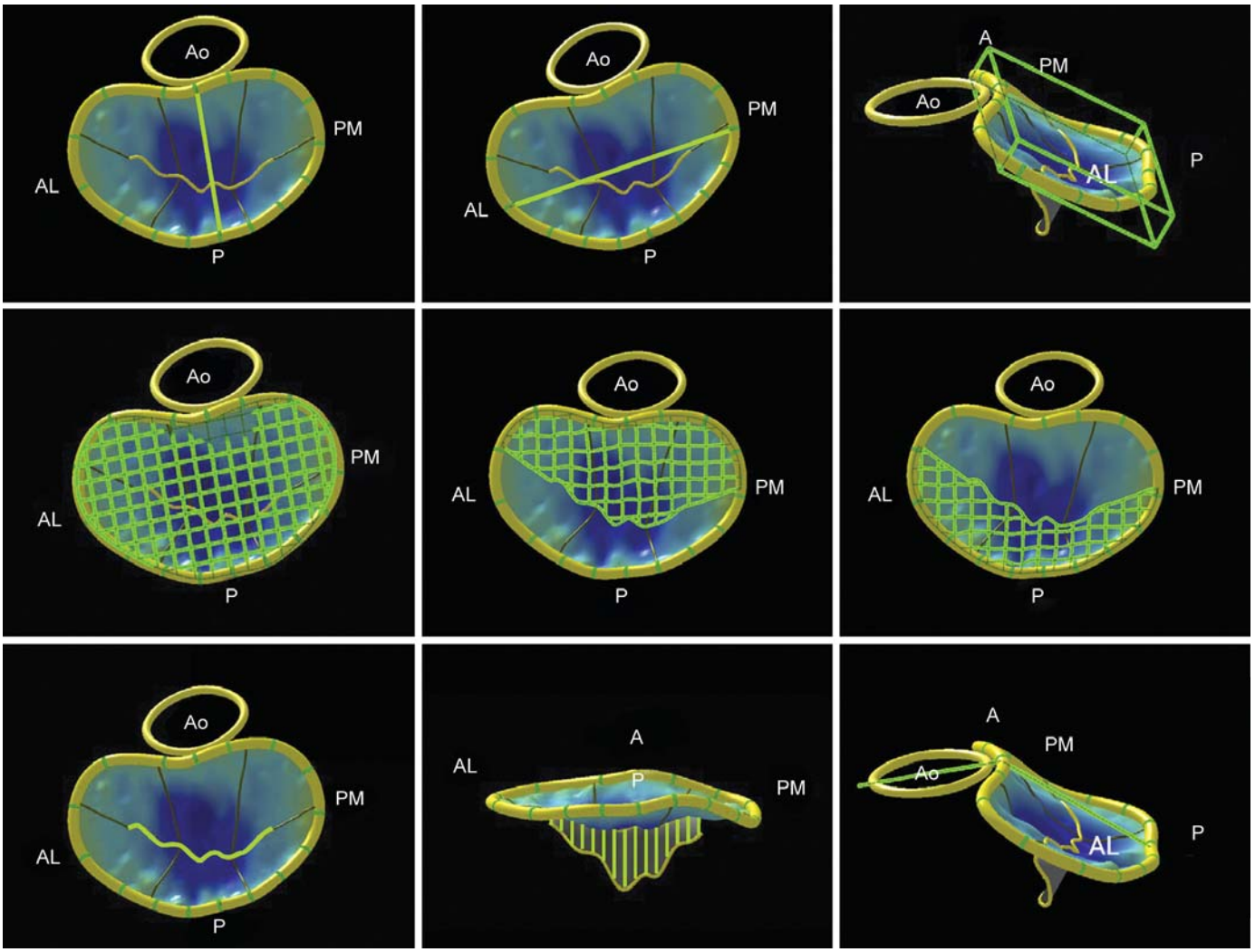
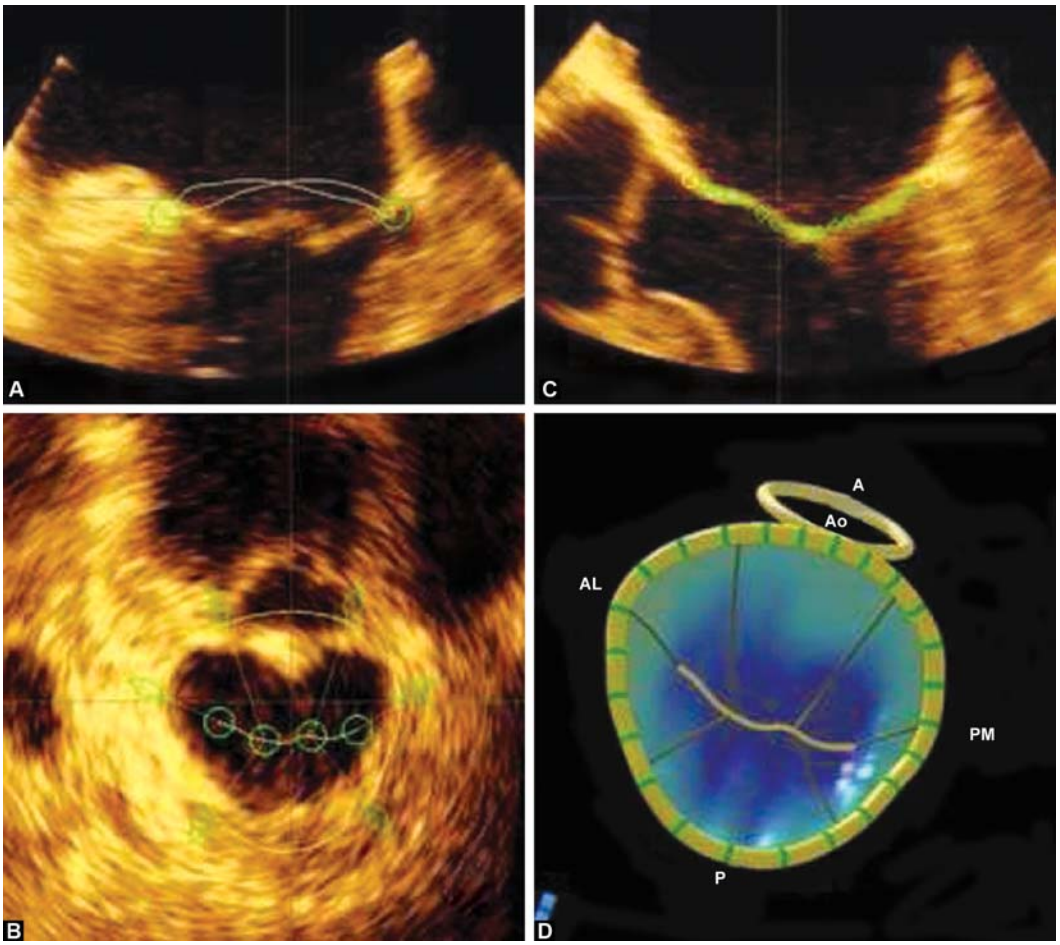


FIGURE 15: Three-dimensional reconstruction of the MV, from which several parameters were automatically calculated. From top to bottom, left to right: anteroposterior diameter of the mitral annulus; mitral annular anterolateral (AL)–posteromedial (PM) diameter; mitral annular height, defined as the height of the bounding box of the MV in the atrial-ventricular direction; mitral annular area, as the area of the minimal surface spanning the annulus; exposed area of the anterior (A) leaflet; exposed area of the posterior (P) leaflet; coaptation length, as the length of the coaptation line projected to approximate leaflet surface; coaptation area, as the area of the region where the leaflets are overlapped, and coaptation height as the mean height of the same region; the aortic (AO) to mitral plane angle. (*Source:* Modified from Maffessanti, et al[69])

the *en face* plane with the narrowest mitral valve orifice, by serial cropping of the full volume dataset from the ventricular perspective. 3D guided planimetry of the mitral valve orifice area for quantification of mitral stenosis is considered a first line recommendation by experienced users.[7,92] In addition, 3DE best agreed with invasive mitral orifice area calculations derived using the Gorlin formula in rheumatic heart disease patients (Figs 21A to C, Videos 6A to C).[93] Intraobserver and interobserver variabilities were also low compared to other echocardiographic modalities. RT3DE is accurate in determination of mitral stenosis severity in calcific mitral stenosis, by planimetry of the orifice at the most restrictive portion. The narrowest orifice is not necessarily at the tips of the leaflets in contrast to that of rheumatic mitral stenosis.[94] Data acquisition for assessment of mitral stenosis can be performed either from apical or parasternal windows of a TTE or mid-esophageal or transgastric long axis views of a TEE for this purpose.

The realistic *en face* views obtained by RT3DE also enable accurate assessment of leaflet thickness, calcification and extent of commissural fusion in rheumatic mitral stenosis. The subvalvular apparatus can be evaluated especially from the transgastric long axis views. Information regarding chordal length, thickness, calcification and fusion can all be obtained. A score akin to Wilkins score has been proposed based on detailed 3D analysis of the mitral valve and subvalvular apparatus;[95] its utility beyond the traditional Wilkins score is yet to be investigated at this time. RT3D TEE in addition also increases the spatial resolution and ease of acquisitions and, in combination with live imaging, makes possible the immediate assessment of mitral valve structure and function. The ability to evaluate commissural splitting (Figs 22A to C), mitral valve area and mitral regurgitation online in the cardiac catheterization laboratory makes this a desirable technique for intraprocedural monitoring during percutaneous balloon mitral valvuloplasty.[91,96]



FIGURES 16A TO D: (A) Morphological 3D analysis of a normal mitral valve. Mitral annulus is manually initialized in one plane. (B) Then repeated in multiple rotated planes and interpolated. (C) MV leaflets are manually traced from commissure to commissure in multiple parallel planes. (D) The resultant surface is displayed as a color-coded 3D rendered valve surface. (*Source:* Modified from Chandra, et al[70])

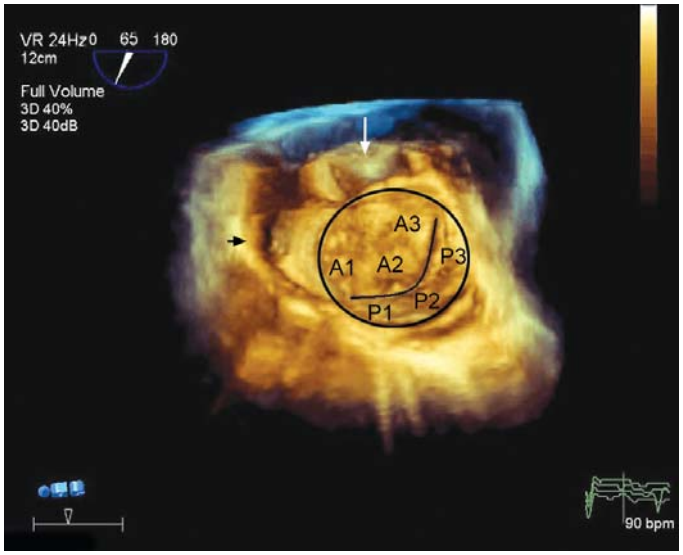


FIGURE 17: Real time three-dimensional echocardiography of the mitral valve (MV) viewed from the left atrium oriented to surgeon's view with the aortic valve (arrow) at 12 O'clock position and the left atrial appendage (arrowhead) at 9 O'clock position. The curved line overlies the MV commissure and the circle overlies the MV annulus. (Abbreviations: A1: Lateral; A2: Middle; A3: Medial scallops of the anterior mitral leaflet; P1: Lateral; P2: Middle; P3: Medial scallops of the posterior mitral leaflet)

Aortic Valve

Planimetry of the aortic valve at peak systole by 3D TEE has been shown to be superior to 2DE in calculating the severity of aortic valve stenosis (Fig. 23).[97] RT3DE similarly is a promising tool from the initial experience in the assessment of aortic valve stenosis mainly due to its ability to identify the perpendicular plane at which the area is the narrowest.[98-100] It has been shown to complement 2DE in identifying other aortic valve and root pathologies (Figs 24A to D, Video 7) including regurgitant lesions.

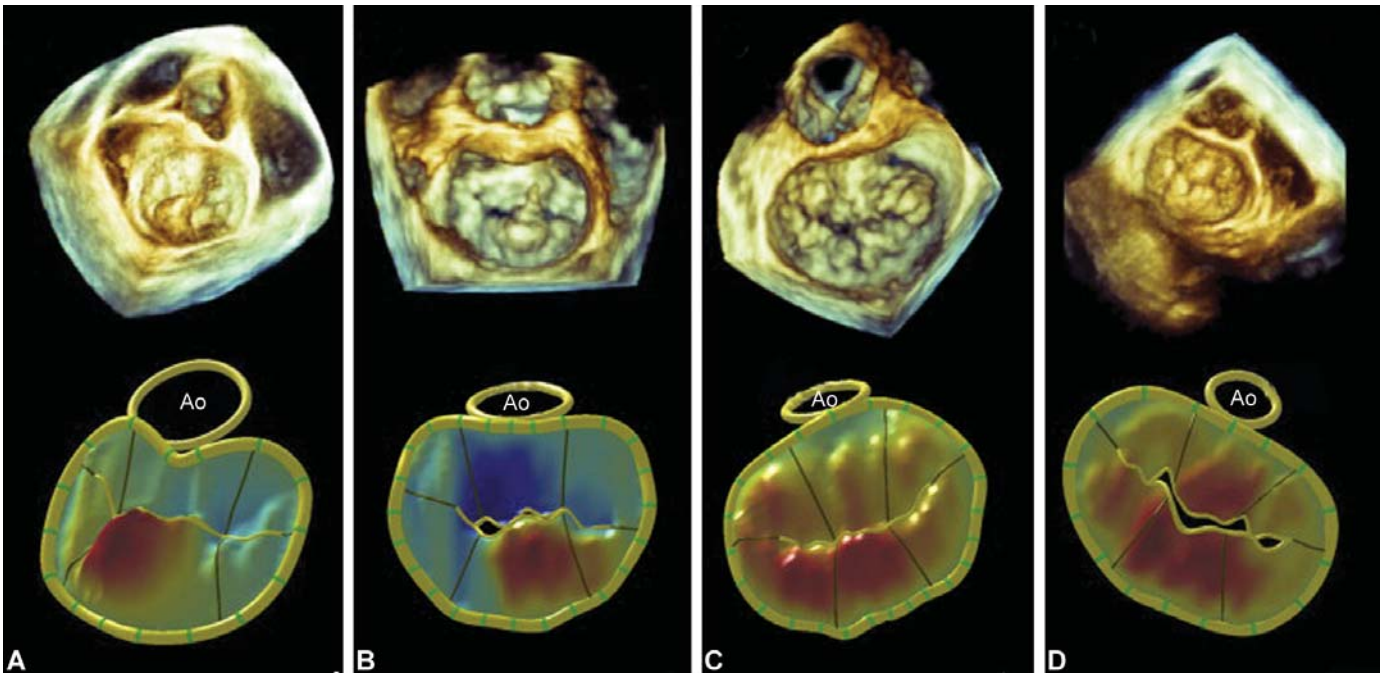
Other Valves

Due to its unique ability to visualize the complex tricuspid valve *en face* (Figs 25A and B), RT3DE has incremental value over 2DE in delineating complex tricuspid valve pathologies including carcinoid disease, Ebstein's anomaly, rheumatic disease (Figs 26A to D), prolapse, chordae rupture and regurgitation.[101,102]

RT3DE makes possible the visualization of pulmonic valve *en face* (Fig. 27)[103] and merits further exploration for its use especially in congenital conditions.[104]

Prosthetic Valves

In the hands of the experienced, RT3DE is superior to conventional 2D and Doppler echocardiography in assessing St Jude



FIGURES 18A TO D: Example of volume-rendered mitral valve (MV) (top) as seen from the left atrium in patients with varying distribution, severity and extent of MV prolapse. The 3D representations (bottom) clearly show the morphology of the MV and the region and severity of prolapse in red: isolated P2 scallop (A and B) versus diffuse prolapse with redundant tissue (C and D). (Abbreviation: Ao: Aorta). (*Source:* Modified from Maffessanti, et al[69])

mechanical prosthetic valve structure and function. The presence of concurrent, brisk motion of both the leaflets (Figs 28A and B, Video 8), at times difficult to demonstrate on a single plane 2DE, can be made possible by diligent cropping of the RT3DE datasets. This takes away the reliance on Doppler gradients, which at times are misleading.[105] Its application to other prosthetic valves remains to be assessed better but preliminary experience is promising.[106]

Prosthetic valve complications such as fracture, dehiscence, paravalvular leak (Figs 29A to D, Videos 9A to C), pannus, thrombosis, vegetation, abscess, fistulae can all be better assessed with a 3D technique especially RT3D TEE.[107-112]

MISCELLANEOUS CONDITIONS

Mass lesions such as thrombi or tumors occurring in the heart can undoubtedly be better imaged by RT3DE compared to 2DE, due to its volume rendering abilities. It helps define the origin, size, structure (brightness indicative of fibrosis;[113] echolucency characteristic of clot lysis (Figs 30A and B),[114] vascularity[115] and cysts[116]) it can demonstrate the extent, volume, mobility and attachments of a mass,[117] along with hemodynamic significance that can result from obstruction to flow. These observations based on RT3DE can possibly translate into better treatment decisions.

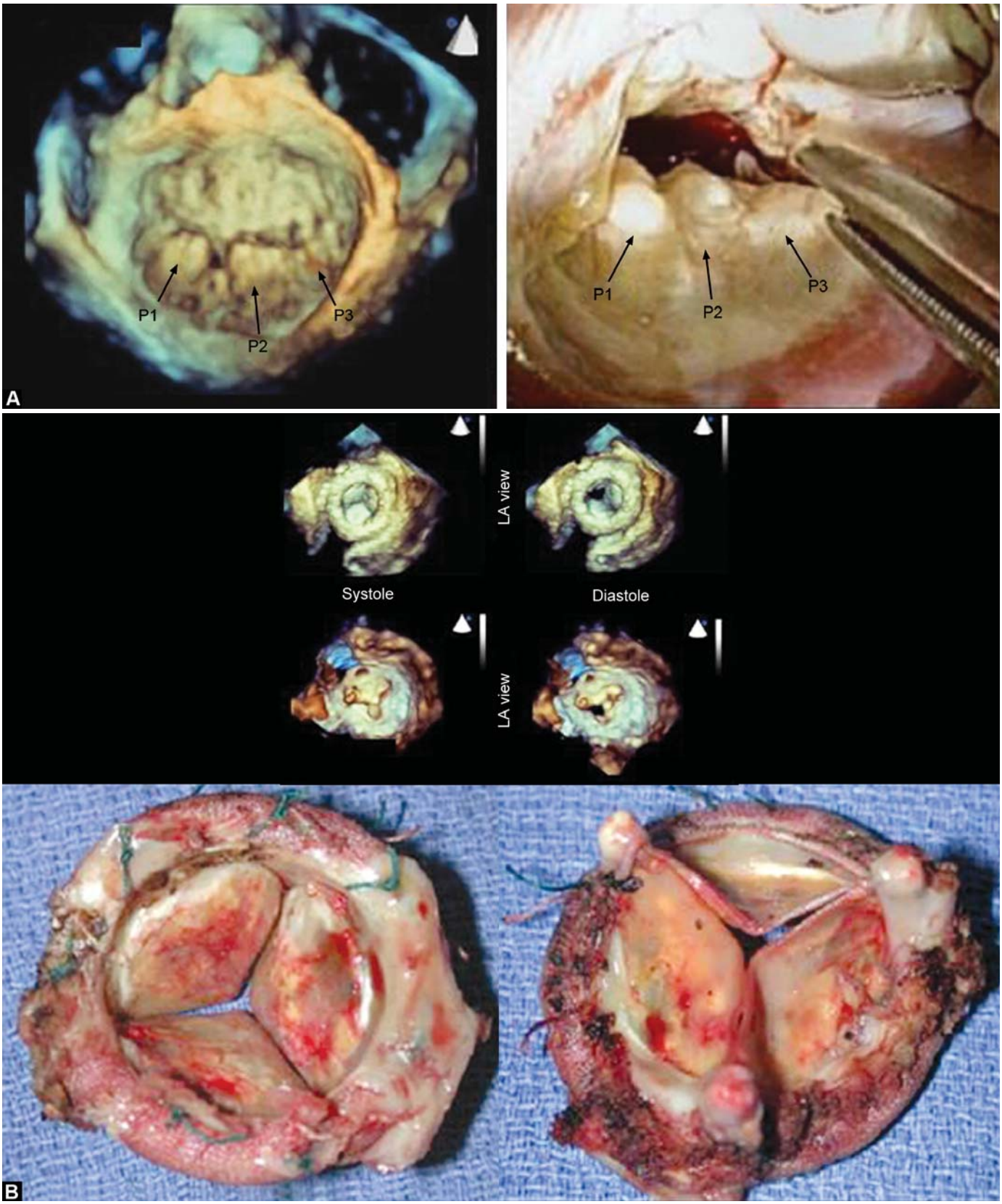
Evaluation of the interatrial septum is a common indication for TEE. RT3D TEE in a literal sense has multiplied the magnitude of information echocardiography can provide in accurate assessment of anatomy, treatment planning, guidance and post-procedural or surgical evaluation of atrial septal defects (ASD). The determination of the location, extent, adequacy of the aortic rim is crucial in planning appropriate therapeutic strategy in these patients. The TUPLE, tilt-up-then-left (rotate-left-in-Z-axis), maneuver when acquiring 3D TEE datasets at 0° from mid-esophageal view (Figs 31A to C); tilt up, rotate counter-clockwise in Z-axis till superior vena cava (SVC) at 12 O'clock (ROLZ) and then turn left to see the left atrial aspect maneuver when acquiring at higher angles has been proposed as a standard maneuver to facilitate accurate diagnosis and description purposes to ensure meaningful communication between imagers, interventionalists and the surgeons.[118] Figure 32 illustrates the effect of higher angles on the orientation of SVC and hence the need for integration of ROLZ maneuvers into TUPLE while imaging at higher angles. RT3DE has not been studied as a tool for shunt quantification across the ASD.

Likewise, RT3DE can also evaluate the size, location and complexity of the ventricular septal defect (VSD) in addition to displaying it *en face* and guide corrective procedures as described below.[119]

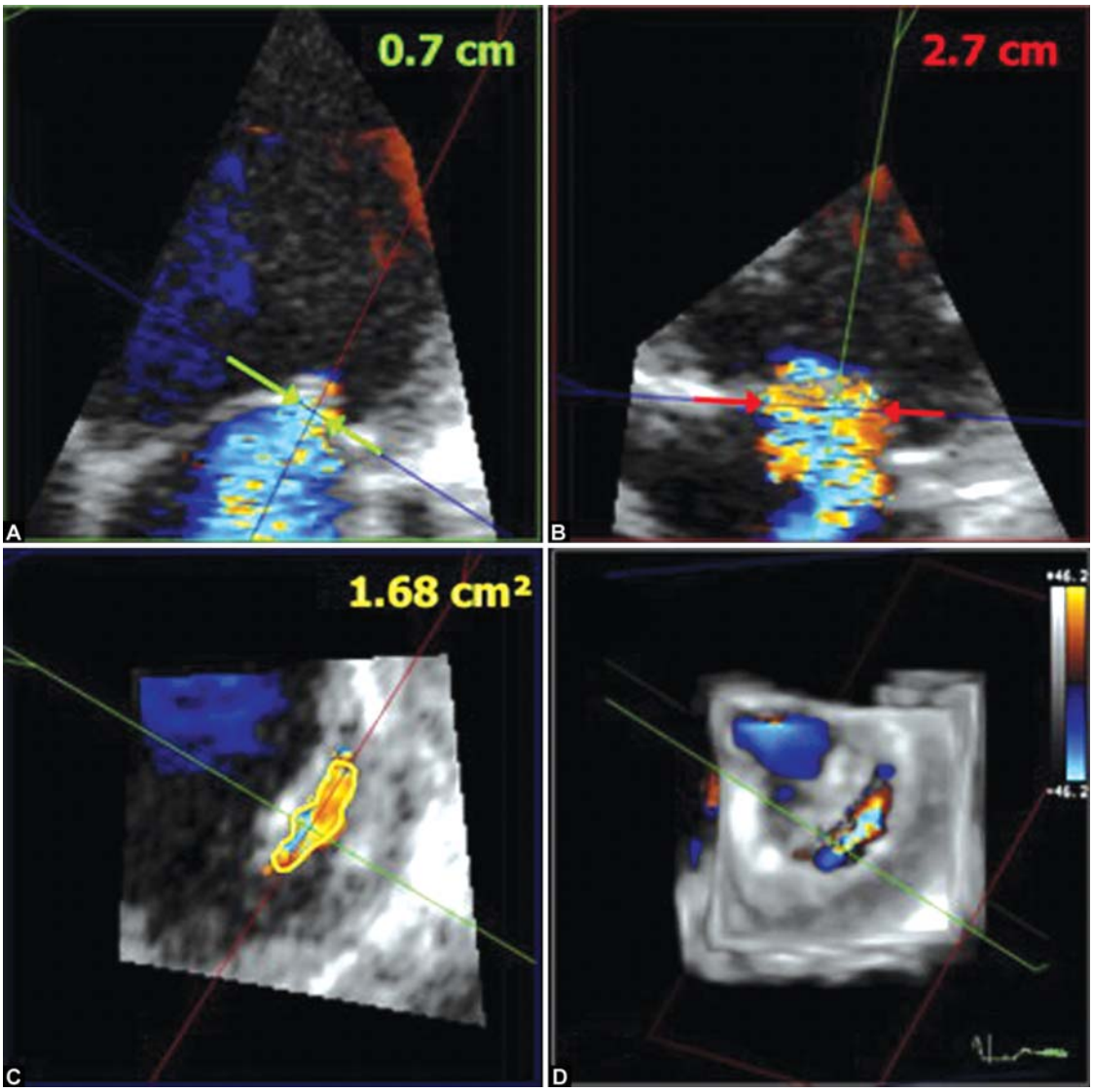
RT3DE can be used to identify any structure that is in the vicinity of the ultrasound beam by examining its 3D relations and meticulous cropping (Figs 33A to C).[120] This technique is also of evolving importance in the evaluation of congenital heart diseases and is beyond the scope of this chapter.

GUIDANCE OF PERCUTANEOUS PROCEDURES

As the technology and the skill of operators evolve, more and more complex percutaneous procedures are being performed on the beating heart. Although these procedures are routinely performed under fluoroscopy, real time 2DTEE and intracardiac echocardiography (ICE) are commonly used to provide important visualization of soft tissue structures of the heart; these cannot usually be otherwise obtained in a cardiac catheterization



FIGURES 19A AND B: (A) Example of a patient with multiscallop mitral valve prolapse of the posterior leaflet (as usually seen in Barlow's syndrome) visualized using three-dimensional matrix transesophageal echocardiographic imaging (left) and a corresponding surgical view (right) (P1—Lateral; P2—middle; P3—medial). (B) Example of systolic and diastolic still frames of three-dimensional (3D) matrix transesophageal real time volume renderings of a bioprosthetic mitral valve (MV) as visualized from the left atrial (LA) (top) and left ventricular (LV) (bottom) perspectives. Note the well-visualized struts in the LV views of the valve. (Right) Explanted stenotic bioprosthetic MV, confirming the 3D matrix transesophageal echocardiographic findings. (*Source:* Modified from Sugeng, et al[86])

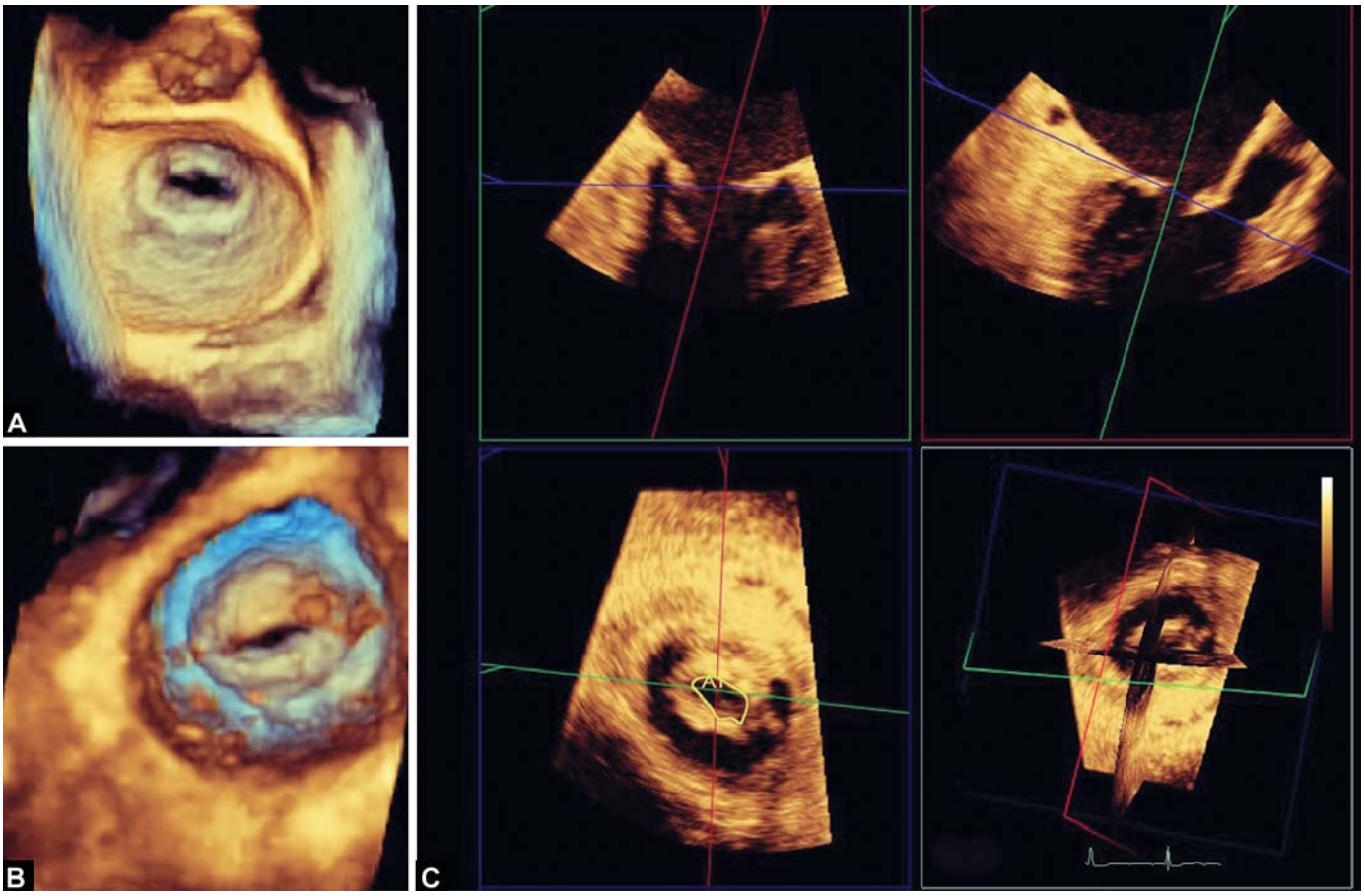


FIGURES 20A TO D: Example of measurement of VC dimensions in a cross-sectional plane through the VC in a patient with functional MR caused by leaflet tethering using onboard 3D analysis software (QLAB, Philips Medical Systems, Andover, MA): (A) 4CH view with measurement of narrow 3D VCW-4CH; (B) 2CH view with measurement of broad 3D VCW-2CH; (C) Cross-sectional plane through the VC with direct planimetry of VCA. The green and the red line indicate the orientation of the 4CH plane (panel 1A, green frame) and the 2CH plane (panel B, red frame); (D) 3D *en face* view of VCA. (Abbreviations: CH: Chamber; MR: Mitral regurgitation; VC: Vena contracta; VCA: Vena contracta area; VCW: Vena contracta width). (*Source:* Modified from Kahlert, et al[87])

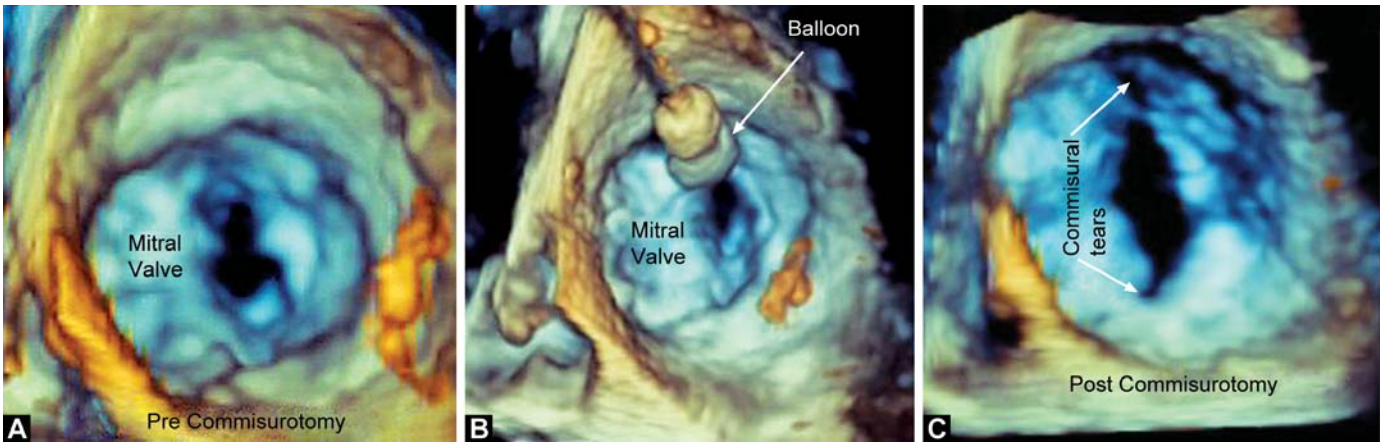
suite. In the past, however, the echocardiographer was limited in the views obtained by 2D single plane technique to guide a procedure that is occurring in 3D. With the advent of RT3DE, especially TEE, easily comprehensible views can be obtained in real time that guide precise wire, catheter or instrument positioning, making the procedure safe and successful. While additional venous access is not needed as with ICE, general anesthesia may be required for prolonged RT3D TEE guidance. Several studies have shown the incremental value of RT3DE during device deployments for patent foramen ovale, ASD (Figs 34A to F), VSD, paravalvular leaks, LAA occlusion (Figs 35A and B), balloon mitral valvuloplasty, percutaneous edge to edge mitral valve repair (Figs 36A to C), aortic valvuloplasty, percutaneous (Figs 37A to C) and transapical aortic valve implantation.[91,121-123]

Endomyocardial biopsy can also be safely performed under RT3DE guidance not only to ensure avoidance of injury to the valvular apparatus but also to monitor for complications as with other procedures. It has been shown to be of incremental value in proper bioptome positioning.[124] Transatrial septal puncture and pulmonary vein isolation procedures have been successfully guided by RT3DE.[91]

Catheter positioning in the first proximal septal perforator is crucial to the success of alcohol septal ablation. If the operator is not diligent, an alternative coronary branch can be mistaken for the first septal perforator, which may lead to inadvertent iatrogenic MI of innocent myocardium. RT3DE can localize the complete extent and distribution of contrast better, clearly delineating the area intended for controlled infarction by alcohol injection.[91]



FIGURES 21A TO C: Rheumatic mitral stenosis by RT3D TEE: (A) zoom mode acquisition obtained from the mid esophageal transducer position cropped transversely viewed from the left atrium and left ventricle (Video 6A); (B) shows the stenotic mitral valve orifice (Video 6B); (C) the cropping in 3D needed to obtain *en face* view of the limiting mitral valve orifice and planimetry of its area labeled A1 in the left lower panel (Video 6C)



FIGURES 22A TO C: Mitral balloon valvuloplasty: (A) *en face* view of a stenosed mitral valve, with restricted opening, as seen from the left atrial perspective (3D zoom mode acquisition); (B) guiding catheter with a balloon placed across the mitral valve commissures, as seen from the left atrium (3D zoom mode acquisition); (C) *en face* view of the mitral valve after commissural tears have been created as seen from the left atrial side. The mitral valve orifice is visibly larger than it was before commissurotomy (3D zoom mode acquisition). (*Source:* Modified from Perk, etal[91])

Procedural guidance is an actively evolving advanced application of RT3DE and is yet to be validated well on a larger scale. RT3DE is currently underutilized due to several factors including the potential need for general anesthesia, lack of standardization of 3D echocardiographic views, prolongation of the procedure time (but less radiation/contrast exposure), the

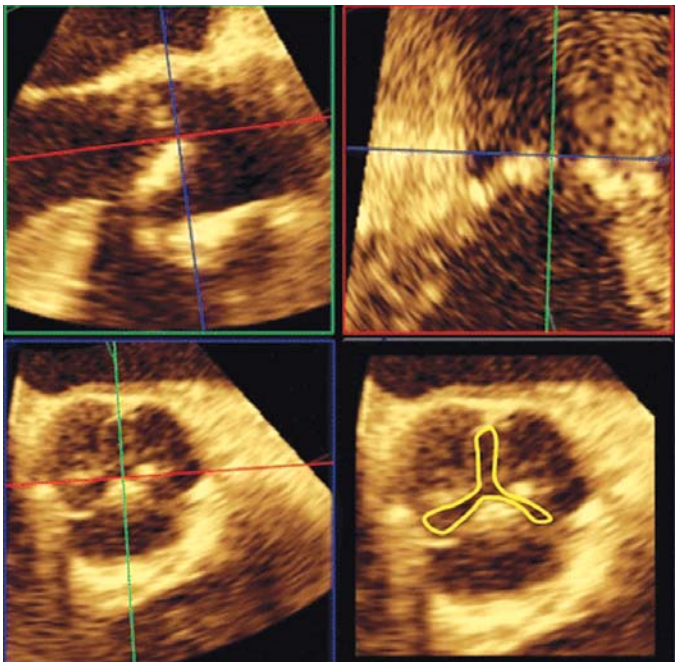
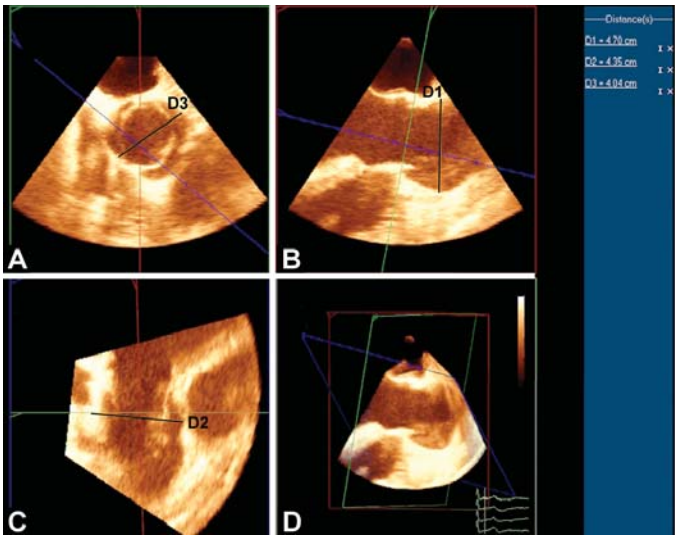


FIGURE 23: Measurement of aortic valve anatomic area (AVA) by volumetric three-dimensional transoesophageal echocardiography. Two orthogonal long-axis views of the aortic valve (green quadrant; anterior-posterior projection, red quadrant; medial-lateral projection) were extracted using multiplanar reconstruction mode. Third plane perpendicular to the other two long-axis planes was the cross-sectional view of the aortic valve for the correct tracing of aortic valve area. Aortic valve area was traced when the optimal cross-section of the valve is achieved during its maximal systolic opening. (*Source:* Modified from Nakai H, Takeuchi M, Yoshitani H, et al. Pitfalls of anatomical aortic valve area measurements using two-dimensional transoesophageal echocardiography and the potential of three-dimensional transoesophageal echocardiography. Eur J Echocardiogr. 2010;11:369-76)

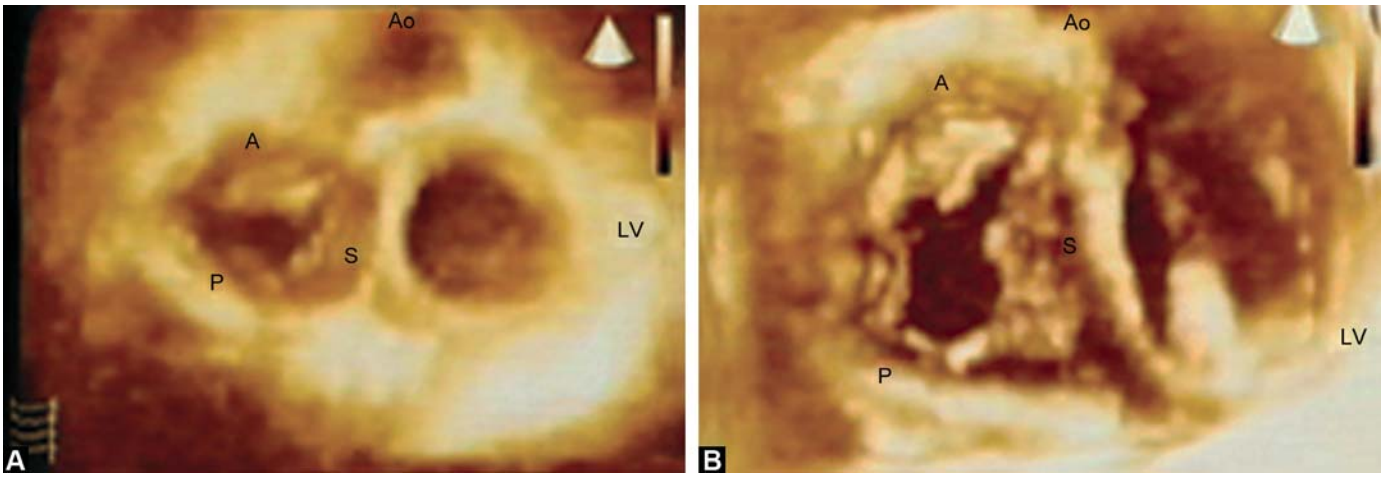


FIGURES 24A TO D: Measurement of the size of aortic enlargement in multiple axes by 3D TEE in a patient with ascending aortic aneurysm and bicuspid aortic valve (Video 7)

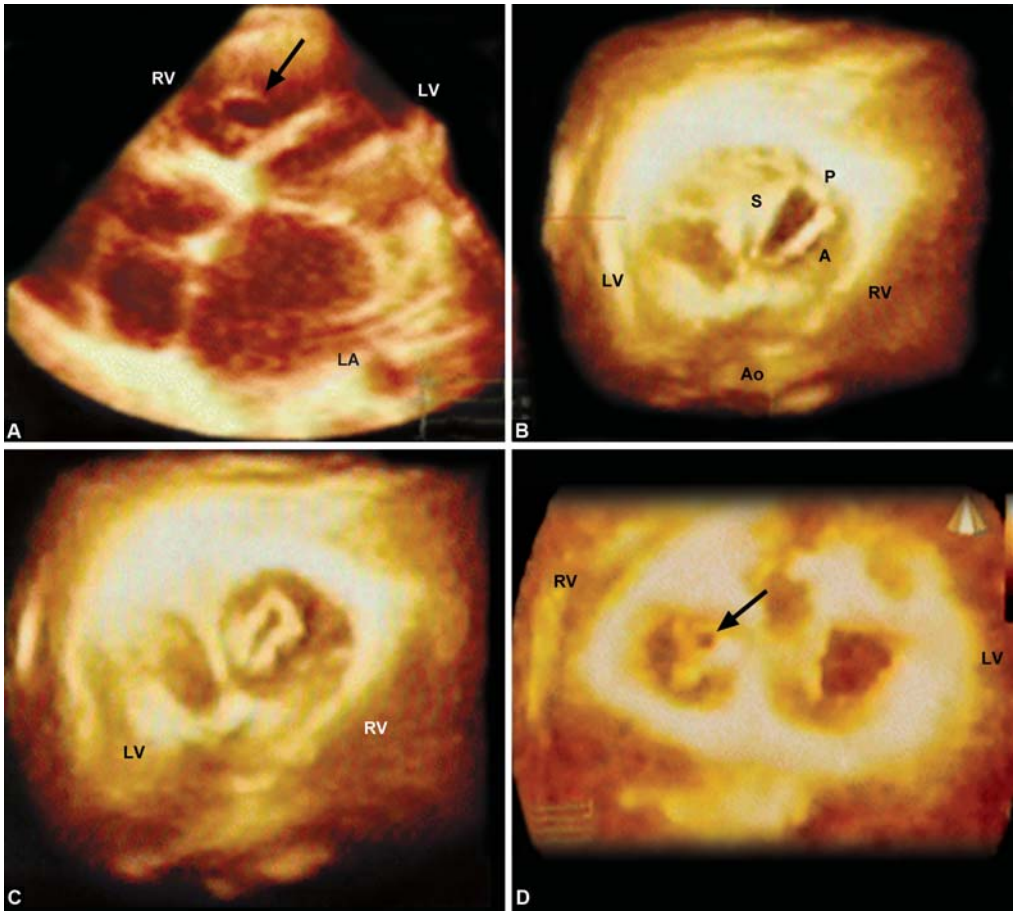
interventional or electrophysiologist's need to integrate continuously the multimodality visual feedback to catheter manipulation, lack of adequate trained operators in advanced echocardiography and the lack of standard nomenclature conventions to describe the position of the device in space, that could lead to potential harm.

FUTURE DIRECTIONS

Since its advent in 2002, RT3DE has plunged forward holding interest of the advanced imagers, and now with the integration of the miniaturized matrix probe with the TEE probe, the indications for its use in valvular and procedural applications are exploding. Further advances in this technology will allow for a probe with smaller footprints, better spatiotemporal resolution, wider acoustic angle, single beat wide angle and color flow acquisition capabilities, eliminating artifacts and patient discomfort to a large extent. Undersampling issues will be resolved with higher frame rates. A comprehensive echocardiogram can potentially be completed in a fraction of a time needed now, as one can eliminate the different 2D views currently acquired, thereby improving the workflow in the echocardiographic laboratory. Stress echocardiograms may possibly be performed solely in a 3D format or in combination with single photon emission computerized tomography, as the



FIGURES 25A AND B: Live or real time three-dimensional transthoracic echocardiography. Three leaflets of the tricuspid valve. (A and B) *En face* views in two different patients showing all three tricuspid valve leaflets in the open position. (Abbreviations: A: Anterior leaflet; Ao: Aorta; LV: Left ventricle; P: Posterior leaflet; S: Septal leaflet). (*Source:* Reproduced with permission from Pothineni, et al[101])



FIGURES 26A TO D: Live or real time three-dimensional transthoracic echocardiography. Rheumatic tricuspid valve stenosis or tricuspid regurgitation. (A) The arrow points to the tricuspid orifice in a patient with tricuspid valve stenosis. The orifice area measured 2.02 cm^2 in diastole. (B and C) *En face* views in another patient with mild tricuspid stenosis but severe tricuspid regurgitation. The tricuspid orifice area measured 2.4 cm^2 in diastole (B). Systolic frame (C) shows non-coaptation of tricuspid valve leaflets. This measured 0.4 cm^2 in area and resulted in severe tricuspid regurgitation as assessed by two-dimensional color Doppler. (D) *En face* view from the ventricular aspect showing systolic non-coaptation (arrow) of the tricuspid valve in a third patient with rheumatic heart disease. (Abbreviations: A: Anterior leaflet; Ao: Aorta; LA: Left atrium; LV: Left ventricle; P: Posterior leaflet; RV: Right ventricle; S: Septal leaflet). (*Source:* Reproduced with permission from Pothineni, et al[101])

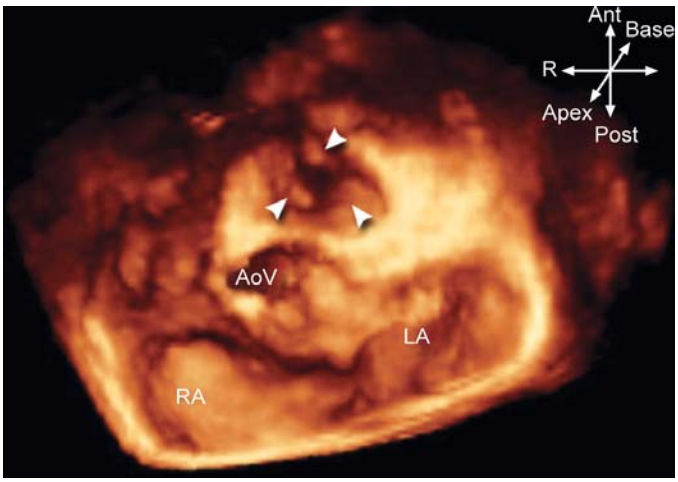
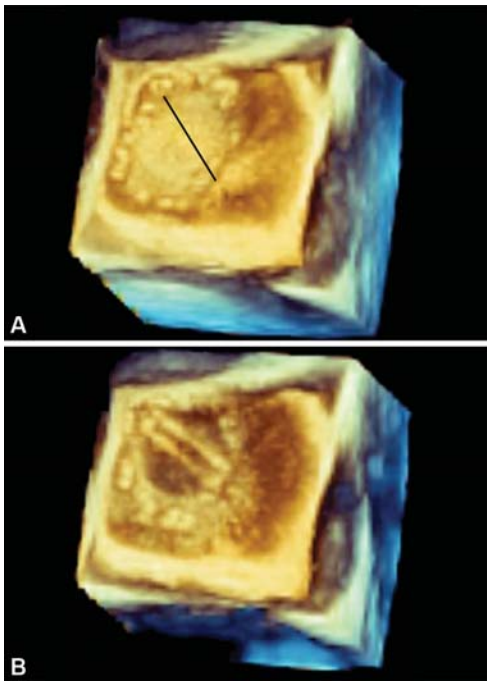
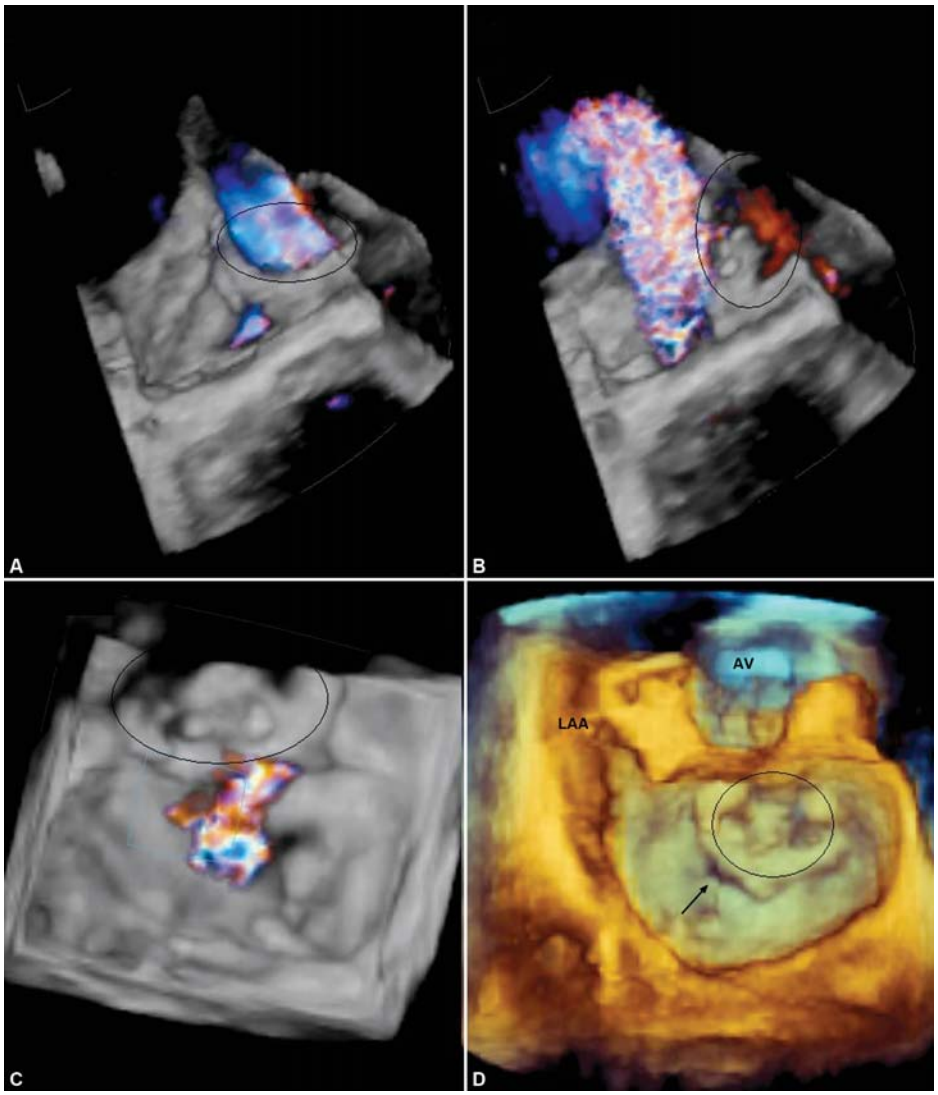


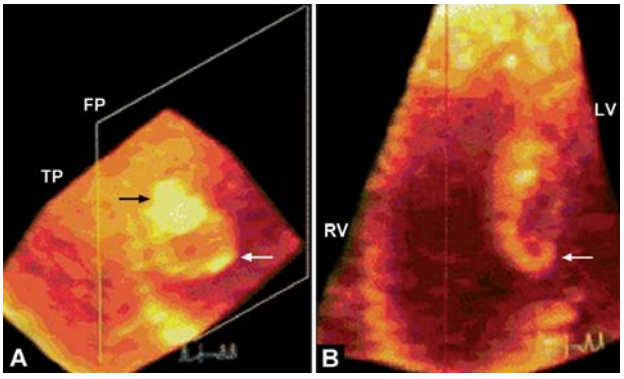
FIGURE 27: Real time three-dimensional echocardiography. Carcinoid syndrome: *en face* view from right ventricular perspective showed thickened and retracted annulus and cusps of pulmonary valve (arrowheads). (Abbreviations: Ant: Anterior; AoV: Aortic valve; L: Left; LA: Left atrium; Post: Posterior; R: Right; RA: Right atrium). (*Source:* Modified from Lee, et al[103])



FIGURES 28A AND B: Left atrial view of St Jude mechanical mitral prosthesis in (A) systole and (B) diastole by RT3D TEE (Video 8). The black line overlies the central closure line



FIGURES 29A TO D: Paravalvular leak in a patient with bioprosthetic mitral valve replacement (MVR) imaged by real time three-dimensional transesophageal echocardiography. Color Doppler datasets viewed from left atrium (LA) in (A) diastole; (B) systole (Videos 9A and B) *en face*; (C) the diastolic mitral inflow occurs through the MVR ring as in A (overlaid with a black circle,) while the systolic mitral regurgitation as in B and C occurs primarily through the posteriorly located paravalvular perforation (arrow in D) Full volume dataset without color oriented to surgeon's view, viewed from LA (Video 9C) (Abbreviations: AV: Aortic valve; LAA: Left atrial appendage)



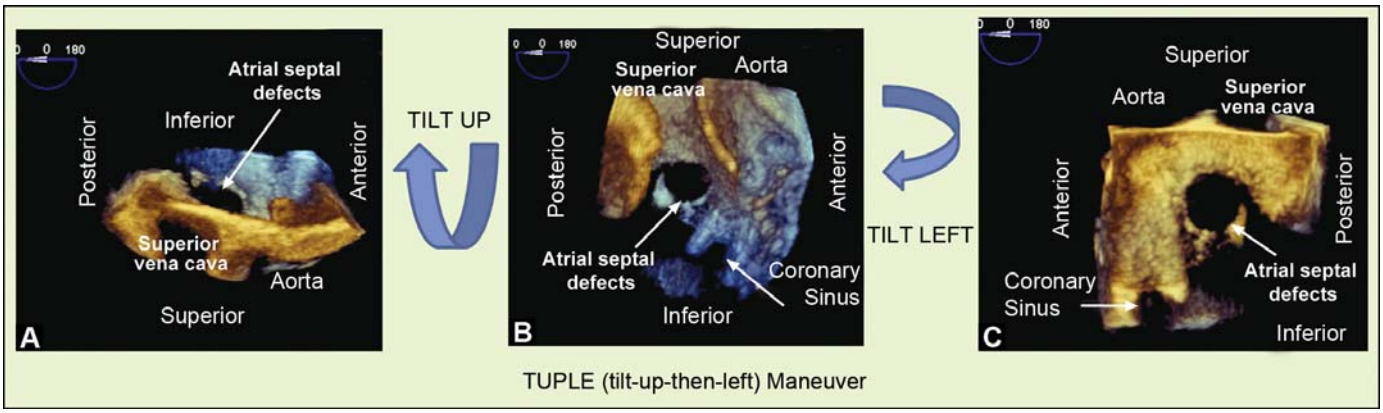
FIGURES 30A AND B: Cropped 3D dataset obtained from apical 4-chamber view with a left ventricular (LV) thrombus attached to the LV apex. Cropping with the transverse plane (TP) shows the absence of echolucency indicative of clot lysis in the stalk (arrow) (A) cropping with frontal plane (FP) shows the presence of echolucency within the body of the thrombus indicative of clot lysis or potential therapeutic efficacy. (Abbreviation: RV: Right ventricle). (*Source:* Modified from Sinha, et al[114])

temporal resolution improves. Myocardial perfusion echocardiography applications should emerge with this 3D technique as further evidence gathers. RT3DE will discover its applications and limitations in determining regional RV volumes in various conditions affecting the RV.

3D speckle or strain imaging, making possible the extension of robust strain derived information to three dimensions will find its applications in a variety of conditions. Similar integration to contraction front mapping in electrophysiological procedures would allow for RT3DE guided ablation procedures, along with RT3DE guided placement of the LV lead to obtain an optimal response to CRT.

The user interface will be further refined and made user friendly with ability to crop in a more intuitive fashion. The advent of real time triplane imaging will eliminate the cropping time while retaining the advantage of imaging in three dimensions that may be adequate for evaluation of certain conditions such as aortic stenosis and stress imaging. As more operators are trained in RT3DE, this modality has the potential to become the standard of care especially in the interventional laboratory and the operating room.

Further advances in technology may make possible stereoscopic vision display (3D display as opposed to the current 2D display of 3D images) of RT3DE to better guide intracardiac beating-heart procedures or surgery.



FIGURES 31A TO C: Imaging of a secundum ASD at 0°. The TUPLE maneuver is applied to the imaging of a secundum ASD: (A) the initial 3D TEE image (opening scene); (B) the right atrial aspect of the ASD; (C) the left atrial aspect of the ASD. (Abbreviations: ASD: Atrial septal defects; SVC: Superior vena cava). (*Source:* Modified from Saric, et al[114])

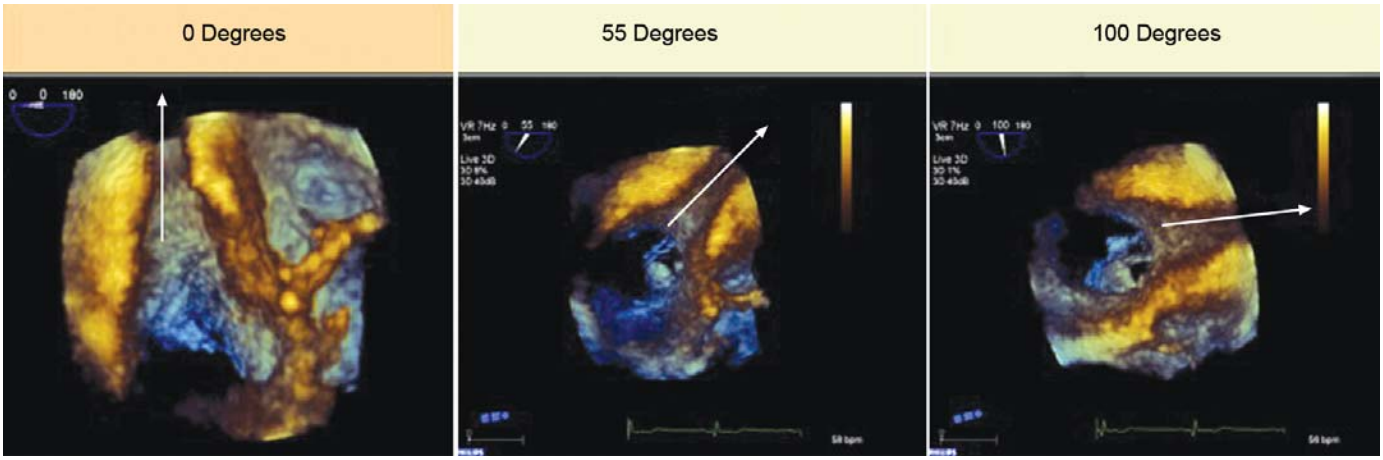
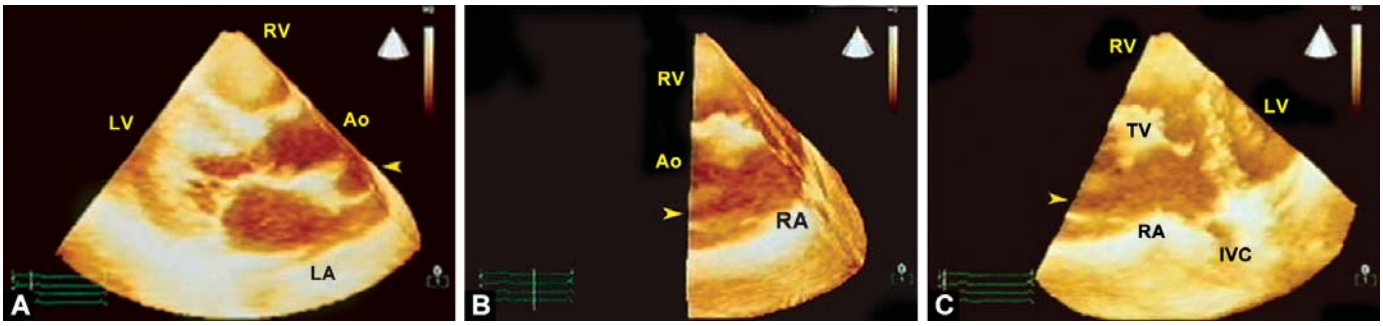


FIGURE 32: Imaging at intermediate angles. The impact of various acquisition angles on the 3D images of the interatrial septum is demonstrated. Each image demonstrates the right atrial aspect of the interatrial septum. Note that as the angle of image acquisition increases, the position of the SVC rotates progressively in the clockwise rotation (see text). (*Source:* Modified from Saric, et al[114])

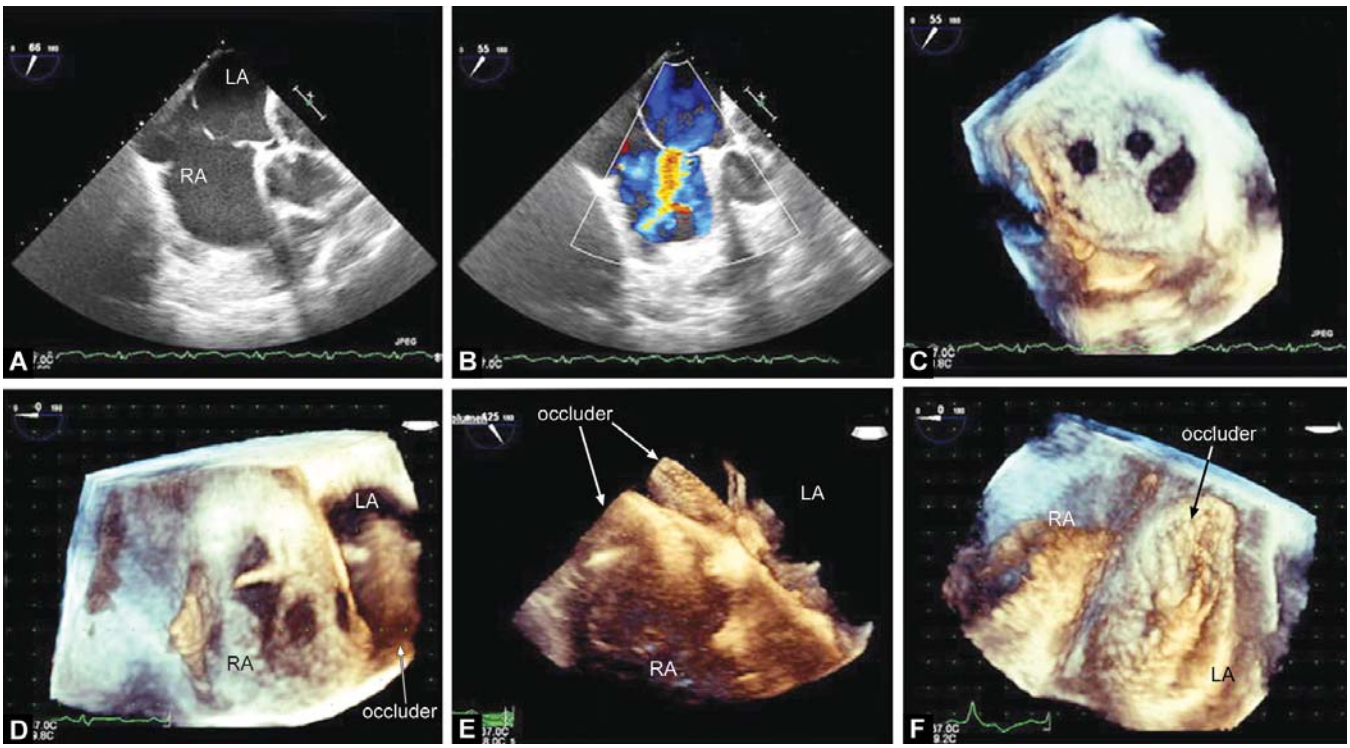


FIGURES 33A TO C: (A) Bounded echo-free space behind the aorta imaged in parasternal long-axis view. (B) Live three-dimensional transthoracic echocardiography. (C) Tilting of the full volume 3D dataset shows the bounded echo-free space (arrowhead) to be continuous with the RA. This is consistent with SVC. (Abbreviations: Ao: Aorta; IVC: Inferior vena cava; LA: Left atrium; LV: Left ventricle; RA: Right atrium; RV: Right ventricle; SVC: Superior vena cava; TV: Tricuspid valve). (*Source:* Modified from Burri, et al[120])

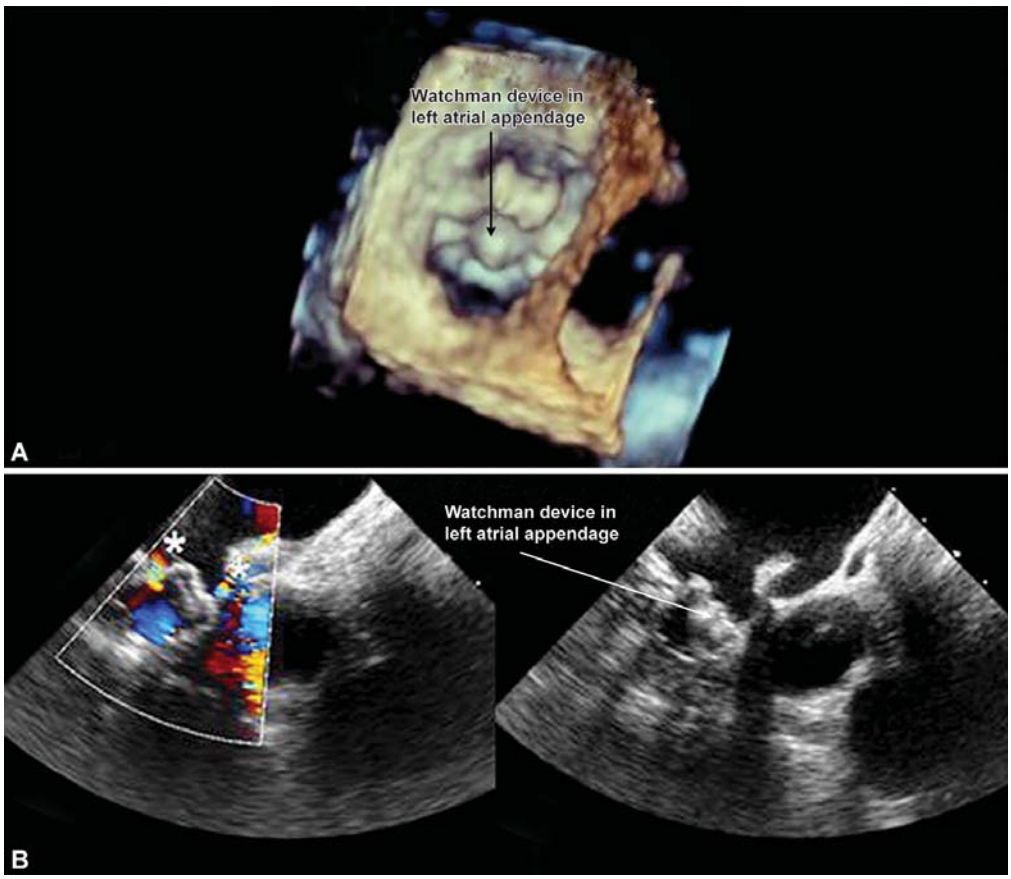
LIMITATIONS

The main limitation of RT3DE is the need for advanced expertise of the operator which calls for independent judgment and problem solving skills similar to that demanded by 2DE. As with any newly developed technique, there is a substantial learning curve. At this time, not all institutions offer training in RT3DE. Guidelines for training requirements are yet to be established.

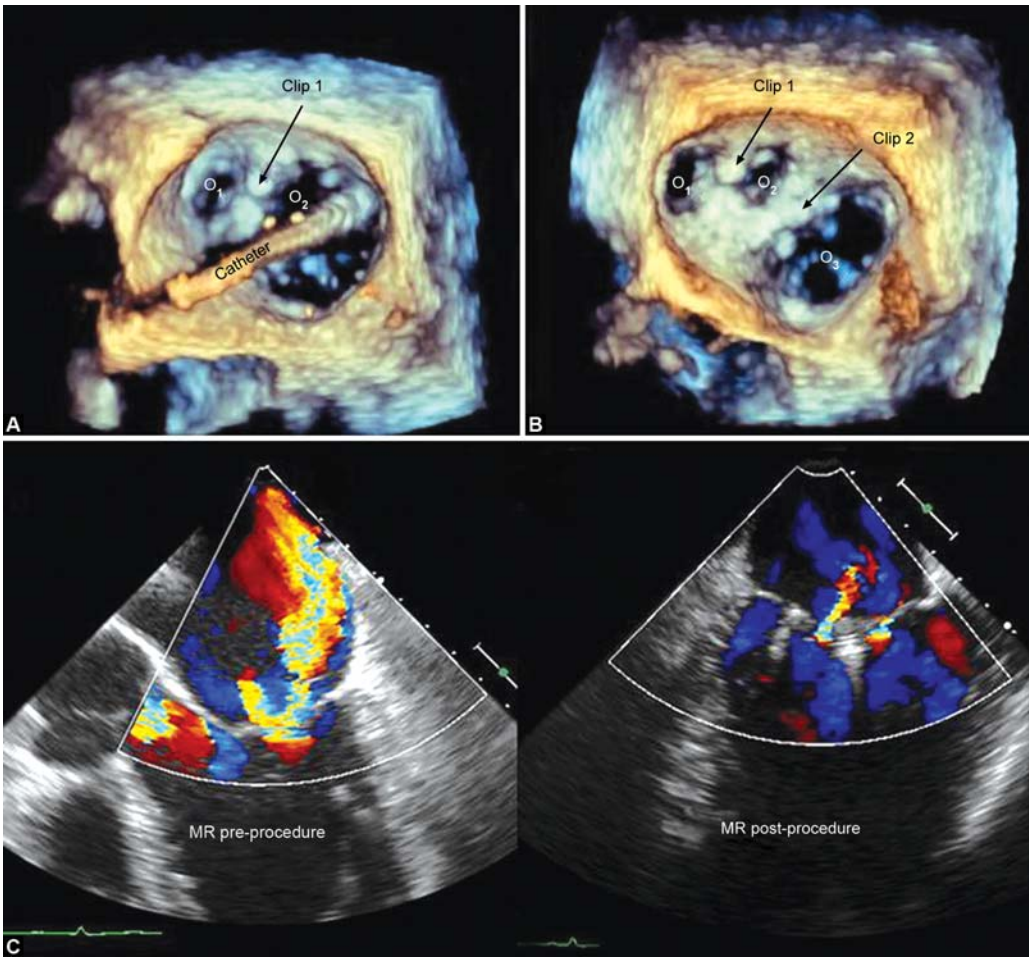
Quality of the 2DE image dictates the quality of the 3D dataset. Most of the currently used 3D probes have compromised spatial and temporal resolution (especially with color Doppler)



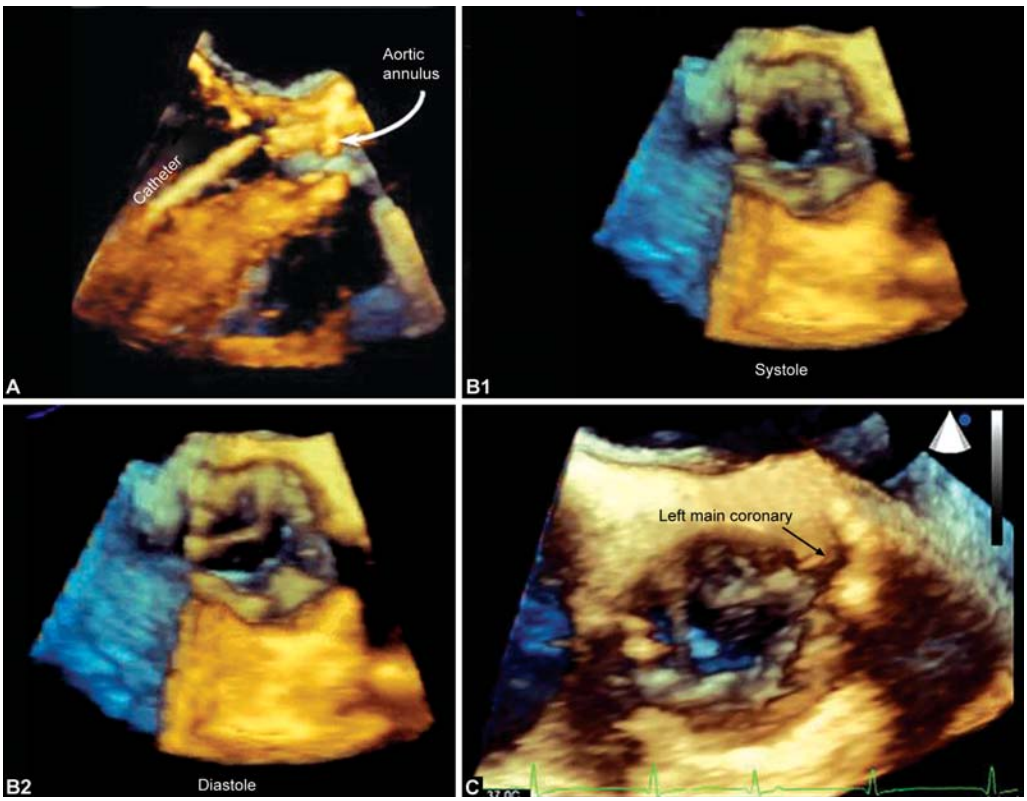
FIGURES 34A TO F: Real time 3D TEE guided closure of three atrial septal defects: (A) 2D imaging suggested more than 1 defect of a mobile interatrial septum with; (B) left-to-right shunt obtained by color Doppler; (C) a 3D left atrial view more detailed demonstrated three separated defects; (D) the septum was crossed under 3D guidance and a 34 mm Amplatzer occluder (occluder) was advanced from the left atrium (LA); (E and F) online 3D imaging allowed positioning the left-sided disc so that it covered all defects and assuring secure placement of the right sided disc (Abbreviation: RA: Right atrium). (*Source:* Modifie from Dodos, et al[123])



FIGURES 35A AND B: LAA obliteration with suboptimal positioning: (A) *en face* view from the left atrium into the LAA showing off-angle LAA occlusion device. The device is not perpendicular to the opening of the LAA, and a residual potential communication between the LAA and the main left atrium is still noticeable (3D zoom mode acquisition); (B) two-dimensional imaging of the off-angle closure device with color Doppler (asterisk) demonstrating residual flow between the LAA and the main left atrium. (*Source:* Modified from Perk, et al[69])



FIGURES 36A TO C: Mitral valve clipping with two clips: (A) mitral valve with the first clip in place seen from the left atrium. A double orifice mitral valve has been created (O_1 and O_2). However, color Doppler interrogation demonstrated significant residual mitral regurgitation (MR), so a second clip was deemed necessary. The guiding catheter is seen directed toward the larger part of the mitral valve orifice (O_2) to place another clip in the mitral valve (3D zoom mode acquisition); (B) two clips have been deployed in the mitral valve, resulting in a three-orifice mitral valve. The image shows an *en face* view of the mitral view, as seen from the left atrium. The three orifices (O_1, O_2 and O_3) are noted (3D zoom mode acquisition); (C) color Doppler demonstration of the result of the procedure. (Left) Before the procedure, severe MR is clearly demonstrated. (Right) After the procedure, only mild MR can be seen (*Source:* Modified from Perk, et al[69])



FIGURES 37A TO C: Percutaneous aortic valve replacement: (A) guiding catheter seen passing through the aortic valve (3D zoom mode acquisition); (B_1) systolic and (B_2) diastolic frames of a percutaneously implanted aortic valve as seen from the left ventricular perspective (3D zoom mode acquisition); (C) the proximal left main coronary artery, as seen from the left ventricular perspective. Patency of the ostium of the left main coronary artery is confirmed after valve implantation (3D zoom mode acquisition). (*Source:* Modified from Perk, et al[69])

compared to their 2D counterparts. The 3D dataset is displayed in 2D and hence the depth perception is limited during procedural guidance. Novel displays provide differential color hues with respect to depth of the image; however, unless one performs carefully calibrated depth measurements by manipulating the image to display the Z-axis (depth) parallel to the screen, certainty of depth perception is questionable. The analysis of the volumetric data can be time consuming.

Artifacts that are seen with 2DE are all common to 3DE as well. In addition, stitch artifacts in space or time, as alluded to previously, can be seen due to respiratory motion or due to irregular heart rates respectively, during the acquisition of pyramidal subvolumes of a full volume dataset.

VIDEO LEGENDS

Videos 1A and B	Modalities of live/real time three dimensional echocardiographic imaging: narrow angle real time imaging (A) and wide angle/full volume acquisition (B)
Videos 2A and B	Common artifacts during full volume acquisition in live/real time three dimensional echocardiography: a temporal (A) and a spatial stitch artifact (B)
Videos 3A and B	Semiautomated quatification of global (A) and regional (B) left ventricular function and corresponding time volume curves for all the phases of cardiac cycle
Videos 4A and B	Color-coded display of 16 left ventricular segments depicted in a cast display, in a normal (A) and a heart failure (B) patient
Videos 5A and B	Semiautomated right ventricular endocardial tracing in axial, sagittal and coronal planes of a full volume dataset (A) Three dimensional cast representation of the right ventricle (RV) providing RV volumes and ejection fraction (B)
Videos 6A and B	Zoom mode RT 3DTEE acquisition cropped transversely and viewed from left atrium (A) and left ventricle (B) in a patient with rheumatic mitral stenosis
Video 6C	The cropping in 3D needed to obtain the limiting mitral valve orifice area on an *en face* view (left lower panel) in rheumatic mitral stenosis
Video 7	RT 3DTEE in a patient with bicuspid aortic valve
Video 8	Left atrial view of St Jude mechanical mitral prosthesis by RT 3DTEE
Videos 9A to C	(A and B) Color Doppler RT 3DTEE of paravalvular regurgitation in a patient with a bioprosthetic mitral valve. (C) The relationship of the paravalvular regurgitation (posterior) to the valve is shown. The aortic valve is seen anteriorly.

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Chapter 20

Intravascular Coronary Ultrasound and Beyond

Teruyoshi Kume, Yasuhiro Honda, Peter J Fitzgerald

Chapter Outline

- Intravascular Ultrasound
  - Basics of IVUS and Procedures
  - Normal Vessel Morphology
  - IVUS Measurements
  - Tissue Characterization
  - Insights into Plaque Formation and Distribution
  - Interventional Applications
  - Preinterventional Imaging
  - Balloon Angioplasty
  - Bare Metal Stent Implantation
  - Drug-Eluting Stent Implantation
  - Safety
  - Future Directions
- Optical Coherence Tomography
  - Imaging Systems and Procedures
  - Image Interpretation
  - Clinical Experience
  - Detection of Vulnerable Plaque
  - Safety and Limitations
  - Future Directions
- Angioscopy
  - Imaging Systems and Procedures
  - Image Interpretation
  - Clinical Experience
  - Detection of Vulnerable Plaque
  - Safety and limitations
  - Future Directions
- Spectroscopy
  - Imaging Systems and Procedures
  - Experimental Data
  - Clinical Experience
  - Safety and Limitations
  - Future Directions

INTRODUCTION

Intravascular ultrasound (IVUS) is widely used as a major diagnostic and assessment technique that provides detailed cross-sectional imaging of blood vessels in the cardiac catheterization laboratory. The first ultrasound imaging catheter system was developed by Bom and his colleagues in Rotterdam, the Netherland, in 1971.[1] By the late 1980s, the first images of human vessels were recorded by Yock and his colleagues.[2] Since then, IVUS has become a pivotal catheter-based imaging technology that can provide scientific insights into vascular biology and practical guidance for percutaneous coronary interventions (PCIs) in clinical settings. In this chapter, IVUS and the other catheter-based imaging devices—optical coherence tomography (OCT), angioscopy and spectroscopy—are described. These newly developed imaging technologies provide supplemental and unique insights into vascular biology as well.

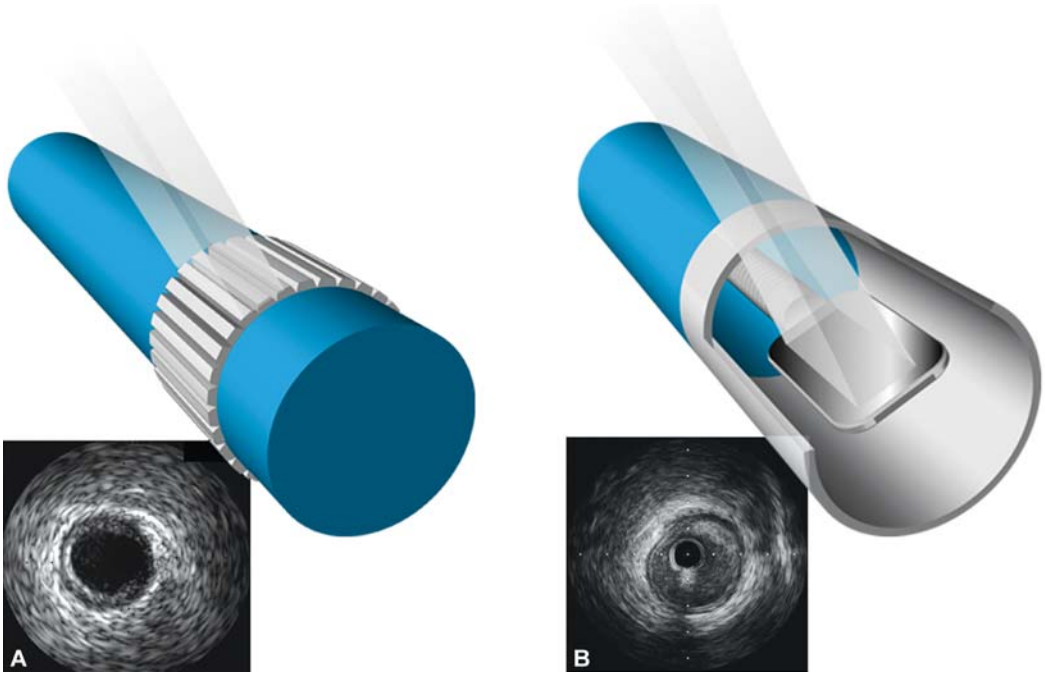
INTRAVASCULAR ULTRASOUND

BASICS OF IVUS AND PROCEDURES

The IVUS imaging systems use reflected sound waves to visualize the vessel wall in a two-dimensional format analogous to a histologic cross-section. In general, higher frequencies of ultrasound limit the scanning depth but improve the axial resolution, and current IVUS catheters used in the coronary arteries have center frequencies ranging 20–45 MHz. There are two different types of IVUS transducer systems: (1) the solid-state dynamic aperture system (the electronically switched multi-element array system) and (2) the mechanically rotating single-transducer system (Table 1 and Figs 1A and B). Several types of artifacts can be observed common or unique to each system (Figs 2A to D). With both systems, still frames and video images can be digitally archived on local storage memory or a remote server using digital imaging and communications in medicine (DICOM) Standard 3.0. Regardless of IVUS system used in the patient, both require preprocedural administration of intravenous heparin (5,000–10,000 U), or equivalent anticoagulation along with intracoronary nitroglycerin (100–300 μg), to reduce the potential for coronary spasm.

NORMAL VESSEL MORPHOLOGY

The interpretation of IVUS images is possible as the layers of a diseased arterial wall can be identified separately. Particularly in muscular arteries, such as the coronary tree, the media of the

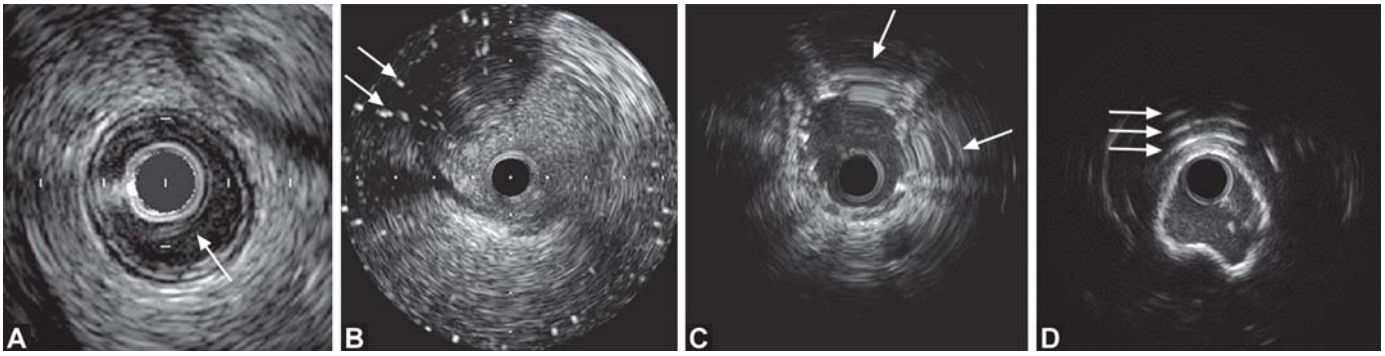


FIGURES 1A AND B: Diagrams of two basic imaging catheter designs: (A) solid state and (B) mechanical. (A: bottom) an Image obtained using a solid-state catheter imaging system. (B: bottom) an image obtained using a mechanical catheter imaging system

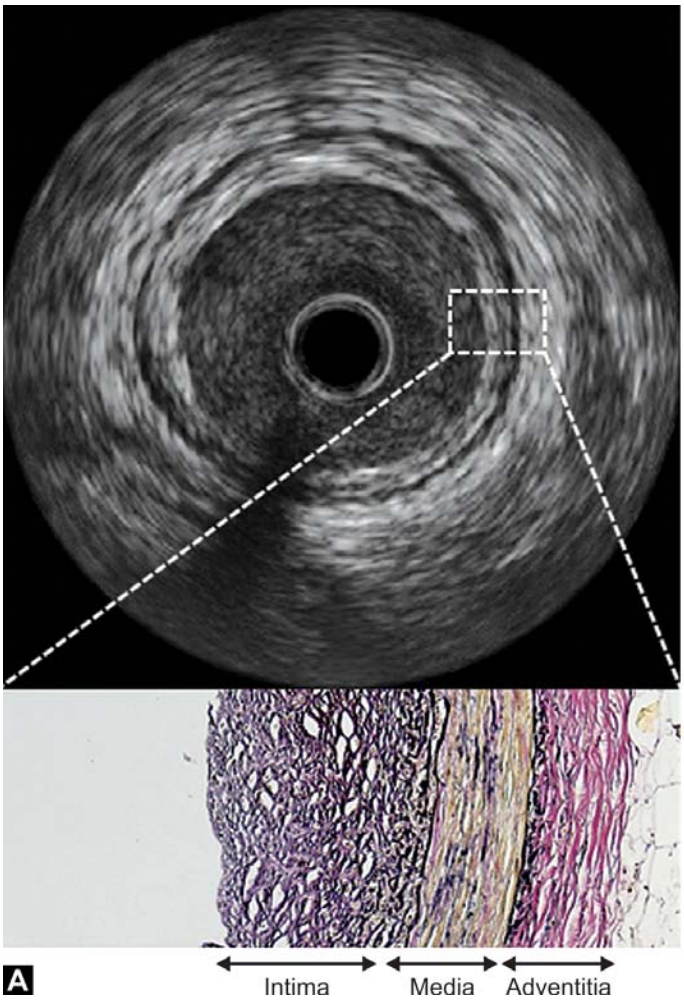
TABLE 1

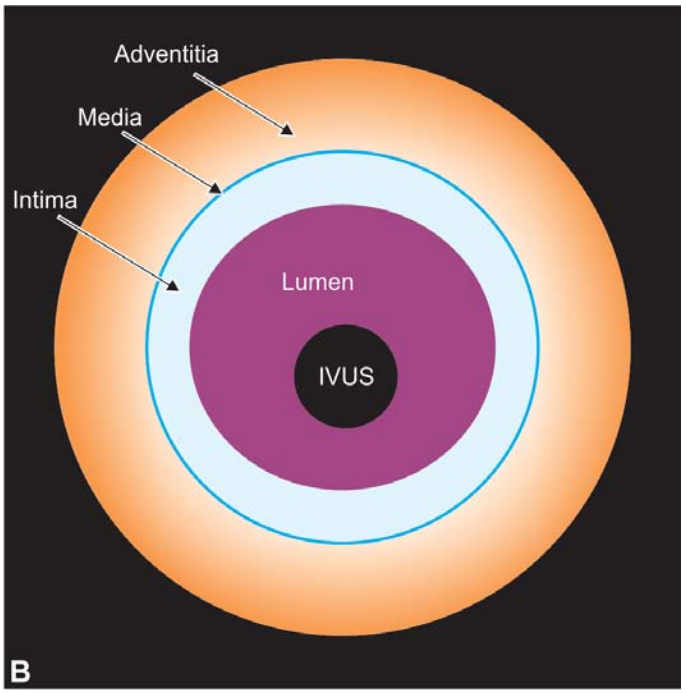
Comparison of two IVUS designs

	Solid-state dynamic aperture system	*Mechanically rotating single-transducer system*
Basics	An electronic solid state catheter system with multiple imaging elements at its distal tip, providing cross-sectional imaging by sequentially activating the imaging elements in a circular way	A mechanical system that contains a flexible imaging cable which rotates a single transducer at its tip inside an echolucent distal sheath
Products	One system is commercially available (Volcano Corporation, Inc., Rancho Cordova, CA)	Several systems are commercially available (Boston Scientific Corporation, Natick, MA; Volcano Corporation, Inc., Rancho Cordova, CA; Terumo Corporation, Tokyo, Japan)
Features	The imaging catheter has 64 transducer elements arranged around the catheter tip and uses a center frequency of 20 MHz The outer shaft diameter of IVUS catheters in a rapid-exchange configuration is 2.9 Fr and thus compatible with a 5 Fr guide catheter	The imaging catheter uses a 40- or 45 MHz transducer with a distal crossing profile of 3.2 Fr (compatible with 6 Fr guide catheters)
Image quality	This imaging catheter has better scanning depth but poorer axial resolution compared with the mechanical systems	Higher frequencies improve the axial resolution. Therefore, mechanical transducers have traditionally offered advantages in image quality compared with the solid-state systems
Artifacts	The guidewire runs inside the IVUS catheter thereby preventing guidewire artifact This system does not require flushing with saline	The guidewire runs outside the IVUS catheter, parallel to the imaging segment, resulting in guidewire artifact This system requires flushing with saline before insertion to eliminate any air in the path of the beam. Incomplete flushing artifact may result in poor image quality
	This system eliminates nonuniform rotational distortion (NURD)	The NURD can occur when bending of the drive cable interferes with uniform transducer rotation, causing a wedge-shaped, smeared image to appear in one or more segments of the image
	Since the solid-state transducer has a zone of “ring-down artifact” encircling the catheter, an extra step is required to form a mask of the artifact and subtract this from the image	The imaging catheters have excellent near-field resolution and do not require the subtraction of a mask
Others	Short transducer-to-tip distance (10.5 mm) facilitates visualization of distal coronary anatomy	The pullback trajectory is stabilized and it reduces the risk of a nonuniform speed in a continuous pullback



FIGURES 2A TO D: Common IVUS image artifacts: (A) A "halo" or a series of bright rings immediately around the mechanical IVUS catheter is usually caused by air bubbles that need to be flushed out. (B) Radiofrequency noise appears as alternating radial spokes or random white dots in the far-field. The interference is usually caused by other electrical equipment in the cardiac catheterization laboratory. (C) Nonuniform rotational distortion (NURD) results in a wedge-shaped, smeared appearance in one or more segments of the image (between 12 O'clock and 3 O'clock in this example). This may be corrected by straightening the catheter and motor drive assembly, lessening tension on the guide catheter, or loosening the hemostatic valve of the Y-adapter. (D) Circumferential calcification causes reverberation artifact between 10 O'clock and 1 O'clock





FIGURES 3A AND B: Cross-sectional format of a representative IVUS image. The bright-dark-bright, three-layered appearance is seen in the image with corresponding anatomy as defined. The "IVUS" represents the imaging catheter in the vessel lumen. Histologic correlation with intima, media and adventitia are shown. The media has lower ultrasound reflectance owing to less collagen and elastin compared with neighboring layers. Since the intimal layer reflects ultrasound more strongly than the media, there is a spillover in the image, resulting in slight overestimation of the thickness of the intima and a corresponding underestimation of the medial thickness

vessel is characterized by a dark band compared with the intima and adventitia (Figs 3A and B). Differentiation of the layers of elastic arteries, such as the aorta and carotid, can be problematic because media are less distinctly seen by IVUS. However, most of the vessels currently treated by catheter techniques are muscular or transitional arteries. These include the coronary, iliofemoral, renal and popliteal systems. Therefore, it is usually easy to identify the medial layer.

The relative echolucency of media compared with intima and adventitia gives rise to a three-layered appearance (bright-dark-bright), first described in vitro by Meyer and his colleagues.[3] Due to the lack of collagen and elastin compared to neighboring layers, the media displays lower ultrasound reflection. "Blooming", a spillover effect, is seen in the IVUS image because the intimal layer reflects ultrasound more strongly than the media. This results in a slight overestimation of the

thickness of the intima and a corresponding underestimation of the medial thickness. On the other hand, the media/adventitia border is accurately rendered, because a step-up in echo reflectivity occurs at this boundary and no blooming appears. The adventitial and periadventitial tissues are similar enough in echoreflectivity that a clear outer adventitial border cannot be defined.

Several deviations from the classic three-layered appearance are encountered in clinical practice. The echoreflectivity of the intima and internal lamina may not be sufficient to resolve a clear inner layer in truly normal coronary arteries from young patients. This is particularly true when the media has a relatively high content of elastin. However, most adults seen in the cardiac catheterization laboratory have enough intimal thickening to show a three-layered appearance, even in angiographically normal segments. At the other extreme, patients with a significant plaque burden have thinning of the media underlying the plaque. As a result, the media is often indistinct or undetectable in at least some part of the IVUS cross-section. This problem is exacerbated by the blooming phenomenon. Even in these cases, however, the inner adventitial boundary (at the level of the external elastic lamina) is always clearly defined. For this reason, most IVUS studies measure and report the plaque-plus-media area as a surrogate measure for plaque area alone. The addition of the media represents only a tiny percentage increase in the total area of the plaque.

The determination of the position of the imaging plane within the artery is one important aspect of image interpretation. For example, an IVUS beam penetrates beyond the coronary artery, providing images of perivascular structures, including the cardiac veins, myocardium and pericardium (Figs 4A to C). These structures provide useful landmarks regarding the position of the imaging plane because they have a characteristic appearance when viewed from various positions within the arterial tree. The branching patterns of the arteries are also distinctive and help to identify the position of the transducer. In the left anterior descending (LAD) coronary artery system, for example, the septal perforators usually branch at a wider angle than the diagonals. On the IVUS scan, the septals appear to bud away from the LAD much more abruptly than the diagonals (Figs 5A to D). The branching pattern and perivascular landmarks, once understood, can provide a reference to the actual orientation of the image in space.

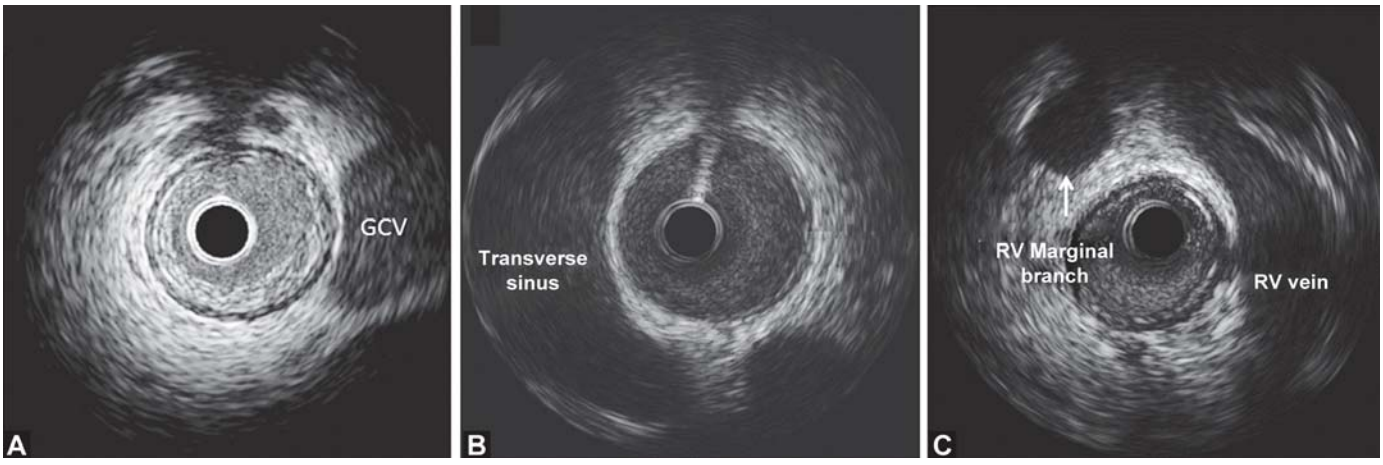
IVUS MEASUREMENTS

The IVUS images have an intrinsic distance calibration, which is usually displayed as a grid in the image. Electronic caliper (diameter) and tracing (area) measurements can be performed at the tightest cross-section, as well as at reference segments located proximal and distal to the lesion.

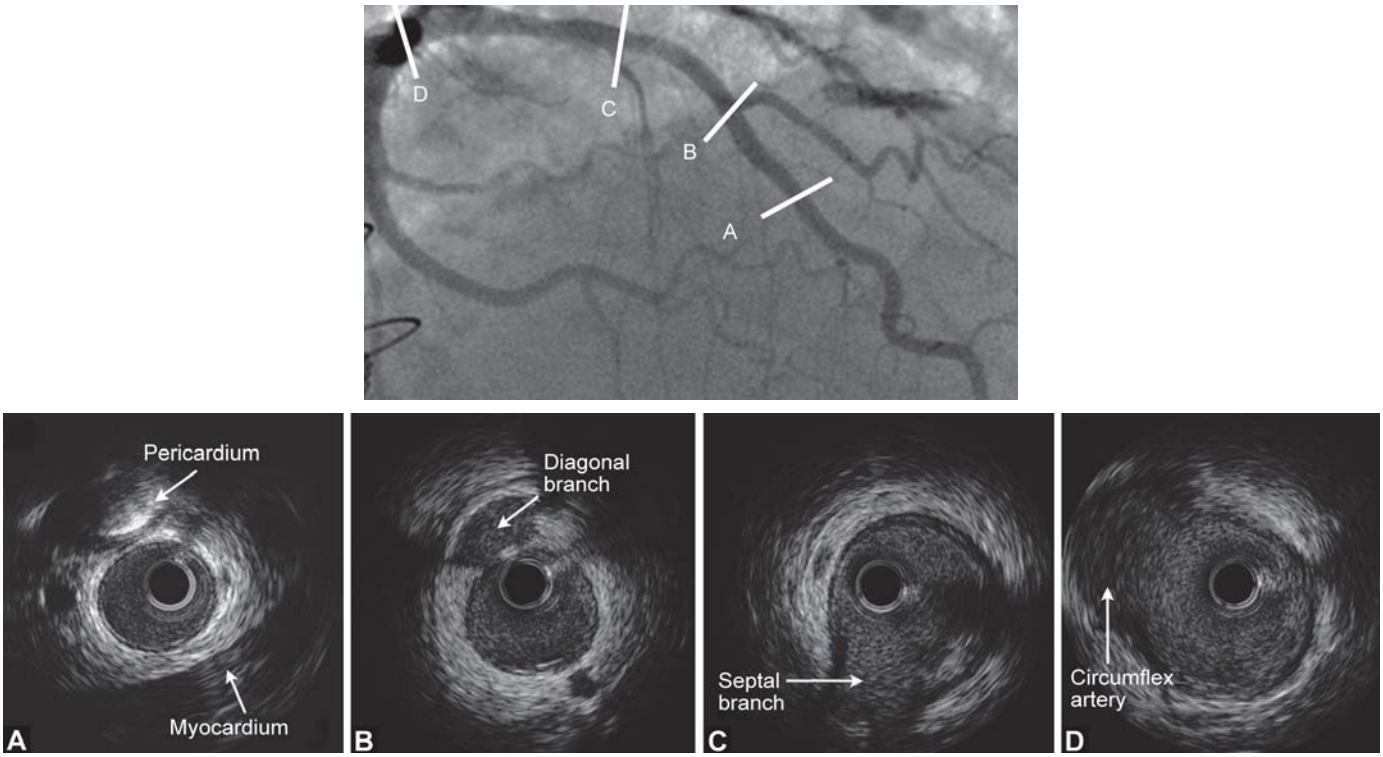
In everyday clinical practice, where accurate sizing of devices is needed, vessel and lumen diameter measurements are important. The maximum and minimum diameters (i.e. the major and minor axes of an elliptical cross-section) are the most widely used dimensions. The ratio of maximum to minimum diameter defines a measure of symmetry. Area measurements are performed with computer planimetry; lumen area is determined by tracing the leading edge of the blood/intima border, whereas vessel or external elastic membrane (EEM) area is defined as the area enclosed by the outermost interface between media and adventitia. Plaque area or plaque-plus-media area is calculated as the difference between the vessel and lumen areas; the ratio of plaque to vessel area is termed percent plaque area, plaque burden or percent cross-sectional narrowing. Area measurements can be added to calculate volumes using Simpson's rule with the use of motorized pullback. In general, the investigator selects the most normal-looking cross-section (i.e. largest lumen with smallest plaque burden) occurring within 10 mm of the lesion with no intervening major side branches as the reference segment.[4]

TISSUE CHARACTERIZATION

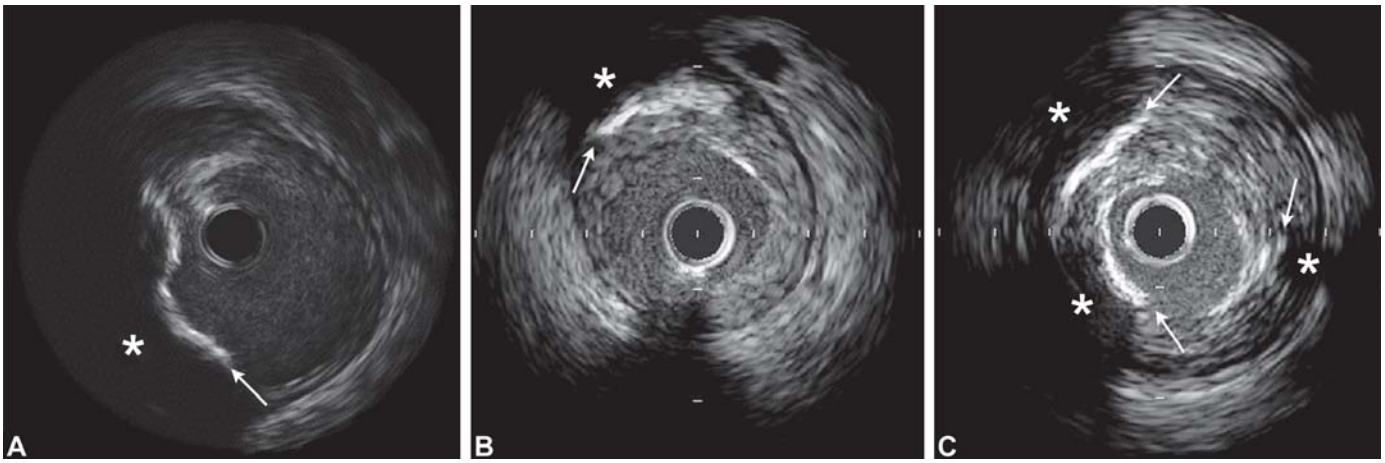
The IVUS can provide detailed information about plaque composition. Regions of calcification are very brightly echo-reflective and create a dense shadow more peripherally from



FIGURES 4A TO C: Perivascular landmarks: (A) The great cardiac vein (GCV), running superiorly to the left circumflex coronary artery (LCx), appears as a large, low-echoic structure with fine blood speckle. Recurrent atrial branches emerge from the LCx in an orientation directed toward the GCV, whereas the obtuse marginal branches emerge opposite the GCV and course inferiorly to cover the lateral myocardial wall. (B) In the proximal portion of the left main coronary artery, a clear echo-free space filled with pericardial fluid, called the transverse sinus, is found adjacent to the artery, immediately outside of the left lateral aspect of the aortic root. (C) At the level of the middle right coronary artery, the veins arc over the artery, typically at a position just adjacent to the right ventricular marginal branches



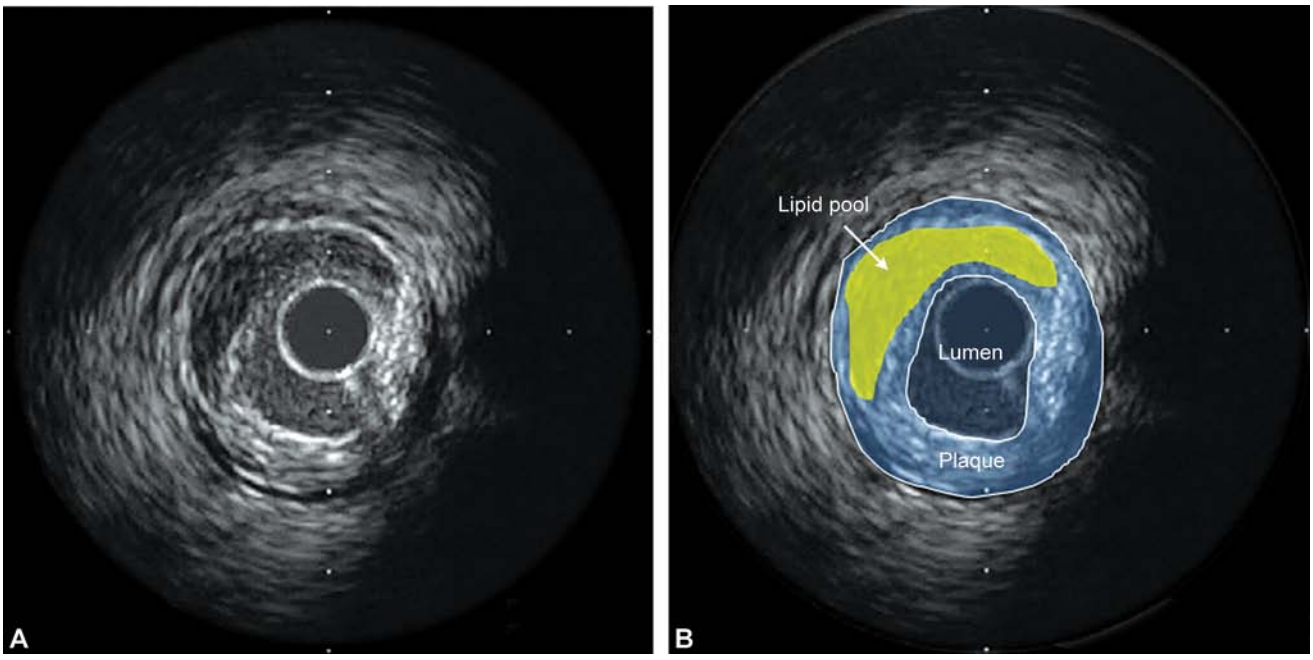
FIGURES 5A TO D: Pullback imaging sequence from mid to proximal portion of the left anterior descending (LAD) artery: (A) The mid and distal portions of the LAD often lie deeper in the sulcus than the proximal LAD and myocardium may be observed. The pericardium is seen at the opposite site of myocardium. (B and C) The septal branches emerge opposite to the pericardium, but the diagonal branches take off more superiorly. The angle between the septal and the diagonal branches usually increases to as much as 180 degrees. (D) The left circumflex artery emerges on the same side as the emergence of the diagonal branches



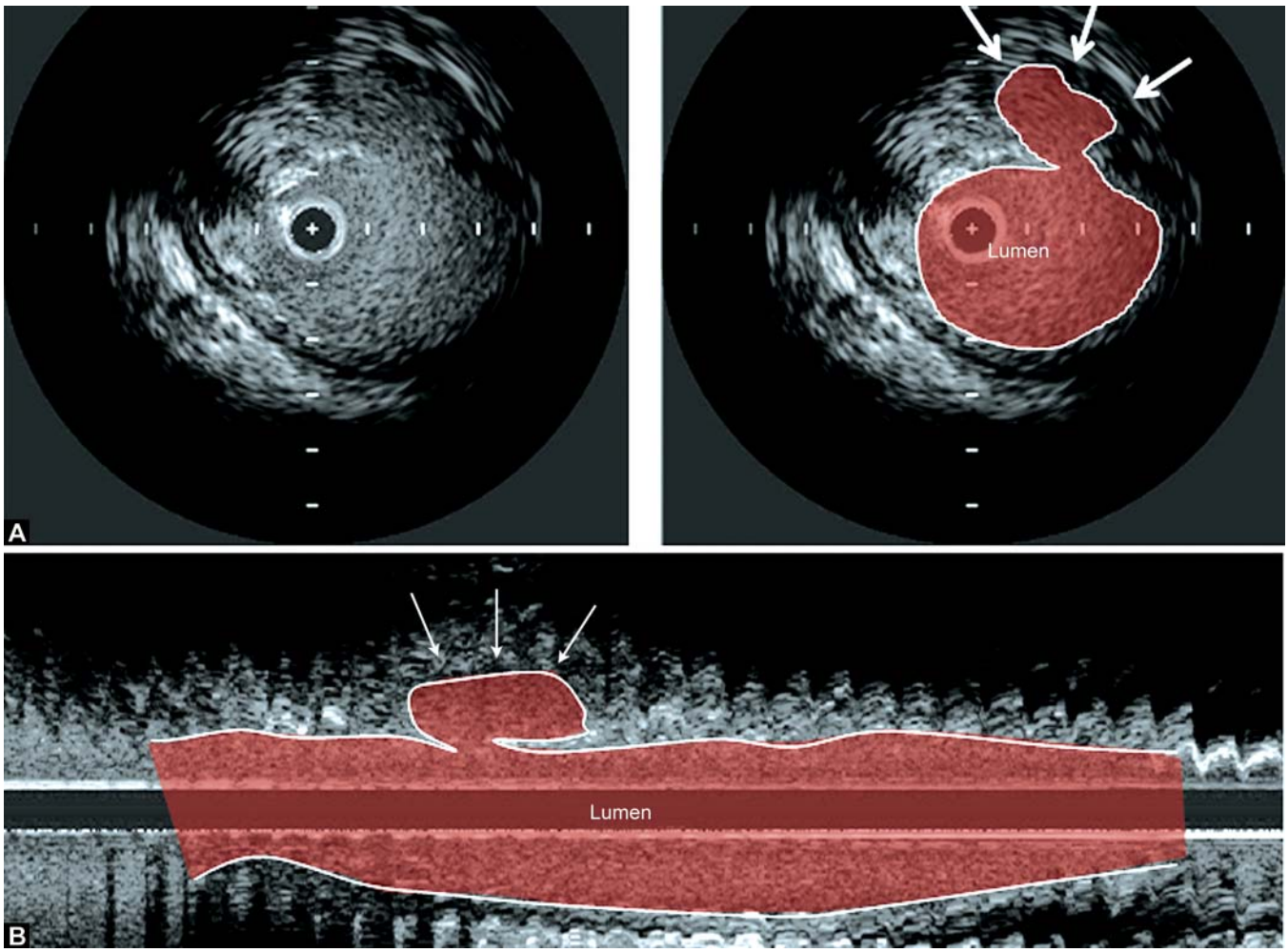
FIGURES 6A TO C: Examples of coronary calcification: (A) Superficial calcification is seen between 6 O'clock and 10 O'clock. The deeper vessel structure is obscured by the shadowing of the calcium layer (acoustic shadowing: asterisk). (B) Deep deposit of calcium is seen in a rim of fibrous plaque. (C) There are superficial and deep calcium deposits with acoustic shadowing

the catheter, a phenomenon known as "acoustic shadowing" (Figs 6A to C). Shadowing prevents determination of the true thickness of a calcific deposit and precludes visualization of structures in the tissue beyond the calcium. Reverberation is another characteristic finding with calcification. It causes the appearance of multiple ghost images of the leading calcium interface, spaced at regular intervals radially (Fig. 2D). Like calcium, densely fibrotic tissue appears bright on the ultrasound scan. Fatty plaque is less echogenic than fibrous plaque. The brightness of the adventitia can be used as a gauge to discriminate between predominantly fatty from fibrous plaque. Therefore, an area of plaque that appears darker than the adventitia is fatty. In an image of extremely good quality, the presence of a lipid pool can be inferred from the appearance of a dark region within the plaque (Figs 7A and B). Furthermore, the "hot" lesions like ruptured plaques responsible for unstable angina or acute coronary syndromes can be observed by IVUS (Figs 8A and B).

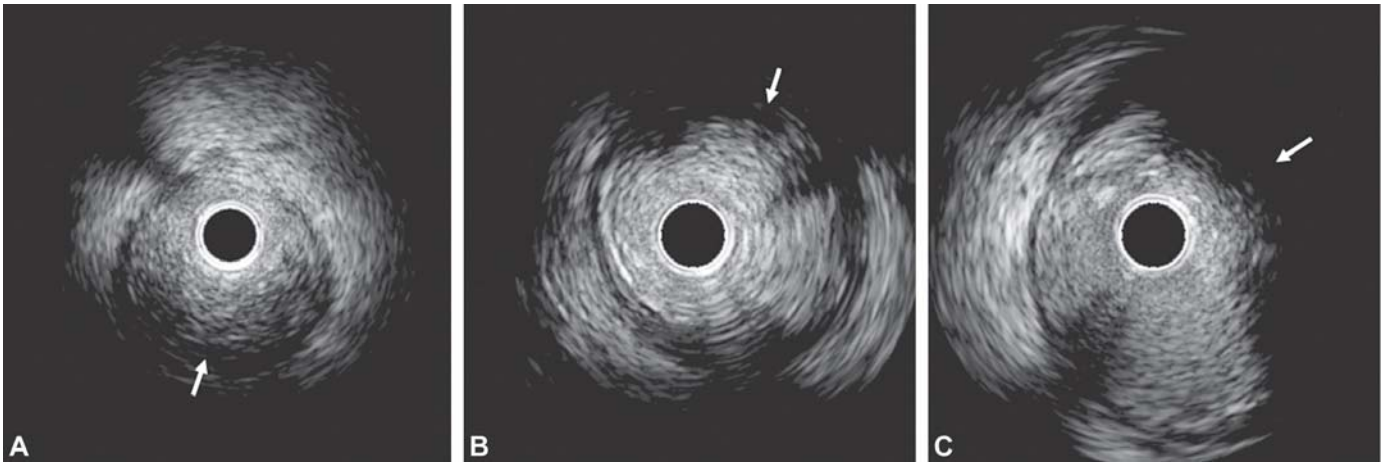
Recently, the clinical impact of attenuated plaques characterized as hypoechoic plaque with ultrasound attenuation



FIGURES 7A AND B: Atherosclerotic plaque with lipid pool. Lipid pool is defined as an echolucent area within the plaque and observed at 8-2 O'clock in this IVUS image



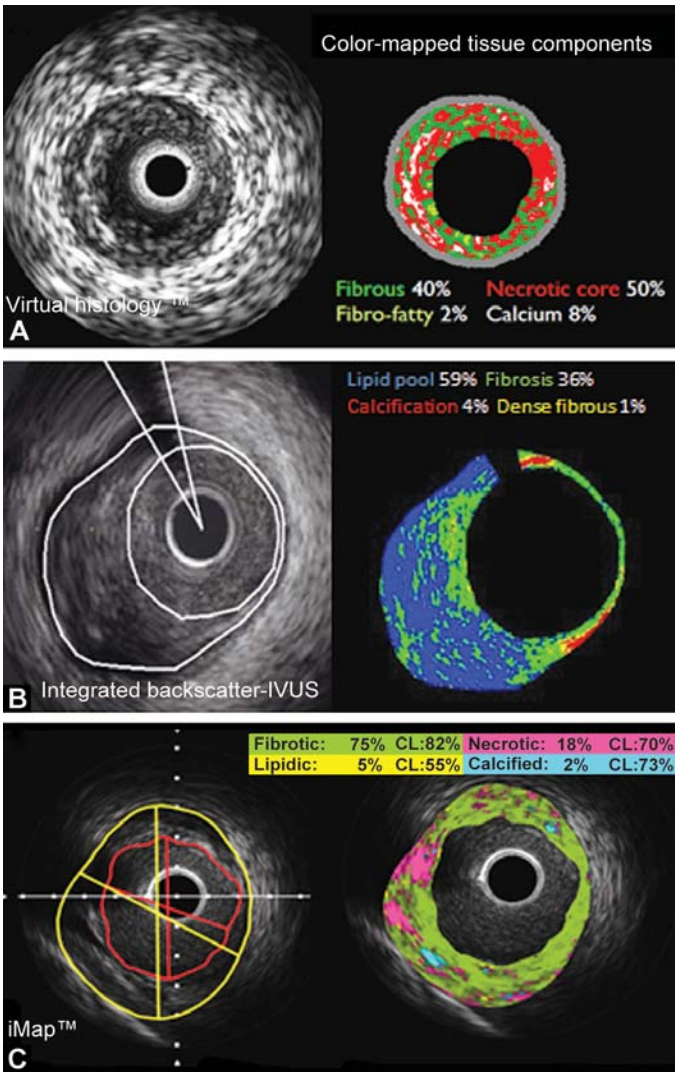
FIGURES 8A AND B: Example of plaque rupture. On the cross-sectional IVUS images (A), a cavity in contact with the vessel lumen is observed. The longitudinal IVUS image (B) shows a spatial representation of the plaque rupture. The rupture occurs in an eccentric plaque and has a residual thin flap that probably corresponds to a thin fibrous cap



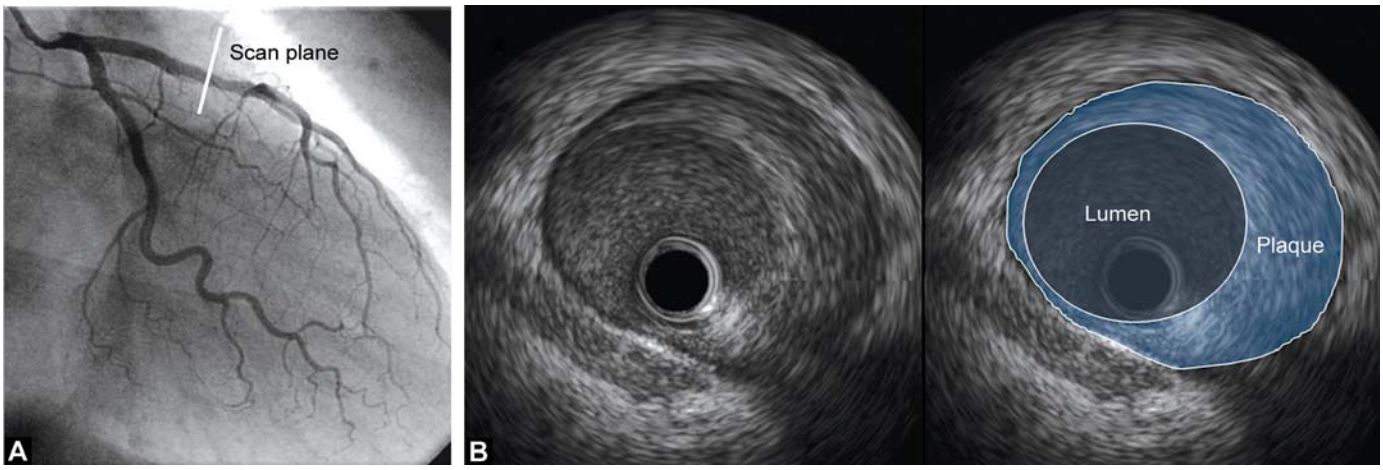
FIGURES 9A TO C: Examples of attenuated plaques. Attenuated plaque was defined as plaque with deep ultrasonic attenuation despite absence of bright calcium

despite little evidence of calcium has been reported (Figs 9A to C). These specific plaques are more often seen in patients with acute coronary syndromes than in those with stable angina and are characterized by positive remodeling and nearby calcification.[5] Clinical studies have indicated that attenuated plaques are associated with no reflow and creatine kinase-MB elevation after PCI because of distal embolization.[6,7] This novel defined plaque may contain microcalcification, thrombus or cholesterol crystals.[8]

Visual interpretation of conventional grayscale IVUS images is limited in the detection and quantification of specific plaque components. Therefore, computer-assisted analysis of raw radiofrequency (RF) signals in the reflected ultrasound beam has recently been developed (Figs 10A to C). Virtual Histology™ (VH) IVUS (Volcano Corporation, Rancho Cordova, California,) is recognized as the first commercialized RF analysis technology. A classification algorithm developed from ex vivo human coronary data sets can generate color-mapped images of the vessel wall with a distinct color for each category: fibrous, necrotic, calcific and fibro-fatty.[9] Another mathematical technique used in RF ultrasound backscatter analysis is Integrated Backscatter (IB) IVUS (YD Corporation, Nara, Japan). This method utilizes IB values, calculated as the average power of the backscattered ultrasound signal from a sample tissue volume. The IB-IVUS system constructs color-coded tissue maps, providing a quantitative visual readout as four types of plaque composition: calcification, fibrosis, dense fibrosis and lipid pool.[10] Similar to these RF-based tissue characterization techniques, iMap™ (Boston Scientific Inc, Natick, Massachusetts) has recently been introduced as an up-to-date tissue characterization method that is compatible with the latest 40-MHz mechanical IVUS imaging system (as opposed to VH-IVUS with 20-MHz solid-state IVUS system). The iMap allows identification and quantification of four different types of atherosclerotic plaque components: fibrotic, necrotic, lipidic and calcified tissues with accuracies at the high level of confidence (95%, 97%, 98% and 98% for fibrotic, necrotic, lipidic and calcified tissues, respectively).[11] Recently, multiple investigators have been trying to elucidate the clinical utility of RF analysis technology, particularly for prediction of future adverse coronary events. Providing regional



FIGURES 10A TO C: Color-mapped images of the coronary plaque. Conventional grayscale IVUS images (left). (A) Virtual Histology ™ shows a distinct color for each of the fibrous, necrotic, calcific and fibro-fatty. (B) Integrated Backscatter-IVUS can provide a quantitative visual readout as four types of plaque composition: calcification, fibrous, dense fibrosis and lipid pool. (C) iMap™ allows identification of four different types of plaque components (fibrotic, necrotic, lipidic and calcified tissue) with a confidence level assessment of each plaque component. (*Source:* Figure A Dr Kenji Sakata)



FIGURES 11A AND B: Angiographically silent disease: (A) An angiogram of the left coronary artery suggests minimal disease. (B) IVUS images show significant eccentric plaque. The lumen is well preserved, round and regular, accounting for the benign angiographic appearance

observations to study predictors of events in the coronary tree (PROSPECT) trial is one of the largest natural history trials to employ three-vessel imaging with VH-IVUS in 700 acute coronary syndrome patients. Multivariate analysis identified VH-IVUS determined thin-cap fibroatheroma (TCFA) (common type of vulnerable plaque defined as the presence of a confluent, necrotic core greater than 10% of plaque in contact with lumen at more than 30 degrees) at baseline as one of the independent predictors of future cardiac events (cardiac death, cardiac arrest, myocardial infarction, unstable angina or increasing angina) (HR = 3.35, P <0.001).[12]

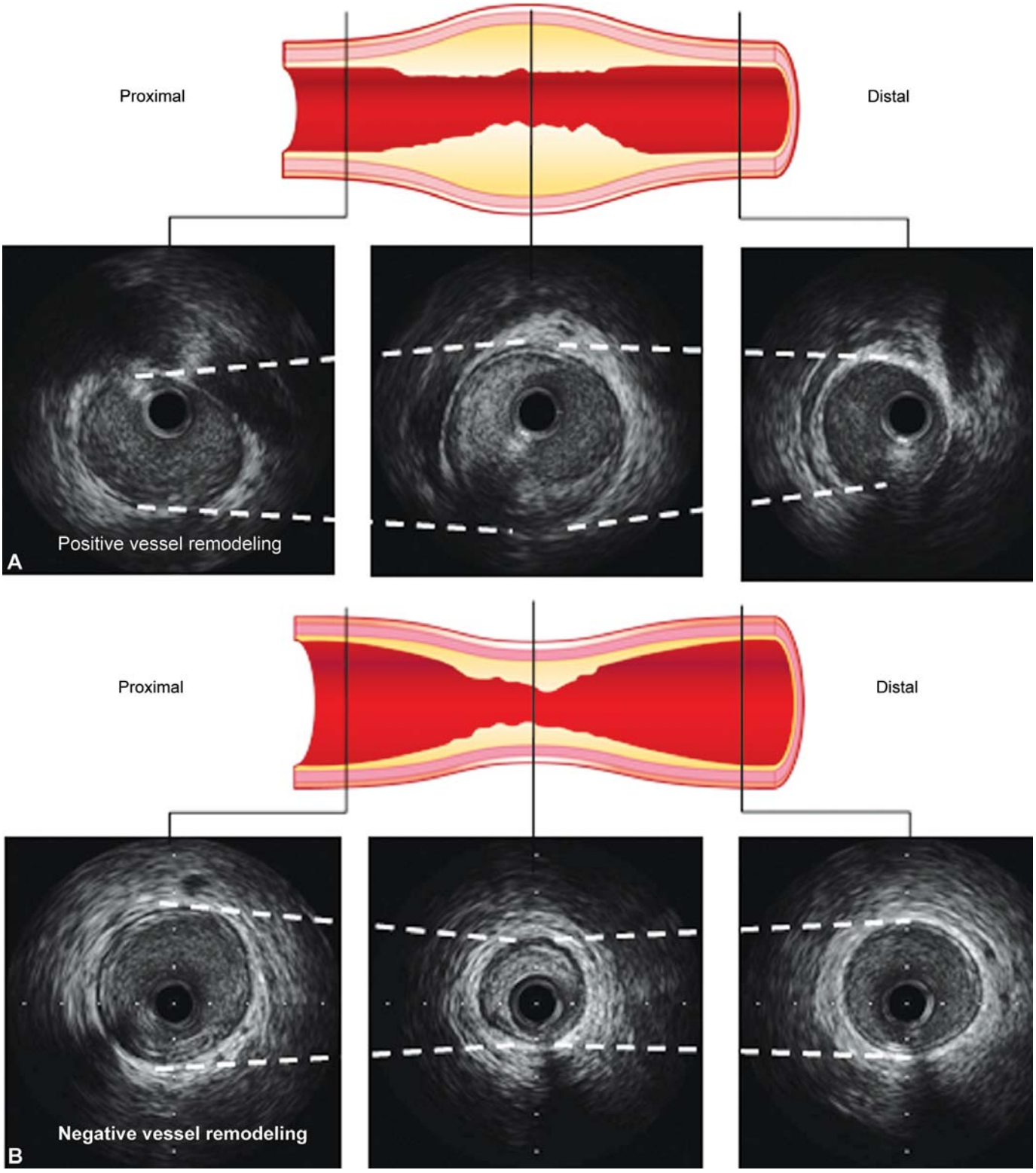
INSIGHTS INTO PLAQUE FORMATION AND DISTRIBUTION

Some of the classic pathologic findings in arterial disease have been "rediscovered" *in vivo* by IVUS. In a vessel that appears to have a discrete stenosis by angiography, IVUS almost invariably shows considerable plaque burden throughout the entire length of the vessel (Figs 11A and B). In fact, IVUS studies have shown that the reference segment for an intervention which by definition is normal or nearly normal angiographically has, on average, 35–51% of its cross-sectional area occupied by plaque.

The phenomenon of remodeling, first described in human coronary specimens by the pathologist Glagov, is well illustrated *in vivo* by IVUS (Figs 12A and B).[13,14] The IVUS studies have also added to the original descriptions in the pathology literature by demonstrating that the remodeling response is in fact bidirectional, with some segments showing the positive remodeling of the typical Glagov paradigm and others showing negative remodeling, or constriction, in the area of lumen stenosis (Figs 12A and B).[14] One important issue in evaluating this heterogeneous process by IVUS is the methodology used to quantify and categorize arterial remodeling. Although remodeling was originally conceptualized as a change in vessel size in response to plaque accumulation over time, most histomorphometric or IVUS studies have relied on measurements of reference sites as a surrogate for the size of the vessel before it became diseased. Therefore, results can vary distinctly according to the choice of reference site as well as the manner of addressing vessel tapering.[15] Theoretically, the use of the proximal reference, rather than the distal reference or the average of proximal and distal references, should preclude the potential influence of distal flow and pressure disturbance due to the presence of the IVUS catheter in the stenotic site. A remodeling index (the ration of vessel area at the lesion site to that at the reference site) as a continuous variable may also be preferable to categorical classifications, because arterial remodeling is considered to be a continuous biologic process. In fact, this remodeling index has been shown to conform to the normal frequency distribution in patients with chronic stable angina.[16] The assessment of remodeling is clinically important, not only for optimal therapeutic device sizing but also for risk stratification regarding plaque rupture or evaluating procedural and long-term outcomes of intervention. The vulnerable lesions responsible for acute coronary syndromes have usually undergone extensive positive remodeling. A histopathologic study by Pasterkamp and his colleagues supported these clinical IVUS observations by demonstrating that positive remodeling is frequently associated with large, soft, lipid-rich plaques with increased inflammatory cell infiltrate.[17] One IVUS study reported an association between preinterventional positive remodeling and creatine kinase elevation after intervention—a marker of distal embolization and future adverse cardiac events.[18] Furthermore, other investigators directly showed that preinterventional positive remodeling assessed by IVUS predicts target lesion revascularization after coronary interventions.[19] Although the predictive values of these parameters in the context of stenting have not been established with certainty, preinterventional IVUS may identify lesions with significant positive remodeling, providing triage information for increased risk of unfavorable outcomes and possible need of adjunctive biologic modalities for antirestenosis therapy in specific patients.

INTERVENTIONAL APPLICATIONS

According to the 2005 American College of Cardiology/American Heart Association/Society for Cardiovascular Angiography and Interventions (ACC/AHA/SCAI) 2005 Guideline Update for PCI, it is reasonable to use IVUS: (a) to assess the adequacy of coronary stent deployment, including the extent of apposition and minimum luminal diameter within the stent; (b) to determine the cause of stent restenosis and guide



FIGURES 12A AND B: IVUS images showing remodeling: (A) Positive remodeling with localized expansion of the vessel in the area of plaque accumulation. (B) Negative remodeling or shrinkage where the lesion has a smaller media-to-media diameter than the adjacent less diseased sites

selection of appropriate therapy; (c) to evaluate coronary obstruction in a patient with a suspected flow-limiting stenosis when angiography is difficult because of location and (d) to assess a suboptimal angiographic result after PCI.[20] In addition, not only after PCI but also before PCI, IVUS is a useful application to assess lesion characteristics.

PREINTERVENTIONAL IMAGING

Preinterventional IVUS has been used to clarify situations in which angiography is equivocal or difficult to interpret (especially in ostial lesions or tortuous segments in which the angiogram may not lay out the vessel well for interpretation).

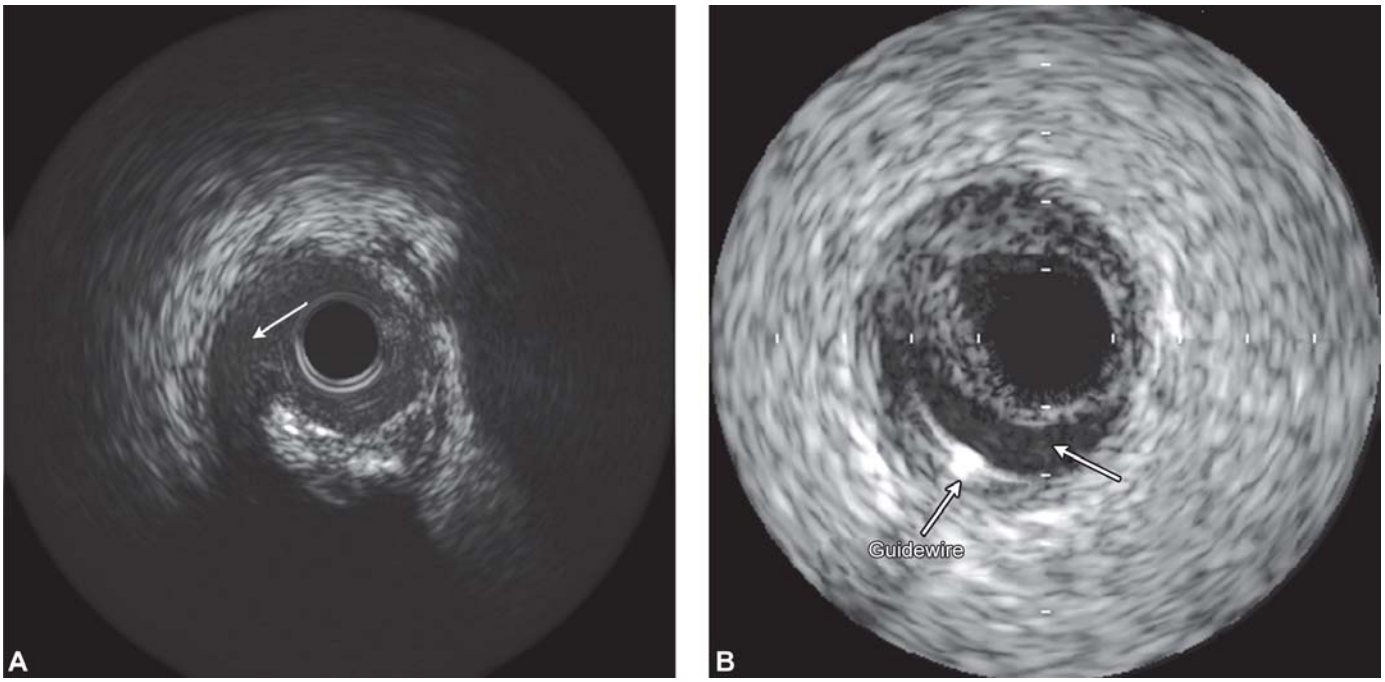
In addition, intermediate coronary lesions identified by angiography (40–70% angiographic stenosis) represent a challenge for revascularization decision-making. Although anatomic evaluation does not provide direct estimation of hemodynamic significance of a given coronary lesion, minimum lumen area (MLA) measured by IVUS demonstrated good correlation with results from physiologic assessment. The ischemic MLA threshold is 3.0–4.0 mm^2 for major epicardial coronary arteries,[21,22] and 5.5–6.0 mm^2 for the left main coronary artery,[23] based on physiologic assessment with coronary flow reserve, fractional flow reserve or stress scintigraphy.

Validated fractional flow reserve data have shown that deferring interventions in lesions with intermediate severity that are not considered hemodynamically significant (> 0.8 mm^2) have a favorable clinical prognosis.[24] Similarly, patients with intermediate coronary lesions in whom intervention was deferred based on IVUS findings (MLA >4.0 mm^2) showed that the rate of the composite endpoint was only 4.4% and target lesion revascularization 2.8%.[25] As a result, IVUS imaging appears to be an acceptable alternative to physiological assessment in patients presenting with intermediate coronary lesions.

Preinterventional IVUS imaging is also useful in determining the appropriate catheter-based intervention strategy. With current IVUS catheters, most of the significant stenoses can be safely imaged before intervention providing detailed information about the circumferential and longitudinal extent of plaque as well as the character of the tissue involved. This can lead to a change in interventional strategy in 20–40% of cases.[26,27] In particular, the presence, location and extent of calcium can significantly affect the results of balloon angioplasty, atherectomy and stent deployment. The amount and distribution of plaque can be accurately determined and may favor atheroablative procedures as primary or adjunctive treatment. Precise measurements of lesion length and vessel size can guide the optimal sizing of devices to be employed. Detailed assessment of target lesion anatomy in the coronary tree is also useful to prevent major side branch encroachment by intervention.

BALLOON ANGIOPLASTY

The IVUS imaging of percutaneous transluminal coronary angioplasty (PTCA) sites demonstrates plaque disruption or dissection more often than angiography does (40–70% of cases versus 20–40% by angiography).[28,29] The IVUS is able to characterize the depth and extent of dissections created by balloon inflation with relatively high accuracy. Although the extent of dissections is relatively unpredictable, it is frequently possible to predict where tears will occur, based on certain morphologic features shown by IVUS. If a plaque deposit is eccentric, tears usually occur at the junction between the plaque and the normal wall (Figs 13A and B). This is presumably because the non-diseased wall is more elastic than the plaque, and, with balloon inflation, it stretches away from the plaque, creating a cleavage plane running either within the media or within the plaque substance, close to the media. Another important factor in determining the location of tears is the presence of localized calcium deposits. During balloon inflation, shear forces are highest at the junction between the calcium and the softer, surrounding plaque. This creates an "epicenter" for the start of a tear, which then extends out to the lumen. In lesions with localized calcification, cutting balloon angioplasty may be preferable, owing to its controlled tearing, to avoid the risk of unfavorable large dissections. Creating dissections in a controlled manner may also be beneficial to lessen acute elastic recoil after balloon angioplasty. Data from phase I of the GUIDE trial showed that lesions with tears had less recoil than lesions that had not torn, suggesting that plaque tearing may effectively



FIGURES 13A AND B: Examples of dissections: (A) A superficial dissection starts at 8 O'clock and extends counterclockwise. (B) Eccentric plaque with deeper dissection is seen between 4 O'clock and 9 O'clock. A guidewire is seen inside the cavity of dissection

act to release the diseased segment from the mechanical constriction process caused by the plaque.[28]

Guidance of Procedures

A direct approach to balloon sizing, based on IVUS images, was pursued by the Clinical Outcomes with Ultrasound Trial (CLOUT) investigators, who reasoned that more aggressive balloon sizing might be more safely accomplished using the "true" vessel size and plaque characteristics as determined by IVUS.[30] In this prospective, nonrandomized study, balloon sizes were chosen to equal the average of the reference lumen and media-to-media diameters for cases in which the plaques were not extensively calcified. This led to an average 0.5 mm "oversizing" of the balloon compared with sizing based on standard angiographic criteria, and resulted in a significant decrease in post-procedure residual stenosis (from 28% to 18%). Importantly, there was no increase in clinically significant complications from this aggressive balloon sizing approach. One-year follow-up of this trial showed a late adverse event rate (death, myocardial infarction or target lesion revascularization) of 22%.[31] This IVUS-guided aggressive PTCA strategy was expanded and confirmed by two single-center studies of provisional stenting, wherein balloon sizing was performed based on IVUS measurements of media-to-media diameter at the lesion site.[32,33] Angiographic or clinical follow-up of these studies also showed long-term outcomes equivalent to those of elective stenting.

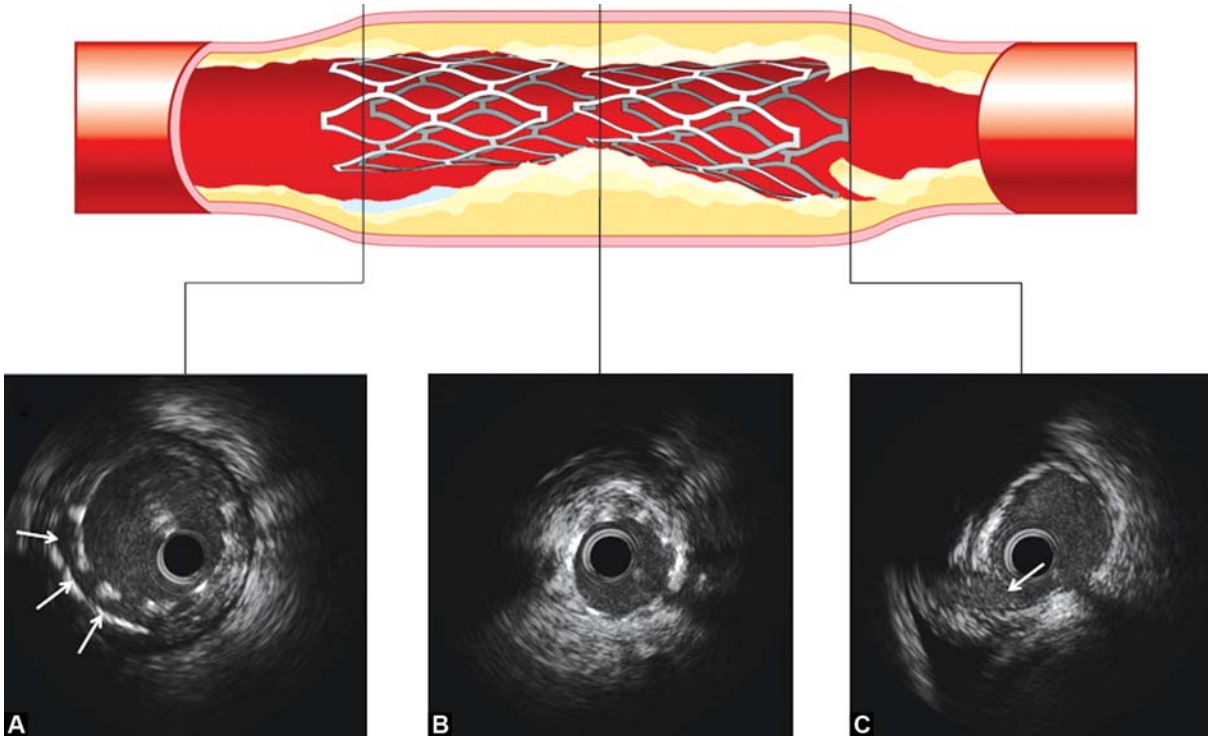
BARE METAL STENT IMPLANTATION

The IVUS clearly visualizes stent struts as bright, distinct echoes. Stents essentially provide a rigid scaffold against the force of vessel recoil. During stent implantation, axial extrusion of noncalcified plaque into the adjacent reference zones can occur.[34] However, commensurate with the ability of the stent to enlarge and hold open the treated segment, the extrusion effect in stenting may be more prominent than for balloon angioplasty. Extrusion of plaque may also contribute to the step-up/step-down appearance on angiography, as well as some of the side branch encroachment seen after stent deployment.

Guidance of Procedures

The IVUS has identified several stent deployment issues, including incomplete expansion and incomplete apposition (Figs 14A to C). Incomplete expansion occurs when a portion of the stent is inadequately expanded compared with the distal and proximal reference dimensions, as may occur where dense fibrocalcific plaque is present. Incomplete apposition (seen in 3–15% of stent cases) occurs when part of the stent structure is not fully in contact with the vessel wall, possible increasing local flow disturbances and the potential risk for subacute thrombosis in certain clinical settings. Tobis and Colombo developed the current high-pressure stent deployment technique after their collaboration in the early 1990s revealed an unexpectedly high percentage of these stent deployment issues.[35,36]

After stent implantation, tears at the edge of the stent (marginal tears or pocket flaps) occur in 10–15% of cases (Figs 13A and B).[37] These tears have been attributed to the shear forces created at the junction between the metal edge of the stent and the adjacent, more compliant tissue or to the effect of balloon expansion beyond the edge of the stent (the "dog-bone" phenomenon). Although minor nonflow-limiting edge



FIGURES 14A TO C: The IVUS-detected problems with stent deployment: (A) Incomplete stent apposition with a gap between a portion of the stent and the vessel wall between 6 O'clock and 10 O'clock. (B) Incomplete stent expansion relative to the ends of the stent and the reference segments. (C) An edge tear or "pocket flap" with plaque disruption at the stent margin

dissections may not be associated with late angiographic in-stent restenosis, significant residual dissections can lead to an increased risk of early major adverse cardiac events.[38] The current practice in our laboratory is to determine from the IVUS image whether the tear appears to be flow-limiting (i.e. whether there is an extensive tissue arm projecting into the lumen), and, if so, an additional stent is placed to cover this region.

Over the past decade, a number of studies have shown that IVUS-guided stent placement improves the clinical outcome of bare metal stents.[39–44] In the landmark trial, Multicenter Ultrasound-guided Stent Implantation in Coronaries (MUSIC) trial, three main IVUS variables were considered for assessing optimal stent deployment: (1) complete stent apposition over the entire stent length; (2) in-stent minimum stent area (MSA) greater than or equal to 90% of the average of the reference areas or 100% of the smallest reference area and (3) symmetric stent expansion with the minimum/maximum lumen diameter ratio greater than or equal to 0.7.[45] This study highlights that appropriate evaluation of stent deployment by IVUS impacts restenosis rate.

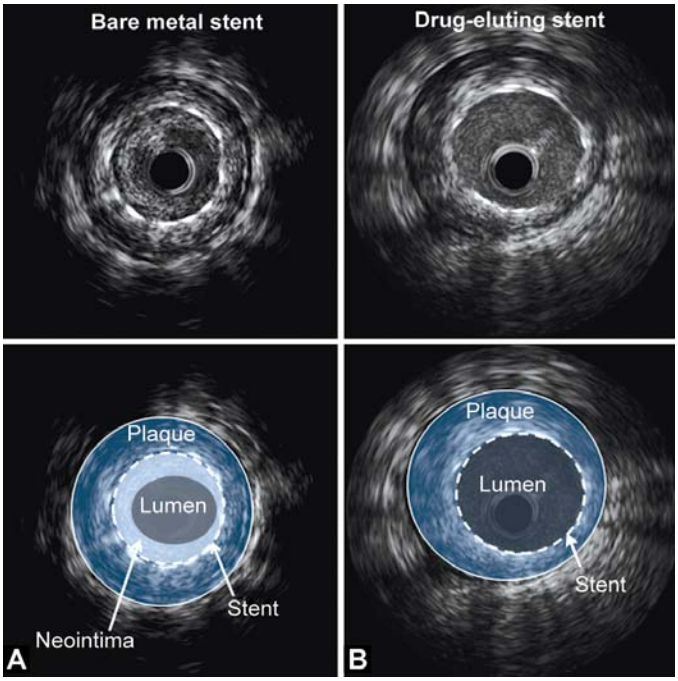
A subacute thrombosis rate of less than 2% was believed to represent a reduction compared with nonguided deployment, although, with current antiplatelet regimens, similar results can usually be achieved by high-pressure postdilation without IVUS confirmation. Nevertheless, a number of studies have suggested a link between suboptimal stent implantation and stent thrombosis, including the predictors and outcomes of stent thrombosis (POST) registry, which demonstrated that 90% of thrombosis patients had suboptimal IVUS results (incomplete apposition, 47%; incomplete expansion, 52% and evidence of thrombus, 24%), even though only 25% of patients had abnormalities on angiography.[46] In a more recent study by Cheneau and his colleagues, these observations were replicated suggesting that mechanical factors continue to contribute to stent thrombosis, even in this modern stent era, with optimized antiplatelet regimens.[47] Although the use of IVUS in all patients for the sole purpose of reducing thrombosis is clearly not warranted given the costs, IVUS imaging should be considered in patients who are at particularly high risk for thrombosis (e.g. slow flow) or in whom the consequences of thrombosis would be severe (e.g. left main coronary artery or equivalent).

The MSA, as measured by IVUS, is one of the strongest predictors for both angiographic and clinical restenosis after bare metal stenting.[48–50] Kasaoka and his colleagues indicated that the predicted risk of restenosis decreases 19% for every 1 mm^2 increase in MSA and suggested that stents with MSA greater than 9 mm^2 have a greatly reduced risk of restenosis.[49] In the can routine ultrasound improve stent expansion (CRUISE) trial, IVUS guidance by operator preferences increased MSA from 6.25 mm^2 to 7.14 mm^2, leading to a 44% relative reduction in target vessel revascularization at 9 months, compared with angiographic guidance alone.[42] In the angiography versus IVUS-directed stent placement (AVID) trial, IVUS-guided stent implantation resulted in larger acute dimensions (7.54 mm^2) than angiography (6.94 mm^2), without an increase in complications, and lower 12-month target lesion revascularization rates for vessels with angiographic reference diameter less than 3.25 mm, severe stenosis at preintervention (> 70% angiographic diameter stenosis), and vein grafts.[51] However, some IVUS-guided stent trials produced controversial results,[52,53] presumably due to differing procedural end points for IVUS-guided stenting, and the various adjunctive treatment strategies that were used in these trials in response to suboptimal results. Overall, a meta-analysis of nine clinical studies (2,972 patients) demonstrated that IVUS-guided stenting significantly lowers 6-month angiographic restenosis [odds ratio = 0.75, 95% confidence interval (CI), 0.60–0.94; P = 0.01] and target vessel revascularization (OR = 0.62; 95% CI, 0.49–0.78; P = 0.00003), with a neutral effect on death and nonfatal myocardial infarction, compared to an angiographic optimization.[54]

Insights into Long-Term Outcomes

Intimal proliferation rather than chronic stent recoil primarily causes in-stent restenosis. Growth of neointima is usually greatest in areas with the largest plaque burden,[55] and the intimal growth process seems to be more aggressive in diabetic patients.[56] The IVUS can be helpful to differentiate pure intimal ingrowth from poor stent expansion in the treatment of in-stent restenosis (Figs 15A and B). Using serial IVUS immediately before and after balloon angioplasty for in-stent restenosis, Castagna and his colleagues[57] demonstrated in 1,090 consecutive in-stent restenosis lesions that 38% of lesions had an MSA of less than 6.0 mm^2. Even with minimal neointimal hyperplasia, stent underexpansion can result in clinically significant lumen compromise. For this type of in-stent restenosis, mechanical optimization is appropriate in most cases.

The IVUS can also track the response to treatment, with evidence that angioplasty of in-stent restenosis is followed by early lumen loss due to decompression and/or reintrusion of tissue immediately after intervention. This phenomenon was more prominent in longer lesions and in those with greater



FIGURES 15A AND B: The IVUS images 8 months after stent deployment: (A) A conventional bare metal stent shows a considerable amount of neointima inside the stent. (B) In contrast, significant suppression of instent neointimal proliferation is observed when a drug-eluting stent was used

in-stent tissue burden, perhaps accounting for the worse long-term outcomes in diffuse versus focal in-stent restenosis. Direct tissue removal, rather than tissue compression/extrusion through the stent struts, may help minimize early lumen loss due to this phenomenon. Several investigators have reported a considerable reduction in angiographic and/or clinical recurrence of in-stent restenosis in patients with diffuse in-stent restenosis treated with ablative therapies (directional coronary atherectomy, rotational atherectomy or laser angioplasty) compared with PTCA alone.[58–60]

DRUG-ELUTING STENT IMPLANTATION

In current clinical experience, IVUS observations of antiproliferative drug-eluting stents (DES) have shown a striking inhibition of in-stent neointimal hyperplasia (Fig. 15). Thus, it comes as no surprise that since the introduction of DES, both the rate of restenosis and need for repeat revascularization have been dramatically reduced. Moreover, both statistical and geographic distributions of neointimal hyperplasia can be significantly different between biologic (DES) and mechanical (bare metal) stents, despite mechanical performances of DES being similar to those of conventional bare metal stents.[61] In general, neointimal volume (as a percentage of stent volume) within bare metal stents follows a near-Gaussian or normal frequency distribution, with a mean value of 30–35%. The standard deviation of this statistical distribution represents biologic variability in vascular response to acute and/or chronic vessel injury as a result of interventions. In contrast, biologic modifications through DES often result in a non-Gaussian frequency distribution, with variable degrees of the tail ends. Since restenosis corresponds to the right tail at the end of the distribution curve, a discrepancy between mean neointimal volume and binary or clinical restenosis can occur in DES trials. Similarly, bare metal stents show a wide individual variation in geographic distribution of neointima along the stented segment, whereas some types of DES demonstrate predilection of in-stent neointimal hyperplasia for specific locations (e.g. proximal stent edge). In serial IVUS studies with multiple long-term follow-ups, neointima within nonrestenotic bare metal stents showed mild regression after 6 months.[62] In contrast, both sirolimus- and paclitaxel-eluting stents showed a slight but continuous increase in neointimal hyperplasia for up to 4 years.[63–65]

Guidance of Procedures

The value of MSA remains as a powerful predictor for in-stent restenosis in the DES era.[66,67] A recent IVUS work by Sonoda and his colleagues demonstrated that sirolimus-eluting stents showed a stronger positive relation, with a greater correlation coefficient between baseline MSA and 8-month MLA, compared to control bare metal stents (0.8 vs 0.65 and 0.92 vs 0.59, respectively).[66] The utility of IVUS to ensure adequate stent expansion cannot be overemphasized, particularly if there are clinical risk factors for DES failure (e.g. diabetes, renal failure). In this context, preinterventional IVUS can provide useful information about plaque composition. In particular, calcified plaque is important to identify, because the presence, degree and location of calcium within the target vessel can substantially affect the delivery and subsequent deployment of coronary stents (Fig. 6). One important advantage of online IVUS guidance is the ability to assess the extent and distance from the lumen of calcium deposits within a plaque. For example, lesions with extensive superficial calcium may require rotational atherectomy before stenting. Conversely, apparently significant calcification on fluoroscopy may subsequently be found by IVUS to be distributed in a deep portion of the vessel wall or to have a lower degree of calcification (calcium arc < 180 degrees). In these cases, stand-alone stenting is usually adequate to achieve a lumen expansion large enough for DES deployment.

The stent deployment techniques on clinical outcomes of patients treated with the cypher stent (STLLR) trial demonstrated that geographic miss (defined as the length of injured or stenotic segment not fully covered by DES) had a significant negative impact on both clinical efficacy (target vessel and lesion revascularization) and safety (myocardial infarction) at 1 year after sirolimus-eluting stent implantation.[68] These findings suggest that less aggressive stent dilation and complete coverage of reference disease may be beneficial, as long as significant underexpansion and incomplete strut apposition are avoided. Another single center study showed optimal stent longitudinal positioning of sirolimus-eluting stents using unique stepwise IVUS criteria (mainly targeting the sites with plaque burden < 50%). In this study, plaque burden in the reference lesion was the strongest predictor of stent margin restenosis.[69] Online IVUS guidance can facilitate both the determination of appropriate stent size and length and the achievement of optimal procedural end points, with the goal being to cover significant pathology with reasonable stent expansion while anchoring the stent ends in relatively plaque-free vessel segments. The efficacy of DES is related not only to the pharmacological (drug and polymer) kinetics but also to how well the stent is deployed within the coronary artery.

Insights into Long-Term Outcomes

Several large studies have assessed the impact of IVUS guidance during DES implantation on long-term clinical outcomes. In a single-center study of IVUS-guided DES implantation versus propensity score matched control population with angiographic guidance alone, a higher rate of definite stent thrombosis was seen in the angiography-guided group at both 30 days (0.5% vs 1.4%, P = 0.046) and 12 months (0.7% vs 2.0%, P = 0.014).[70] In addition, a trend was seen in favor of IVUS guidance in 12-month target lesion revascularization (5.1% vs 7.2%, P = 0.07). In addition, recent results of the revascularization for unprotected left main coronary artery stenosis: comparison of percutaneous coronary angioplasty versus surgical revascularization (MAIN-COMPARE) registry showed significantly lower 3-year mortality in the IVUS-guidance group as compared with the conventional angiography-guidance group (4.7% vs 16.0%, log-rank P = 0.048) in patients treated with DES.[71] Despite the growing evidence of the benefits of IVUS-guided DES implantation, few multicenter studies have been conducted to prove this hypothesis in a randomized controlled fashion. The Angiographic versus IVUS Optimization (AVIO) study was the first randomized trial designed to establish modern, universal criteria for IVUS optimization of DES implantation in complex coronary lesions.[72,73] This study proposed unique optimization

criteria in which the target stent area was determined according to the size of a post-dilation, noncompliant balloon chosen on the basis of IVUS-measured media-to-media diameters at multiple different sites within the stented segment. Post-procedure minimum lumen diameter, as the primary endpoint of this study, was significantly larger in the IVUS-guided group, particularly when optimal IVUS criteria were met, with no increased complication as compared to the angiography-guided group (target IVUS criteria met: 2.86 mm, target IVUS criteria not met: 2.6 mm, angiography alone: 2.51 mm). Further studies with a larger population are required to determine whether this acute benefit in complex lesions can translate into improved long-term clinical outcomes.

Due to the low incidence of DES failure, clarification of its exact mechanisms awaits the cumulative analysis of large clinical studies. Nevertheless, suboptimal deployment or mechanical problems appear to contribute to the development of both restenosis and thrombosis. Particularly, the most common mechanism is stent underexpansion, the incidence of which has been reported as 60–80% in DES failures. In a study of 670 native coronary lesions treated with sirolimus-eluting stents, the only independent predictors of angiographic restenosis were postprocedural final MSA and IVUS-measured stent length (OR = 0.586 and 1.029, respectively).[67]

Recurrent restenosis after DES implantation for bare metal stent restenosis was also recently investigated using IVUS. In a series of 48 in-stent restenosis lesions treated with sirolimus-eluting stents, 82% of recurrent lesions had an MSA of less than 5.0 mm^2, compared with only 26% of nonrecurrent lesions (P = 0.003).[74] In addition, a gap between sirolimus-eluting stents was identified in 27% of recurrent lesions versus 5% of nonrecurrent lesions. These observations emphasize the importance of procedural optimization at DES implantation for both *de novo* and in-stent restenosis lesions.

Although published data on DES thrombosis are further limited, one single-center IVUS study reported stent underexpansion (P = 0.03) and a significant residual reference segment stenosis (P = 0.02) as independent multivariate predictors of sirolimus-eluting stent thrombosis (median time, 14 days after implantation).[75] The IVUS features of stent thrombosis from another single-center IVUS study appear analogous to the previous observations.[76]

For very late DES thrombosis (> 12 months), another investigator group has suggested incomplete stent apposition as a possible risk factor.[77] Late-acquired incomplete stent apposition with DES has been reported in both experimental (paclitaxel)[78] and clinical (sirolimus and paclitaxel) studies (Fig. 16).[79–82] Several IVUS studies have indicated that the main mechanism is focal, positive vessel remodeling (Figs 17A and B).[79,81] In addition, there is strong suggestion that incompletely apposed struts are seen primarily in eccentric plaques, and that gaps develop mainly on the disease-free side of the vessel wall. Thus, the combination of mechanical vessel injury during stent implantation and biologic vessel injury with pharmacologic agents or polymer in the setting of little underlying plaque may predispose the vessel wall to chronic, pathologic dilation (Figs 18A and B). Despite a recent meta-analysis suggesting an increased risk of late/very late stent thrombosis in patients with late-acquired incomplete stent apposition,[83] it remains

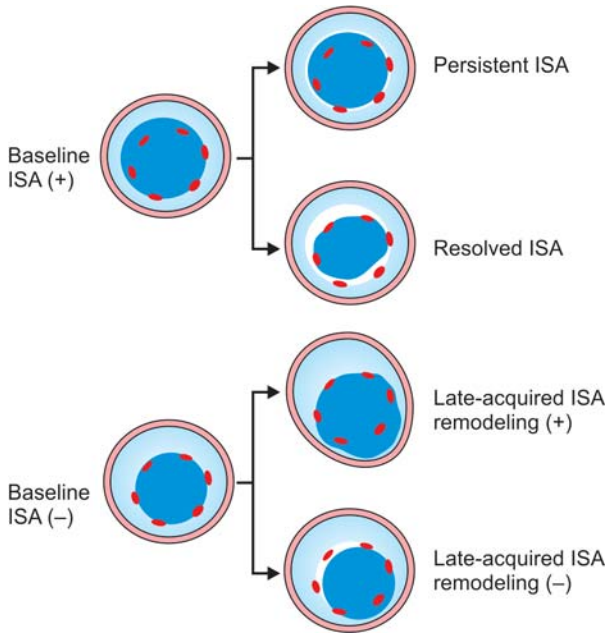


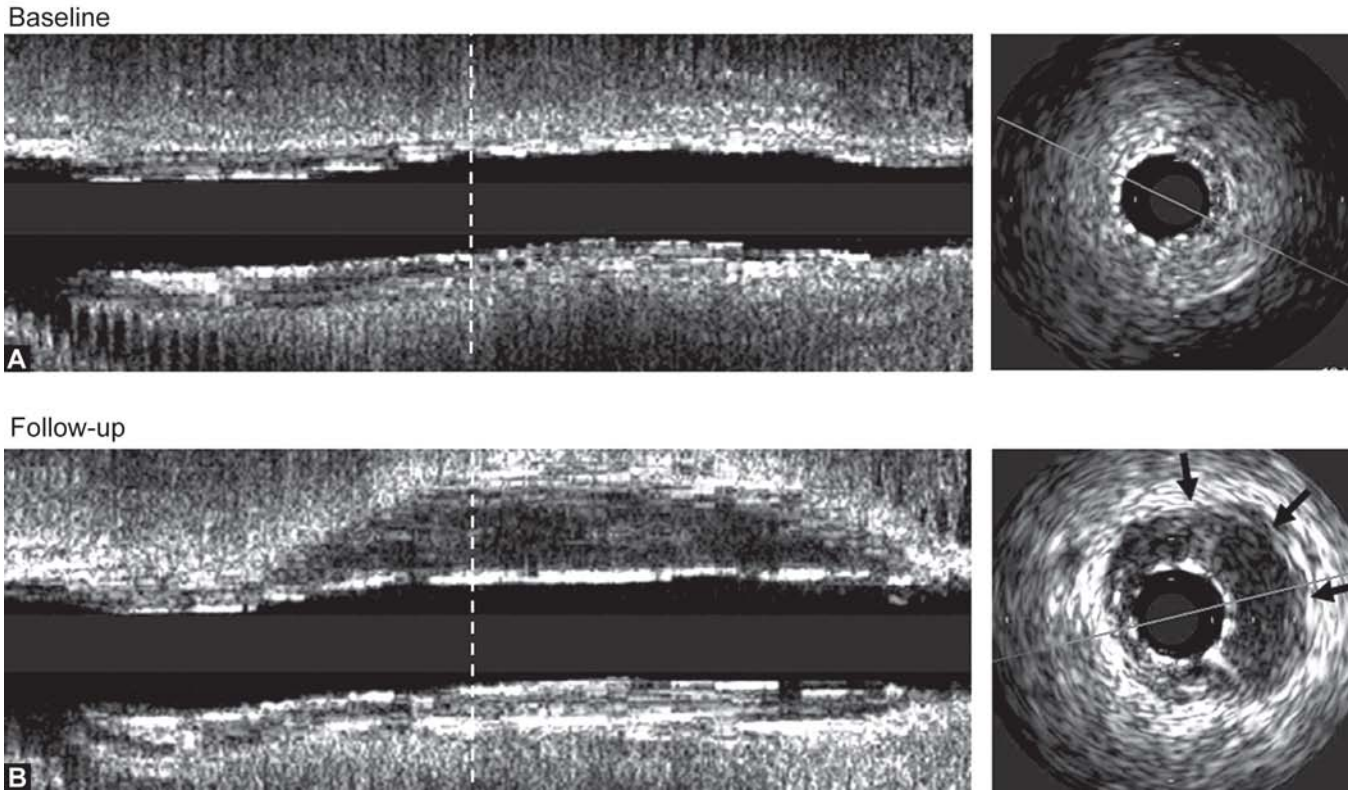
FIGURE 16: Classification of incomplete stent apposition (ISA). The ISA observed at follow-up is either persistent from baseline or late acquired. Late-acquired ISA without vessel remodeling is typically seen in thrombus-containing lesions, whereas late-acquired ISA with focal, positive vessel remodeling is more characteristic to drug-eluting stents

controversial whether this morphologic abnormality independently contributes to the occurrence of stent thrombosis.[84–86]

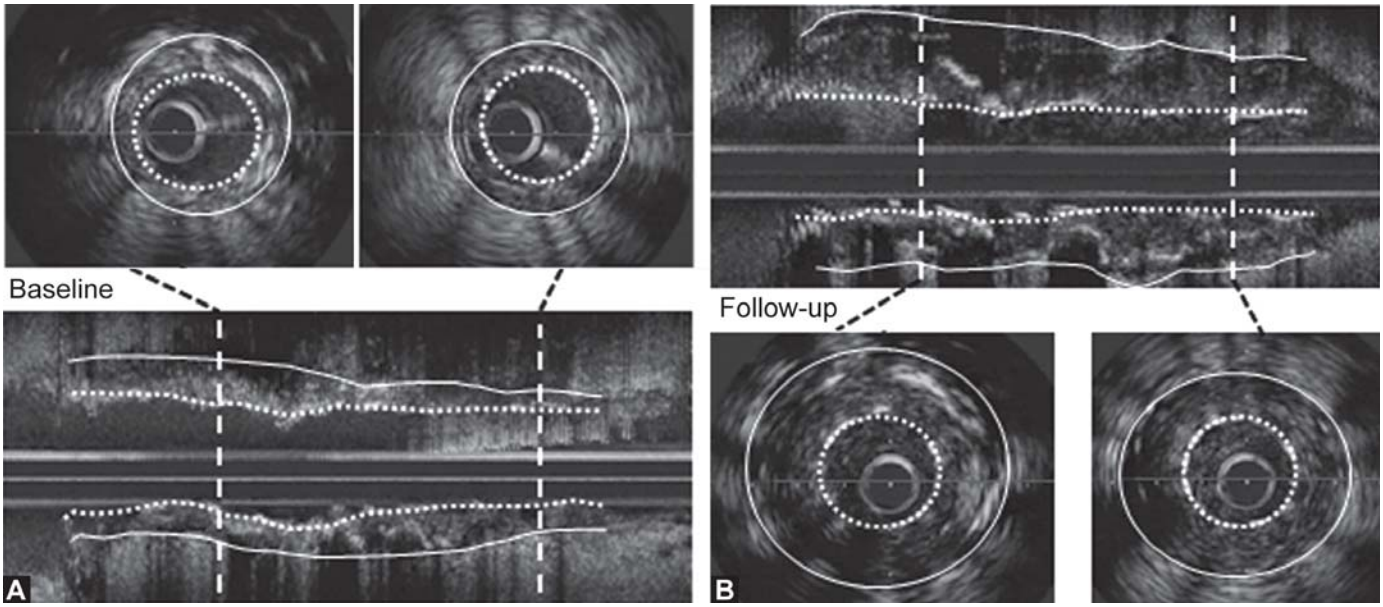
Other IVUS-detected conditions that may be of importance in DES include nonuniform stent strut distribution and stent fractures after implantation (Figs 19A and B). Theoretically, both abnormalities can reduce the local drug dose delivered to the arterial wall, as well as affecting the mechanical scaffolding of the treated lesion segment. By IVUS, strut fracture is defined as longitudinal strut discontinuity and can be categorized based upon its morphological characteristics: (1) strut separation; (2) strut subluxation or (3) strut intussusceptions (Fig. 20).[87] A recent IVUS study of 24 sirolimus-eluting stent restenosis cases identified the number of visualized struts (normalized for the number of stent cells) and the maximum interstrut angle as independent multivariate IVUS predictors of both neointimal hyperplasia and MLA.[88] In addition, angiographic or IVUS studies have reported the incidence of DES fracture as 0.8–7.7%, wherein in-stent restenosis or stent thrombosis occurred at 22–88%.[89] The exact incidence and clinical implications of strut fractures remain to be investigated in large clinical studies.

SAFETY

As with other interventional procedures, the possibility of spasm, dissection and thrombosis exists when intravascular imaging catheters are used. In a retrospective study of 2,207 patients, Hausmann and his colleagues identified spasm in 2.9% of patients, and other complications, including dissection, thrombosis and abrupt closure with "certain relation" to IVUS, in 0.4%.[90] Another multicenter European registry revealed 1.1% complications were reported (spasm, vessel dissection or guidewire entrapment) in a total of 718 examinations.[91] These studies were performed with first-generation catheters in the 1990s, and it is likely (although not documented) that the



FIGURES 17A AND B: Serial IVUS images of late-acquired incomplete stent apposition: (A) Baseline IVUS shows excellent post-procedure results of a mid-left anterior descending coronary artery lesion treated with a drug-eluting stent. (B) At 6 months, focal increase in vessel size is observed in the longitudinal IVUS image (left). On the cross-sectional IVUS images (right), stent struts are separated from the vessel wall which was not seen at stent implantation



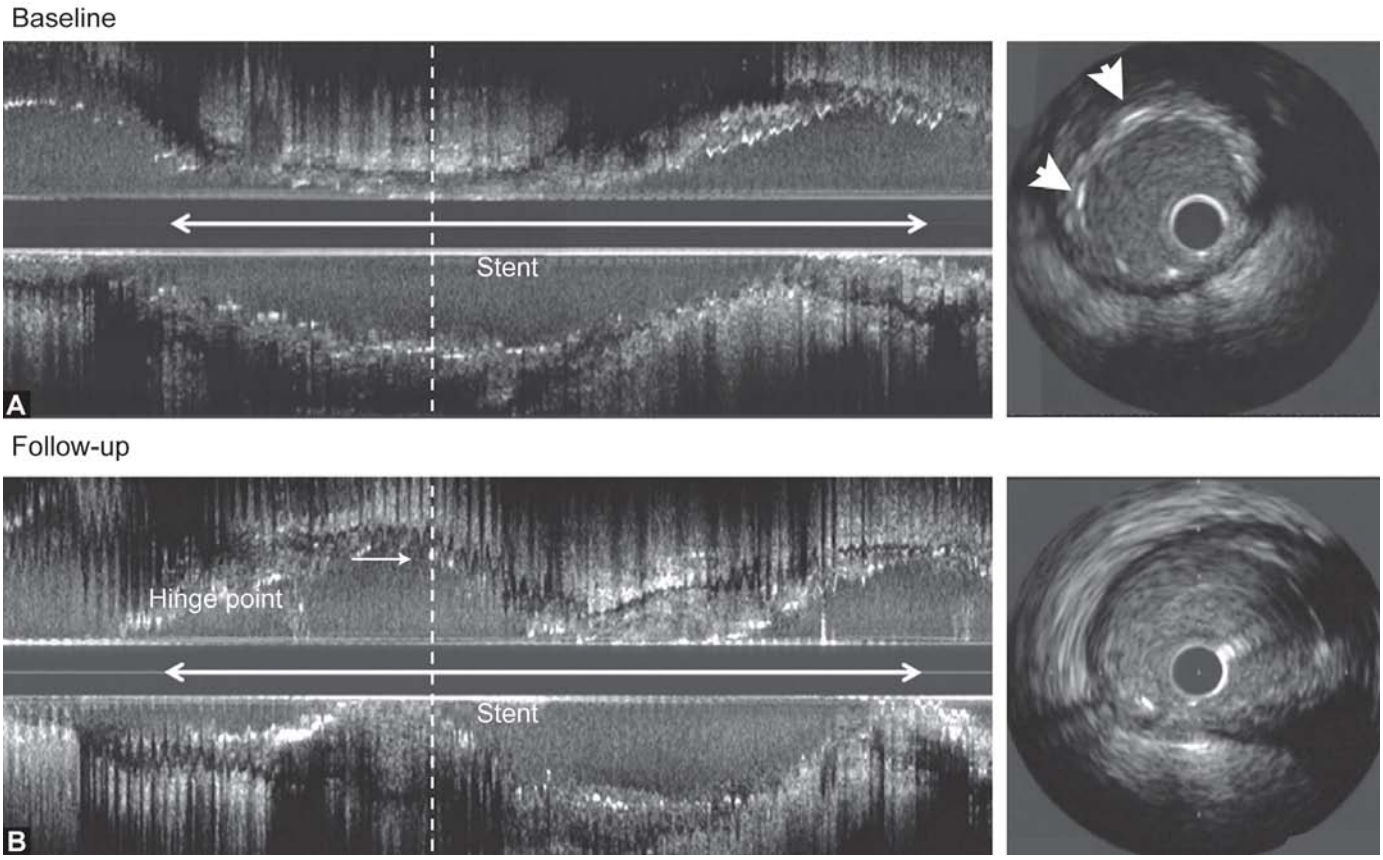
FIGURES 18A AND B: Positive vessel remodeling associated with very late stent thrombosis. Serial IVUS examination shows a significant increase in vessel size 3 years after stent deployment (dotted line: stent contour; solid line: vessel contour)

incidence of spasm and other complications is substantially lower with the current generation of catheters.

FUTURE DIRECTIONS

An interesting approach would be to combine IVUS with a therapeutic device, such as balloon catheter. In 2010, one angioplasty balloon catheter to integrate IVUS imaging (Vibe™ RX, Volcano Corporation, Rancho Cordova, California) gained CE-mark clearance in Europe. This new device can provide precise IVUS-guided balloon dilatation with immediate confirmation of interventional results without additional catheters or catheter exchanges.

Another interesting device iteration is "forward-looking" IVUS which can visualize the vessel wall in front of the imaging



FIGURES 19A AND B: Stent strut discontinuity (fracture) observed 8 months after deployment. On the cross-sectional IVUS images (B, right), partial separation of the stent, not seen at implantation (A, right), is detected at a portion of the mid stent. The longitudinal IVUS image (left) shows an acute-angled bend at follow-up

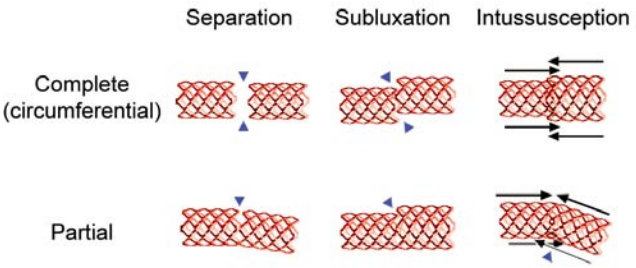


FIGURE 20: Classification of stent strut fracture. By IVUS, strut fracture is defined as longitudinal strut discontinuity and can be categorized based on morphological characteristics

catheter thereby having the potential to visualize the true and false lumens in chronic total occlusion (CTO) lesions. This enhanced visualization could be used to improve CTO crossing by continually maintaining and directing the catheter or wire toward the true lumen.[92]

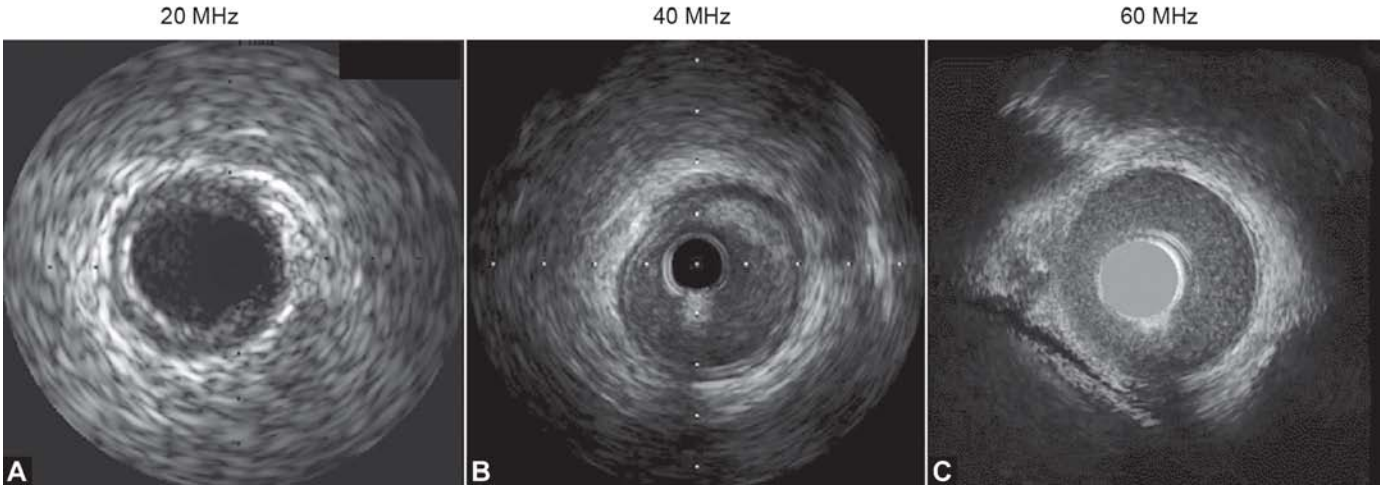
Currently, commercially available IVUS catheters used in the coronary arteries have center frequencies ranging from 20 MHz to 45 MHz with the highest frequency IVUS being the 45 MHz Revolution™ IVUS catheter (Volcano Corporation, Inc., Rancho Cordova, California). In general, higher frequencies of ultrasound improve the axial resolution. On the other hand, higher frequency IVUS may result in stronger scattering echoes from the blood, hampering visualization of the vessel lumen and thereby limiting the scanning depth. Therefore, IVUS frequencies higher than the current 45 MHz range IVUS may have inherent limitations. By overcoming these limitations, the next generation higher frequency IVUS catheter will enable better axial resolution (Figs 21A to C). Theoretically, an increase of center frequency from 40 MHz to 50 MHz corresponds to a 25% improvement in axial resolution if the design is similar.

OPTICAL COHERENCE TOMOGRAPHY

The principal technology was developed and first described by researchers at the Massachusetts Institute of Technology in 1991.[93] Since then, optical coherence tomography (OCT) has been applied clinically in ophthalmology, dermatology, gastroenterology and urology. Currently, intracoronary OCT has emerged as an *in vivo* optical microscopic imaging technology, as it generates real-time tomographic images from backscattered reflections of infrared light. Thus, the use of optical echoes by OCT can be regarded as an optical analog of IVUS, with its greatest advantage being its significantly higher resolution (10 times or greater) compared to conventional pulse-echo and other ultrasound-based approaches.

IMAGING SYSTEMS AND PROCEDURES

The imaging catheter includes a fiberoptic core with a microlens and prism at the distal tip to generate a focused scanning beam perpendicular to the catheter axis, thereby providing circumferential imaging of the arterial wall. In standard OCT systems,

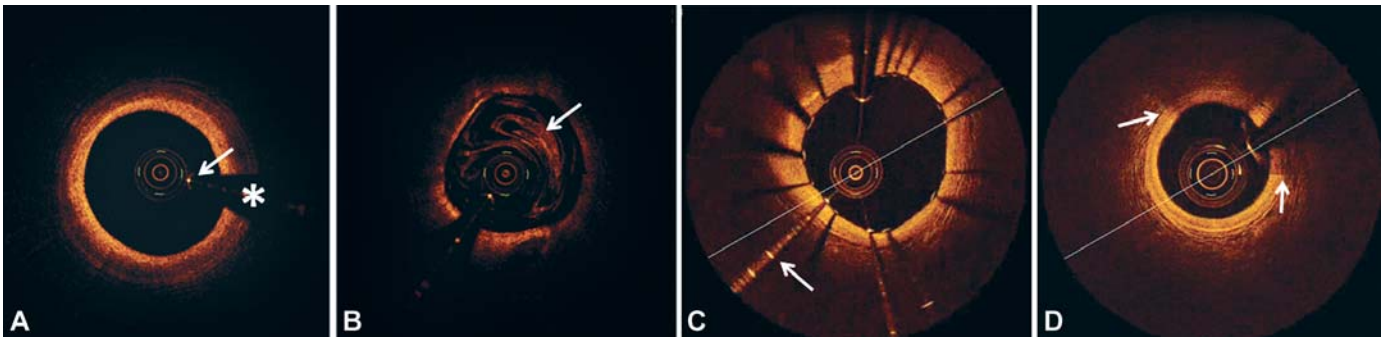


FIGURES 21A TO C: Comparing variable frequency IVUS images. Higher frequency IVUS can produce improved image quality due to higher resolution (60 MHz IVUS image). (*Source:* Silicon Valley Medical Instrument, Inc., CA)

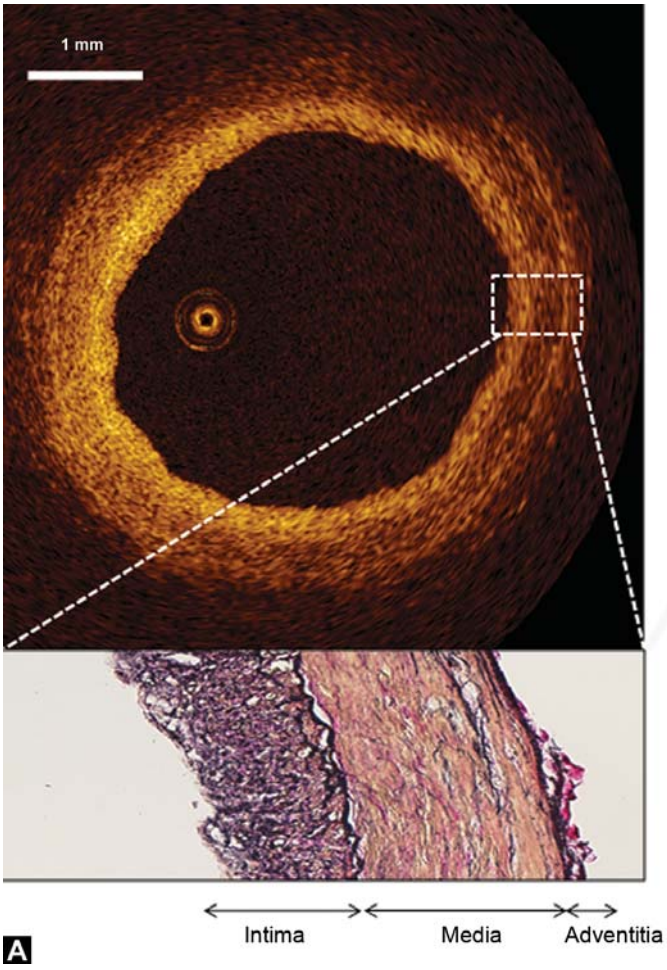
the optical engine includes a superluminescent diode as a source of low coherent, infrared light, typically with a wavelength around 1300 nm. The first commercialized intravascular OCT device (St. Jude Medical, Inc. St. Paul, Minnesota) consisted of a guidewire-based imaging catheter with a profile of 0.014 inches, a proximal low-pressure occlusion balloon catheter, and a system console containing the optical imaging engine and computer for signal acquisition, analysis and image reconstruction. The imaging procedure of intravascular OCT is similar to that of IVUS except that blood must be displaced by saline or contrast medium while imaging. Technically, this is because the dominant mode of signal attenuation in OCT is multiple scattering, so that additional scattering by red blood cells results in very large signal loss (Fig 22B). During OCT image acquisition, blood flow is interrupted by inflating the balloon with a modest amount of liquid flush from the distal flush exit ports of the occlusion catheter. The balloon inflation is performed at a low pressure to avoid unnecessary vessel stretching. Although this first generation intravascular OCT system was not approved by the United States Food and Drug Administration, the Fourier-domain OCT system (the so-called second generation OCT system) (St. Jude Medical, Inc.) was approved in 2010. Other companies have been developing similar rapid-scan OCT systems, referred to as optical frequency-domain imaging (OFDI). This technique measures optical echo time delay using a light source whose light output can be rapidly swept over a range of wavelengths (e.g. 1,260–1,360 nm). Fourier transform techniques enable conversion of the frequency-domain (or wave length dependent) data to be converted to a time-domain representation. While first generation OCT (time-domain OCT) systems have a frame rate of 4–20 frames/sec, the Fourier/frequency-domain OCT achieves 80–110 frames/sec acquisition, allowing comprehensive scanning of long arterial segments during one bolus flush through the guide catheter without the need for occlusion. Since the OCT catheter has a short guidewire lumen at the distal portion of the catheter tip, the guidewire can be seen as a point artifact with shadowing (Figs 22A to D).

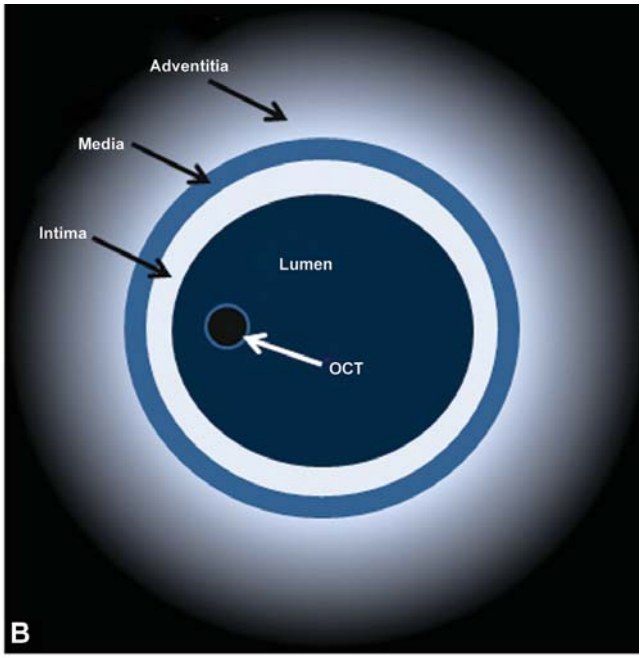
IMAGE INTERPRETATION

The higher resolution of OCT can often provide superior delineation of each structure compared with IVUS. The OCT can reliably visualize the microstructure (i.e. 10–50 µm, vs 150–200 µm for IVUS) of normal and pathologic arteries. Typically, the media of the vessel appears as a lower signal intensity band than the intima and adventitia, providing a three-layered appearance similar to that seen by IVUS (Figs 23A and B). Atheromatous lesions and fibrous plaques exhibit homogeneous, signal-rich (highly backscattering)



FIGURES 22A TO D: Common image artifacts: (A) A guidewire (arrow) produces a radial invisible part formed in the circumferential direction (asterisk). (B) Residual blood inside the vessel lumen causes deterioration of OCT image quality. (C) Highly reflective objects, like stent struts, can produce a series of ghost reflections that appear as a replica at a fixed distance away from the primary image of an object. (D) The silicone fluid gap inside the OCT catheter causes scatter of the light beam, casting a shadow in OCT image





FIGURES 23A AND B: Example of cross-sectional image format of OCT. The bright-dark-bright, three-layered appearance is seen in the image with corresponding anatomy as defined. Histologic correlation with intima, media and adventitia are shown. The OCT shows the three layer appearance of normal vessel wall, with the muscular media being revealed as a low signal layer comprised between intima and adventitia

regions; lipid-rich plaques exhibit signal-poor regions (lipid pools) with poorly defined borders and overlying signal-rich bands (corresponding to fibrous caps); and calcified plaques exhibit signal-poor regions with sharply delineated borders (Figs 24A to C). The OCT has the advantage of being able to image through calcium without shadowing, as would be seen with IVUS. On the other hand, signal penetration through the diseased arterial wall is generally more limited (no more than 2 mm with current OCT devices), making it difficult to investigate deeper portions of the artery or to track the entire circumference of the media-adventitia interface. Plaque characteristics of OCT versus IVUS are listed in Table 2.

TABLE 2

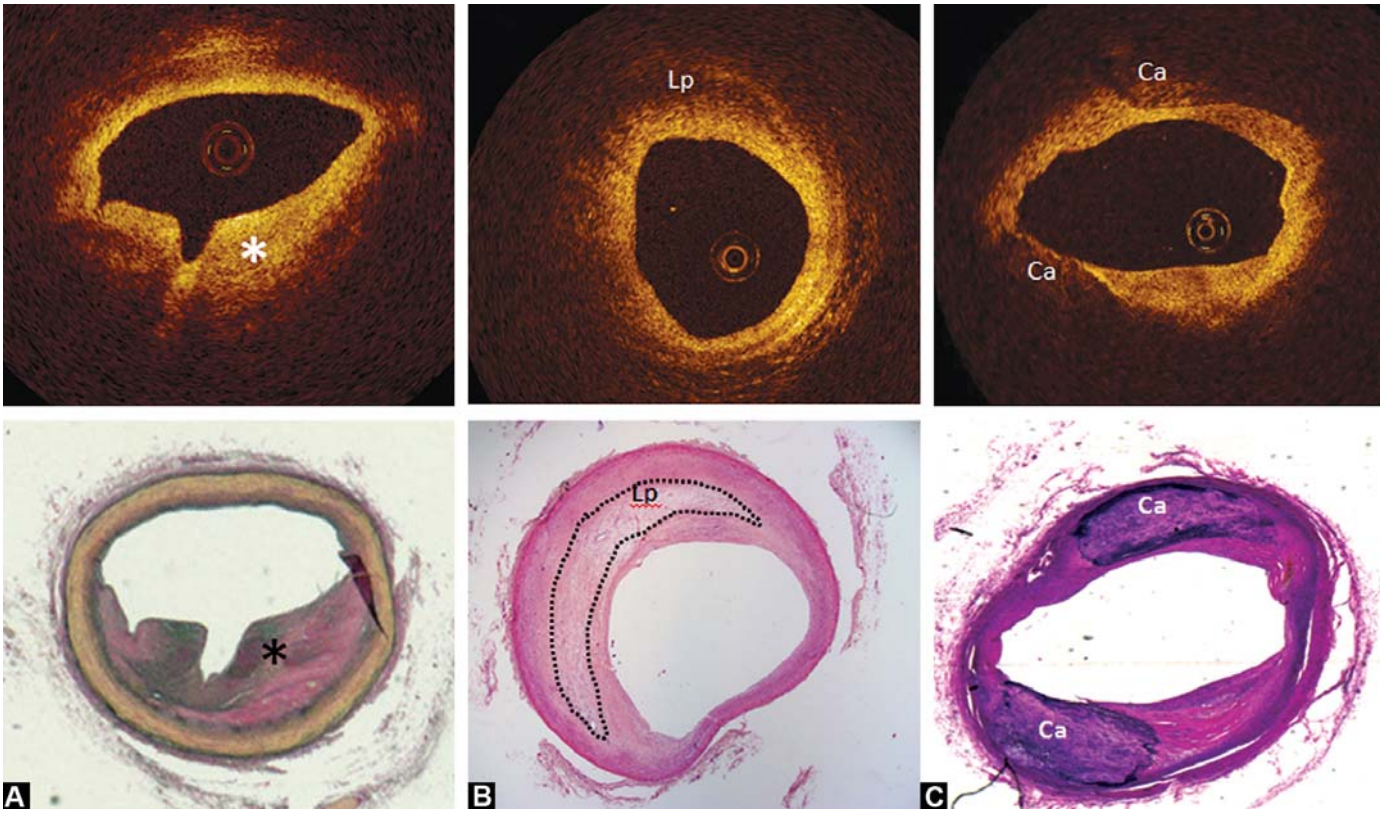
Plaque characteristics of OCT versus IVUS

Tissue type	*OCT*	*IVUS*
Fibrous	Homogeneous Signal-rich (highly backscattering)	Homogeneous High echogenicity
Calcium	Sharply delineated borders Signal-poor	Very high echogenicity Shadowing
Lipid	Poorly defined borders Signal-poor	Low echogenicity

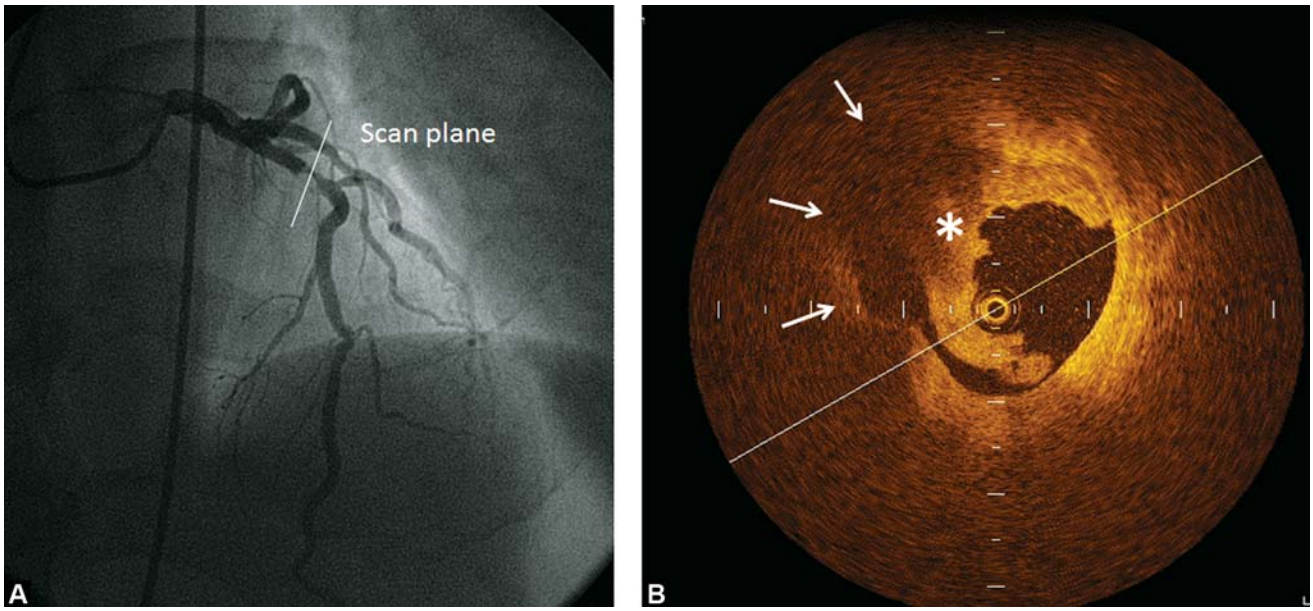
The diagnostic accuracy of OCT for the above plaque characterization criteria was confirmed by an ex vivo study of 307 human atherosclerotic specimens including aorta, carotid, and coronary arteries.[94] Independent evaluations by two OCT analysts demonstrated a sensitivity and specificity of 71–79% and 97–98% for fibrous plaques; 90–94% and 90–92% for lipid-rich plaques and 95–96% and 97% for fibrocalcific plaques, respectively (overall agreement vs histopathology, κ values of 0.88–0.84). The interobserver and intraobserver reproducibility of OCT assessment was also high (κ values of 0.88 and 0.91, respectively).

CLINICAL EXPERIENCE

In the first coronary OCT study in humans reported by Jang and his colleagues, 17 coronary segments in 10 patients were imaged with 3.2F OCT catheters (modified IVUS catheters) during intermittent saline flushes through the guide catheter.[95] The maximum penetration depth of OCT imaging measured 1.25 mm versus 5 mm for IVUS. *In vivo* axial resolutions, determined by measuring the full-width half-maximum of the first derivative of a single axial reflectance scan at the surface of the tissue, were 13 ± 3 μm with OCT versus 98 ± 19 μm with IVUS. All fibrous plaques, macrocalcifications and echolucent regions identified by IVUS were visualized in corresponding OCT images. Intimal hyperplasia and echolucent regions, which may correspond to lipid pools, were identified more frequently by OCT than by IVUS.

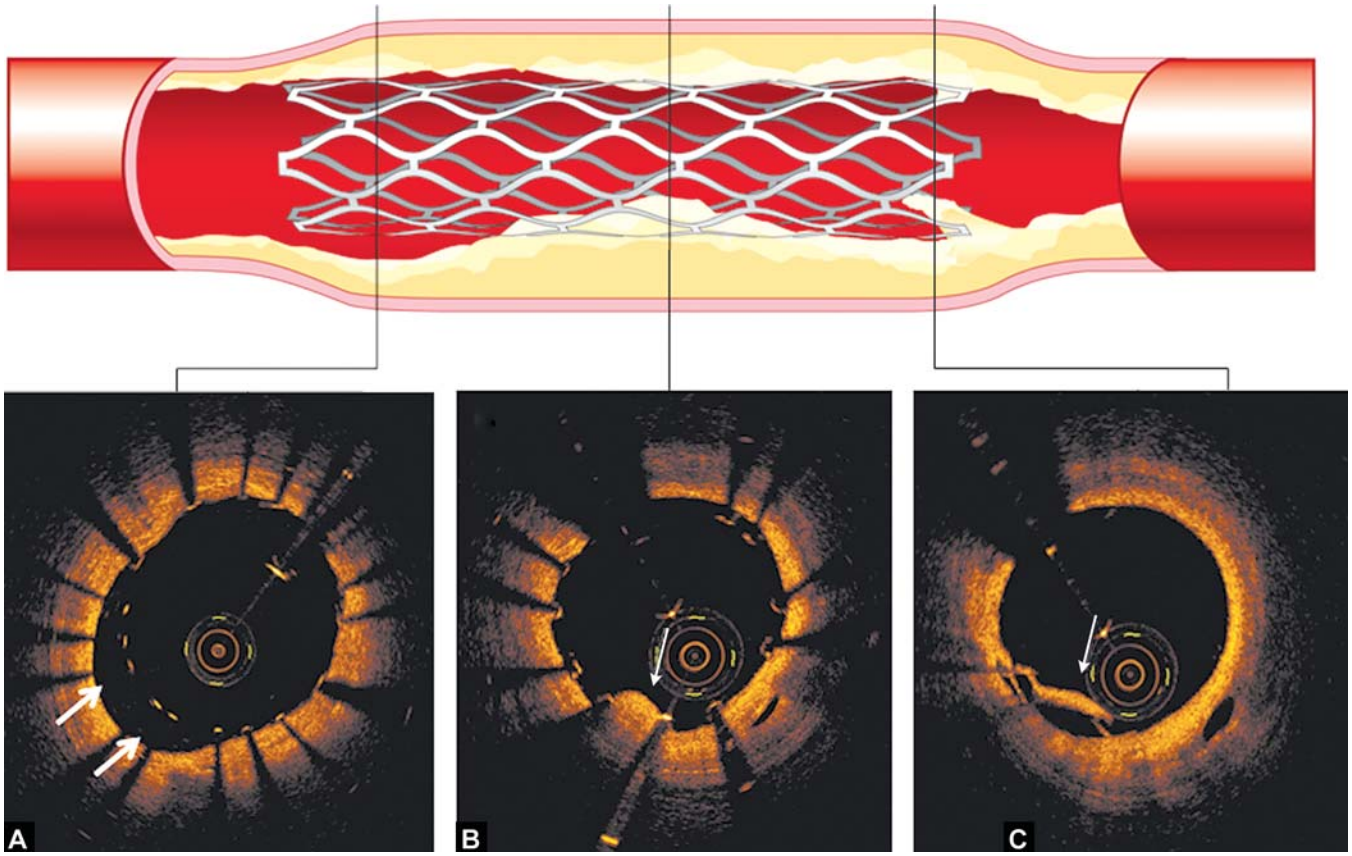


FIGURES 24A TO C: The OCT images (top) and corresponding histology (bottom) for (A) lipid-rich, (B) fibrous and (C) calcific plaques. In fibrous plaques, the OCT signal is observed to be strong and homogenous (asterisk). In comparison, both lipid-rich (Lp) and calcific (Ca) regions appear as a signal-poor region within the vessel wall. Lipid-rich plaques have diffuse or poorly demarcated borders, whereas the borders of calcific nodules are sharply delineated (Histologic stainings: elastica van Gieson for left, hematoxylin and eosin for middle and right, respectively)



FIGURES 25A AND B: Culprit lesion in the left anterior descending (LAD) artery in a patient with unstable angina: (A) Coronary angiogram shows significant lumen narrowing at the proximal portion of LAD. (B) OCT clearly visualizes the protruded thrombus (asterisk) attached to the plaque rupture site (arrow)

In addition, recent clinical reports by the same investigator group showed that intravascular OCT detected lipid-rich plaques and thrombus more frequently in acute myocardial infarction or unstable angina than in stable angina lesions.[96] In a recent study using the first commercialized OCT system, Kubo and his colleagues reported that the plaque rupture and thrombus in patients with acute myocardial infarction were identified more frequently by OCT than by IVUS (73% vs 40%, P = 0.009, and 100% vs 33%, P < 0.001) (Figs 25A and B).[97]

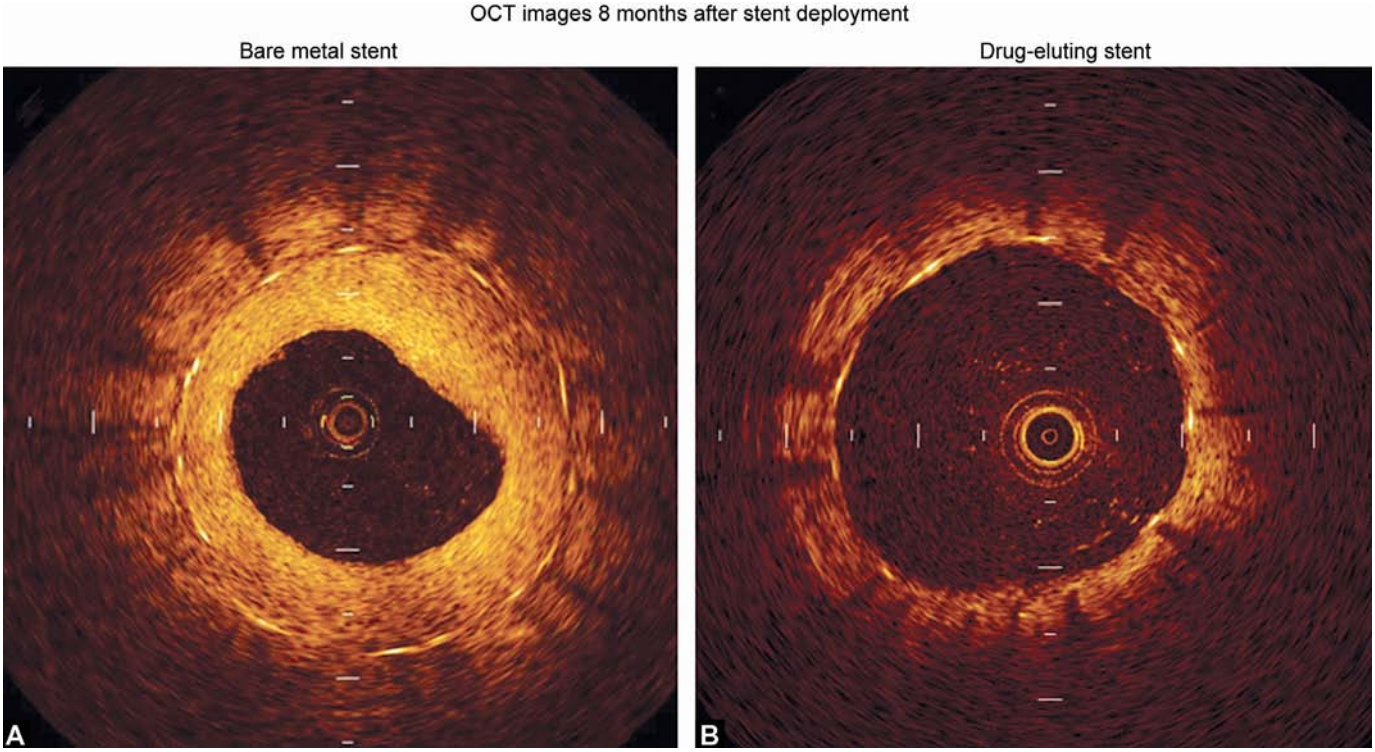


FIGURES 26A TO C: Stent deployment problems detected by OCT: (A) Incomplete stent apposition, in which there is a gap between a portion of the stent and the vessel wall between 6 O'clock and 10 O'clock. (B) Tissue prolapse between the stent struts at 6 to 7 O'clock. (C) An edge tear or "pocket flap" with a disruption of plaque at the stent margin

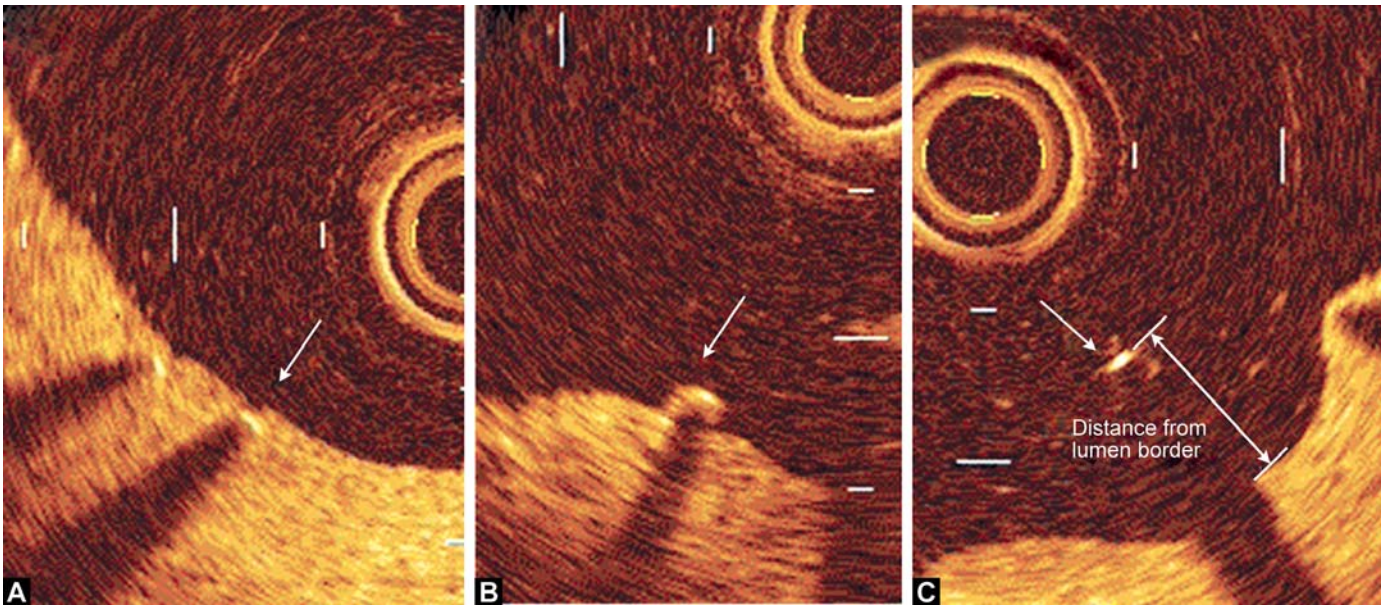
Encouraging preliminary results have been reported in the assessment of coronary interventions as well. Bouma and his colleagues successfully imaged 42 coronary lesions before and immediately after stenting.[98] In this series, OCT detected dissections, instent tissue prolapse and incomplete stent apposition more often than IVUS (Figs 26A to C). With a dedicated OCT catheter, Grube and his colleagues reported a follow-up OCT examination 6 months after drug-eluting stent implantation for the treatment of instent restenosis.[99] The high resolution of OCT allowed clear visualization of the overlapped stents (stent-in-stent), distinctly identifying each stent strut as well as a very thin neointimal layer covering the drug-eluting stent struts (Figs 27A and B). More recently, some investigator groups have reported that OCT images can visualize the thin neointima on each stent strut and quantify its thickness after drug-eluting stent implantation.[100,101] The OCT revealed the majority of stent struts were covered by a thin neointima layer less than 100 μm thick, which is beyond IVUS resolution capabilities, 6 months after sirolimus-eluting stent implantation.[100] In addition, Otake and his colleagues reported that subclinical thrombus after sirolimus-eluting stenting was significantly associated with longer stents, a larger number of uncovered struts, and greater average of neointimal unevenness score (maximum neointimal thickness in the cross section/average neointimal thickness of the same cross section).[102] Although the exact clinical impact of intravascular OCT findings requires systematic evaluation, these preliminary reports have confirmed that this new imaging technology has the potential to provide a new level of anatomic detail, not only as a research technique but also as a clinical tool (Figs 28A to C). In fact, OCT has been used as a tool for evaluating neointimal proliferation after commercially available stents or newly developed stents in some multicenter trials.[103–106] OCT for DES SAfety (ODESSA) reported the frequency of uncovered stent struts at 6 months in overlapped segments (sirolimus-eluting stent, 8.7 ± 13.3%; paclitaxel-eluting stent, 8.3 ± 20.9%; zotarolimus-eluting stent, 0.05 ± 0.19%; bare metal stents, 1.8 ± 4.0%) and in non-overlapped segments (sirolimus-eluting stent, 7.9 ± 11.3%; paclitaxel-eluting stent, 2.3 ± 4.1%; zotarolimus-eluting stent, 0.01 ± 0.05%; bare metal stents, 0.5 ± 2.2%).[103] In the OCT in acute myocardial infarction (OCTAMI) study, uncovered stent struts were reported in 0.00% of zotarolimus-eluting stent and in 1.98% of bare metal stents (P = 0.13) 6 months after stent implantation in patients with ST-segment elevation myocardial infarction.[106]

DETECTION OF VULNERABLE PLAQUE

One of the most valuable challenges for OCT is its role in the detection of vulnerable plaque. OCT is often able to identify a thin fibrous cap of vulnerable plaque, the thickness of which (< 65 μm) is technically below the image resolution of IVUS (~ 150 μm). The TCFA, that is the primary plaque type at the site of plaque rupture, exists in nonculprit lesions and is



FIGURES 27A AND B: OCT images 8 months after stent deployment: (A) OCT visualizes the stent struts covered by a thick neointima that appeared as a bright luminal layer surrounding the stent struts after bare metal stent implantation. (B) The OCT shows stent struts and thin, bright reflective tissue coverage after drug-eluting stent implantation



FIGURES 28A TO C: Strut assessment by OCT in relation to the vessel wall. Due to a blooming effect of metal struts, the highest intensity point within the strut image should be used for the measurement. Strut apposition to the vessel wall is determined by measuring the distance from the stent strut surface to the vessel wall as compared to the nominal strut thickness (Nominal strut thickness; Cypher®, Cordis, Johnson and Johnson Co, Miami, FL; 154 µm, TAXUS Liberté®, Boston Scientific Inc, Natick, MA; 115 µm, Endeavor®, Medtronic, Santa Rosa, CA; 96 µm, Xience™V, Abbott Vascular, Santa Clara, CA; 89 µm)

distributed in all three coronary arteries. Fujii and his colleagues performed three-vessel OCT examination in patients with ischemic heart disease and showed that TCFAs tend to cluster in predictable spots within the proximal segment of the LAD artery yet develop relatively evenly in the left circumflex and right coronary artery.[107] These data were similar to prior histologic data indicating that TCFAs were concentrated in the proximal portions of the LAD artery and more uniformly distributed in the right coronary artery.[108] The unique capabilities of OCT as an investigational tool for high-risk lesions will serve the cardiology community well, as it advances us toward a better understanding and identification of vulnerable plaque

thereby improving our ability to more precisely treat our patients, both acutely and for the long term.

SAFETY AND LIMITATIONS

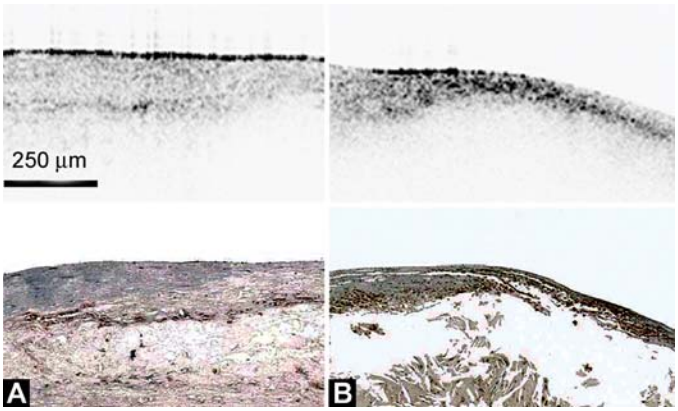
Since the biologic safety of applied energies in OCT has been well established in other medical fields, potential issues predominantly derive from the mechanical designs of intravascular devices (imaging catheters and flush delivery system) and transient ischemia during coronary imaging.

Preliminary experiences of first generation OCT system with both occlusive and nonocclusive images acquisition showed the technique to be safe. No major complications or arrhythmias were reported in a study of 60 patients examined using the non-occlusive technique.[109] Ischemic ECG changes were transient and occurred in 21 patients (35%), with ST depression in 17 (28%) and ST elevation in 4 (7%). Another multicenter study reported on the safety of the occlusive image acquisition technique in 76 patients with coronary artery disease. There were no significant procedural complications including ventricular tachycardia or ventricular fibrillation, acute vessel occlusion, dissection, thrombus formation, or vasospasm.[110] Second generation OCT systems have faster frame rates and can obtain a scan of up to 50 mm of a vessel within 3 seconds. Therefore, OCT images can be acquired with the smaller volume of flush in shorter pullback acquisition time without blood flow occlusion. A preliminary study reported the Fourier-domain OCT system had better safety results than the first generation time-domain OCT system.[111]

Although OCT has a higher image resolution than IVUS, OCT is not capable of studying tissue at a cellular level. Therefore, OCT cannot discriminate the different kinds of tissues covering stent strut (i.e. endothelium, smooth muscle cells, fibrin, etc.) after stent implantation.

FUTURE DIRECTIONS

One interesting aspect of OCT regarding in-depth plaque characterization is macrophage quantification in the fibrous cap of atherosclerotic plaques. This signal-processing technique is based on the hypothesis that macrophage-infiltrated caps may have a higher heterogeneity of optical refraction index, exhibiting stronger optical scattering with a higher signal variance than less infiltrated fibrous caps (Figs 29A and B). In an *ex vivo* study of 26 lipid-rich atherosclerotic arterial segments, Tearney and his colleagues compared the standard deviation of the OCT signal intensity with cap macrophage density quantified by immunohistochemistry.[112] Prior to analysis, the computation background and speckle noises were filtered out and the standard deviation was normalized by the maximum and minimum OCT signals in the image. There was a high degree of positive correlation between OCT and histologic measurements of fibrous cap macrophage density ($r = 0.84$, $p < 0.0001$). A range of OCT signal standard deviation thresholds (6.15–6.35%) yielded 100% sensitivity and specificity for identifying caps containing more than 10% CD68 staining. Based on this signal-processing technique, several clinical studies reported that macrophage density was significantly higher in vulnerable plaque features such as rupture sites or positive vessel remodeling sites.[113,114] Despite direct visualization of individual mononuclear macrophages being limited with current intravascular OCT devices, advanced image-processing algorithms, as shown in these studies, may be of great utility in the assessment of plaque instability.

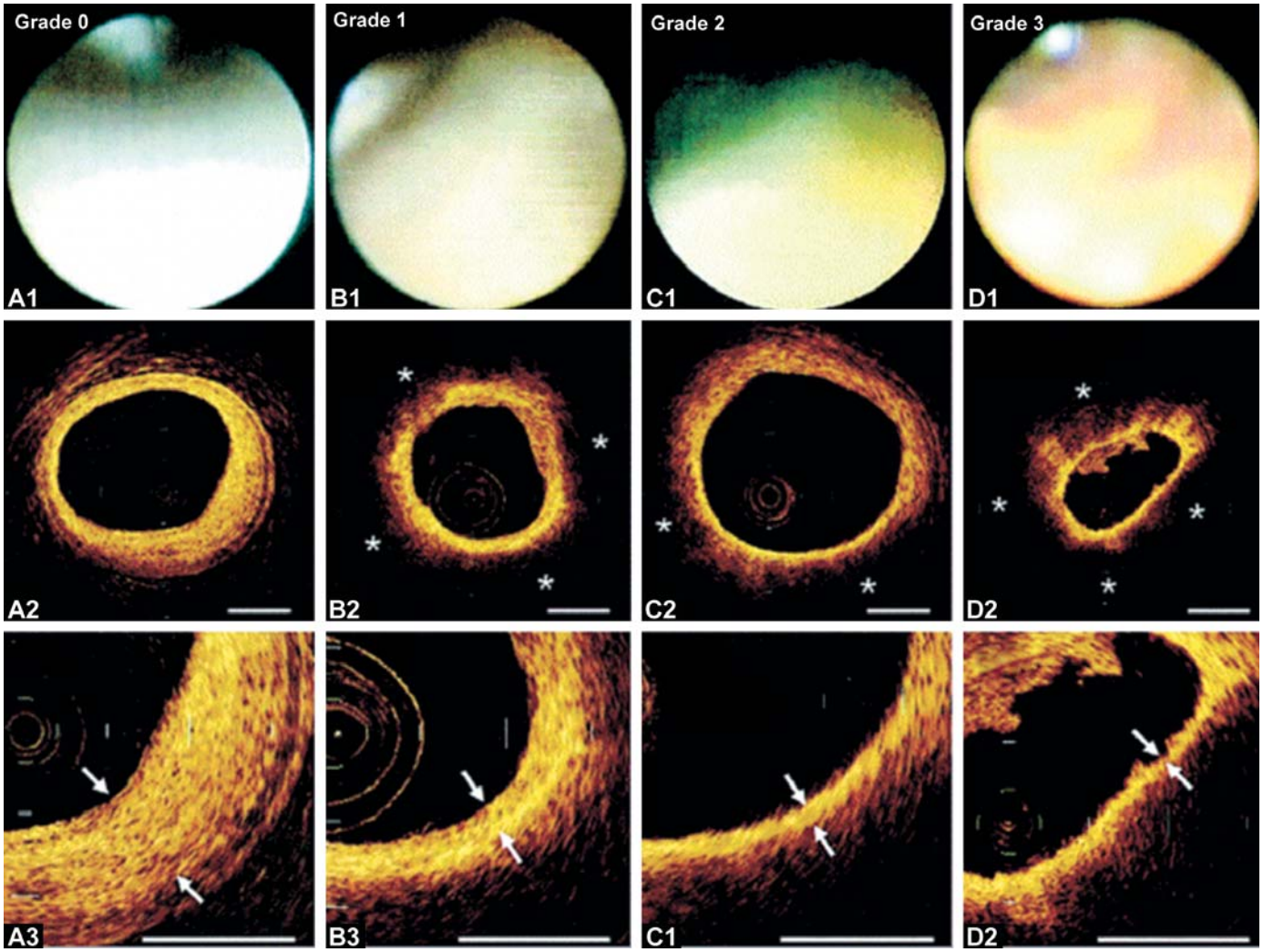


FIGURES 29A AND B: The OCT images (top) and corresponding histology (CD68 immunoperoxidase; original magnification 100X, bottom) of (A) a fibroatheroma with a low macrophage density within the fibrous cap and (B) a fibroatheroma with a high macrophage density within the fibrous cap. (*Source:* Tearney GJ, et al. Quantification of macrophage content in atherosclerotic plaques by optical coherence tomography. Circulation. 2003;107:113-9, with permission)

Spectroscopic analysis is another interesting assessment tool. It uses a spectrum of infrared light reflected from the structures to color code the information on tomographic images providing insights into the biochemical contents of the tissue. Polarization analysis, measuring the degree of birefringence in the tissue, may also be helpful in plaque component discrimination, since regions with highly oriented fibrous or smooth muscle cell components are more sensitive to the polarity of the imaging light than degenerated atheromatous regions with randomly oriented cells. The OCT Doppler and elastography are analogous to those of ultrasound-based approaches but may offer improved sensitivity, owing to higher resolution and contrast. In addition, viscoelasticity of the structure may be accurately assessed based on its intrinsic properties using laser speckle analysis.

ANGIOSCOPY

Intracoronary angioscopy is an endoscopic technology that allows direct visualization of the surface color and superficial morphology of atherosclerotic plaque, thrombus, neointima, or stent struts. In 1985, the first clinical experience of intracoronary angioscopy was reported[115] and since then, technical improvements have occurred resulting in image quality enhancement, catheter miniaturization and development of subselective catheterization systems. Although the Food and Drug Administration has not yet approved any coronary angioscopy system for use in the United States, clinical investigators worldwide have been using this unique diagnostic modality to provide considerable information in the pathophysiology of coronary lesions, particularly in the field of acute coronary syndromes.



FIGURES 30A TO D: An example of yellow plaque grading by angioscopy and corresponding optical coherence tomography images. The surface color represents a lipid-rich core seen through a fibrous cap, and its intensity rises as the fibrous cap thins and becomes increasingly transparent (Top, grade 0 to 3). OCT has demonstrated that the fibrous cap is thinner in the more intensively yellow plaques (Bottom; enlarged images, scale bar; 1 mm). Thickness of the fibrous cap is indicated by the two arrows. (*Source:* Kubo T, et al. Implication of plaque color classification for assessing plaque vulnerability: a coronary angioscopy and optical coherence tomography investigation. JACC Cardiovasc Interv. 2008;1:74-80, with permission)

IMAGING SYSTEMS AND PROCEDURES

In general, intracoronary angioscopy consists of an external optical engine incorporating a light source and a charge coupled device (CCD) camera; a fiberoptic catheter for illumination and imaging; a subselective delivery catheter system and a video monitor with an image recording system. The light source emits a high-intensity white light to illuminate the target object through the fiberoptic catheter. The imaging catheter contains a flexible fiber optic bundle of several thousand pixels; the latest-generation catheter, which incorporates 6,000 fibers, is 0.75 mm in outer diameter with a microlens that provides a 70° field of view and a focused depth that ranges from 1 mm to 5 mm. Although conventional delivery systems are equipped with a distal balloon to create a blood-free field for optical imaging, an alternative system uses a smaller catheter to continuously flush an optically clear liquid in front of the angioscope tip for transient blood displacement.

IMAGE INTERPRETATION

Similar to gastrointestinal angioscopy, coronary angioscopic images are interpreted based on the surface color and endoluminal morphology of vessel walls or structures. The normal coronary artery surface appears as grayish white and smooth in contour without any protruding structure whereas atherosclerotic plaques can show varying degrees of yellowish color (Figs 30A to D) with or without visible irregularities of the luminal surface. The yellow plaque surface signifies a lipid-rich core seen through a fibrous cap, and the yellow intensity rises as the fibrous cap thins and becomes increasingly transparent. Dissections are characterized as visible cracks or fissures on the luminal surface and/or sail-like white protruding structures that can be loose or immobile inside the lumen. Intimal flaps are visualized as thin, faint, highly mobile fronds of white tissue. Both structures are generally contiguous and of similar appearance to the adjacent vessel wall. Thrombi are recognized

as masses that are red, white or mixed in color, which adhere to the intima or protrude into the lumen. Red masses, not dislodged by flushing, are considered as fibrin/erythrocyte-rich thrombi, whereas white granular cotton-like appearances are characteristics of platelet-rich thrombi. Subintimal hemorrhage may be detected as distinct, demarcated patches of red coloration that are clearly within the vessel wall. To circumvent subjectivity of color interpretation, quantitative colorimetric methods have been proposed. The Ermenonville classification was established by a European coronary angioscopy working group, featuring several parameters, such as image quality, lumen diameter, surface color, atheroma, dissection and thrombus, graded in 3–5 categories.[116] In addition, κ values for chance-corrected intraobserver and interobserver agreement of diagnostic items were low at 0.51–0.67 and 0.13–0.29, respectively. On the other hand, the important items, such as red thrombus and dissection, were shown to have a good intraobserver and acceptable interobserver agreement when recorded more simply as either present or absent. Similarly, relatively simple classifications by other investigators resulted in good reproducibility.[117]

CLINICAL EXPERIENCE

Angioscopy has contributed valuable information of the underlying mechanisms of acute coronary syndromes. Angioscopically, most culprit lesions show occlusive or mural thrombi frequently overlying disrupted yellow plaque. The thrombi are predominantly white, but can turn into red or mixed once they become occlusive. On the other hand, the majority of ruptured plaques at the angiographically mild to moderate stenosis may remain subclinical.

The detailed healing process of infarct-related, disrupted plaques has also been evaluated in vivo by serial angioscopy. In a study by Ueda and his colleagues,[118] culprit lesions were examined immediately after PCI and/or thrombolysis and at 1, 6 and 18-month follow-up. Thrombus was detected in 93% at baseline and in 64% even 1 month after the onset of acute myocardial infarction, suggesting prolonged and persistent thrombogenicity at the culprit lesion. The prevalence of thrombus, however, markedly decreased at the following time points, accompanied by a significant reduction in visually graded yellow color intensity of the plaque. Interestingly, these stabilization processes were significantly impaired in patients with diabetes mellitus or hyperlipidemia.

Assessment of lesions before or after coronary intervention represents another commonly reported application of coronary angioscopy. One early study, for example, evaluated 122 patients undergoing conventional PCI and revealed that angioscopic thrombus was strongly associated with in-hospital adverse outcomes (either a major complication or a recurrent ischemic event) after PCI (relative risk, 3.11; 95% CI, 1.28–7.60; P = 0.01).[119]

Coronary angioscopy may significantly contribute to our understanding of new interventional devices or pharmacologic interventions as well. In coronary stenting, for example, several investigators have evaluated *in vivo* vessel response to bare metal stent implantation by serial angioscopy. Unlike animal models, these human studies suggested that, in some cases, several months may be required for visible completion of neointimal coverage over the metal struts. In-stent neointima became thick and nontransparent up to 6 months but completely disappeared by 3 years, indicating that functional neointimal maturation may require several months following stent implantation. A more recent study investigated the effect of stenting on infarct-related lesions as well.[120] At baseline, most lesions had complex morphology (96%) and yellow plaque color (96%), most of which still being observed even 1 month after stenting. At 6-month follow-up, the plaque shape and color mostly turned into smooth (97%) and white (93%), suggesting that stent implantation may lead to a sealing of unstable plaque with neointimal proliferation. Similar changes in plaque color have also been reported with lipid-lowering interventions.[121] As for drug-eluting stents, angioscopy revealed a difference in neointimal formation pattern between sirolimus- and paclitaxel-eluting stents.[122] In this study, paclitaxel-eluting stents showed more heterogeneous neointimal coverage and higher incidence of thrombus formation (70% vs 11%, P < 0.001) as compared with sirolimus-eluting stents at 18 months after stent implantation. The same investigator group reported similar results in a comparison to bare metal stents: paclitaxel-eluting stents showed the most heterogeneous neointimal formation and the highest incidence of thrombus formation at 6 months after stent implantation (50% in paclitaxel-eluting stent, 12% in sirolimus-eluting stent and 3% in bare metal stent, p < 0.001).[123]

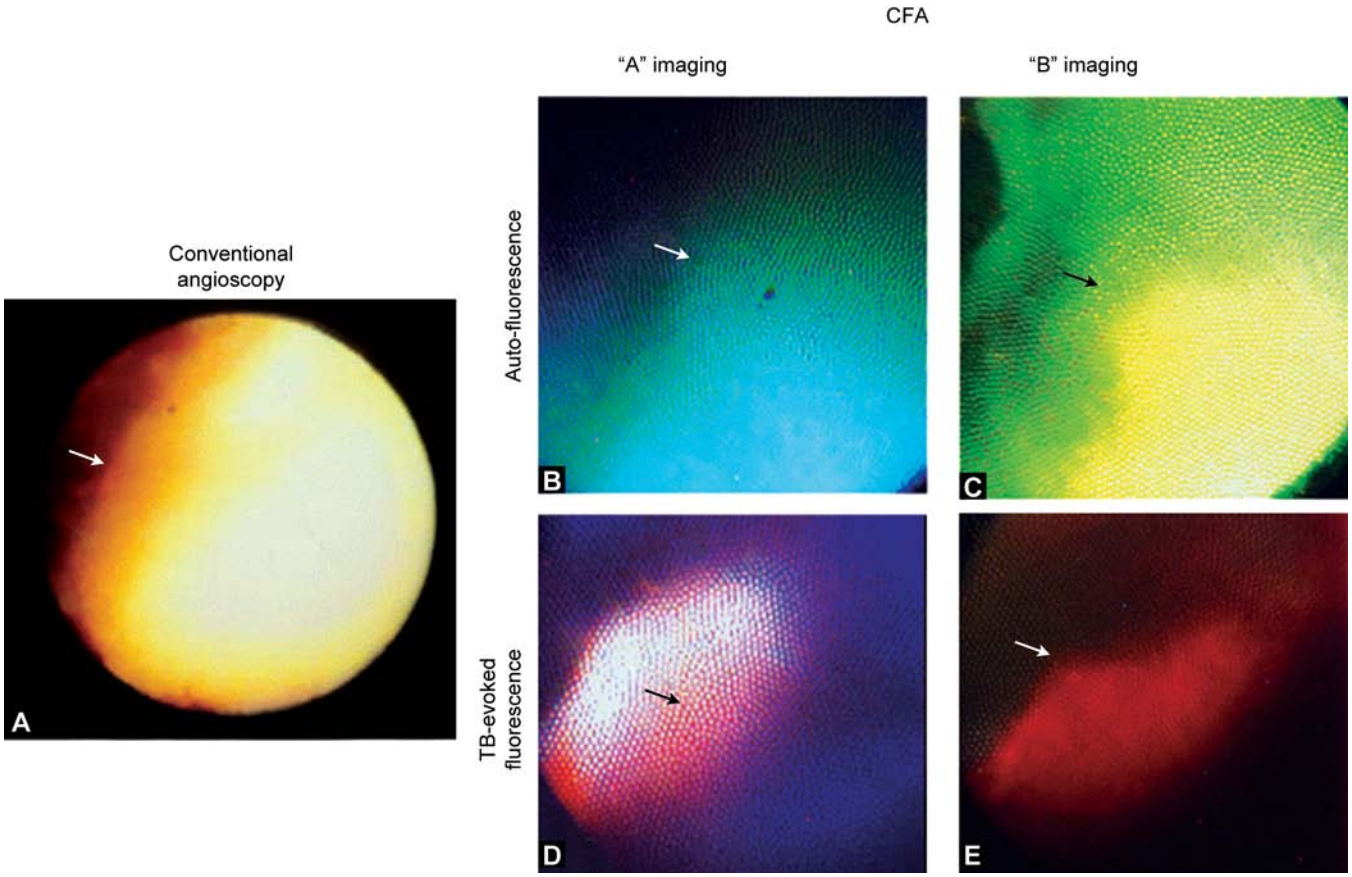
Another investigator group reported that serial angioscopic examination immediately after the 10 months of sirolimus-eluting stent implantation (n = 57) showed significant increase in the yellow color grade of the stented lesion from baseline to follow-up.[124] Lesions with yellow color grade had significantly higher prevalence of thrombus than with white color grade (25% vs 5%, P < 0.01). These data may suggest that sirolimus-eluting stents promote formation of yellow plaque and is associated with an increased incidence of mural thrombus in stented lesions at 10 months follow-up.

DETECTION OF VULNERABLE PLAQUE

To date, a number of angioscopic studies have suggested that intensive yellow surface color of plaque is associated with unstable lesion morphology or clinical presentations. An early clinical study showed that yellow plaques were more common in patients with acute coronary disorders (50%) than in those with stable angina (15%) or old myocardial infarction (8%).[125] In a more recent study of 843 patients who underwent cardiac catheterization for suspected coronary disease, 1,253 yellow plaques were detected at nonstenotic (diameter stenosis < 50%) segments and were graded as 1–3 (from light to intensive yellow) using prespecified color samples.[126]

Pathophysiologic mechanisms for this association may be partly explained by structural and mechanical characteristics of yellow plaques. An experimental study using a bovine model of lipid-rich plaque showed an inverse correlation between angioscopic percent yellow saturation and histologic plaque cap thickness.[127] A similar correlation was also reported in a clinical study by comparing angioscopic surface colors and plaque cap thickness measured by OCT (Figs 31A to E).[128]

On the other hand, yellow surface color of individual plaques alone may not have a sufficiently high predictive value for future



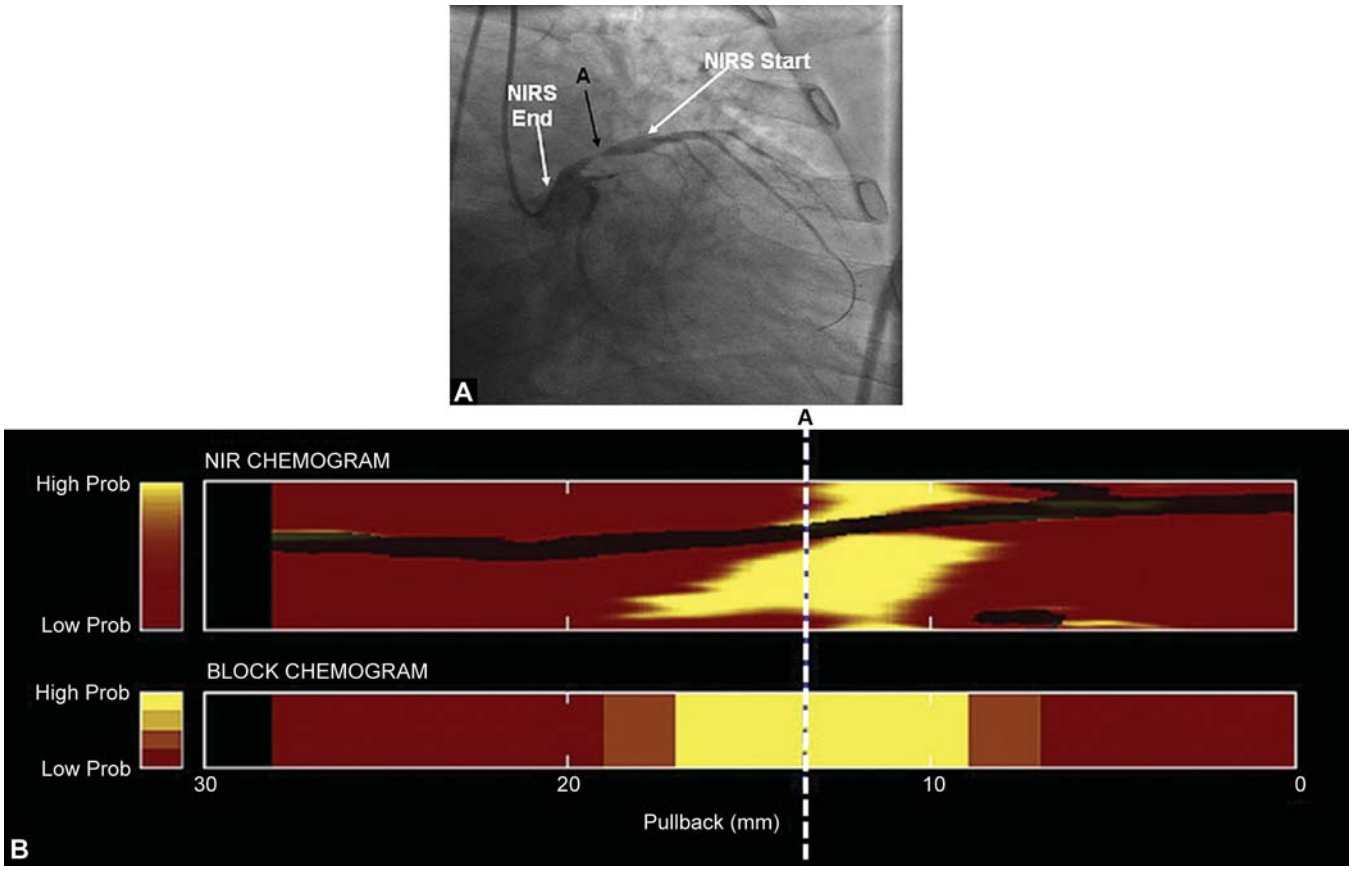
FIGURES 31A TO E: Lysophosphatidylcholine in a coronary plaque imaged by a color fluorescence angioscopy system (CFA). (A) Yellow plaque imaged by conventional angioscopy. (B and C) The CFA image of the same plaque before administration of Trypan blue dye (TB). (D and E) The CFA images after administration of TB. The plaque showed red fluorescence by both "A" and "B" imaging, indicating the existence of lysophosphatidylcholine. (*Source:* Uchida Y, et al. Imaging of lysophosphatidylcholine in human coronary plaques by color fluorescence angioscopy. Int Heart J. 2010;51:129-33)

clinical events, presumably owing to the presence of "silent" plaque rupture as well as the need of additional factors for triggering the events. Uchida and his colleagues reported the first prospective 12-month follow-up study and found that acute coronary syndromes occurred more frequently in patients with yellow plaques than in those with white plaques.[129] Moreover, the syndromes occurred more frequently in patients with glistening yellow plaques than in those with nonglistening yellow plaques, but the positive predictive values of overall yellow and glistening yellow plaques were only 28% and 69%, respectively. More recently, Asakura and his colleagues performed extensive angioscopic examination of all three major coronary arteries in patients undergoing follow-up cardiac catheterization 1 month after myocardial infarction.[130] Both infarct-related and non-infarct related coronary arteries showed equally prevalent, multiple yellow plaques (3.7 ± 1.6 vs 3.4 ± 1.8 plaques per artery, respectively), indicating a pan-coronary process of vulnerable plaque development. Clinical follow-up (931 ± 107 days) of the enrolled patients showed a secondary event rate of only 20%. On this basis, the same investigator group proposed a plaque index (number of yellow plaques multiplied by maximum color grade) and found that patients who suffered another acute event during 5-year follow-up had a higher index at baseline than patients who did not (9.5 ± 6.8 vs 4.4 ± 4.0, P = 0.02). Although angioscopic examination of the entire coronary tree is not practical in clinical settings, angioscopic plaque characterization has the potential to offer unique complementary information in the field of vulnerable plaque/patient investigation and risk stratification.

SAFETY AND LIMITATIONS

The light source of angioscopy provides a high intensity but "cold" light (low infrared content) to avoid thermal damage to the illuminated vessel wall. On the other hand, mechanical designs of the angioscope and its delivery catheter can significantly affect the safety profile of this invasive imaging tool. To date, several complications have been reported related to the occlusion cuff of the delivery catheter or transient ischemia owing to flow obstruction during imaging. Another complication is so-called wire-trapping caused by a loop formation of the guidewire between the two monorail wire channels of a particular angioscopy system. With the new over-the-wire system with no occlusion cuff, one experienced group reported a complication rate less than 1% during 1,200 procedures, but no comprehensive report of a large multicenter experience currently exists.

Despite recent technical advances, angioscopy is still limited in evaluating small vessel segments or imaging across tight stenoses. Other technical limitations include its limited



FIGURES 32A AND B: Near-infrared spectroscopy scan of a patient and corresponding angiogram. (A) Coronary angiogram of the left coronary artery of a 71-year-old man with post-infarct angina. There is a severe culprit stenosis (A) in the proximal left anterior descending artery. (B) the corresponding chemogram reveals a prominent, circumferential lipid core-containing coronary plaque signal between 8 mm and 18 mm in the area of the culprit lesion. The narrowest area of luminal stenosis is approximately 14 mm and demarcated in the chemogram (A). The block chemogram shows that the strongest lipid core-containing coronary plaque signals extended from 9–17 mm. (*Source:* Waxman S, et al. In vivo validation of a catheter-based near-infrared spectroscopy system for detection of lipid core coronary plaques. J Am Coll Cardiol Imag. 2009;2:858-68, with permission)

capability to assess inner tissue structures and the subjectivity of qualitative interpretation that potentially results in relatively large intraobserver and/or interobserver variability.

FUTURE DIRECTIONS

One technical solution to the subjective color interpretation is a quantitative colorimetric analysis of angioscopic images. In addition to the variability of lumen color perception, hardware-induced chromatic distortions can occur depending on angioscopic systems, individual catheters, illuminating light settings and spatial location of the object within the view field. Quantitative colorimetric methods measuring coronary plaque color after proper adjustment for brightness can overcome these limitations, and excellent measurement reproducibility with this technique has been reported in preliminary clinical studies.[131,132]

Molecular imaging of coronary plaques by fluorescence angioscopy is another interesting challenge. Fluorescence 'excited' through a specific band pass filter can visualize lysophosphatidylcholine, which is a major component of oxidized low-density lipoprotein and acts as a proatherogenic agent in the presence of trypan blue dye (Figs 32A and B).[133] If these molecular substances are visualized *in vivo* by using fluorescence angioscopy, more information can be acquired about the exact mechanisms of the progression of atherosclerosis.

SPECTROSCOPY

Spectroscopy determines the chemical composition of plaque substances based on the analysis of spectra induced by interaction of electromagnetic radiation, or light, with the tissue materials. To date, several forms of photonic spectroscopy have been adapted for characterization of atherosclerotic plaques, including diffuse reflectance near-infrared (NIR), Raman and fluorescence spectroscopy. When tissues are exposed to a light beam containing a broad mixture (spectrum) of wavelengths, those wavelengths absorbed by the illuminated molecules will be missing from the spectrum of the original light after it has traversed the tissue. Diffuse reflectance NIR spectroscopy analyzes the amount of this absorbance as a function of wavelengths within the NIR window (700–2,500 nm). On the other hand, Raman spectroscopy uses a light beam of a single wavelength and monitors shifts in wavelength as some of the incident photons interact with the molecules so as to gain or lose energy (i.e. shift in wavelength). Raman spectroscopy measures this inelastic scattering, or so-called Raman scattering, since it contains unique information on the substance with which the photons interacted. Under certain conditions, the photons can excite molecules to a higher energy level, the decay from which releases the energy difference in the form of light. The Raman shift is more specific for individual chemicals than is

diffuse NIR reflectance, but the signal is much weaker and therefore more difficult to detect in vivo.

Fluorescence spectroscopy uses photoluminescence or luminescent emission to identify the properties of the tissue being illuminated. Each technique has shown promising ex vivo results and is under active investigation for in vivo coronary applications.

IMAGING SYSTEMS AND PROCEDURES

Development of a catheter-based spectroscopy system for percutaneous coronary applications has faced several technical challenges. First, NIR light must be delivered to the artery and collected with minimal risk to the patient. Second, the undesirable effect of blood on the signal must be overcome. Third, the effect of coronary motion on spectra must be managed. Fourth, a scan of all major coronary arteries is needed for clinical use. One coronary catheter system overcame these problems and was approved by the United States Food and Drug Administration in 2008 (Intravascular Chemogram™, InfraReDx, Inc., Cambridge, Massachusetts). The 3.2F NIR catheter contains fiberoptic bundles for delivery and collection of light within a protective outer sheath. The rapid-exchange platform of the catheter enables advancement to the coronary segment of interest using a standard interventional technique, and can direct light to the vessel wall with a mirror, located at the tip, to acquire spectra within 20 milliseconds through flowing blood. This configuration allows not only circumferential data collection but also a complete longitudinal scan of the target segment using controlled pullback of the probe. The collected light is analyzed by a spectrometer; using a diagnostic algorithm, the processed data are color coded and displayed in a grid pattern with the spatial (circumferential and longitudinal) information. Signal acquisition is performed through a 6F guide catheter without the need for artery occlusion or blood displacement, and the process is similar in use to IVUS.

Although further improvement is still required prior to clinical testing, a miniaturized fiberoptic probe with a real-time analysis system has been developed for future intravascular application of Raman spectroscopy as well. The probe (Visionex, Atlanta, Georgia) consists of a central fiber (core diameter: 400 μm) for laser delivery and seven collection fibers (core diameter: 300 μm) around the central fiber. Both fibers have a dielectric filter to block the Raman signal generated by the fiber material. The system uses an 830 nm diode laser (Process Instruments Diode Laser, Salt Lake City, Utah) as a light source, and spectra acquisition times were reported to be 3–5 seconds for reliable detection of cholesterol and 1 second for calcium in an ex vivo setting. Although this prototype is a forward-viewing system, other investigators are also developing side-viewing catheter probes suitable for intravascular Raman scattering or fluorescence measurements.

EXPERIMENTAL DATA

Over the past decade, a number of experimental studies have reported the ability of biospectroscopy (reflectance, Raman and fluorescence) to identify the basic chemical components of atherosclerotic plaques in animal models or human arterial samples. Particularly, intensive efforts are now focused on the characterization of the specific features of plaque vulnerability. Using diffuse reflectance NIR spectroscopy, Moreno and his colleagues examined 199 human aortic samples and compared the findings with corresponding histology.[134] A diagnostic algorithm was constructed with 50% of the samples used as a reference set; blinded predictions of plaque composition were then performed on the remaining samples. The sensitivity and specificity of NIR spectroscopy for histologic plaque vulnerability were 90% and 93% for lipid pool, 77% and 93% for thin fibrous cap (< 65 μm), and 84% and 89% for inflammatory cell infiltration, respectively. Similar promising results of NIR spectroscopy to identify lipid-rich plaques have been reported in human carotid endoatherectomy[135] and coronary autopsy specimens[136] as well. Whereas these ex vivo studies were performed in a blood-free laboratory setup, a recent in vivo study using a 1.5 mm fiber-bundle NIR catheter system also showed the feasibility of intravascular NIR spectroscopy through blood.[137] In this rabbit aortic model, the catheter-based system identified lipid areas greater than 0.75 mm^2 with 78% sensitivity and 75% specificity.

Although Raman spectroscopy has a theoretical advantage in direct quantification of individual plaque components, only a small percentage of photons are recruited into the Raman shift, resulting in a low signal-to-noise ratio and poor tissue penetration. However, recent exclusive use of the NIR wavelength laser (750–850 μm), coupled with enhanced CCD array cameras, may significantly improve the signal-to-noise ratio. In addition, mathematical tools have been developed to separate the contribution of background fluorescence in the Raman spectrum. In an ex vivo study of human coronary specimens, Romer and his colleagues also demonstrated that a tissue layer of 300 μm attenuates the Raman cholesterol signals by 50% at 850 nm excitation,[138] indicating that a lipid core up to 1–1.5 mm from the lumen could still be detected with this technique. Accordingly, the first in vivo application of catheter-based, intravascular Raman spectroscopy was demonstrated by Buschman and his colleagues.[139] This experimental study showed that the in vivo intravascular Raman signal obtained from an aorta was a simple summation of signal contributions of the vessel wall and blood. More recently, a compact fiberoptic-based Raman system for in vivo applications has been developed.[140] In autopsy studies of human coronary arteries and aortas, the system detected cholesterol and calcification, indicating that Raman spectroscopy has the potential to perform plaque characterization in patients if problems of in vivo measurement can be overcome.

On the other hand, the strong fluorescence of arterial tissue is a potential advantage of fluorescence spectroscopy over Raman analysis, permitting good signal-to-noise ratio with rapid spectra acquisition. Nevertheless, the encouraging ex vivo studies with fluorescence spectroscopy has not been translated into successful in vivo applications of this technique. This is in part owing to the significant spectra attenuation and distortion by the interplay of absorption and scattering at the presence of hemoglobin. Recently, a combined approach using fluorescence and diffuse reflectance spectroscopy has been proposed to minimize this technical limitation.

TABLE 3

Characteristics of catheter-based imaging devices

	IVUS	*OCT*	*Angioscopy*	*Spectroscopy*
Resolution	100–250 μm	10–20 μm	N/A	1 mm
Penetration depth	4–8 mm	1.5–2 mm	Surface only	Several millimeter
Vessel occlusion	No	No/Yes	No/Yes	No
Morphological information	Yes	Yes	Yes	No
Remodeling/plaque distribution	+++	+	-	-
Lipid identification	+	++	+	+++
Inflammation	-	+	-	+
Thrombus	+	++	+++	-
Stent struts distribution	++	+++	+	-
Stent struts apposition	+	+++	-	-

CLINICAL EXPERIENCE

Clinical experience has been collected since a prototype device of intravascular NIR spectroscopy was developed in 2001.[141] In the preliminary study, however, substantial motion artifact was present. In 2006, the new NIR catheter system was used in patients with stable coronary artery disease at the time of PCI and showed that signals obtained in the artery differ from those obtained in blood alone.[142] This system (Intravascular Chemogram™) developed and manufactured by InfraReDx is the only commercially available NIR spectroscopy system for coronary imaging at present.[143] Initial results of the SPECTroscopic Assessment of Coronary Lipid (SPECTACL) study were reported in 2009.[144] This study was the first multicenter study designed to demonstrate the applicability of the lipid core-containing plaques detection algorithm in patients with stable coronary artery disease or acute coronary syndrome. SPECTACL trial showed spectral similarity between acquired spectra in vivo and those from autopsy data sets in 40 of 48 spectrally adequate scans (83% success rate, 95% confidence interval: 70–93%, median spectral similarity/pullback: 96%, interquartile range 10%) (Fig. 32). These findings suggest the feasibility of invasive detection of coronary lipid core-containing plaques with this NIR spectroscopy system. Although the current NIR spectroscopy system can provide compositional information but not structural information like IVUS, intravascular investigation of chemical composition of a coronary plaque has the possibility to offer useful insights into risk stratification and clinical management of vulnerable plaques/patients. Table 3 shows characteristics of NIR spectroscopy and in comparison with other light-based diagnostic techniques.

SAFETY AND LIMITATIONS

The preliminary study of the NIR spectroscopy system confirmed that clinical outcomes did not differ from those expected with stenting and IVUS usage.[144] No device-related adverse events occurred. However, the safety of NIR spectroscopy has not been well established in a large number of patients. In addition, unacceptably high rates of failure to obtain adequate data were seen in early clinical experience.

FUTURE DIRECTIONS

A catheter-based spectroscopy device combined with another structural imaging modality, such as IVUS or OCT, may allow comprehensive plaque evaluation by providing both chemical and anatomical information. In fact, one combined coronary catheter system (NIR spectroscopy combined with IVUS) has been developed and is under clinical evaluation (LipiScan IVUS system™, InfraReDx, Inc).[145]

Another interesting concept is to use diffuse reflectance NIR spectroscopy for in situ measurement of tissue pH or lactate concentration in atherosclerotic plaques. These metabolic parameters may indicate the activity of macrophages and other inflammatory cells, offering additional functional measures of plaque vulnerability. The feasibility of this technique has been demonstrated in an ex vivo study using human carotid endoatherectomy specimens,[146] and further technical refinements are awaited for future clinical applications.

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Chapter 21

Cardiovascular Nuclear Medicine—Nuclear Cardiology

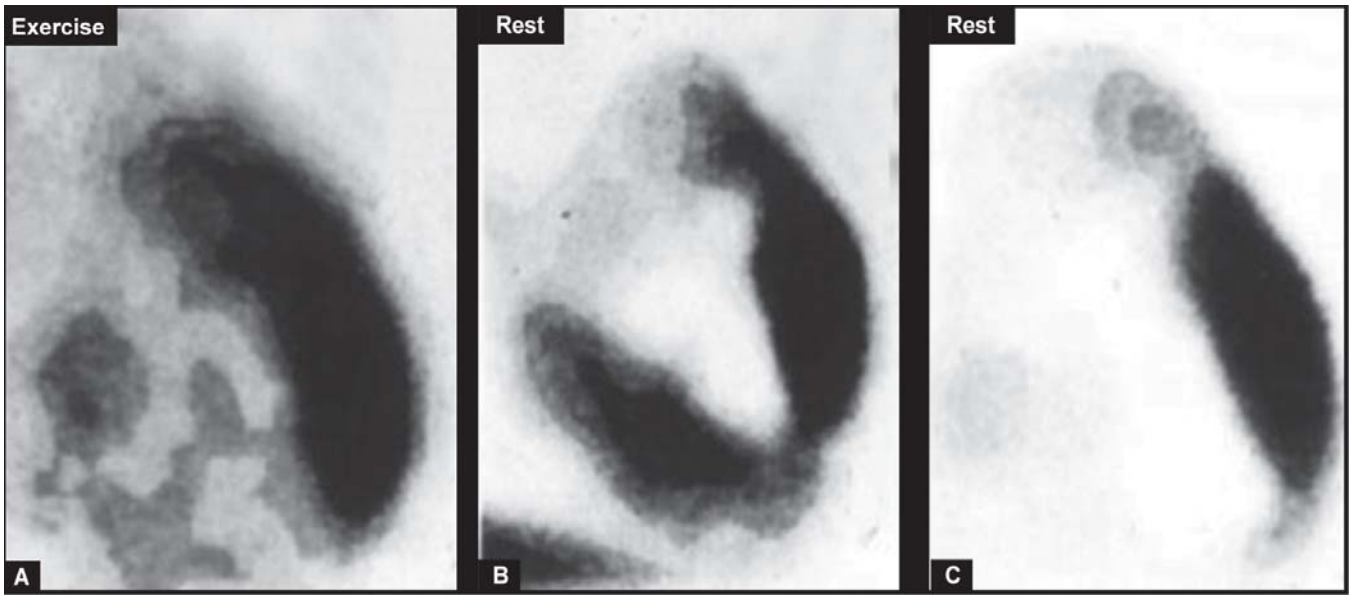
Elias H Botvinick

Chapter Outline

- Pathophysiologic Considerations
  - Lesion Severity
  - Owing to Stress Testing Deficiencies
  - The Ischemic Cascade
  - Stress Testing
- Myocardial Perfusion Imaging
  - Image Acquisition Protocols
  - Image Display
  - Gated—Myocardial Perfusion Imaging
  - Interpretation
  - Diagnostic Accuracy and Cost Effectiveness
  - Indicators of Multivessel Coronary Artery Disease and Related Risk
  - Nonperfusion Indicators of CAD-Related Risk—Lung/Heart Ratio
  - Transient Ischemic Dilation
  - Dense Cavitary Photopenia
  - Clinical Applications of Myocardial Perfusion Imaging in the Emergency Department—with Acute Chest Pain Syndromes
  - Unstable Angina/Non-ST Elevation Myocardial Infarction
  - Follow-up after Initial ACS Evaluation Strategy
- Risk Assessment of General and Specific Patient Populations
  - General Principles
  - Preoperative Evaluation for Noncardiac Surgery
  - The Evaluation of CAD in Women
  - Diabetics
  - Myocardial Perfusion Imaging in the Elderly
  - Postrevascularization
  - Heart Failure
  - Appropriateness Criteria for Perfusion Imaging
- Positron Emission Tomography Perfusion and Metabolism
  - PET and SPECT Technology
- Imaging Myocardial Viability
  - The Principles
  - Nonscintigraphic Imaging Options
  - Scintigraphic Imaging Options—Perfusion Related
  - Scintigraphic Imaging Options—Metabolism Based
- Imaging Perfusion
  - Rubidium (^{82}Rb) Chloride
  - Nitrogen (^{13}N) Ammonia
- Quantitation of Regional Coronary Flow and Flow Reserve
- Blood Pool Imaging—Equilibrium Radionuclide Angiography and First Pass Radionuclide Angiography
  - Guidelines
  - Introduction
  - Labeling the Blood Pool
- First Pass Curve Analysis
  - Ventricular Function
  - Left-to-Right Shunt Analysis
- Equilibrium Gated Imaging—ERNA
- The Value of Functional Imaging
- Phase Analysis
- Imaging Myocardial Sympathetic Innervation
- Radiation Concerns

INTRODUCTION

The primary advantage of nuclear medicine methods is their ability to image physiology.[1] Nowhere is this more apparent and valued then in their cardiac applications. Approximately 8,000,000–10,000,000 nuclear cardiology studies are performed each year in the USA. Most of these are stress single photon emission computed tomography (SPECT) perfusion studies performed for the diagnosis, localization and risk stratification of coronary artery disease (CAD). With its growing availability of positron emission tomography (PET) myocardial perfusion studies are increasingly applied. Positron emission tomography, with its added resolution, accuracy and quantitative ability, competes with SPECT studies and the increasingly diverse choice of noninvasive imaging methods in CAD. These and other scintigraphic methods used to evaluate ventricular function, myocardial synchrony, metabolism, innervation and necrosis are evolving. The field is invigorated by new instrumentation, new acquisition, processing and display hardware and software, new stress testing (ST) and imaging agents and the



FIGURES 1A TO C: Myocardium at ischemic risk. Shown are digital enhanced, (A) planar exercise and (B) rest myocardial perfusion scintigrams from a patient with right coronary artery (RCA) stenosis estimated to be 40%. Although somewhat contoured by the processing, the scintigrams clearly reveal evidence of reversible inferior ischemia. (C) Subsequently, the patient had a spontaneous infarction of the same region, as shown on the rest image. This study illustrates the difference between angiographic anatomy and scintigraphic pathophysiology, and provides one form of evidence for the ability of scintigraphy to identify myocardium at ischemic risk. (*Source:* Goris M, MD, Stanford University, Palo Alto, CA)

integration of computed tomographic methods. Scintigraphic methods are finding new applications in acute coronary syndromes (ACSs), heart failure and electrophysiologic conditions. This review will consider these methods in their current and potential clinical roles, with reflection on the principles of cardiac and coronary physiology in which they are based.

PATHOPHYSIOLOGIC CONSIDERATIONS

LESION SEVERITY

(See Chapter "Changing focus in global burden of cardiovascular diseases") Some studies support the assumed relationship between lesion severity and events, and directly relate the presence of a severely stenotic lesion to regional ischemic risk[2] (Figs 1A to C). However, several angiographic studies demonstrate that acute coronary occlusion and resultant myocardial infarction (MI), not uncommonly relate to vessels which may not have "significant" coronary lesions when assessed a variable time before that event.[3,4] Many of these studies are biased by their retrospective nature, the lack of coronary evaluation shortly prior to the event and the exclusion of patients with the most severe lesions and prior revascularization. When analyzed quantitatively, on a vessel-by-vessel basis, since severely stenotic vessels are far less frequent than those with modest narrowing, the likelihood of an event precipitated by occlusion of a tightly stenotic vessel far exceeds the likelihood of an event related to occlusion of any insignificantly stenotic vessel, even when most events occur in relation to less stenotic vessels.[5] Nonetheless, coronary occlusion may, not uncommonly, involve vessels which are not significantly stenotic and in such cases, coronary occlusion and related prognosis is determined by some condition other than the degree of coronary stenosis. Yet clinically, coronary related risk is clearly correlated with the extent and severity angiographic stenosis as revealed by myocardial perfusion imaging (MPI) defect extent and severity, the timing, severity and extent of stress induced ST changes and wall motion abnormalities. The prognostic value of methods based on lesion severity is well established and strongly relied upon in clinical decision making. So how can these apparently mutually exclusive observations be reconciled? How can coronary events be predicted based on findings which relate directly to the severity and extent of CAD when these events do not necessarily relate to even flow limiting lesions?

The conclusion that coronary occlusion may occur in vessels with stenosis of varying significance is unavoidable and may relate to factors regulating the stability of atheromata. Perhaps the relationship of ischemic parameters to prognosis and events is due to the fact that severe ischemic disease identified by these methods, also likely occurs in the presence of numerous lesser lesions, which occur in some proportion to lesion severity. All contribute to the "total ischemic burden"[6] and it is this factor linking events to lesion severity.[7]

In any given patient, the likelihood of a coronary occlusion varies directly with the "ischemic (or plaque) burden", the full extent of myocardium subtended by all atherosclerotic vessels and presumably representing all myocardium which may be involved with an acute coronary occlusion and event. It appears that cardiac risk is directly, or indirectly, related to the "ischemic burden", the extent and pathophysiologic, but not necessarily anatomic, severity of coronary lesions. A more physiologic index, the "ischemic burden" generally correlates well with the magnitude of the vascular hyperemic response, the coronary

TABLE 1

Scintigraphic evidence of extensive myocardium at ischemic risk and related poor prognosis based on gated single-photon perfusion imaging

- Extensive, severe, reversible defects
- Modest or severe defects at a low level of stress or accompanied by extensive fixed defects
- Perfusion defects outside the infarct zone in patients with prior MI
- Stress related lung uptake or cavitary dilation
- Extensive, stress induced wall motion abnormalities or a reduced LVEF or increased LV end-diastolic volume with stress, especially with stress induced perfusion defects
- Reduced rest LVEF with extensive, severe CAD with limited fixed or reversible defects

flow reserve (CFR). As a measure of CFR, MPI is a noninvasive measure of the presence of flow limiting coronary lesions, of the extent of myocardium at ischemic risk[8] and, indirectly, of the "ischemic burden". Studies which reveal a relationship between the severity of coronary stenosis, a measure of the extent of "myocardium at ischemic risk", and events, may reflect their ability to image the "ischemic burden". However neither the quantitative measure of coronary stenosis nor its effect on CFR permits the prediction of plaque rupture and an acute coronary event.[9]

OWING TO STRESS TESTING DEFICIENCIES

(See Chapter "Electrocardiogram") MPI is being increasingly applied to identify and monitor high risk CAD patients (Table 1), and assess the varied benefits of medical versus revascularization therapy.[10] It presents the possibility of differentiating those at risk for death versus acute MI, with their different preventive and treatment measures. This differentiation presents a basis for management decisions among high risk CAD patients.[11-12a]

THE ISCHEMIC CASCADE

(See Chapter "Evaluation of chest pain") The high resistance of the coronary bed at rest normally permits vigorous flow augmentation of three to five times rest levels, with stress induced dilation. This augmentation represents the CFR. Compensatory vasodilation in the presence of significant stenoses, supports normal flow at rest until stenosis becomes subtotal and compensation fails.[14] The dilated resistance bed of the stenotic vessel has reduced or blunted flow reserve compared with that of the patent vessel, which maintains its full vasodilator reserve. A reduced hyperemic response with stress or reduced CFR is the primary abnormality exposed with ST and relates to myocardial ischemia with the increased flow demands of exercise testing and to flow heterogeneity, generally without ischemia, when imposed by direct coronary dilation. When ischemia is induced with exercise or with occasional vasodilator related "coronary steal", the ischemic indicators of reduced perfusion, diastolic dysfunction, systolic dysfunction, electrocardiographic (ECG) changes and pain, will appear in this sequence as described by the "ischemic cascade". This sequence can be seen during percutaneous intervention (PCI) and provides an explanation for: breathlessness as an early ischemic indicator; the occurrence of "silent ischemia"; and the fact that the perfusion ischemic indicator on ST, the earliest ischemic change, has proven to be the most diagnostic and prognostic parameter for clinical decision making.

STRESS TESTING

Dynamic Exercise Testing

(See Chapter "Electrocardiogram")[12] Image findings must be interpreted in the light of the findings on related stress test. Exercise testing seeks to incrementally augment exercise workload and related myocardial oxygen demands, heart rate and afterload, or its surrogate, systolic blood pressure. These then increase flow demands, and so tests the CFR. Tests are generally *maximal*, that is performed to a symptom or safety limited endpoint. An *adequate* or *inadequate* exercise test simply indicates that the test did or did not adequately address the clinical question for which it was indicated and ordered. An *optimal* or *suboptimal* exercise test indicates that the test did or did not fully test the CFR, stimulating maximal coronary vasodilation by reaching a high level of myocardial oxygen and flow demand. This optimal level generally requires the attainment of 85% of predicted heart rate for age or a double (rate x pressure) product in the range of 20,000–25,000. Maximal tests, especially when negative, may yet be inadequate and suboptimal. In such cases and others, where patients cannot perform exercise stress adequately for the clinical need, pharmacologic ST is indicated.

Pharmacologic Stress Testing

The direct coronary vasodilators adenosine, regadenoson, an adenosine analog and dipyridamole[12,13] (Figs 2 and 3) act directly on the coronary resistance vessels to augment coronary flow and test the CFR (Tables 2 and 3). They uncommonly cause myocardial ischemia by a "coronary steal" mechanism, where reduced resistance in the normal bed, eliminates the pressure gradient driving collateral flow, resulting in ischemia in beds perfused by severely stenotic vessels. Ischemic ST changes, induced with "steal" in the setting of vasodilator stress are very

TABLE 2

The mechanism of stress testing (testing the CFR—the hyperemic flow response

Direct tests of CFR (Vasodilator stress agents)
- Seeks to provoke flow heterogeneity
- Best suited for the perfusion ischemic endpoint
- Less likely influenced by beta blockers
- Strongest, most reproducible tests of CFR

Indirect tests of CFR (Exercise/dobutamine)
- Seek to provoke ischemia (perfusion or wall motion abnormality)
- Suites either perfusion of function ischemic endpoint
- Vary in ability to augment flow demands and test CFR
- Permit serial function analysis

Source: Botvinick EH. Stress imaging: Current clinical options for the diagnosis, localization and evaluation of coronary artery disease. Med Clin N Amer. 1995;79:1025-61

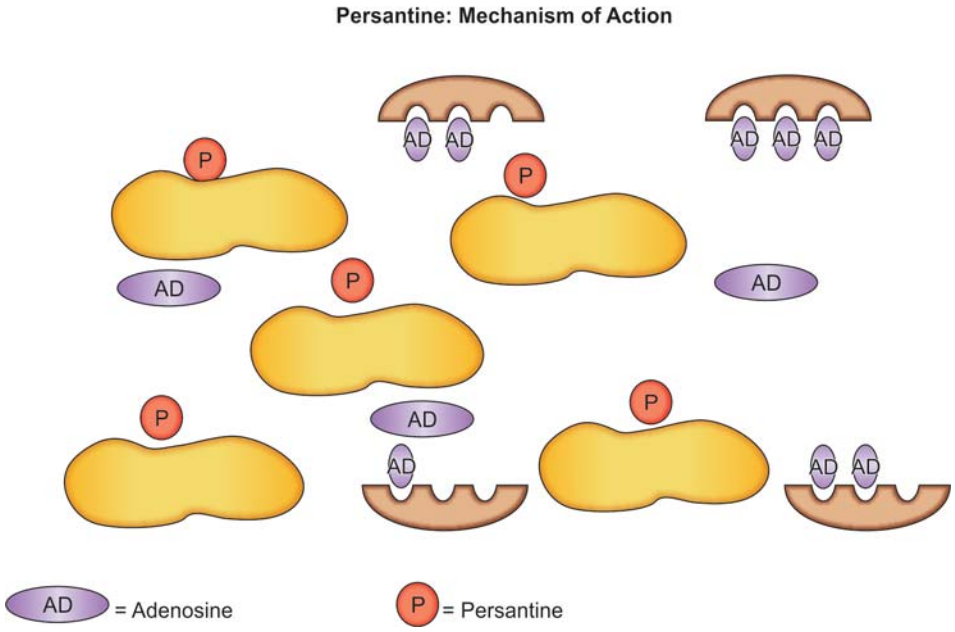


FIGURE 2: Dipyridamole effect. The elevated blood adenosine levels produced by dipyridamole (persantine, P) induced inhibition of adenosine degradation, find coronary endothelial binding sites and cause vigorous coronary dilation (*Source:* Modified from Self Study Program III; Nuclear Medicine: Cardiology Topic 2-Pharmacologic Stress and Associated Topics. Soc Nucl Med Publ. 1998)

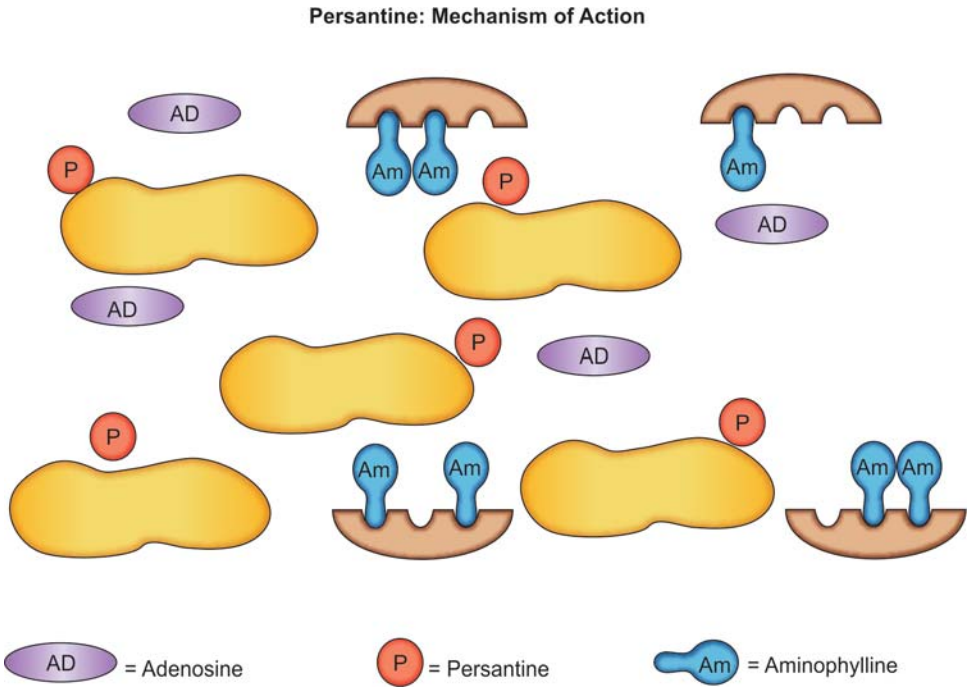


FIGURE 3: Vasodilator antidote. The effects of adenosine can be terminated, and the effects of vasodilation and pharmacologic stress ended by the administration of aminophylline which preferentially binds the adenosine binding site. Dipyridamole continues active for an additional 30–60 minutes, however, and adenosine levels remain elevated for 30–60 minutes theoretically, vasodilation can recur if aminophylline effects subside while dipyridamole persists and before adenosine levels fall. Such a prolonged effect can be avoided with direct adenosine infusion or use of Regadenoson, Lexiscan (*Source:* Modified from Self Study Program III; Nuclear Medicine: Cardiology Topic 2-Pharmacologic Stress and Associated Topics. Soc Nucl Med Publ. 1998)

specific for ischemia.[14] More typically the method produces heterogeneous coronary flow augmentation with related abnormalities on MPI in the absence of induced ischemia. Regardless of the mechanism, the diagnostic and prognostic value of vasodilator stress imaging is equal to that of maximal and optimal exercise stress imaging, well able to induce abnormalities of the CFR generally without inducing ischemia. These vasodilators are the most widely applied pharmacologic stress agents in the nuclear medicine laboratory (Tables 2 and 3). Dobutamine, an ischemic stress agent, is widely applied for pharmacologic stress in the echocardiography laboratory but less frequently in the nuclear lab due to the presence of better and safer agents. It is prohibited in the setting of a variety of ischemic, hypertensive and other conditions which are aggravated by its effects. The 3 minute "stages" of the incremental titration dobutamine stress protocol are a poor match for its 2.4 minutes half time, bringing a delayed, poorly controlled and sometimes dangerous response. Even with these inclusions, the mortality and morbidity of dobutamine stress has been shown to be about tenfold greater than that of vasodilator or exercise stress.[15] Although some European investigators advocate its use, vasodilator agents are not generally applied with echocardiography which seeks a decremental wall motion response, a marker for true ischemia

TABLE 3

Pharmacologic stress agents

	Dipyridamole	*Adenosine*	*Regodenoson*	*Dobutamine*
Source	Synthetic	Natural	Synthetic	Synthetic
Mechanism	Tests CFR	Tests CFR	Tests CFR	Ischemic stress
Action of CFR	Indirect	Direct	Indirect	Indirect
Administration	IV infusion	IV infusion	Bolus	IV infusion
Agent preparation	Mix mg/kg dose	Mix mg/kg dose	Single dose ampule	Mix mg/kg dose
Agent duration	Prolonged	Very short	Short	Short
Stress test duration (uncomplicated)	7 min	< 6 min	5 min	> 15 min
Prognostic value	High	High	NA	Modest
Patient exclusions	Rare	Rare	Rare	Common
Patient tolerance	High	High	Very high	Modest
Arrhythmia	Rare	Rare	Rare	Not infrequent
Safety	Like ETT	Like ETT	Like ETT	Less than ETT (many patient exclusions)
End test/Antidote	Aminophylline	Discontinue/ Aminophylline	Aminophylline	Beta blocker
Speed of reversal	Minutes	Seconds	Seconds	Minutes
Diagnostic indicator	Perfusion	Perfusion	Perfusion	Perfusion/wall motion

which is rarely induced by these agents. In the absence of a reliable perfusion marker and any other alternative stress method, dobutamine is applied widely by those who seek to use echocardiography as the stress imaging modality, but used rarely in the nuclear lab in selected patients when the risk of vasodilators is prohibitive. Many of the prohibitions of vasodilator stress which serve as justification for some to apply dobutamine relate to the potential for bronchospasm and can be overcome with an incrementally titrated infusion of adenosine or the new agent regadenoson. Of course dobutamine perfusion scintigraphy, while less desirable than vasodilator pharmacologic stress imaging, has demonstrated greater sensitivity for CAD detection than dobutamine stress echocardiography.[16]

MYOCARDIAL PERFUSION IMAGING

IMAGE ACQUISITION PROTOCOLS

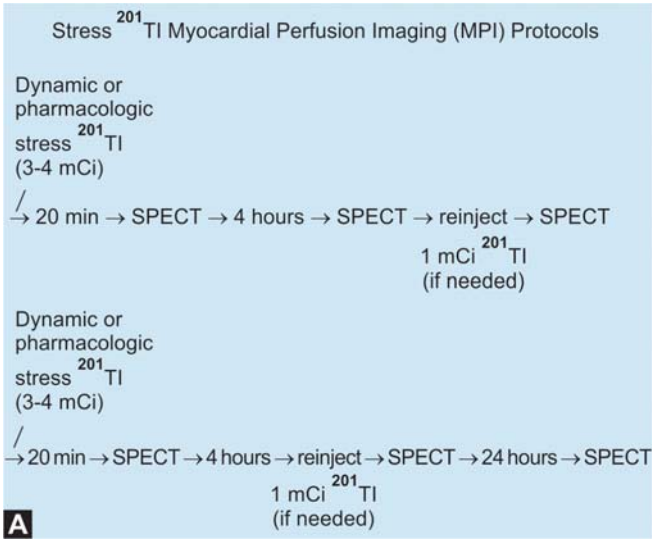
Protocols for ST with exercise, regadenoson, adenosine, dipyridamole and dobutamine have been established. The imaging protocols, whether one or two day, applying ^{99m}Tc-based sestamibi or tetrofosmin or combined radiotracers, performed in the sequence of rest versus stress or the reverse, are varied and may be individualized to the patient and laboratory[17] (Figs 4A to D). Adding low level exercise to vasodilator stress appears to reduce background image activity, but adds nothing to diagnostic accuracy. Although there are differences in linearity with flow, excretion pattern and target to background ratio,[18] (Figs 5 and 6) ^{99m}Tc sestamibi and ^{99m}Tc tetrofosmin have similar diagnostic sensitivity and clinical utility. Each protocol has its advantages and disadvantages. However ^{201}Tl has fallen from use due to its low emission energy, long half-life and related poor image resolution and relatively high radiation exposure. Regardless of the protocol employed, the scintigraphic method, as all, remains imperfect.

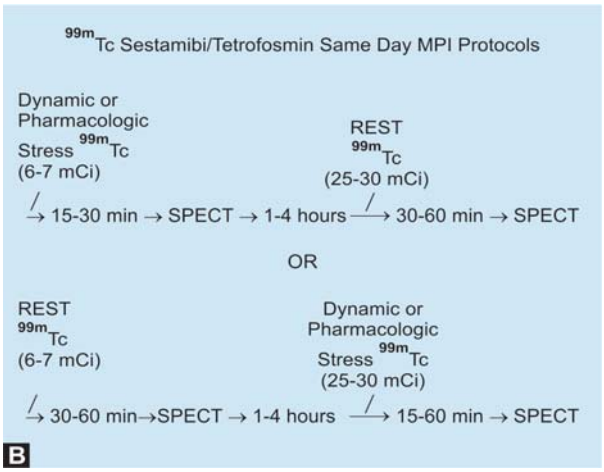
IMAGE DISPLAY

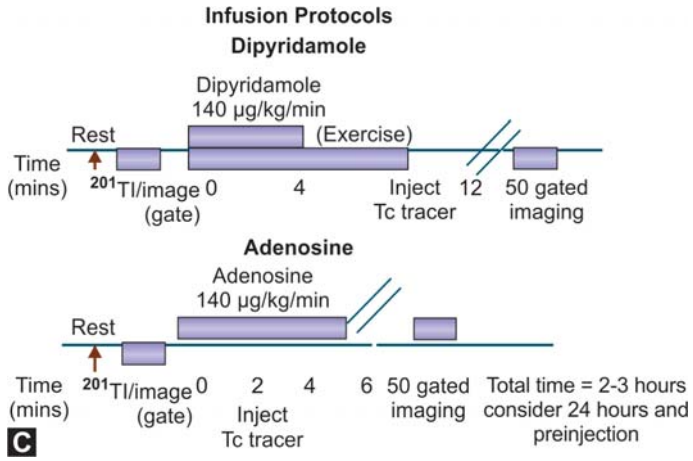
The perfusion image display divides the left ventricular (LV) myocardium into 17 or 20 segments which may be grouped to represent the distribution of the three coronary arteries on a polar map of regional LV activity[19] (Figs 7 to 10). An objective 5-point semi-quantitative scoring system is applied in each segment to grade the severity and together, the extent, of regional and global myocardial perfusion defects. The resultant summed stress scores (SSS), summed rest scores (SRS) and summed difference or reversibility scores (SDS) have established prognostic value. Here a score of 9–13 relates to an increased infarct risk in the year after testing and scores greater than 13 relate to an increased incidence of death, generally recommending selective coronary angiography (SCA) and, where appropriate, coronary revascularization. A standard image formatting method for nuclear medicine, cardiology, radiology and all of medicine, digital imaging and communications in medicine (DICOM), has been established and is compatible with other imaging modalities, display devices and data storage systems.[20]

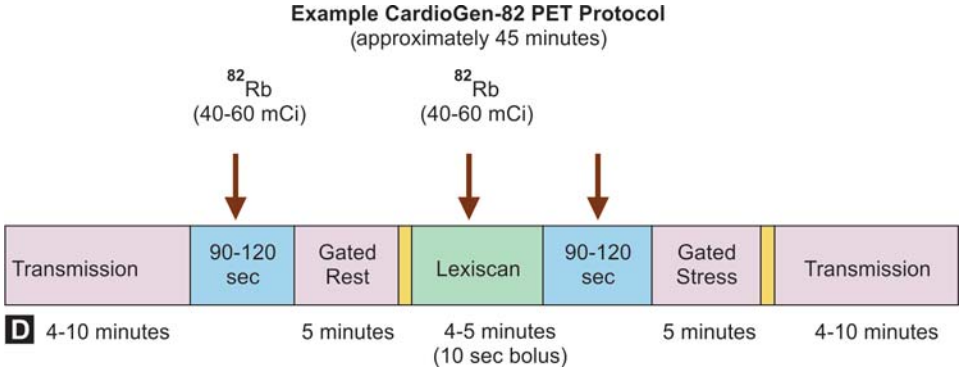
GATED—MYOCARDIAL PERFUSION IMAGING

^{99m}Tc-based perfusion tracers permit a high injected dose and allow acquisition of gated studies with adequate count statistics in each of 8 or 16 frames. Gated studies and their assessment of LV systolic function add to the ability of the perfusion method to risk stratify CAD where decremental left ventricular ejection fraction (LVEF) with stress, raises dramatically the prognostic risk related to any image perfusion defect.[21] The "partial volume effect"[22] produces intensity changes linearly related to myocardial wall thickening, the basis for accuracy in the measurement of percent wall thickening on gated perfusion images (Figs 11 and 12). The intensity variation accompanying myocardial thickening closely correlates with percentage wall thickening. Calculation of diastolic dysfunction is possible, but beset with pitfalls. Gating aids the differentiation of perfusion









FIGURES 4A TO D: (A) ^{201}Tl based protocols—shown diagrammatically is the sequence of stress-rest ^{201}Tl perfusion imaging protocol. A number of permutations may be applied for delayed redistribution and reinjection in order to capture the full extent of myocardial viability. Two such possibilities are illustrated; (B) ^{99m}Tc based protocols—shown diagrammatically is the sequence of the stress-rest and rest-stress 1 day protocols. The latter is preferred since it provides an uncontaminated rest image and gives the highest dose of the imaging agent during stress, where image resolution is most required and gating most beneficial. Each of these is aided by the higher radionuclide dose. Radiation exposure may best be limited in relatively low likelihood patients by performing a stress only study. Rest imaging may be performed subsequently only if needed; (C) Dual isotope sequential perfusion imaging protocol—shown diagrammatically is the sequence of the dual isotope sequential perfusion imaging protocol. With expectation of image abnormality at rest, prior infarction or known abnormal left ventricular wall motion and patient access, ^{201}Tl can be injected the day before stress imaging. The subsequent rest ^{201}Tl image will have been "preinjected". Imaged 24 hours later, before stress ^{99m}Tc administration, these delayed ^{201}Tl images will provide the ultimate for viability evaluation. The protocol is quick and cost-effective in busy labs. Until recently, this was the most popular, most widely applied protocol. Some have now raised concerns regarding the related radiation exposure when compared with other, ^{99m}Tc based protocols (see radiation concerns in the text); (D) ^{82}Rb PET MPI protocol—shown diagrammatically is the ^{82}Rb PET MPI protocol with Regadenoson, Lexiscan as the pharmacologic stress agent. The method employs the CardioGen Rb-82 generator. Owing to the short half-life of the radionuclide, it can be used only for pharmacologic stress evaluation (*Source:* (4A to C) Botvinick EH, MD, UCSF, San Francisco, CA; (4D) Modified from DiCarli MF. Major achievements in nuclear cardiology XI. Advances in positron emission tomography. J Nucl Cardiol. 2004;11:719-32)

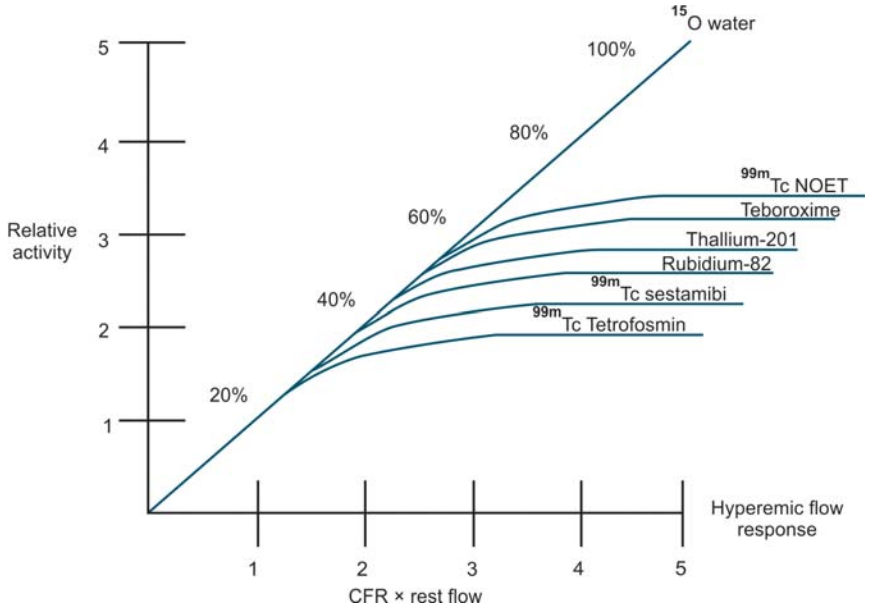


FIGURE 5

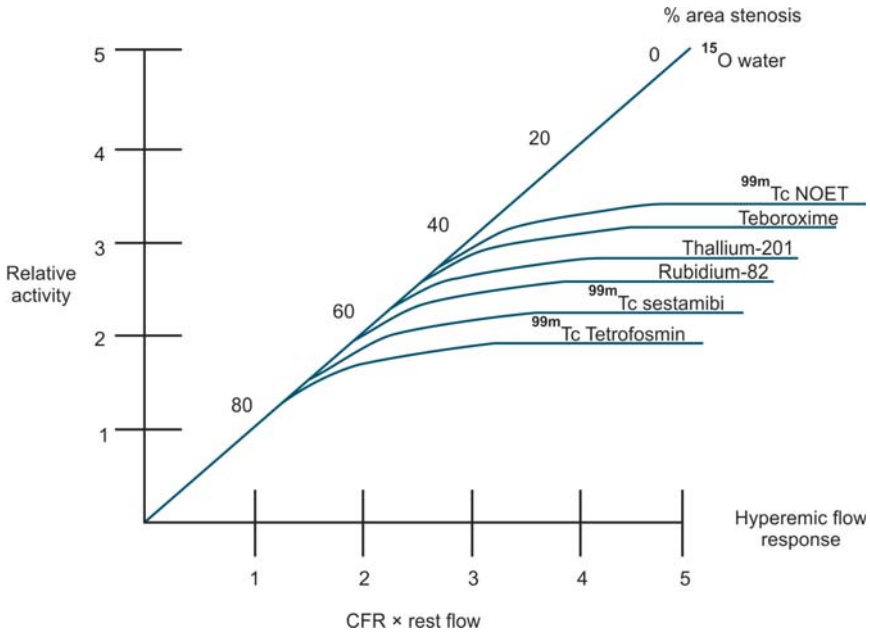


FIGURE 6

FIGURES 5 AND 6: Linearity with flow. Shown diagrammatically in both the figures is the relationship between their myocardial uptake and regional myocardial blood flow or coronary flow reserve, measured in multiples of resting flow (CFR x Rest Flow), for a variety of the available and proposed perfusion agents. Each agent departs from the diagonal line of identity or complete flow linearity, at the approximate limit of their specific linearity with flow. In Figure 5, the line of linearity is labeled with the percentage of the CFR reflecting a linear flow relationship at any given level. In Figure 6, the perfusion agents are similarly plotted, but now the range of percent stenosis related to the CFR is approximated. All agents have a high sensitivity for tight, severely stenotic, lesions. However, less severe, less flow limiting agents will be best identified by agents with greater flow linearity. As is evident here, agents with better linearity with flow are needed. While ^{15}O water demonstrates absolute linearity with flow, it is not used clinically owing to its short half-life and other unfavorable properties. The preservation of radionuclide distribution in a linear relationship to flow is an important indicator of its success as a marker of the regional myocardial perfusion. When the blunted hyperemic flow response related to a given level of stenosis exceeds the level of tracer linearity with flow, the tracer concentration and image intensity matches that of the normal flow response and so cannot be identified as abnormal. The greater the tracer flow linearity the higher it can track the blunted hyperemic response. Greater obstruction brings greater abnormalities of the hyperemic response and greater compatibility with the linearity of the agents, making the identification of tighter lesions more successful. Differences in flow linearity relate to the ability of the tracer to identify abnormal responses related to less stenotic vessels in the higher range of the abnormal flow response. Thus, all other factors being equal, the greater the linearity with flow the greater the ability of the agent to identify less severe, but significant lesions, and the higher its expected sensitivity. This data again indicates the fact that the high prognostic value of the method appears to relate to the fact that most events do, in fact, relate to the presence of a severe stenosis, somewhere in the coronary bed. ^{99m}Tc Teboroxime is an FDA approved perfusion imaging agent which has been withdrawn from the market when its rapid extraction feature was found to be incompatible with the slower rate of SPECT acquisition. However it seems quite optimal for rapid dynamic methods of SPECT acquisition now being studied to gain quantitation of regional perfusion. ^{99m}Tc NOET (bis (N-ethoxy, N-ethyl dithiocarbamato) nitrido ^{99m}Tc (V)) (TcN-NOET) is a member of a new group of cardiac imaging agents with a technetium nitido core. It is a neutral lipophilic cardiac perfusion imaging agent with the highest linear relationship to flow among all agents so far evaluated. Not yet FDA approved, it promises to be a “hot spot” label for ischemic and viable myocardium with traits similar to ^{201}Tl including redistribution, and the additional advantages of its ^{99m}Tc label (*Source:* Botvinick EH, MD, UCSF, San Francisco, CA)

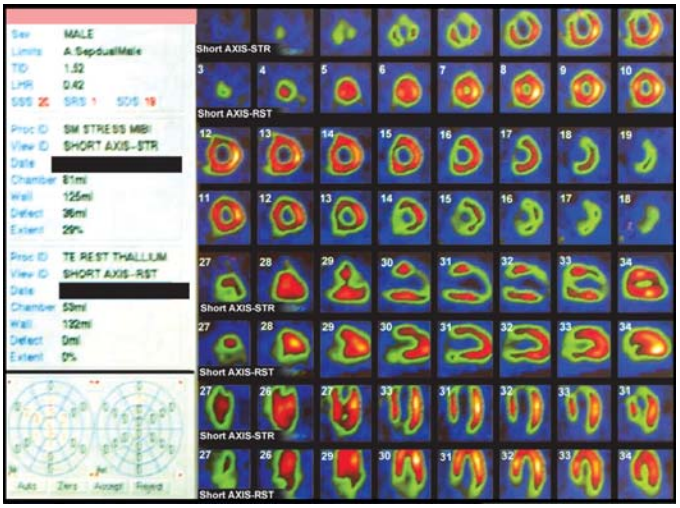


FIGURE 7

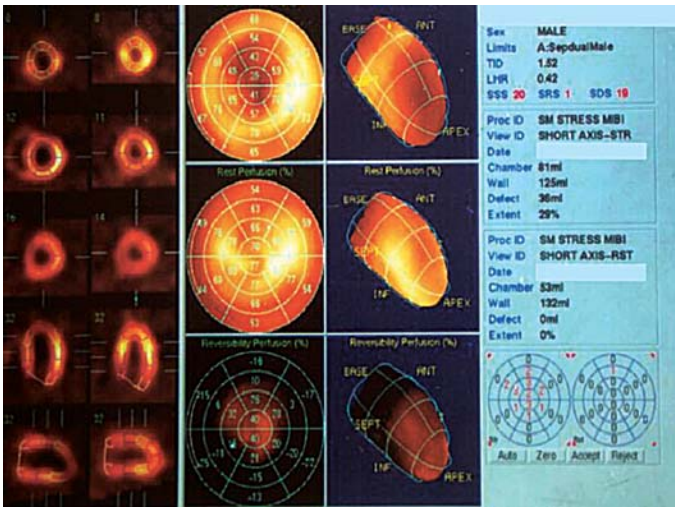


FIGURE 8

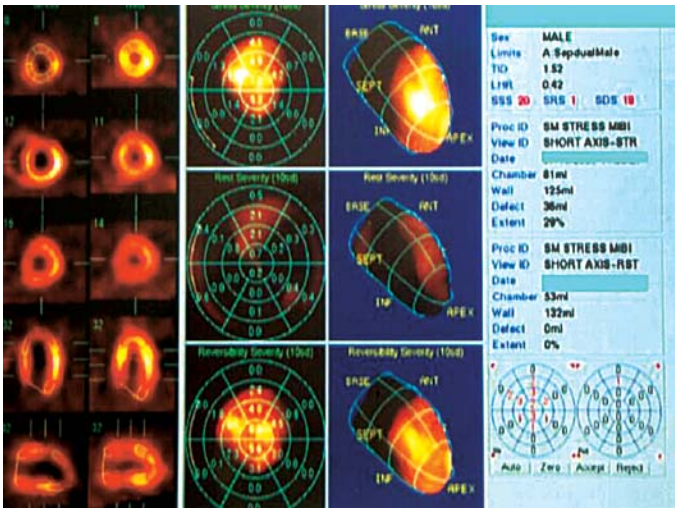


FIGURE 9

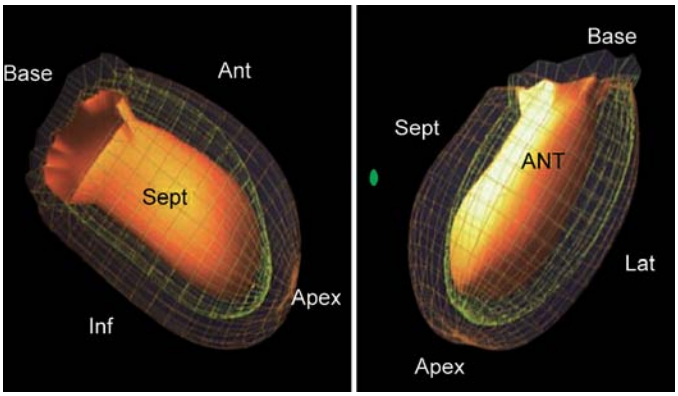


FIGURE 10

FIGURES 7 TO 10: Gated perfusion imaging identification of critical coronary disease and a high prognostic risk. AutoQuant (Cedars Sinai Medical Center, LA) is one of the several commercially available software packages for quality assurance, analysis, quantitation and display of myocardial perfusion images and related data.

Shown in Figure 7 in the first 4 rows according to the standard AutoQuant formatted display are: short axis slices from apex (left) to base (right), vertical long axis slices from septum (left) to lateral wall (right) in the next 2 rows, and horizontal long axis slices, from inferior wall (left) to anterior wall (right), in the bottom 4 rows, in a 49-year-old man with atypical chest pain and no other apparent coronary risk factors. In each image set exercise stress related ^{99m}Tc sestamibi images are above, while the rest ^{201}Tl images are below, in this study acquired by the dual isotope sequential rest ^{201}Tl /^{99m}Tc sestamibi gated SPECT protocol. The patient exercised 10 minutes of a standard Bruce protocol, stopping with shortness of breath, with ST changes suggesting ischemia. Unlike the stress test, here the image gives a clear reading and sets a clinical management approach. A large, clear reversible defect in the distribution of the left anterior descending coronary artery is suggested with accompanying cavitary dilation. A review of associated images and materials suggested no technical issues in this man of normal size. The polar map summed stress score (SSS) of 20 (*Source:* Reproduced from Botvinick EH, MD, UCSF, San Francisco, CA)

Figure 8 demonstrates the AutoQuant display of regional perfusion related activity data, QPS, and the method of quantitation and standardization of perfusion defect size. Sample rest and stress slices are shown in the left 2 panels. Here, in the third panel, a 20 segment polar map is used. In the top frame, relative activity is painted on the stress polar map, with a similar map for the rest study below. At bottom, the difference map is shown. These values are painted on a model left ventricle at right and patient related and study generated information is shown at far right. Chamber, defect and wall volumes are presented, as is the polar map scores for rest and stress images at lower right where the SSS = 20 and SRS (summed rest score) = 1 or normal. Also shown at upper right are the lung-heart ratio (LHR) and the transient ischemic dilation ratio (TID). With the dual isotope protocol, this ratio could be as high as 1.30 owing to the different scatter and resolution of the tracers and the apparent differences in resultant wall thickness and cavitary size. This figure presents regional polar data in segmental standard deviations (SD) from the normal values generated by application of the protocol to gender matched normal subjects. These SD values are translated by an established table to the polar map scores at lower right (*Source:* Botvinick EH, MD, UCSF, San Francisco, CA)

Figure 9 presents regional polar data in segmental standard deviations (SD) from the normal values generated by application of the specific protocol to gender matched normal subjects. These SD values are translated by an established table to the polar map scores at lower right (*Source:* Botvinick EH, MD, UCSF, San Francisco, CA)

Figure 10 illustrates the left ventricular contour derived from the epicardial (orange mesh), and endocardial contours at end diastole (yellow mesh) and end systole (solid orange region) derived from the gated stress perfusion images in the patient illustrated in Figures 7 to 10. A clear septal wall motion abnormality is seen. Rest wall motion was normal here and this stress induced wall motion abnormality at once confirms the perfusion defect and the presence of coronary disease and also adds to its prognostic risk (Abbreviations: ANT: Anterior wall; INF: Inferior wall; SEPT: Septal wall; LAT: Lateral wall) (*Source:* Botvinick EH, MD, UCSF, San Francisco, CA)

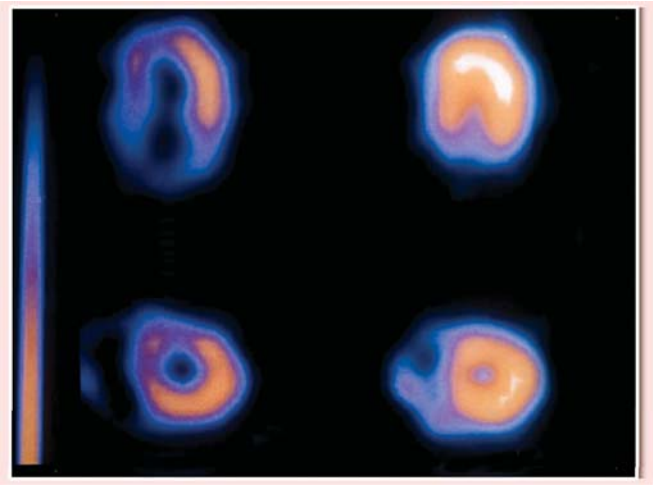


FIGURE 11: Gated sestamibi imaging. Shown are end diastolic (left) and end systolic (right) gated ^{99m}Tc sestamibi perfusion images in a normal heart in selected short (above) and horizontal long axis (below) SPECT slices. Inward systolic motion is evident as well as brightening, or increased intensity during systole. The latter, a result of partial volume effect, is well correlated with myocardial thickening (*Source:* Modified from Botvinick EH, Dae M, O'Connell JW, et al. The scintigraphic evaluation of the cardiovascular system. In: Parmley WW, Chatterjee K (Eds). Cardiology. Philadelphia: JB Lippincott; 1991)

defects and attenuation artifacts, where preserved regional motion in areas of "fixed" defects suggests attenuation; coronary and noncoronary cardiomyopathies, where segmental defects suggest the former; and the identification of the postpericardiotomy patient,[23] where an anterior LV "swing", paradoxical septal motion with preserved thickening indicates intrinsically normal septal contraction and suggests the unrestricted ventricular motion of the condition. Recently, there has been an outburst of new acquisition and analysis technology focused on the field of nuclear cardiology.[24]

INTERPRETATION

Myocardial perfusion imaging presents a map of regional myocardial perfusion. Normal images are rarely the result of artifacts, but abnormal images are not uncommonly, based in artifact.[25] The polar map objectively identifies and compares areas of reduced activity to a normal gender matched normal control set (Figs 7 and 10). However areas of reduced activity unrelated to perfusion may relate to patient motion, attenuation by the breast, chest wall or diaphragm and must be clarified. SPECT attenuation correction (AC)[26] and prone imaging[27] have been used to distinguish such effects and improve diagnostic accuracy. AC methods aid viability evaluation, help overcome ambiguities related to high background activity, aid security in the evaluation of stress only studies and improve the accuracy of quantitative image parameters. AC is optional for SPECT image acquisition but is mandatory for PET which requires AC to fix the errors introduced by the gross loss of data intrinsic to its 360° acquisition.

Several commercial AC methods are approved and applied in routine practice. While each improves image specificity, AC methods vary and differ in their accuracy. Prone imaging has also been shown to improve the specificity of CAD diagnosis as it eliminates attenuation effects of the diaphragm and the breast, while often resolving motion artifacts with a second acquisition in a more stable position. ECG-gated SPECT imaging permits identification of wall motion abnormalities which help to identify true perfusion defects and allows the measurement of LVEF. Additionally, specific image patterns support a technical cause of the finding including: a normal polar map; defects worse at rest than stress; nonsegmental, shifting defects or those which improve on AC or prone imaging; and the findings on raw data. Expert readers use these tools, their relationships and their experience in image interpretation.

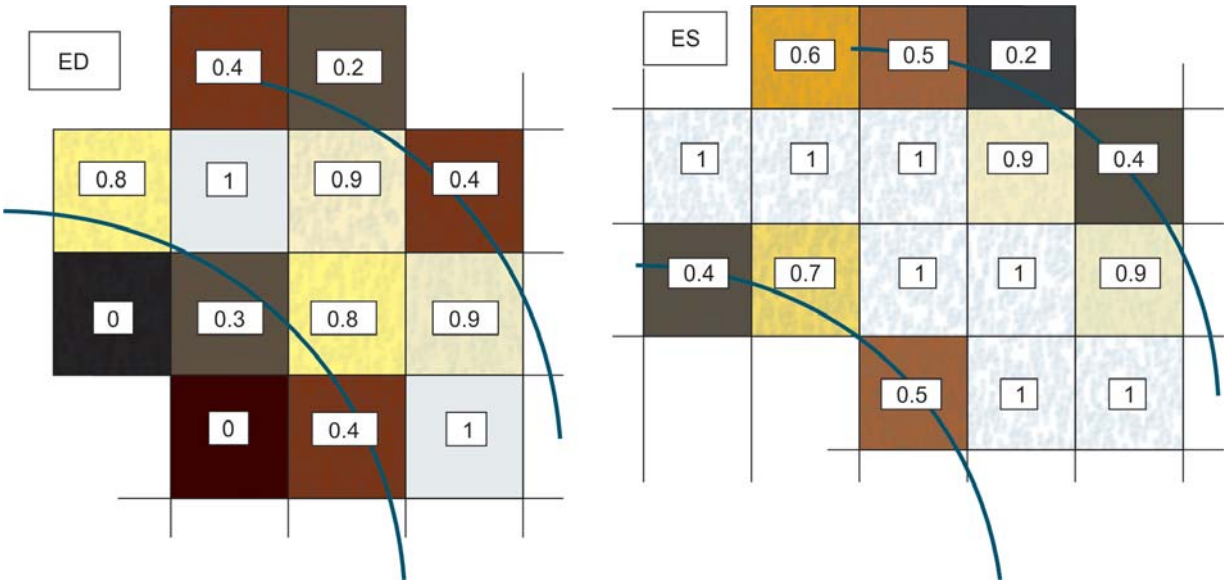


FIGURE 12: Brightening, wall thickening and the partial volume effect. Shown diagrammatically is a myocardial region in end diastole (ED) and end systole (ES). The squares represent pixels which are color coded for and labeled with the percentage of the pixel occupied by the myocardium. Thickening brings more pixels fully or more fully filled by the myocardium and related to a brighter (lighter) intensity response (*Source:* Modified from Botvinick EH, Ratzlaff N, Hoffman JIE, et al. Self Study Program III; Nuclear Medicine: Cardiology Topic 5-Myocardial Perfusion Scintigraphy by Single Photon Radionuclides-Planar and Tomographic (SPECT)-Technical Aspects. Soc Nucl Med Publ. 2003)

PET and SPECT may be combined with CT for both increased anatomic resolution and AC.

Raw images, the processed SPECT "splash" slice display, polar maps, gated images with thickening and quantitative data including cavitary and wall volumes, LVEF, AC or prone image findings should all be included in the study evaluation.

DIAGNOSTIC ACCURACY AND COST EFFECTIVENESS

No other stress imaging method has been so thoroughly studied for its CAD diagnostic and prognostic value in a variety of clinical subgroups. MPI plays an integral role in the evaluation of CAD in all its clinical variations. As with all such tests, apparent MPI accuracy and clinical value will vary with the pretest CAD probability. The test accuracy and choice will vary as well with the interpretability for ischemia of the baseline ECG, and the ability of the ST method to test the CFR (Figs 13 and 14). MPI sensitivity to CAD increases with disease extent, severity, the vigor of the stress test and other factors. Stress MPI has been well established to have a very high negative predictive diagnostic value in thousands of study patients, in those with a high pretest probability (> 85%), where the CAD diagnosis is known or highly likely. For those with a low pretest probability of CAD (< 15%), an interpretable ECG, and the ability to exercise adequately, an exercise test alone is all needed for diagnostic purposes. MPI is of greatest diagnostic value in those with an intermediate pretest CAD likelihood (between 15% and 85%) and of greatest prognostic value, rivaling that of SCA. Applied in this way, MPI is a cost-effective method associated with a reduced length of hospital stay and decreased number of cardiac catheterizations performed (Table 4).

TABLE 4

When is perfusion imaging cost-effective for CAD diagnosis and prognosis

Extensive population studies indicate that myocardial perfusion scintigraphy is generally of clinical value and cost-effective • *For CAD diagnosis:* In the presence of an intermediate pre-test CAD likelihood With an abnormal baseline electrocardiogram • *For CAD prognosis:* In the presence of an intermediate or high pre-test CAD likelihood In association with pharmacologic stress
Source: Botvinick EH, Maddahi J, Hachamovitch R, et al. Self-study program III; Nuclear medicine: Cardiology, topic 6: myocardial perfusion scintigraphy by single photon radionuclides–planar and tomographic (SPECT), clinical aspects. With permission of the Soc Nuc Med Publcns, 2004.

Stress test results interact strongly with image findings to determine CAD prognosis. The event rate related to a given MPI defect size varies inversely with the achieved heart rate and imposed myocardial flow demands (Fig. 15). Event rate is further increased in relation to any defect size in diabetics and other high risk populations. A normal stress MPI has a high predictive value of a benign course (< 1% annual risk of cardiac death or MI) in the general population. The high predictive prognostic value of an optimally performed negative stress MPI reduces the likelihood of coronary events among symptomatic patients with no known CAD to that of the general asymptomatic

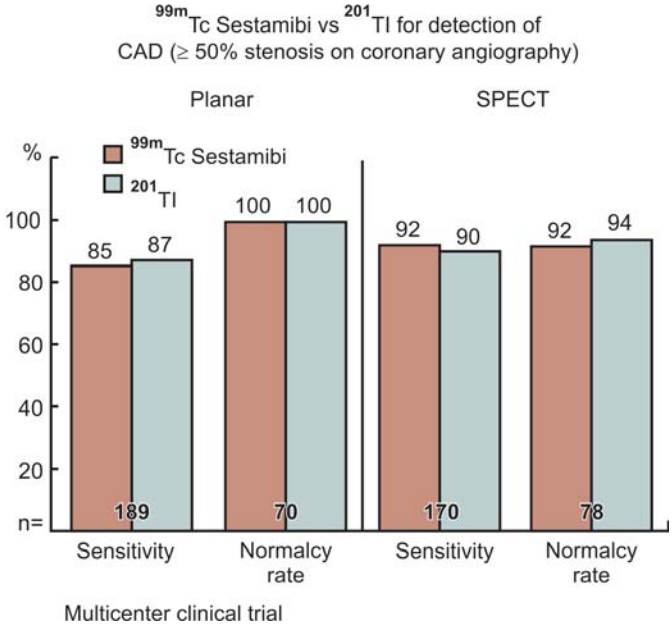


FIGURE 13

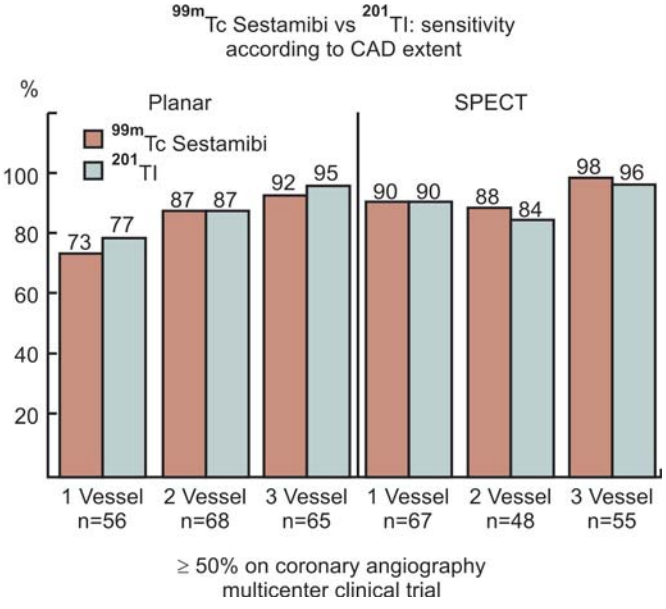


FIGURE 14

FIGURES 13 AND 14: Accuracy of ^{99m}Tc based perfusion imaging. Shown in Figure 13 are the results of an early multicenter trial evaluating the diagnostic sensitivity and normalcy of planar and SPECT ^{201}Tl and ^{99m}Tc sestamibi stress perfusion images. SPECT sensitivity was significantly higher than planar while preserving specificity. In the same way, Figure 14 compares sensitivity and specificity of ^{201}Tl and sestamibi planar and SPECT imaging for the identification of disease according to its extent. Unlike planar imaging, SPECT was equally sensitive to 1, 2 and 3 vessel coronary artery disease. Surprisingly, in this study, there was no difference in diagnostic accuracy between ^{201}Tl and ^{99m}Tc studies. However ^{99m}Tc agents provide best image quality and improved sensitivity and specificity, especially in large patients and women (*Source:* Modified from Taillefer R, Lambert R, Dupras G, et al. Clinical comparison between thallium-201 and technetium-99m methoxyisobutyl isonitrile (hexamibi) myocardial perfusion imaging for detection of coronary artery disease. Eur J Nucl Med. 1989;15(6):280-6)

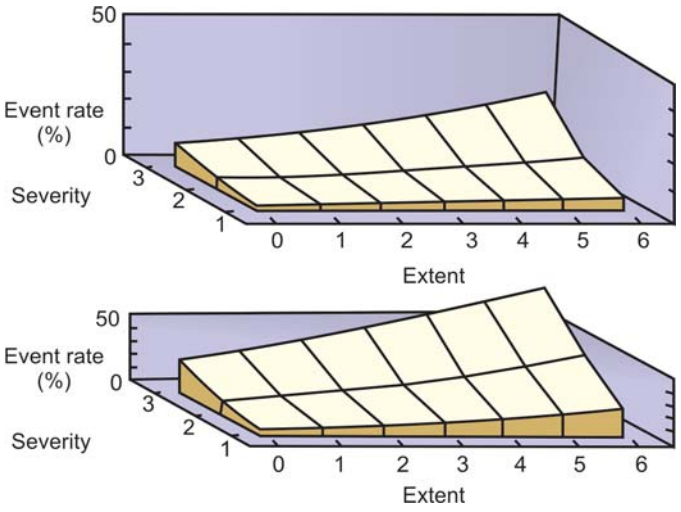


FIGURE 15: Relationship to prognosis. Shown in this 3-dimensional plot drawn from results generated in a large patient population, is the relationship between induced perfusion image defect extent (size, on the abscissa), severity (density, on the ordinate) and event rate (prognosis, on the vertical axis). Note the almost exponential relationship. The data are divided into two plots, above in patients who achieved 85% of predicted heart rate for age, and below, in those who failed to reach that level. The suggestion is that defects of similar conformation have a much higher event rate and relate to a graver prognosis when acquired in association with a lesser stress and test of the coronary flow reserve. The impact of image data must be related to the associated stress (*Source:* Modified from Ladenheim ML, Pollock BH, Rozanski A, et al. Extent and severity of myocardial hypoperfusion as predictors of prognosis in patients with suspected coronary artery disease. J Am Coll Cardiol. 1986;7:464-71)

population and generally permits a conservative approach to management. However, the predictive value of a normal stress MPI varies with the pretest CAD likelihood (Fig. 15). For the same reason, the high predictive value of a negative test has a varying warranty period with retesting required at intervals of 1–3 years to maintain appropriate surveillance depending on pretest CAD likelihood.

Myocardial perfusion imaging is also of value with a low pretest probability in the presence of a baseline ECG uninterpretable for ischemia as with ventricular pacing, left bundle branch block (LBBB), LV hypertrophy with "strain" or baseline ST abnormalities, an initial stress test with unexpected or ambiguous ST changes or an inadequate stress test. When the stress test is suboptimal and the patient cannot exercise adequately to gain the rate and pressure response needed to test the CFR and so address the clinical question, vasodilator pharmacologic stress would be helpful. While relatively uncommon, the likelihood of a coronary event rises to clinical concern when a markedly positive stress ECG, with greater than or equal to 2 mm within the first 6 minutes of a standard Bruce protocol, or the equivalent, accompanies a normal MPI.

INDICATORS OF MULTIVESSEL CORONARY ARTERY DISEASE AND RELATED RISK

Although greater than 90% of those with high risk, multivessel or left main CAD present with abnormal stress MPI, only 40–60% of these are identified by a reversible perfusion defect subtending over 15% of the LV or a total defect greater than 30%. Although superior to stress imaging with other modalities, the sensitivity of SPECT MPI for the specific identification of those at highest coronary risk based only on the extent, severity and distribution of defects, is suboptimal. While the method can identify some ischemic abnormality in more than 90% of those with extensive CAD, stress MPI may underestimate disease involvement, and in only about 2 of 3 patients with left main or three vessel disease, at most, will an image pattern of extensive, high risk, multivessel disease be demonstrated.[28] Exceeded by PET methods, the sensitivity of SPECT MPI to high risk CAD benefits from findings unrelated to the character of the perfusion defect. These "nonperfusion" indicators of coronary risk include increased post-stress lung uptake of ^{201}Tl or less commonly ^{99m}Tc sestamibi or tetrofosmin with an increased lung/heart ratio (LHR), transient ischemic dilation (TID) of the LV and induced cavitary photopenia. Owing to their difference in physical characteristics, resolution and resultant apparent wall thickness, the cavity size may normally appear more than 30% greater on ^{99m}Tc stress than on ^{201}Tl rest images. A relative augmentation of activity at the usually deficient ventricular base, basal uptake or augmented right ventricular (RV) uptake in the absence of RV hypertrophy, suggest an extensive relative deficiency of activity and perfusion elsewhere in the LV consistent with extensive, high risk CAD. In conjunction with the defect score, the LHR, TID and induced cavitary photopenia further enhance the diagnostic accuracy and predictive value of SPECT MPI for the specific identification of severe, high risk CAD to a sensitivity of roughly 65–70%. The findings of induced wall motion abnormalities or falling LVEF with gated stress SPECT MPI, yields a further increment in diagnosis certainty and prognostic risk.

The extent of perfusion defect, regardless of its distribution or relationship to multivessel disease, provides the most reliable measure of the myocardium at ischemic risk which relates well to CAD risk. Quantitative stress MPI objectifies the severity and risk related to functionally significant CAD in those with chronic stable angina and other clinical CAD subgroups.[29] The SSS, introduced above, presents a quantitative measure of stress image defect extent and intensity, the amount of infarcted, ischemic or jeopardized myocardium, with proven abilities to identify risk of infarction or death. Hachamovitch R and his coworkers have presented retrospective and prospective studies demonstrating the value of stress related defect size, not only for prognosis but also for guidance in patient management. Defect size is greater than or equal to 12% of LV mass related to an unacceptably high risk of death in the year following the study and was related to improved survival with revascularization in comparison with medical management. Patients of both sexes with such image findings, but not necessarily those with smaller defects, would benefit from intervention and aggressive management.[30] Other multicenter studies which evaluate CAD prognosis with varying forms of treatment also indicate a benefit from scintigraphic analysis.[31] Stress induced dysfunction adds to this risk.[12,24,32]

NONPERFUSION INDICATORS OF CAD-RELATED RISK—LUNG/HEART RATIO

Increased LHR is due to prolonged pulmonary transit with increased radionuclide extraction. In the presence of known or suspected CAD, this finding suggests extensive stress-induced

LV dysfunction and multivessel CAD. It has been most thoroughly studied with ^{201}Tl where an increased LHR greater than 0.4 appears to correlate with more extensive CAD and lower LVEF at rest, with exercise, as well as vasodilator pharmacologic stress. The relationship has been studied with ^{99m}Tc-based perfusion agents where lung uptake occurs less frequently. However, with these agents as well, an increased LHR has been associated with more severe and extensive CAD than in the presence of a normal LHR and reduced LV function.

TRANSIENT ISCHEMIC DILATION

Transient ischemic dilation (TID), LV dilation with stress greater than 1.2 in single and greater than 1.4 in dual isotope protocols, is determined on the basis of calculated LV volumes, but supplemented by visual assessment. The measure correlates with extensive multivessel disease or severe high-grade coronary stenosis. TID with stress suggests stress induced LV dysfunction and has been found to be an independent predictor of total cardiac events. Its presence aids in the identification of those with reversible ischemia and who are most likely to benefit from revascularization. The finding has a high sensitivity, specificity and accuracy (91%, 77% and 84% respectively) regardless of the stress method.[33] In the presence of lung uptake or cavitary photopenia, the CAD risk related to any stress induced defect is increased.[34]

Left ventricular (LV) cavitary dilation may be global, consistent with functional compensation for a severe, presumably ischemic, reduction in ventricular function or local and associated with an apparent regional "thinning" of the LV wall. The local condition often presents a resultant apparent visual shift of the cavity from the LV center toward the perfusion abnormality in an "arrowhead" configuration with the tip pointing to the defect.

DENSE CAVITARY PHOTOPENIA

Although the perfusion agent is almost completely extracted from the blood pool, the LV cavity is rarely without intensity in a SPECT MPI. This relates to the incomplete tomographic nature of the SPECT study and the fact that slices are contaminated by the intense activity of the contracting perfused overlying and adjacent walls. Dense cavitary photopenia then relates to massive LV dilation, reduced wall motion or and/or severe regional underperfusion, each of which reduces the potential "contamination" of the cavity by the overlying myocardial wall and promotes cavitary photopenia. When seen only at stress it is yet another indicator of extensive myocardium at ischemic risk.

CLINICAL APPLICATIONS OF MYOCARDIAL PERFUSION IMAGING IN THE EMERGENCY DEPARTMENT—WITH ACUTE CHEST PAIN SYNDROMES

(See Chapter "Coronary syndrome I: unstable angina and non-ST segment elevation myocardial infarction diagnosis and early treatment")[35,36] Standard methods of clinical evaluation have been found to be unsatisfactory as a triage tool of the 8 million patients presenting each year to the emergency department (ED) with chest pain (CP) of suspected cardiac origin. There are 5 million patients admitted with acute or possible MI, 3 million of which are eventually shown to have noncardiac pain, while 3 million other patients are sent home, erroneously discharged with an ongoing ACS and 40,000 with a heart attack (MI)!

^{99m}Tc-based MPI is a useful tool in the triage and evaluation of patients in the acute ED setting. Rest MPI has been shown to be as accurate as serum enzyme analysis for MI diagnosis and has the advantage of speed, where two troponin determinations over 6 hours after CP onset are required to exclude an event. Rest MPI has a high negative predictive value, 99–100%, for the exclusion of acute MI or subsequent cardiac events. Acute rest MPI is especially useful in patients with acute CP and normal or nonspecific rest ECGs. Of course, the full extent of myocardium at ischemic risk is most certainly determined with subsequent stress MPI. The study may remain diagnostic with radionuclide injection as long as 6 hours after cessation of symptoms. However, the delay between the cessation of symptoms and the time of radionuclide injection may result in a missed diagnosis of ischemia and so injection should optimally be made no more than 2 hours after symptoms have abated. The method appears cost effective as well with accelerated triage time, reduced admissions and duration of hospital stay. As in other clinical settings, the method appears useful in diabetics, the elderly and in women presenting to the ED. Recently, Cancer Treatment Centers of America (CTCA), a diagnostic method based in anatomy, has taken a pivotal role in the ED triage of CP patients. However its superiority has yet to be established. An editorial considers the varied imaging options in the ED setting. Guidelines are available for the application of both planar and SPECT MPI.

Myocardial perfusion imaging (MPI) can be done safely 2–5 days post-MI with submaximal exercise or, most completely, with vasodilator pharmacologic agents to determine the amount of myocardium at risk prior to or early after discharge. This is a safe and valuable method of predischarge risk stratification in those where cardiac catheterization is not planned.

UNSTABLE ANGINA/NON-ST ELEVATION MYOCARDIAL INFARCTION

(See Chapter "Acute coronary syndrome II: ST-elevation myocardial infarction and postmyocardial infarction complications and care") The presence and extent of reversible perfusion defects on MPI is a useful tool in predicting future cardiac events.[35] If no recurrent ischemia or signs of congestive heart failure (CHF) are evident, vasodilator pharmacological stress MPI may be recommended in those patients with unstable angina/non-ST elevation myocardial infarction (UA/NSTEMI) to assess inducible ischemia and help to decide whether an early invasive strategy is warranted. For ACS (UA/NSTEMI, STEMI or CP syndrome) with coronary angiogram and stenosis of uncertain significance, MPI can again be helpful in determining the significance of the lesion. Unlike the rest ECG which may be quite benign in the setting of even an extensive infarction or with a large amount of myocardium at ischemic risk, the rest MPI is often demonstrative of the area involved.

FOLLOW-UP AFTER INITIAL ACS EVALUATION STRATEGY

The initial goal of evaluating patients with suspected ACS and nonischemic ECG results in the ED, through use of either resting MPI or serial cardiac serum markers, is to determine the likelihood of ACS and to stratify patient risk. Subsequent assessment of symptoms and risk usually requires some form of ST. Decisions about the type of stress used (treadmill exercise or pharmacologic stress) and the type of analysis performed (ECG testing alone or ECG testing in conjunction with gated MPI) can be made based on well-established clinical protocols such as those outlined in the American College of Cardiology (ACC)/American Heart Association (AHA) Stable Angina Guidelines. It is recommended either that such ST is performed in the ED before the patient is discharged or that the patient is discharged with an appointment for an outpatient stress test within 1 week. A thorough review of this subject was written by Kontos and his coworkers.[37]

RISK ASSESSMENT OF GENERAL AND SPECIFIC PATIENT POPULATIONS

GENERAL PRINCIPLES

The appropriateness of MPI in the general population is highly dependent upon the patient's likelihood for CAD based on the Framingham risk criteria and as outlined above. The time frame recommended for repeat study varies with the initial findings and clinical condition (See "warranty period" above). CT coronary calcium score may provide further guidance. However, studies have shown that stress MPI and CT may provide complementary rather than duplicate data. Criteria of test appropriateness have been formulated.

PREOPERATIVE EVALUATION FOR NONCARDIAC SURGERY

Identification and preoperative management of high risk CAD patients is best accomplished with the teamwork of the primary care physician, the surgeon, anesthesiologist and, where needed, a cardiologist. Noninvasive testing should only be done where results could influence management and outcome. Indications for coronary angiography are generally those as in the nonoperative setting with timing dependent on the urgency of noncardiac surgery, patient risk as evidenced by the history, physical examination and related testing, and the risk of the surgery to be done. The consultant should plan management for both the short (upcoming surgery) and the long term. The clinical predictors of increased cardiovascular risk, MI, CHF and death are presented in the ACC/AHA guideline update for perioperative cardiovascular evaluation for noncardiac surgery.[38,39] In these guidelines, noncardiac surgical procedures are risk stratified, a stepwise approach to perioperative cardiac risk assessment is presented, and a summary of long-term survival after vascular surgery is reviewed. The guidelines present the results of studies assessing the perioperative risk by ST as well as by stress MPI and the factors governing the choice of the stress test in perioperative cardiac risk stratification.

Appropriate use criteria for cardiac radionuclide imaging in the perioperative and in all clinical settings have been developed and updated.[40,41] These and other guidelines discussed below, further address the application of stress MPI. Almanaseer and his coworkers, from this same group, demonstrated that "Implementation of the ACC/AHA guidelines for cardiac risk assessment prior to noncardiac surgery in an internal medicine preoperative assessment clinic led to a more appropriate use of preoperative ST and beta-blocker therapy while preserving a low rate of cardiac complications".

THE EVALUATION OF CAD IN WOMEN

Special consideration for women and CAD detection has long been acknowledged. As presented above, stress MPI has incremental benefit in detecting and risk stratifying CAD in women.[30,42-44] With enhanced interpretive skills, ^{99m}Tc-based perfusion agents, tomographic, prone, attenuation corrected and gated images, SPECT MPI has demonstrated diagnostic and prognostic equality and even superiority to its application in men. Consensus statements on the role of MPI in the detection of CAD in women are available. The clinical role of stress MPI in the management of women with suspected CAD has been reviewed extensively, as well as its role in women with diabetes and CHF.

DIABETICS

Type 2 diabetics is considered a coronary disease equivalent. Such diabetics have a 2–4-fold increased risk of coronary events compared to the nondiabetic population and the MI risk in a diabetic patient is equal to the risk of reinfarction in a non-diabetic with a prior MI. Silent angina and MI is more common among diabetics and diabetics are more likely to die from their MI than those without diabetes. Coronary disease is the leading cause of death in type 2 diabetics. This risk is compounded and exaggerated by the epidemic of obesity worldwide. The need to identify early atherosclerosis and coronary disease in such people is well recognized and stress MPS can contribute to this end. Work has highlighted the high risk of even asymptomatic diabetic patients.[45] Noninvasive cardiac imaging with exercise or pharmacologic stress is cost effective in many categories applicable to large populations of diabetic patients.

MYOCARDIAL PERFUSION IMAGING IN THE ELDERLY

Left ventricular functional data assessed during myocardial gated SPECT provide independent and incremental information above clinical and perfusion SPECT data for the prediction of cardiac and all-cause death in patients aged 75 years or older referred for myocardial SPECT imaging.[46] Vasodilator pharmacologic stress SPECT MPI is safe and most useful for evaluating myocardial ischemia in this group.

POSTREVASCULARIZATION

Regardless of the time frame, MPI is recommended for those who are symptomatic postrevascularization, either by PCI or by coronary artery bypass graft (CABG). Guidelines[39,40] suggest that routine MPI is not indicated prior to hospital discharge

postrevascularization if asymptomatic nor if asymptomatic within 1 year post-PCI or within 5 years post-CABG. However, MPI is recommended even if the patient is asymptomatic greater than 5 years after CABG. It is more a matter of individual judgment, whether MPI should be routinely performed in asymptomatic patients greater than 2 years after PCI. After bypass surgery or with any pericardiectomy, the unrestrained heart "swings" anteriorly in the chest giving the appearance of a septal wall motion abnormality. However, septal thickening and systolic function is preserved.[23]

HEART FAILURE

(See Chapter "Systolic heart failure and diastolic heart failure—epidemiology, risk factors, evaluation, diagnosis and management)[47] Patients with newly diagnosed CHF, whether in the setting of CP syndrome or not, should undergo MPI to determine the likelihood of CAD and assess for potential reversible ischemia.[48] The combination of reversible perfusion abnormalities and regional wall motion provides a 94% accuracy for the differentiation of ischemic from nonischemic cardiomyopathy.[49] Those with ischemic cardiomyopathy who are eligible for revascularization with known CAD on SCA should have assessment of myocardial viability. Additionally, those who are receiving potentially cardiotoxic therapy (i.e. doxorubicin) should undergo baseline and serial measurements of ventricular function.

APPROPRIATENESS CRITERIA FOR PERFUSION IMAGING

An appropriateness review was conducted for gated SPECT MPI[40,41] under the auspices of the American College of Cardiology Foundation (ACCF) and the ASNC. The review assessed the risks and benefits of SPECT MPI for 52 selected indications or clinical scenarios grading them as a reasonable approach, a generally reasonable approach and not a reasonable approach. The 52% of indications rated as appropriate, were derived more often, 89% of the time, from existing clinical practice guidelines than was the case for the 23% of uncertain indications, or for the 25% of inappropriate indications. The findings here confirmed and consolidated earlier findings. The guidelines text categorizes the appropriateness of SPECT MPI for the detection of CAD in the presence of an intermediate pretest CAD likelihood and for prognostic value in the setting of an intermediate or high risk pretest CAD likelihood. There is a wide and appropriate MPI application in the presence of CP, especially with an uninterpretable ECG except when CAD was very unlikely or, very likely. It also is quite applicable, especially with pharmacologic stress, in the setting of LBBB. In the absence of CP, the study was found to be appropriate for risk stratification with a high pretest CAD likelihood or a moderate likelihood in the setting of new onset arrhythmia, heart failure or valvular disease, with other worsening symptoms, with long-standing high CAD likelihood or known CAD, an ambiguous stress test, ACS with stenosis of unclear significance and after thrombolytic therapy. Ambiguous results of stress ECG, ST and CTCA, as well as a high coronary calcium score may also be appropriately resolved by MPI. MPI is of value after incomplete or remote revascularization, in the presence of silent ischemia and for the evaluation of myocardial viability.

POSITRON EMISSION TOMOGRAPHY PERFUSION AND METABOLISM

PET AND SPECT TECHNOLOGY

Compared with SPECT, PET has superior image resolution.[50] A number of factors make it most accurate for CAD diagnosis and prognosis and the index imaging method for assessment of myocardial viability. Major advances in PET technology add to its intrinsic physical advantages over SPECT and have contributed to its rapid growth and current application. Crystal options and camera design have moved from laboratory to the bedside and present a growing list of equipment options now available. Combined PET/CT instruments have proliferated widely for use in oncology making the instrumentation more available and the application of PET MPI possible. Reimbursement makes it practical. PET MPI combined with calcium scoring and CTCA add to its interest among practitioners. PET quantitation of flow reserve adds advantages beyond other methods and raises excitement for the future. High energy, 511 keV, PET studies require no extrinsic collimation where AC is performed in all studies generally using X-ray sources making PET quite advantageous in large patients.

Compared with SPECT, PET suffers a sparsity of commercial PET software to assess and correct for motion, alignment of emission and transmission images and perform a host of other tasks to assure quality control and aid acquisition and display. PET tracers are plentiful but suffer from their generally short half-life and their generation in cyclotrons rather than generators. Among PET perfusion agents, only ^{82}Rb is generator produced and available to institutions without a cyclotron. However its short half-life makes only vasodilator pharmacologic stress possible and relatively untested for flow reserve quantitation. ^{13}N ammonia is cyclotron produced and well applied for flow quantitation. Each has physical, kinetic and flow related advantages beyond ^{99m}Tc-based radiotracers. While PET technology remains more expensive, its greater clinical advantages, rapid throughput and extracardiac applications make it cost effective in specific applications, even now.

Single photon emission computed tomography (SPECT) technology is moving rapidly, seeking to equal or surpass the advantages of PET. New instruments, imaging methods and computer software provide new solid state detectors with rapid camera rotation and list mode acquisition. New detector materials provide increased sensitivity with improved energy resolution and reduced scatter. With these methods SPECT perfusion image acquisition may be accelerated to as brief as two minutes with high sensitivity, improved energy resolution and the potential for quantitation and simultaneous dual ^{99m}Tc stress/^{201}Tl rest imaging. Recent methods seek to measure the CFR by SPECT MPI.[51]

With approximately 10 million myocardial perfusion scans, 1.35 million PET scans and 100 million CT scans done each year in the USA, radiation dosage delivered by all methods is again under careful scrutiny (see below—radiation concerns).

TABLE 5

Spectrum of myocardial pathophysiology and viability

Myocardial state	*Rest wall motion*	*Rest/stress perfusion*	*Metabolism*
Normal	Normal	Normal	Normal
Scar	Abnormal	Abnormal—fixed defect	Abnormal
Ischemia	Normal	Abnormal—reversible defect	Normal
Stunned (Transient, post-ischemic dysfunction)	Abnormal	Normal	Normal
Hibernating (dysfunction due to marginal blood supply, serial stunning)	Abnormal	Reversible or fixed defects	Preserved

However, while studies must be performed only with proper indications[40,41] and all must be done to minimize radiation dosage, the tests are safe and should be applied when indicated. The linear extrapolation of risk from highest to lowest radiation exposure now suddenly popular is still not proven and, in some publications, suggests that (cancer) risk from a stress perfusion imaging study rivals that of the stress test. Yet we only request patient's permission for the latter and the benefits of low dose radiation (hormesis) is well established.[52]

IMAGING MYOCARDIAL VIABILITY

THE PRINCIPLES

When myocardium demonstrates systolic dysfunction, the question of myocardial viability arises. Dysfunctional myocardium may be scarred and beyond salvage, or it may be viable in one of several forms. Viable but dysfunctional myocardium may be ischemic, even in the absence of overt ischemic symptoms or signs, or "stunned" or "hibernating". Dysfunctional but viable myocardium is salvageable and may be restored to function with revascularization; a non inconsequential consideration in patients with systolic dysfunction and severe CHF (Tables 5 to 7). Here, with failure of medical treatment, reversal of dysfunction in extensive "hibernating" areas could be life saving and present an important and preferred choice to heart transplantation, which too often is not an available option.

"Stunning" represents transient postischemic dysfunction, generally requiring nothing more than recognition, patience and supportive care, after the ischemic episode passes. After bypass surgery "stunned" myocardium may persist for weeks (Figs 16 and 17). It may last minutes to hours after a positive exercise

TABLE 6

The basis for imaging myocardial viability

Viatility method	*Principles*
^{201}Tl perfusion imaging/ MR contrast enhancement	Membrane integrity
MIBI/Tetrafosmin perfusion imaging	Mitochondrial integrity
Low dose dobutamine/ MR imaging	Inotropic contractile response
PET	Preserved metabolism

TABLE 7

Scintigraphic evidence of myocardial viability and functional reversibility (in the presence of rest wall motion abnormalities and related coronary disease)

- Evidence of preserved perfusion in a dysfunctional segment
- Extensive reversible perfusion abnormalities in a region of abnormal wall motion
- Delayed redistribution of ^{201}Tl in a region with abnormal wall motion
- Post-reinjection ^{201}Tl uptake
- Modest fixed defect in a region with extensive wall motion abnormalities
- PET perfusion-metabolism mismatch
- Evidence of fatty acid uptake (metabolism)

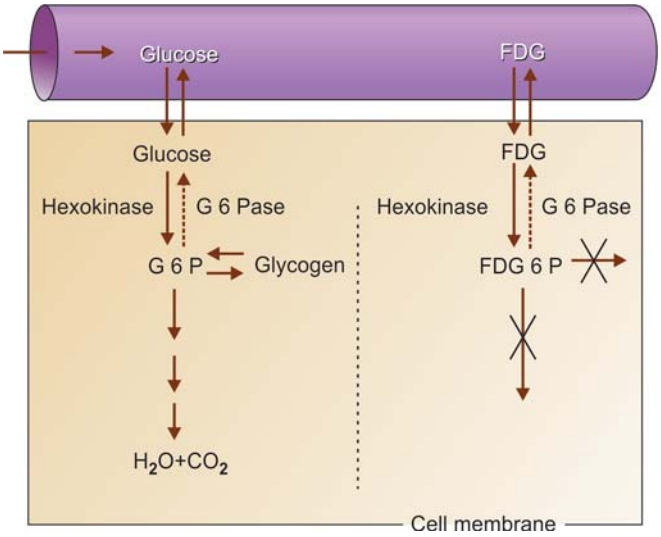


FIGURE 16: Mechanism of FDG localization. Shown diagrammatically is the action of FDG. Transported actively across the cell membrane as is glucose, it is not a substrate for hexokinase and so is not phosphorylated to FDG 6 phosphate (FDG 6 P), as is glucose to glucose 6 phosphate (G 6 P) (Abbreviation: FDG: ^{18}F-deoxyglucose G 6 Pase: enzyme glucose 6 phosphatase). Trapped in the cell it serves as a marker of membrane and energy metabolism integrity and cell viability (*Source:* Modified from Botvinick EH, Dae M, O'Connell JW, et al. The scintigraphic evaluation of the cardiovascular system. In: Parmley WW, Chatterjee K (Eds). Cardiology. Philadelphia: JB Lippincott; 1991)

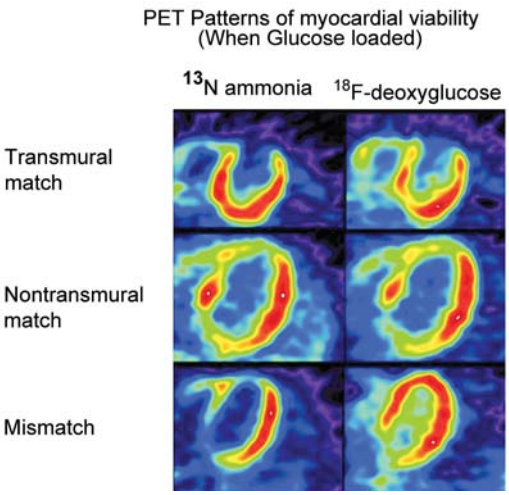


FIGURE 17: Patterns of FDG uptake. Shown on perfusion (left) and FDG metabolism images are matching patterns of varying intensity and the classic, perfusion-metabolism mismatch, suggesting viability. The severe matched defect suggests scar. The matched area with modest uptake on both perfusion and metabolism images suggest potential viability which varies directly with the intensity of FDG and perfusion uptake (*Source:* Reproduced from Maddahi J, UCLA, Los Angeles, CA, with permission)

test, and forms the basis for exercise stress echocardiography. It is characterized by preserved perfusion and metabolism with normal pathology on light microscopy. The cause of related post-ischemic dysfunction is unclear, but has been related to altered energy metabolism.

"Hibernation" has been called "chronic ischemia", a condition hard to imagine and difficult to produce in an animal model. Yet clinically, it may occur at any time and in any clinical setting in the absence of overt ischemia. It must be recognized, differentiated from other causes of systolic dysfunction, and the ischemic cause reversed. It may come and go and is thought to relate to repetitive "stunning". This is the form of occult, potentially reversible ischemic dysfunction, which image viability assessment seeks.

NONSCINTIGRAPHIC IMAGING OPTIONS

The improvement of wall motion with low dose dobutamine stress echocardiography is a more subjective noninvasive alternate manner of determining myocardial viability. MRI and delayed (gadolinium) contrast enhancement, indicating scar on MRI, are another alternative methods for viability assessment. However, SPECT and PET methods remain the most frequently applied, best documented and most trusted methods for determination of myocardial viability. They stand as the comparative gold standard for all other methods and the one to which they aspire.

SCINTIGRAPHIC IMAGING OPTIONS—PERFUSION RELATED

Most prominent among scintigraphic indicators of viability is the maintenance of regional perfusion. The presence of ^{201}Tl or ^{82}Rb, potassium analogs which enter the cell by energy requiring active transport, or any of the ^{99m}Tc perfusion tracers, which enter viable cells by diffusion, indicates viability. Here, the level of radiotracer uptake is directly proportional to the likelihood of viability and restoration of function after revascularization. ^{201}Tl is initially distributed to the myocardium in proportion to regional flow. With time the intracellular ^{201}Tl distribution parallels intracellular space or viability. These distributions are generally the same, but if viable cells are ischemic at rest, an initial rest related perfusion defect may "fill in" or normalize with time. Delayed ^{201}Tl imaging at 4 and 24 hours or the delayed "reinjection" of a small dose of the radionuclide may normalize perfusion, an indicator of viability. The time to redistribution is directly proportional to the severity of the stenosis and related flow abnormality. Reinjection and related viability detection appear to be augmented with nitroglycerin. Reinjection of the radionuclide too close to the time of redistribution imaging may re-establish an already resolved defect and result in an underestimation of viability. Administration of nitrates has been advocated to increase radiotracer uptake and optimize the evaluation of viability with single photon perfusion agents.

SCINTIGRAPHIC IMAGING OPTIONS—METABOLISM BASED

With fasting or with ischemia, myocardial metabolism shifts from its primary metabolite, fatty acids, to glucose. Imaging a radiolabeled analog of glucose, ^{18}F-deoxyglucose (FDG), which is trapped in the myocyte but not metabolized, remains the noninvasive imaging standard for myocardial viability. Scintigraphically, the density of a perfusion defect at rest has been found proportional to the likelihood of viability. However, even severe PET perfusion defects are roughly divided between those which are and those which are not, viable (Figs 16 and 17). Here, viability is determined by evidence of ^{18}F-FDG uptake, revealing a perfusion-metabolism mismatch and indicating active metabolism in the area of underperfusion[53] (Figs 16 and 17). When present in a major mass of dysfunctional myocardium, the "mismatch" pattern is highly predictive of functional and symptomatic improvement and reduced mortality after revascularization where a failure to revascularize such ventricles relate to increased mortality. However, the smaller the extent of mismatch, the larger the "matched", scarred area, the more prolonged the dysfunction, the more delayed is revascularization, or a baseline LVEF too low, less than 30%, end diastolic volume (LVEDV) too high with LVED diameter greater than or equal to 6 cm each has an adverse effect on the outcome and relates to an increased risk with revascularization, particularly CABG. The complexity of predicting postrevascularization functional improvement has been reviewed.[54] The advantages of viability evaluation by PET perfusion with ^{13}N-ammonia compared with ^{99m}Tc-based perfusion tracers were analyzed.[55] Most recently, the identification of infarcted myocardium on a contrast MRI study has engendered excitement as a more direct manner of determining regional myocardial viability, although with only modest ability to assess myocardium at ischemic risk. Guidelines have been published for application of cardiac PET studies as well as for qualifications to practice cardiac PET.[53]

IMAGING PERFUSION

RUBIDIUM (^{82}Rb) CHLORIDE

Strontium generator produced ^{82}Rb (T 1/2 = 75 sec) is being applied with increasing frequency for pharmacologic stress MPI.[56-59] Compared with current ^{99m}Tc-based agents it has improved imaging characteristics and better spatial resolution, superior flow linearity, shorter acquisition time with imaging begun at the time of radionuclide administration and completed within 1 hour, more rigorous AC and ready availability. The review of ^{82}Rb PET MPI presented in the PET guidelines[53] notes an overall diagnostic sensitivity of 89% and specificity of 86% for CAD, superior to SPECT MPI. The method is clearly advantageous for use in heavy patients and women where issues of attenuation often cloud interpretation. SPECT ^{99m}Tc sestamibi and PET ^{82}Rb MPS gated rest/pharmacologic stress studies have been compared in patient populations matched by gender, body mass index, and presence and extent of CAD PET demonstrated higher image quality, diagnostic accuracy and interpretive confidence in both men and women, in obese and nonobese patients, and for correct identification of multivessel CAD. Similar to SPECT perfusion imaging, the PET method also gains significant prognostic value with added functional information with gated acquisition. As opposed to stress SPECT, where gated images are acquired post-stress, the PET ^{82}Rb method acquires true peak stress gated images, with evaluation of LV wall motion and ejection fraction (EF). This can be compared with rest images for a better diagnosis and prognosis of induced ischemia and CAD, where lack of stress induced LVEF augmentation could indicate occult evidence of an ischemic response. Dynamic image acquisition could permit quantification of the regional stress related augmentation of perfusion and CFR. An editorial considers the clinical roles of SPECT and PET perfusion imaging. The method is highly cost effective in high volume laboratories which can utilize the continuous and endless availability of the ^{82}Rb generator at a cost of $28,000 monthly. Unlike SPECT studies, there is a dearth of commercial PET software to assess and correct for motion, compare with a normal database, score defects or provide other analytic tools. Nonetheless, the potential benefits of PET compared to SPECT are extensive. While a dedicated PET cardiac camera is not practical in most imaging practices, cardiac cases can be well integrated with oncology demands to fill spaces in PET camera schedules with collaboration between referring internists and cardiologists and imaging radiologists and nuclear physicians.

NITROGEN (^{13}N) AMMONIA

With cyclotron produced ^{13}N (T 1/2 = 75 sec) ammonia, the longer agent half-life permits the performance of gated exercise MPI. However excellent coordination with an on-site cyclotron is needed. These considerations may favor the choice and more widespread application of ^{82}Rb in spite of the better imaging characteristics of ^{13}N ammonia. The availability of either agent will provide PET rather than SPECT perfusion to compare with FDG metabolism, an important for the evaluation of myocardial viability.

Guidelines have been developed for patient preparation for data acquisition, interpretation and reporting of both ^{18}F-FDG cardiac PET for myocardial viability and for PET perfusion imaging performed with generator produced ^{82}Rb as well as with cyclotron produced ^{13}N ammonia. Future applications with PET/CT scanners could find PET perfusion and CT coronary anatomy fused noninvasively into an image with optimal information content.

The reimbursement of PET stress MPI appears well justified by its accuracy, better localizing value with a clearer roadmap of CAD involvement, relative ease of performance, its added speed and reduced radioactivity exposure compared to ^{99m}Tc-based perfusion agents. Then should PET MPI replace SPECT? This may not necessarily be the case as SPECT methods have also gained accuracy. However, those with equivocal SPECT studies, obese subjects, those with more complicated coronary anatomy and high likelihood or known CAD post-MI, PCI or CABG, those with a known cardiomyopathy of ischemic or unknown cause are likely to benefit most from PET perfusion evaluation.

However, if exercise is needed, in the absence of a cyclotron, SPECT MPI is required even in an obese patient weighing over 250 lbs. If SPECT images are suboptimal then ^{82}Rb PET MPI with vasodilator stress becomes an option. The ready availability of generator produced ^{82}Rb, its rapid throughput and the safety of vasodilator stress make it appropriate for ED evaluation.

QUANTITATION OF REGIONAL CORONARY FLOW AND FLOW RESERVE

Currently, perfusion imaging is evaluated as a "heterogeneity map" and read as abnormal based on the degree and extent of intensity or counts heterogeneity. The ability to accurately and reproducibly quantitate absolute regional myocardial stress induced hyperemia would increase diagnostic sensitivity beyond the relative visual method of perfusion imaging.[60-62] Calculation of the exact regional flow at rest and stress in absolute ml/min/g of tissue could evaluate each region independently but presents greater technical obstacles and imaging challenges which are not currently in the realm of standard clinical imaging. However, flow quantitation with identification of regional CFR and the increase in hyperemic compared to normal flow is a relative yet superior value, which is likely within the technical abilities of most well-disciplined clinical imaging labs. CFR quantitation would free regional sampling from the insensitivity resulting when abnormal regions are best perfused, yet underperfused. The grossest example of this problem relates to the occurrence of the oft-noted but rarely observed example of "balanced ischemia", where all regions may be similarly underperfused and so could appear homogeneous and normal on standard relative perfusion imaging. This could result in normal scans in the setting of triple vessel disease. To a lesser degree this relative intensity comparison is a reason for underestimating the full extent of disease by such relative regional analysis. It should be noted, however, that MPI sensitivity increases with the severity and extent of CAD and the strong prognostic value of the method also argues against the frequent error in the diagnosis of multivessel, high risk CAD. Even with balanced ischemia, the scintigraphic method would be expected to reveal heterogeneity in long axis slices where regions proximal to the stenoses are more intense than those distal. Of

course, even with misleading balanced intensities, the nonperfusion indicators of extensive disease including cavitary dilation and lung uptake, induced cavitary photopenia in addition to ischemic symptoms and ECG changes could present clues to the severity of the condition and the reader must always consider the image in the overall context of stress test findings. Of course, MPI sensitivity directly parallels the level of stress applied as a test of the CFR. While not common, there is a higher incidence of reported normal images with adequate stress and extensive CAD in selected studies. Of course, any level of such error is unacceptable and anything which can practically be done to increase the diagnostic and prognostic yield, even in relation to "suboptimal" stress tests, should be applied. PET perfusion quantitation presents the best noninvasive hope. Some advocate CTCA to identify this group and even suggest its application to asymptomatic subjects. Those who do, assume a high specificity of the CTCA method, not supported to date, set aside copious data supporting the high predictive value of a negative stress perfusion image over the spectrum of clinical presentations and overlook the already documented high prognostic value and superior cost effectiveness of the physiologic compared with the anatomic evaluation of coronary disease. In other settings, such measures of CFR may help identify an altered coronary vasoreactivity in the absence of flow limiting stenoses, in those with advanced atherosclerosis or other condition and provide insight into disease pathophysiology and symptoms in a variety of vascular diseases and cardiomyopathies. For these reasons quantitation of perfusion is important. With the clinical proliferation of PET perfusion imaging, quantitation is sure to follow as a widely or selectively applied method.

BLOOD POOL IMAGING—EQUILIBRIUM RADIONUCLIDE ANGIOGRAPHY AND FIRST PASS RADIONUCLIDE ANGIOGRAPHY

GUIDELINES

Guidelines have been formulated for the acquisition and clinical application of first pass radionuclide angiography (FPRNA) and equilibrium radionuclide angiography (ERNA).[63,64] Although in recent years these methods have often been relegated to a supportive or confirmatory role, they are highly quantitative and reproducible for the evaluation of biventricular wall motion and EF. With greater effort absolute volumes can be calculated. Popular clinical applications relate to those scenarios where accuracy and reproducibility in serial measurements are required as for the monitoring of chemotherapy induced cardiotoxicity.[65] Here starting from a normal LVEF, greater than or equal to 55%, a fall in LVEF of 10% or to less than or equal to 50% is significant and requires ERNA monitoring before subsequent doses. Chemotherapy should be interrupted for a period of recovery if LVEF falls a further 10% or to lesser than 40% with careful monitoring thereafter or the patient risks a permanent loss of LV systolic function. Exercise LVEF can also help identify cardiotoxicity when the LVEF at rest is normal but there are no specific guidelines.

The method now seems to be gaining increased importance in the serial evaluation of patients with CHF due to systolic dysfunction and particularly to evaluate ventricular synchrony as cardiac resynchronization therapy (CRT) is applied to improve severe systolic dysfunction, CHF symptoms and outcomes.[66]

INTRODUCTION

Two radionuclide based techniques have been used to measure ventricular function for over three decades.[67] One method employs tracers that label the myocardial walls (e.g. ^{99m}Tc-MIBI, ^{18}F-FDG, etc.) and examines wall thickening and motion throughout the cardiac cycle. Here, wall thickening is proportional to cyclical intensity changes while volumes and LVEF are based in calculations based geometric chamber analysis. This is the principle applied to gain functional information in perfusion imaging, as discussed above. Alternatively, the blood can be labeled and imaged in two ways, by first pass or equilibrium methods. In the FPRNA, ventricular volumes and function are assessed from the passage of the radionuclide through the chamber, while in ERNA, calculations are based on the fact that counts are proportional to volume. In both methods, geometric analysis may be applied or more appropriately and more accurately, volumes and EF can be calculated from chamber counts and systolic wall motion and sequence can be determined by an examination of the changes in the intensity and configuration of the ventricular blood pool through the cardiac cycle. The latter method has been discussed below.

LABELING THE BLOOD POOL

This method has the advantage of providing a direct measure of ventricular volumes. In the ideal circumstance with truly quantitative imaging, measurement of absolute volume can be obtained directly from the images, where:

LV volume = Total cavitary radioactivity/
Activity in the blood.

The ability to make accurate quantitative measurements from images of cavitary activity is currently limited to PET. SPECT blood pool techniques have greater inaccuracies of attenuation and scatter, and cannot currently be used to quantitate ventricular volumes from image data alone. PET and SPECT volumetric methods are most arduous, require blood sampling and counting, and are not done clinically. However, nearly all clinical applications, simply seek to make relative measurements of ventricular function and LVEF which depend only on the relative accuracy of the imaging modality. Planar imaging methods can do this quite well, whereas SPECT offers some advantages for regional function evaluation. The most commonly used tracer for ERNA is ^{99m}Tc labeled red blood cells but any tracer which passes through the lungs may be used for FPRNA.[63] Thus one can obtain LV function data from FPRNA data acquired with a study done for some other purpose, as bone scans. Commercial kits are available and generally applied. PET is not used for clinical blood pool imaging where LVEF is readily generated with perfusion imaging by analysis of the myocardial label.

FIRST PASS CURVE ANALYSIS

VENTRICULAR FUNCTION

First pass radionuclide angiography (FPRNA) can be accurately performed with as little as 1–2 mCi of any agent which stays in

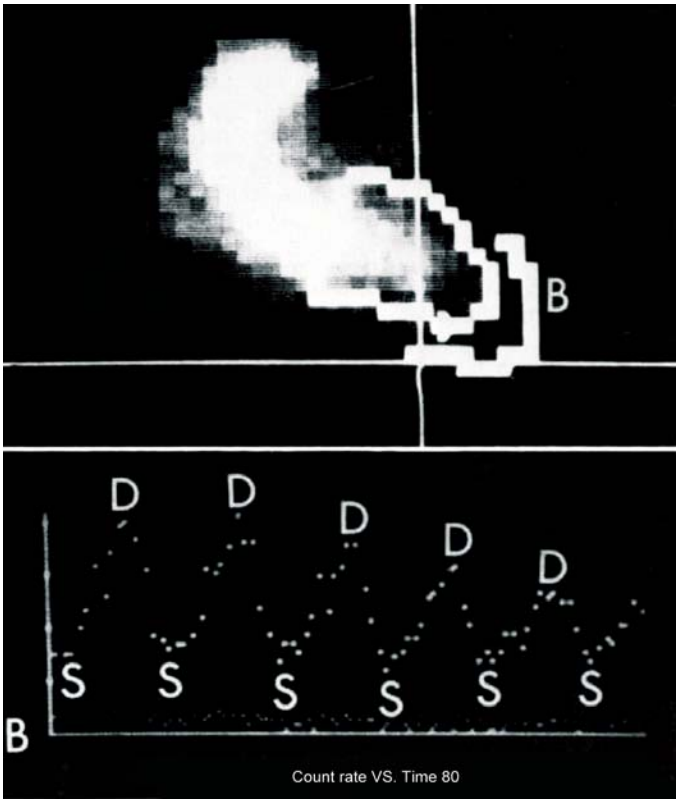


FIGURE 18: First pass analysis of the levophase. An irregular region of interest is drawn (top) on the levophase of the first pass ventriculogram. High temporal sampling of the left ventricular data produces the curve shown below. Correcting for background activity, the diastolic peaks (D) and systolic valleys (S) are compared to calculate the LVEF (*Source:* Modified from Botvinick EH (Ed). Radionuclide angiography: equilibrium and first pass methods. Self-Study Program III; Nuclear Medicine: Cardiology, Soc Nucl Med.)

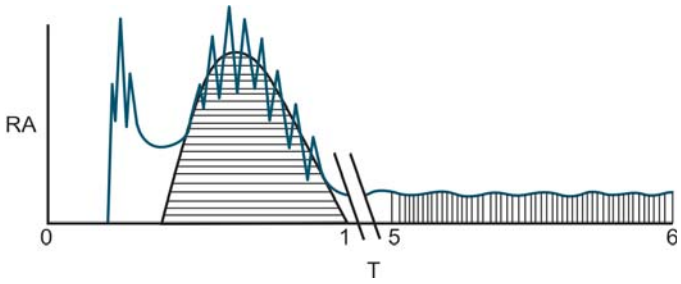


FIGURE 19: First pass analysis. The figure presents a sketch of a first pass time (T), versus radioactivity (RA) curve. The area under the left ventricular component (horizontal lines) is proportional to cardiac output and is calibrated for volume by dividing it into the integrated area under one minute of the equilibrium time versus radioactivity curve (vertical lines), acquired when the radiotracer is thoroughly mixed in the blood. Alternatively, volumes may be calculated from ventricular outlines using geometric considerations (*Source:* Modified from FA Davis Co. Botvinick EH, Glazer HB, Shosa DW. What is the reliability and utility of scintigraphic methods for the assessment of ventricular function? Cardiovasc Clin. 1983;13:65-78. Legend adapted with permission from Botvinick EH (Ed). Radionuclide angiography: equilibrium and first pass methods. Self-Study Program III; Nuclear Medicine: Cardiology, Soc Nucl Med Publ.)

the blood pool for the first circulation, but, with this low dose, images are not available (Figs 18 and 19).

"First pass" imaging presents an alternative method of blood pool acquisition with imaging the subject while injecting the tracer as a bolus. Nearly all the considerations discussed for standard gating of MPI, above, can be applied to this first pass methodology. Regardless of its ultimate disposition, during its brief first transit through the heart, most tracers stay in the arterial blood for seconds to minutes, before they are taken up by the myocardium or other tissues. During that brief transit time, the tracer behaves as though it were a blood pool tracer. When the tracer is injected as a bolus, gating is necessary in order to capture the EF. For first pass studies only a few beats of data need be added together. In addition, it is possible to position the gamma camera in an RAO view and obtain early gated images during the passage of the radioisotope through the RV, prior to contamination by counts from the LV. One of the disadvantages of the first transit is that one usually must obtain all the LV function information from only a small number of beats. This means a rapid bolus injection must be given, resulting in very high count rates during passage of the tracer through the cardiac chambers. Such high count rates require state of the art cameras. Additionally, the EF, calculated from the average values based on the magnitude of the peak counts, proportional to ED volume, and the valleys, proportional to ES volume, correcting for background activity, is based on few samples and so is prone to greater variability. Fewer samples relate to right ventricular ejection fraction (RVEF) evaluation and so require a tight RV bolus passage.

First pass radionuclide angiography (FPRNA), like ERNA, may be applied to evaluate the effects of exercise on ventricular function and were earlier applied with great frequency to evaluate the functional reserve in aortic valvular disease and for the diagnosis of CAD. These applications have been largely replaced by the echo-Doppler evaluation of valve disease and by MPI.

LEFT-TO-RIGHT SHUNT ANALYSIS

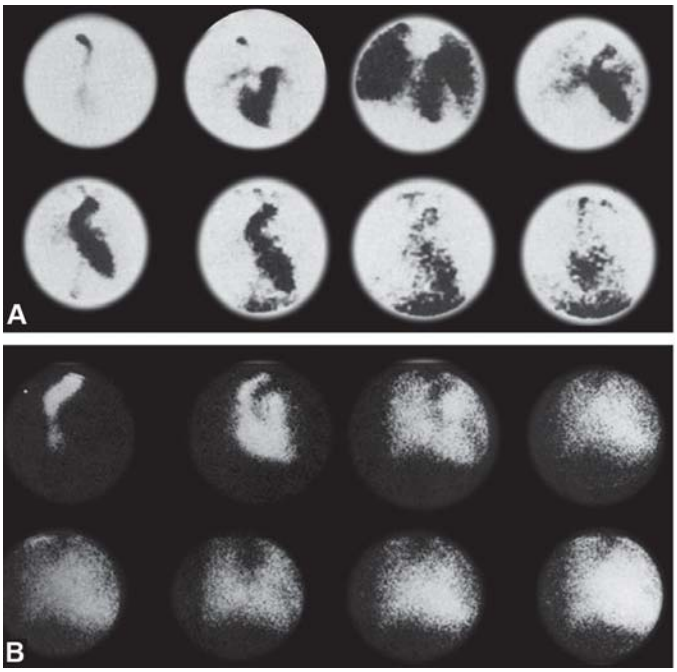
First pass radionuclide angiography (FPRNA) remains a method for the quantitation of left-to-right intracardiac shunts (Figs 20A and B). It demonstrates the calculation of the pulmonic to systemic (Qp/Qs) flow ratio; the left-to-right shunt magnitude in a patient with an atrial septal defect according to the method of Maltz and Treves. Here, by the principles of "dye dilution" analysis, the area under the first fitted curve, Area 1, is proportionate to systemic flow while the area under the second passage curve, Area 2, is proportional to the shunt flow. As shown diagrammatically in the following Figure, Area 1 = Qs (systemic) and Area 2 = Qsh (shunt). Thus, Qp = Qs - Qsh and

$$Qp/Qs = \frac{Qp}{Qs - Qsh} = \frac{Area\ 1}{Area\ 2 - Area\ 1}$$

The method is not a diagnostic tool but one meant for accurate quantitation of such shunts between Qp/Qs of 1.2–3, and so is useful in prognosis and management. It is another scintigraphic method which is underutilized owing to the widespread availability and capabilities of echo-Doppler examination.

EQUILIBRIUM GATED IMAGING—ERNA

The method of equilibrium gated blood pool image acquisition is demonstrated here, often called ERNA.[63] ERNA requires a



FIGURES 20A AND B: First pass images in normal patient and in a patient with left to right shunt. Shown in panel (A) are serial images acquired during the first passage of the radioactive bolus through the central circulation with a normal heart. Note lung clearance in frame 4 and the teardrop shape of the left ventricle in frames 4–6. In panel (B) are similar images taken in a patient with a significant left to right shunt. The lungs never clear due to continued recirculation of the bolus. As a result, the left ventricle teardrop and the levophase are not seen. This "smudge sign" generally relates to a left to right shunt with "Qp/Qs e" 1.5 (*Source:* Modified from Botvinick EH (Ed). Physical and technical aspects of nuclear cardiology. Self-Study Program III; Nuclear Medicine: Cardiology, Soc Nucl Med Publ. 2009)

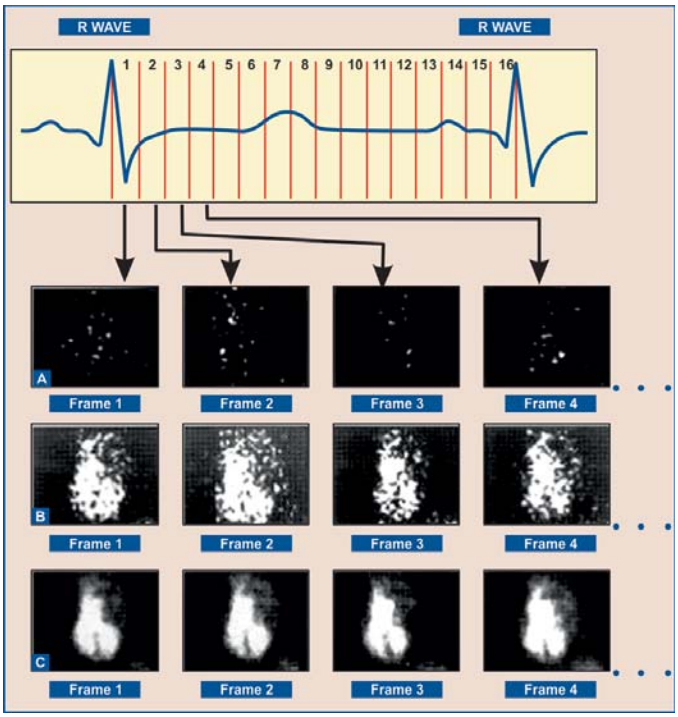


FIGURE 21: Computer acquisition of the equilibrium study (see text) (*Source:* Modified from Parker DA, Karvelis KC, Thrall JH, et al. Radionuclide ventriculography: methods. In: Gerson MC (Ed). Cardiac Nuclear Medicine, 2nd edn. Legend adapted with permission from Botvinick EH (Ed). Physical and technical aspects of nuclear cardiology. Self-Study Program III; Nuclear Medicine: Cardiology, Soc Nucl Med Publ.)

blood pool agent, typically labeled red blood cells, which are injected, and then allowed to mix with the 5–6 liters of blood in a typical subject. After 3 or 4 minutes of mixing, the tracer will be uniformly distributed, and the tracer is then said to be "in equilibrium". If a single heart beat were 960 msec long (i.e. a heart rate of about 63 bpm), we could divide that single beat into 16 images, each 60 msec long. The first image would be acquired for 60 msec and then the second would acquire all the data in the next 60 msec, etc. Each image would reflect a different portion of the cardiac cycle, from end diastole through systole, and back again. Unfortunately, an acquisition that was only 60 msec long would have too few counts to make an interpretable image. With the typical activities injected in a patient (10–30 mCi, or 370–1,110 MBq for either blood pool or myocardial imaging), one would need to acquire each image many 100s of times longer—perhaps 10–20 seconds or longer. To solve this problem, we use the technique of ECG gating. Here, an ECG is connected to the patient, and its output is put through a "trigger" device which generates a "gating" signal at each R wave peak, for example. For the first 60 msec after the first R wave, all the photons are sorted into the first image. After 60 msec have elapsed, all data are then sorted into the second image, and so on. Finally, at the next R wave, signifying the beginning of the next cardiac cycle, the process is repeated, and the next 60 msec of data are again added to the first image (called image 1 in the Figure), and similarly for all the subsequent images. If this process continues for 300 beats, then each image is acquired for (60 msec/beat)*300 sec = 18 seconds. Note that the total acquisition time for collecting data is not determined directly by the imaging time, but rather by the number of beats times the duration of each frame. At high heart rates, then, this time builds up more quickly than at low heart rates. Computer acquisition of the ERNA is illustrated in Figure 21. Shown is the relationship between the cardiac cycle or R-R interval acquired over 16 separate frames or intervals and the related images in each frame over the course of the acquisition. The counts acquired during the frame 2 are stored in frame 2; those acquired during frame 3 are stored in frame 3 and so on. Only data accumulated over the first four frames is illustrated here. Owing to the low count rate in this study, 750 counts per frame, there is little to see after acquisition over a single cycle (A). However, after the accumulation and addition of the counts from 20 R-R cycles, now with 15,000 counts per frame, the cardiac chambers are taking from (B). With the addition of counts acquired over 400 cycles and 300,000 counts per frame, image quality is excellent and the acquisition is over (C). A typical but relatively high frequency ERNA time versus radioactivity curve is shown in Figure 22.

A RV region of interest can be applied to an end diastole and end systole region of interest in an equilibrium blood pool study to calculate RVEF. Overlap of the right atrium reduces accuracy of RVEF calculation but the method compares well with other methods for RVEF measurement, a difficult task by all methods due to the position and shape of the chamber.

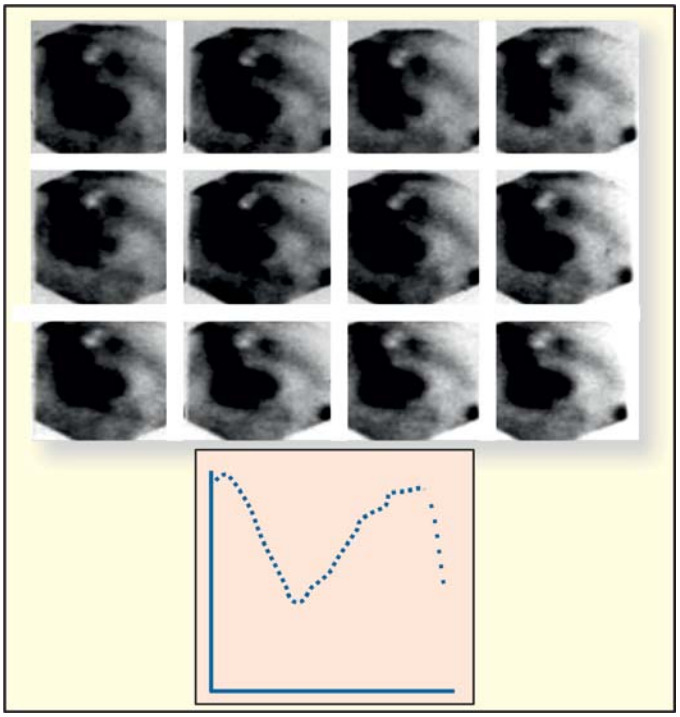


FIGURE 22: Equilibrium radionuclide angiography images and time versus radioactivity curve. Shown above, in the "best septal" projection are 12 selected frames from a multiple-gated equilibrium study. End diastole is shown at upper left, with contraction progressing left to right and top to bottom. End systole is in frame 5, below end diastole. A clear halo around the left ventricular images here relates to the myocardial boundaries, suggesting hypertrophy in this case. The area of reduced radioactivity in the region of the septum is of normal thickness, as may be seen with pericardial effusion. However the halo does not extend to the pericardial reflections, as is commonly seen with a large, nonloculated effusion. Below is the time versus radioactivity curve derived from counts in the left ventricular region in this study where peak counts are proportional to end diastolic volume and lower counts are proportional to end systolic volume. Terminal count fall-off relates to irregularity of the cardiac rhythm and R-R interval over the acquisition period, where short cycles do not add data to the terminal frames (*Source:* Modified from Green MV, Ostrow HG, Douglas MA, et al. High temporal resolution ECG-gated scintigraphic angiocardiography. J Nucl Med. 1975;16:95-8. Legend adapted with permission from Botvinick EH (Ed). Physical and technical aspects of nuclear cardiology. Self-Study Program III; Nuclear Medicine: Cardiology, Soc Nucl Med Publ.)

THE VALUE OF FUNCTIONAL IMAGING

There are many useful clinical parameters which can be extracted from the LV volume curve shown in the previous figures. The most useful measure is EF, defined as stroke volume (SV)/ED volume = (ED counts - ES counts)/ED counts, where the counts are corrected for background. Many other parameters can be extracted from this curve including the peak ejection rate and its time of occurrence, the time to end systole and the peak filling rate. A variety of functional images are illustrated in Figure 23.

Equilibrium radionuclide angiography (ERNA) functional or parametric images are of value in adding objectivity to the interpretation of studies to evaluate exercise evaluation of possible coronary disease (Figs 24A to C), the pathophysiologic significance of aortic regurgitation or other valve lesion (Figs 25 and 26). A regurgitant index, quantitating the relative regurgitant volume can be accurately calculated.[68]

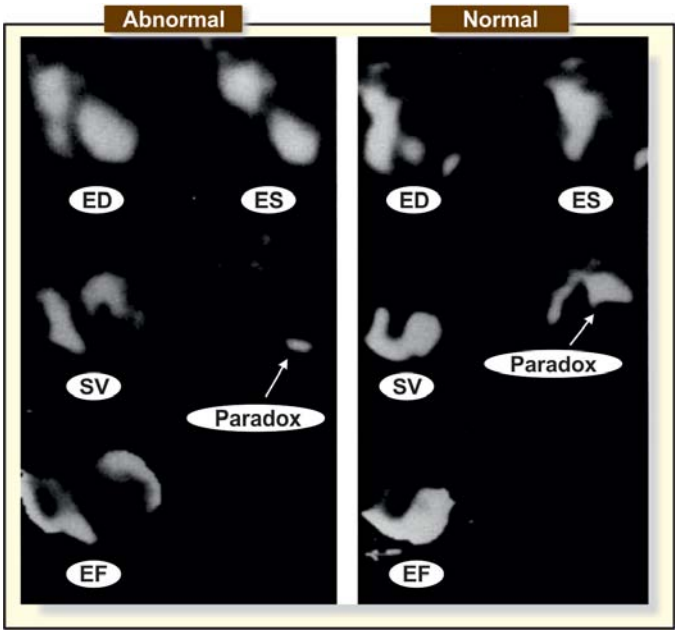


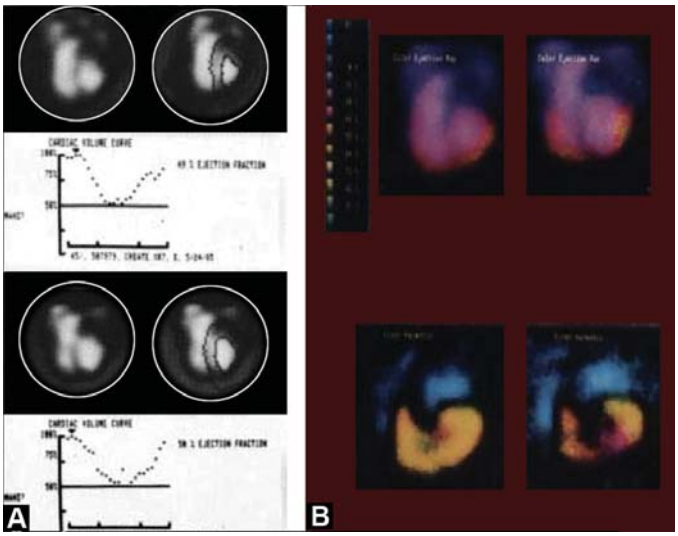
FIGURE 23: Functional or parametric images. Shown in the left panel above are end diastolic (ED) and end systolic (ES) frames from a normal equilibrium blood pool study. In the center row are stroke volume (SV) and paradox images. The former represents the pixel-by-pixel representation of the difference in ED and ES counts, while the latter represents the converse. Since ES-ED represents a positive value in the atrial regions, they are evident in the paradox but not in the SV image. Conversely, ventricular regions are well seen in the SV image but present negative values in the paradox image and are absent. Unlike SV and paradox images, amplitude images are sign neutral and will proportionately present any region that changes counts (volume) with the cardiac cycle, regardless of its phase. The bottom row shows the ejection fraction (EF) image, where each pixel of the SV image has been divided by per pixel ED counts, yielding an image comprised of pixel-by-pixel, intensity coded EF. At right are the same parametric images derived from a patient with a left ventricular apical aneurysm (*Source:* Modified from Botvinick EH (Ed). Radionuclide angiography: equilibrium and first pass methods. Self-Study Program III; Nuclear Medicine: Cardiology, Soc Nucl Med Publ.)

PHASE ANALYSIS

Phase image analysis is based on functional images derived from the gated ERNA. They have been successfully applied to characterize the sequence of ventricular contraction. While ERNA is a long established method, this application promises added clinical value in the assessment of the newest treatment of advanced heart failure, CRT. The basis for the method and some applications are illustrated in Figures 27 and 28.

IMAGING MYOCARDIAL SYMPATHETIC INNERVATION

Metaiodobenzylguanidine (MIBG) is an analog of norepinephrine and can be radiolabeled to reveal a map of the scattered presynaptic terminals throughout the rich myocardial sympathetic innervation. Autonomic abnormalities may be a common final pathway for sudden cardiac death, taking 300,000–400,000 yearly. Normal values have been established.[69-72] Extensive studies have demonstrated that scintigraphic evaluation of ^{123}I labeled MIBG intensity and distribution can aid risk stratification and therapy in patients with heart failure of any cause.[73-77] The agent is now completing Phase III evaluation and will, pending



Rest		Exercise
127	EDV(cc)	158
65	ESV(cc)	79
62	SV(cc)	79
49	LVEF(%)	50
65	HR(bpm)	126
4	CO(1/min)	10
	Workload 400 kpm	

C

FIGURES 24A TO C: The value of functional imaging. In (A), at left shows the automated left ventricular edge fit to the equilibrium blood pool image of a patient with coronary disease, above, at rest, and below during peak reclining bicycle exercise. The LVEF showed no significant change. However induced wall motion abnormalities are clearly seen in (B), with a loss of septal intensity at stress, right, compared to rest, left, in the color ejection images, with a break in the "ejection shell" above, and with reduced amplitude, an analog of regional stroke volume, the red color in the septum of the stress image, right, compared to rest, left, in the color amplitude images, below. Shown in (C) are the volumes calculated from this blood pool data at rest and stress, where end diastolic (EDV) and end systolic volume (ESV) increased. Note the blunted LVEF response with a rise in ESV with exercise (Abbreviations: CO: Cardiac output; HR: Heart rate; LVEF: Left ventricular ejection fraction; SV: Stroke volume) (*Source:* Modified from Botvinick EH, Dae MW, O'Connell JW. Blood pool scintigraphy. Cardiol Clin. 1989;7:537-63. Legend adapted with permission from Botvinick EH (Ed). Radionuclide angiography: equilibrium and first pass methods. Self-Study Program III; Nuclear Medicine: Cardiology, Soc Nucl Med Publ.)

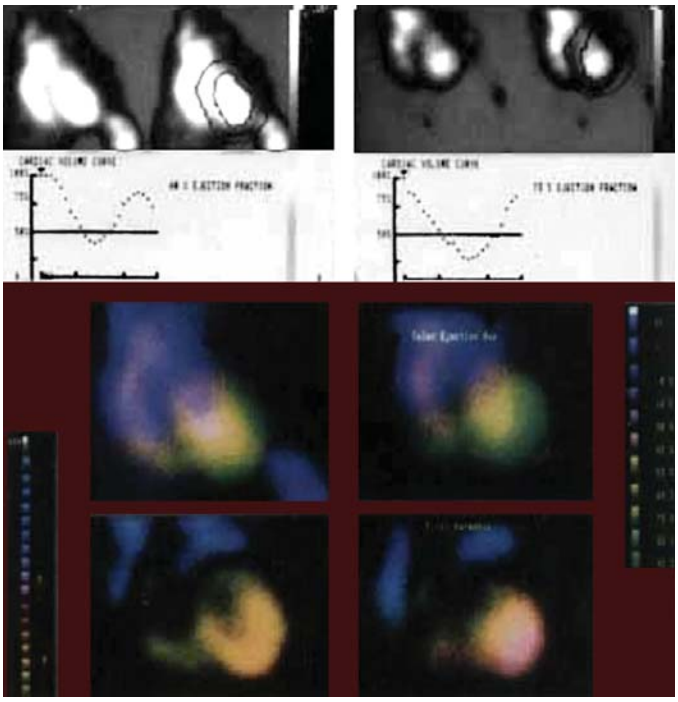
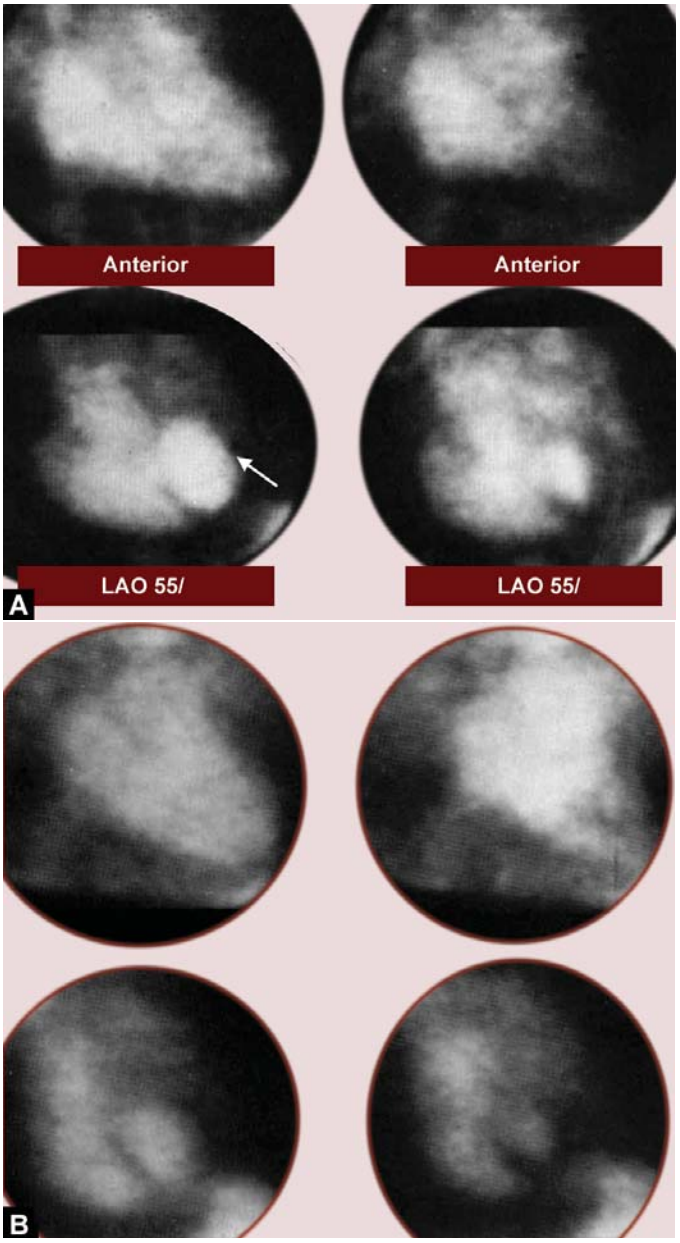


FIGURE 25: Equilibrium blood pool assessment of aortic regurgitation. Shown are left ventricular time versus activity curves derived from a left ventricular region of interest (top panel); ejection fraction images, color-coded for regional ejection fraction (middle panel); and phase-amplitude images (bottom panel), at rest (left) and with maximal exercise (right) in a young patient with severe aortic regurgitation. Here, the left ventricular edge is derived between the limits of the edges drawn, and background is taken within these geometric boundaries. Dual color and intensity coded images, shown here, permit the integration of multiple parameters in a single image and are an example of the analytic and display potential of the scintigraphic modality. The LVEF increases with exercise. This is supported by the increased area covered by yellow and green and high ejection fraction values in the ejection fraction image. Although colors shift to later phase angles as heart rate increases, amplitude, intensity, is maintained and apparent ventricular size decreases in all images, consistent with a normal response to exercise. The uniform phase shift, related to increased symmetry of the time versus radioactivity curve with increased heart rate and shortening of end diastole, represents a normal finding, as do all the image results shown here (*Source:* Modified from Botvinick EH, Dae MW, O'Connell JW. Blood pool scintigraphy. Cardiol Clin. 1989;7:537-63. Legend adapted with permission from Botvinick EH (Ed). Radionuclide angiography: equilibrium and first pass methods. Self-Study Program III; Nuclear Medicine: Cardiology, Soc Nucl Med Publ.)

likely early FDA approval, soon be available. A large prognostic multicenter trial including 55 in the United States and 25 in the European medical centers, studies New York Heart Association Class II–III CHF patients with LVEF less than 35% by SPECT MIBG. In heart failure, a low heart/mediastinal (H/M) MIBG ratio less than 1.2 or a slow myocardial washout less than 27% per hour indicates a poor prognosis, even in the absence of CAD. Diabetics are at an increased risk since the condition appears to effect autonomic innervation in an independent manner. In some studies, the H/M was a more significant predictor of death than the LVEF. Improvement in this ratio could serve to demonstrate the beneficial effects of heart failure therapy (Figs 29 and 30). Evidence suggests that denervated regions with preserved perfusion, an MIBG/perfusion mismatch, place the patient at greatest risk. The combination of heart rate variability, another reflection of autonomic innervation, and MIBG washout appears to reflect survival and varies with treatment in CHF patients. This combination of heart rate variability and MIBG distribution differentiated between those with implanted defibrillators who did or did not receive a shock on follow-up evaluation. PET imaging of perfusion and the norepinephrine analog 11C-HED could add yet greater resolution and quantitation to this evaluation, but would require an on-site cyclotron. The potential role for MIBG in the clinical evaluation of the heart failure patient is presented above (Figs 29 and 30). MIBG image findings may well impact too on the state of chemotherapy induced cardiotoxicity.

RADIATION CONCERNS

When taken in the context of natural background radiation, man-made radiation represents 18% of that delivered. Yet, this is primarily medical in origin and, of course, may be controlled



FIGURES 26A AND B: Gated blood pool studies pre- and post-repair of mitral regurgitation. Panel (A) illustrates end diastolic (left) and end systolic (right) images in the anterior (top) and "best septal" (bottom) projections in the equilibrium blood pool study in a patient with a systolic murmur, breathlessness and fatigability. The arrow points to the enlarged left ventricle in this patient presenting with severe mitral regurgitation. Panel (B) illustrates the study post-mitral valve replacement, in the same format. The size and relative intensity, indicators of volume, of the left ventricle, are dramatically reduced. The obvious visual difference between right and left ventricular stroke volume present on the preoperative study is no longer evident after surgery (*Source:* Modified from Botvinick EH, Dae MW, O'Connell JW. Blood pool scintigraphy. Cardiol Clin. 1989;7:537-63. Legend adapted with permission from Botvinick EH (Ed). Radionuclide angiography: equilibrium and first pass methods. Self-Study Program III; Nuclear Medicine: Cardiology, Soc Nucl Med Publ.)

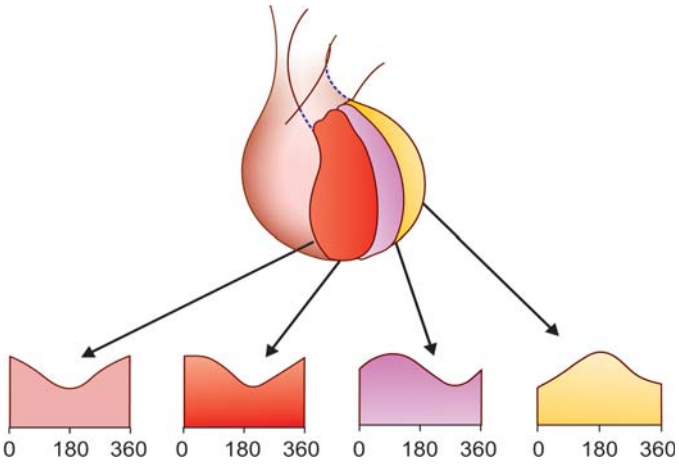


FIGURE 27: Phase analysis. This diagram presents a ventricle that is gray scale coded for increasing delay in contraction sequence from septum to lateral wall. The resultant cosine curves, fitted to the regional time-versus-radioactivity curve, are shown below. The septum and its corresponding curve begin contraction at the R wave. The region has a phase angle of 0° and is coded dark gray. The lateral wall and its related cosine curve fill when the ventricle should empty. This wall would demonstrate paradoxical motion and the curve would have a phase angle of 180° (*Source:* Modified from Exerpta Medica, Inc. from Frais MA, Botvinick EH, Shosa DW, et al. Phase image characterization of ventricular contraction in left and right bundle branch block. Am J Cardiol. 1982;50:95-105)

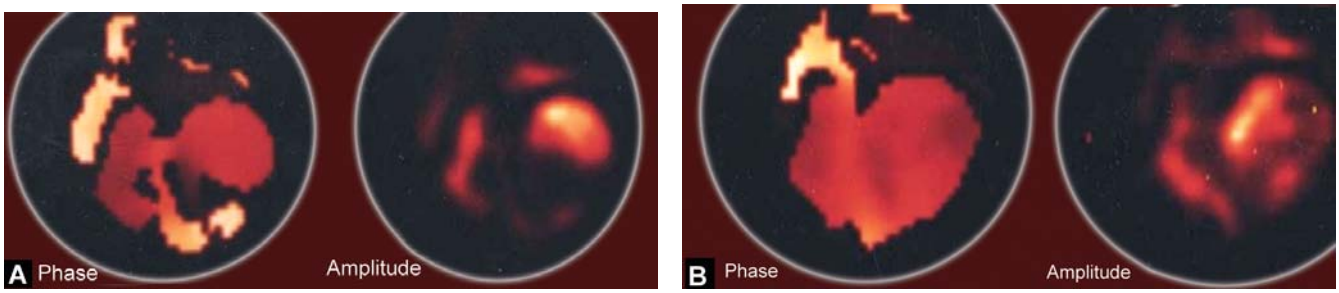
by design and application of diagnostic and therapeutic methods. The seventh report of the National Research Council's Committee on the Biological Effects of Ionizing Radiation (BIER) on the medical effects of low dose ionizing radiation was released in 2005.[78] It assumes a linear dose response relationship between exposure to ionizing radiation and the development of solid and hematologic cancers in humans. Absorbed radiation dose refers to the amount of energy deposited by exposure to the ionizing radiation per patient unit mass. Units of absorbed radiation dose are rads or milliards in conventional units or gray in international system of units (SI). The effective dose is expressed in conventional units of rem or millirem or the SI units of sievert (Sv) or millisievert (mSv). Since the effects of low dose radiation, from 0 to 100 mSv (millisieverts), are small and so difficult to measure, a linear response is extrapolated from high dose effects. Although such extrapolation and these related effects are controversial, they are not inconsequential and must be considered in ordering and performing any test with such potential effects. The full body effective dose is highest for MPI performed with ^{201}Tl or with the dual isotope ^{201}Tl rest-^{99m}Tc stress protocol and less when performed exclusively with ^{99m}Tc-based agents or ^{82}Rb. Of course, stress only ^{99m}Tc or ^{82}Rb studies present lowest dose (Tables 8 and 9). A 64 slice modified discrete cosine transform (MDCT) without ECG pulsing but with retrospective gating

TABLE 8

Radiation dosage of selected exposures

Study	*Total body effective dose (mSv)*
Chest radiographs in 2 views	0.08
Mammogram	0.13
Average US background radiation	3.0/y
Smoking cigarettes	2.8/y
Air travel	0.01 per 1000 miles

Source: Thompson RC, Cullom SJ. Radiation dosage of cardiac nuclear and radiography procedures. J Nucl Cardiol. 2006;13:19-23.



FIGURES 28A AND B: Phase image analysis of synchrony before and after biventricular pacing. Shown are examples of phase and amplitude images, left and right in each panel, respectively, derived from gated blood pool scintigrams in a patient with heart failure. Panel A shows images acquired from the patient at baseline, with evidence of gross regional dyssynchrony in the phase image at left (white color in the septum and apex) and with reduced amplitude in most of the distal LV, as shown by the low intensity regions of the amplitude images at right. In panel B, color is more homogeneous and phase is more synchronous, with much improvement in the intensity of the amplitude image following biventricular pacemaker insertion. Not surprisingly, the patient was much improved clinically after the procedure (*Source:* Modified from Rosenquist M, Botvinick EH, Dae M, et al. Left ventricular function during pacing: the relative importance of activation sequence compared to AV synchrony. J Nucl Med. 1990;31:752)

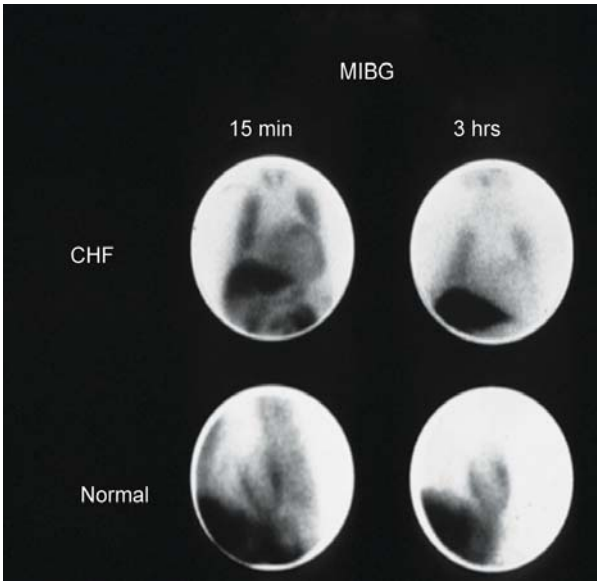


FIGURE 29: MIBG imaging in congestive heart failure (CHF). Shown in these anterior planar images is the distribution of ^{123}I MIBG in a patient with CHF and a normal patient. The CHF distribution is marked by the presence of a markedly enlarged heart with dense lung uptake on both early and late imaging, poor myocardial tracer localization on early imaging and near complete washout on late imaging. This stands in contrast to the normal cardiac contour, brisk myocardial localization and excellent target to lung background on the delayed images in the normal patient (*Source:* Courtesy of Dae M, MD, UCSF, San Francisco, CA)

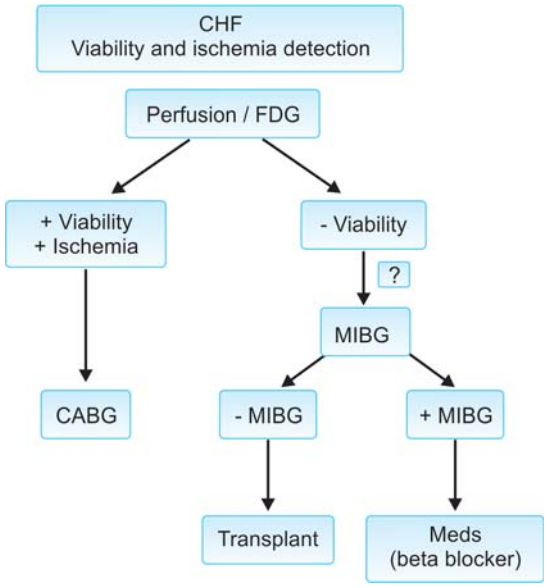


FIGURE 30: Possible role of MIBG in the management of severe congestive heart failure (CHF) with systolic dysfunction. First a determination must be made of the myocardial viability of abnormally contracting and poorly perfused segments. In those with coronary disease, evident ischemia, and "sufficient" viable myocardium, coronary artery bypass (CABG) or percutaneous catheter intervention, stent, may be performed. In those without viability or in the absence of coronary disease which may be revascularized, MIBG imaging may be performed. MIBG uptake indicates preserved neuronal binding sites and the potential for improvement and reduced risk with beta blockers and medical therapy. In the absence of MIBG uptake, heart transplantation would be the remaining option (*Source:* Courtesy of Dae M, MD, UCSF, San Francisco, CA)

optimizes the accuracy of the CTCA method but presents a much higher effective dosage, while CT applied only as a transmission source delivers a very low exposure. The radiation exposure from CT to females is much greater than to males and the CT exposure to the female breast, intervening between X-ray source and target and a focus of the delivered X-ray, is high and far exceeds that of scintigraphic methods, where the dose is delivered more uniformly body wide and to the target organ. While the risks are real, they are relatively small in patients in the coronary disease age range, increasing cancer mortality from 0.01 to 0.05%. Further, this increment is applied over the life of a patient and decreases in impact with increasing age at application. They are far less significant in the elderly. The cardiovascular risk addressed by many such studies is much greater, and focused on a brief period of decision and management. Physicians working with these methods must be fully informed regarding the dosimetry and the technical aspects of the diagnostic test. The basic principle to keep dosage as low as possible must be observed. However, as clinicians, they must also weigh the clinical need and risks versus benefits, in order to apply to the patient the proper evaluation with greatest accuracy and least ambiguity. Preferably the test selected will make others (which give yet further radiation exposure)

TABLE 9

Radiation dosage of cardiovascular radionuclide studies

Study	*Total body effective dose (mSv)*
^{99m}Tc trofosmin rest-stress (10 mCi + 30 mCi)	10.6
^{99m}Tc sestamibi 1-day rest-stress (10 mCi + 30 mCi)	12
^{99m}Tc sestamibi-stress only (30 mCi)	8
^{99m}Tc sestamibi 2-day stress-rest (30 mCi + 30 mCi)	17.5
^{201}Tl stress and reinjection (3.0 mCi + 1.0 mCi)	25.1
Dual-isotope (3.0 mCi ^{201}Tl (30 mCi ^{99m}Tc)	27.3
^{82}Rb PET myocardial perfusion (45 mCi + 45 mCi)	16
Ge-68 or Gd-153 transmission for PET (approximate)	0.08
CT transmission source for PET (low-dose CT protocol)	0.8
Fluorine 18 FDG PET viability (10 mCi)	7
ERNA, ^{99m}Tc -labelled RBCs (20 mCi ^{99m}Tc)	5.2
Ventilation/perfusion lung (200 MBq ^{99m}Tc MAA + 70 MBq ^{99m}Tc aerosol)	2.8

unnecessary. A stimulating overview of this issue has recently been published.[79] Also to be considered and addressed is the general public phobia of all things radioactive. While the public attitudes toward nuclear power as a method of energy generation had recently been mellowed with realization of its benefits, an increased and almost certainly exaggerated concern has emerged with the recent events related to the natural disaster in Japan. This has reignited the ever present phobia which certainly extends to the medical use of nuclear methods and must be addressed through a rational consideration of events, alternatives and public education. The involved, informed physician advocate must take the educational lead. While concerns are not without basis, they must be kept in perspective. Patients must not be permitted to discard a useful and beneficial diagnostic or therapeutic method simply because it is "nuclear". Unfair and biased use of this public fear and prejudice by other physicians for their own benefit must not be permitted. The public must be made aware that radiation is a fact of life to which they are exposed constantly with increased exposure at altitude and even when sleeping with their partner. While all accept these as reasonable and even necessary exposures with an acceptable risk, so too are appropriately applied diagnostic nuclear imaging and radiographic methods.

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Chapter 22

Cardiac Computed Tomography

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Chapter Outline

- Technical Aspects
  - Basic Principles of Computed Tomography
  - Radiation
  - Image Analysis
  - Image Quality and Artifacts
  - Contrast
- Coronary Artery Disease
  - Noncontrast CT and Coronary Calcifications
  - Contrast CT Coronary Angiography
  - Coronary Stent
  - Coronary Bypass Grafts
  - Anomalous Coronary Arteries
  - Other Coronary Findings
- Myocardium and Chambers
- Pulmonary Veins
- Cardiac Veins
- Valvular Disease
- Pericardium
- Masses
  - Malignant Cardiac Neoplasm
  - Noncancerous Masses
- Incidental Findings
- Future
- Guidelines

INTRODUCTION

Soon after Sir Godfrey Hounsfield first developed his prototype computed tomography (CT) scanner in the early 1970s,[1] there was interest in imaging the heart. The first scientific report of CT of the heart was in 1976.[2] Reports of EKG gated image acquisition[3] and the concept of "stop-action" heart imaging occurred in 1977.[4] The first scanners acquired data over several minutes, and image analysis was done overnight by assistance of primitive computer technology. The initial CT scanners were affected by low temporal and spatial resolution. Ultrafast CT, also called electron beam CT, was introduced in the 1980s and allowed for temporal resolution that was a fraction of a second. This allowed for reliable imaging of the heart but spatial resolution was suffering. Its greatest strength was detection of coronary calcifications and coronary stenosis analysis was less reliable. Greater spatial resolution was obtained by helical multidetector row CT technology.[5] Multidetector row technology allowed for subsecond temporal resolution and submillimeter spatial resolution. First multicenter trial was done in 2004 with 16 detector row scanner[6] and following this a progressive increase in number of detector rows has currently peaked at 320 with spatial resolution of 0.4 mm and temporal resolution of 150–200 ms. Dual source CT has further improved temporal resolution to about 80 ms by adding a second set of generator and detector. With the advent of multidetector row technology the radiation exposure was initially increased but with progressive improvements in image acquisition protocols there has been dramatic reduction in radiation. Current top of the line scanners can acquire a single phase image of the whole heart within a fraction of a second with radiation dose that is 60–80% less than a standard abdominal or chest CT.[7,8]

Due to progressive improvement in CT technology, both hardware and software, the image acquisition can be done in a few seconds and computerized processing of raw data takes a few minutes resulting in thousands of images covering the whole heart from different parts of the cardiac cycle. With multiphase imaging the door has been open not only to evaluation of the coronary anatomy but also to comprehensive analysis of other heart structures including chamber sizes, biventricular systolic function, regional wall motion abnormalities, valve pathology, cardiac masses and congenital anomalies.

TECHNICAL ASPECTS

BASIC PRINCIPLES OF COMPUTED TOMOGRAPHY

Image acquisition during CT relies on catching X-ray beams as they travel through the body. This requires an X-ray generator and X-ray detector. To produce an axial image or a "slice" of the body, with minimal artifacts, the X-ray beam has to travel through the body at multiple angles, and images are produced from the attenuation pattern of X-rays as they reach the detectors.

X-ray beams are generated identically to X-rays during standard chest X-ray or invasive coronary angiography. X-ray generator will produce X-ray beams of differing *energy* [kilovoltage (kV)] profiles and *current* [milliamperes (mA)]. Most commonly used energy profile is 100 or 120 kV based on patient size. Imaging acquisition done simultaneously with multiple energy profiles (ranging 80–140 kV) can allow for better tissue discrimination (e.g. dual energy imaging).

The X-ray detectors generate images by the assistance of complex mathematical models calculated by computer, hence

the prior nomenclature of computer assisted tomography or "CAT" scanning. Current high-end CT detectors have multiple rows of detectors that can capture 64–320 slices or images during partial rotation. Collimation typically used during cardiac images aims at smallest possible slice thickness of about 0.5–0.75 mm. In combination with standard reconstruction algorithm using 50% overlapping, the *spatial resolution* can be as low as 0.4 mm.

Gantry of the CT scanner refers to the circular or doughnut shaped structure that holds the X-ray generator and detectors. The gantry rotates around the patient and current high-end CT systems will complete a full rotation of 360° in 270–500 ms. The patient is placed within the middle of the gantry on a table that will move in a longitudinal plane most often referred to as the *Z-axis.* Longitudinal movement of the scan table in *Z-axis* in relationship to the detector size is referred to as *pitch*. Formula for pitch is table movement during image acquisition divided by detector length.

In most scanners the detector length or combined coverage of all detector rows is less than the longitudinal length of the heart in *Z-axis*. Two modes of scanning exist to allow for this shortcoming. One called *helical* (or *spiral*) *scanning* where continuous radiation is generated with continuous image acquisition. Typically this is done with very slow motion of the CT table in *Z-axis* (low pitch of 0.2–0.5). Slow motion of the scan table makes for low pitch and redundant data collection with an increased radiation. This allows for flexibility in postprocessing reconstruction algorithms where, if the patient has an ectopic beat, the EKG editing tool can give an option to remove the raw data related to the ectopic beat. This can improve image quality substantially and allows for greater reliability of acquiring diagnostic images. More recently dual source scanners have allowed for a unique high pitch mode of 3.4 ("FLASH" mode, Siemens) where there is a minimal redundancy of raw data and considerable lowering of radiation with image acquisition time for the whole heart of about 280 ms.

Second mode is *axial scanning.* During this mode, the CT table does not move during image acquisition and images are acquired in axial mode only. No spiral scanning is done. While moving to the next position the radiation is turned off. When the CT table has reached the next segment it will stop and wait until the correct portion of the EKG is reached. When the predetermined cardiac cycle is reached, axial images are acquired again. This sequence of events is frequently referred to as "step and shoot" as the scanner first steps and then shoots the radiation. This mode is used primarily when heart rate is less than 65 bpm as diastasis is then long enough to allow for motion free image acquisition.

To produce an image with minimal artifacts most scanners will need to cover more than 180° or half rotation plus the detector fan beam angle. *Temporal resolution* is dependent on gantry rotational speed that is limited by centrifugal forces and rotational time of about 300–400 ms. As such single source CT scanners (single set of generator and detector) will have temporal resolution of greater than 150 ms during axial imaging. Dual source CT scanners have two sets of generator/detector. This allows for rapid image acquisition and temporal resolution of 83 ms during axial imaging.

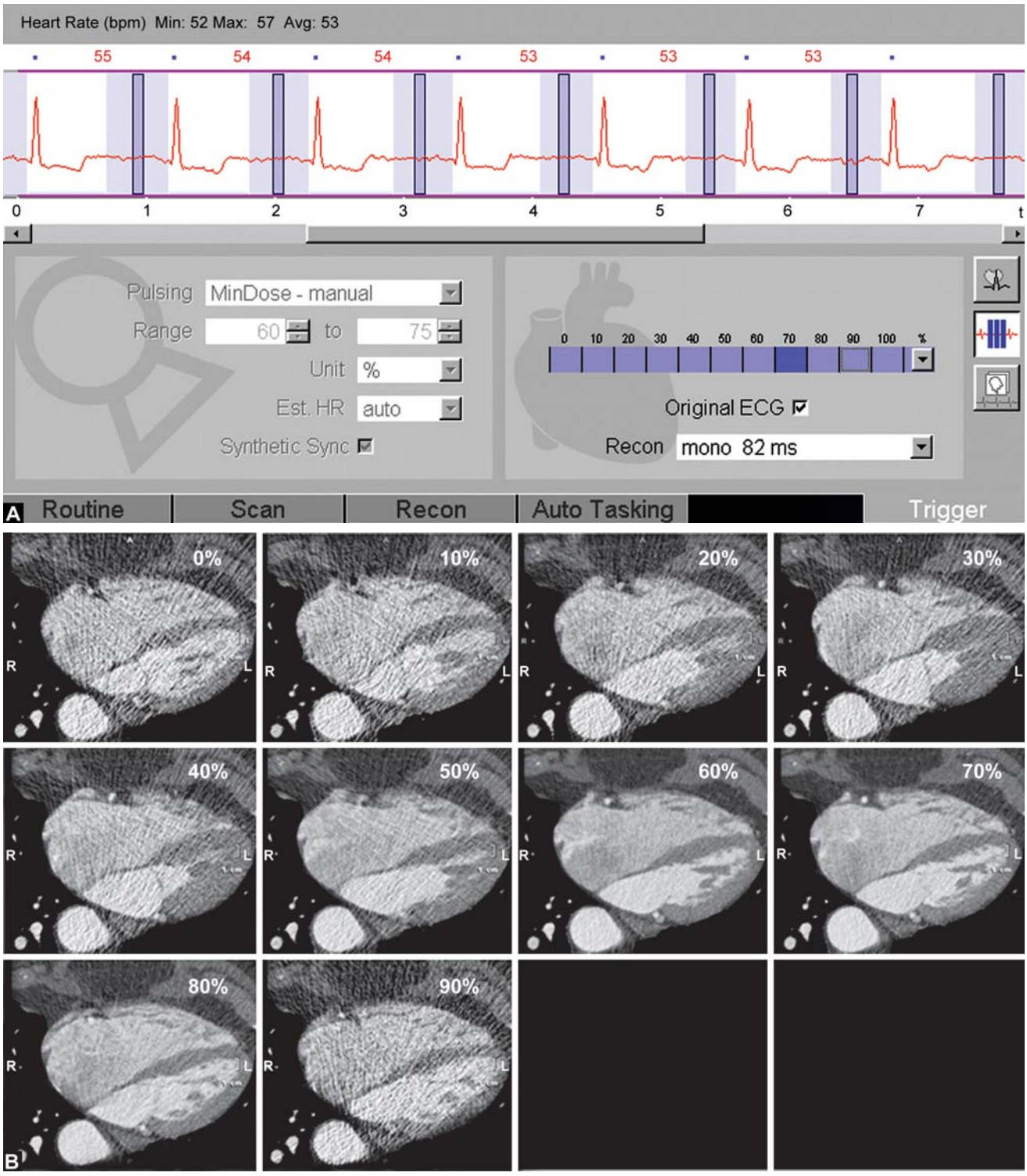
Single source CT scanners can attempt to improve temporal resolution by a postprocessing method called *multi-segment* or *multi-cycle reconstruction*. This requires use of continuous helical (spiral) scanning mode at low pitch (< 0.5) and post-processing methods which include partial data from several cardiac cycles and at different adjacent angles but within near identical phase of the cardiac cycle. This method can lower temporal resolution 2–3 fold but this requires minimal heart rate variability that is typically only seen with heavy beta-blockage, in transplanted hearts or in patients with severe cardiomyopathy.

Due to cardiac motion it is essential to have EKG gating during image acquisition and reconstruction. As images are always acquired with EKG data present and reconstruction of raw data is always done based on the corresponding EKG, it could be stated that all cardiac CT is done with retrospective gating (Table 1). But in general, when referring to prospective or retrospective EKG gating a reference is made to how the X-ray generation is controlled. Early CT protocols would not allow for prospective EKG-gated radiation modulation and continuous radiation was produced and protocol called only

TABLE 1

CT protocol terms

General protocol terms	*Scan mode*	*Pitch*	*Prospective EKG gated X-ray generation*	*EKG editing*	*Image reconstruction*	*When used*	*Radiation*
Retrospective	Helical mode	0.2–0.5	No	Yes	Retrospective	Irregular heart rhythm, e.g. Atrial fibrillation	Highest
Dose modulated	Helical mode	0.2–0.5	Yes—Prospective modulation of current (mA)	Yes	Retrospective	Coronary and ventricular function analysis	Intermediate
FLASH or high pitch	Helical mode	3.4	Yes—Prospective during diastole only	No	Retrospective	Coronary analysis when heart rate is below 65 bpm	Lowest
Prospective or Step and Shoot	Axial mode	1	Yes—Prospective interrupted mode (on and off)	If padding (window) is increased	Retrospective	Coronary analysis when heart rate is below 65 bpm	Lowest
Sequential adaptive	Axial mode	1	Yes—Mix of modulation and interrupted mode	Limited	Retrospective	Coronary analysis when heart rate is below 65 bpm	Low—Intermediate



FIGURES 1A AND B: (A) EKG gating and dose modulation. Helical scanning allows for variable dose of radiation during the cardiac cycle, hence radiation dose modulation. The pictures show an example of dose modulation where full dose of radiation is only administered during diastolic phases (light blue 60–90%). In this example, the 70% phase (dark blue) is selected for reconstruction. (B) Phase selection. Sample of image from 10 equally spaced phases. Dose modulation with radiation reduction is caused for granular images in several phases. The 70% phase shows the least motion of the RCA and was selected for coronary analysis

"*retrospective*". This protocol is currently used only for patients with very irregular rhythm, such as atrial fibrillation, where EKG editing is frequently required.

Other image acquisition protocols utilize EKG gating to decrease radiation in a prospective manner. EKG from prior cardiac cycles is used to predict when it is optimal to generate radiation. The common protocols are "dose modulation" and axial scanning. The "*dose modulation*" protocol (Figs 1A and B) is done with helical scanning, and during image acquisition the scanner will prospectively lower the current (mA) by 80–96% during a selective portion of the cardiac cycle (frequently late diastole and early systole) and allow full dose

during the motion less part of the cardiac cycle, late systole (isovolemic relaxation) and/or mid-diastole (diastasis). The *axial* protocol frequently termed "*prospective*" "*axial-sequential*" or "*step and shoot*" protocol are based on EKG of prior beats and the X-rays are only generated during specific portion of the cardiac cycle (e.g. diastasis) where X-ray generation is done with table/patient stationary and, while X-ray generation is turned off, the table moves patient to allow imaging of another portion of the heart. In the new table position, the X-ray generation is not started until the quiescent portion of the EKG is reached. Newer protocols with novel features are "FLASH" and "sequential adaptive". The "FLASH" mode has been described earlier and the sequential adaptive protocol is an example of a mixed protocol that does both axial imaging and dose modulation without spiral scanning. The last two protocols are specific to Siemens equipment.

RADIATION

Utilization of medical imaging with ionizing radiation is rapidly growing. Radiation with each modality alone is considered low (< 50–100 mSv) but serial imaging and cumulative exposure is of concern. Medical personnel exposed to radiation are limited to an exposure of 50 mSv per year. Calculation of risk for cancer with ionizing radiation is based on data from World War II atomic bombing, with substantially higher radiation doses than are seen in medical imaging. The assumption of a linear relationship between very low level radiation exposure and cancer risk are not accepted by all societies.[9]

Technical advancements have allowed for considerable lowering of radiation with cardiac CT. The most advanced scanners are able to perform cardiac CT with an equal or lower dose than annual background radiation (2–4 mSv). Less advanced CT scanners are now able to use protocols with radiation that is comparable or lower than invasive angiography, nuclear studies or standard CT of chest or abdomen[10,11] (Table 2).

When considering the use of cardiac CT the risk-benefit ratio with radiation and contrast need to be weighed against the benefit of correct diagnosis. For example, the risk of missing the diagnosis of acute coronary syndrome in an emergency room patient is 2.1% and theoretical estimated lifetime risk of cancer following dose modulated cardiac CT is less than 0.5%.[12]

TABLE 2

Radiation with CT and other modalities[10,11]

Examination	*Representative Effective dose value (mSv)*	*Range of reported Effective dose value (mSv)*
Chest X-ray PA and lateral	0.1	0.05–0.24
CT chest	7	4–18
CT abdominal	8	4–25
CT pelvis	6	3–10
Coronary calcium CT*	3	1–12
Coronary CT angiogram	16	5–32
64-Slice coronary CTA		
without tube current modulation	15	12–18
with tube current modulation	9	8–18
with lower energy—100 kV	8.4	—
Dual-source coronary CTA		
with tube current modulation	13	6–17
Prospectively triggered coronary CTA	3	2–4
Diagnostic invasive coronary angiogram	7	2–16
Percutaneous coronary intervention or radiofrequency ablation	15	7–57
Myocardial perfusion study		
Sestamibi (1-day) stress/rest	9	—
Thallium stress/rest	41	—
F-18 FDG	14	—
Rubidium-82	5	—

IMAGE ANALYSIS

Current multidetector technology gives isotropic image reconstruction where each pixel in an image can be viewed as a voxel with equal resolution in x-, y- and z-axis. This isotropic image resolution allows for image analysis from any view (axial/sagittal/coronal) without distortion. This was not possible with prior electron beam technology. Each image pixel has designated CT value or density value also named Houndsfield unit (HU). In routine imaging of the body (at 120 kV) these density values can differentiate accurately between soft tissue and bone where bone will have density value from 130 to more than 1,000. Fat tissue has negative HUs (–20 to –150). Muscle and blood will have similar density 30–70 HU. Intravenous contrast administration allows for differentiation of blood and muscle. Contrast administration will increase density of blood pool to 100–500 HU depending on contrast type, rate of administration and mixture. Contrast administration will also increase density of soft tissue depending on vasculature of the tissue.

Energy level (kV) during image acquisition will affect density values of contrast, soft tissue and bone. Lower energy level to 80–100 kV will make for denser images where contrast enhanced blood will have higher density (HU) and calcium or bone will have density above 150–200 HU. The effect of differing density with differing energy levels can be used to differentiate between tissues and extract contrast ("iodine mapping") or to differentiate better between contrast and calcium.

Viewing of raw images is done in gray scale. This scale can be manipulated to allow for better tissue characterization. Density value range of lung tissue and the heart is very different and requires different gray scale range for evaluation. Center (or level) of image density (HU) and window width (or range) determine image brightness and ease of differentiation and analysis of differing tissues. In coronary analysis where there are very dense objects, such as metallic stents or calcium, it is important to increase the window width further (Figs 2A to C). This reduces somewhat the blooming artifact related to dense objects but at the same time decreases

the ability to evaluate softer density structures such as non-calcified atherosclerotic plaque or clot.

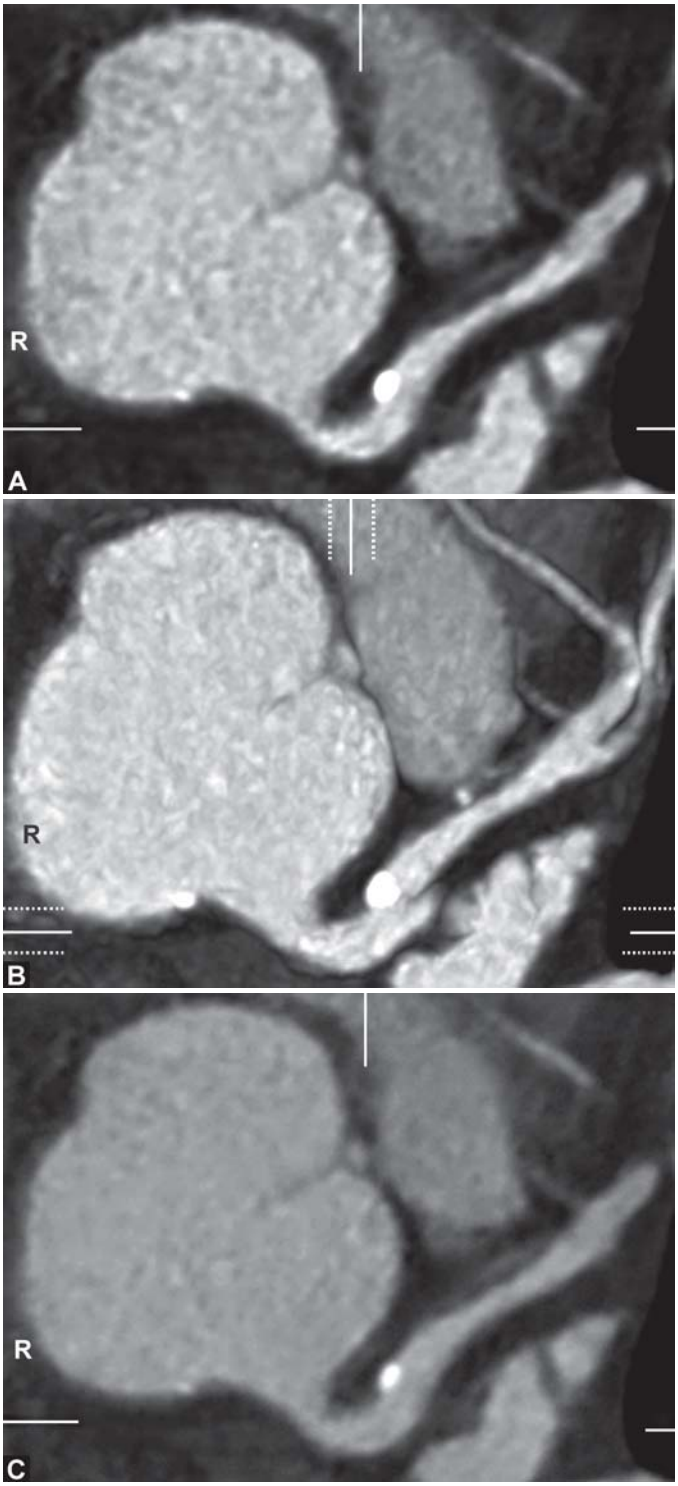
Raw images of the heart are typically around 300 and reconstructed in axial plane. The most simple viewing software allows for evaluation of these images in only the axial plane but more sophisticated viewing software will combine images to allow for evaluation of thicker images in any plane. Thickening of the image slice will reduce image noise but can also result in loss of information. There are three basic modes of thickening images—(1) MIP, (2) MinIP and (3) Average.

Maximum intensity projection (MIP) will display only the highest density value within a thickened image. *Minimum intensity projection* (MinIP) will display the lowest density value within the thickened image. *Average* will display the average of all values seen within the designated image thickness. MIP view is frequently used for coronary stenosis analysis with image thickness of 5 mm (Figs 2A to C). Higher or lower image thickness can also be used depending on the software. MIP view allows the contrast-filled vessel to be viewed in single frame and can simplify stenosis analysis and images will represent more of an angiographic view. The downside of MIP analysis is underestimation of non-calcified plaque and overestimation of calcium related stenosis. Calcified coronary plaque in MIP images can also give artificial appearance of calcium within the mid lumen of a vessel (Figs 2A to C). MinIP projection is primarily used for evaluation of thinner low density structures that are surrounded by higher density contrast-filled structures such as valves. Thickening images and averaging the density within the thickened images are primarily used in analysis of the myocardium and for assessment of the contrast density of the myocardium. Myocardium also be assessed by MinIP to increase sensitivity for detection of scars on first pass images and MIP to emphasize the contrast enhancement within the myocardium in delayed contrast enhancement analysis.

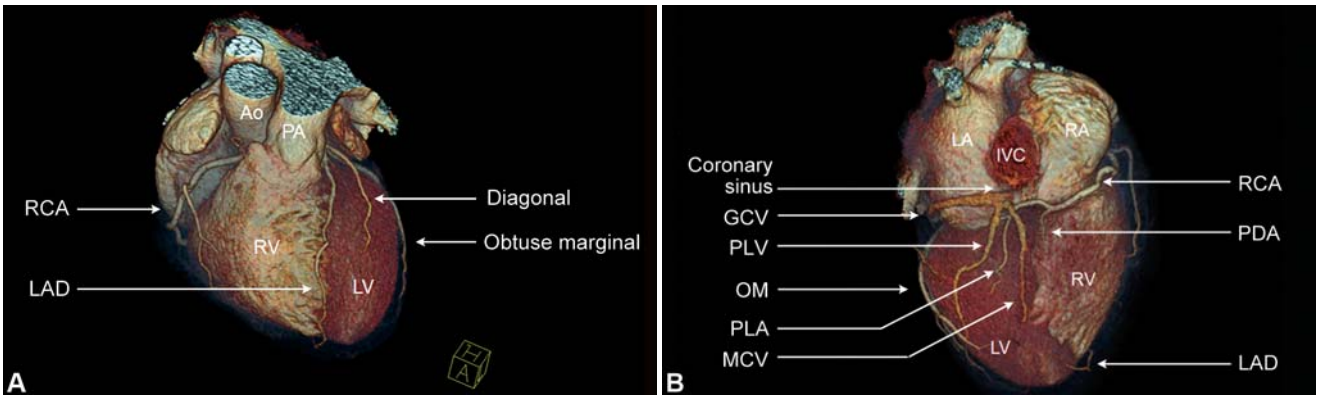
A stack of axial images (typically around 300) can be combined to make a 3D model of the heart (Figs 3A and B). This type of representation has limited benefit when analyzing coronary stenosis but can sometimes allow for better understanding of relationship between the adjacent structures such as in complex congenital heart disease or for analyzing anomalous coronary vessels.

The basic viewing planes (axial/sagittal/coronal) can be sufficient to analyze the heart but to allow for displaying a coronary vessel in a single image (Fig. 4), an oblique view is necessary. Multi planar reconstruction (MPR) is a compilation of oblique views that allow for depicting of an entire vessel through its whole length in orthogonal views.

Image reconstruction of a single data set is typically done by reconstruction of a phase within the cardiac cycle. The phases are defined based on dividing the cardiac cycle into relative lengths (percents between the R waves) where the full cardiac cycle is 100% and the middle of cardiac cycle is 50% into the cardiac cycle (Figs 1A and B). This type of reconstruction requires minimal heart rate variability where length of each cardiac cycle during image acquisition is mostly constant. Low heart rate (below 65 bpm) allows for reconstruction within diastasis (phase 65–75%). Of note the definition of phases varies between image vendors where some define the phase based on the beginning of the reconstruction interval and other based on the middle of the reconstruction interval. If there is increased heart rate variability, such as in atrial fibrillation, a fixed interval from the R wave will allow for better image assessment.



FIGURES 2A TO C: Single plane image of the left main coronary artery and proximal left anterior descending artery (LAD). LAD with ostial calcium and mixed plaque (calcified and noncalcified) in the proximal segment. (A) Thin slice image (0.75 mm) with narrow window (W750/C250). (B) Thick slice (5 mm) maximum intensity projection (MIP) image with narrow window (W750/C250). Calcium becomes prominent and artifically appears to occlude vessel. Minor calcium within soft plaque is noted. (C) Thin slice image with wide window (W1800/C400). Calcium smaller and plaque less prominent



FIGURES 3A AND B: Volume-rendering technique. Normal 3D anatomy. (A) Anterior view shows left ventricle (LV), right ventricle (RV), pulmonary artery (PA) and aorta (Ao). Coronary arteries visualized are left anterior descending (LAD), diagonal artery, obtuse marginal artery and right coronary artery (RCA). (B) Inferior/Posterior view shows left ventricle (LV), right ventricle (RV), inferior vena cava (IVC), right atrium (RA) and left atrium (LA). Coronary arteries visualized are left anterior descending (LAD), obtuse marginal (OM) artery, right coronary artery (RCA), posterior descending coronary artery (PDA) and posterolateral artery (PLA). Cardiac veins are coronary sinus, great cardiac vein (GCV), middle cardiac vein (MCV) and posterolateral vein (PLV)

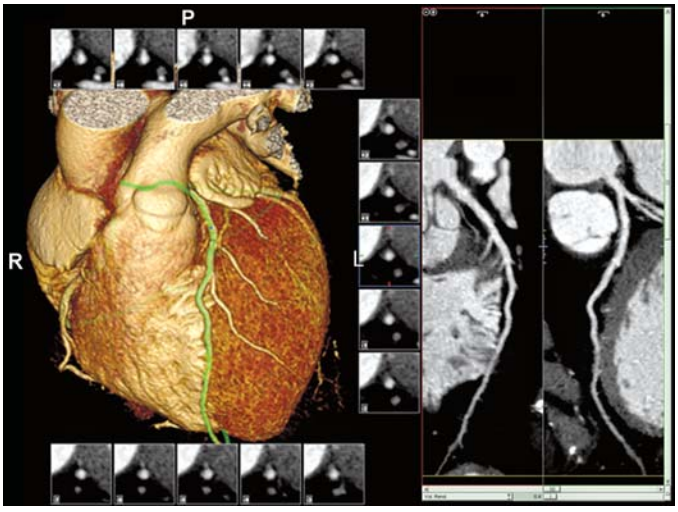


FIGURE 4: Volume-rendering technique (VRT) and curved multi-planar reconstruction (cMPR) for coronary analysis. Sample of how VRT in combination with cMPR allows for orthogonal views of the LAD and short axis views of the coronary lumen and vessel wall

IMAGE QUALITY AND ARTIFACTS

The image quality is determined by multiple factors—scanner type, protocol selection, patient size, contrast protocol, patient co-operation and heart rhythm. Currently the community standard for multidetector CT scanners is 64 detector row scanners with sub-millimeter collimation and gantry speed less than half a second (< 500 ms) where spatial resolution is 0.5–0.8 mm and temporal resolution 75–190 ms. Optimal scanners are also required to have high current output to allow imaging of larger patients and avoid photon starvation. Selection of acquisition protocol takes into consideration patient's heart rate and the clinical question. Contrast rate and amount is also individualized and suboptimal contrast opacification will lead to low signal to noise ratio with decreased diagnostic quality. High heart rate and arrhythmia can lead to motion artifacts and misalignment artifacts that can sometimes be corrected or reduced with postprocessing and EKG editing.

Patient preparation always involves selection of patients that can comply with breath holding and patients where use of radiation and contrast is justified based on the clinical question. Ideally patient could be consented prior to scanning but at this time it is not common practice. Knowledge of patient's size, renal function and history of contrast allergy is important for all studies irrespective of scanner type and protocol. Patients with higher heart rate and irregular heart rhythm might be better assessed in scanners with high temporal resolution.

Common practice is to use beta-blockers to lower heart rate prior to image acquisition as this allows for better image quality through longer diastasis, less motion of the vessel and lower heart rate variability. It also allows the use of imaging protocols with very low radiation when heart rate is less than 60–65 bpm (Table 1). Oral administration of beta-blocker is done an hour or sometimes several hours prior to scanning and intravenous administration is done a few minutes prior to scanning while patient is on the CT table or in adjacent patient care area. In patients who do not tolerate a beta-blocker, a nondihydropyridine calcium channel blocker can work as an alternative.

Nitroglycerin is also commonly administered just prior to scanning. It is thought to allow for better visualization of the whole coronary tree including smaller vessels (around 1.5 mm).

All patients are required to have intravenous access for contrast administration. Ideally patients have large bore needle, such as 18G in anticubital vein, to allow for contrast administration rate up to 6–7 ml/min but in smaller patients (BMI < 40) a rate of 4–5 ml/min is sufficient and this requires only 20G access.

CONTRAST

Contrast is required to assess the chambers and vessels of the heart. Without contrast it is not possible to assess coronary artery obstruction or chamber sizes. Allergic reaction to contrast and renal failure are the most common side effects of contrast administration.

High iodine concentration of the contrast is important to allow for less contrast dose and improve signal to noise ratio during vessel or chamber opacification. In the United States iopamidol (Isovue-370) has the highest concentration (370 mg/ml) and in Europe even higher concentrations are used. Iso-osmolar contrast with lower iodine concentration (i.e.

iodixanol) is also used when concerns are for increased risk of renal failure such as in diabetic patients.

Timing of contrast injection is critical to image quality. The contrast transit time varies between subjects based on location of IV catheter, injection rate and patient's hemodynamic state. Some institutions use test bolus method where a single test bolus is given and density curve done to guide timing of the main imaging. A simpler contrast protocol is bolus tracking where a region of interest is drawn within the descending or ascending aorta and when the density has increased by 100 HU the scanning starts.

Contrast protocols are dependant on the clinical question. When the clinical question relates primarily to the coronaries and possible left ventricular systolic function a biphasic protocol where saline is administered during second phase can be sufficient. Tri-phasic protocol can allow for assessment of right ventricle and pulmonary arteries. In this tri-phasic mode additional 30 ml of contrast in mixture with 30 ml of water (50% mix) can be sufficient to allow diagnosis of pulmonary embolism or volumetric assessment of right ventricular systolic function.

When ordering a noncontrast CT to assess for coronary calcium, it is important to know that it is currently not covered by insurance companies in many states and patients frequently pay out of pocket to have this performed. Noncontrast CT is frequently performed prior to contrast enhanced CT to determine feasibility of contrast enhanced CT. The practice of cancelling contrast injection based the quantity of coronary calcium (Agatston score 400–1000) varies between clinical facilities and also depends on the clinical question.

Contrast enhanced CT can be divided into comprehensive versus coronary analysis alone. During imaging of the coronaries alone information is also gained of adjacent structures. Axial scanning only gives a single cardiac phase and does not allow for analysis of left ventricular ejection fraction. Multiphase imaging opens the door for *comprehensive cardiac CT* that allows for assessment of left and right ventricular systolic function in addition to coronaries, cardiac veins, valves and pericardium.

"Triple rule out CT" refers to contrast enhanced CT where imaging is done of the aortic arch, pulmonary vasculature and the heart in a single scan.

CORONARY ARTERY DISEASE

The coronary arteries can be evaluated by CT both with and without contrast. Noncontrast CT is best suited for assessment of coronary calcifications in primary prevention. Contrast CT angiography is reserved for symptomatic patients primarily to exclude presence of obstructive disease. Patients with previously known coronary disease have less benefit from contrast CT due to blooming artifacts from coronary calcifications.

NONCONTRAST CT AND CORONARY CALCIFICATIONS

Noncontrast CT can estimate atherosclerotic burden but has limited value in predicting coronary stenosis. The magnitude of coronary calcifications correlates well with atherosclerotic burden in histologic studies[13,14] but not as well with stenosis analysis.[14] Assessment of coronary calcium by CT was first done in the late 1980s[15] and proposal for a quantification method was presented by Agatston et al. in 1990.[16] The Agatston scoring method is a weighted sum score based on plaque area and density. This can be done with semi-automated software that is widely available. The Agatston score is generally referred to as "calcium scoring". Other methods to quantify the coronary calcifications are based on volume and mass[17] but these are not used in clinical practice.

Multiple retrospective and prospective studies have consistently shown that calcium scoring is an independent predictor of future cardiovascular events. These studies have also shown that its power of prediction exceeds current standard Framingham risk scoring.[18,19]

The greatest clinical value of calcium scoring is in patients at intermediate Framingham risk for future cardiovascular events where reclassification by Agatston scoring might allow for better determination of which patients might benefit from more intense medical therapy.[20,21] Current primary prevention guidelines support the use of calcium scoring in patients at intermediate risk for coronary events.[22]

In general, Agatston score less than 100 is considered to convey low risk and greater than 300–400 high risk. In patients at intermediate Framingham risk, a calcium score above 400 is associated with 2.4% annual risk for cardiac death or myocardial infarction.[18] Serial calcium scans to monitor the effect of medical therapy is thought to have limited value.

CONTRAST CT AND CORONARY ANGIOGRAPHY

EKG gated contrast enhanced CT is primarily used to exclude the presence of obstructive coronary disease in patients with chest discomfort. Patients with known coronary disease are generally not considered good candidates for CT due to blooming artifacts from coronary calcium that can limit stenosis analysis. Contrast enhanced CT differs from invasive angiography since it not only determines stenosis but also assesses the presence of atherosclerotic plaque and type of plaque similar to intravascular ultrasound (IVUS).

Careful selection of patients for coronary CT is very important to minimize risk to the patient and optimize appropriate use. Due to high sensitivity and high negative predictive value, CT is best suited for symptomatic patients with intermediate or low risk for obstructive coronary disease.[23]

Limitations in spatial resolution affect the overall accuracy of CT in stenosis analysis. Currently the spatial resolution is 0.4–0.8 mm. This makes evaluation of coronary branches (i.e. diagonal and obtuse marginal) less accurate as these vessels are frequently less than 2 mm in diameter.[24] In patients with low prevalence of coronary disease, CT has high sensitivity and specificity for stenosis detection (Table 3) but in patient with increased prevalence of coronary disease the specificity of stenosis analysis is decreased and false positive rate is increased.[25-28] Ratio between false positives and false negatives can be 6:1 or greater, and the most common reason for false positive findings are artifacts from calcium or motion.[27]

Temporal resolution is also an important factor for accuracy of CT. Coronary vessels within the atrioventricular grooves [right coronary artery (RCA) and left circumflex (LCX)]

TABLE 3

Patient-based analysis for detection of greater than 50% stenosis in (a) multicenter trials with 64 detector row scanners, (b) meta-analysis using 12 detector row or greater scanners published in 2010 and (c) meta-analysis of low dose scanning methods published in 2011

		N	*Sens*	*Spec*	*NPV*	*PPV*	*Prev*	*Uneval*
(a)	Accuracy[26]	230	95%	83%	99%	64%	24%	1.3%
	Core 64[25]	291	85%	90%	83%	91%	56%	1.7%
	Meijboom[27]	360	99%	64%	97%	86%	68%	0%
(b)	Meta-analysis[23]	7516	97%	87%				
(c)	Low dose[28]	960	100%	89%				9.5%

(Abbreviations: N: Number; Sens: Sensitivity; Spec: Spacificity; NPV: Negative predictive value; PPV: Positive predictive value; Prev: Prevalence; Uneval: Unevaluable)

experience considerable motion during the cardiac cycle and slowing heart rate with beta-blockers allows for near motion free imaging. Dual source CT scanners with temporal resolution of 70–90 ms allow for reliable imaging without beta-blockers.

Left main coronary artery evaluation with CT is considered highly accurate. This is due to the combination of large diameter of the vessel and limited motion.

In general, CT is highly sensitive for detection of coronary disease and has the ability to detect disease before a vessel has hemodynamically significant stenosis. This might allow earlier preventive measures, an advantage not shared by stress testing or other noninvasive functional imaging. Data from the CONFIRM registry shows that patients with nonobstructive coronary disease by CT angiography are at increased mortality risk.[29]

CT is able to characterize coronary plaque into—calcified, noncalcified and mixed plaque (mixture of calcified and non-calcified plaque elements). Reliable differentiation of soft and fibrous plaque has not yet materialized and this is due to limitations in spatial resolution. Additionally there appears to be systemic underestimation of noncalcified plaque size due to partial volume effect.[30,31] Despite this, the number of segments with atherosclerotic plaque is associated with future prognosis.[32,33] Current CT technology does not allow for direct visualization of thin fibrous plaque but it can detect positive remodeling and low attenuation plaque that in a single cohort study have been associated with the increased risk of acute coronary syndrome.[34]

The greatest strength of CT is the low event rate of 0.17–0.37% [29,35] in patients with a normal coronary CT. This is comparable to the background event rate among healthy low-risk individuals (< 1%). In patients with coronary stenosis (> 50%) the number of vessels and location of stenosis predict future cardiac events.[29,32,33,35]

Appropriate Indications

Correct selection of patients for contrast enhanced coronary CT is very important and requires a physician's evaluation to minimize risk to patients and optimize appropriate use. Due to high sensitivity and very high negative predictive value, CT is best suited for symptomatic patients with intermediate or low risk for obstructive coronary disease.[36] Patients with atypical chest pain and no increase in cardiac enzymes in the ER setting are also good candidates as performing of CT can be done earlier than traditional tests. Studies comparing CT to standard stress testing in the emergency room showed significant shortening of hospital stay and subsequent reduction in cost.[37-40]

Patients with left bundle branch block are good candidates for CT[41] as they frequently have false positive imaging stress tests and are not suitable for stress testing with EKG alone. This might also be the case for patients with WPW but it has not yet been investigated. Other clinical scenarios are patients with new onset heart failure[42] and preoperative evaluation including patients planned for valve surgery.[43]

Currently published appropriateness criteria[36] suggest that patient with known coronary disease, chronic stable angina or history of myocardial infarction are not good candidates for CT.

Two large randomized multicenter comparative effectiveness trials, the PROMISE and the RESCUE trial, will assess the clinical value of cardiac CT in comparison to stress testing in symptomatic patients.

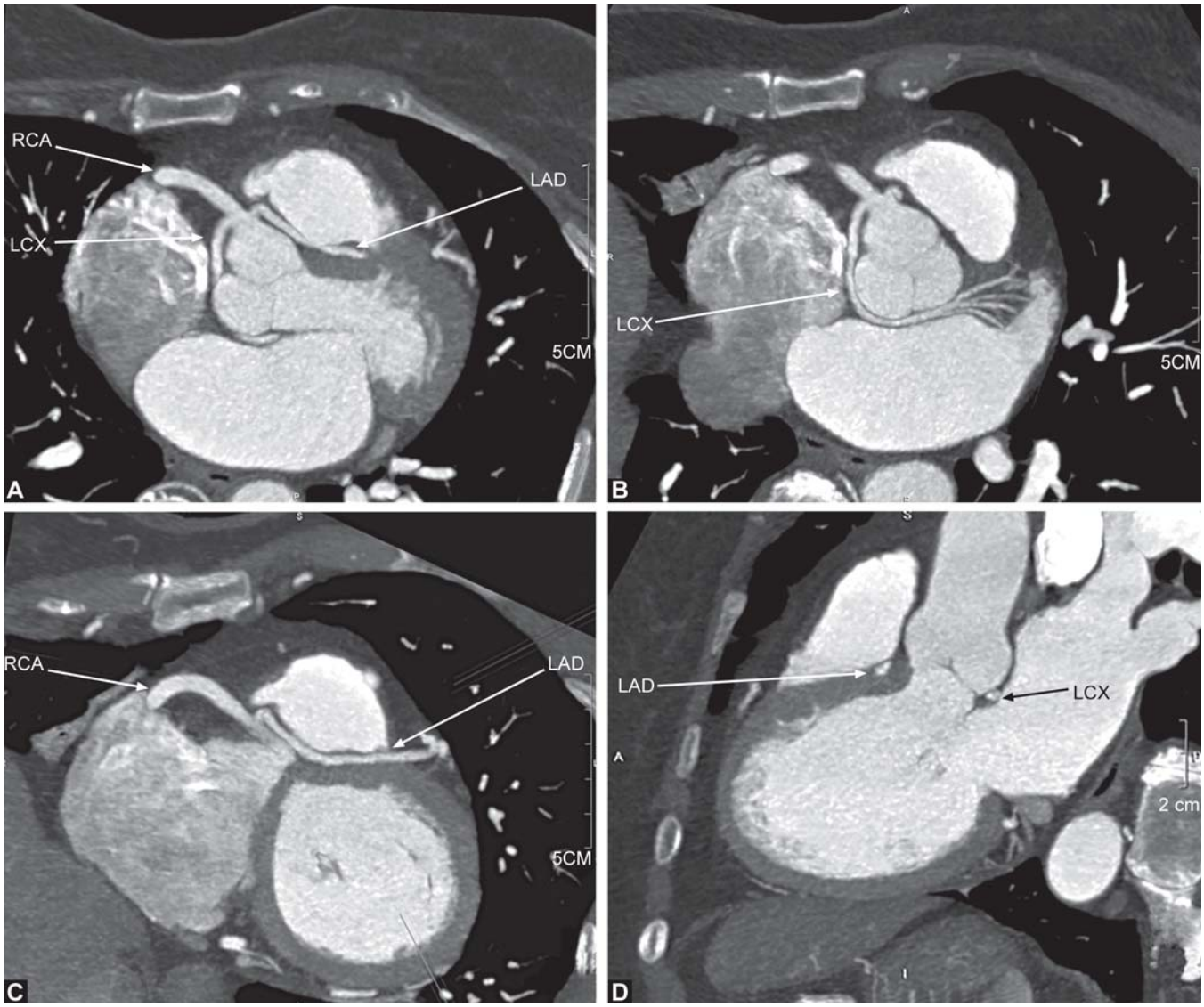
CORONARY STENT

Coronary stent evaluation by CT is limited by blooming artifacts. The stent size, design and metal type will have varying effect on artifacts. Stents with diameter greater than 3–3.5 mm[44] are better suited than smaller stents. Asymptomatic patients with stents are not appropriate for cardiac CT but selected symptomatic patients with adequate stent size and possible equivocal stress test results, combined with peripheral vascular disease or history of stroke might be candidates for CT to avoid higher risk invasive angiography.

CORONARY BYPASS GRAFTS

Coronary bypass grafts can be evaluated by contrast CT with good results due to large diameter of the grafts and lack of motion. Metal clip artifacts and severe native coronary disease with diffuse coronary calcifications have limited the clinical applicability. As such cardiac CT has limited clinical use in routine evaluation of bypass graft patency.

CT is considered appropriate in presurgical planning prior to redothoracic or cardiac surgery where it can accurately account for location of prior bypass grafts in relationship to sternum and sternal wires. Additionally it will assess the distance of the right ventricular free wall from the sternum. Routine use of CT has been shown to decrease surgical complications, transfusion and hospital stay.[45] Additionally, in patients with



FIGURES 5A TO D: Anomalous coronary arteries. (A) Oblique planar images with anomalous left anterior descending (LAD) and left circumflex (LCX) arising from the right coronary sinus of Valsalva adjacent to the right coronary artery (RCA). (B) LCX travels posterior to the aorta. (C) LAD travels below the pulmonic valve within the left ventricular myocardium. (D) LAD with intramyocardial course. LCX travels posterior to the aorta

history of stroke where there can be concerns for engaging the left internal mammary artery (LIMA) with coronary catheter or there is clinical concern for left subclavian stenosis, a CT scan can evaluate the origin of the LIMA graft and assess the subclavian artery at the same time.

ANOMALOUS CORONARY ARTERIES

Screening for anomalous coronary vessels with EKG gated contrast CT is considered Class I indication.[46] CT allows for more accurate evaluation of the course of the vessels where exclusion of inter-arterial course is paramount.[47,48] The anomalous vessels are of great variety and the course of the proximal portion of each vessel determines the clinical significance. A course anterior to the pulmonary artery, or posterior to the aortic root, is benign where as an inter-arterial course, between the aorta and the pulmonary artery, is frequently considered malignant.[49] Left main coronary anomaly arising from right sinus of Valsalva and traveling between the pulmonary artery and the aortic root is considered malignant but when the vessel travels below the pulmonic valve and is within the myocardium (Figs 5A to D) it is considered a benign finding.[48] RCA with inter-arterial course[50] is considered an indication for surgery when ischemia is present.[46] LCX arising from the right sinus of Valsalva and traveling posterior to the aortic root is considered a benign variant (Figs 5A to D).

OTHER CORONARY FINDINGS

Coronary aneurysms are well characterized by CT and can be found in association with atherosclerosis, Kawasaki disease, Takayasu arteritis and cocaine use.[51]

Myocardial bridging of the coronary arteries is a common finding on CT, and more commonly detected by CT compared to invasive angiography.[52] Clinical importance of myocardial bridging is under debate.[53] Noncalcified plaques at the site of the myocardial bridge could theoretically be missed on CT as noncalcified plaque could have similar density as the adjacent myocardium.

Coronary fistulas can be evaluated by CT.[54] Small fistulas are of limited clinical significance but larger fistulas benefit from characterization prior to surgical interventions. Coronary fistula to low pressure chambers such as atrium or cardiac veins are frequently dilated due to increased flow. During invasive angiography, it is sometimes difficult to determine the course, due to lack of selective contrast filling but with high resolution CT a detailed evaluation is possible.

MYOCARDIUM AND CHAMBERS

The first report of CT of the heart in 1976 involved imaging of myocardial contrast perfusion defects in an animal model of myocardial infarction.[2] Since then there has been progressive improvement in spatial and temporal resolution that now allows for accurate assessment of ventricular ejection fraction plus regional systolic wall thickening.[55] Due to radiation involved with CT, other techniques, such as echocardiography and magnetic resonance imaging (MRI), are considered first line imaging techniques for assessing the myocardium and chambers. Temporal resolution with *single source* CT has been considered suboptimal leading to concern that it was unable to accurately capture the end-systolic phase thus underestimating the stroke volume and left ventricular ejection fraction.[56] *Dual source* CT scanners have been able to show excellent image quality irrespective of heart rate and during phantom imaging able to assess global function with greater accuracy than MRI.[57] Right ventricular systolic function can also be assessed by CT with equal or better interobserver and intraobserver variability than MRI.[58,59] Low radiation (equal to MUGA) and low contrast protocols exist for analyzing simultaneously left and right ventricular systolic function but due to general availability of alternative modalities there has been limited adoption of this.[60] Left ventricular ejection fraction measured by CT has prognostic value that can supplement clinical history and coronary findings.[33]

Qualitative and quantitative myocardial perfusion analysis can be performed by CT.[61] Research dating back to the 1980s suggested that despite significant diffusion of contrast into the interstitial space there was still a fairly linear relationship between myocardial contrast enhancement and myocardial perfusion.[62] Artifacts affected the myocardial analysis by electron beam CT.[62] Multidetector CT has less artifacts and this has renewed interest in myocardial perfusion analysis by CT. Radiation with myocardial perfusion imaging is expected to be similar or less than radiation with nuclear perfusion studies.[61] Technology exists to acquire analysis of myocardial blood flow with reasonable radiation burden but at this time most research is focused on qualitative evaluation of myocardial contrast enhancement.[61] Combining coronary analysis with myocardial contrast enhancement and wall motion analysis improves accuracy of coronary analysis[63] and is expected to be a cost effective way of analyzing ischemic heart disease in the future. Extensive research including multicenter trial, underway for analysis of myocardial contrast enhancement during adenosine infusion.[61]

For image evaluation of myocardial perfusion defects the image settings are different than during coronary evaluation (center ~100 and width of 150–200). Additionally increased

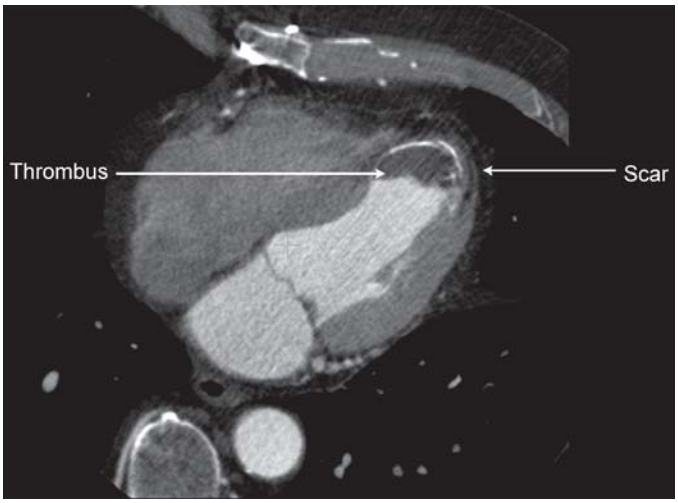


FIGURE 6: Myocardial scaring of the apex with thinning, calcification, fatty transformation and large thrombus

images thickness (5–10 mm) with average or MinIP has superior contrast to noise ratio compared to MIP and thin slices images.[64]

Assessment of myocardial scaring can be done by CT. Wall thinning and fatty transformation of scar (Fig. 6) can be readily detected by CT where the fatty tissue will have negative CT density (HU –30 to –60).[65] More subtle signs of myocardial scaring without wall thinning can also be detected by CT and delayed contrast enhancement imaging.[66] Animal studies of recent myocardial infarction suggest that good correlation exist between delayed enhancement detect by CT and MRI. Limitations of CT are contrast to noise ratio between areas of delayed enhancement and normal myocardium.

Currently evaluation of myocardial contrast enhancement is not part of established clinical care as there is not yet consensus for ideal protocol and clinical research is still limited. During the comprehensive evaluation of the myocardium, there is a general agreement for using the "stress" adenosine infusion and, during the initial image acquisition, and this is then followed by "non-stress" contrast imaging and later by delayed enhancement imaging.

Current clinical use for detection of myocardial scar by CT is aimed at patients who are not able to undergo MRI due to presence of an ICD. These are typically patients with reoccurring ventricular tachycardia awaiting catheter ablation therapy.[67] In these cases, CT can possibly detect the location of scar by hypoenhancement during the first pass imaging, wall thinning, delayed enhancement and exclude mural thrombus. Additionally the CT images can be used for anatomic mapping for the ablation procedure, similar to common practice of mapping left atrium during ablation of atrial fibrillation.

Another indication for delayed enhancement with cardiac CT could be perimyocarditis where young individuals with clinical diagnosis for pericarditis and elevated troponin could get cardiac CT to rule out the coronary anomaly or disease in addition to analyzing left ventricular function and detection of delayed enhancement.[68]

Left ventricular thrombus can be easily accessed by CT and apical thrombus is frequently detected on non-gated contrast enhanced CT of the chest.[69] Due to high spatial and temporal resolution of cardiac CT, it is congenial for detection of left

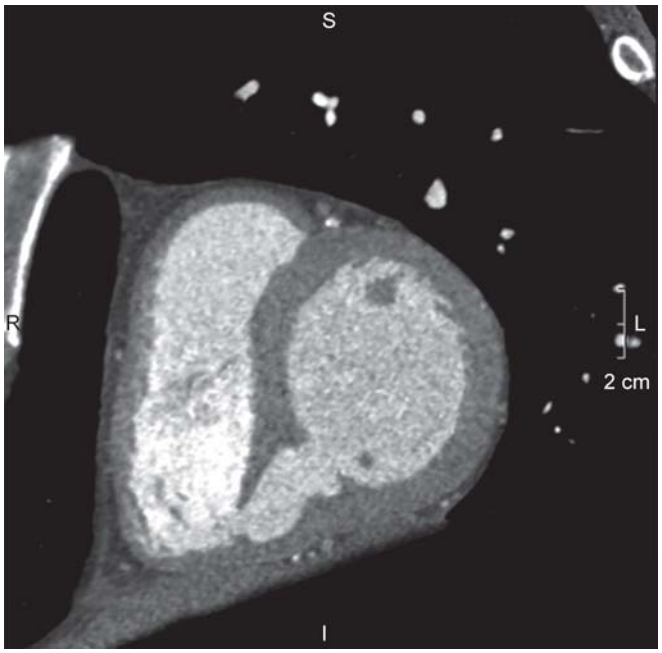


FIGURE 7: Postinfarction ventricular septal defect

ventricular thrombus. High contrast to noise ratio between the thrombus (HU density 30–60) and contrast mixed blood (HU density of 200–500) allows for detection of small clots that can be missed by echocardiography.

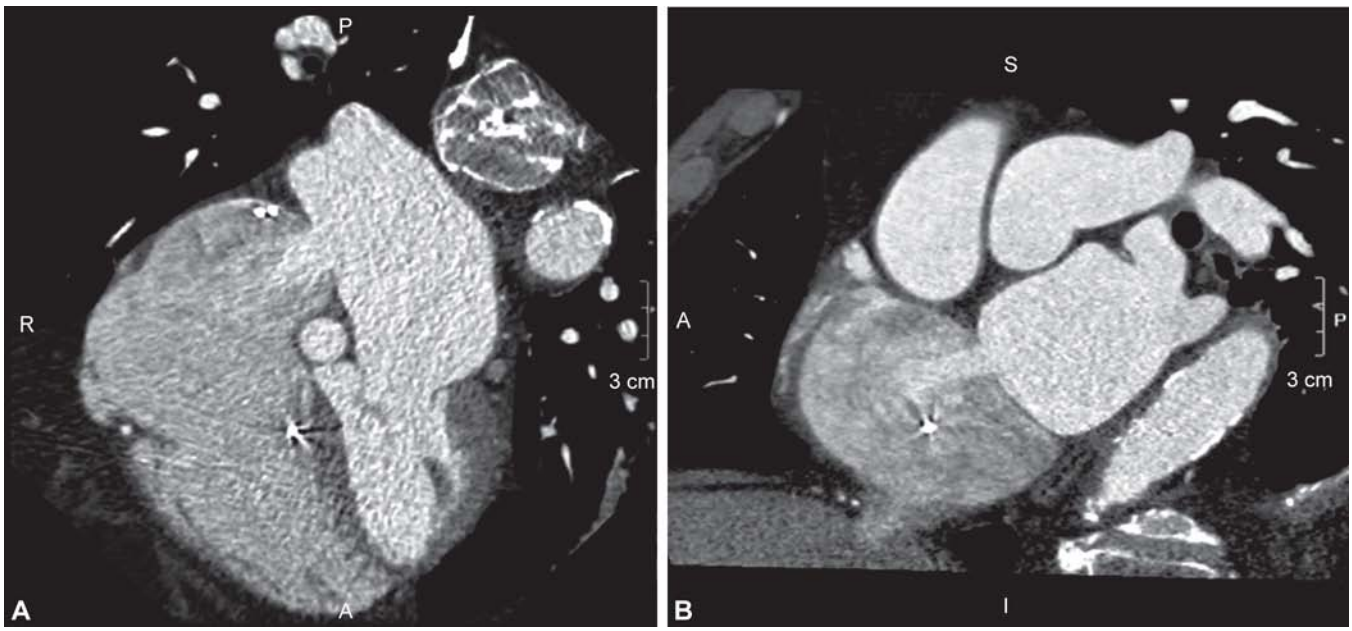
Due to high affinity of CT for detection of fatty tissue and high spatial resolution, cardiac CT might be ideal for assessing the right ventricular dysplasia.[70] Few publications exist on this matter and this will require dedicated contrast bolus timing for the right ventricle that is frequently avoided during the coronary imaging. Additionally software for analyzing the right ventricular systolic function is currently limited.

Ventricular (Fig. 7) and atrial (Figs 8A and B) septal defects can be detected by CT.[71] Other reported findings on cardiac CT are hypertrophic cardiomyopathy, noncompaction, congenital heart disease and ventricular aneurysm.[72,73]

PULMONARY VEINS

With the advent of radiofrequency ablation for atrial fibrillation, there is an increased need for visualization of the left atrium, left atrial appendage and pulmonary veins. Other imaging modalities, such as transesophageal echocardiography, intracardiac echocardiography and MRI can also delineate these structures. CT is frequently the test of choice due to its widespread availability and the ease of performance. The excellent contrast to noise ratio of CT images makes them well-suited for developing a 3D map of the highly variable anatomy of the left atrium, appendage and pulmonary veins prior to the ablation procedure (Fig. 9). Integration of the 3D map with electroanatomic mapping and real-time location of ablation catheters is thought to increase safety and efficacy of the procedure in addition to facilitating shorter periprocedural fluoroscopic time.[74,75] CT can exclude the presence of the left atrial appendage thrombus (Fig. 10) and determine the relationship between the atrium and the esophagus, as ablation adjacent to the esophagus can result in catastrophic perforation with atrial-esophageal fistula. Additionally a detailed EKG gated CT is able to detect accessory atrial appendages and other possible recesses that could be sites for an increased risk of catheter induced perforation.[76] Following the ablation procedure, a patient can undergo repeat imaging to exclude pulmonary vein stenosis and CT is considered the optimal modality.[77]

CT prior to ablation can be done both with and without EKG gating.[78,79] EKG gating of CT in patients in atrial fibrillation does currently not allow for radiation reduction protocols such as prospective dose modulation or sequential scanning.[79] This might change in the future with more sophisticated EKG detection software. By using the "retrospective EKG gating", the postprocessing allows for motion free end-systolic (atrial diastolic) visualization of the



FIGURES 8A AND B: Atrial septal defect with contrast traveling from left atrium to right atrium. Enlargement of right ventricle and both atria

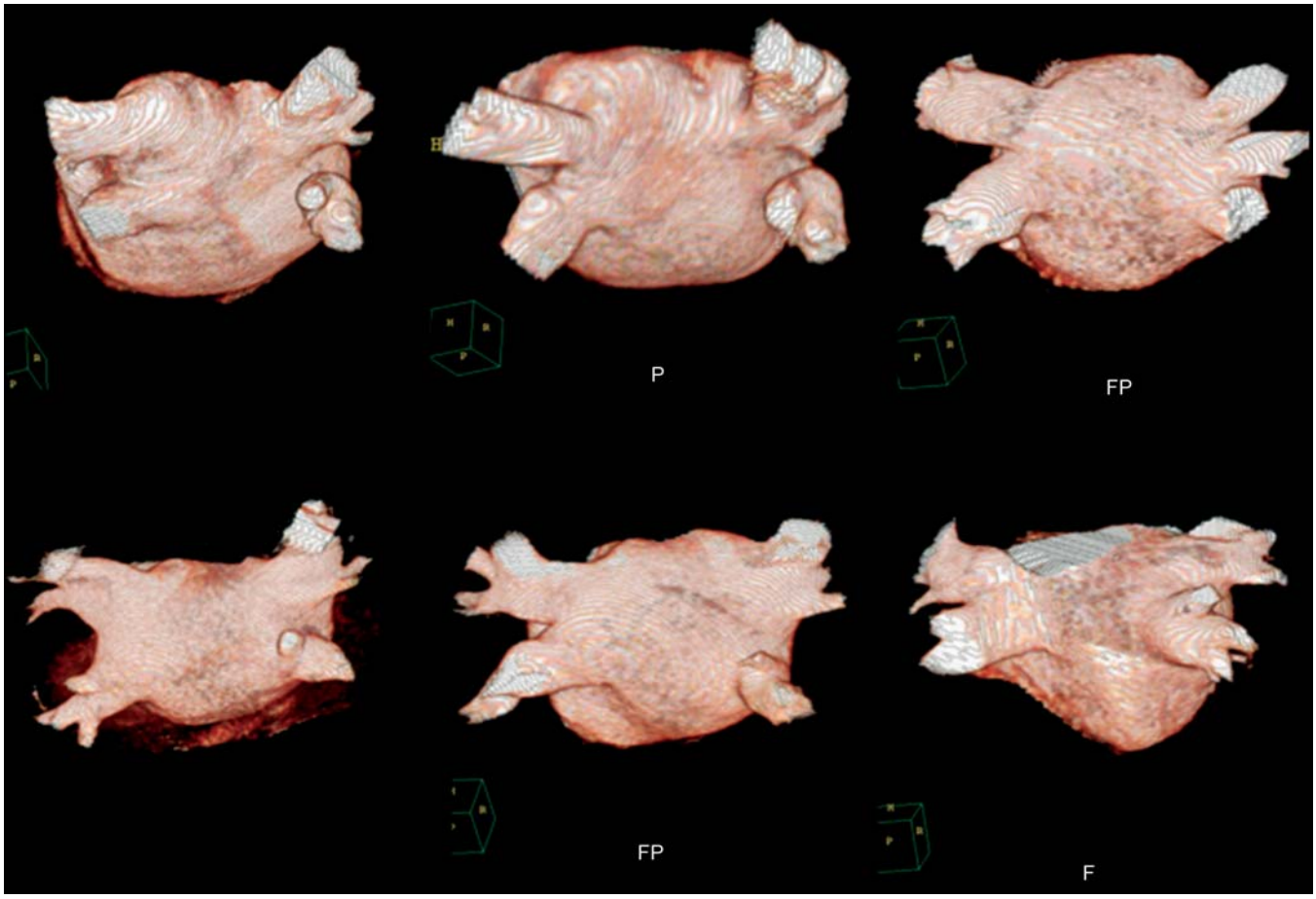


FIGURE 9: Left atrial and pulmonary venous anatomy is highly variable as is demonstrated in these six examples

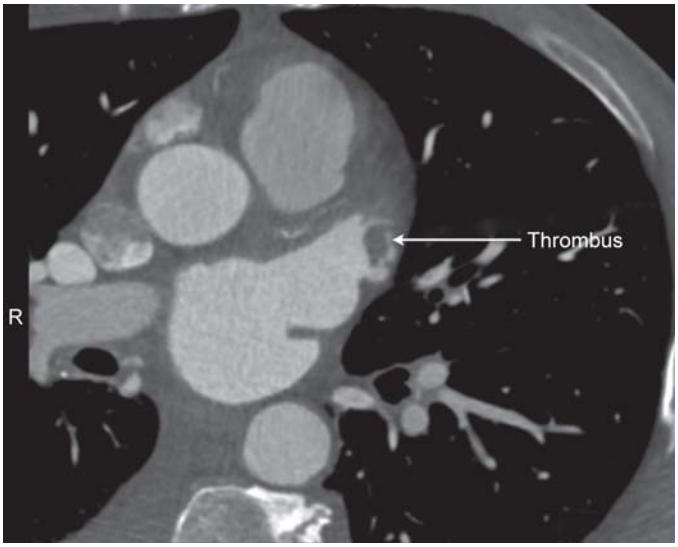


FIGURE 10: Thrombus within the left atrial appendage

left atrium by reconstruction of images 275–350 ms following the R-wave.[80] This type of reconstruction has also been termed "absolute delay reconstruction". Radiation associated with nongated CT is less but motion artifacts affecting the left atrial appendage would make exclusion of thrombus less reliable. Nongated CT might be sufficient in patients with CHADS^2 score less than 1.[79] Patients with left ventricular systolic dysfunction, dilatation of the left atrium and low blood flow frequently have partial contrast filling of the left atrial appendage during the first pass imaging.[81] This often necessitates repeat scanning within 60–90 seconds of the first scan to exclude pseudothrombus.[82] On review of the delayed images, the density ratio between the left atrial appendage and the ascending aorta can be used to quantitatively assess for thrombus.[82] Additionally it has been proposed that prone imaging might also facilitate contrast filling of appendage and prevent the problem of partial filling.[83]

CARDIAC VEINS

Cardiac venous anatomy is readily assessed by CT. This requires slight delay of image acquisition time to allow adequate levophase maturation. Cardiac venous anatomy is highly variable and theoretically it could be assessed prior to placement of the left ventricular pacemaker lead. The anterior cardiac vein originates in the anterior interventricular groove parallel to the left anterior descending coronary and empties into the great cardiac vein in the atrioventricular groove which empties into the coronary sinus and finally the right atrium. Middle cardiac vein runs within the posterior interventricular groove and also joins the coronary sinus prior to emptying into the right atrium. The posterolateral cardiac vein

(Figs 3A and B), which is frequently used for resynchronization therapy is frequently absent in ischemic heart disease.[84]

Combining assessment of left ventricular dyssynchrony and cardiac venous anatomy prior to insertion of a biventricular pacemaker has been proposed[85,86] with favorable results in smaller studies. Large randomized prospective trials have not been completed. Assessment of cardiac venous anatomy is more commonly done following failure to place a left ventricular lead as this can both explain the cause for a failed procedure and aid in planning for epicardial lead placement. Additionally CT can be used prior to consideration of resynchronization therapy in patients with complex congenital heart disease.[87]

VALVULAR DISEASE

Evaluation of valves by CT is, in general, done as a byproduct of coronary analysis. Echocardiography remains the gold standard for valvular assessment due to safety, lack of radiation, higher temporal resolution and ability to assess the functional significance of valvular lesions. CT is considered appropriate when the significant valvular dysfunction is suspected and other noninvasive methods are inadequate.[36]

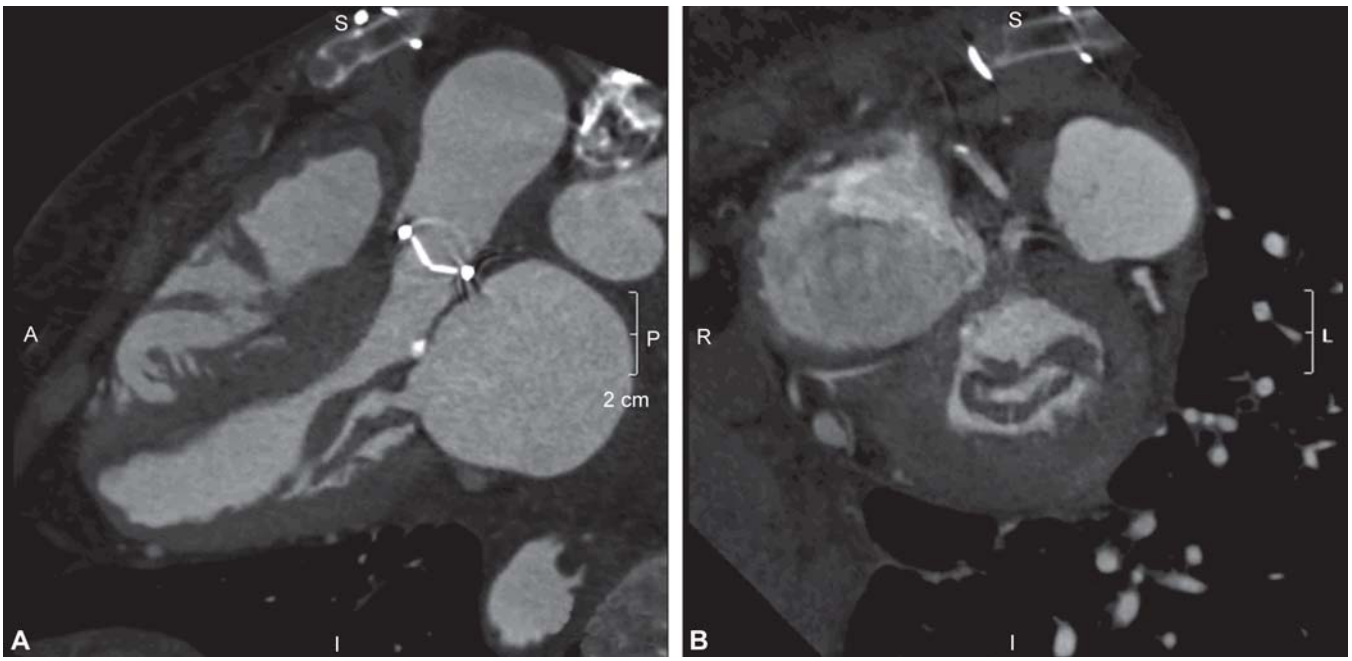
Imaging protocol for valvular assessment requires higher radiation as data from most of the cardiac cycle is needed and dose modulation can be detrimental. Imaging with prospective single phase protocol limits the valvular analysis substantially. Contrast opacification of the right ventricle can also be helpful for functional assessment and this will lead to overall increased contrast dose. Image analysis benefits from thicker image slabs (3–10 mm) with MinIP. This allows for better evaluation of thin leaflets both for stenotic and regurgitant orifice area measurements. Three- and four-dimensional image analysis with so-called blood pool inversion volume-rendering technique can allow for easier morphologic evaluation but thin leaflets are not always well visualized.[88]

Left-sided valves are better visualized than right-sided valves and stenotic orifice areas are better measured than regurgitant lesions.[89] CT can readily detect the number of aortic valve leaflets, aortic valve stenosis, mitral valve stenosis (Figs 11A and B) and mitral valve prolapse. Aortic valve area during mid-systole and mitral valve area during early diastole can be assessed with fairly good accuracy. Assessment of aortic valve stenosis has been validated by multiple studies and some studies suggest that valve area is systematically larger by CT than with echocardiography and this could be due to erroneous systematic underestimation of left ventricular outflow tract (LVOT) area by echocardiography.[90,91]

CT imaging can quantify valvular calcifications better than other imaging modalities and this can be valuable prior to percutaneous valvuloplasty.[92] In patients with mitral valve stenosis, during preprocedural planning, CT can also detect left atrial appendage thrombus, valvular, subvalvular thickening and calcifications. Right-sided valve analysis is limited by spatial resolution, thin leaflet structures and contrast mixing artifacts. Procedural planning for percutaneous interventional treatment of mitral valve with a coronary sinus device can be done by cardiac CT. The contrast enhanced EKG gated images can assess the location of target vein and adjacent LCX and thus assess the risk of circumflex compression injury.

Assessment of valves by CT is primarily done by morphologic evaluation, and functional assessment is limited. Estimations of flow by combination of volume and area measurements over time are still investigational and expected to be limited by temporal resolution and assumption of intact integrity of other valves.[91] Estimation of regurgitant volume and regurgitant fraction can be done by analyzing right and left ventricular volumes in patients with single valve disease.[93]

Mechanical valves can be visualized by contrast and non-contrast enhanced CT (Figs 11A and B). Evaluation of metallic valves by echocardiography and MRI suffers from metal



FIGURES 11A AND B: Mitral valve disease with bileaflet thickening and calcification of anterior leaflet. Prosthetic mechanical bileaflet aortic valve. Right ventricle dilated with hypertrophy

artifacts making image analysis frequently inadequate. Artifacts during CT are less prominent. Similar to simple fluoroscopy a cardiac CT without contrast has the potential to show mechanical leaflet motion with great accuracy. Contrast enhanced CT allows for detection of thrombus formation and pannus in addition to assessment of leaflet immobility. Additionally CT can delineate pseudoaneurysm, quantify dehiscence of a prosthesis and rocking motion.[94]

A limited number of publications exist on assessment of endocarditis by CT.[95] Size and possible contrast opacification of the vegetation will limit detectability. Additionally vegetative lesions are highly mobile and conventional assessment of mid-diastolic or end-systolic phases might not be sufficient. Small perforation of thin valve leaflets can also be difficult to appreciate by CT. At this time, it is unclear what additional information can be obtained over standard echocardiography.

The future role of cardiac CT in evaluation of valvular disease appears to be more as a complimentary tool to echocardiography. The areas where it would be expected to give the greatest benefit would be during procedural planning of valvular surgery or transcatheter interventions.

PERICARDIUM

Superior spatial resolution of CT allows for excellent visualization and characterization of pericardial pathology. Initial imaging modality for pericardial disease is echocardiography but CT offers advantages over echocardiography in regards to superior spatial resolution, detection of calcification (Fig. 12) and characterization of adjacent intrathoracic structures.[96] High spatial resolution and separation of myocardium from pericardium by epicardial fat allows for accurate measurements of pericardial thickness. Normal pericardial thickness is less than 2–4 mm.[97] Assessment of the pericardium is best adjacent to the right ventricular free wall and can be difficult over the left ventricular free wall due to the lack of epicardial fat. Selection of systolic phases can allow for better separation of pericardium from myocardium. CT is highly sensitive for detection of pericardial effusion and multiphase cine imaging allows for assessment of dynamic changes during the cardiac cycle.

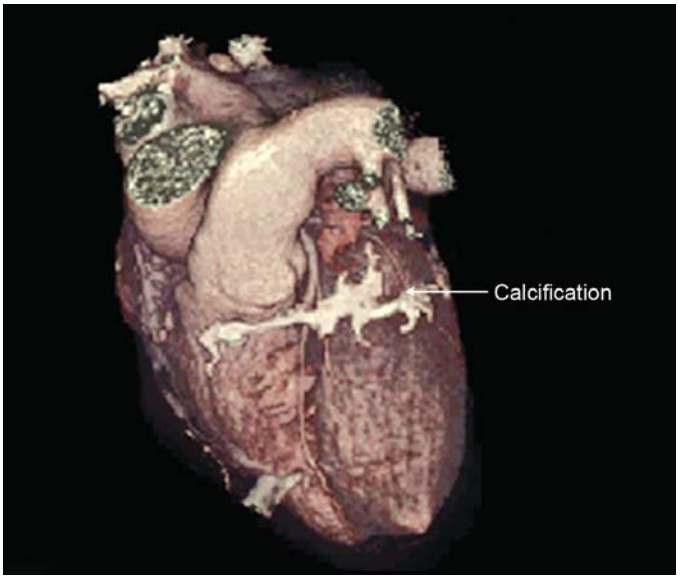


FIGURE 12: Pericardial calcification visualized by volume rendering technique

Constrictive cardiomyopathy with thickening of the pericardium can be easily diagnosed by CT. Contrast administration is not necessary but it can facilitate better separation between pericardium and adjacent structures. Thickness greater than 4 mm is suggestive for constriction, and greater than 6 mm thickness would be considered highly specific. Calcification of the pericardium is also a very specific finding strongly associated with constrictive physiology. Constriction caused by thin pericardium has been described and invariably is associated with deformation of the cardiac chambers that is best seen with contrast administration.[98,99] Additional signs of constrictions could be dilatation of the IVC, ascites and pleural effusion.

In patients with established diagnosis of constrictive cardiomyopathy CT can assist in preoperative planning by accurately delineating the extent of pericardial calcification. It also allows for assessment of the relationship between the pericardium and the sternum or coronaries.

Pericardial effusion can be easily detected by CT and quantified volumetrically if necessary. Characterization of the fluid can be done by CT image density (HU). Serous, transudative, fluid has density between 0–30 HU and exudative 30–70 HU. Hemorrhagic effusion can have variable density ranges from 32–70 HU. Hemopericardium complicating aortic dissection can be readily diagnosed by CT and thus prevent impending catastrophe with pericardiocentesis. Chylous effusion might have negative HU due to fatty content but a mix of chylous fluid with high protein content or exudative fluid could give measurements in the normal range.[100,101] Diagnosis of tamponade is primarily a clinical diagnosis but some features of tamponade physiology can be detected by CT such as right-sided chamber collapse. Reflux of contrast into the inferior vena cava has been considered a sign of tamponade but specificity of this finding is low.

Enhancement of the pericardial layers can be seen in pericarditis. Sensitivity and specificity of this finding is unknown. Small amount of pericardial fluid can make this finding more prominent. The inflammatory enhancement of the pericardial layers is also seen in effusion secondary to malignancies. Both pyogenic and malignant effusion would be expected to have signal density of 30–70 HU.

Pericardial tumors such as metastatic disease or primary cardiac tumors will enhance during contrast administration.[102] Nonenhancing tumor may be a pericardial cyst. Typical features of pericardial cysts are thin walls without septation and signal density of 0–30 HU. The most common pericardial tumors are metastatic disease from breast and lung cancer.

Congenital absence of pericardium is rare. Findings, such as interposition of lung tissue between the ascending aorta and the pulmonary artery or left ward displacement of the heart, are features that depend on the degree of absence. Partial or complete absence of pericardium is associated with other congenital defects such as atrial septal defect, patent ductus arteriosus and tetralogy of Fallot.

Echocardiography is the most widely used modality for evaluating or detecting a cardiac mass but it is limited by poor acoustic windows, operator dependency and limited tissue characterization ability. Additionally it is limited in assessing extracardiac extent of lesions. Some of the limitations of poor acoustic windowing can be overcome by transesophageal echocardiography. Magnetic resonance imaging (MRI) has been the imaging modality of choice for tissue characterization of the majority of cardiac tumors due to better spatial resolution in addition to high contrast resolution and multi planar image reconstruction capacity.

Cardiac computer tomography is highly rated in the ACCF/SCCT/ACR/AHA/ASE/ASNC/NASCI/SCAI/SCMR 2010 appropriateness criteria for evaluation of cardiac mass, in patients with technically limited echocardiography or MRI, due to high spatial and temporal resolution and complete coverage of the heart and adjacent organs.[36]

EKG gated CT scanning improves soft tissue characterization similar to MRI and can better identify fatty content, and calcification compared to echocardiography. Additionally it can aid in evaluating the vascular supply of tumors.[103]

Image acquisition protocols for evaluation of a cardiac mass might be best done in three phases; noncontrast scanning, "first-pass" contrast imaging and delayed enhancement imaging. The noncontrast and delayed enhancement imaging can be done with axial protocols to lower overall radiation dose.[104] The noncontrast images are ideal for detection of calcium within the tumor. The "first-pass" contrast images allow assessment of blood supply and possible tumor necrosis. The delayed images allow for assessment of inflammation and low flow state within the tumor or adjacent structures. Large field of view reconstructions are well suited for assessment of extracardiac metastatic disease.

Myxomas are the most common benign cardiac tumor and can be detected by CT based on a common location within the left atrium with attachment to the atrial septum adjacent to the fossa ovale. Occasionally calcifications are seen within the myxoma. More "gelatinous", friable, poorly defined and mobile myxomas are associated with embolism, fever and weight loss.

Lipomas are the second most common benign primary cardiac tumors with variable location within the heart. On CT, they are characteristically with negative signal density and may be located in the cardiac chamber, the myocardium or the pericardium.

Fibromas are a common primary benign cardiac neoplasm in children with calcifications and they usually arise in the interventricular septum or the anterior ventricular wall.

Hemangiomas are vascular tumors that mostly occur in the lateral wall of the left ventricle. On noncontrasted CT, it is usually a well-defined, round or oval mass with heterogeneous attenuation and interspersed fat. A common characteristic of hemangiomas are calcified thrombi.

Fibroelastomas are the most common valvular tumors (Fig. 13). The differential diagnosis for valvular tumor would include vegetation, thrombus or myxoma. Most patients are asymptomatic and when symptoms occur, they are likely due to thromboembolic event.

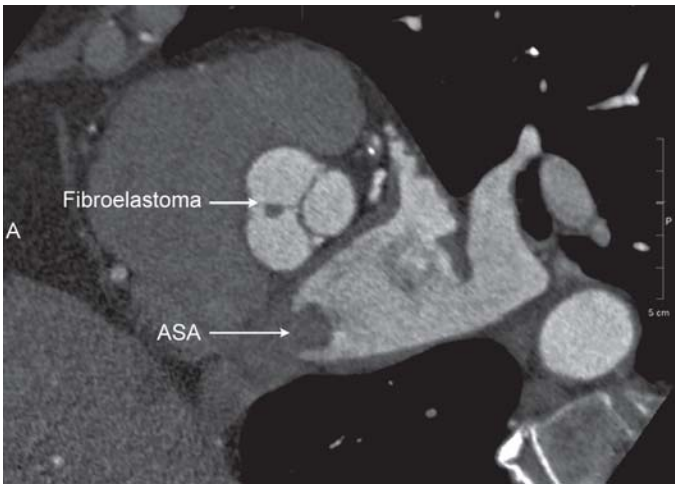


FIGURE 13: Fibroelastoma of the aortic valve attached to the noncoronary sinus of Valsalva. (Abbreviation: ASA: Atrial septal aneurysm).

MALIGNANT CARDIAC NEOPLASM

Angiosarcomas are malignant and usually arise from the right atrium with associated pericardial or pleural effusions, metastatic lung lesions and right-sided heart failure. On CT, it is often broad-based with heterogeneous enhancement or a low-attenuated mass which might be nodular or irregular.

Myxosarcomas are a rare form of a primary malignant cardiac tumor and very difficult to differentiate from a myxoma on CT. It is characterized by local recurrence and has been shown to involve the pulmonary artery, pericardium, pleura or distant metastasis, especially to the brain.

Primary cardiac lymphoma is rare and commonly affects the subepicardial fat, the right atrium, pericardium, and AV groove. Pericardial effusion is sometimes the only finding. When visualized, it may present as a large focal mass, multiple nodules or diffuse soft tissue infiltration with heterogeneous enhancement. Extracardiac findings may include mediastinal lymphadenopathy.[103]

Liposarcomas are rare and on CT they are usually a large solitary mass with mostly fatty and soft tissue components, infiltrating cardiac chambers and pericardium with mild contrast enhancement.

Metastatic cardiac tumors make up the bulk of malignant cardiac tumors. Most of the tumors originate through direct or transvenous invasion from the lungs, breasts, esophagus or other mediastinal tumors. Transvenous spread may also occur through the inferior vena cava from an adrenal or kidney tumor. Bronchogenic carcinoma can spread through the pulmonary vein to the left atrium. CT findings of metastatic malignant tumors are usually nonspecific and PET scanning can help to determine the extent of tumor spread or even localize the primary tumor.

NONCANCEROUS MASSES

Intracardiac thrombus is the most common intracardiac mass.[105] Most intracardiac thrombi occur in the setting of hypercoagulable state which can be as a result of left ventricular wall motion abnormality, presence of artificial devices (like mechanical valves) or atrial fibrillation. The major concern about an intracardiac thrombus is the propensity

for embolization with a 15% risk of embolic stroke. Thrombus is most commonly found in the left side of the heart.

CT can be used in patients with suspected left-sided thrombus who are not candidates for transesophageal echocardiogram. On CT, left atrial thrombus usually appears as a round or oval filling defect commonly found in the atrial appendage. The draw back of CT for left atrial thrombus differentiation is the phenomenon of "pseudo-filling" defect or mixing artifact. The pseudo-filling defects occur in cases with circulatory stasis, as can be seen with atrial fibrillation, and is due to incomplete mixing of blood with contrast. The problem of pseudo-filling defect can be overcome by delayed imaging, that is done in 60–90 seconds after the initial contrast scan because thrombus persist in both early and late phases, while pseudo-filling defect does not.[106]

Ventricular Thrombus

These are seen as crescent shaped filling defects close to infarcted or dyskinetic areas. Attenuation is usually less than that of the myocardium, but greater than fatty tissue. Chronic or long-standing thrombus may appear laminated or become calcified (Fig. 6). Thrombus can be differentiated from myxoma based on the location and also most thrombi are immobile.

Hiatal Hernia

This can be identified by the presence of gastric folds.

Lipomatous Hypertrophy of Intra-Atrial Septum

This occurs frequently in older and obese individuals. Patients are usually asymptomatic, but a few may develop arrhythmias. This is characterized by the accumulation of mature fat cells in the intra-atrial septum. CT findings are bilobed, dumb-bell shaped intra-atrial septum that is usually greater than 2 cm in transverse diameter. Attenuation is usually in the range of fatty tissue (–110 HU). The fossa ovale is characteristically spared.

INCIDENTAL FINDINGS

Integral part of cardiac CT is the evaluation of the adjacent organs to the heart. Multiple studies have assessed the incidental noncardiac findings and the reported incidence varies greatly ranging from 3% to 40%.[107] The most important incidental findings, such as aortic dissection, pulmonary embolism and cancer, are rare. Additionally findings of esophageal hiatal hernia and lung nodules are more common. Granulomatous disease with nodular calcifications is considered benign, but other noncalcified lung nodules, especially in patients with history of smoking are of concern. Patients with lung nodules are advised to undergo follow-up scans based on the Fleischner criteria that determine frequency and number of the follow-up studies.[108] Until recently, incidental lung nodule findings were, by some, considered a nuisance with limited clinical benefit,[109] but a randomized prospective study on smokers suggests there is a mortality benefit in the use of screening CT[110] and this might translate into benefit to patients who undergo a cardiac CT. Of note, a standard cardiac CT does not cover the whole lung field, and a half of incidental lung cancer findings could be missed.[111,112] At this time, it is not a common practice to offer full chest CT as an additional radiation would be expected with EKG gating and low pitch protocols.

FUTURE

The future of cardiac CT is very promising. The fast pace of technology has allowed a progressive improvement in CT scanning methods. Moore's law for annual increase in transistor computational power appears to apply for the CT technology. In the last decade, we have reached sub-millimeter spatial resolution and sub-second temporal resolution. At current time, we are able to acquire an image of the whole heart within a third of a second and with considerably less radiation than is used by other standard tests such as SPECT, CT chest, CT abdomen and CT of the head.

Cardiac CT has reached a state where its image quality is competitive with other imaging modalities such as SPECT, PET, echocardiography and MRI. Two randomized multicenter trials are in progress that will compare the anatomic assessment by CT with functional tests in patients with chest discomfort. These trials, the PROMISE and the RESCUE,are expected to solidify the clinical usefulness of Cardiac CT.

Research with myocardial perfusion CT is very promising and likely to be highly successful. Cardiac CT already allows for comprehensive evaluation of the heart by simultaneous anatomic assessment of the coronary arteries, cardiac chambers and valves. With successful myocardial perfusion imaging CT could become the primary test for evaluation of patients with chest pain.

With progression of technology, we can expect to see better spatial resolution, lower radiation and better tissue characterization. Multi-energy detectors with photon counting are under development and could allow for better detection of vulnerable plaque and discrimination between calcium and contrast within the coronary arteries. This would allow for more accurate stenosis analysis and improve prognostication of future cardiac events.

Cardiac CT has been embraced by cardiologist worldwide but due to concerns for overuse and presence of competing imaging modalities, the insurance companies have aggressively regulated and prevented the current use within the United States. Comparative effectiveness studies are expected to give the evidence based platform for future use of cardiac CT within the United States.

GUIDIELINES
2010 ACCF/AHA GUIDELINES FOR ASSESSMENT OF CARDIOVASCULAR RISK IN ASYMPTOMATIC ADULTS

Recommendations for Calcium Scoring Methods

Class IIa level of evidence: B	Measurement of coronary artery calcium (CAC) is reasonable for cardiovascular risk assessment in asymptomatic adults at intermediate risk (10–20% 10-year risk).
Class IIb level of evidence: B	Measurement of CAC may be reasonable for cardiovascular risk assessment in persons at low to intermediate risk (6–10% 10-year risk).
Class III level of evidence B	Person at low risk (< 6% 10 year risk) should not undergo CAC measurements for cardiovascular risk assessment

Recommendation for Coronary Computed Tomography Angiography

Class III Level of evidence: C	Coronary computed tomography angiography is not recommended for cardiovascular risk assessment in asymptomatic adults

Source: Greenland P, Alpert JS, Beller GA, et al. American College of Cardiology Foundation; American Heart Association. 2010 ACCF/AHA guidelines for assessment of cardiovascular risk in asymptomatic adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2010;56(25):e50-103.

AHA SCIENTIFIC STATEMENT 2006
ASSESSMENT OF CORONARY ARTERY DISEASE BY CARDIAC COMPUTED TOMOGRAPHY

Coronary Calcium Assessment

Class IIb Level of evidence: B	Coronary artery calcium (CAC) assessment may be reasonable for the assessment of symptomatic patients, especially in the setting of equivocal treadmill or functional testing
	Patients with chest pain with equivocal or normal EKGs and negative cardiac enzyme studies may be considered for CAC assessment
	There are other situations when CAC assessment might be reasonable. CAC measurement may be considered in the symptomatic patient to determine the cause of cardiomyopathy
Class III Level of evidence: C	Serial imaging for assessment of progression of coronary calcification is not indicated at this time

CT Coronary Angiography

Class IIa Level of evidence: B	CT coronary angiography is reasonable for the assessment of obstructive disease in symptomatic patients
Class IIa Level of evidence: C	CT coronary angiography reasonable to use CT as one of the first-choice imaging modalities in the workup of known and suspected coronary anomalies
Class IIb Level of evidence: C	Clinically, however, it might be reasonable in most cases not only to assess the patency of the bypass graft but also the presence of coronary stenoses in the course of the bypass graft or at the anastomotic site as well as in the native coronary artery system
Class III Level of evidence: C	Several small studies have assessed the value of EBCT and MDCT for detecting restenosis after stent placement. At this time, however, imaging of patients to follow-up stent placement cannot be recommended
	The use of both CT modalities to evaluate noncalcified plaque (NCP) is promising but premature. There are limited data on variability but none on the prognostic implications of CT angiography for NCP assessment or on the utility of these measures to track atherosclerosis or stenosis over time; therefore, their use for these purposes is not recommended
	CT coronary angiography is not recommended in asymptomatic persons for the assessment of occult CAD

Hybrid Nuclear/CT Imaging

Class III Level of evidence: C	The incremental benefit of hybrid imaging strategies will need to be demonstrated before clinical implementation, as radiation exposure may be significant with dual nuclear/CT imaging. Therefore, hybrid nuclear/CT imaging is not recommended

Source: Budoff MJ, Achenbach S, Blumenthal RS, et al. Assessment of coronary artery disease by cardiac computed tomography: a scientific statement from the American Heart Association Committee on Cardiovascular Imaging and Intervention, Council on Cardiovascular Radiology and Intervention, and Committee on Cardiac Imaging, Council on Clinical Cardiology. Circulation. 2006;114:1761-79.

ACCF/SCCT/ACR/AHA/ASE/ASNC/NASCI/SCAI/SCMR 2010 APPROPRIATE USE CRITERIA FOR CARDIAC COMPUTED TOMOGRAPHY

Detection of CAD in Symptomatic Patients without Known Heart Disease Symptomatic—Non-acute Symptoms Possibly Representing an Ischemic Equivalent

- Intermediate pretest probability of CAD

OR

- Low pretest probability of CAD
- EKG uninterpretable or unable to exercise

Detection of CAD in Symptomatic Patients without Known Heart Disease Symptomatic—Acute Symptoms with Suspicion of ACS (Urgent Presentation)

- Normal EKG and cardiac biomarkers
- Low pretest probability of CAD

OR

- Nondiagnostic EKG or equivocal cardiac biomarkers
- Intermediate pretest probability of CAD

Detection of CAD in Other Clinical Scenarios—New-Onset or Newly Diagnosed Clinical HF and No Prior CAD

- Reduced left ventricular ejection fraction
- Low pretest probability of CAD

OR

- Reduced left ventricular ejection fraction
- Intermediate pretest probability of CAD

Detection of CAD in Other Clinical Scenarios—Preoperative Coronary Assessment Prior to Non-coronary Cardiac Surgery

- Coronary evaluation before non-coronary cardiac surgery
- Intermediate pretest probability of CAD

Use of CTA in the Setting of Prior Test Results—Prior EKG Exercise Testing

- Normal EKG exercise test
- Continued symptoms

OR

- Prior EKG exercise testing
- Duke Treadmill Score—intermediate risk findings

Use of CTA in the Setting of Prior Test Results—Sequential Testing after Stress Imaging Procedures

- Discordant EKG exercise and imaging results

OR

- Stress imaging results: equivocal

Use of CTA in the Setting of Prior Test Results—Prior Coronary Calcium Score (CCS)

- Diagnostic impact of coronary calcium on the decision to perform contrast CTA in symptomatic patients
- CCS < 100

OR

- Diagnostic impact of coronary calcium on the decision to perform contrast CTA in symptomatic patients
- CCS 100–400

Use of CTA in the Setting of Prior Test Results—Evaluation of New or Worsening Symptoms in the Setting of Past Stress Imaging Study

- Previous stress imaging study normal

Risk Assessment Postrevascularization (PCI or CABG)—Symptomatic (Ischemic Equivalent)

- Evaluation of graft patency after CABG

Risk Assessment Postrevascularization (PCI or CABG)—Asymptomatic—Prior Coronary Stenting

- Prior left main coronary stent with stent diameter 3 mm

Evaluation of Cardiac Structure and Function—Adult Congenital Heart Disease

- Assessment of anomalies of coronary arterial and other thoracic arteriovenous vessels

OR

- Assessment of complex adult congenital heart disease

Evaluation of Cardiac Structure and Function—Evaluation of Ventricular Morphology and Systolic Function

- Inadequate images from other noninvasive methods
- Evaluation of left ventricular function
- Following acute MI or in HF patients

OR

- Quantitative evaluation of right ventricular function

OR

- Assessment of right ventricular morphology
- Suspected arrhythmogenic right ventricular dysplasia

Evaluation of Cardiac Structure and Function—Evaluation of Intracardiac and Extracardiac Structures

- Characterization of native cardiac valves
- Suspected clinically significant valvular dysfunction
- Inadequate images from other noninvasive methods

OR

- Characterization of prosthetic cardiac valves
- Suspected clinically significant valvular dysfunction
- Inadequate images from other noninvasive methods

OR

- Evaluation of cardiac mass (suspected tumor or thrombus)
- Inadequate images from other noninvasive methods

OR

- Evaluation of pericardial anatomy

OR

- Evaluation of pulmonary vein anatomy
- Prior to radiofrequency ablation for atrial fibrillation

OR

- Noninvasive coronary vein mapping
- Prior to placement of biventricular pacemaker

OR

- Localization of coronary bypass grafts and other retrosternal anatomy
- Prior to reoperative chest or cardiac surgery

Source: Taylor AJ, Cerqueira M, Hodgson JM, et al. ACCF/SCCT/ACR/AHA/ASE/ASNC/NASCI/SCAI/SCMR 2010 Appropriate use criteria for cardiac computed tomography: a report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, the Society of Cardiovascular Computed Tomography, the American College of Radiology, the American Heart Association, the American Society of Echocardiography, the American Society of Nuclear Cardiology, the North American Society for Cardiovascular Imaging, the Society for Cardiovascular Angiography and Interventions, and the Society for Cardiovascular Magnetic Resonance. J Am Coll Cardiol. 2010;56:1864-94.

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Chapter 23

Cardiovascular Magnetic Resonance

Robert M Weiss

Chapter Outline

- Introduction
  - Information Provided by CMR
- Diagnosis of Epicardial Coronary Artery Stenosis
- Assessment of Global and Regional Left Ventricular Function at Rest and During Inotropic Stress
- Myocardial Perfusion Imaging
- Cardiovascular Magnetic Resonance Coronary Angiography
- Unrecognized Myocardial Infarction
- Dilated Cardiomyopathy
  - Etiology
  - Prognosis
- Hypertrophic Cardiomyopathy
  - Diagnosis
  - Prognosis
  - Correlative Findings
- Restrictive Cardiomyopathy
  - Diagnosis
  - Etiology
- Cardiovascular Magnetic Resonance-guided Therapy
- Valvular Heart Disease
  - Valve Stenosis
  - Valvular Regurgitation
- Diseases with Right Ventricular Predominance
  - Intracardiac Shunt
  - Pulmonary Artery Hypertension
  - Arrhythmogenic Right Ventricular Cardiomyopathy
- Miscellaneous Conditions
  - Cardiac Thrombi
  - Cardiac Masses
  - Left Ventricle Trabeculations and Noncompaction
  - Pericardial Disease

INTRODUCTION

The history of magnetic resonance imaging (MRI) for characterization of cardiovascular morphology and function has been one of continuous innovation and refinement for over 25 years. Advancements in device design, image acquisition methodology and image analysis are rapidly translated into standardized methods for broad application in clinical cardiovascular medicine and cardiovascular research.

The fundamental principles of MRI are described in exquisite detail elsewhere.[1] The purpose of this chapter is to acquaint clinicians and clinical researchers with the ways that cardiovascular magnetic resonance (CMR) can solve problems in cardiovascular medicine.

INFORMATION PROVIDED BY CARDIOVASCULAR MAGNETIC RESONANCE

Morphology, kinematics and tissue characterization together form the crux of cardiovascular assessment with CMR. Assessments of left and right ventricular volumes and mass are highly reproducible and, when indexed for body habitus, are able to report relatively narrow reference ranges[2-4] (Table 1). It is important to note, however, that reference ranges depend somewhat upon the specific CMR image acquisition method,[5] and vary by sex and ethnic lineage.[4]

TABLE 1

Normal values for CMR using true-FISP acquisition

	*Males**	*Females**
LVEDV (ml)	168.5 ± 33.4	134.9 ± 19.3
LVESV (ml)	60.8 ± 16.0	48.9 ± 10.7
LVSV (ml)	107.7 ± 20.7	86.0 ± 12.3
LVEF (%)	64.2 ± 4.6	64.0 ± 4.9
LV Mass (g)	133.2 ± 23.9	90.2 ± 12.0
LV EDV/BSA (ml/m²)	82.3 ± 14.7	77.7 ± 10.8
LV Mass/BSA (g/m²)	64.7 ± 9.3	52.0 ± 7.4
LV EDV/HT (ml/m)	95.0 ± 17.3	82.6 ± 10.9
LV Mass/HT (g/m)	75.1 ± 12.3	55.3 ± 7.0
RVEDV (ml)	176.5 ± 33.0	130.6 ± 23.7
RVESV (ml)	79.3 ± 16.2	52.3 ± 9.9
RVSV (ml)	97.8 ± 18.7	78.3 ± 16.9
RVEF (%)	55.1 ± 3.7	59.8 ± 5.0
RV EDV/BSA (ml/m²)	86.2 ± 14.1	75.2 ± 13.8
RV EDV/HT (ml/m)	99.5 ± 16.9	80.0 ± 14.2

*mean ± SD

(Abbreviations: LV: Left ventricle; RV: Right ventricle; EDV: End-diastolic volume; ESV: End-systolic volume; SV: Stroke volume; EF: Ejection fraction; BSA: Body surface area; HT: Height; true-FISP: True fast imaging with steady-state precession). (*Source:* Alfakih, Plein S, Thiele H, et al. Normal human left and right ventricular dimensions for MRI as assessed by turbo gradient echo and steady-state free precession imaging sequences. J Magn Reson Imaging. 2003;17:329-9, with permission)

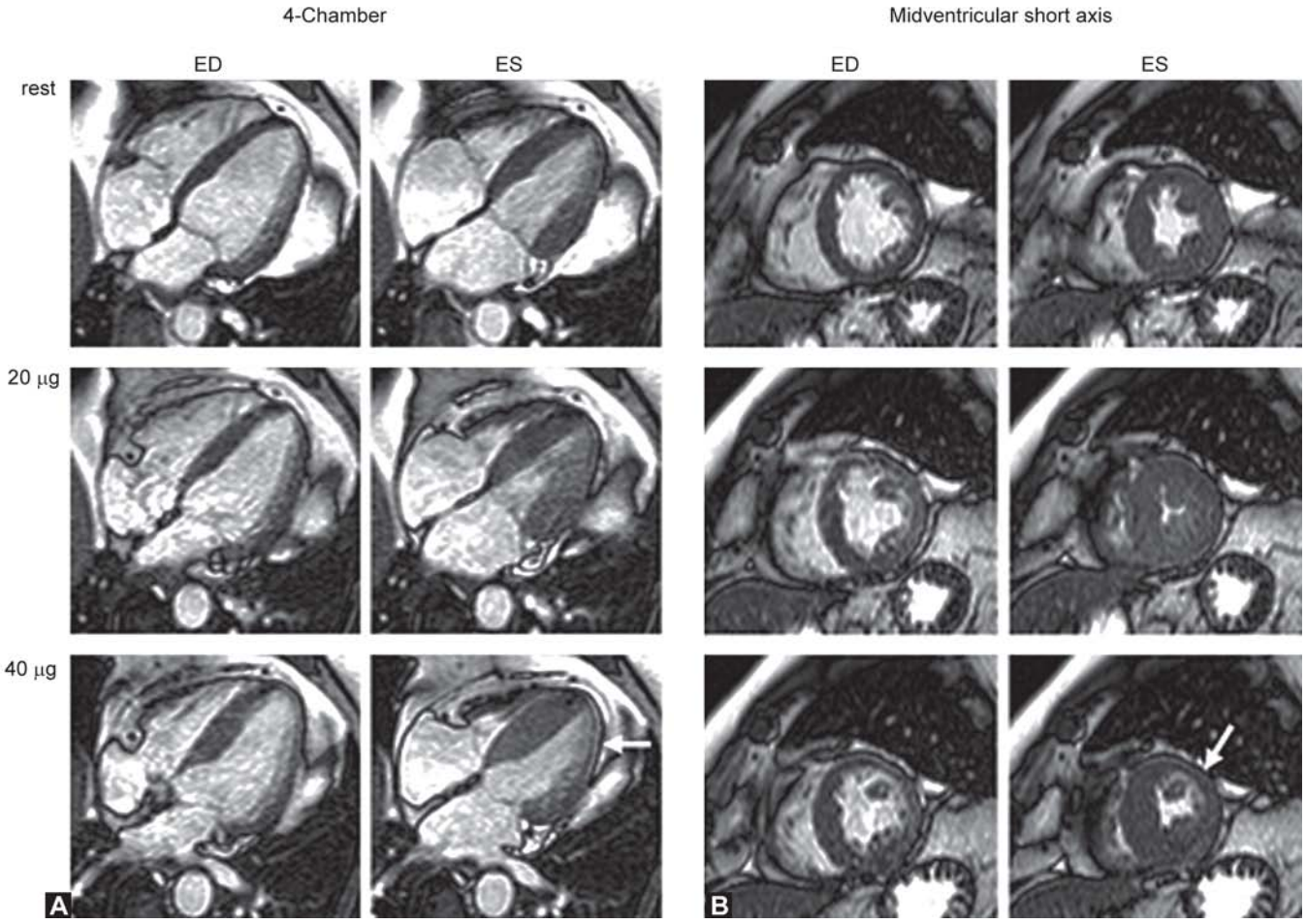
The superior quantitative accuracy of CMR characterization of ventricular anatomy and function does not depend on any assumptions regarding chamber geometry, a distinct advantage over purely planar techniques. The CMR has emerged as a reference standard against which the accuracy of newer applications using conventional methods (e.g. 3-dimensional echocardiography) can be compared.[6] The high reproducibility and narrow reference ranges of CMR ventriculographic data have been utilized in clinical trials for about 20 years.[7] The CMR offers increased statistical power and drastically reduces the necessary sample size in clinical trials, compared to echocardiography.[8] A search of a public database using the terms "heart and magnetic resonance" returns 436 ongoing or recently completed clinical trials.[9]

DIAGNOSIS OF EPICARDIAL CORONARY ARTERY STENOSIS

Myocardial infarction caused by flow limitation in epicardial coronary arteries [coronary artery stenosis (CAS)] is responsible for about one-sixth of all deaths in the United States.[10] Since myocardial infarction and sudden cardiac death (SCD) are often not preceded by intractable symptoms, a diagnostic armamentarium has been developed for the purpose of detecting disease in the epicardial coronary arteries. The CMR techniques for CAS detection, by and large, recapitulate established approaches using other techniques: functional evaluation at rest and during inotropic stress; perfusion assessment during vasodilator stress and coronary angiography.

ASSESSMENT OF GLOBAL AND REGIONAL LEFT VENTRICULAR FUNCTION AT REST AND DURING INOTROPIC STRESS

Ischemia is detected when the increased myocardial oxygen demand induced by inotrope infusion exceeds its supply, resulting in a wall motion abnormality (Figs 1A and B). In the twenty years following a small demonstration-of-principle study,[11] assessment of global and regional left ventricular systolic function during stepped infusion of the inotrope dobutamine has emerged as the CMR method most widely employed for detection of CAS. Subsequent series, involving thousands of patients, consistently report diagnostic performance and safety record that compares favorably to other noninvasive methods for detection of CAS.[12,13] Optimal diagnostic sensitivity is achieved when heart rate is raised to greater than or equal to 85% of predicted maximum, which often requires coadministration of the muscarinic blocker atropine.



FIGURES 1A AND B: End-diastolic (ED) and End-systolic (ES) SSFP images at rest and during stepped infusion of dobutamine in an individual with flow-limiting stenosis of the left circumflex coronary artery. During high-dose infusion (40 µg/kg/min), a wall motion abnormality appears in the mid- and apical lateral wall (arrows) (*Source:* Wahl A, Paetsch I, Gollesch A, et al. Safety and feasibility of high-dose dobutamine-atropine stress cardiovascular magnetic resonance for diagnosis of myocardial ischemia: Experience in 1000 consecutive cases. Eur Heart J 2004;25:1230-6, with permission)

At centers with significant expertise, CMR can be particularly useful for stress studies in patients with suboptimal acoustic access for echocardiography.[14] Unsuitability for an echocardiographic stress study can be ascertained at rest—avoiding the need to subject a patient to the repetitive risks and discomfort of inotropic stress. Use of echocardiography for assessment of the presence of residual CAS in patients with resting wall motion abnormalities is challenging. In that setting CMR can provide higher diagnostic yield for CAS.[15] The diagnostic accuracy of stress CMR can be incrementally improved when myocardial tagging is employed.[16] The incremental prognostic power of stress CMR has been established. Subjects who complete an inotropic stress protocol without CMR evidence of inducible ischemia have an excellent prognosis, whereas subjects with inducible ischemia are at greater risk of major adverse cardiac events.[17]

Since the intent of inotropic stress is to provoke and recognize myocardial ischemia, personnel and equipment must be available to manage its consequences, including myocardial infarction, malignant arrhythmia and shock.[18] Identification and treatment of complications can be more challenging in a CMR environment than in others, due to restricted patient contact. Recognition of ischemia requires frequent sampling and prompt assessment of left ventricular wall motion. Convenient access to emergency drugs and resuscitation equipment by experienced personnel is critically important in the CMR setting.[13]

MYOCARDIAL PERFUSION IMAGING

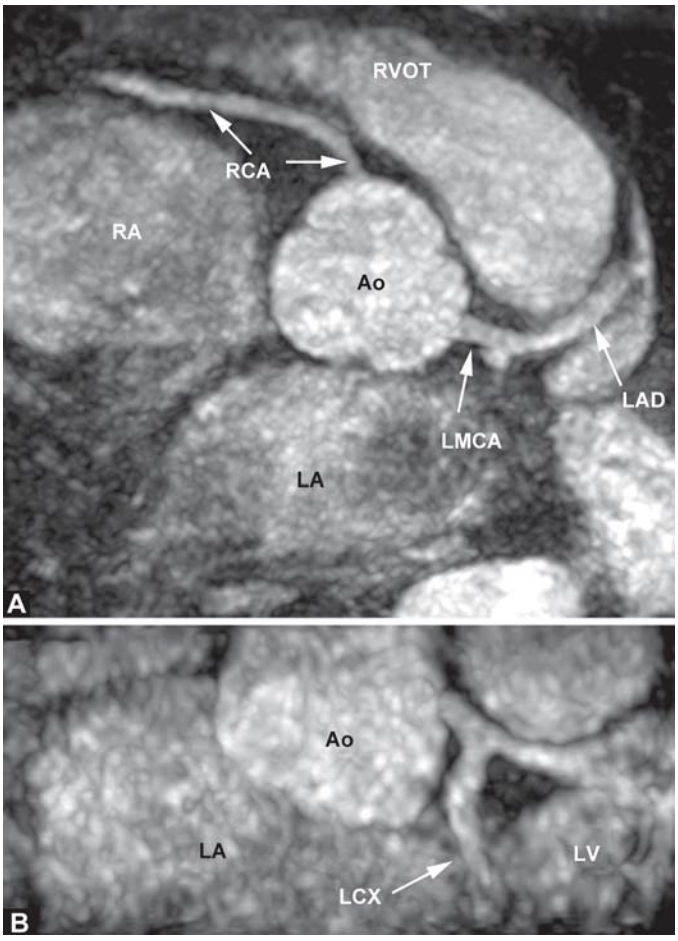
Adenosinergic drugs cause vasodilation in coronary resistance vessels. In the presence of flow-limiting epicardial coronary stenosis, resistance arteries will be at least partially dilated at rest, in order to maintain normal myocardial perfusion. During vasodilator stress, then, the incremental increase in tissue perfusion will be diminished in regions subserved by a stenotic epicardial vessel, compared to regions subserved by nonstenotic epicardial vessels, forming the basis for recognition of CAS.

In experienced centers, adequate diagnostic accuracy for CAS has been achieved using CMR to assess regional myocardial perfusion and perfusion reserve, during adenosine infusion.[19,20] A comprehensive CMR evaluation which includes perfusion assessment during adenosine stress provides incremental prognostic information, over and above consideration of routine clinical variables.[21]

As with inotrope stress, vasodilator stress can result in intractable ischemia, malignant arrhythmia and shock. Thus, similar precautions for recognition and management apply.[18] In addition, there is concern that recognition of ischemia during vasodilator stress may require computation of regional myocardial perfusion, which could delay remedial measures to a greater degree than visual recognition of ischemic wall motion abnormalities during inotrope stress.

CARDIOVASCULAR MAGNETIC RESONANCE CORONARY ANGIOGRAPHY

The CMR is useful to identify the origin and proximal course of the coronary arteries for the purpose of confirming or rejecting the presence of anomalies[22,23] (Figs 2A and B). The CMR has been employed to identify the presence of coronary



FIGURES 2A AND B: Free-breathing True-FISP 3-D coronary angiogram from a young man with chest pain, dyspnea, abnormal ECG, and elevated serum cardiac troponin-T. The origins and courses of the proximal coronary arteries are normal, effectively ruling out coronary anomaly as the etiology of the patient's clinical findings (Abbreviations: Ao: Aorta; RA: Right atrium; LA: Left atrium; RVOT: Right ventricular outflow tract; LV: Left ventricle; LMCA: Left main coronary artery; LAD: Left anterior descending coronary artery; LCX: Left circumflex coronary artery; RCA: Right coronary artery) (*Source:* Alan H. Stolpen, MD, PhD, Department of Radiology, University of Iowa Carver College of Medicine)

aneurysms in patients with Kawasaki disease.[24,25] Coronary artery bypass graft patency can be ascertained with high diagnostic accuracy.[26]

Detection of stenoses in native coronary arteries generally requires specialized 3-D methods.[23,27] Discrimination between clinically significant gradations in the severity of stenoses can be problematic, possibly rendering CMR coronary angiography more of a "screening tool", identifying patients who may benefit from evaluation of the physiological significance of identified lesions. However, in some highly specialized centers, CMR coronary angiography attains diagnostic yield comparable to other noninvasive methods for detecting CAS.[28]

UNRECOGNIZED MYOCARDIAL INFARCTION

At least 20% of incident myocardial infarctions occur in the absence of recognizable symptoms.[10] The condition often comes to a clinician's attention by virtue the appearance of pathological Q-waves on an elective electrocardiogram. More recently, it has become clear that a significant number of prior silent infarctions

do not produce such findings and are only detected by characteristic findings on CMR-late gadolinium enhancement (LGE) with subendocardial predominance, in a typical distribution of a major coronary artery branch. That finding contributes significantly to the overall diagnostic sensitivity of CMR for detection of CAS.[29] Furthermore, the finding is a powerful independent predictor of future major adverse cardiac events, even in patients with known CAD.[30,31]

DILATED CARDIOMYOPATHY

Despite advances in prevention and treatment, the prevalence and impact of heart failure are increasing in Western Societies.[10] Dilated cardiomyopathy (DCM) is the most common cause of heart failure, and the most frequent reason for referral for heart transplantation or mechanical cardiac assist device implantation.[32,33]

Although management strategies for patients with DCM have matured over the past decade, clinicians continue to be presented with significant challenges for the management of individual patients.[34] Applications of established CMR methods can be useful in decision-making in selected patients with DCM.

ETIOLOGY

The DCM can arise from diverse processes—genetic or environmental—and can be a presenting feature of systemic diseases such as atherosclerosis, hypertension or endocrine imbalance. The CMR is useful for directing therapy designed to treat the underlying cause of DCM in a number of instances where generic treatment of "heart failure" would be expected to yield a suboptimal outcome.

Coronary Artery Stenoses

In patients presenting with systolic heart failure due to DCM, it is incumbent upon the clinician to ascertain the presence or absence of flow-limiting coronary artery stenoses (CAS). As noted above, CMR can be useful for identifying patients with DCM due to CAS. Equally important, CMR confers the ability to precisely define the extent and severity of ischemic myocardial fibrosis in patients with DCM.[35,36]

Several decades ago, a landmark clinical trial reported that patients with DCM and symptomatic stenoses of the three major epicardial coronary branches, and those with flow-limiting stenosis of the left main coronary artery, fared better with revascularization than with medical therapy alone.[37] More recently, this longstanding paradigm has been refined so as to suggest that the benefits of revascularization are most likely for patients who demonstrate a limited extent of ischemic scar in regions with systolic dysfunction (viable myocardium). The unique ability of CMR to depict the transmural extent of ischemic scar allows accurate prediction of functional recovery after successful revascularization,[38-40] and directly influences prognosis in patients with ischemic DCM.[41,42] Some experts advise consideration of performing assessment of myocardial viability in patients with heart failure, with an eye toward revascularization, even when angina pectoris is not present.[43] The surgical treatment for ischemic heart failure (STICH) study is a multicenter clinical trial designed to determine whether the potential benefit of surgical revascularization in patients with DCM and CAS is dependent on the presence of viable myocardium.[44] Early results indicate that echocardiographic or scintigraphic confirmation of myocardial viability did not forecast improved outcome in patients who underwent surgical revascularization for CAS with DCM, compared to patients without viable myocardium. At this time it is not known whether the superior quantitative precision of CMR for identification of ischemic scar would result in improved identification of patients who would derive the most benefit from surgical revascularization for ischemic DCM.

Myocarditis

The actual incidence of myocarditis is not known. The clinical manifestations of the disease can be nonspecific—fever, myalgias, exercise intolerance—and its course is usually mild and self-limited. However, patients with fulminant disease, and those with chronic indolent myocarditis, can present with incident heart failure, and require special attention.

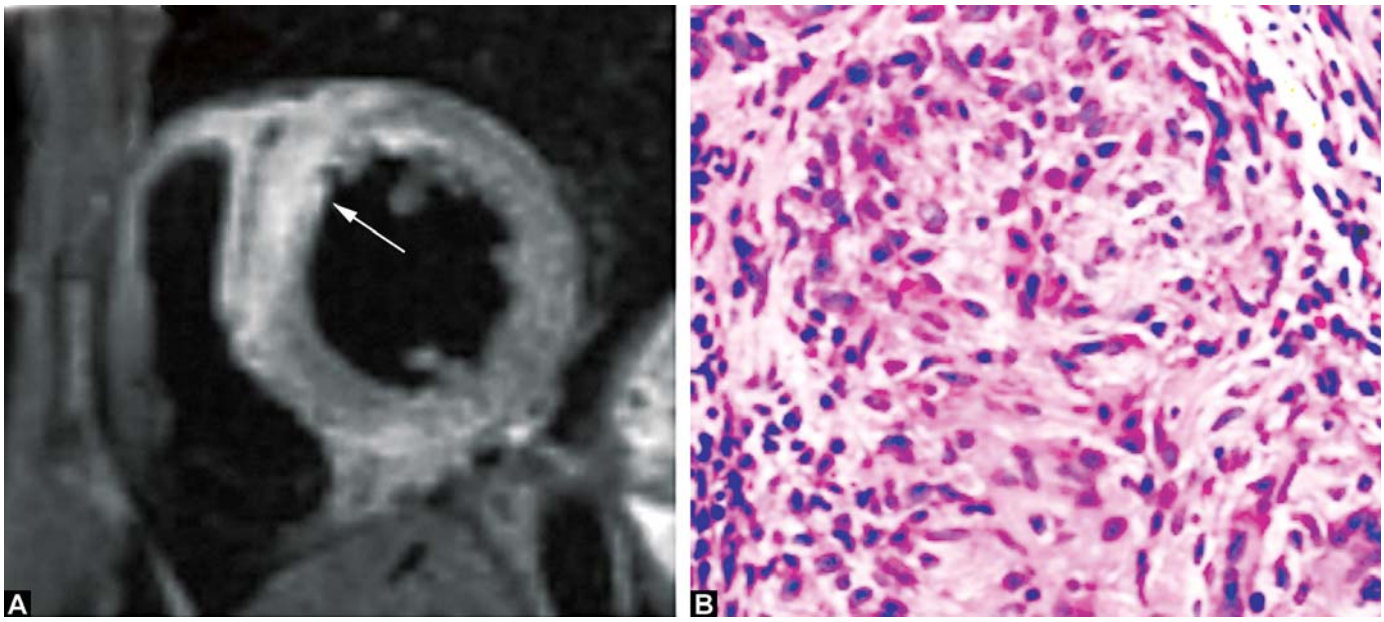
Patients with incident heart failure due to fulminant myocarditis require admission to the hospital, continuous ECG-monitoring and aggressive supportive care. Although early mortality is relatively high (~ 10%), those surviving to hospital discharge have an excellent prognosis[45] findings which emphasize the importance of early diagnosis. Patients with giant cell myocarditis often develop fulminant progression of disease with very poor prognosis, if untreated.[46] The CMR can facilitate diagnosis of giant cell myocarditis by identifying sentinel features of inflammation—edema and expansion of the extracellular space (Figs 3A and B).

Indolent myocarditis is characterized by subacute or chronic cardiac dysfunction and poor long-term prognosis.[45] No broadly applied treatment regimen has demonstrated efficacy for the treatment of all patients with indolent myocarditis.[48] However, emerging evidence suggests that confirmation of the diagnosis of myocarditis and subsequent etiology-specific treatment can favorably influence the prognosis for some patients.

In a nonrandomized prospective study of patients with chronic lymphocytic myocarditis, those for whom infectious etiologies were identified fared worse with immunosuppressive therapy than those for whom infectious etiologies were excluded.[49] A subsequent randomized study in patients with non-viral lymphocytic myocarditis demonstrated improved left ventricular systolic function in patients treated with an immunosuppression regimen, compared to patients who received placebo.[50]

The diagnosis of myocarditis itself can be problematic. Electrocardiographic and echocardiographic findings may be nonspecific or absent, and blood enzymology is not sufficiently sensitive.[51] Referral for endomyocardial biopsy requires a very high level of clinical suspicion, and that procedure can be subject to low diagnostic yield, presumably due to the patchy nature of the disease in many cases.[52]

In addition to providing quantitatively precise assessment of global and regional ventricular function, CMR findings point to a diagnosis of myocarditis by virtue of visualizing expansion of the myocardial extravascular space, reflecting edema, inflammation or fibrosis. T2-weighted (black blood) imaging



FIGURES 3A AND B: Giant cell myocarditis. (A) Short-axis double inversion-recovery image from a young man with acute heart failure. Bright signal in the anterior interventricular septum indicates myocardial edema (arrow). (B) Hematoxylin and eosin stain of endomyocardial biopsy specimen shows abundant inflammation and several multi-nucleated giant cells (*Source:* Berry CJ, Johnson FL, Cabuay BM, et al. Evanescent asymmetrical septal hypertrophy and rapidly progressive heart failure in a 32-year-old man. Circulation. 2008;118:e126-8, with permission)

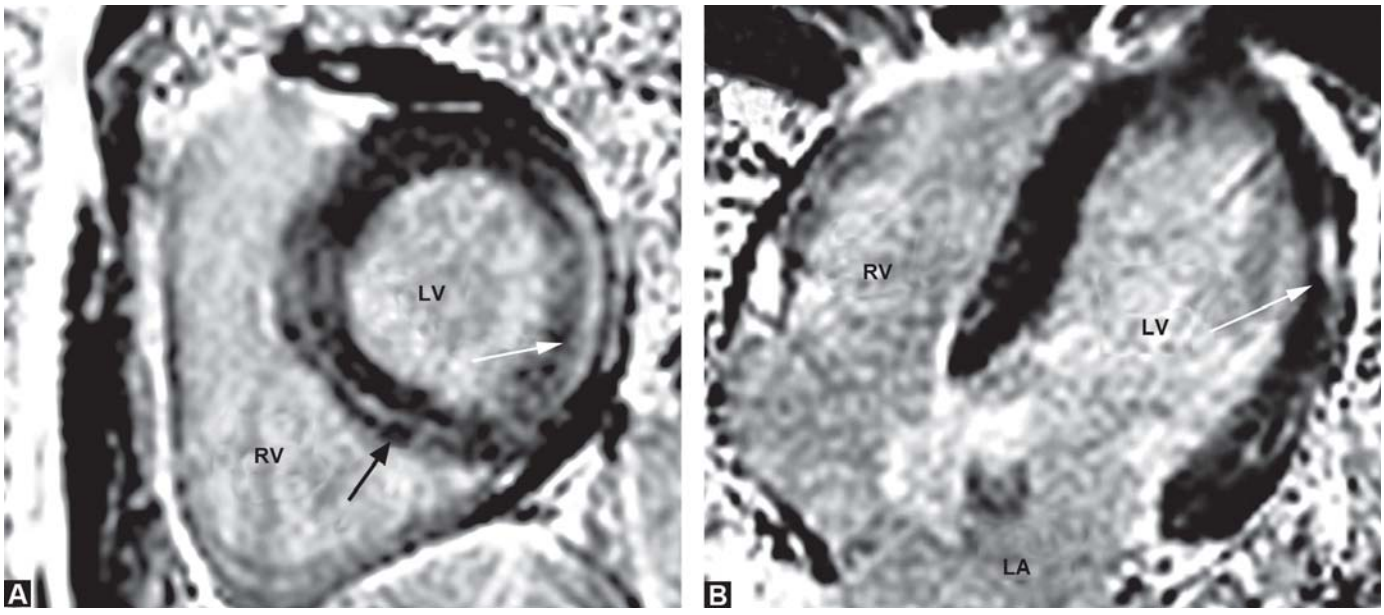
produces increased signal intensity in regions with unrestrained extravascular water (Figs 3A and B). Exclusion of other causes of myocardial edema—ischemic injury, trauma, toxin exposure—guides the clinician toward a diagnosis of myocarditis. The CMR techniques which utilize LGE also produce increased signal intensity in regions with expansion of the extracellular extravascular space (Figs 4A and B), and are preferred in some settings, due to greater signal-to-noise ratio than T2-weighted imaging.

The CMR is emerging as the diagnostic procedure of choice for identification of myocarditis in patients presenting with incident left ventricular dysfunction. In relatively small series, CMR has demonstrated very high sensitivity and specificity for detection of myocardial inflammation.[53,54] The CMR localization of myocardial inflammation has been found to improve the diagnostic yield of endomyocardial biopsy in some,[55] but not all,[56] studies.

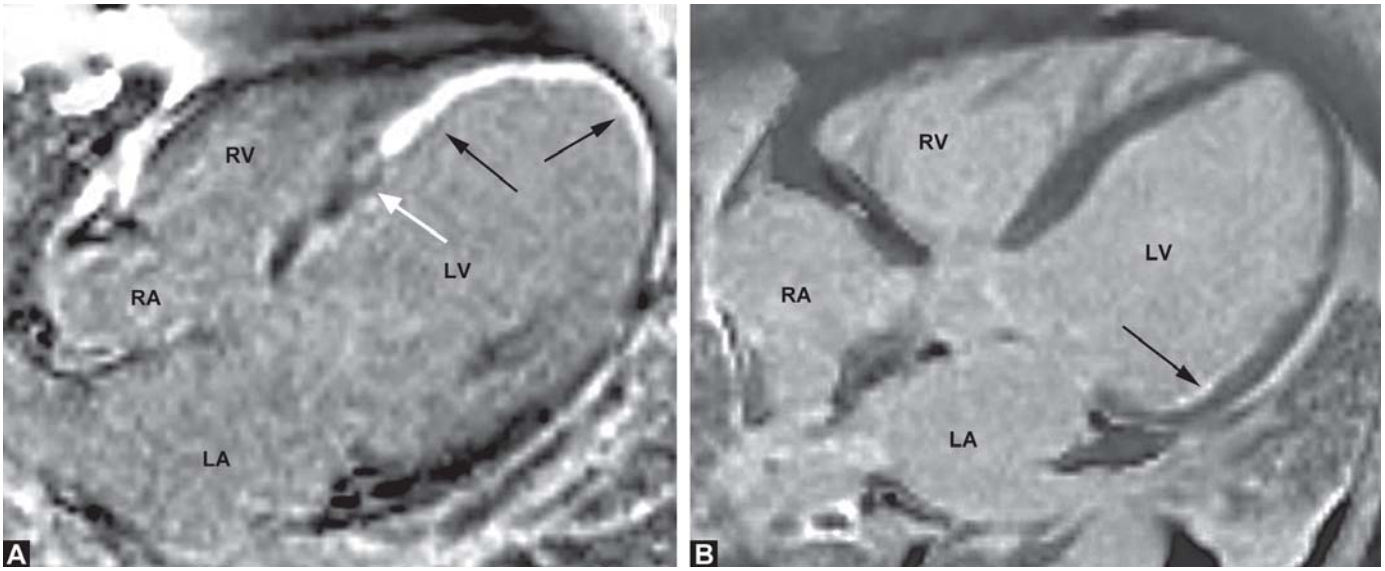
PROGNOSIS

Ischemic Dilated Cardiomyopathy

In patients with DCM due to CAS, the extent of irreversibly injured myocardium (scar) varies widely (Figs 5A and B). Prognosis is directly related to the extent of ischemic scar, independent of the severity of left ventricular systolic dysfunction, or the decision to undergo revascularization.[57,58]



FIGURES 4A AND B: Indolent myocarditis. A young male presented with chest pain, abnormal ECG and troponinemia one week following a viral prodrome. (A) Short-axis and (B) Four-chamber phase-sensitive inversion recovery images acquired 10 minutes following administration of Gd-DTPA. Dense LGE with epicardial predominance appears in the lateral LV wall, with streaky midmyocardial LGE in the septum (arrows)



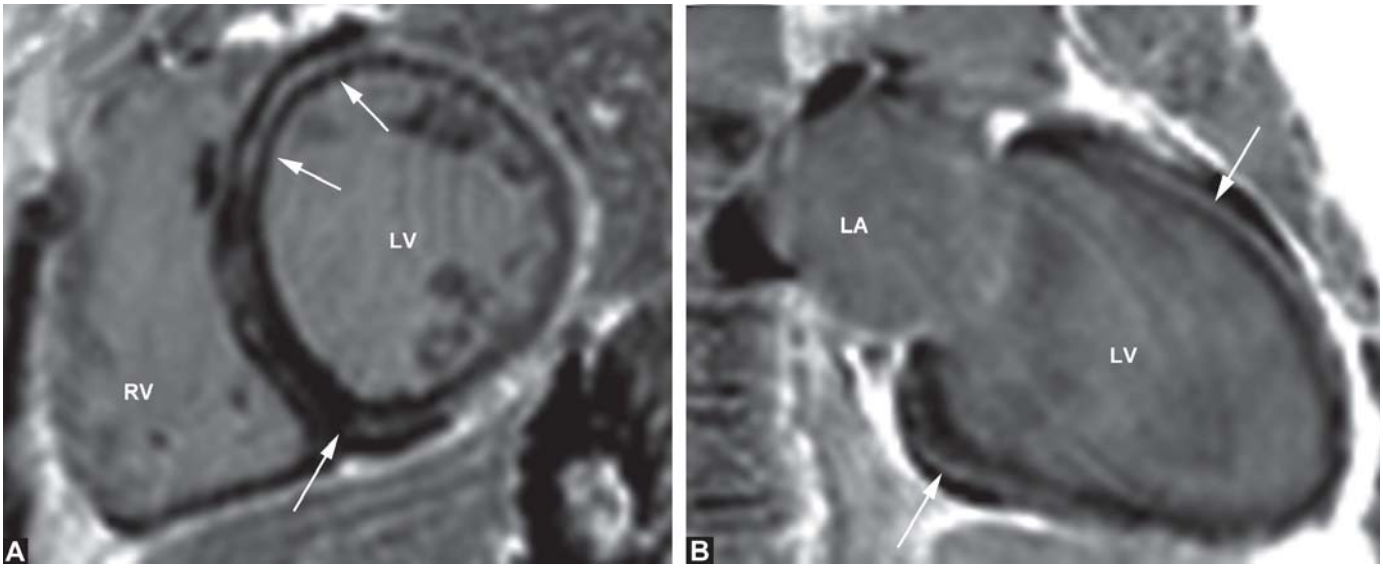
FIGURES 5A AND B: Four-chamber phase-sensitive inversion recovery images 10 minutes after administration of Gd-DTPA from two patients, each with 3-vessel CAS, LV dilation and LVEF < 0.30. (A) In Patient A there is transmural infarction (black arrows) in the septum and apex, including microvascular obstruction in the basal septum (white arrow). The findings forecast little benefit of revascularization in those regions. (B) In Patient B there is only subendocardial infarction in the basal lateral wall (black arrow), indicating a high likelihood of functional improvement following successful revascularization

Patients with ischemic DCM and extensive ischemic scar are more likely to incur ventricular tachycardia during programmed electrical stimulation, than patients with little or no LGE.[59] Preliminary studies indicate that the extent of LGE in patients with ischemic DCM may have independent utility for identifying patients at risk of SCD. A study designed to determine whether CMR assessment of scar burden is an appropriate indication for implantation of a cardioverter-defibrillator is in progress.[60]

Prognosis in Idiopathic Dilated Cardiomyopathy

In patients with DCM that is not associated with CAS, CMR provides powerful prognostic information. Morphology and systolic function of the right ventricle (RV) are not optimally characterized by planar techniques, but exert a strong influence on prognosis in patients with DCM.[61] The superior quantitation of right ventricular abnormalities of CMR thus provides improved prognostic power, compared to conventional methods.

Although idiopathic DCM was previously thought to invariably entail abundant myocardial fibrosis, recent evidence indicates substantial variability in the degree of fibrosis among patients with DCM—an attribute linked to prognosis and the likelihood of therapeutic response to therapeutic intervention.[62] Myocardial fibrosis in idiopathic DCM is often visualized as midmyocardial LGE (Figs 6A and B). The CMR depiction of LGE, representing myocardial fibrosis, is associated with increased risk of death or hospitalization in patients with DCM, compared to patients with DCM without LGE, and the association is more pronounced in patients with abundant scar.[63]



FIGURES 6A AND B: Myocardial fibrosis in dilated cardiomyopathy. Phase-sensitive inversion recovery images acquired 10 minutes following administration of Gd-DTPA in a 31-year-old man with idiopathic DCM. (A) Short-axis, and (B) Two-chamber long-axis views demonstrate midmyocardial LGE in the anterior and inferior LV walls (arrows)

In patients with systolic heart failure due to non-ischemic DCM, SCD or appropriate intervention by an implantable cardiac defibrillator (ICD) are fourfold more likely in patients with LGE than in patients without LGE.[64]

Although these studies in patients with DCM strongly support the prognostic power of CMR in patients with DCM, the role of CMR in clinical decision-making, e.g. whether or not to refer an individual patient for ICD placement, has not been definitively determined.

HYPERTROPHIC CARDIOMYOPATHY

Hypertrophic cardiomyopathy (HCM) is a leading cause of sudden death in young people and in competitive athletes.[65] The disease is usually characterized by morphologic left ventricular hypertrophy (LVH) in the absence of pressure-overload or volume-overload or systemic conditions associated with cardiac hypertrophy. Genetic testing reveals cardiac sarcomere-related mutations in about 50% of cases.[66,67] Cellular hypertrophy with myocyte disarray and increased interstitial collagen are histopathologic hallmarks of the disease.[68] Clinical manifestations include diastolic heart failure, arrhythmic and neurogenic syncope and SCD.[69] The diagnosis is most often suspected based on clinical and family history, physical examination and electrocardiography, and is most often confirmed by echocardiography. Since sudden death commonly occurs in the absence of intractable symptoms, risk stratification algorithms have been proposed and are in continuous evolution.

DIAGNOSIS

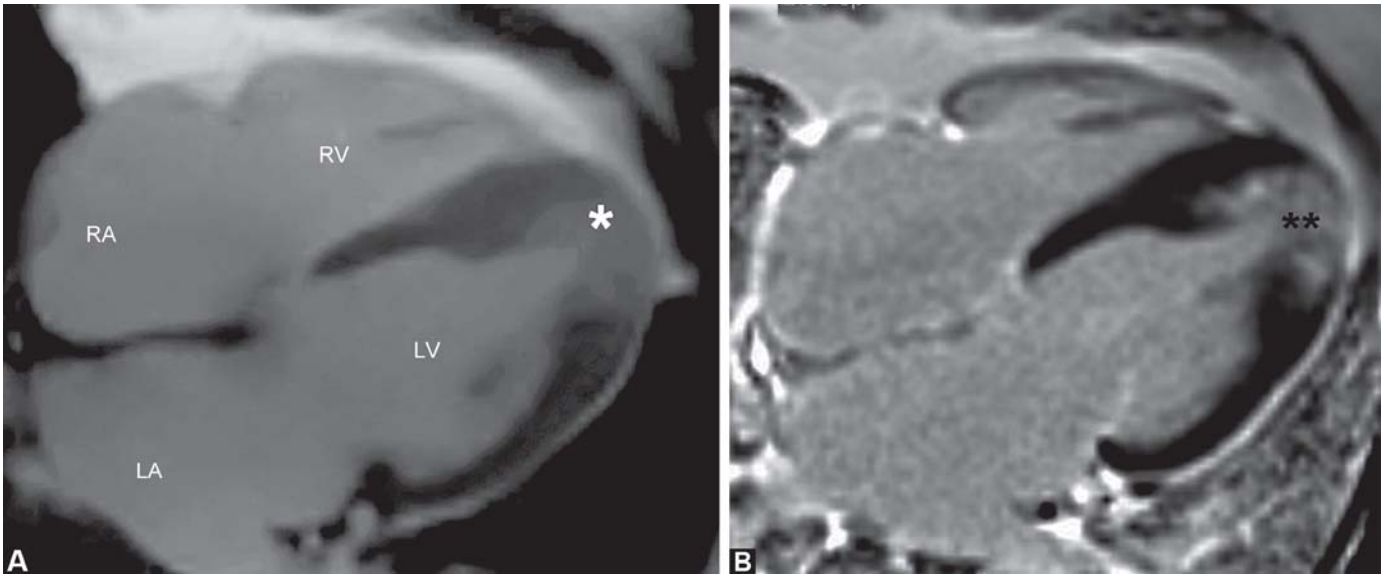
The CMR can offer higher diagnostic sensitivity for HCM than echocardiography. This is more often the case when the left ventricular region of hypertrophy occurs in a location other than the basal interventricular septum,[70] or when visualization of the heart with echocardiography is suboptimal.[71] Echocardiographic visualization of the left ventricular apex with sufficient clarity to ascertain wall thickness can be problematic in some patients with suboptimal acoustic windows. The CMR can provide diagnostic certainty in such cases, where the clinical suspicion of apical HCM is high.[72] In some cases, CMR can be useful to definitively discriminate between apical HCM and left ventricular noncompaction (LVNC) (Figs 7A and B). In patients with HCM, there is frequently involvement of the RV,[73] a finding of uncertain clinical significance.

The clinical course of carriers of HCM-associated gene mutations who do not manifest morphologic HCM can be unclear. Strijack et al. report a case of a gene-positive carrier with a family history of sudden death, with multiple morphology-positive first-degree relatives, whose echocardiogram showed normal wall thickness and left ventricular mass.[74] On CMR examination, the individual demonstrated abundant LGE, indicating ongoing disease in the absence of morphologic LVH (Figs 8A and B). However, in a later series, CMR was found to be nondiagnostic in gene-positive morphology-negative patients who demonstrated biochemical evidence of myocardial collagen turnover.[75]

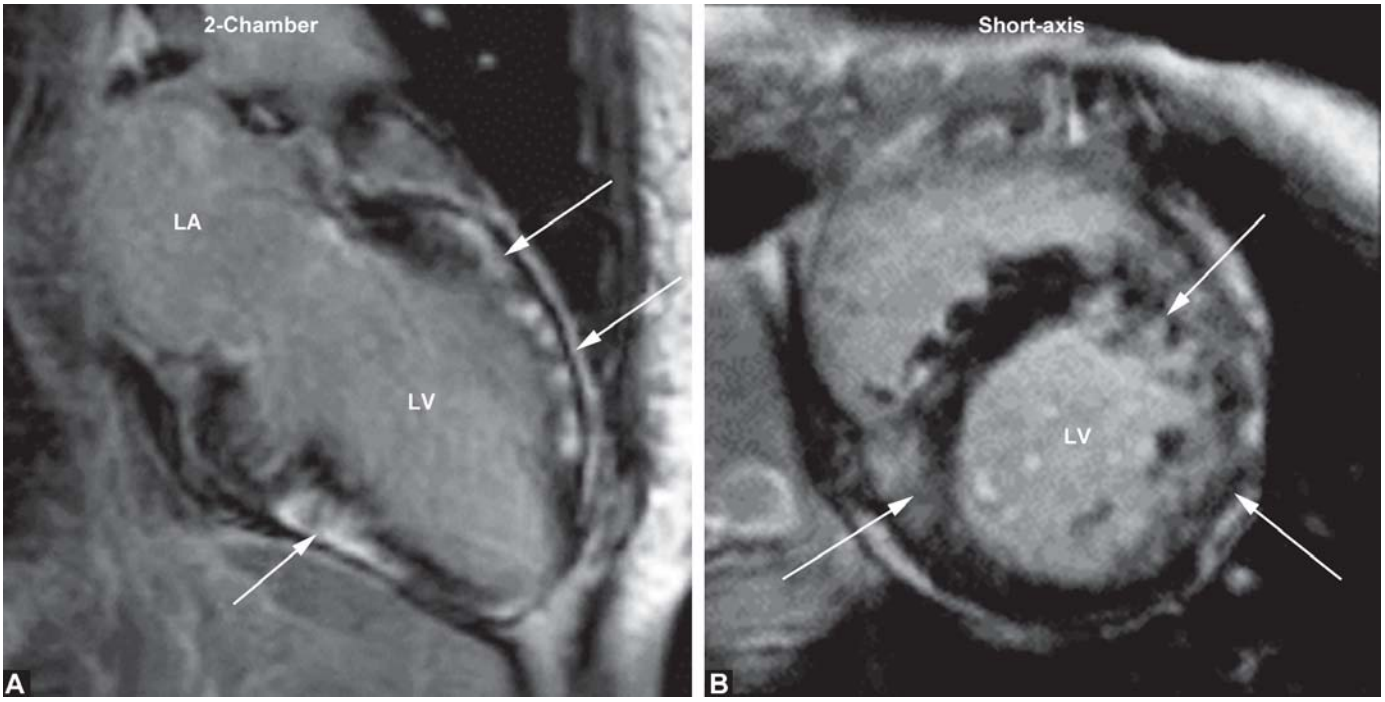
PROGNOSIS

Established risk factors for SCD in patients with HCM include: prior arrhythmic cardiac arrest, spontaneous sustained or nonsustained ventricular tachycardia, family history of unexplained SCD, regional diastolic left ventricular wall thickness greater than 3 cm and abnormal blood pressure response to exercise. The presence of multiple SCD risk factors is associated with incremental risk.[76]

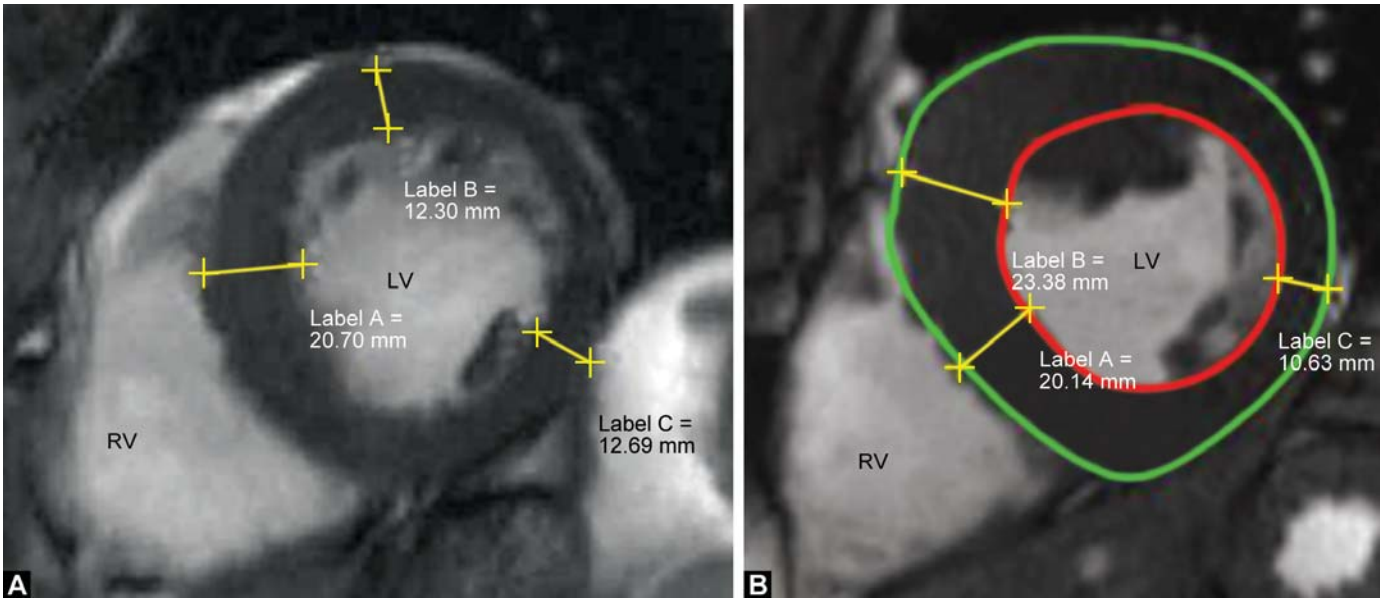
The CMR can be helpful in elucidating the risk profile in individual patients. In addition to higher diagnostic sensitivity for the disease itself, Rickers et al. reported that CMR identified patients with wall thickness greater than 3 cm in 10% of cases where echocardiography did not.[70] In patients



FIGURES 7A AND B: Apical HCM. A 57-year-old man complained of chest pain and dyspnea on exertion. Coronary angiography revealed no CAS. Echocardiography raised the question of apical HCM vs LVNC. (A) Four-chamber true-FISP image at end-diastole reveals grossly thickened apical myocardium (*). (B) Phase-sensitive inversion recovery image acquired 10 minutes after administration of Gd-DTPA reveals abundant LGE in apical myocardium (**). Endomyocardial biopsy from the LV apex revealed myocyte hypertrophy and disarray with profound interstitial fibrosis, in the absence of inflammation or infiltration—confirming the diagnosis of apical HCM



FIGURES 8A AND B: Inversion recovery images late after administration of Gd-DTPA from a patient who is gene-positive, but morphology negative for HCM. Arrows indicate abundant LGE within LV myocardium (arrows) [Images reprinted with permission from the Society of Cardiovascular Magnetic Resonance (Strijack, et al[73])]



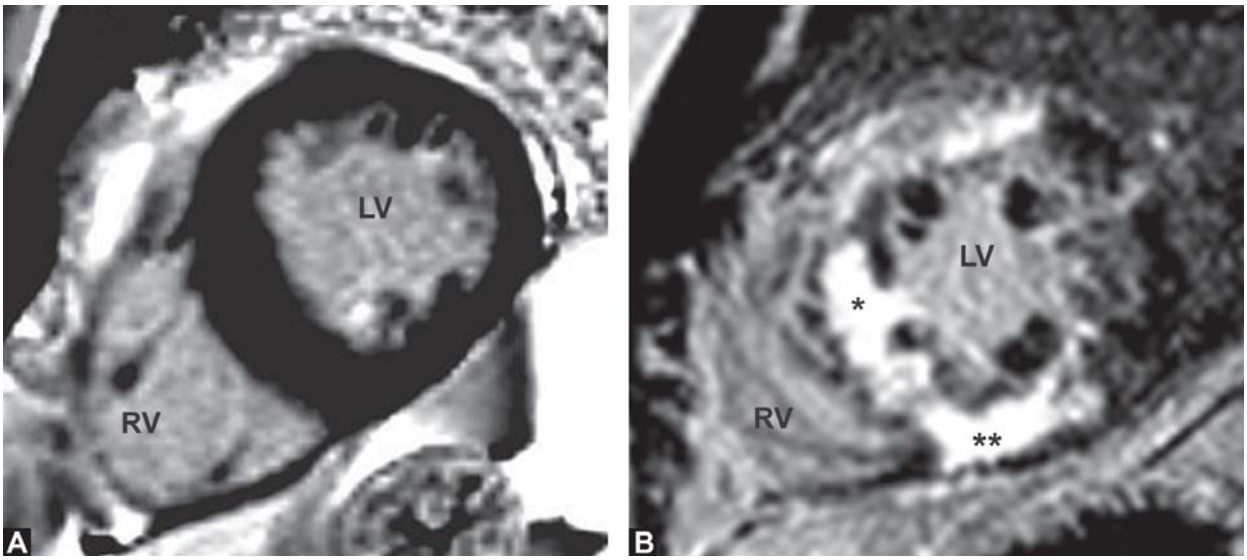
FIGURES 9A AND B: Differing extent of regional left ventricular hypertrophy in two patients with HCM. Mid-septal wall thicknesses are similar in both patients, ~ 20–21 mm. However, profound hypertrophy extends into the anterolateral LV wall in Patient B, a finding occasionally not appreciated on echocardiography.[70] In addition, LV mass index is > 4 SD above the normal mean, a finding which has been linked to worse prognosis[77]

with HCM, CMR-derived total left ventricular mass demonstrates greater than twofold greater sensitivity for prediction of SCD, compared to echo-derived maximum wall thickness, and there is a relatively weak correlation between the two parameters[77] (Figs 9A and B).

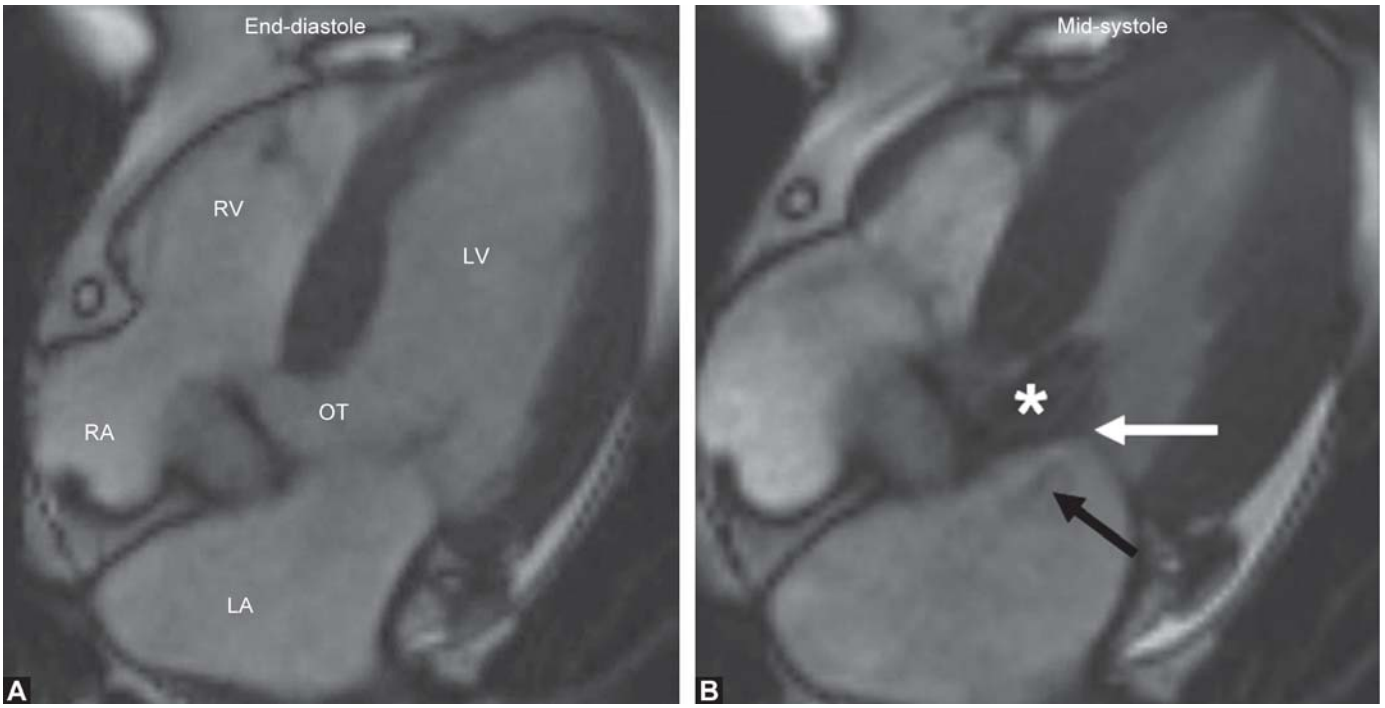
The presence and extent of LGE varies widely among patients with HCM (Figs 10A and B). The presence of LGE is associated with the occurrence of malignant arrhythmias.[78] The extent of myocardial LGE is positively correlated with the likelihood of a composite "adverse outcome" (heart failure progression or SCD).[79-82]

CORRELATIVE FINDINGS

The CMR provides dynamic evidence of left ventricular outflow obstruction (Figs 11A and B), which may be useful for planning ablative or surgical procedures, and can provide follow-up confirmation of the efficacy of the procedure.[83] Mitral valve regurgitation frequently complicates the course of patients with



FIGURES 10A AND B: Late gadolinium enhancement in HCM. Phase-sensitive inversion recovery imaging 10 minutes after administration of Gd-DTPA. Two patients with similar magnitude of septal hypertrophy. In Patient A, no myocardial LGE is detected, while in Patient B, there is extensive LGE in the septum (*) and posterior wall (**)



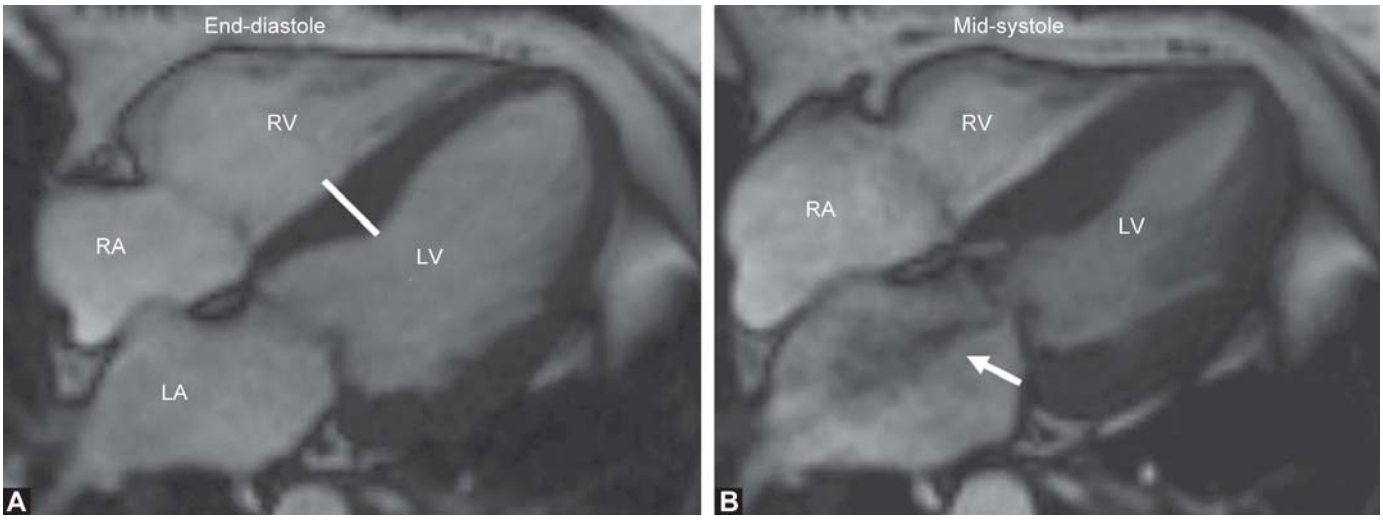
FIGURES 11A AND B: Four-chamber true-FISP images from a patient with concentric LVH with basal predominance. During systole, the point of mitral leaflet coaptation is drawn toward the septum (white arrow). Flow acceleration in the outflow tract (OT) results in dephasing of the blood signal (*), and a trace of mitral regurgitation occurs (black arrow)

HCM, and can be quantitated using CMR, thus assisting in the decision to refer for mitral valve replacement or repair (Figs 12A and B).

HCM is associated with functional abnormalities of the microcirculation, which may correlate with its clinical course.[84,85] Abnormalities of myocardial energetics can be ascertained in patients with HCM, and often precede onset of symptoms.[86]

RESTRICTIVE CARDIOMYOPATHY

Restrictive cardiomyopathy (RCM) comprises a diverse set of conditions which often entail a long period of clinical latency, followed by progressive cardiac dysfunction and death due to refractory heart failure or SCD. Symptoms consist of pulmonary and systemic venous congestion and inability to raise cardiac output during exertion, all of which can be ascribed to decreased compliance of one or both ventricles.



FIGURES 12A AND B: Four-chamber true-FISP images from a young woman with focal septal hypertrophy (white bar = 1.7 cm). During systole there is mitral regurgitation demonstrated by dephasing of the blood signal (arrow)

DIAGNOSIS

Symptoms, signs and hemodynamic findings of restrictive cardiomyopathies often mimic those which occur with constrictive pericarditis.[87] The CMR can be useful for discriminating between the two conditions. Constrictive pericarditis is readily identified using methods described below. In a patient with a clinical diagnosis of heart failure, CMR provides quantitative corroboration of the salient features of restrictive cardiomyopathy early in the course of disease—normal or decreased left ventricular end-diastolic volume, normal or increased left ventricular mass, preserved or only mildly decreased left ventricular ejection fraction.

ETIOLOGY

Although disease-specific treatment is not available for many patients with RCM, effective treatments have been developed for some disease etiologies—forming a justification for a rigorous diagnostic strategy. In addition to morphologic and functional data, CMR can identify expansion of the extracellular space—a common finding in restrictive cardiomyopathy caused by amyloidosis,[88] Fabry's disease,[89] sarcoidosis[90] and hypereosinophilic syndromes.[91] The CMR methods for RCM assessment resemble those for detection of myocarditis (which can also manifest as restrictive cardiomyopathy). Double inversion-recovery ("black blood") techniques identify myocardial edema. Phase-sensitive inversion-recovery (PSIR) imaging is used to depict LGE, in a manner similar to methods employed to detect myocardial infarction (Figs 13A to F).

Iron overload states represent a special case for the diagnosis of restrictive cardiomyopathy. Clinically important levels of iron deposited in myocardium can sufficiently alter the local CMR signal so as to be diagnostic. Special techniques have been developed which compare T2*-weighted signal intensity to routine T2*-weighted signal. When tissue iron is abundant, local effects serve to diminish T2 intensity, rendering myocardium darker in areas of infiltration.[92]

CARDIOVASCULAR MAGNETIC RESONANCE-GUIDED THERAPY

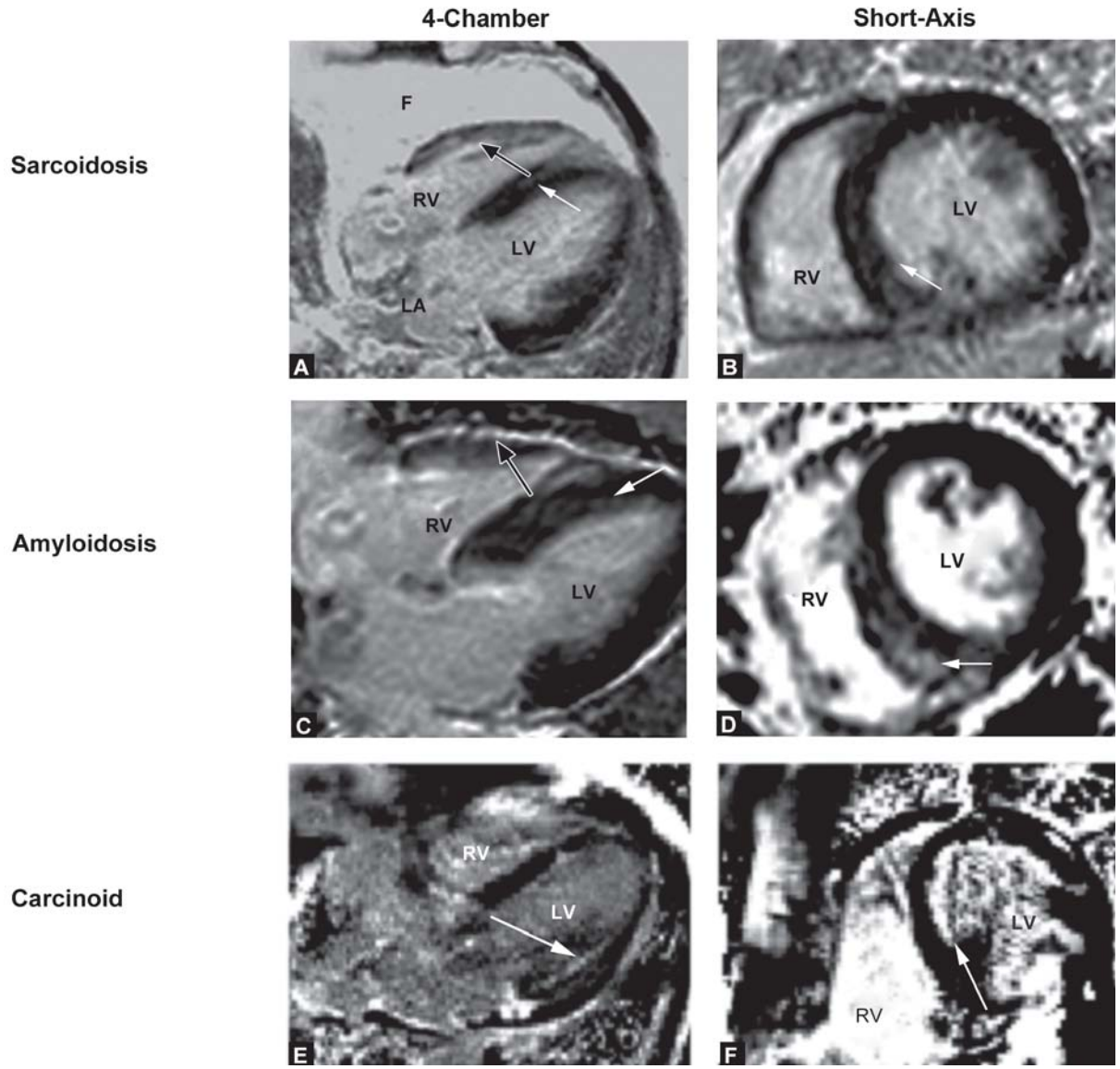
In some cases, e.g. hypereosinophilia, therapeutic decisions are guided by routine clinical assessments and laboratory testing. In other cases, longitudinal CMR studies can help optimize management of chronic conditions responsible for restrictive cardiomyopathy.

Immunosuppressive therapy for sarcoidosis may result in sustained disease quiescence or, in some cases, may convert active granulomatous inflammation to interstitial fibrosis—a process which could hypothetically increase or decrease susceptibility to malignant arrhythmia. For that reason, Mehta et al. have proposed a stepped diagnostic regimen which utilizes CMR to triage patients for invasive electrophysiologic studies.[93] The algorithm demonstrated high predictive power for identifying patients who subsequently received appropriate ICD shocks.

Plasma cell dyscrasias can cause restrictive cardiomyopathy via deposition of immunoglobulin components in myocardium—a form of amyloidosis. Available treatments entail a significant risk of systemic and cardiac toxicity. The CMR can identify the extent of cardiac amyloidosis in such patients, along with critical cardiac function data, which guide therapy. Tissue iron overload is a frequent complication of chronic anemias that require periodic transfusion, and is the most common cause of death in thalassemia major.[94] The CMR is useful for identification of patients at risk of heart failure due to iron overload, and longitudinal CMR studies are useful to determine efficacy of chelation therapy.[95]

VALVULAR HEART DISEASE

Echocardiography, via transthoracic or transesophageal approaches, is most often the procedure of choice for assessment of the morphology of the cardiac valves. The CMR studies usually require compilation of image data over multiple cardiac cycles, in order to achieve sufficient signal-to-noise ratios—a



FIGURES 13A TO F: Restrictive cardiomyopathy. Phase-sensitive inversion recovery images in four-chamber view (left) and short-axis (right) planes 10 minutes after administration of Gd-DTPA. (A and B) sarcoidosis, (C and D) amyloidosis, (E and F) carcinoid tumor. There is late gadolinium enhancement in left ventricular myocardium (white arrows) and in the right ventricular free wall (dark arrow). Abundant epicardial fat (F) is present in the patient with sarcoidosis, a common finding in patients receiving long-term corticosteroid therapy

requirement not ideally suited to visualization of thin structures exhibiting complex motion during the cardiac cycle. "real-time" CMR techniques have been applied, but do not generally offer improved valve visualization compared to best-quality echocardiographic images.

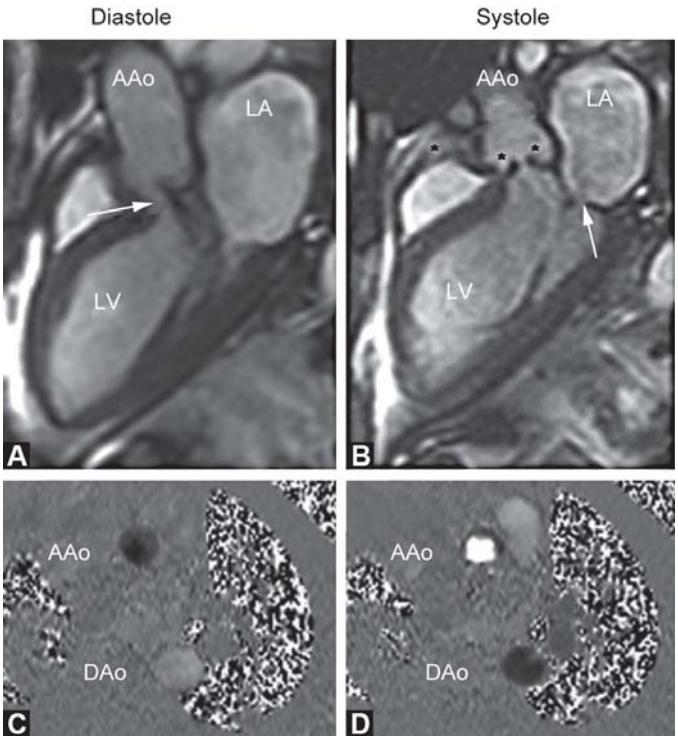
The CMR can be useful for assessment of valve morphology and function when echocardiographic images are suboptimal, but is more often utilized to characterize the impact of valve disease upon cardiac chamber morphology and function. In patients with mitral or aortic regurgitation, left ventricular size and systolic function are key determinants of the timing of valve surgery.[96] In cases where the left ventricle (LV) demonstrates pathological remodeling and/or impaired systolic function, the contribution of valve regurgitation to those processes can be quantitatively ascertained using CMR methods[97] (See below). In cases where there is regurgitation of multiple valves, complementary CMR techniques can be employed to discern the relative contributions of the individual valve lesions.

VALVE STENOSIS

The CMR assessment of valve stenosis is preliminarily approached by visualization of valve leaflet motion during the cardiac cycle, best accomplished using multiple planes. Limitation of leaflet excursion and high velocity blood dephasing, identify a stenotic valve[98] (Figs 14A to D). More advanced methods have been introduced, which utilize velocity encoding in a manner similar to established Doppler echocardiography methods, in order to estimate transvalvular gradients.[99] In general, these CMR methods do not yield greater accuracy for assessment of stenosis severity than Doppler techniques, except in cases where echocardiography is technically suboptimal.

VALVULAR REGURGITATION

Regurgitant flow across a cardiac valve causes turbulent dephasing in "white blood" CMR images, facilitating qualitative or semi-quantitative assessment of the magnitude of back



FIGURES 14A TO D: Complex Valve Disease: (A and B) True-FISP images from a middle-aged man with dyspnea on exertion. In diastole, there is a broad jet of dephased blood crossing the aortic valve (arrow), indicating aortic regurgitation. In systole, thickened aortic valve cusps with restricted excursion are evident (*). There is also a small regurgitant jet across the mitral valve (arrow). (C and D) Velocity encoding, where cephalad flow is depicted in white and caudal flow is depicted in black. Antegrade flow in the ascending aorta (AAo) was 116 ml/cycle, and retrograde AAo flow was 46 ml, yielding a regurgitant fraction of 40%. Confirmation of the hemodynamic significance of aortic regurgitation is supported by observation of faint cephalad (retrograde) flow in the descending aorta (DAo) during diastole. Subsequent comparison of net ventriculographic stroke volumes from the LV (70 ml) and from the RV (63 ml) yielded a mitral regurgitant fraction of 10%

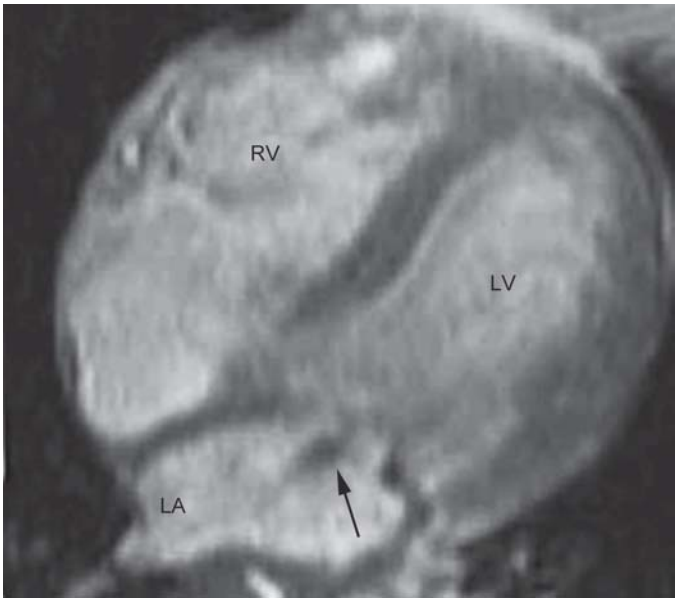
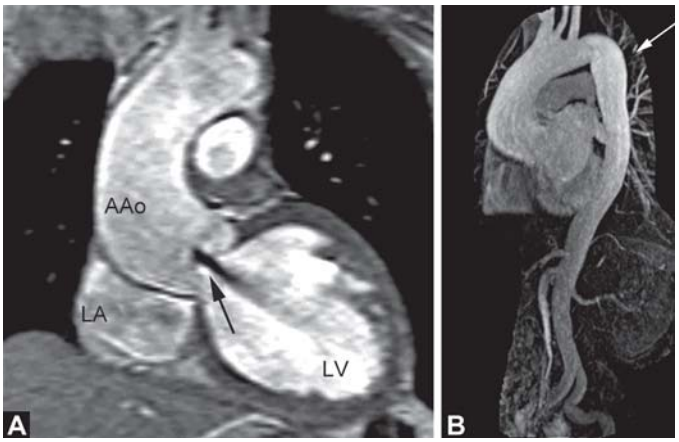


FIGURE 15: Four-chamber cine-FLASH image in mid-systole from a patient with DCM. Dephasing of blood crossing the mitral valve (arrow) indicates mild mitral regurgitation



FIGURES 16A AND B: (A) Coronal oblique true-FISP image during mid-diastole from a patient with ascending aortic (AAo) aneurysm. Dephasing of blood crossing the aortic valve indicates moderate-severe aortic valve regurgitation (black arrow). In this patient with univalvular regurgitation, stroke volume analysis revealed a regurgitant volume of 96 ml, and a regurgitant fraction of 52%. (B) Gadolinium enhanced aortagram, after 3-D rendering, reveals extent of aortic dilation, including the proximal descending thoracic aorta (white arrow) (*Source:* Alan H. Stolpen, MD, PhD, Department of Radiology, University of Iowa Carver College of Medicine)

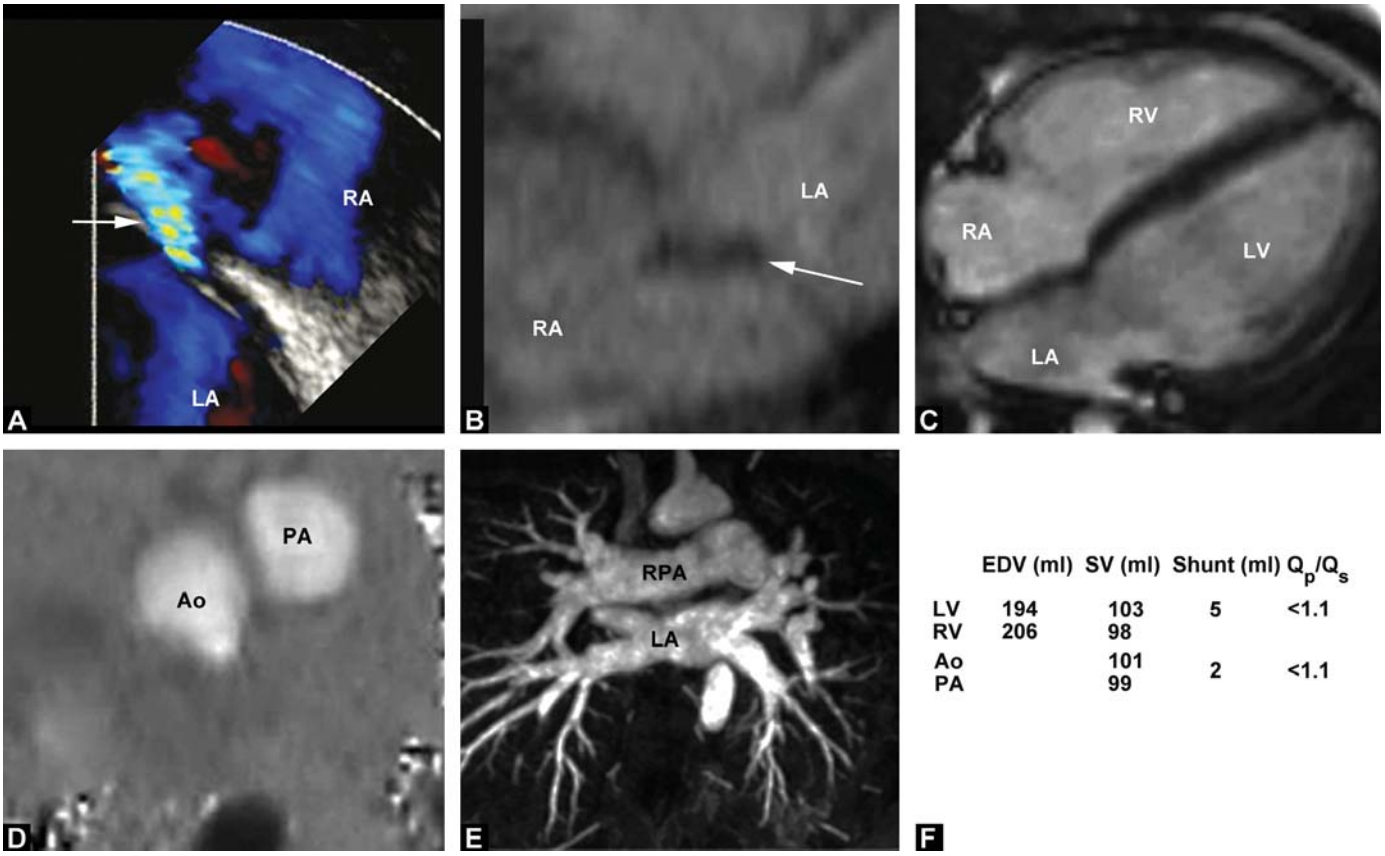
flow[100] (Figs 14 to 16). In cases where clinically significant regurgitation is limited to one valve and no shunts are present, quantitation of regurgitant volume is most readily achieved by comparing left and right ventricular stroke volumes (Figs 16A and B).

Velocity mapping studies in the proximal pulmonary artery and in the aortic root can be used to produce measurements of net forward stroke volume for each ventricle. The findings can be used to corroborate findings in cases of univalvular regurgitation. When multivalvular regurgitation is present, velocity mapping can be used in combination with ventriculographic data to parse regurgitant flow measurements among the individual valves (Figs 14A to D).

Integration of CMR into decision-making paradigms for patients with valvular heart disease depends largely upon local expertise and practice patterns. Consensus about its utility arises when echocardiographic evaluation is technically suboptimal or inconclusive.[101] The CMR can provide clinically useful additions to more conventional assessments in patients with valve disease that is associated with pathology of the aorta (Figs 16A and B). Advocacy of CMR for longitudinal clinical evaluations in patients with valvular heart disease is based on its superior quantitative accuracy, whereas the requirement for CMR in such cases is not yet firmly established.[101]

DISEASES WITH RIGHT VENTRICULAR PREDOMINANCE

Right ventricular morphology and function are often altered in patients with left ventricular disease. In addition, a number of conditions exert preferential effects on the RV, with relative sparing of the LV. The superior quantitative accuracy of CMR characterizations of right ventricular volumes and mass facilitate evaluation with a high degree of confidence. In addition, techniques capable of quantitating through plane blood velocity



FIGURES 17A TO F: Comprehensive evaluation of a young woman with palpitations, in whom echocardiography detected an atrial septal defect (ASD) and possible RV enlargement. (A) Transesophageal echocardiogram demonstrating left-to-right flow across the ASD (arrow). (B) Cine-FLASH four-chamber CMR image with dephasing (black) of ASD flow (arrow). (C) End-diastolic four-chamber true-FISP image showing near-equal sizes of right and left heart chambers, respectively. When normalized for body surface area, all four cardiac chamber volumes are within normal limits. (D) Velocity-encoded images used for calculation of right- and left-heart flows (Q_p and Q_s, respectively). (E) Pulmonary venous angiogram demonstrating normal locations of the ostia of all four pulmonary veins—effectively excluding anomalous venous return. (F) Volumetric flow calculations showing very good agreement between methods, and effectively excluding simple left-to-right intracardiac shunting as an explanation for the patient's symptoms (Abbreviations: RPA: Right pulmonary artery; LA: Left atrium)

(velocity encoding) provide useful information in cases where left and right ventricular stroke volumes are unequal, and where there is significant valvular regurgitation.

INTRACARDIAC SHUNT

In adults with intracardiac shunting of blood, clinical decision-making and prognosis depend critically upon right ventricular morphology and function. Clinical decision-making is also strongly influenced by the magnitude and direction of shunting. The shape of the RV defies simple characterization, which creates difficulty in obtaining quantitative assessments with techniques, such as echocardiography, which acquire images on only a few planes.

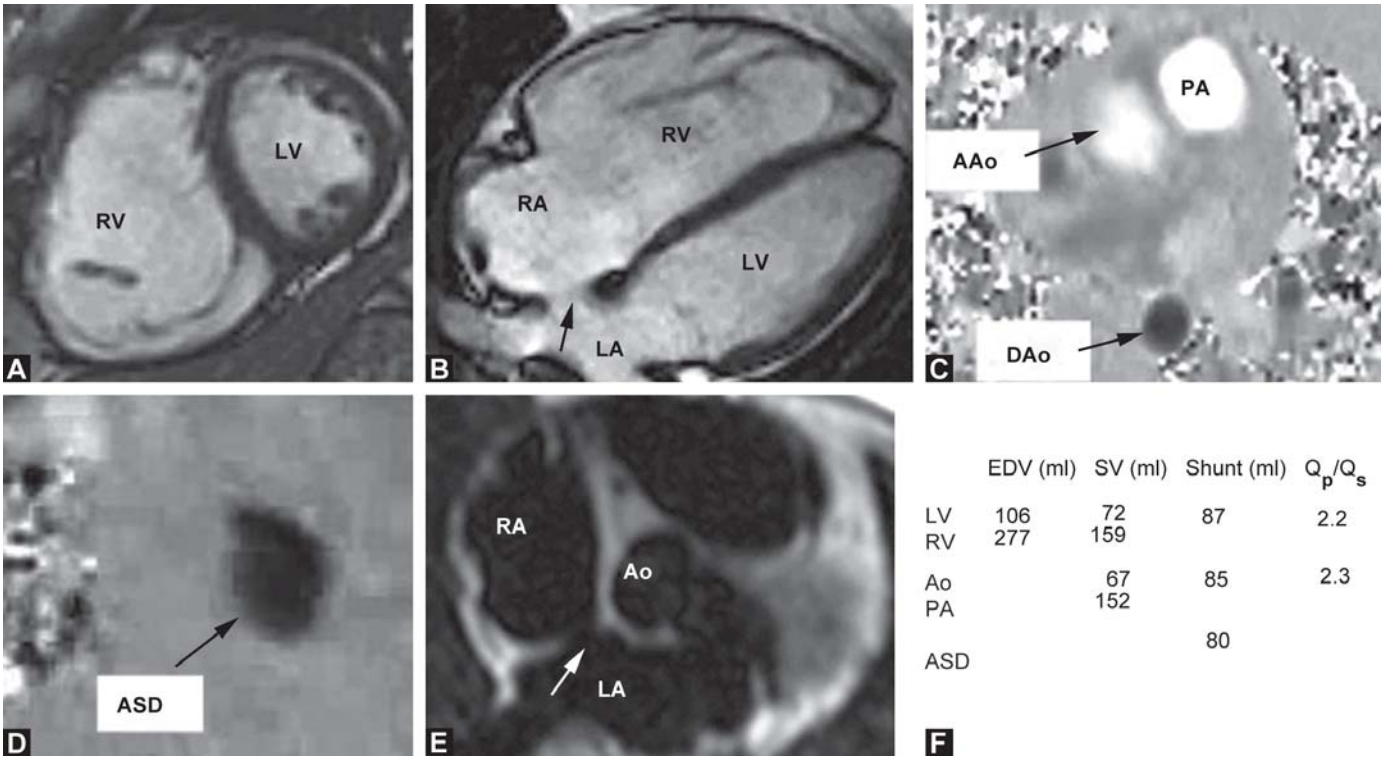
The CMR provides quantitative evaluation of intracardiac shunting utilizing three complementary and corroborative methods: (1) ventriculographic comparison of left and right ventricular stroke volumes, (2) calculation of stroke volumes in the main pulmonary artery and ascending aorta by means of velocity encoding techniques and (3) calculation of volumetric flow in the shunt itself using velocity encoding techniques (Figs 17 and 18).

PULMONARY ARTERY HYPERTENSION

Primary pulmonary hypertension is a progressive disease of resistance arteries in the lungs, in the absence of a systemic disease known to affect pulmonary artery pressure. Secondary pulmonary hypertension can develop as a complication of diverse disease processes—collagen vascular disorders,[102] pulmonary embolism, congenital malformations of the heart or great vessels, cor pulmonale or mass effects.

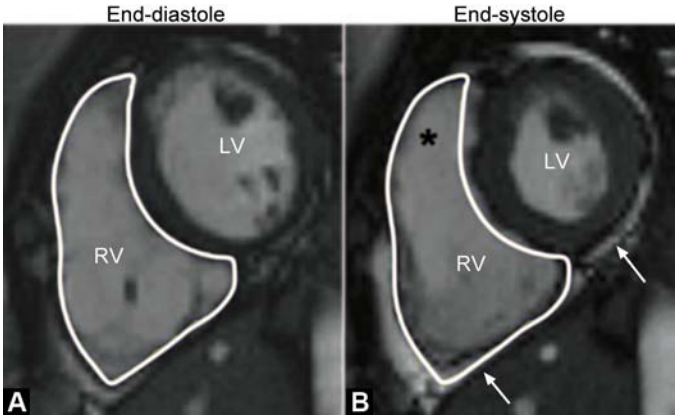
Historically, treatment and prognosis were guided by measurement of pulmonary artery pressure itself; along with determination of cardiac output.[103] Subsequently, echo Doppler methods have replaced the need for repetitive invasive measurement of pulmonary artery systolic pressure. More recently, with the introduction of reliable methods, assessments of right ventricular morphology and systolic function have emerged as critical tools for management.[104,105]

Although advanced 3-D echocardiographic techniques are under development to address this need, CMR methods continue to serve as the reference standard for such methods, and CMR yields superior reproducibility with lower interobserver bias.[106]



	EDV (ml)	SV (ml)	Shunt (ml)	Q_p/Q_s
LV	106	72	87	2.2
RV	277	159		
Ao		67	85	2.3
PA		152		
ASD			80	

FIGURES 18A TO F: Comprehensive CMR studies from a young man with exertional dyspnea. (A) Short-axis end-diastolic true-FISP image showing RV enlargement. (B) Four-chamber end-diastolic true-FISP image showing RV and RA enlargement and an interatrial communication (arrow). (C) Short-axis velocity-encoded image where cephalad flow is depicted in white and caudal flow is depicted in black. (D) Velocity-encoded image of left-to-right flow across the atrial septal defect (ASD, black). (E) Short-axis double inversion-recovery image demonstrating the size and location of the ASD (arrow). (F) Volumetric flow calculations, demonstrating very good agreement between the three methods for shunt quantitation (Abbreviations: RA: Right atrium; LA: Left atrium; AAo: Ascending aorta; PA: Pulmonary artery; DAo: Descending aorta)



FIGURES 19A AND B: Short-axis true-FISP images from a young woman with recurrent syncope due to ventricular tachycardia. The RV end-diastolic silhouette is shown in both end-diastolic and end-systolic frames, in order to accentuate akinesis/dyskinesis in the more anterior region of the RV (*). RVEF = 0.29 and RVEDV index = 120 ml/m^2, fulfilling a major criterion for the diagnosis of arrhythmogenic right ventricular cardiomyopathy.[109] Epicardial fat abuts the myocardium of both ventricles (arrows)—a nonspecific finding not useful in making the diagnosis of ARVC[110]

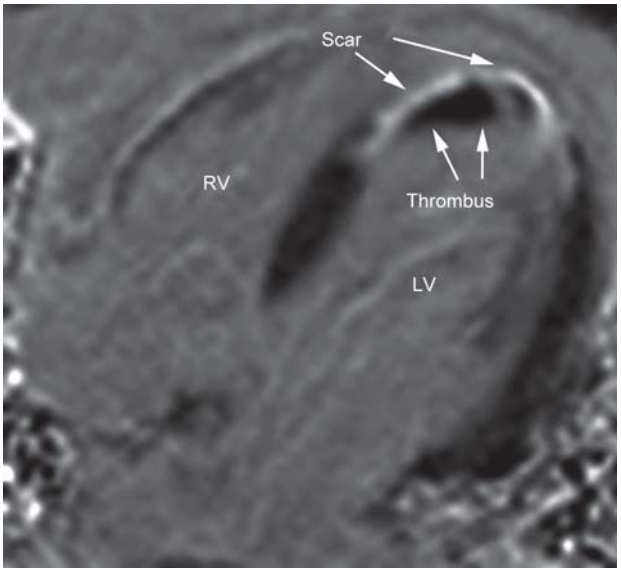
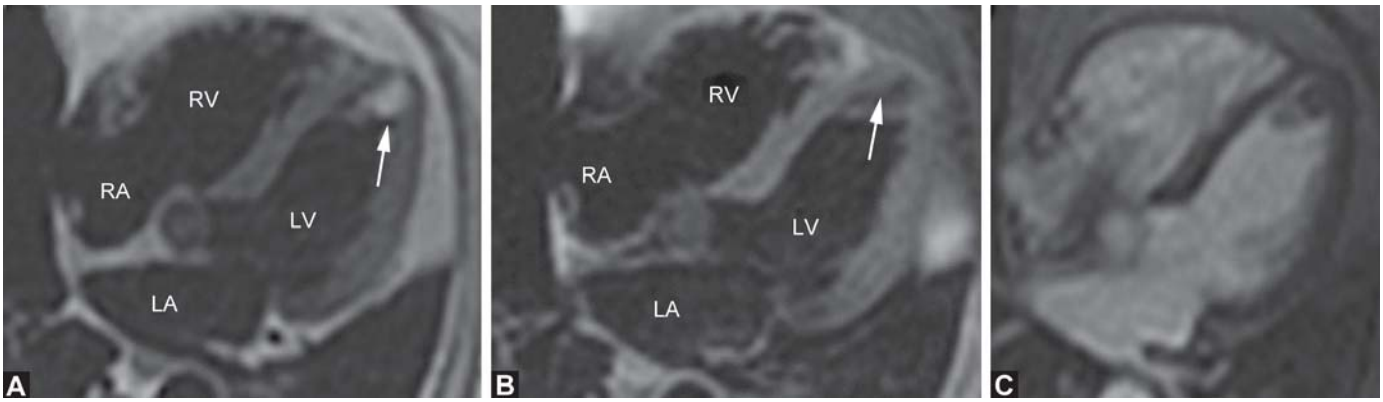


FIGURE 20: Four-chamber phase-sensitive inversion-recovery image acquired 10 minutes after administration of Gd-DTPA. There is a mural thrombus overlying a zone of transmural infarction (scar)

ARRHYTHMOGENIC RIGHT VENTRICULAR CARDIOMYOPATHY

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a genetically determined disorder characterized by myocyte loss and fibrofatty replacement in right ventricular myocardium.[107] Left ventricular involvement ranges from negligible to predominant.[108] The disease is manifest by symptomatic arrhythmias, including SCD, often not preceded by progressive heart failure. The diagnosis, or its exclusion, requires a careful search for characteristic abnormalities of the electrocardiogram



FIGURES 21A TO C: Four-chamber views from a middle-aged woman with an apical mass discovered incidentally by echocardiography. (A) Double inversion (IR) recovery sequence reveals a mass in the LV apex exhibiting high signal intensity (arrow). (B) Double IR with a "fat saturation" pulse completely attenuates the mass signal, indicating a high lipid content. (C) Image acquired during first-pass of Gd-DTPA reveals absence of enhancement of the mass—indicating low vascularity. The findings support a diagnosis of benign lipoma, and the patient was managed conservatively

during sinus rhythm and during episodes of ventricular tachycardia, right ventricular morphology and function and right ventricular histology, along with a definitive family history and/or genetic testing.[109] Unfortunately, absence of any one feature is not sufficient to exclude the disease, nor to support a benign prognosis over the long-term.

The CMR is useful to define the presence or absence of morphologic and functional features of the disease[110] (Figs 19A and B), and can provide a basis for more intensive subsequent investigation. Since arrhythmias can precede overt morphologic changes in ARVC, CMR can be useful for longitudinal studies when the initial evaluation is negative or inconclusive.[111]

MISCELLANEOUS CONDITIONS

CARDIAC THROMBI

The diagnosis of LV mural thrombus is usually based on clinical suspicion and confirmation of characteristic findings on echocardiography; echogenic mass protruding into the LV cavity from a myocardial region after ischemic insult. More recently, CMR has been shown to provide increased diagnostic accuracy in patients at high-risk for mural thrombus and consequent systemic embolization[112] (Fig. 20). The CMR has diagnostic accuracy similar to transesophageal echocardiography for detection of left atrial appendage mural thrombi, and is less invasive.[113]

CARDIAC MASSES

The CMR can be useful to discriminate between solid-tissue cardiac masses and mural thrombi. Information regarding tissue character and vascularity augment decisions about treatment and prognosis (Figs 21A to C).

LEFT VENTRICLE TRABECULATIONS AND NONCOMPACTION

The LVNC is a genetic disorder characterized by failure of coalescence of myocardium during fetal development.[114] Improvements in imaging technology have facilitated its diagnosis, and the morphologic phenotype appears to be far more common than the sum of known genetic abnormalities, raising the question of whether LVNC can be acquired postnatally.[115,116]

In some cases, the echocardiographic diagnosis is unclear, and CMR can provide confirmation or rejection of its presence[117] (Fig. 22).

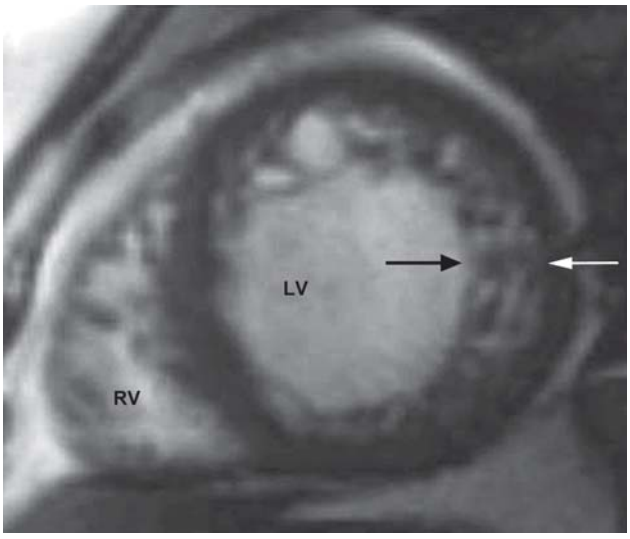
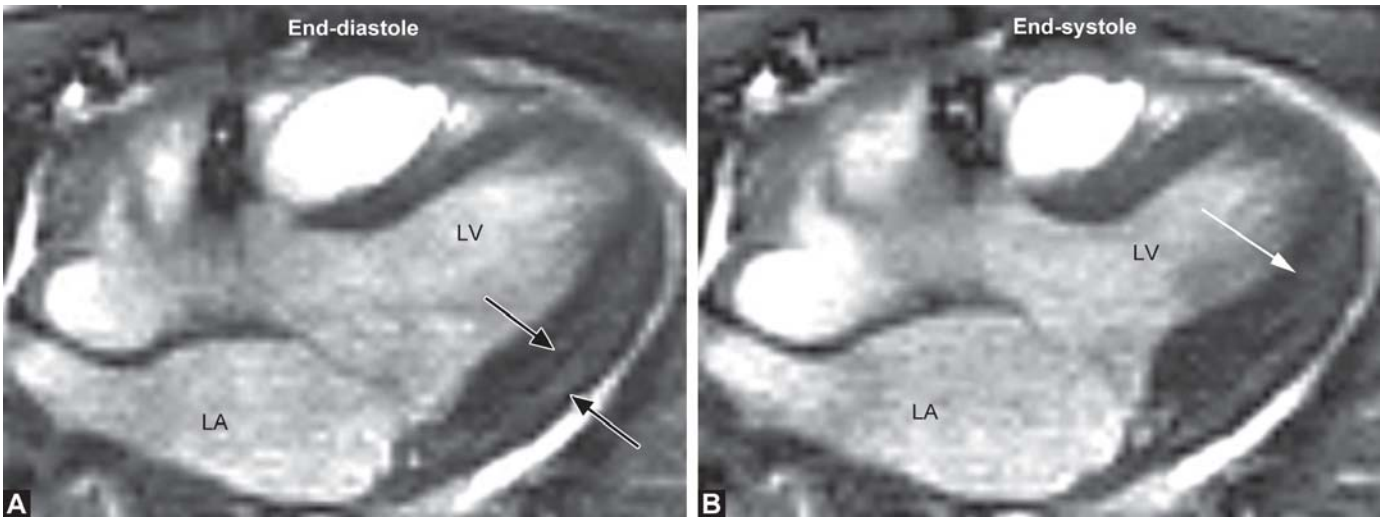


FIGURE 22: End-diastolic short-axis true-FISP image from a 27-year-old man with heart failure. There is abundant trabeculation and thinning of the compacted myocardium, most prominent in the lateral LV wall (arrows)

PERICARDIAL DISEASE

The CMR is a useful adjunct for assessment of pericardial disease and its functional consequences[118] (Figs 23A and B). The CMR can estimate pericardial effusion. However echocardiography is the imaging technique of choice and clinical application of CMR for the diagnosis and management of pericardial effusion is limited. However, CMR can be used to assess pericardial thickness in patients with suspected constrictive pericarditis.



FIGURES 23A AND B: Axial true-FISP images from a patient with lower extremity edema and ascites. Visceral and parietal pericardial layers are thickened (maximum = 8 mm; black arrows), and are fused along the apical lateral wall (white arrow)

ABBREVIATIONS

ARVC: Arrhythmogenic right ventricular cardiomyopathy
CAS: Coronary artery stenosis
CMR: Cardiovascular magnetic resonance
DCM: Dilated cardiomyopathy
HCM: Hypertrophic cardiomyopathy
LGE: Late gadolinium enhancement
LV: Left ventricle
PSIR: Phase-sensitive inversion-recovery
RCM: Restrictive cardiomyopathy
RV: Right ventricle
SCD: Sudden cardiac death
SSFP: Steady-state free precession
True-FISP: True fast imaging with steady-state precession.

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Chapter 24

Molecular Imaging of Vascular Disease

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Chapter Outline

- Molecular Imaging Fundamentals
- Molecular Imaging Modalities
- Molecular Imaging of Vascular Disease Processes
  - Atherosclerosis
  - Thrombosis
  - Aneurysm
  - Vascular Injury
  - Outlook

INTRODUCTION

With the discovery of new molecular targets and pathways that both expand our knowledge base and refine classical teachings, there is an ongoing role for technological advances to illuminate these areas by offering improved diagnostic and therapeutic clinical tools. Molecular imaging aims to capitalize on these advances by employing small molecules and nanoparticles, which are coupled with imaging agents to visualize cellular and molecular events in living subjects, complementing clinical, anatomical and physiological imaging modalities. Clinical applications of molecular imaging in cardiovascular disease can provide novel insight into disease mechanisms, risk stratification, prognosis and the in vivo efficacy of biotherapeutics. In addition, molecular imaging is poised to alter the landscape of cardiovascular disease by offering targeted, personalized therapy and facilitating small scale clinical trials that can readily feedback important biological parameters that mark treatment response or disease progression. In this chapter, we focus on promising translational and clinical advances in molecular imaging of vascular disease.

MOLECULAR IMAGING FUNDAMENTALS

The specific detection and reporting of in vivo biological targets is the underlying goal of all molecular imaging strategies.[1,2] In order to achieve this goal, certain fundamental issues require attention by the investigator. First, an appropriate cellular or molecular target must be identified that can delineate the desired process and be targeted with a specific high-affinity ligand. Second, an imaging agent with advantageous biopharmacokinetic properties must be chosen that can be linked to and report on the target. Finally, an imaging system with appropriate resolution and sensitivity to detect the imaging target is needed.

As the range of potential cellular and molecular targets available for detection is vast, appropriate determination of the desired target is of critical importance. Ideal targets are those that reported on important biological processes and possess a unique biological signature that can be exploited, and abundant enough to enable in vivo detection. In certain cases, amplification schemes can be employed to boost a low-level signal, such as with internalizing receptors, enzymes or reporter gene approaches; however, other less easily accessed targets on DNA, RNA or proteins, expressed at low concentrations, can be more challenging. While both intracellular and extracellular targets are possible to sense, extracellular targets are generally more accessible as they avoid charge, size and solubility issues that limit intracellular targeting agents traversing the plasma membrane. Examples of cellular targets successfully identified in vascular disease include macrophages, lymphocytes and stem cells in atherosclerosis. Molecular targets are predominantly investigated and include cell surface receptors, neovessel epitopes and tissue enzymatic processes. Table 1 provides a list of explored molecular and cellular targets in vascular diseases that are either currently FDA-approved for clinical use or hold significant promise for clinical translation in the coming years.

Just as the numbers of potential cellular and molecular targets are large, there are even greater numbers of smaller molecules that can be employed in molecular imaging strategies as high-affinity ligands to detect the desired target. As with a lock and key, these small molecules should bind specifically to the cell or molecule of interest, in most cases, without disrupting its function, although there are certain instances where alteration or frank disruption of function may be an advantageous property. They must interact in such a fashion as to specifically identify the biological process in question and minimize nonspecific binding that reduces the signal-to-noise ratio (SNR). The most well-known example of binding partners are antibody-antigen combinations; however, antibodies have several suboptimal properties that make their use in molecular imaging strategies less desirable, such as relatively large size leading to steric hindrance and poor conjugation density when coupled to the imaging agent.

TABLE 1

Promising molecular imaging agents in vascular disease

Application	*Agent*	*Modality**	*Multi-channel*	*Primary target*	*Primary use*	*Clinical*
Atherosclerosis	^{18}FDG (18-fluoro-deoxygulcose)	PET	No	Glucose transporter-1, hexokinase	Metabolism	Yes
	^{111}In-oxine (indium-111-oxyquinolone)	SPECT	No	Monocytes/macrophages	Inflammation	Yes
	USPIOs (Ferumoxtran)	MRI	No	Monocytes/macrophages	Inflammation	Yes
	^{99m}Tc-annexin A5	SPECT	No	Annexin-A5/macrophages	Apoptosis	Yes
	^{18}F-Galakto-RGD	PET	No	Integrins/endothelial cells	Neovascularization	Yes
	$\alpha_v\beta_3$ magnetic nanoparticles	MRI	No	$\alpha_v\beta_3$ integrins/ endothelial cells	Neovascularization	Promising
	^{99m}Tc-interleukin-2	SPECT	No	Interleukin-2/lymphocytes	Inflammation	Yes
	ProSense	NIRF, IVM	Yes	Cysteine protease activity	Inflammation	Promising
	MMPsense	NIRF, IVM	Yes	Matrix metallo-proteinase activity	Inflammation	Promising
	OsteoSense	NIRF	Yes	Hydroxyapatite	Calcification	Promising
	N1177	CT	No	Monocytes/macrophages	Inflammation	Promising
	Gadofluorine-M	MRI	No	Monocytes/macrophages	Inflammation	Promising
	P947	MRI	No	Matrix metalloproteinase activity	Inflammation	Promising
	VCAM-1 microbubbles	CEU	No	VCAM-1	Inflammation	Promising
	Tri-modality nanoparticle	MRI, PET, NIRF	Yes	Monocytes/macrophages	Inflammation	Promising
	Bis-5HT-DTPA (Gd)	MRI	No	Myeloperoxidase activity	Inflammation	Promising
	^{99m}Tc-RP805	SPECT	No	Matrix metalloproteinase activity	Inflammation	Promising
Thrombosis	^{99m}Tc-apcitide (AcuTect)	SPECT	No	GPIIb/IIIa receptor	Platelet activity	Yes
	EP-2104R	MRI	No	Fibrin	Coagulation factors	Yes
	Activated factor XIII (FXIIIa)	MRI, SPECT, NIRF	Yes	FXIIIa activity	Coagulation factors	Promising
Aneurysm	^{18}FDG (18-fluoro-deoxygulcose)	PET	No	Glucose transporter-1, hexokinase	Metabolism	Yes
	di-5-hydroxytryp-tamide of gado-pentetate dimeglumine	MRI	No	Myeloperoxidase activity	Inflammation	Promising
Vascular Injury	^{111}In-RP782	SPECT	No	Matrix metalloproteinase activity	Inflammation	Promising
Myocardial infarction	^{99m}Tc-NC100692	SPECT	No	$\alpha_v\beta_3$ integrins/ endothelial cells	Angiogenesis	Yes
	^{18}F-Galakto-RGD	PET	No	Integrins/endothelial cells	Angiogenesis	Yes
	^{99m}Tc-CRIP	SPECT	No	Collagen	Fibrosis	Promising
	^{99m}Tc-collagelin	SPECT	No	Collagen (type I and III)	Fibrosis	Promising
	EP-3533	MRI	No	Collagen (type I)	Fibrosis	Promising
	AnxCLIO-Cy5.5	MRI, fluorescence	No	Annexin/myocardial cells	Apoptosis	Promising
	^{19}F perfluorocarbons	MRI	No	Monocytes/macrophages	Inflammation	Promising
Cardiomyopathy	AnxCLIO-Cy5.5	MRI, fluorescence	No	Annexin/myocardial cells	Apoptosis	Promising
Transplant rejection	USPIOs (Ferumoxtran)	MRI	No	Monocytes/macrophages	Inflammation	Yes
Cardiac regeneration	Firefly luciferase Sodium-iodide symporter (NIS)	BLI PET	Yes No	Luciferin gene expression NIS gene expression	Reporter gene construct Reporter gene construct	Promising Promising
	Herpes simplex virus thymidine kinase (HSV-tk)	SPECT	No	HSV-tk gene expression	Reporter gene construct	Promising
	USPIOs (Ferumoxtran)	MRI	No	Monocytes/macrophages	Inflammation	Yes
	^{18}FDG (18-fluoro-deoxygulcose)	PET	No	Glucose transporter-1, hexokinase	Metabolism	Yes
	Gadofluorine-M-Cy3	MRI, fluorescence	No	Monocytes/macrophages	Inflammation	Promising

(* for modality abbreviations, see Table 2)

TABLE 2

Comparison of small animal molecular imaging modalities

Technique	*Resolution*	*Depth*	*Sensitivity*	*Scan time*	*Multi-channel*	*Agents*	*Clinical*
Computed tomography (CT)	50 μm	Unlimited	+	Seconds to minutes	Yes	Iodine moieties	Yes
Magnetic resonance imaging (MRI)	10–100 μm	Unlimited	++	Minutes to hours	Yes	Paramagnetic and magnetic particles	Yes
Contrast-enhanced ultrasound (CEU)	50 μm	Centimeters	++	Seconds to minutes	No	Microbubbles	Yes
Single photon emission computed tomography (SPECT)	0.3–1 mm	Unlimited	+++	Minutes	Dual	Radiolabeled compounds (^{99m}Tc, ^{111}In, ^{131}I, ^{67}Ga, ^{201}Tl)	Yes
Positron emission tomography (PET)	1–2 mm	Unlimited	+++	Seconds to minutes	No	Radiolabeled compounds (^{18}F, ^{64}Cu, ^{11}C, ^{68}Ga)	Yes
Bioluminescence imaging (BLI)	3–5 mm	Millimeters	+++	Seconds to minutes	Multiple	Luciferase, luminol	Potential
Fluorescence reflectance imaging (FRI)	1 mm	Millimeters	+++	Seconds to minutes	Multiple	Fluorophores, photoproteins	Yes
Fluorescence mediated tomography (FMT)	1 mm	Centimeters	++	Minutes	Multiple	Near-infrared fluorophores	Developing
Intravital microscopy	1 μm	Micrometers	++	Seconds to hours	Multiple	Fluorophores, photoproteins	Developing

+ millimolar or less; ++ micromolar; +++ nanomolar or greater

More often, bioengineered nanoparticles or oligopeptides with superior pharmacokinetics are utilized that deliver specific target identification and allow higher probe-coating densities due to their smaller physical size.

Once a molecular or cellular target has been identified, a corresponding imaging agent must be selected. The choice of imaging agent must consider the various advantages and disadvantages of each imaging detection modality, as well as the characteristics of the imaging platform that will be used for detection (Table 2). Tradeoffs between spatial resolution, sensitivity and tissue penetration among other factors must be considered carefully for each biological application. Signal amplification strategies to boost the detection capability of certain probes are also possible, such as sequestration/cellular trapping and "activatable" probes that report on biologically functional enzymes.[3] Ever more frequently, investigators are creating flexible chemical backbones that can incorporate two or even three different imaging agents on a single molecular probe for multimodality imaging.[4] These multimodality agents thus harness the strengths of the complementary imaging technologies in a single probe and also offer the attractive possibility of multifunction "theranostic" probes that can deliver a therapeutic drug or other payload in concert with diagnostic imaging, all packaged in a single injectable agent.[5]

MOLECULAR IMAGING MODALITIES

A wealth of different imaging modalities have been utilized for cardiovascular molecular imaging, each of which offers certain advantages and limitations as outlined in (Table 2). Factors of importance include sensitivity, spatial and temporal resolution, depth penetration, scan time, radiation exposure and cost among others. Compared to other applications, such as cancer detection, cardiovascular molecular imaging also poses significant additional difficulties due to cardiac and respiratory motion artifacts for myocardial imaging, small vessel size for coronary plaque detection and competing signals from adjacent blood flow. Nevertheless, through improvements in newer generation imaging systems including faster scan times and gating of cardiac and respiratory motion, as well as enhancements of software packages and motion detection or correction strategies, these barriers continue to be overcome.

Of the imaging strategies in current clinical practice, superparamagnetic nanoparticles for magnetic resonance imaging (MRI) and ^{18}F-fluorodeoxyglucose (FDG) for positron emission tomography (PET) provide illustrative examples of the technical tradeoffs inherent to all of the different modalities. Imaging strategies, such as ^{18}FDG-PET, offer high sensitivity of detection but relatively poor spatial resolution, whereas MRI provides high spatial resolution and soft tissue contrast but relatively poor sensitivity of probe detection.

Combinatory use of multiple imaging modalities into hybrid imaging strategies is frequently utilized to overcome the limitations of a single imaging platform, such as with the commonly used hybrid SPECT-CT sequence or more recently with the advent of simultaneous PET-MRI following the development of solid-state photodetectors that are not affected by magnetic field variations.[6] Other molecular imaging modalities include contrast-enhanced ultrasound imaging with ligand-coated microbubbles and optical imaging strategies that utilize fluorescence (intravital microscopy, fluorescence molecular tomography, intravascular catheter-based imaging) and bioluminescence reporter gene imaging.

MOLECULAR IMAGING OF VASCULAR DISEASE PROCESSES

With an ever growing armamentarium of molecular imaging probes available for use and in development, there has been extensive growth of molecular imaging applications in vascular disease. High-priority areas include atherosclerosis, thrombosis, aneurysmal disease and vascular injury. While most molecular imaging probes are in preclinical testing and development phases, and only a few agents that are FDA approved are present, this balance is likely to shift significantly in the coming years with the translation of these new emerging agents into the clinical arena.

ATHEROSCLEROSIS

Atherosclerotic vascular disease, fueled by lipid deposition, endovascular inflammation and leukocytic infiltration of the vessel wall, is an important and well-studied focus of molecular imaging studies. Histopathologically, atherosclerosis represents the end result of a potent combination of lipid, chronic inflammation, cellular proliferation, apoptosis and necrosis, leading to progressive plaque expansion within the vessel wall that may encroach on the vessel lumen, obstructing blood flow or acutely rupturing and exposing thrombogenic elements that cause abrupt vessel occlusion. Atherosclerosis is a top priority within molecular imaging, with the goal of early detection and preventative treatment of lipid-rich "vulnerable" plaques that have the highest likelihood to rupture, resulting in an acute coronary syndrome, peripheral arterial occlusion or cerebrovascular accident. High-risk features of vulnerable atheroma include necrotic lipid cores, neovascularization, apoptosis and inflammation, and each of these components has been successfully targeted by molecular imaging strategies. Molecular imaging of atherosclerosis thus has the potential to offer high-yield complementary clinical information to that of current anatomic and physiologic imaging methods such as coronary angiography and exercise stress testing. Following detection, serial noninvasive molecular imaging has the potential to directly monitor atherosclerotic plaque evolution over time in an individual patient during pharmaceutical therapy.

From a clinical perspective, there are presently two major platforms for atherosclerosis detection, ^{18}FDG-PET imaging and ultrasmall superparamagnetic iron oxide (USPIO) nanoparticle-enhanced MRI, both of which can identify inflammatory foci in larger caliber arteries such as the carotid, aorta and femoral beds. Coronary artery atheroma, however, are less easily imaged due to their small size but emerging technologies that also detect inflammation such as an intravascular catheter for near-infrared fluorochrome detection[3] and new ^{18}FDG-PET protocols to suppress obscuring background myocardial tissue uptake,[7] hold promise. Finally, there exist multiple new emerging atherosclerosis molecular imaging agents (Table 1) that with further testing hold significant potential for translation to clinical practice.

Inflammation

Large arteries (e.g. carotid, aorta and iliofemoral): Infiltration of the vessel wall with leukocytes in atherosclerosis predominantly composed of the key effector cells monocytes and macrophages, represent tissue sites of active inflammation and vessel remodeling.[8] In patients experiencing sudden cardiac death, the culprit ruptured plaque often contains an abundant monocyte/macrophage burden,[9] thus making these sites excellent targets for clinical imaging agents of vulnerable plaques.

Ultrasmall superparamagnetic iron oxide: Clinical ultrasmall superparamagnetic iron oxide (USPIO) are magnetic nanoparticles composed of a 3 nm superparamagnetic iron oxide core that induce MRI tissue contrast by strongly influencing local signals in T2- and T2*-weighted images. An external dextran-coating over the iron oxide core promotes phagocytosis of the agent, primarily by mononuclear cells, (monocytes and macrophages) allowing USPIO to hone to sites where these cells accumulate such as atherosclerotic plaques.[10-14] To allow sufficient tissue accumulation and blood pool washout of nonspecific circulating signal, MRI is performed 24–36 hours following USPIO injection and the images are collected over 1–2 hours. Due to its T2 relaxation effects, USPIO are detected as dark "negative" reductions in MRI signal. While a negative-contrast agent can be more challenging in low SNR environments such as in vessel wall MRI, in many cases, the dark lumen and brighter soft tissue components in the vessel wall offer sufficient contrast density differences to facilitate adequate detection. However, while USPIO-based MRI has advantages in spatial resolution, it has relatively lower sensitivity, limiting its ability to detect smaller inflammatory foci in the carotid arteries or aorta. This limitation is particularly problematic in the much smaller coronary arteries, but may be addressable with intravascular MRI catheters.[15]

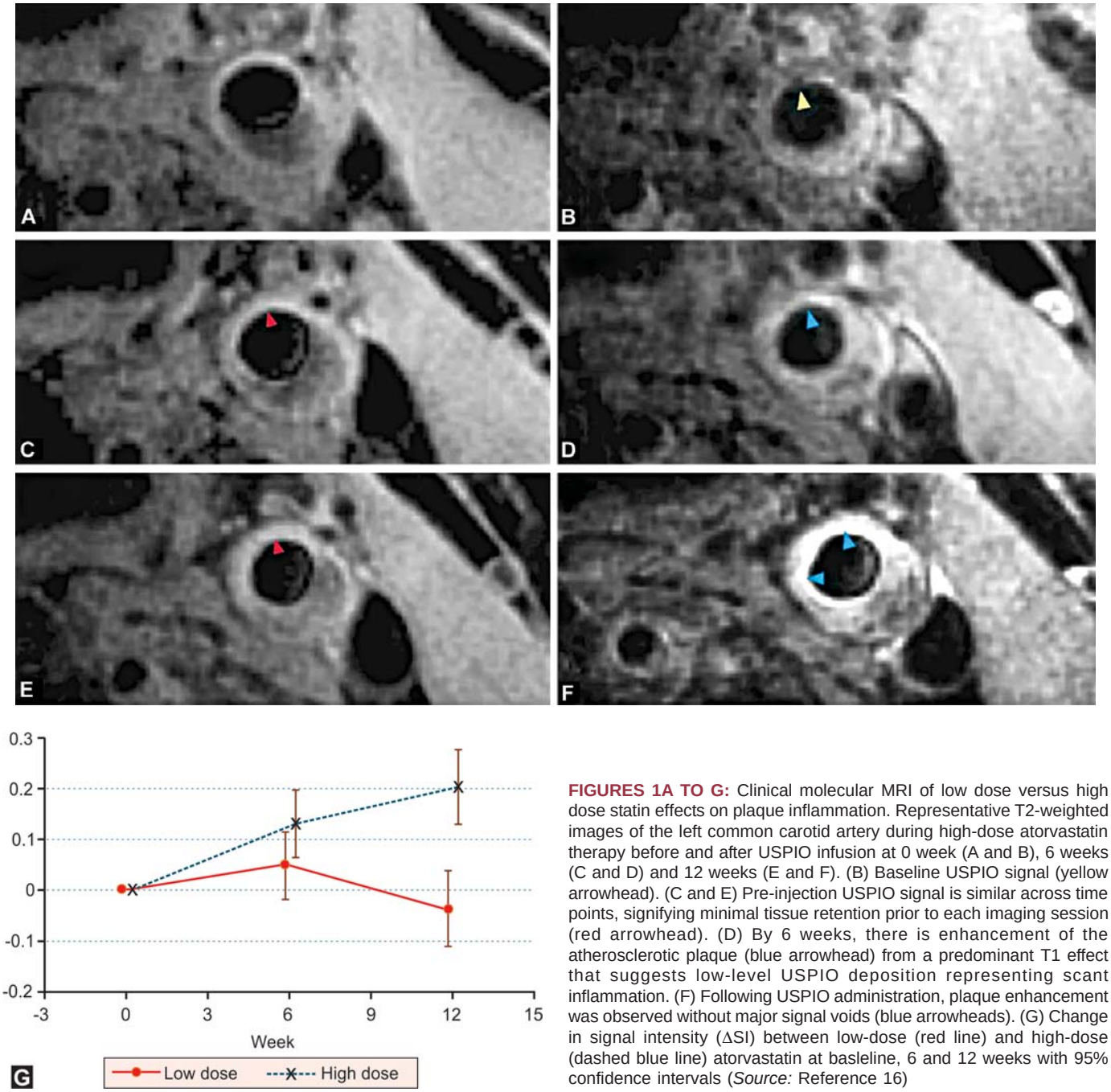
Effects of pharmacotherapy: Several noninvasive molecular imaging studies have demonstrated changes in plaque biology in response to pharmacotherapy treatment and, in particular, statins. Statin treatment promotes atherosclerotic plaque stabilization via lipid depleting and anti-inflammatory effects, and has the potential to halt or perhaps even cause regression of atheroma burden. Molecular imaging approaches can identify inflammatory components that define high-risk plaques. Although plaque inflammation represents a surrogate clinical marker, changes in inflammation may guide future outcome studies and provide valuable in vivo insights into the mechanisms of action of putative anti-inflammatory agents.

Of note, the utility of clinical USPIOs to evaluate carotid plaque inflammation following dose-modulated stain therapy was examined in the "atorvastatin therapy: effects on reduction

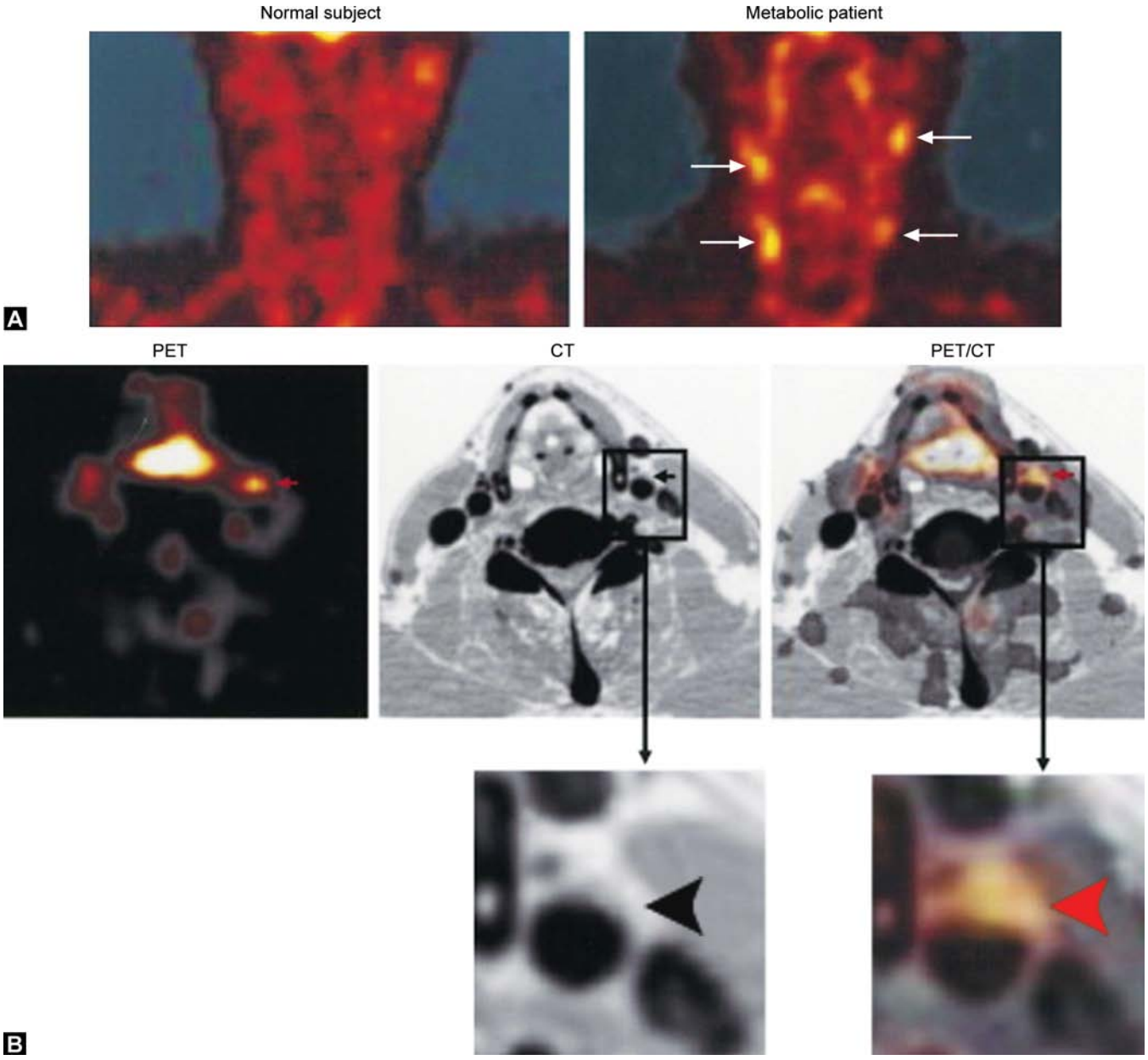
of macrophage activity" (ATHEROMA) trial.[16] In this study, 47 patients were randomized to 80 mg (high-dose) or 10 mg (low-dose) atorvastatin. Treatment with high-dose atorvastatin decreased USPIO-MRI detectable carotid plaque inflammation after only 12 weeks of statin pharmacotherapy (Figs 1A to G). Importantly, decreased inflammation correlated with fewer carotid emboli measured by transcutaneous Doppler.

^{18}F-Fluorodeoxyglucose: The other major clinical atherosclerosis molecular imaging platform features ^{18}FDG-PET. ^{18}FDG is a glucose analog that becomes concentrated within metabolically active cells where it emits positrons (110 minute half life) for detection by clinical PET scanners. Intracellular concentration of ^{18}FDG occurs following active transport of the agent into the cytosol through normal glucose transport pathways where it becomes trapped upon phosphorylation by the enzyme hexokinase. Studies with ^{18}FDG have particularly become more prominent in recent years with the widespread availability of clinical ^{18}FDG-PET systems spurred by the growth of cancer imaging studies and the development of a broad radiopharmaceutical delivery network. Compared to USPIO-enhanced MRI, ^{18}FDG-PET is significantly more sensitive but must be coupled with coregistered CT (or other anatomical modality) to provide the high degree of spatial resolution required to enable precise tissue localization, which exposes the patient to additional ionizing radiation.

^{18}FDG has been shown to be upregulated at inflammatory foci in the carotid and other larger arterial beds and correlates with monocyte/macrophage plaque content on histopathology.[17-21] Patients with the metabolic syndrome also



FIGURES 1A TO G: Clinical molecular MRI of low dose versus high dose statin effects on plaque inflammation. Representative T2-weighted images of the left common carotid artery during high-dose atorvastatin therapy before and after USPIO infusion at 0 week (A and B), 6 weeks (C and D) and 12 weeks (E and F). (B) Baseline USPIO signal (yellow arrowhead). (C and E) Pre-injection USPIO signal is similar across time points, signifying minimal tissue retention prior to each imaging session (red arrowhead). (D) By 6 weeks, there is enhancement of the atherosclerotic plaque (blue arrowhead) from a predominant T1 effect that suggests low-level USPIO deposition representing scant inflammation. (F) Following USPIO administration, plaque enhancement was observed without major signal voids (blue arrowheads). (G) Change in signal intensity (ΔSI) between low-dose (red line) and high-dose (dashed blue line) atorvastatin at basleline, 6 and 12 weeks with 95% confidence intervals (*Source:* Reference 16)



FIGURES 2A AND B: Augmented ^{18}FDG-PET-based plaque inflammation in patients with the metabolic syndrome. Representative coronal carotid artery ^{18}FDG-PET images from a patient with the metabolic syndrome and a control subject: (A) Red arrows identify areas of focal ^{18}FDG uptake; (B) Transaxial PET, contrast-enhanced CT and co-registered PET/CT images show ^{18}FDG signal (red arrowhead) in the carotid artery vessel wall (black arrowhead) of the metabolic syndrome patient. (*Source:* Reference 22)

demonstrate elevated ^{18}FDG signals in carotid atheroma (Figs 2A and B).[22] The prevalence of ^{18}FDG-identified carotid inflammation was further assessed in a series of 100 consecutive asymptomatic patients undergoing screening carotid ultrasonography. In patients with evidence of atherosclerosis (41%), approximately one-third had elevated ^{18}FDG uptake on PET/CT imaging, possibly identifying patients with inflamed plaques at a higher risk of future events.[23] Importantly for future application to clinical practice and trials, ^{18}FDG-PET/CT has demonstrated excellent reproducibility at least over the short term in a small series of high-risk patients.[24]

Pathophysiologically, human ^{18}FDG-PET imaging studies demonstrate greater uptake in patients with known vascular disease and primarily colocalize with non calcified, inflammatory loci.[25] Furthermore, not only upregulated expression of proinflammatory mRNA, particularly CD68, but also cathepsin K, matrix metalloproteinase (MMP-9) and interleukin (IL-18) are correlated with ^{18}FDG plaque uptake in ten carotid endarterectomy patients.[26] In multimodal carotid plaque studies, a report with ^{18}FDG-PET/MRI revealed that lipid-containing atheroma had greater ^{18}FDG uptake than collagen-rich fibromuscular or calcified plaques; [27] however, a separate investigation had only provided weak correlation between ^{18}FDG-PET signal and CT or MRI-guided plaque tissue composition.[28]

Recent clinical data has correlated ^{18}FDG plaque signals and future vascular events. In a retrospective 200 patient trial, the ^{18}FDG positive plaque number was correlated with the

number of cardiovascular risk factors, and was found to be inversely related to statin pharmacotherapy.[29] An observational ^{18}FDG-PET/CT trial in 932 asymptomatic cancer patients demonstrated that averaged ^{18}FDG signal uptake from the aorta, iliac and carotid arteries was the strongest indicator of a future vascular event over 29 months, notably being fourfold more predictive than atherosclerotic plaque calcification on co-registered CT images.[30] In a pharmacotherapeutic study, ^{18}FDG signal in human carotid plaques lessened over time with moderate dose simvastatin therapy, compared to dietary changes alone (Figs 3A to C).[31] Similar to the ATHEROMA study utilizing USPIOs, this study demonstrates the potential to assess reductions in carotid plaque inflammation using noninvasive molecular imaging.

Coronary arteries: Coronary atherosclerotic plaque imaging is highly challenging due to the small size of the vessels, the motion of surrounding myocardium during systole and diastole, as well as respirophasic variations. To overcome these challenges, imaging modalities must have both high spatial and temporal resolution, as well as high sensitivity, a combination not easily found in a single entity. However, several emerging technologies, including ^{18}FDG-PET/CT with myocardial suppression, macrophage-targeted molecular CT imaging and intravascular near infrared fluorescence (NIRF) imaging show promise for clinical investigation.

^{18}FDG: While ^{18}FDG targeted imaging of coronary arterial plaques is limited by high background signal from the adjacent highly metabolically active myocardium, there is recent evidence that noninvasive coronary molecular imaging may be possible with ^{18}FDG-PET/CT utilizing a specialized myocardial suppression protocol.[7,32] To suppress the myocardial ^{18}FDG signal, patients consumed a high fat and low carbohydrate meal, the night before the study, and then drank a vegetable oil formulation on the morning of the study. While not all subjects obtained optimal myocardial suppression; however, in those with a good response, ^{18}FDG uptake was successfully observed in coronary artery segments. Patients with angiographically confirmed coronary artery disease tended to have more positive ^{18}FDG segments. Given the limitations of cardiac motion and lower resolution, it is envisioned that ^{18}FDG-PET imaging will assess the left main coronary artery and possibly the very proximal coronary arterial beds.

Molecular CT imaging: Macrophages can be targeted with N1177, an iodinated nanoparticle CT contrast agent dispersed with surfactant.[33,34] Atherosclerotic-prone rabbits subjected to aortic balloon-mediated injury demonstrated N1177 contrast enhancement within the injured aortic wall 2 hours after intravenous injection (Figs 4A to G). Comparison of N1177 signal with both ^{18}FDG-PET uptake in the same animals imaged one week later and histopathologic macrophage density showed general quantitative agreement. Given the excellent spatio-temporal resolution of modern multidetector CT imaging systems, already in clinical use for coronary artery imaging and the potential to discriminate atherosclerotic plaque constituents such as calcium versus fibrous tissue or lipid,[35,36] the addition of molecular targeted imaging agents, such as N1177 to coronary CT assessment, offers heightened ability to identify high-risk macrophage-laden coronary atherosclerotic plaques that may prove future use in preventing ischemic events.

NIRF imaging: Intravascular molecular imaging technologies are also being advanced, exemplified by the development of a prototype intravascular catheter that allows real time, high resolution in vivo NIRF sensing of atherosclerotic plaque through flowing blood (Figs 5A to G).[3] Evaluation in atherosclerosis-laden rabbit iliac arteries, of similar size to human coronary vessels, was performed after intravenous administration of a cysteine protease-activatable NIRF imaging agent (ProSense750) that can detect vascular inflammation. Real time pullbacks of the NIRF catheter revealed multifold increases in protease activity in atheroma as compared to control atherosclerotic animals injected with saline. In vivo NIRF results correlated with histopathological macrophage infiltration and the cysteine protease cathepsin B. New detection and imaging processing algorithms[37], as well as the advent of novel 2D NIRF rotational imaging catheters[38] are likely to continue to improve the yield of this technique.

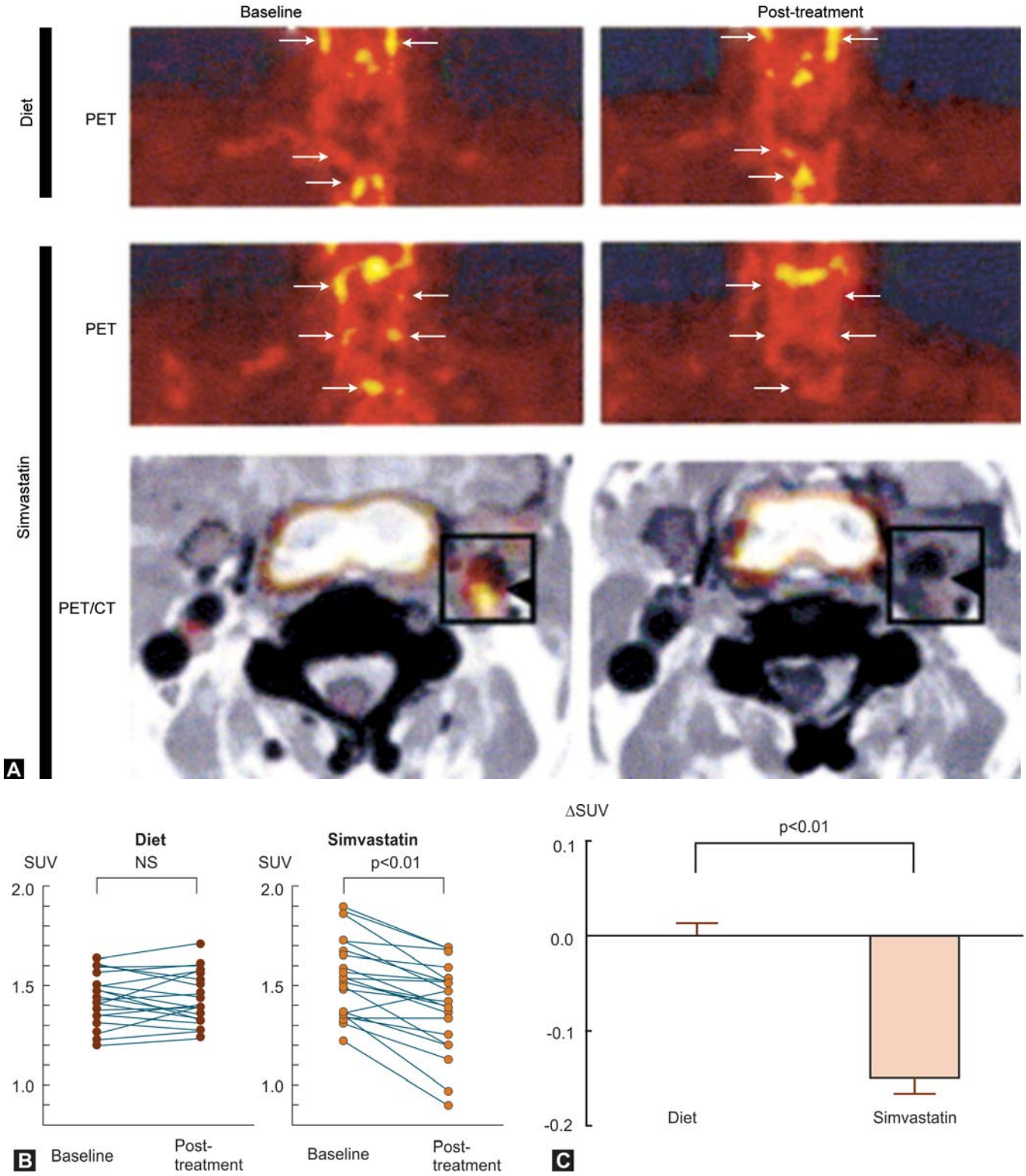
Additional promising preclinical molecular imaging strategies: Newer high sensitivity and novel agents are being developed at a rapid pace in preclinical studies.

Macrophages: A lipid-based gadolinium MRI probe shows strong affinity for the macrophage scavenger receptor-B (CD36), to enable noninvasive positive contrast MRI of plaque macrophages.[39] Agents with multimodality detection capabilities are becoming more prevalent, such as the trimodality nanoparticle for MRI, PET and NIRF detection of macrophages (Figs 6A to L).[4]

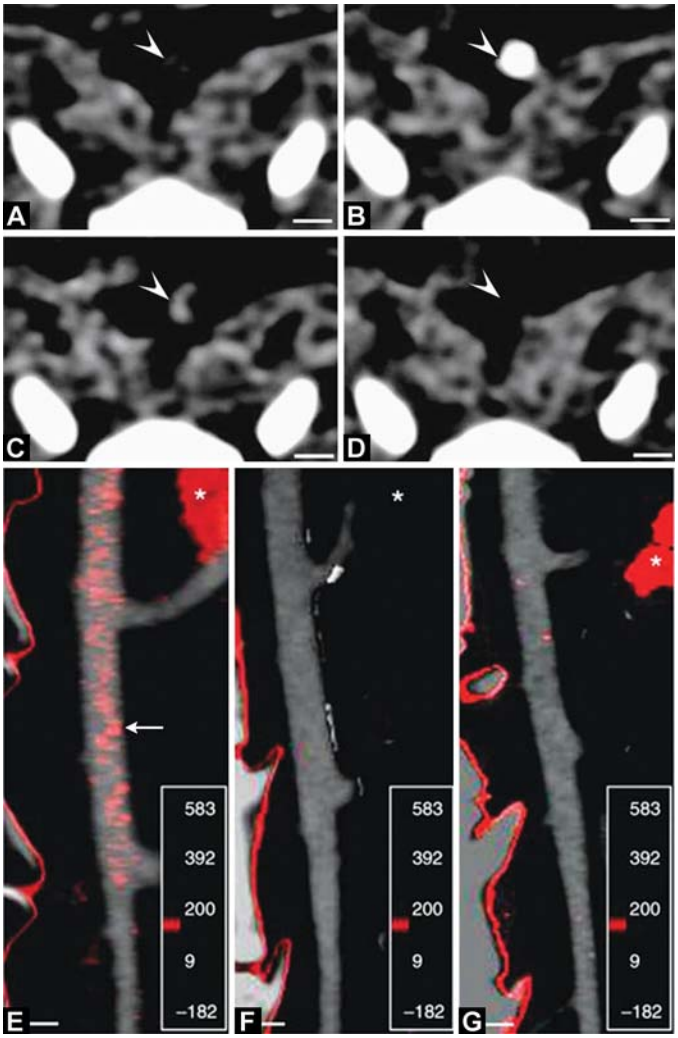
Proteases: There is also a particular focus on detecting enzymatic activity as a marker of active inflammatory changes and tissue destruction. In addition to cathepsin protease imaging, MMPs are frequently pursued targets on multiple platforms including an NIRF protease activity sensor,[40] a positive-contrast gadolinium chelate p947 for MRI[41,42] and the radionuclide SPECT tracers ^{111}In-RP782[43] and ^{99m}Tc-MMP.[44,45] Not only can MMP inflammatory activity be detected with these agents, but can also be measured over time following an intervention, such as that observed in hypercholesterolemic rabbits[44] and transgenic mice[45] where MMP-derived inflammation measured by ^{99m}Tc-MMP SPECT decreased with fluvastatin therapy or dietary modification. Customized enzymatic protease nanosensors (5–40 nm diameter) for optical molecular imaging have also been developed.[46]

Adhesion molecules: Endothelial surface glycoprotein receptors upregulated during inflammation, such as VCAM-1, E-selectin and P-selectin, have also been targeted using phage-display derived VCAM-1 specific nanoparticles (Figs 7A to H),[47] coated microbubbles for contrast-enhanced ultrasound,[48] iodine-containing liposomes conjugated to a receptor binding peptide with CT,[49] microparticles of iron oxide[50] and ^{18}F-labeled small affinity ligand.[51]

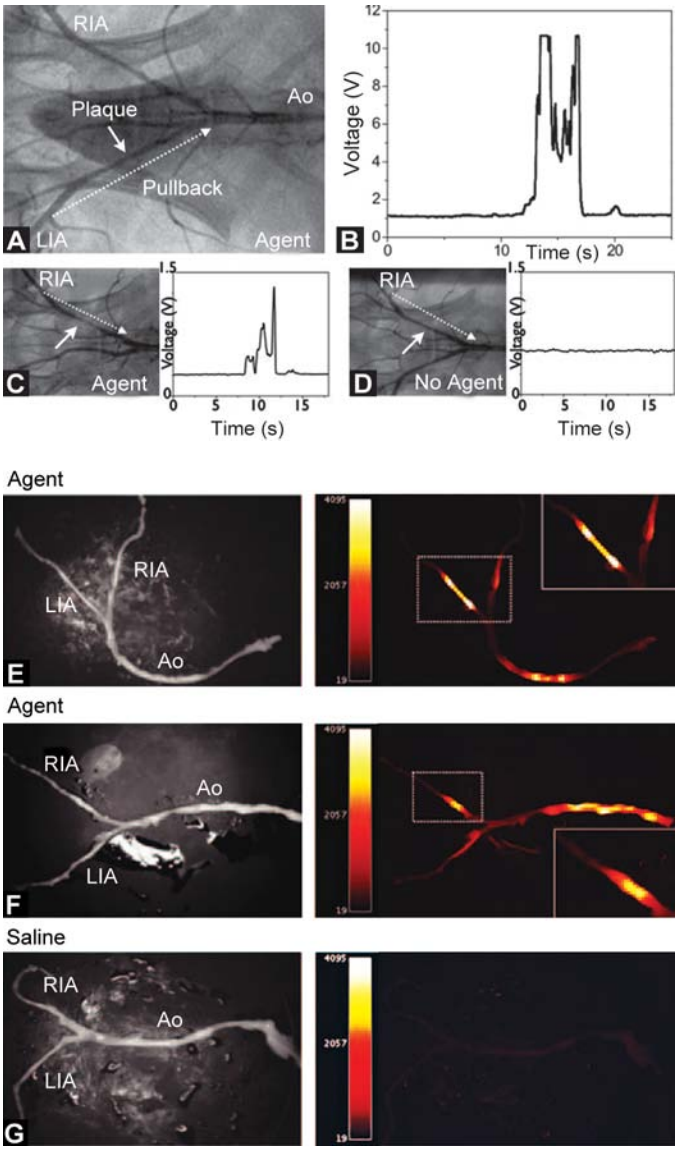
Cell tracking: Using adoptively transferred monocytes tagged with the clinical FDA-approved radionucleide tracer indium-111-oxyquinolone (^{111}In-oxine) and co-registered SPECT/CT



FIGURES 3A TO C: The effects of simvastatin therapy on atherosclerotic plaque inflammation assessed by serial ^{18}FDG-PET imaging. (A) Representative baseline images compared to post-treatment (3 months) showed no effect of altered diet alone on ^{18}FDG uptake (arrows, top images); however, simvastatin therapy diminished ^{18}FDG-detected plaque inflammation (middle images). Co-registered PET/CT identified areas of plaque ^{18}FDG disappearance after 3 months of simvastatin therapy (arrowheads, bottom images). (B) Quantitative anaylsis of ^{18}FDG plaque signal (average maximum standardized uptake values, SUVs) in individual subjects at baseline and after 3 months of simvastatin treatment. (C) Comparative change in plaque SUV from baseline demonstrated significant reductions with simvastatin therapy but not dietary modification alone. Bar = 1 SD (*Source:* Reference 31)



FIGURES 4A TO G: Molecular CT imaging of plaque inflammation in rabbits. Axial images of an aortic atherosclerotic plaque (white arrowheads) (A) before, (B) during and 2 hours following (C) N1177 nanoparticle administration or (D) a conventional contrast agent. Prior to contrast injection, the unvisualized atherosclerotic plaque becomes apparent once N1177 enhancement occurs, but is not seen with the conventional contrast agent. Color fusion image overlays onto the aortic plaques representing the density of vessel wall contrast enhancement demonstrated (E) focal regions of high signal intensity in atherosclerotic plaques after N1177 injection that was not observed with (F) a conventional contrast agent or (G) a non atherosclerotic control rabbit administered N1177. The insert shows the density color scale in HU. White asterisk identifies the spleen. Scale bar, 5 mm. (*Source:* Reference 33)

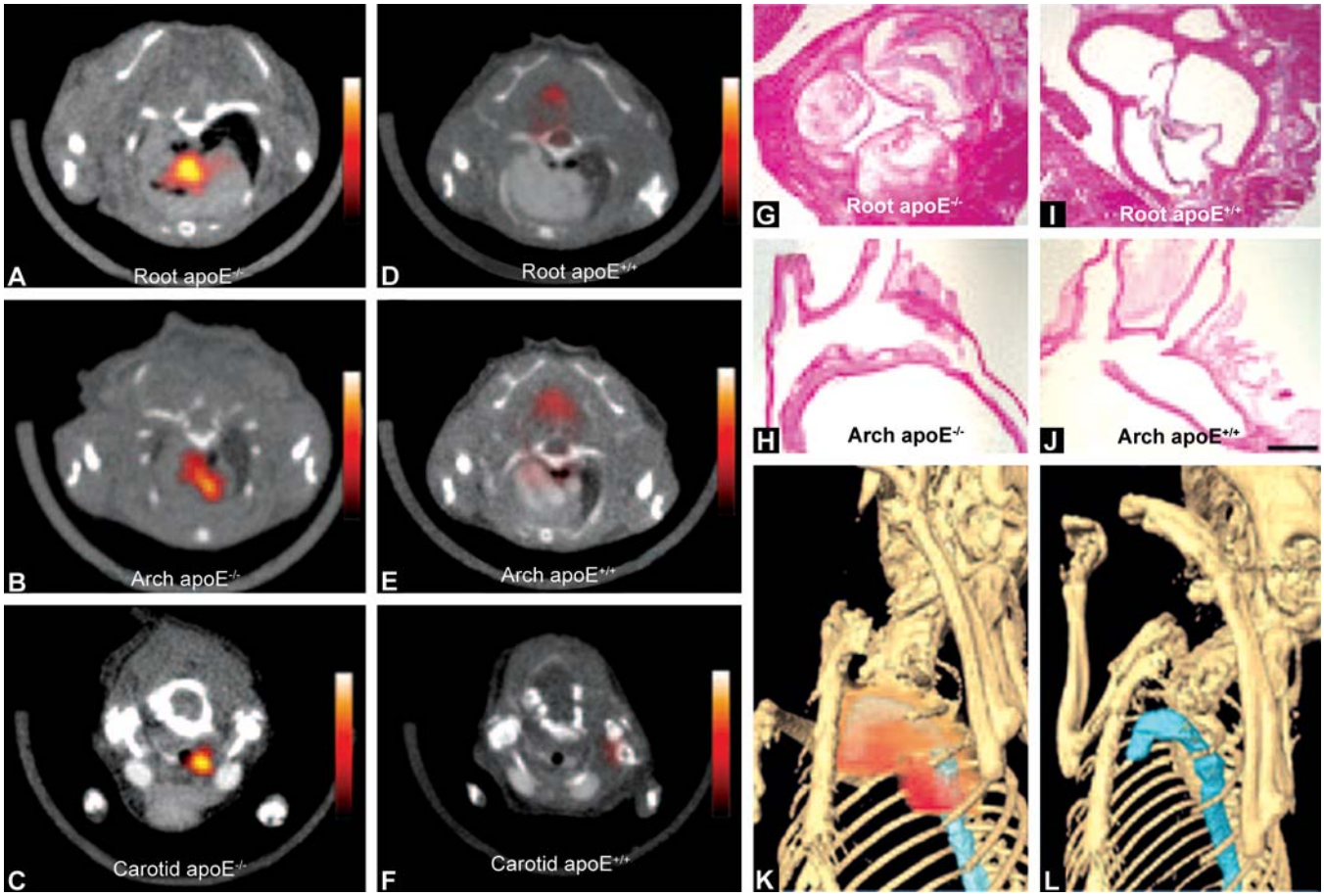


FIGURES 5A TO G: Atherosclerosis inflammation detected with in vivo real time NIR fluorescence intravascular sensing catheter. (A) Manual NIRF catheter pullback (trajectory defined by dotted arrow) in rabbit iliac arteries. (B and C) Protease-activatable NIRF activity following injection 24 hours before imaging, demonstrated significant fluorescence reporter activity (average TBR 6.8) at angiographically identified atheroma. (D) Saline injected control rabbits, exhibited significantly lower amplitude of NIRF signal. (E and F) Ex vivo arterial transmitted light and NIRF images revealed enhanced plaque protease fluorescence activity that was absent in (G) control animals that were administered saline (Abbreviations: RIA: Right iliac artery; LIA: Left iliac artery; Ao: Aorta). (*Source:* Reference 3)

molecular imaging, less monocyte trafficking to aortic plaques was observed in mice were treated with acute statin therapy.[52]

Oxidative Stress

The oxidation of phospholipids in atheroma contributes to the activation and recruitment of monocyte/macrophages and the production of enzymes, such as MMP, that degrade local tissue strength thus destabilizing plaque constituents. Detection of proinflammatory oxidative products by noninvasive molecular imaging may provide prospective information on the risk of individual plaques for future events or on the efficacy of therapeutics. Enzymatic detection agents for myeloperoxidase (MPO), a macrophage-derived product, have been evaluated by blue light bioluminescence using a small molecule luminol that activates fluorescence when oxidizing species are present,[53] as well as by MRI with the gadolinium agent bis-5HT-DTPA(Gd).[54] Another example of an oxidative species detection agent is gadolinium-retaining nanomicelles (20 nm diameter) with surface monoclonal antibodies that detect specific configurations of oxidized lipoproteins in atheroma.[55] Although presently untested, in the future combining information from oxidative stress imaging, in concert with more traditional macrophage or monocyte molecular imaging strategies, may bolster understanding of the underlying inflammatory state.

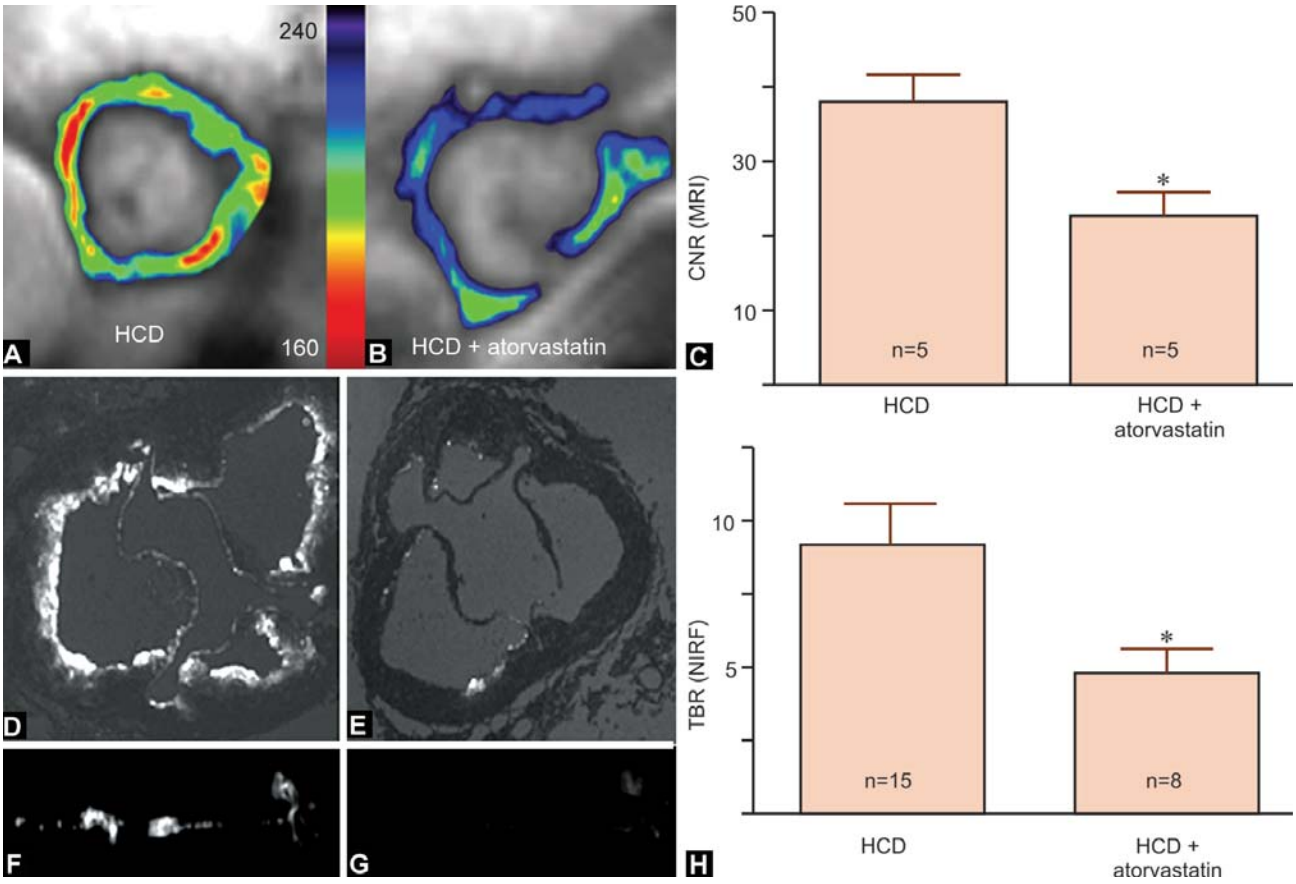


FIGURES 6A TO L: PET imaging of atherosclerotic plaque inflammation with a trimodality nanoparticle, ^{64}Cu-TNP. In atherosclerotic-prone ApoE$^{-/-}$ mice, ^{64}Cu-TNP PET imaging demonstrates enhancement in the (A) aortic root, (B) aortic arch and (C) carotid artery on co-registered CT fusion images identifying loci of inflammatory plaques. (D to F) On the contrary, wild type mice without atherosclerosis show no significant ^{64}Cu-TNP PET uptake. Hematoxylin and eosin histologic staining of excised aortas reveal advanced plaque burden in (G and H) ApoE$^{-/-}$ mice that is absent in (I and J) wild type controls (400 x magnification for G and I; 200 x magnification for H and J; bar 0.4 mm). Rendered three dimensional maximum intensity fused data set reconstructions show (K) proximal thoracic aorta (blue) focal ^{64}Cu-TNP PET signal (red) in ApoE$^{-/-}$ mice that is not seen in (L) control wild type mice. (*Source:* Reference 4)

Neovascularization

New vessel formation occurs during states where growth factors, such as vascular endothelial growth factor (VEGF) and others, are released stimulating endothelial and other supporting cells to create new blood channels. Endothelial cells organizing into interconnected vascular tubes and networks are anchored to extracellular matrix proteins in part through expression of the $\alpha_V\beta_3$integrin surface receptor, a common target for neovascularization molecular imaging studies. While in certain clinical scenarios angiogenesis can be beneficial, such as myocardial preconditioning from ischemia-reperfusion injury, in atherosclerotic disease, neovascularization highlights underlying plaque instability where it may promote intraplaque hemorrhage. Although clinical neovascularization studies have not been performed, a number of promising agents have been preclinically tested, including many agents for integrin $\alpha_V\beta_3$, which can be detected by the peptide sequence RGD or RGD mimetics. Noninvasive plaque angiogenesis imaging was initially shown with paramagnetic integrin $\alpha_V\beta_3$-targeted agents for MRI.[56] Other approaches include PET imaging with ^{18}F labeling[57] or ^{76}Br on a degradable nanoparticle shell.[58] Other, novel agents, such as gadofluorine-M for MRI, have been developed.[59]

Plaque neovascularization is one area within cardiovascular molecular imaging in which investigators have formulated agents that have the capability for both diagnostic detection and therapeutic purposes, a strategy termed “theranostics”. One such agent was created by combining the endothelial mycotoxin fumagillin with an angiogenesis-specific magnetic nanoparticle, $\alpha_V\beta_3$-MNP that targets the $\alpha_V\beta_3$ integrin receptor and contains gadolinium for MRI detection.[5,56] In an atherosclerosis rabbit study,[60] administration of the fumagillin theranostic nanoparticle followed by serial MR imaging over 4 weeks with the diagnostic $\alpha_V\beta_3$-MNP demonstrated significantly diminished neovascularization in the animals treated with the theranostic agent compared to controls. In comparison, atorvastatin pharmacotherapy without administration of the fumagillin theranostic nanoparticle did not reduce angiogenesis, but in combination helped sustain the fumagillin effect. The ability to diagnose, monitor and treat a diseased state with a single injectable agent demonstrates the potential power of a theranostic molecular imaging approach, a strategy that will undoubtedly gain increased attention with the



FIGURES 7A TO H: MRI detection of VCAM-1 expression on activated endothelial cells and the effects of statin therapy. VINP-28 injection, which targets endothelial VCAM-1 expression, revealed enhancement (color scale: red maximum and blue minimum signal) in the aortic root (short axis images) of (A) hypercholesterolemic ApoE$^{-/-}$ mice that was lessened in (B) an atorvastatin treated cohort. (C) Quantitative contrast-to-noise ratio (CNR) comparison demonstrated a significant reduction in atorvastatin treated mice compared to untreated controls (mean ± SD; P < 0.05 vs HCD). (D and E) Aortic root NIRF microscopy of the sections depicted in panels A and B show circumferential plaque VINP-28 fluorescence that was greater in non-atorvastatin fed mice. Fluorescence reflectance imaging in excised aortic specimens of (F) controls demonstrated greater NIRF signal than (G) atorvastatin treated mice, which correlated with (H) target-to-background ratios (TBR; mean ± SD; P < 0.05 vs HCD). (*Source:* Reference 47)

development of next generation clinical agents. Furthermore, theranostic strategies have the potential to locally deliver drugs at a fraction of the required systemic dose, limiting nonspecific tissue toxicity.

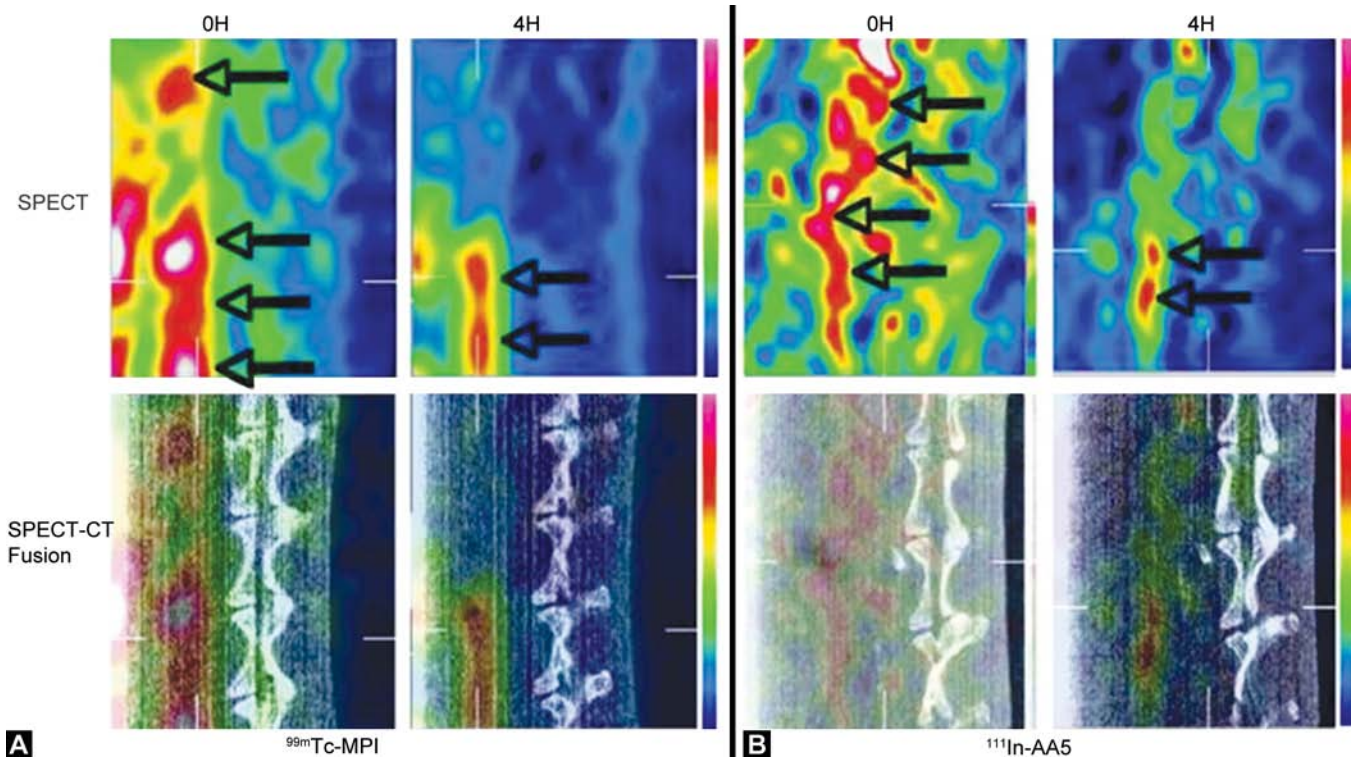
Apoptosis

Programmed cell death or apoptosis contributes to weakening of the fibrous cap via smooth muscle cell loss and facilitates expansion of the unstable lipid-filled necrotic core. Molecular signaling markers can identify cells destined for apoptotic demise, via annexin protein binding to exposed phosphatidylserine residues or via components of the caspase enzyme family that activate and execute the apoptotic cascade. The most widely utilized annexin-based imaging agents for apoptosis detection are high sensitivity SPECT-based tracers, such as ^{99m}Tc-annexin and ^{111}In-annexin, and can be combined with other readouts such as ^{18}FDG-derived inflammation[61] or MMP presence.[62] Inhibition studies with caspase blocking agents in atherosclerotic rabbits that diminish histologic plaque apoptosis have demonstrated the ability of ^{99m}Tc-annexin A5 SPECT imaging to discriminate between regions of different apoptotic activity.[63] Imaging of apoptosis has yielded insights into the salutary benefit of statin therapy in atherosclerosis (Figs 8A and B).[62] Optical imaging with fluorescently labeled caspases have been developed with the opportunity for NIRF or preclinical FMT imaging applications.[64]

In a limited number of patients with transient ischemic attacks scheduled for carotid endarterectomy, ^{99m}Tc-annexin A5 SPECT imaging has illuminated the relationship between apoptotic activity and carotid plaque instability (Figs 9A to D).[65] ^{99m}Tc-annexin A5 SPECT signal was detectable only in those patients with recent clinical events (within 4 days), where it localized to the culprit lesion. In comparison, subjects with remote transient ischemic attacks had no significant carotid ^{99m}Tc-annexin A5 uptake, nor did the non-cuprit stenotic contralateral carotid lesions in patients with recent events. Postoperative immunohistopathologic specimens confirmed increased tissue macrophage content and hemorrhage associated with enhanced macrophage annexin A5-binding suggesting accelerated local apoptosis.

Calcification

Vascular calcification is increasingly linked to chronic vascular inflammation, likely representing the terminal phase of



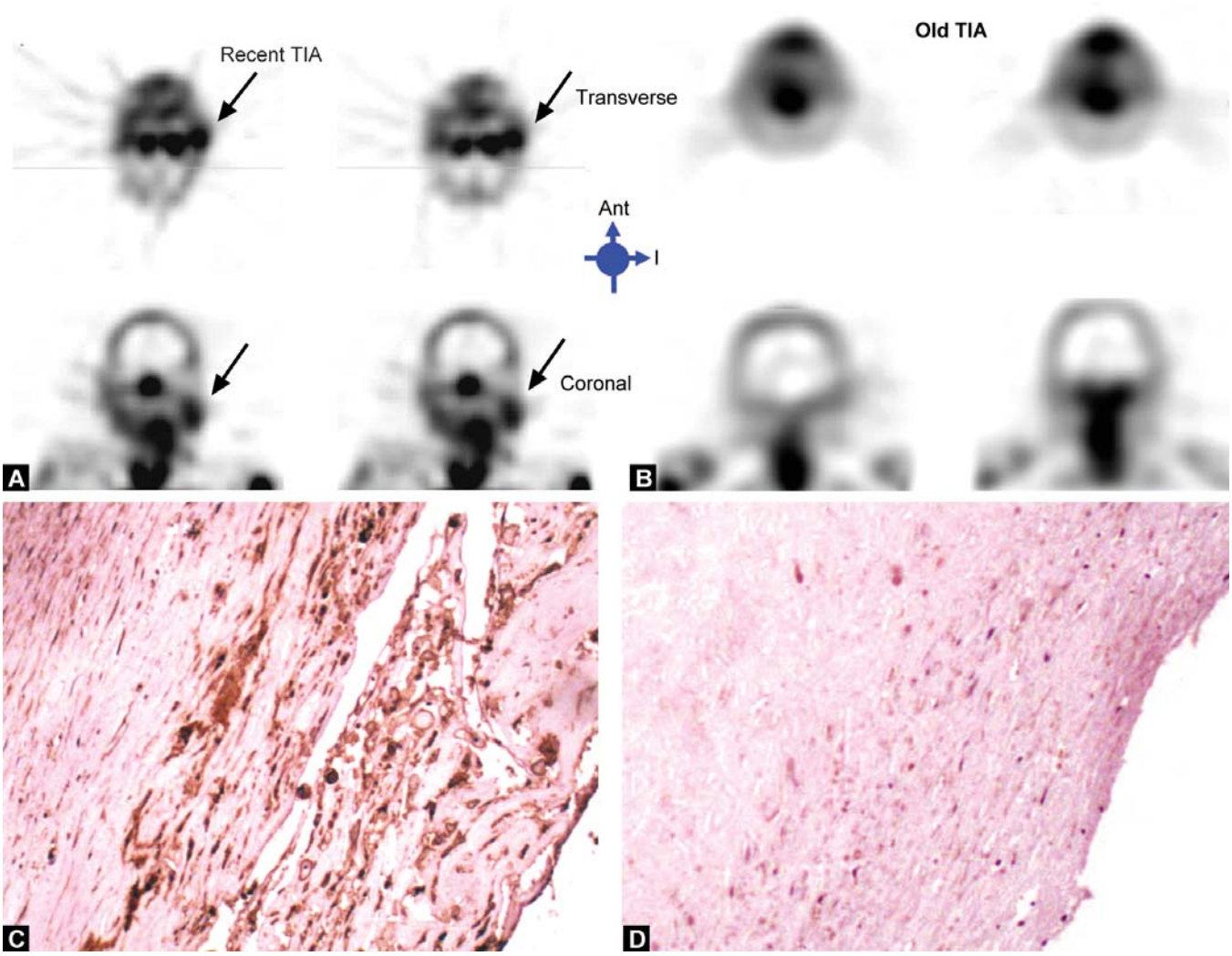
FIGURES 8A AND B: SPECT radionuclide imaging of atherosclerotic plaque MMP activity and apoptosis. Serial dual-target micro-SPECT radionuclide imaging of (A) matrix metalloproteinase (MMP) activity via the tracer ^{99m}Tc-MPI and (B) apoptosis with ^{111}In-Annexin (AA5) in atherosclerotic prone rabbits demonstrated aortic plaque target localization at 4 hours (arrows, right panels) following blood pool agent washout (left panels). The top panels show SPECT radiotracer uptake and the bottom panels SPECT-CT fusion images. (*Source:* Reference 62)

inflammatory lesions. In atherosclerosis, microcalcifications within plaques portend a greater risk for rupture and on a larger scale global coronary calcium scoring correlates with risk of future cardiovascular events. Another commonly encountered clinical scenario is calcification of the heart valves and supporting structures, such as aortic stenosis, which has many histopathological similarities to atherosclerosis and results in considerable cardiovascular morbidity and mortality particularly in an aging global population. The mechanisms of calcification in these disease states remain poorly understood as evidenced by the lack of effective nonsurgical management options, offering excellent opportunities for further research with in vivo molecular imaging. Currently available probes include optical agents such as fluorescently labeled enzymes substrates that identify the bone mineral component hydroxyapatite.[66]

The mechanism of bone mineral deposition in atherosclerotic calcification has been explored in molecular imaging studies of hypercholesterolemic mice with surgically induced renal failure to accelerate osteogenesis.[67] Using multichannel intravital fluorescence molecular imaging with a fluorescent quenched substrate for cathepsin S (CatS) and an optical bone mineral targeting agent (osteosense), the time course of enzymatic protease activity and bone deposition in arterial vascular and aortic valvular calcification was evaluated. Optical molecular imaging signals were then correlated with coinjected fluorescent USPIO nanoparticles that identified plaque macrophages. Results have demonstrated that the extent of calcification correspond to CatS activity. Mice deficient in CatS had less calcification but similar atherosclerotic plaque size, suggesting that CatS mediated tissue elastin peptide degredation contributed to local mineralization. A similar intravital microscopic study in the carotid plaques of atherosclerotic prone mice coinjected with NIRF, USPIOs and osteosense illustrated that macrophage infiltration and subsequent local inflammatory changes occurred prior to tissue osteogenesis and that bone mineral activity could be detected prior to histological or CT evidence of calcification (Figs 10A and B).[68]

THROMBOSIS

While the activation of circulating plasma clotting factors and platelets is key to vascular hemostasis and repair following tissue injury, arterial and venous thrombosis syndromes are worldwide leading causes of cardiovascular morbidity and mortality. Molecular imaging of key thrombus-associated molecules and cells has the potential to biologically refine anatomical imaging methods such as ultrasound or CT. Moreover, molecular imaging strategies may provide additional guidance into optimal therapeutic strategies to treat fibrin-rich or platelet-rich thrombi. Other advantages include the ability to replace invasive thrombosis imaging strategies with noninvasive options. For example, intracardiac thrombus formation, as may occur in the atrial appendage from atrial fibrillation, often requires transesophageal echocardiography for diagnosis. Another clinical arena of importance is arteriolar thrombosis syndromes, where flow-based diagnostic methods may be limited due to spatial resolution and possibly nephrotoxic contrast material and radiation exposure. The diagnosis

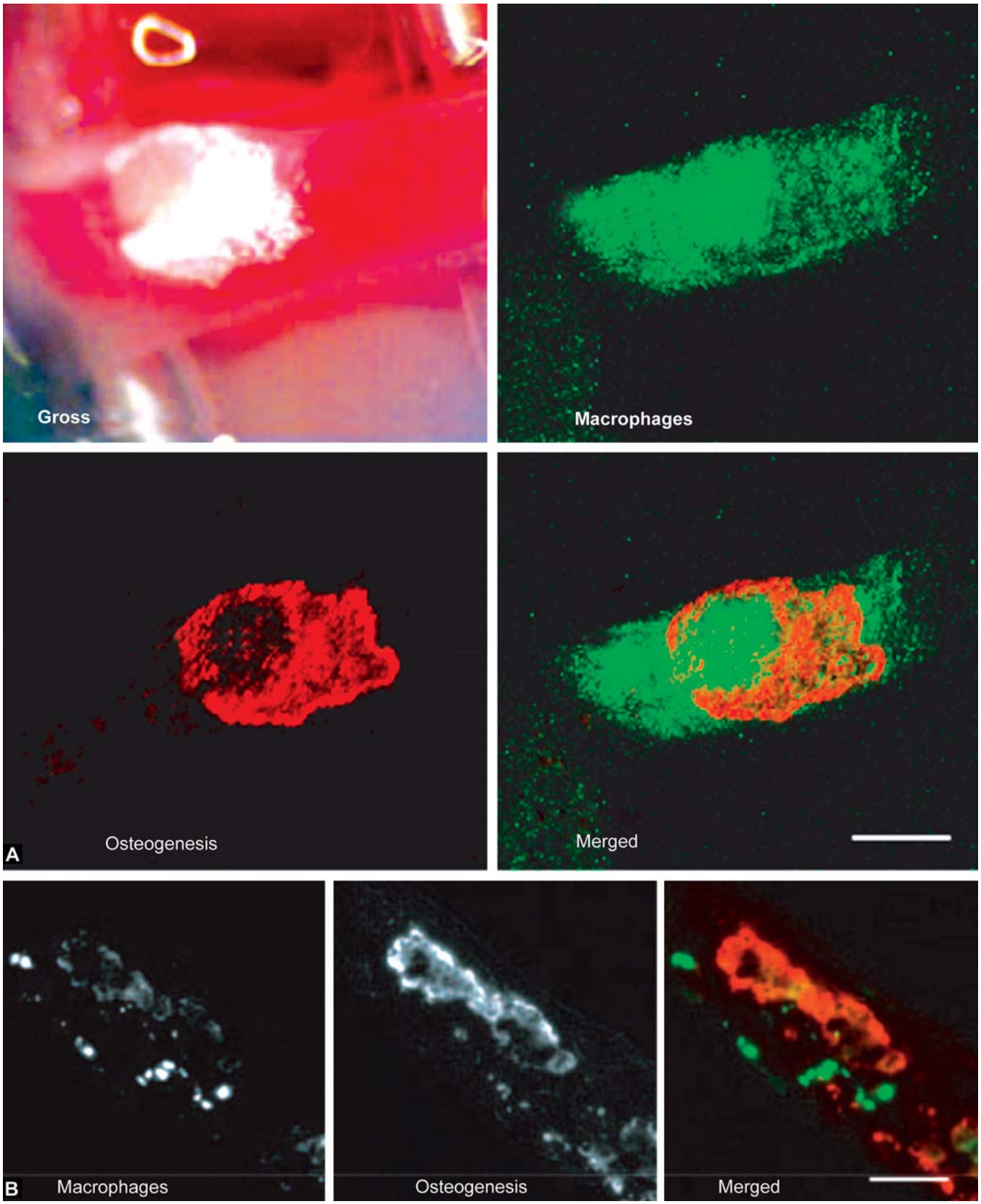


FIGURES 9A TO D: Clinical SPECT imaging of carotid plaque apoptosis in four patients with recent or remote TIA. (A) The apoptosis-targeted sensor ^{99m}Tc-annexin A5 was injected and was found to accumulate in the carotid lesion of a patient with recent TIA. (B) Immunohistochemical annexin A5 staining was pronounced in the surgically resected plaques (400 x magnification). A patient with remote TIA, in contrast had (C) minimal ^{99m}Tc-annexin A5 carotid plaque uptake and (D) annexin A5 immunochemical signal that was similar to background nonspecific staining. (Abbreviations: Ant: Anterior; L: Left). (*Source:* Reference 91)

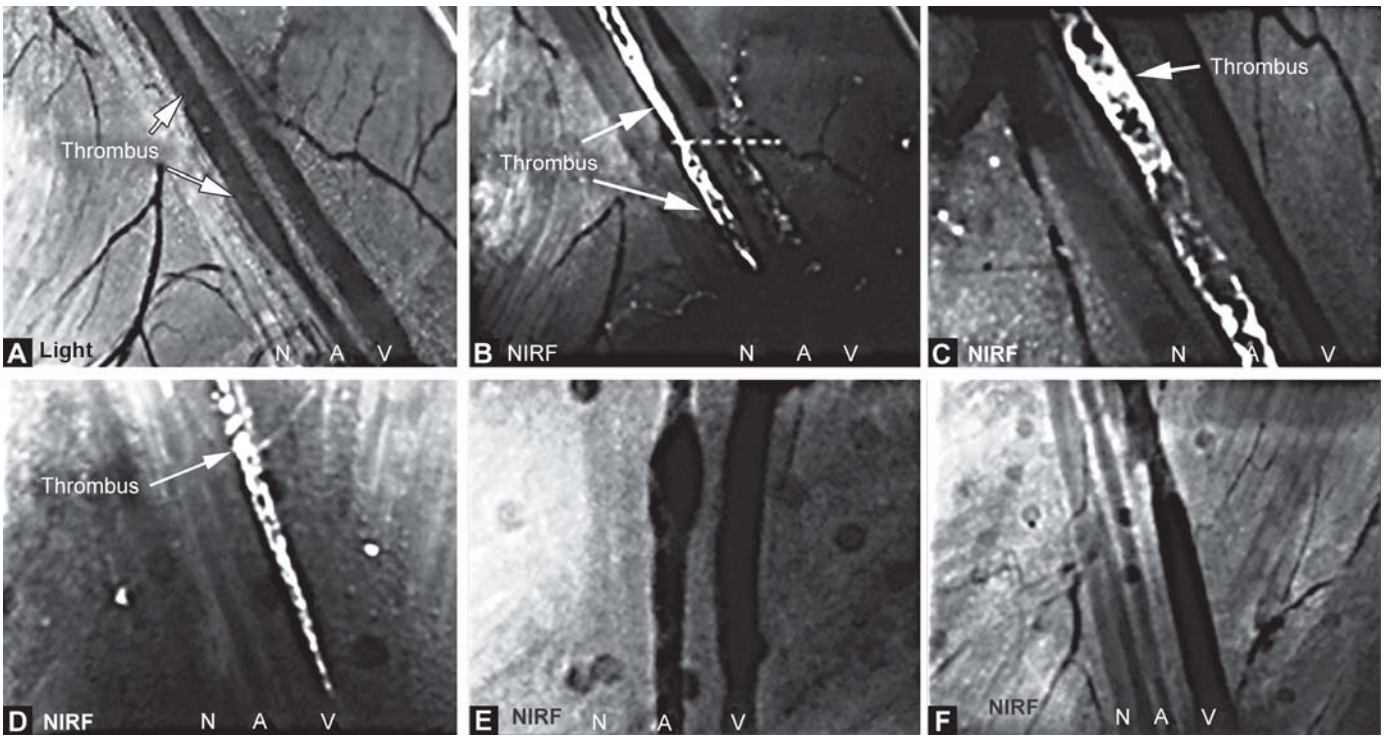
of new thrombi over prior existing thrombi is also challenging for anatomic imaging methods and represents another opportunity for molecular imaging of thorombosis. Furthermore, subclinical arterial thrombi which may be present in unstable carotid or aortic plaques following recent non occlusive rupture or intraplaque hemorrhage can be difficult to detect due to small size and surrounding complex plaque constituents such as calcium-related artifact in CT scans that obscures local tissue contrast. The development of specific molecular imaging markers of arterial and venous thrombosis has the potential to improve detection characteristics in each of these categories and diminish patient-specific risks, facilitating serial imaging studies that can visually document thrombus resolution following definitive therapy.

Clinical Imaging of Fibrin-Rich Thrombi

Of the molecular imaging thrombosis detection agents in development, the fibrin-targeted peptide EP-2104R has completed a multicenter phase II human clinical trial.[69,70] The EP-2104R peptide has been derivatized with four gadolinium molecules per peptide, providing signal amplification necessary for MRI detection. Prior to clinical studies, the EP-2104R agent underwent extensive preclinical evaluation, and showed a high degree of specificity and robustness for fibrin imaging.[71-75] In patients with recently identified venous (n = 14) or arterial (n = 38) thrombi, the administration of EP-2104R followed by a 2–6 hour imaging agent blood pool washout delay prior to MRI resulted in increased thrombus detection at areas of gadolinium enhancement that were not apparent on non-contrast imaging studies. While there were very few reported adverse reactions to EP-2104R and the total gadolinium dose was significantly less than typical clinical MRI studies, a majority of venous (71%) and many arterial (16%) thrombi were undetected by EP-2104R, possibly secondary to impaired penetration of the agent into more organized and contracted thrombi. With additional optimization of dose and imaging parameters, EP-2104R has clinical potential to detect thrombi



FIGURES 10A AND B: Multichannel NIRF image of macrophages and osteogenesis in murine atherosclerosis. (A and B) ApoE$^{-/-}$ mice with heavily calcified carotid artery atherosclerotic plaques demonstrated correlative gross morphology with intravital fluorescence microscopy of calcification (red) and macrophages (green). Merged fluorescence images show exclusion of macrophages from calcified regions and vice versa. Scale bar, 200 μm. (*Source:* Reference 68)



FIGURES 11A TO F: In vivo molecular imaging of activated transglutaminase FXIII (FXIIIa) via intravital epifluorescence microscopy. (A) Light image reveals dark clots (arrows) within the murine femoral vessels following ferric chloride chemical injury. (B) The FXIIIa targeted optical agent A15 was injected into mice harboring femoral thrombi. NIRF imaging at 82 minutes postinjection shows high TBRs in the arterial and venous vessels (arrows). The dashed line identifies a tissue region used for immunohistopathology (not shown). (C) On higher magnification of another A15-enhanced arterial thrombus (62 minute after injection), greater NIRF signal was observed at the thrombus margins and interface with the vessel wall. (D) A15 NIRF signal was also detected in venous thrombi (83 minute postinjection), but (E) not in older clots (72 minute after injection but 28 hours after thrombus induction), consistent with a time-dependent decrease in FXIIIa activity. (F) NIRF imaging of thrombi after administration of a control agent (AF680 fluorochrome) had minimal thrombus enhancement. (Abbreviations: N: Nerve; A: Artery; V: Vein). (*Source:* Reference 76)

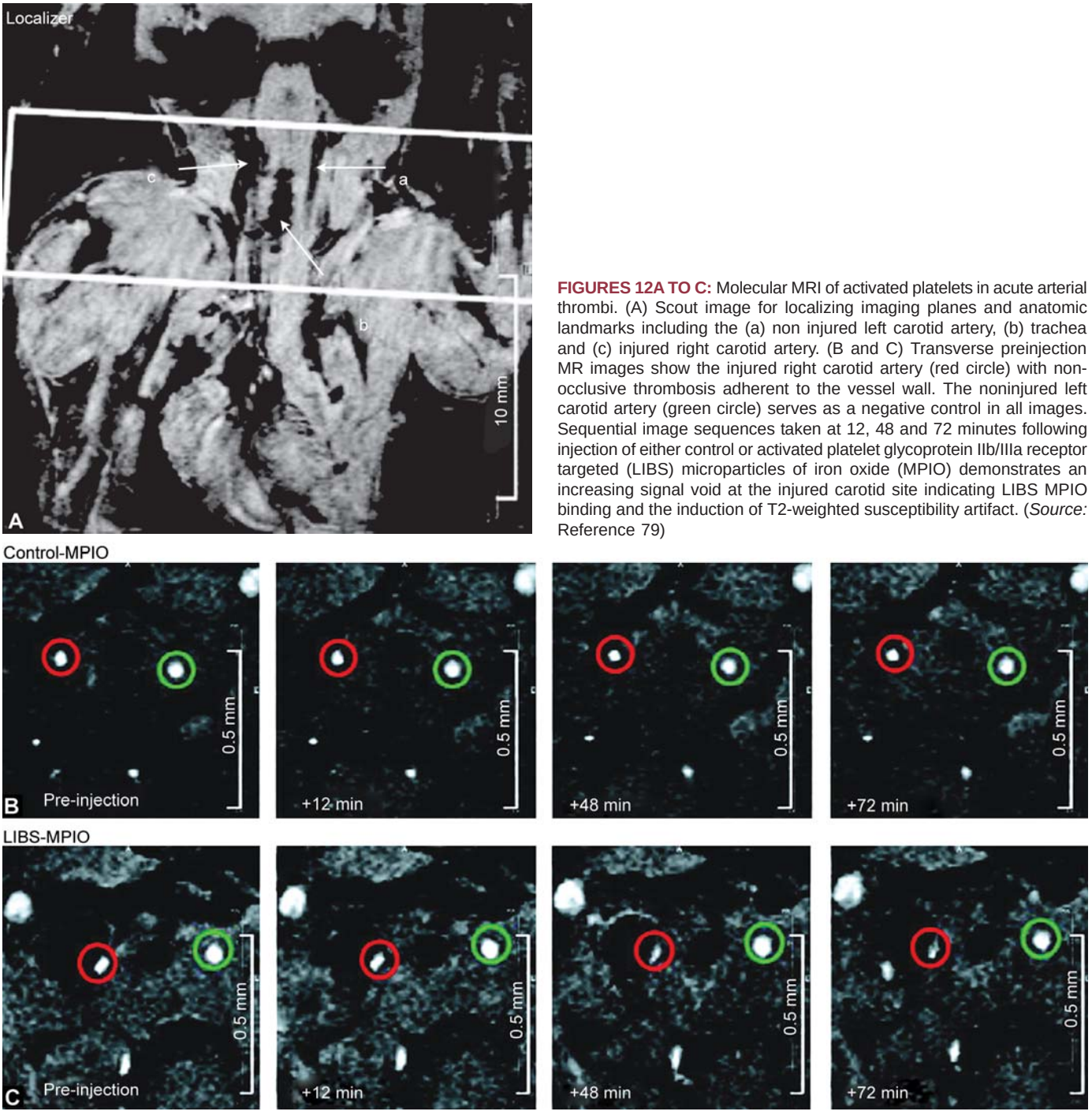
through molecular MRI of fibrin, providing a more specific molecular alternative to current flow-based thrombosis diagnostic imaging methods such as ultrasound and contrast-enhanced CT and MRI.

Preclinical Thrombus Imaging Strategies

Additional preclinical thrombus detection agents targeting both blood clotting factors and platelet receptors are in development for a range of imaging platforms including optical, radionuclide imaging and MRI. Activated transglutaminase factor XIII (FXIIIa) is one example; a circulating clotting factor found within acute thrombi, where it protects against fibrinolysis by cross-linking fibrin strands and α2-antiplasmin into the growing clot. Intravital fluorescence microscopy (IVFM) studies demonstrated the ability of an NIRF FXIIIa-targeted agent to distinguish acute from subacute thrombi (Figs 11A to F)[76] and to evaluate cerebral sinus vein thrombosis.[77] By linking gadolinium and the fluorophore rhodamine to an oligopeptide sequence based on the amino terminus of α2-antiplasmin, a dual platform MRI and optical FXIIIa targeted agent was developed and then validated in a murine chemically induced carotid arterial thrombosis model to identify acute thrombi (90 min after induction), but not more established clots (24–48 hour old).[78] Platelet imaging, which preferentially identifies arterial clots that are relatively platelet-rich compared to venous thrombi, has been established through binding to the surface glycoprotein IIb/IIIa receptor in its activated state with 1 μm diameter microparticles of iron oxide for MRI linked to a single chain monoclonal antibody (Figs 12A to C),[79] as well as by direct fluorescence labeling for NIRF imaging.[80] Serial MRI after non occlusive arterial thrombus formation demonstrated the feasibility of noninvasive monitoring of thrombolysis with this platelet-sensitive agent. Lastly, an optical sensor for thrombin activity imaging in acute thrombi has been evaluated using NIRF imaging.[81]

ANEURYSM

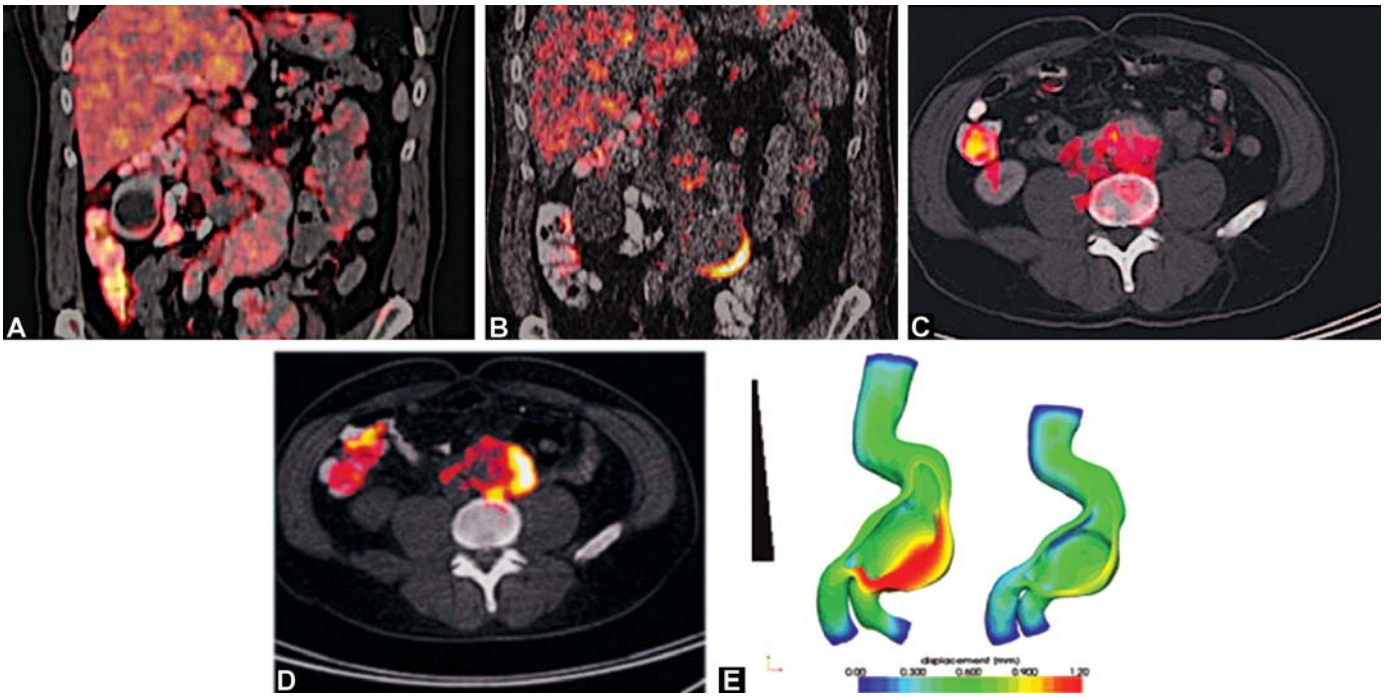
While aneurysms affect multiple arterial beds of varying size and wall thickness, including small intracranial vessels and the large thoracoabdominal aorta, they are similarly characterized by vessel wall weakening and lumen expansion driven by local inflammatory changes and its subsequent byproducts, with the potential for acute rupture and blood content extravasation. Often aneurysmal disease shares many of the same hallmark pathological features as atherosclerosis, which from a molecular imaging standpoint enables significant overlap in the available probes and detection strategies. In particular, inflammation and neovascularization, two important local processes that potentiate aneurysm formation, have been tested with molecular imaging strategies providing useful insight into this vascular disease process.



FIGURES 12A TO C: Molecular MRI of activated platelets in acute arterial thrombi. (A) Scout image for localizing imaging planes and anatomic landmarks including the (a) non injured left carotid artery, (b) trachea and (c) injured right carotid artery. (B and C) Transverse preinjection MR images show the injured right carotid artery (red circle) with non-occlusive thrombosis adherent to the vessel wall. The noninjured left carotid artery (green circle) serves as a negative control in all images. Sequential image sequences taken at 12, 48 and 72 minutes following injection of either control or activated platelet glycoprotein IIb/IIIa receptor targeted (LIBS) microparticles of iron oxide (MPIO) demonstrates an increasing signal void at the injured carotid site indicating LIBS MPIO binding and the induction of T2-weighted susceptibility artifact. (*Source:* Reference 79)

Clinical Aneurysm Inflammation Imaging

The use of ^{18}FDG-PET is an attractive clinical approach to investigate inflammation in aneurysms.[82] Inflammation as a predictor of aneursymal expansion has been evaluated in small-sized human trials. One recent study on 14 male patients with advanced infrarenal abdominal aortic aneurysms (AAA) undergoing surveillance imaging had demonstrated that ^{18}FDG uptake was highest in those that also had CT evidence of inflammatory changes, although there was no correlation with vessel diameter or recent expansion.[83] However, a case report of an asymptomatic patient with an incidentally discovered but rapidly expanding AAA had demonstrated areas of markedly increased ^{18}FDG uptake on serial PET/CT hybrid imaging studies (Figs 13A to E). At surgery, these areas were associated with microscopic collagen and elastin degradation, enhanced MMP expression and increased macrophage number.[84] Conversely, areas of low ^{18}FDG uptake had less histologic tissue inflammation and remodeling, suggesting that there may be AAA subsets that demonstrate detectable increases in ^{18}FDG-derived inflammatory signal as the aneurysms progress clinically. Given its clinical availability, ^{18}FDG-PET readouts of inflammation are well positioned to inform the risk of AAA expansion and rupture.



FIGURES 13A TO E: ^{18}FDG-PET imaging of metabolism/inflammation in a patient with an expanding abdominal aortic aneurysm. (A and C) ^{18}FDG-PET/CT images in the coronal and axial planes of the aneurysm at (A and C) baseline and (B and D) 6 months later. The red arrow indicates maximal glycolytic activity. (E) Three dimensional reconstruction with wall displacement of the smaller baseline aneurysm (left) and larger aneurysm observed at follow-up (right). The color scale identifies high (red) or low (blue) vessel wall displacement. (*Source:* Reference 84)

Preclinical Aneurysm Imaging Investigations

Preclinical studies have utilized many similar imaging strategies also examined for atherosclerotic disease in experimental animal models of large vessel inflammation and aneurysm formation. In experimentally induced intracranial saccular aneurysms, gadolinium-based MPO enzymatic activity representing oxidative stress has been visualized on a clinical strength 3T MRI scanner.[85] In another study, aneurysm neovascularization was assessed using optical imaging and a VEGF-specific probe labeled with an NIR fluorochrome. The VEGF tissue fluorescence in aneurysmal segments correlated positively with AAA diameter measured by ultrasound.[86] Recently endovascular imaging of inflammation in aneurysm disease was performed using NIRF imaging of MMP activity.[87] Additional translation of these and similar agents adopted from atherosclerosis studies will continue to aid in understanding of markers of aneurysm progression that can be utilized clinically to risk stratify those patients who may benefit from more aggressive early surgical or endovascular intervention.

VASCULAR INJURY

Injury of the vessel wall results in a local inflammatory response and smooth muscle cell hyperproliferation similar to atherosclerosis, leading to the formation of a pronounced neointima that progressively impacts oxygenated blood passage. In severe cases, the obstruction to blood movement becomes flow-limiting and causes downstream tissue ischemia and the development of associated symptoms. Diseases such as graft arteriosclerosis, in-stent restenosis and diabetic vasculopathies are characterized by this type of exaggerated neointimal expansion. Vascular injury models typically employing mechanical arterial wall insult with metal catheter guidewires or angioplasty balloons recapitulate many of the inflammatory features of this phenomenon and molecular imaging technologies are poised to allow tracking of the inflammatory and remodeling response over time as these lesions mature.

Due to the dependence of the vascular injury response on tissue remodeling, enzymes, such as MMPs, are prime molecular imaging targets, as they hasten extracellular matrix degradation to promote enhanced fibromuscular cell migration into the developing neointima. SPECT imaging of broad-spectrum MMP activity with ^{111}In-RP782 in the injured carotid arteries of atherosclerotic mice had demonstrated increased MMP signal within weeks of the insult, which correlated positively with the degree of hyperplastic neointimal expansion.[43] Importantly, the contralateral, sham-treated carotid artery showed no significant ^{111}In-RP782 signal uptake. Another ^{111}In labeled-probe, RP748 can identify activated $\alpha_V\beta_3$ integrin expression as a marker of neointimal vascular cell proliferation and has tracked angiogenesis within the expanding vessel wall.[88-91] The development of real-time intravascular catheters for optical NIRF probe detection of fluorescent enzymatic reporters that mark tissue injury and remodeling holds significant promise for clinical translation,[3,38] which in concert with advances in imaging processing protocols, such as normalization algorithms that reduce confounding blood pool fluorescence attenuation,[37] should accelerate the capability of this technology toward imaging of coronary stent-induced vascular injury.

OUTLOOK

Molecular imaging studies are yielding unparalleled in vivo insight into clinical aspects of vascular disease, including atherosclerosis, thrombosis, aneurysm formation and vascular injury. Clinical development of high-yield molecular imaging agents and the development of coronary-artery targeted imaging systems remain top priorities for the field. Preclinically, the emphasis remains on developing new highly sensitive, multifunctional/multimodal imaging agents with excellent safety and pharmacokinetic profiles. For molecular imaging to integrate into routine clinical practice, clear utility beyond functional and anatomical imaging will need to be established. In the near term, molecular imaging will likely assess the biological effects of new pharmacotherapies aimed to mitigate vascular disease. Thereafter, molecular imaging should improve the risk stratification and the clinical management of many vascular disease states.

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Chapter 25

Cardiac Hemodynamics and Coronary Physiology

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Chapter Outline

- Cardiac Catheterization—the Basics
  - Right Heart Catheterization
- Catheterization Computations
  - Cardiac Output
  - Fick Method
  - Indicator Dilution Method
  - Vascular Resistance
  - Intracardiac Shunt Ratio
- Cardiac Cycle Pressure Waveforms
  - Atrial Pressures
  - Ventricular Pressures
- Hemodynamics in Valvular Heart Disease
  - Aortic Stenosis
  - Aortic Regurgitation
  - Mitral Stenosis
  - Mitral Regurgitation
  - Pulmonic Stenosis
  - Pulmonic Regurgitation
  - Tricuspid Stenosis
  - Tricuspid Regurgitation
- Hemodynamics in Cardiomyopathy
  - Hypertrophic Obstructive Cardiomyopathy
  - Restrictive Cardiomyopathy
- Hemodynamics in Pericardial Disease
  - Constrictive Pericarditis
  - Cardiac Tamponade
- Coronary Hemodynamics
  - Fractional Flow Reserve
  - Coronary Flow Reserve
  - Index of Microcirculatory Resistance

INTRODUCTION

The first living human cardiac catheterization was performed in 1929 by a German surgical resident physician, Werner Forssmann, when he inserted a urological catheter into his own antecubital vein, passed it to his right atrium, and then walked to the X-ray room to document the position of the catheter in his heart. Fired for his self-experimentation, Forssmann later won the Nobel Prize for his contributions to physiology and medicine.[1,2] This important step in cardiology demonstrated that cardiac catheterization could safely be performed in humans and opened the door to a more direct understanding of cardiac disease states.

CARDIAC CATHETERIZATION—THE BASICS

Proper cardiac diagnosis and disease management relies on accurate hemodynamic data acquisition. Caution must be applied for adequate flushing of catheters, avoidance of bubbles and equipment calibration. Proper placement of the pressure transducer prevents inaccurate hemodynamic data acquisition. Traditionally, the transducer is placed at the mid-chest level by dividing the patient's anterior-posterior chest diameter by two. However, to avoid the effects of hydrostatic pressure by the fluid filled catheter, the transducer should be optimally aligned to the upper blood level of the cardiac chamber being assessed. Placing the transducer below this level subjects pressure assessment to include the hydrostatic pressure of fluid in the catheter and overestimates cardiac pressure. To minimize this effect, the transducer should be 5 cm below the left sternal border at the level of the fourth intercostal space and secured to a stationary pole.[3] To optimize confidence in data, the clinician should be astute to recognize artifacts that affect data integrity. The catheter, loose equipment connections, transducer, or amplifier and gain settings may create artifacts in pressure waveforms.

Underdampening of pressure waveforms results when either vigorous catheter movement or air bubble oscillation produces artifacts in peaks and dips of the pressure waveform. This is best avoided by repositioning and proper flushing of the catheter, respectively. Catheter kink or blood, contrast media, or air in the catheter can result in reduced pressure transmission and overdampening of the pressure waveform (Figs 1A to C).

Cardiac catheterization is a relatively safe procedure, however, knowledge of the relative contraindications and possible complications of cardiac catheterization are important in assessing the risks and benefits of the procedure (Tables 1 and 2). Furthermore, risk assessment must be performed on an individual basis as the risks associated with each procedure will vary based on the patient's comorbidities.

A common hazard of the cardiac catheterization laboratory is exposure of ionizing radiation to both patients and staff. Stochastic effects of radiation are those whose probability increases with increasing dose of radiation, such as



FIGURES 1A TO C: Left ventricle pressure waveform (A) Underdampening of pressure waveforms results when either excessive catheter movement or air bubble oscillations produce artifacts in peaks and dips of the pressure waveform, with falsely elevated systolic pressure and low diastolic pressure; (B) Catheter kink or blood, contrast media, or air in the catheter can result in reduced pressure transmission and overdampening of the pressure waveform, with smooth contour of the waveform; (C) Normal waveform. (Abbreviations: s: Systolic; d: Diastolic; e: End-diastolic pressure

TABLE 1

Risks of cardiac catheterization and coronary angiography*

Complication	*Risk (%)*
Mortality	0.11
Myocardial infarction	0.05
Cerebrovascular accident	0.07
Arrhythmia	0.38
Vascular complications	0.43
Contrast reaction	0.37
Hemodynamic complication	0.26
Perforation of heart chamber	0.03
Other complications	0.28
Total of major complications	1.70

*Number of patients = 59,792

Source: Scanlon PJ, Faxon DP, Audet AM, et al. ACC/AHA guidelines for coronary angiography: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Coronary Angiography). J Am Coll Cardiol. 1999; 33:1760.

TABLE 2

Relative contraindications to coronary angiography

- Acute renal failure
- Chronic renal failure secondary to diabetes
- Active gastrointestinal bleed
- Unexplained fever, that may be due to infection
- Untreated active infection
- Acute stroke
- Severe anemia
- Severe uncontrolled hypertension
- Severe symptomatic electrolyte imbalance
- Severe lack of patient cooperation, due to psychological or severe systemic illness
- Severe concomitant illness that drastically shortens life expectancy or increases risk of therapeutic intervention
- Patient refusal to consider definitive therapy such angioplasty or coronary artery bypass graft or valve surgery
- Digitalis intoxication
- Documented anaphylactoid reaction to angiographic contrast media
- Severe peripheral vascular disease limiting vascular access
- Decompensated congestive heart failure or acute pulmonary edema
- Severe coagulopathy
- Aortic valve endocarditis

Source: Scanlon PJ, Faxon DP, Audet AM, et al. ACC/AHA guidelines for coronary angiography: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Coronary Angiography). J Am Coll Cardiol. 1999; 33:1760-1.

carcinogenesis. Deterministic effects, such as skin injury, occur after a certain radiation dose threshold is reached. The purpose of radiation safety is to limit both stochastic and deterministic effects. Details of radiation safety are beyond the scope of this chapter, however, the operator must understand radiation physics and apply appropriate safety precautions that limit radiation exposure.

Right heart catheterization is performed for assessment of right-heart pressures, pulmonary arterial and pulmonary arterial wedge pressure (PAWP), which estimates left atrial pressure, and to calculate resistance of systemic and pulmonary vascular beds. This information is useful in studying conditions such as valvular heart disease, cardiac shunts, heart failure, pulmonary hypertension and to establish the etiology of shock.

Catheters are advanced under fluoroscopy through a sheath placed in a large vein, such as the femoral, internal jugular, subclavian or cephalic vein. Femoral venous access should not be used if an inferior vena cava filter is present. Venous systems with arteriovenous fistula (such as in dialysis patients) or suspected thrombus should also be avoided.

Classic woven Dacron catheters for right heart catheterization include the Cournard, which is a single end-hole catheter and the Goodale-Lubin, with two additional side holes. These catheters have excellent torquability, however, their stiffness makes them more traumatic catheters.[4] More commonly used are the flow-directed balloon floatation catheters such as the Swan-Ganz catheter, a balloon-tipped catheter with thermistor for measurement of cardiac output. Cardiac pressures are measured while advancing the catheter with the balloon tip inflated. When withdrawing the pulmonary artery catheter, it is important to keep balloon deflated to prevent trauma to cardiac or venous structures. Blood oxygen saturation sampled during right heart catheterization can be analyzed to assess for the presence of cardiac shunts.

CATHETERIZATION COMPUTATIONS

Assessment of cardiac output, vascular resistance and shunt severity are calculated from computations performed during right heart catheterization.

CARDIAC OUTPUT

Cardiac output is the volume of blood that circulates per unit time and is assessed using either the Fick method or the indicator dilution technique. Normal cardiac output is 5–6 l/min for males and 4–5 l/min for females. Cardiac index is cardiac output proportional to the body surface area.

FICK METHOD

Determination of the oxygen (O_2) content difference between arterial and venous (A-VO_2) blood is required for the Fick method. If no intracardiac shunt is present, pulmonary flow is equivalent to systemic flow and measurement of pulmonary A-VO_2 can be used. Simultaneous blood samples of the pulmonary artery and pulmonary vein (carefully obtained with balloon tip of catheter inflated) reflect venous and arterial content, respectively. In the absence of an intracardiac shunt, systemic arterial oxygen saturation may be used as a surrogate for pulmonary wedge oxygenation. Cardiac output using the Fick method is calculated using the following equation:

$$\text{Cardiac output (l/min)} = \frac{O_2 \text{ consumption (ml/min)}}{\text{Arterial } O_2 \text{ content} - \text{Mixed venous } O_2 \text{ content (ml/l)}}$$

where Oxygen content = 1.36 × Hemoglobin (g/dl) × SO_2 + (0.003 × PaO_2)

SO_2 is the percent oxygenation of arterial or venous blood.

PaO_2 is the arterial partial pressure of oxygen

Normal arterial oxygen content is 17–24 ml/dl and venous oxygen content is 12–17 ml/dl.

Oxygen consumption is measured during a graded exercise test during which the oxygen and carbon dioxide levels of inhaled and exhaled air are measured using a tight-fitting gas exchange mask. Because oxygen consumption determination using this method can be cumbersome, a nomogram is often used to estimate oxygen consumption using the patient's age, gender and heart rate.[5] However, accurate objective measurements of oxygen consumption are used to establish cardiac reserve and prognosis in patients with congestive heart failure, valvular heart disease, and hypertrophic cardiomyopathy, congenital heart disease, and coronary artery disease and risk stratify patients for cardiac transplant. Average oxygen consumption values for young males and females are 3.5 l/min and 2.0 l/min, respectively. The accuracy of the Fick method to determine cardiac output is compromised in the presence of intracardiac shunts due to mixing of oxygenated and deoxygenated blood.

INDICATOR DILUTION METHOD

The dilution of an indicator over time can be used to assess cardiac output. This method originally involved the injection of indocyanine green into one cardiac chamber and detection of its concentration in a downstream cardiac chamber. More commonly used is thermodilution, employing a thermal indicator of cold or room temperature saline. Using a catheter with a thermistor tip placed in the pulmonary artery, a temperature-time curve is generated after the injection of cold saline into the proximal port located in the right atrium. Using a computer model, the area under the thermodilution curve is converted to cardiac output and is inversely proportional to cardiac output. For example, in a low cardiac output state, the area under of the curve is greater as the thermistor senses a change in temperature over a longer period of time (Fig. 2). Conditions that prevent adequate forward flow, such as valve regurgitation, and intracardiac shunts or irregular heart rhythms, preclude the accurate measurement of cardiac output using the thermodilution technique. Hypothermia may also prevent assessment of cardiac output by thermodilution as the thermistor may not be able to detect a change in temperature

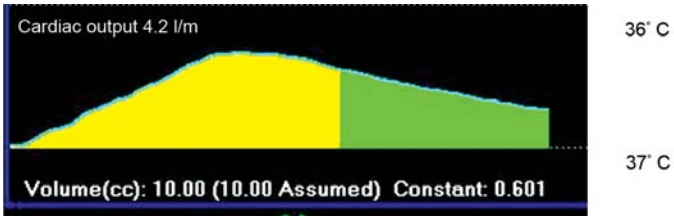


FIGURE 2: Temperature-time curve for cardiac output by thermodilution. A temperature-time curve is generated after the injection of cold saline into the proximal port located in the right atrium and thermistor tip placed in the pulmonary artery. Using a computer model, the area under the thermodilution curve is converted to cardiac output

of cooled normal saline depending on the degree of hypothermia.

VASCULAR RESISTANCE

The mean pressure gradient and flow across a vascular bed reflects the vascular resistance:

$$\text{Systemic Vascular Resistance (Woods units)} = \frac{\text{Mean arterial blood pressure} - \text{Right atrial pressure}}{\text{Cardiac Output (l/min)}}$$

$$\text{Pulmonary Vascular Resistance (Woods units)} = \frac{\text{Mean PA pressure} - \text{Mean PAWP}}{\text{Cardiac Output (l/min)}}$$

(PA = pulmonary artery, PAWP = pulmonary arterial wedge pressure)

1 Woods unit = 1 mm Hg x min/l = 8 MPascals.s/m^3 = 80 dynes.sec/cm^5

An indexed vascular resistance is calculated by multiplying vascular resistance by body surface area. In the presence of an intracardiac shunt, pulmonic and systemic cardiac outputs must be calculated separately when used to calculate PVR and SVR, respectively. See Table 3 for normal pulmonary and systemic vascular resistance.

INTRACARDIAC SHUNT RATIO

Flow across a vascular bed is defined as the oxygen consumption divided by the difference between the arterial and the venous oxygen content across a vascular bed.

Therefore,

$$\text{Pulmonary Flow (Qp)} = \frac{\text{O}_2\text{ Consumption (ml/min)}}{\text{PvO}_2 - \text{PaO}_2 \times \text{Hemoglobin} \times 1.36 \times 10} = \text{l/min/m}^2$$

$$\text{Systemic Flow (Qs)} = \frac{\text{O}_2\text{ Consumption (ml/min)}}{\text{SaO}_2 - \text{MvO}_2 \times \text{Hemoglobin} \times 1.36 \times 10} = \text{l/min/m}^2$$

SaO_2 = systemic arterial oxygen saturation, MvO_2 = mixed venous oxygen saturation, PvO_2 = pulmonary vein oxygen saturation, PaO_2 = pulmonary artery oxygen saturation.

The pulmonary to shunt flow ratio describes the magnitude and direction of an intracardiac shunt by the ratio of pulmonary to systemic blood flow using oximetry:

$$\text{Pulmonary Flow (Qp)} = \frac{\text{O}_2\text{ Consumption}}{\text{PvO}_2\text{-PaO}_2} = \text{SaO}_2 - \text{MvO}_2$$

$$\text{Systemic Flow (Qp)} = \frac{\text{O}_2\text{ Consumption}}{\text{SaO}_2\text{–MvO}_2} = \text{PvO}_2 - \text{PaO}_2$$

Venous blood from the superior vena cava has lower oxygen saturation than the inferior vena cava as more oxygen is extracted from the brain and upper extremities. Therefore, the Flamm formula allows for accurate MvO_2 using the oxygen saturation of the inferior and superior vena cava using the following equation:[6]

$$\text{MvO}_2 = \frac{3\ (\text{SVC O}_2) + \text{IVC O}_2}{4}$$

At rest, normal mixed venous oxygenation is approximately 75%.

In the absence of an intracardiac shunt, pulmonary and systemic flow are equivalent, Qp/Qs = 1. When a left-to-right shunt is present Qp/Qs > 1, with increased pulmonary flow. A Qp/Qs of > 1.5 suggests a more hemodynamically significant left-to-right shunt.

When a step up in blood oxygen saturation is noted from vena cava to the pulmonary artery of ≥ 8% and the systemic arterial oxygen saturation is less than pulmonic vein saturation, a bidirectional shunt should be suspected. To calculate the amount of blood flow shunted in each direction, the effective blood flow (EBF) must be calculated:

$$\text{EBF} = \frac{\text{O}_2\text{ Consumption}}{(\text{Pulmonic vein O}_2\text{ Saturation} - \text{Mixed venous O}_2\text{ Saturation}) \times 10 \times 1.36 \times \text{Hemoglobin}}$$

The difference between the pulmonic blood flow and effective blood flow indicates flow shunted from left-to-right. The difference between the systemic blood flow and the effective blood flow indicates flow shunted from right-to-left.

The indicator dilution method using a dye curve over time also quantifies shunts. The curve of the concentration of dye over time is generated by injecting dye proximal to the shunt and sampling distal to the shunt. For a left-to-right shunt, a second peak occurs due to recirculation of the shunted dye. The area under the two curves is used to calculate the magnitude of the shunt. For a right-to-left shunt, the ascending limb of the curve has a single early peak.

CARDIAC CYCLE PRESSURE WAVEFORMS

ATRIAL PRESSURES

The right atrial pressure tracing exhibits "a" and "v" waves that reflect an increase in the atrial pressure with atrial contraction and filling during ventricular systole, respectively. The "a" wave is followed by a "c" deflection that results from closure of the tricuspid valve during isovolumetric ventricular contraction. During the x-descent, the atrium relaxes with a decline in pressure. The y-descent following the "v" wave reflects atrial emptying after opening of the tricuspid valve (Fig. 3).

Left atrial pressure waveform is similar to the right atrium but with increased amplitude of the "a" and "v" waves. Direct pressure assessment of the left atrium requires retrograde catheterization from the aorta or atrial transeptal puncture by an experienced operator. The PAWP provides an indirect yet reliable assessment of left atrial pressure, in the absence of mitral valve disease.

VENTRICULAR PRESSURES

In the absence of valve stenosis, systolic pressures of the right and left ventricle pressure equal those of the pulmonary artery

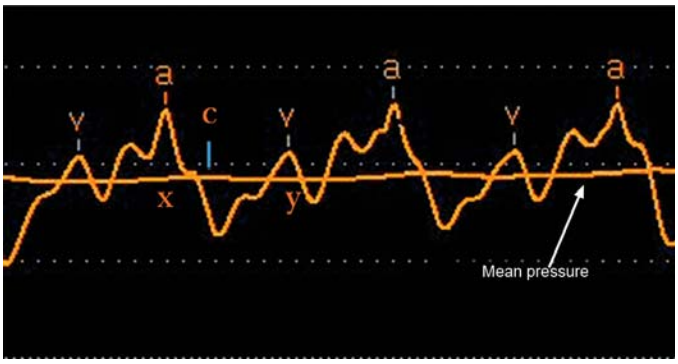


FIGURE 3: Right atrial pressure waveform. The "a" and "v" waves that reflect an increase in the atrial pressure with atrial contraction and filling during ventricular systole, respectively. The "c" deflection results from closure of the tricuspid valve during isovolumetric ventricular contraction. The atrium relaxes with a decline in pressure during the x-descent and the y-descent occurs during atrial emptying

and aorta, respectively. Ventricular diastolic pressures are dependent on myocardial compliance, which is inversely proportional to the slope of the pressure-volume curve. Wall thickness, volume, ischemia and medications affect myocardial compliance by altering the pressure-volume curve. Impaired myocardial compliance results in a "stiffer" chamber and elevation of ventricular end-diastolic pressure.

Left ventricle end-diastolic pressure (LVEDP) is approximately equal to left atrial and PAWP. During left heart catheterization, LVEDP is usually measured using a pigtail catheter placed in the left ventricle. However, if more accurate pressure recordings are required, a high-fidelity manometer can be used instead of a fluid-filled catheter. If a mid-cavity obstruction within the left ventricle is suspected, a straight or angled end-hole catheter should be used to assess left ventricular pressure.

LVEDP is measured on the left ventricular pressure tracing at a point just prior to isovolumetric contraction and immediately after the "a" wave of the PAWP tracing.[7] LVEDP also corresponds to the "R" wave of the electrocardiogram tracing (Fig. 4). If atrial fibrillation is present, the LVEDP of 10 cardiac cycles are averaged. Artifact of elevated diastolic pressure may occur when using a pigtail catheter with multiple holes if the holes are simultaneously partially present in the aorta and left ventricular cavity, producing a falsely elevated combined diastolic pressure. All holes of the pigtail catheter must be within the left ventricular cavity for accurate measurement of LVEDP. Normal cardiac pressures are listed in Table 3.

HEMODYNAMICS IN VALVULAR HEART DISEASE

AORTIC STENOSIS

Valvular AS is most often due to calcific degeneration of the valve seen in the elderly population. Young adults with AS often have a congenital malformation of the valve, such as a bicuspid aortic valve, that contributes to the development of AS. AS may also be supra-valvular or sub-vavular. Supra-valvular AS is usually congenital in etiology. Sub-valvular AS may be present due to basal septal hypertrophy or the presence of a subaortic membrane. Current guidelines discourage invasive hemodynamic evaluation of aortic stenosis when noninvasive findings regarding the severity of aortic stenosis by echocardiography are unequivocal. Invasive evaluation of AS is reserved for situations in which there is a discrepancy between echocardiographic findings and patient's symptoms.[8] Coronary angiography should be performed in patients referred



FIGURE 4: Identification of left-ventricle end diastolic pressure. Left ventricle pressure (yellow) and ECG leads tracing. LVEDP corresponds to the "R" wave of the electrocardiogram tracing. LVEDP may also be measured at a point just prior to isovolumetric contraction and immediately after the "a" wave of the PAWP tracing. (Abbreviation: e: end-diastolic pressure)

TABLE 3

Normal pressures and vascular resistance

	Pressure (mm Hg)
Right atrium	
a wave	6 (2–7)
v wave	5 (2–7)
Mean	3 (1–5)
Right ventricle	
Peak systolic	25 (15–30)
End-diastolic	4 (1–7)
Pulmonary artery	
Peak systolic	25 (15–30)
End-diastolic	9 (4–12)
Mean	15 (9–19)
Pulmonary artery wedge	9 (4–12)
Left atrium	
a wave	10 (4–16)
v wave	12 (6–21)
Mean	8 (2–12)
Left ventricle	
Peak systolic	130 (90–140)
End-diastolic	8 (5–12)
Aorta	
Peak systolic	130 (90–140)
End-diastolic	70 (60–90)
Mean	85 (70–105)
	Resistance (dyne-sec/cm^5)
Systemic vascular resistance	1100 (700–1600)
Pulmonary vascular resistance	70 (20–130)

for aortic valve surgery when a suspicion of coronary artery disease exists.

Hemodynamic measurements in AS reveal a gradient between the systolic aortic and the left ventricular pressures (Fig. 5). In severe aortic stenosis, the ascending limb of the aortic pressure waveform is delayed. One should be careful in using peripheral arterial pressure as a surrogate for central aortic pressure, as they may not always be equal. This is due to pressure waveform summation, different elasticity and size of the vessels, and peripheral vascular disease that often results in a differentiation in peripheral and aortic pressures. Therefore, two arterial catheters or a double lumen catheter may be used for catheterization of the left ventricle and aorta simultaneously. If a peripheral arterial pressure will be used as a surrogate for central aortic pressure, this should be calibrated with the central aortic pressure before crossing the valve. Use of a pigtail catheter with side-holes is discouraged due to pressure artifacts if holes are only partially present in one chamber. To avoid risk of thrombosis, anti-coagulation may be considered especially if measurements are to be taken with catheter placed in the left ventricle for sometime.

Peak aortic and left ventricular pressures are temporally separated. Thus, the gradient between the two can be described as peak-to-peak, peak instantaneous or mean gradient. Peak-to-peak gradient is the absolute difference between peak aortic systolic pressure and peak left ventricular systolic pressure. Peak instantaneous gradient is the maximum pressure gradient between the aorta and left ventricle at a single point in time. The area between the systolic left ventricular and aortic

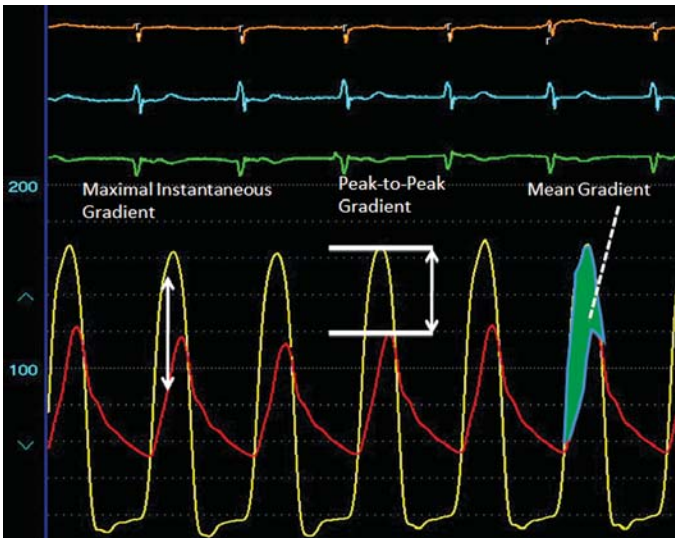


FIGURE 5: Aortic-Left ventricular systolic gradient in aortic stenosis. Maximal instantaneous gradient is the maximum pressure gradient between the aorta (red) and left ventricle (yellow) at a single point in time. Peak-to-peak gradient is the absolute difference between peak aortic systolic pressure and peak left ventricular systolic pressure. Mean gradient is defined by the area between the systolic left ventricular and aortic hemodynamic tracings (green shaded area)

hemodynamic tracings defines the mean gradient and best quantifies the severity of aortic stenosis.

Aortic valve area (AVA) is calculated from hemodynamic data and cardiac output in ml/min using the Gorlin equation:[9]

$$\text{AVA (cm}^2\text{)} = \frac{\text{(Cardiac output [ml/min]/Systolic ejection period [sec] × Heart rate [beats/minute])}}{44.3 \times \surd\text{mean gradient (mm Hg)}}$$

The Hakki formula is a simplified version for AVA:[10]

$$\text{AVA (cm}^2\text{)} = \frac{\text{Cardiac output (l/min)}}{\surd\text{Peak to peak gradient (mm Hg)}}$$

AVA estimation using the Hakki formula is based on the finding that the product of systolic ejection period, heart rate, and the constant are close to 1000. Note that cardiac output in the Hakki formula is reported in liters per minute. If valve regurgitation is present, the Fick method for calculation of cardiac output is more accurate. AVA of lesser than 1 cm^2 and a mean gradient of greater than 40 mm Hg indicate severe AS. An AVA of greater than 1.5 cm^2 and a mean gradient of lesser than 20 mm Hg indicate mild aortic stenosis.

AORTIC REGURGITATION

Although, characterization of aortic regurgitation (AR) by echocardiography is often adequate, aortic angiography provides further information on aortic root size and qualitative information on regurgitation of blood across the aortic valve into the left ventricle. Aortic angiography is performed with a multi-side-hole catheter positioned just above the sinus of Valsalva in the left anterior oblique projection and a power injector is used to inject contrast; approximately 40 ml of

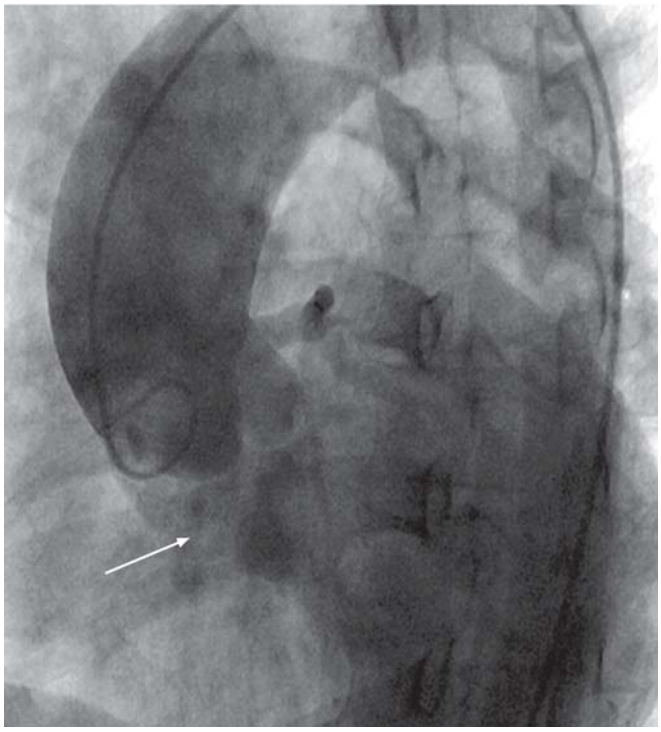


FIGURE 6: Aortic regurgitation on aortic angiography. Aortogram performed with pigtail catheter in the aorta demonstrating Grade 2 aortic regurgitation, with moderate opacification of the left ventricle

contrast at a rate of 20 ml/second. AR is graded on a scale of 1–4: Grade 1 (mild) minimal contrast opacifies the left ventricle; Grade 2 (moderate) opacification of entire left ventricular; Grade 3 (moderately severe) dense opacification of left ventricle over sequential cardiac cycles and Grade 4 (severe) dense opacification of entire left ventricle in one cardiac cycle[11] (Fig. 6). The pathophysiology and cardiac hemodynamics of acute and chronic AR are different. Recognizing the different patterns in the LVEDP and pulse pressure aid in making this distinction and are described below.

Chronic Aortic Regurgitation

As blood volume regurgitates from the aorta to the left ventricular chamber in diastole, arterial diastolic pressure falls. As the severity of AR worsens, the left ventricular end-diastolic volume also increases. An increased left ventricular ejection volume results in augmented arterial systolic pressure. Therefore, the pulse pressure increases as is evident on the aortic pressure waveform. Hemodynamically significant AR results in a bisferiens pulse, which is a double peak of the aortic systolic contour separated by a mid-systolic dip. The bisferiens pulse results from a rapid left ventricular ejection velocity and subsequent reflected wave from the periphery.

Increased wall stress from a chronically volume overloaded left ventricular chamber results in eccentric hypertrophy. The compliance of the left ventricular eventually begins to deteriorate and results in a modest rise in the LVEDP along with an increased slope of the ventricular diastolic waveform.

Acute Aortic Regurgitation

Acute AR may result from aortic dissection involving the aortic root, trauma or valve perforation from endocarditis. Regardless of the etiology, the unconditioned ventricular is suddenly exposed to a substantial increase in diastolic volume and a dramatic increase in LVEDP. Initially, premature closure of the mitral valve occurs. Eventually, the rise in volume and pressure transmits to the left atrium and pulmonary vasculature resulting in congestion and hypotension.

Unlike chronic AR, an increase in the aortic pulse pressure may not be as impressive acutely due to the absence of both an increased ventricular ejection velocity and decreased systemic vascular resistance. Pulsus alternans may be evident on the aortic pressure waveform with beat-to-beat variation in systolic amplitude due to variations in myocardial contraction strength.

MITRAL STENOSIS

Hemodynamic assessment of mitral stenosis (MS) requires simultaneous right and left cardiac catheterization. Mean gradients by doppler methods and valve area by planimetery, may be obtained by echocardiography. It must be emphasized that echocardiography plays a pivotal role in characterizing valvular and sub-valvular features, such as calcification, leaflet mobility and thickness, which help to determine suitability for percutaneous valvuloplasty.[12] During valvuloplasty, resolution of the mitral valve gradient and the undesirable development of mitral regurgitation are monitored by hemodynamics.

Measurement of the mean mitral valve gradient is made by the diastolic area difference between the left atrial and the left ventricular diastolic pressure waveforms (Fig. 7). PAWP approximates left atrial pressure and may be used as a surrogate to limit the risk associated with transeptal puncture. However, since the PAWP waveform is delayed 40–120 msec with respect to the left atrial pressure waveform, the tracing should be phase shifted so that the peak of the PAWP "v" wave is placed on the downslope of the left ventricular pressure tracing. With severe MS, the PAWP, pulmonary artery pressures and pulmonary vascular resistance increase.

Atrial fibrillation has a common association with MS. If atrial fibrillation is present, the mean mitral valve gradients of ten cardiac cycles should be averaged to increase accuracy. Alternatively, temporary pacing for a regular ventricular rhythm may be used to make more accurate measurements. A rapid heart rate also precludes the accurate assessment of the mean gradient as a short R-R interval abbreviates the diastolic period and prevents equilibration of left atrial and ventricular diastolic pressures, overestimating the mitral valve gradient.

Mitral valve area (MVA) is calculated using the Gorlin formula for the mitral valve:[13]

$$\text{MVA (cm}^2\text{)} = \frac{\text{[Cardiac output (ml/min)/Diastolic filling period (sec)} \times \text{Heart rate (beats/min)]}}{44.3 \times 0.85 \times \sqrt{\text{mean gradient (mm Hg)}}}$$

The diastolic filling period is measured at the start of diastole, where the pulmonary arterial wedge and left ventricular

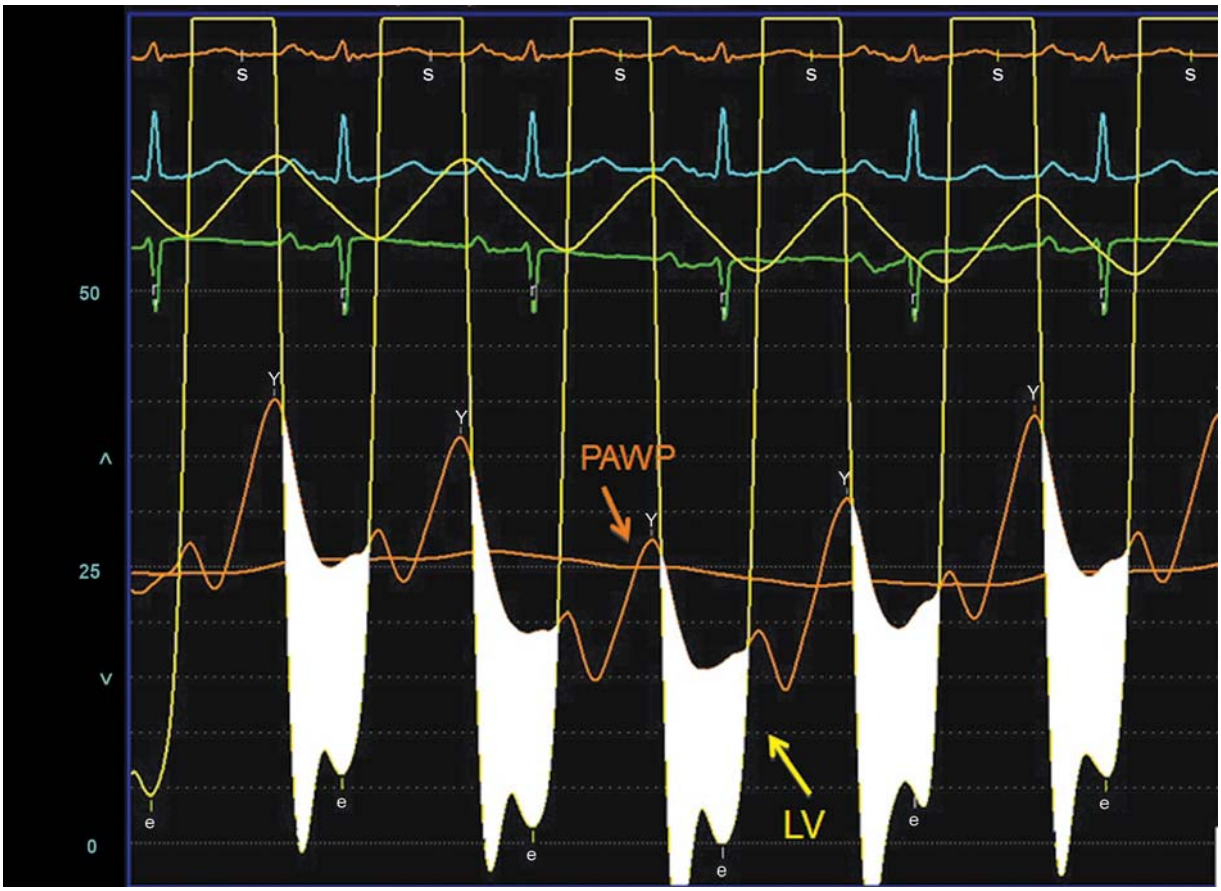


FIGURE 7: Mitral stenosis, diastolic gradient. Mean mitral valve gradient is determined by the diastolic area difference between the pulmonary arterial wedge pressure (PAWP) tracing in orange and left ventricle (LV) pressure tracing in yellow

pressure tracings cross, to end-diastole, identified as peak of the R wave on the electrocardiogram.[14]

MITRAL REGURGITATION

The mitral valve apparatus consists of an annulus and leaflets attached to papillary muscles via chordae tendinae. Disruption of any component of the mitral valve apparatus may result in regurgitation of blood from the left ventricle to the atrium during systole. 2D Echocardiography provides anatomical information on mitral valve structures and doppler calculations quantify mitral regurgitation (MR). Left ventriculography provides a qualitative assessment of mitral incompetence is performed using a pigtail catheter with side-holes in the 30 degrees right anterior oblique projection using 30 ml of contrast at a rate of 10 ml/second. Severity of MR on ventriculography is graded on a scale of 1–4: Grade 1 (mild) contrast partially opacifies the left atrium; Grade 2 (moderate) complete yet faint opacification of left atrium; Grade 3 (moderately severe) opacification of left atrium and left ventricle are comparable and Grade 4 (severely) dense opacification of complete left atrium in one beat[15] (Fig. 8).

Right and left heart catheterizations provide information on the hemodynamic effects of mitral competence. Increased "v" wave amplitude of the PAWP tracing is suggestive of significant MR. Recall that the "v" wave correlates with atrial filling during ventricular systole. Generation of "v" wave amplitude is not only dependent on regurgitant volume, but left atrial compliance and size as well. Therefore, the absence of a tall "v" wave does not necessarily exclude the diagnosis of severe MR.

A comparison of the atrial and ventricular pressures in severe MR reveals the LVEDP to be lower than left atrial

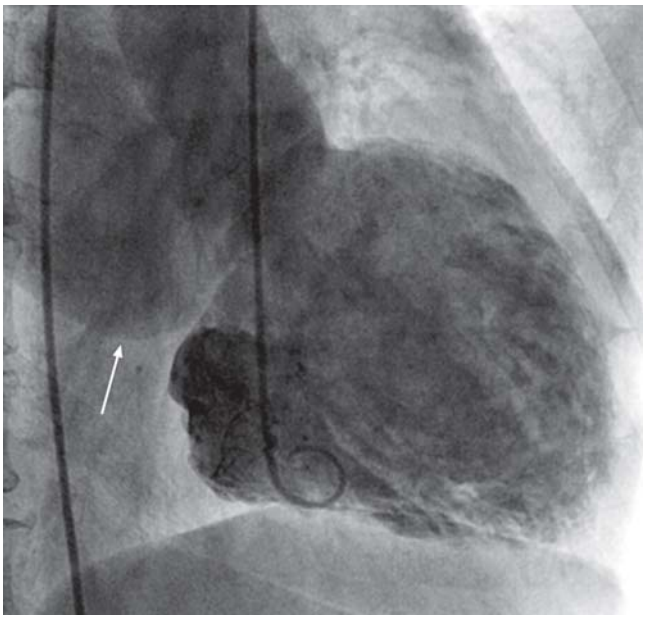


FIGURE 8: Mitral regurgitation, left ventriculography. Grade 3 (moderately severe) with equal opacification of left atrium (arrow) and the dilated left ventricle

pressure or mean PAWP. However, if left ventricular failure is present, the LVEDP may approach mean PAWP.

PULMONIC STENOSIS

Pulmonic stenosis (PS) is rare and most often congenital in etiology. PS may be valvular, supra- or sub-valvular. Echocardiography can be useful in identifying the location of the stenosis and quantifying the gradient. Right ventriculography to evaluate PS may be performed with a pigtail or Berman catheter. This often reveals the site of obstruction and, in valvular PS, may demonstrate the hallmark doming of the pulmonic valve, post-stenotic dilatation of the pulmonary artery, and hypertrophy of the right ventricle.

Catheter pullback from the pulmonary artery to the right ventricle quantifies and locates the obstruction. Quantification of the gradient may also be performed by a double lumen catheter or placement of catheters in the pulmonary artery and right ventricle simultaneously. A gradient across the pulmonic valve of greater than 50 mm Hg indicates severe PS and lesser than 25 mm Hg indicates mild PS. Diastolic pressures provide important diagnostic information to identify the location of the obstruction. Valvular PS reveals a systolic gradient and diastolic pressure difference between the pulmonary artery and the right ventricle (Figs 9A to C). If the obstruction is supra-valvular, the location of the gradient is in the pulmonary artery and thus the diastolic pressures are equal. Likewise, a sub-valvular or infundibular obstruction in the right ventricle would reveal a systolic pressure gradient from the obstruction but the same diastolic pressure of the right ventricle. Balloon valvuloplasty is the procedure of choice for PS.

PULMONIC REGURGITATION

Minimal pulmonic regurgitation (PR) is present in normal individuals. Significant PR may be due to processes involving the pulmonic valve or secondary to pulmonary hypertension. The hemodynamic interaction involving the right ventricle and pulmonary artery is similar to that of the left ventricle and aorta with AR. Significant PR results in a widened pulmonary arterial pulse pressure. A rapid rise in the right ventricular diastolic pressure is evidenced with an elevated RVEDP approaching pulmonary arterial diastolic pressure. However, other causes of elevated RVEDP, such as right ventricular diastolic dysfunction must also be considered.

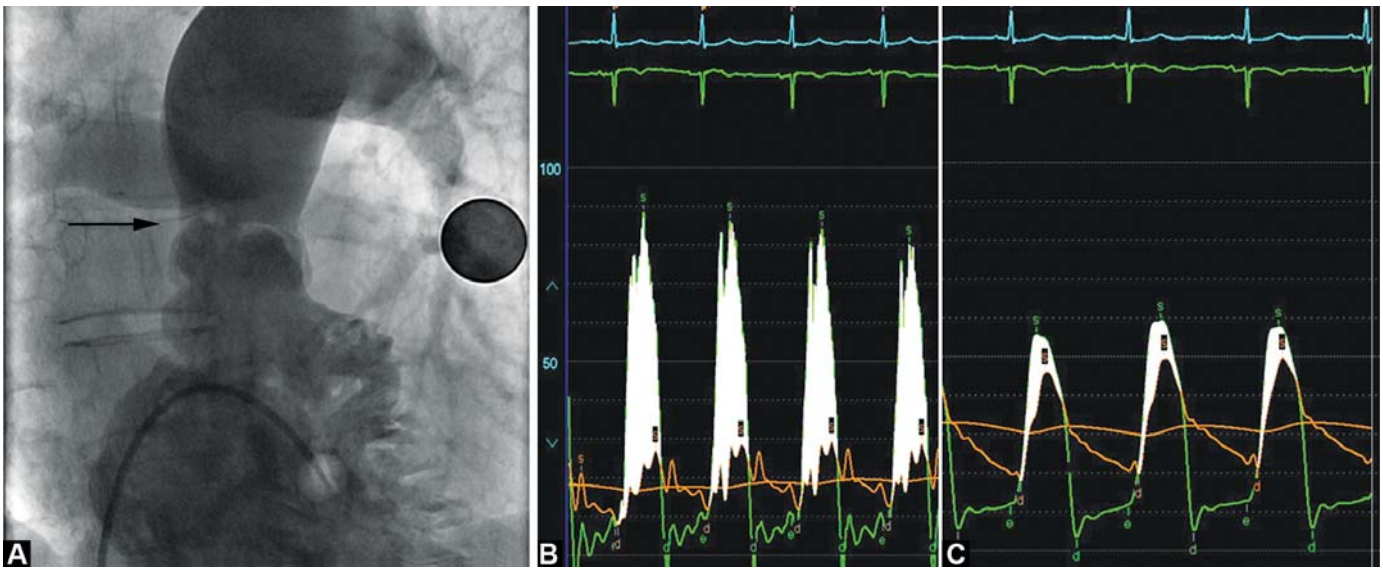
Pulmonary arteriography is of limited value as a catheter across the pulmonic valve causes PR itself. Therefore, echocardiography has greater utility in defining the severity and characteristics of the PR jet.

TRICUSPID STENOSIS

Tricuspid Stenosis (TS) is rare, yet when present, may be congenital in etiology or secondary to rheumatic or carcinoid heart disease. Doppler and 2D echocardiography provide useful information on valve gradient and area, as well as other coexisting valvular heart disease; a finding not uncommon with TS. Hemodynamic tracings reveal elevated right atrial pressure with blunted y-descent due to impairment of right ventricular filling. Simultaneous catheters in the right atrium and right ventricle demonstrate the presence of a discrete diastolic gradient between the right atrium and ventricle. A mean gradient greater than or equal to 5 mm Hg across the tricuspid valve suggest hemodynamically significant TS. Varying degrees of tricuspid regurgitation almost always accompanies TS due to leaflet restriction and incomplete coaptation.

TRICUSPID REGURGITATION

Trace tricuspid regurgitation (TR) is present in normal patients without consequence due to the complex closure of the tricuspid valve leaflets. Primary TR includes processes that directly affect the tricuspid valve apparatus, such as endocarditis, right ventricular myocardial infarction, rheumatic or carcinoid heart disease. Congenital conditions that produce TR include tricuspid valve atresia and Ebstein's anomaly: a



FIGURES 9A TO C: Pulmonic stenosis. (A) Right ventriculography revealing stenotic dilatation of the pulmonary artery. (B and C) Right ventricle and pulmonary artery pressure waveforms before and after balloon valvuloplasty of the stenotic pulmonic valve, respectively. The pulmonic valved peak to peak gradient is reduced from 65 mm Hg to 10 mm Hg after valvuloplasty

condition in which the septal and posterior leaflets are apically displaced. Functional TR may result from right ventricular and tricuspid annular dilatation from cardiomyopathy or pulmonary hypertension. With severe right ventricular dilatation or near complete failure of tricuspid valve leaflet coaptation, the right atrial pressure approaches right ventricular pressure.

Doppler and 2D-echocardiography provide information on jet severity and direction, hepatic vein systolic flow reversal, right ventricular size, valve morphology and the presence of pulmonary hypertension. A negative jet on right atrial angiography or contrast reflux across the tricuspid valve with right ventriculography provides a qualitative assessment of TR.

Hemodynamic tracing of right atrial pressure demonstrates a large "v" wave. However, it is important to note that the height of the "v" wave is also dependent on right atrial size and compliance. Thus, the absence of a tall "v" wave does not exclude the diagnosis of severe tricuspid regurgitation.

HEMODYNAMICS IN CARDIOMYOPATHY

Cardiomyopathy of any cause is usually associated with changes in cardiac hemodynamics, including elevation of end-diastolic pressures in the affected ventricle(s), reduced cardiac output, reduced mixed venous oxygen saturation and elevated atrial pressures. In more advanced cardiomyopathy, alternating higher and lower systolic pressures from one beat to the next can be seen in the affected ventricular tracing or in the aortic pressure wave. This is known as *pulsus alternans* and signifies ventricular dysfunction. In advanced heart failure, reduced aortic systolic pressures are also seen (cardiogenic shock). Hemodynamic tracings can help diagnose cardiomyopathy, assess severity, guide management and assess response to treatment. However, although some forms of cardiomyopathy may have distinct hemodynamic patters, hemodynamic assessment does not necessarily aid in establishing an etiology of the cardiomyopathy. However, some forms of cardiomyopathy may have distinct hemodynamic patterns.

HYPERTROPHIC OBSTRUCTIVE CARDIOMYOPATHY

Hemodynamics in left ventricular cavitary obstruction is amongst the most interesting in diagnostic catheterization. Variants of hypertrophic obstructive cardiomyopathy (HOCM) exist and not all patients with hypertrophic cardiomyopathy have an obstructive component. Likewise, not all patients with intracavitary obstruction have HOCM. For example, myocardial infarction or Takosubo's cardiomyopathy may alter myocardial contractility and generate an intracavitary gradient. When present, the intracavitary obstruction can be localized in the apex, mid-cavity or outflow tract of the left ventricle. Ventriculography provides a visual assessment of cavitary obliteration during systole.

Catheterization set-up for quantifying intracavitary obstruction is similar to that of aortic stenosis. Simultaneous catheters are placed in the aorta and left ventricular cavity. Pullback of a left ventricular end-hole catheter will identify the location as well as quantify the intracavitary gradient. Aortic and left ventricular systolic pressures will be equal in the area above cavitary obstruction. Pressure artifact may be produced if catheter entrapment occurs with the end-hole of the catheter embedded in the myocardium with transduction of intramyocardial pressure.

Intracavitary obstruction is dynamic and dependent on preload and myocardial contractility. Therefore, maneuvers or medications that alter these parameters may elicit an intracavitary gradient when not apparent at rest. An increase in the intracavitary gradient following a premature ventricular contraction (PVC) is seen in HOCM as a result of increased myocardial contractility, known as the Brokenbrough-Braunwald-Morrow sign.[16] In HOCM, the post-PVC beat is associated with a reduction in aortic systolic pressure and pulse pressure (Fig. 10). In comparison, the post-PVC beat in the case of fixed outflow obstruction, such as valvular aortic stenosis, is associated with an increase in the aortic pulse pressure. Furthermore, the upstroke of aortic pressure in systole is brisk in HOCM yet slow in severe aortic stenosis.

Further analysis of the aortic pressure tracing reveals a spike-and-dome contour during systole; generated by ventricular cavitary obstruction in mid-systole. The force generated by the hypertrophic myocardium results in a high velocity jet in the left ventricular outflow tract which generates a drag force on the anterior leaflet of the mitral valve, a phenomenon known as the Venturi effect. The result is a mid-systolic outflow tract obstruction that generates a spike-and-dome in the aortic systolic pressure tracing.

Alterations in preload affect the degree of intracavitary obstruction in HOCM. The Valsalva maneuver increases intrathoracic pressure and thus decreases venous return to the heart. The reduced preload causes further obstruction in the small cavity of the hypertrophied left ventricle and an increase in the intracavitary gradient.

Due to impaired myocardial compliance, left ventricular end-diastolic pressure (LVEDP) is elevated. The rate of diastolic pressure rise of the hypertrophied left ventricle is slow during the passive filling phase in early diastole due to diastolic dysfunction. Atrial systole then results in a prominent "a" wave and elevated LVEDP.[17]

A reduced or possibly abolished left ventricular outflow gradient is observed after percutaneous alcohol septal ablation therapy (Fig. 11). This procedure is a highly effective therapy that requires echocardiography and angiography to identify the septal artery perfusing the hypertrophied septal portion causing obstruction. Once identified, dehydrated alcohol is locally delivered in a controlled fashion through a balloon inflated in the target septal artery. Resolution of the outflow tract gradient is confirmed by the absence of postextrasystolic potentiation.[18,19]

RESTRICTIVE CARDIOMYOPATHY

Restrictive cardiomyopathy (RCM) results from infiltrative myocardial diseases such as amyloidosis, sarcoidosis, hemochromatosis as well as other rare conditions. Direct myocardial involvement of an infiltrative process results in reduced myocardial compliance and biventricular diastolic dysfunction, often with preserved systolic function. Secondary causes of diastolic dysfunction, such as coronary artery disease, must be ruled out prior to the making the diagnosis of restrictive cardiomyopathy.

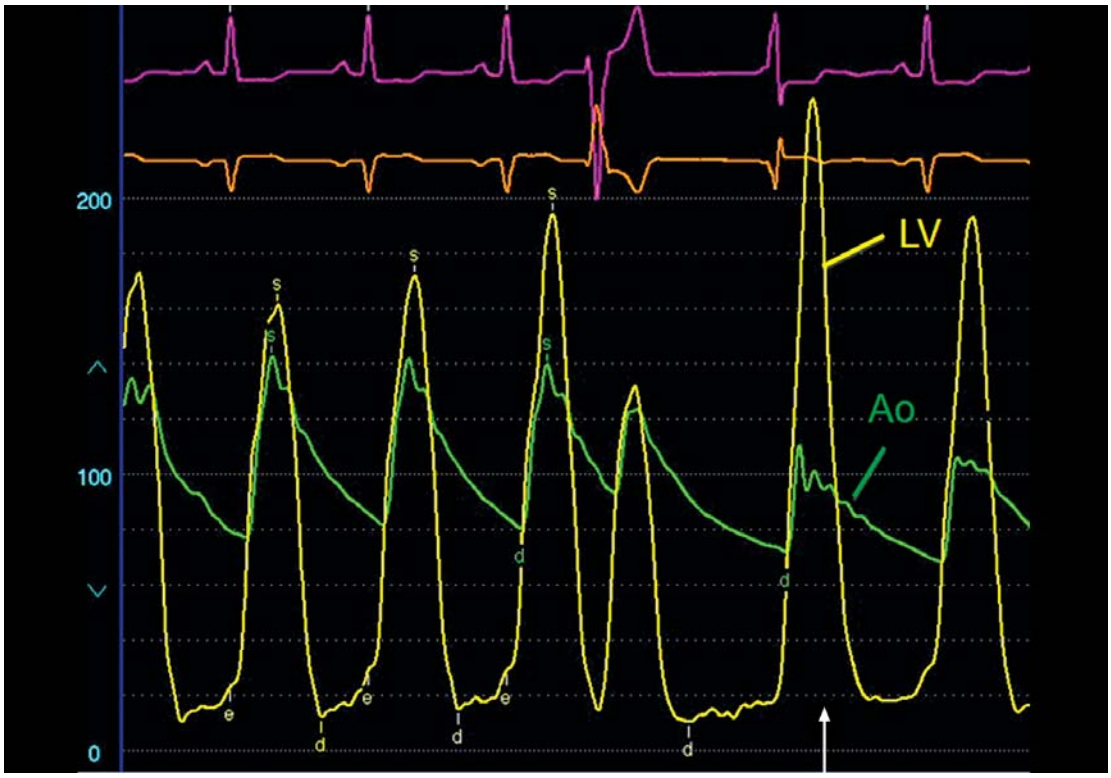


FIGURE 10: Post PVC potentiation in hypertrophic obstructive cardiomyopathy. An increase in the intra-cavitary gradient following a premature ventricular contraction (PVC) is seen in HOCM as a result of inceased myocardial contractility. The post PVC beat (arrow) is associated with a reduction in aortic systolic pressure and pulse pressure known as the Brokenbrough-Braunwald-Morrow sign.[16] (Abbreviations: LV: Left ventricle; Ao: Aorta)

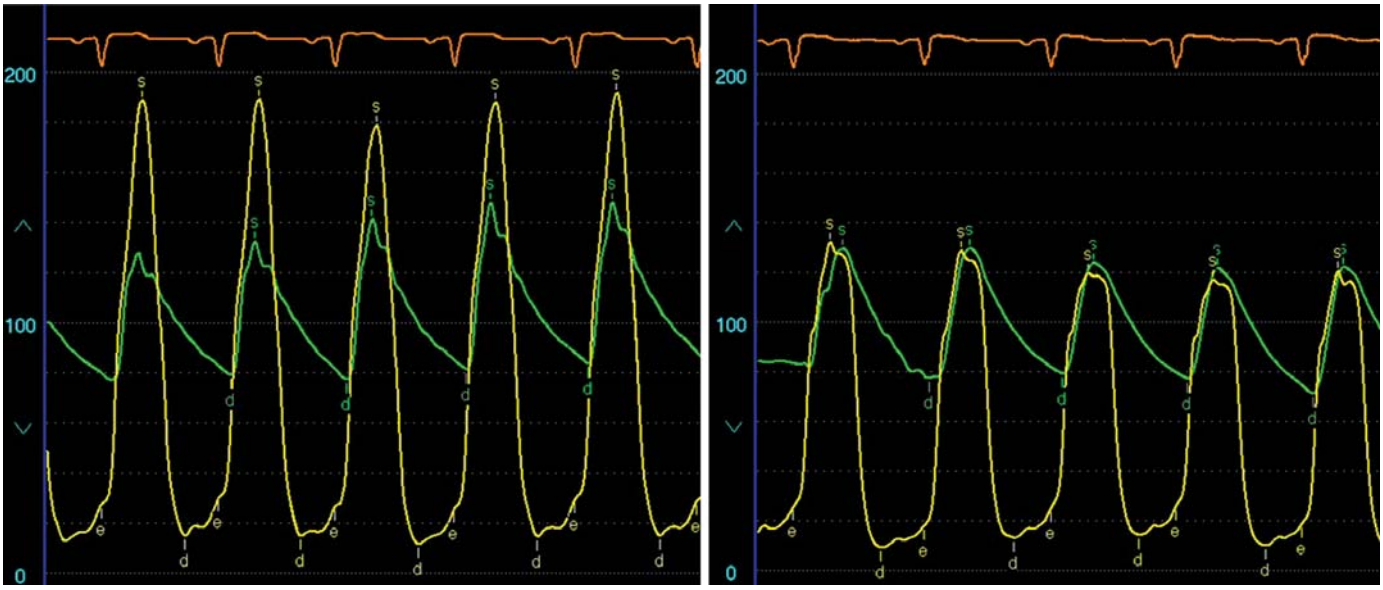


FIGURE 11: Left ventricle outflow gradient pre- and postalcohol septal ablation. Note resolution of the left ventricle-aortic gradient after alcohol administration in an isolated septal coronary artery

Evaluation of hemodynamics in RCM is performed by right heart catheterization to assess right atrial, right ventricular, pulmonary artery and PAWPs. Simultaneous catheters in the right and left ventricles allow analysis of the change in ventricular pressures during the respiratory cycle and help distinguish RCM from constrictive pericarditis; ventricular interdependence that occurs in constrictive pericarditis is not seen in RCM.

Reduced compliance and impedance to ventricular filling results in elevation of ventricular diastolic pressures for any given volume, accompanied by biatrial enlargement. Both right and left atrial pressures are elevated with prominent x- and y-



FIGURE 12: Dip-and-plateau configuration in restrictive or "square root sign" in restrictive cardiomyopathy and constrictive pericarditis. Note that the right ventricle end-diastolic pressure is >1/3 of the right ventricle systolic pressure

descents of the atrial pressure tracings. In the absence of valvular regurgitation, the prominent "v" wave reflects reduced atrial compliance.[20] When atrial fibrillation is present, only the "v" wave and y-descent are present due to the absence of atrial contraction.

Bi-ventricular diastolic pressures in RCM are elevated and often near equal within 5 mm Hg. However, since left ventricular involvement exceeds that of the right ventricle, LVEDP is greater than RVEDP. The ventricular diastolic tracing has a characteristic "dip-and-plateau" or "square-root sign" configuration due to abrupt cessation of ventricular filling followed by a restriction to further filling from impaired relaxation of the ventricle (Fig. 12). Pulmonary artery pressures in RCM are generally high and may exceed 55 mm Hg.

Restrictive cardiomyopathy (RCM) and constrictive pericarditis share many similar properties. However, distinguishing the two conditions is extremely important, as the treatment for the latter is surgical pericardiectomy. Several hemodynamic parameters to better distinguish these conditions have been evaluated (Table 4). Perhaps the most reliable is *respirophasic concordance* in RCM; left and right ventricular pressures follow normal physiologic properties with a decrease in systolic pressure during inspiration and increase in expiration. Respirophasic variation during the normal respiratory cycle occurs as intrathoracic pressures are transmitted to cardiac chambers, a phenomenon that is uncoupled in constrictive pericarditis.[21,22]

Imaging modalities, such as computed tomography and magnetic resonance, may aid in diagnosis if a thick pericardium is present to suggest constrictive pericarditis. The absence of a thickened pericardium, however, does not rule out constrictive pericarditis. If diagnostic uncertainty remains, an endomyocardial biopsy may aid in diagnosis.

HEMODYNAMICS IN PERICARDIAL DISEASE

The pericardium consists of visceral and parietal layers separated by a minimal amount of serous fluid, and extends to cover the heart and great vessels, excluding a portion of the left atrium and pulmonary veins. This anatomical relationship is important in understanding the physiology and hemodynamics of constrictive pericarditis.

Variations in intrathoracic pressures during the respiratory cycle are normally transmitted to the pericardial space and cardiac chambers. During inspiration, a decrease in the intrathoracic pressure is transmitted to the right heart, augmenting venous return. The increase in right ventricular diastolic pressure is transmitted across the intraventricular septum elevating left ventricular filling pressures. The gradient between the pulmonary veins and the left ventricle, the effective filling gradient, remains relatively constant throughout the respiratory cycle as the pericardial and pleural pressures follow intrathoracic pressure. The result is a decrease in left ventricular stroke volume with inspiration and reduced systemic systolic blood pressure.

CONSTRICTIVE PERICARDITIS

In constrictive pericarditis, a rigid thickened pericardium uncouples the pericardial and cardiac pressures from intrathoracic pressures; the variations in pressures with the respiratory cycle are no longer transmitted. Thus, producing an inspiratory increase in jugular venous pressure is also known as Kussmaul's sign. The right atrial pressure tracing reveals a steep y-descent due to rapid filling in early diastole. A prominent "a" wave during atrial contraction occurs due to elevated pressure, followed by a blunted x-descent secondary to impairment in ventricular filling; resulting in an "M" configuration of the right atrial pressure tracing.[21,22]

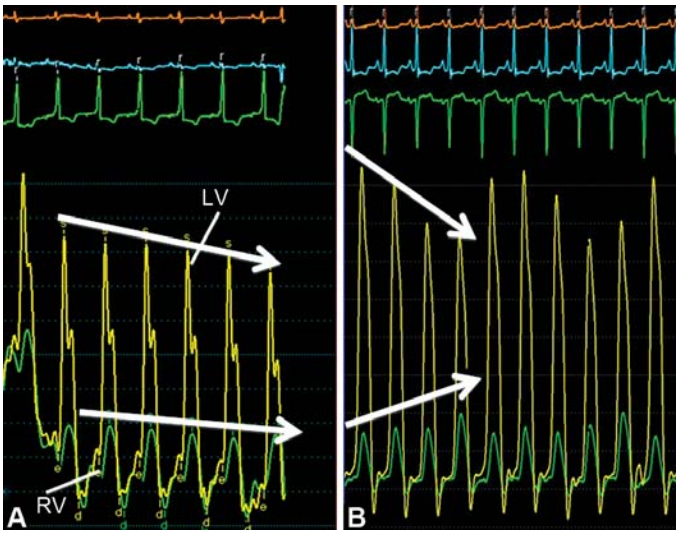
The rigid pericardium impairs the ventricular compliance and diastolic pressures are elevated and near equal. Intra-

TABLE 4

Sensitivity and specificity of hemodynamic parameters in constrictive pericarditis

	Constrictive pericarditis	*Restrictive cardiomyopathy*	*Sensitivity (%)*	*Specificity (%)*
LVEDP-RVEDP*	≤ 5 mm Hg	> 5 mm Hg	60	38
Pulmonary artery systolic pressure	< 55 mm Hg	> 55 mm Hg	93	24
Right ventricular systolic and EDP	> 1/3	≤ 1/3	93	38
Respiratory variation in mean right atrial pressure	Absent	Present	93	48
Left ventricular diastolic rapid filling wave	> 7 mm Hg	≤ 7 mm Hg	93	57
Ventricular interdependence	Present	Absent	100	95

(Abbreviations: *LV: Left ventricle; RV: Right ventricle; EDP: End-diastolic pressure). (*Source:* Hurrell DG, Nishimura RA, Higano ST, et al. Value of dynamic respiratory changes in left and right ventricular pressures for the diagnosis of constrictive pericarditis. Circulation. 1996; 93:2007-13)



FIGURES 13A AND B: Respirophasic waveforms in (A) Restrictive cardiomyopathy with ventricular concordance of right and left ventricle pressures with a parallel change in right ventricle (RV) and left ventricle (LV) pressures (arrows). (B) Constrictive pericarditis demonstrating ventricular discordance of the right and left ventricle pressures

thoracic pressures are transmitted to the pulmonary veins and a portion of the left atrium not encased by the pericardium. However, the pressure of the pericardial bound left ventricle does not vary with intrathoracic pressure as a result of the dissociation from pericardial pressures in constrictive pericarditis. Thus, the effective filling gradient across the mitral valve is decreased in inspiration. With the reduced left ventricular volume and elevated right ventricular diastolic pressure, the interventricular septum shifts to the left. V*entricular interdependence* or *discordance* during the respirophasic cycle is demonstrated by simultaneous catheters in the right and left ventricles (Figs 13A and B). An inspiratory decrease in left ventricular systolic pressure results in an increase in the right ventricular systolic pressure and the reverse occurs during expiration. If atrial fibrillation is present, evaluation with temporary ventricular pacing avoids the hemodynamic variation produced by an irregular rhythm.

Similar to restrictive cardiomyopathy, a "dip-and-plateau" configuration of the ventricular diastolic pressures occurs due to rapid early diastolic filling followed by an abrupt cessation to flow from impaired compliance (Fig. 12). The height of the early diastolic rapid filling wave is usually greater than 7 mm Hg in constrictive pericarditis. Table 4 lists hemodynamic criteria that exist to aid in the diagnosis of constrictive pericarditis with varying sensitivity and specificity.[23]

CARDIAC TAMPONADE

Between the visceral and parietal layers of the pericardium there is the pericardial space that normally contains less than 35 ml of plasma ultrafiltrate, or pericardial fluid. Normal pericardial pressure is between "5 to 5 mm Hg.[19] The pathologic accumulation of excess fluid in the pericardial space increases pericardial pressure and may comprise cardiac function if the pericardial pressure exceeds those of the cardiac chambers. The pericardium stretches to accommodate a higher volume when fluid accumulates chronically. However, rapid accumulation of fluid into the fixed pericardial space quickly compromises cardiac function.

The hemodynamics of cardiac tamponade shares similarities to constrictive pericarditis, with an elevation and near equalization of diastolic pressures. The fluid-filled pericardial space does not transmit intrathoracic pressures to the cardiac chambers. The dissociation of intrathoracic and intracardial pressures leads to ventricular discordance during the respirophasic cycle. The extrapericardial pulmonary veins follow intrathoracic pressure and the pulmonary venous pressure decreases in inspiration. This decreases the left sided effective filling gradient and left ventricular stroke volume. Thus pulsus paradoxsus, or a greater than normal (> 10 mm Hg) decrease in aortic blood pressure with inspiration occurs.[24]

Right atrial pressure is elevated, however, unlike constrictive pericarditis, a blunted y-descent is present on the right atrial pressure waveform in cardiac tamponade. The effect of the increased intrapericardial pressure on impairment atrial emptying is most present when the ventricle is filled in diastole, resulting in a blunted y-descent. The "a" wave is augmented due to elevated pressure in the right ventricle during atrial contraction. The x-descent following the "a" wave is sharp as the atrium relaxes from a higher pressure peak and the volume of the right ventricle decreases in systole, such that the effects of elevated intrapericardial pressure are less pronounced on the atrium.[24]

Unlike constrictive pericarditis, the dip-and-plateau configuration of the diastolic ventricular pressure tracing is not seen in cardiac tamponade. This is due to the lack of sudden restriction to filling.

CORONARY HEMODYNAMICS

Coronary angiography provides information on luminal contrast opacification and visual estimation of luminal diameter stenosis often dictates whether coronary intervention is performed. However, limitations of coronary angiography exist and are important to recognize prior to making clinical decisions regarding coronary intervention. Coronary angiography provides a 2-dimensional image of a 3-dimensional vascular lumen. Based on the angiographic views and plaque characteristics, such as eccentricity, angiography may not capture the area of maximal stenosis. Furthermore, assessment of certain anatomical locations, such as side branch ostial lesions, are often challenging with angiography due to vessel overlap and foreshortening with fluoroscopy. Assessing left main coronary lesions with standard angiography can be especially challenging. Indeed we extrapolate physiological reduction on blood supply based on anatomic measurement from coronary angiography. Knowledge of coronary physiology, using techniques such as fractional flow reserve (FFR) and coronary flow reserve (CFR), improves diagnostic accuracy of coronary lesions producing ischemia, particularly when angiography is limited in its ability to do.

FRACTIONAL FLOW RESERVE

FFR is a physiologic coronary study performed percutaneously at the time of coronary angiography to detect ischemia-producing stenoses. Ohm's law describes flow is equal to the change in pressure divided by resistance; the length of coronary stenosis is inversely proportional to coronary blood flow. Therefore, a lengthy intermediate coronary lesion of intermediate diameter stenosis may compromise coronary blood flow

more than a short high-grade stenosis, a factor that would be difficult to assess using visual information alone. FFR is a comparison of pressure measured distal to the stenosis in question to that proximal to the stenosis. The procedure is performed using a pressure sensor guidewire that is calibrated and then advanced through a guide catheter across the coronary lesion in the target artery. FFR is calculated as the ratio of mean coronary artery pressure distal to the coronary lesion of interest at maximal hyperemia to the mean aortic pressure and is derived as such:[25-29]

$$\text{FFR} = \frac{1 - \text{Mean translesional pressure gradient}}{\text{Mean aortic pressure} - \text{Mean right atrial pressure}}$$

$$= \frac{\text{Mean pressure distal coronary pressure} - \text{Mean right atrial pressure}}{\text{Mean aortic pressure} - \text{Mean right atrial pressure}}$$

$$= \frac{\text{Mean pressure distal to coronary stenosis (Pd)}}{\text{Mean aortic pressure (Pa)}}$$

In order to assess the physiologic significance of coronary stenosis, maximal hyperemia with a vasodilator is required. If vasodilation is submaximal, stenosis severity may be underestimated. A vasodilator, such as adenosine, is administered intravenously 140 and 180 μg/kg/min (each dose administered for two minutes). If intracoronary adenosine is used to induce hyperemia then 15–40 μg is delivered to the left coronary system and 10–30 μg to the right coronary artery. Prior to the use of adenosine, the patient should be screened to ensure no contraindication to the use of adenosine exists such as reactive airway disease.

A FFR of lesser than 0.75 correlates with ischemia when compared to non-invasive stress testing with a sensitivity of 88% and specificity of 100%.[27] Interestingly, the largest study to date using FFR to guide percutaneous intervention in patients with multi-vessel disease, found that using FFR lesser than 0.8 to guide decision making reduced the primary endpoint of death, nonfatal myocardial infarction and repeat revascularization.[25] FFR has great utility for predicting ischemia where angiography is limited in doing so, particularly for intermediate-grade, left main, and ostial side branch stenosis. Figure 14 demonstrates hemodynamic assessment of coronary pressure during maximal hyperemia using FFR.

CORONARY FLOW RESERVE

Similar to FFR, coronary flow reserve (CFR) is a physiologic coronary study performed percutaneously at the time of coronary angiography for the detection of ischemia–producing stenoses. The technique of CFR involves use of a doppler tipped guidewire that transmits ultrasound doppler waves from which coronary flow can be assessed. CFR is the ratio of coronary flow distal to a stenosis at maximal hyperemia to basal coronary blood flow measured in a coronary artery without stenosis. A CFR of lesser than 2 identifies an ischemia-producing stenosis (Fig. 15).

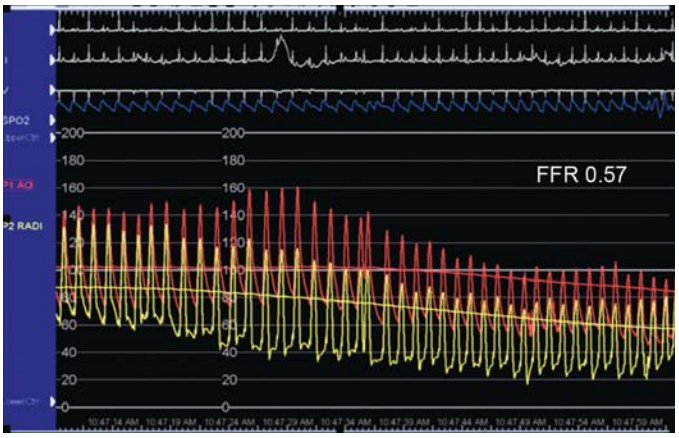


FIGURE 14: Fractional flow reserve. Aortic pressure (red) and coronary artery pressure (yellow) during adenosine infusion. Fractional flow reserve of mid left anterior descending coronary artery 70% angiographic luminal stenosis reveals positie physiological significance with value of 0.57

$$\text{CFR} = \frac{\text{Flow distal to stenosis}}{\text{Basal coronary flow}}$$

Alternatively, CFR may be derived from a coronary thermodilution curve with a pressor sensor wire with proximal and distal thermistors such that a thermodilution curve during the injection of saline is generated. The mean transit time is measured from the thermodilution curve. The ratio of the mean transit time at rest divided by the mean transit time at hyperemia reflects CFR.

Unlike FFR, CFR is influenced by conditions that affect vascular resistance such as microvascular disease and myocardial hypertrophy. Therefore, it has utility in the assessment of microvascular disease, and is an important research tool. Coronary flow is also influenced by hemodynamic variations

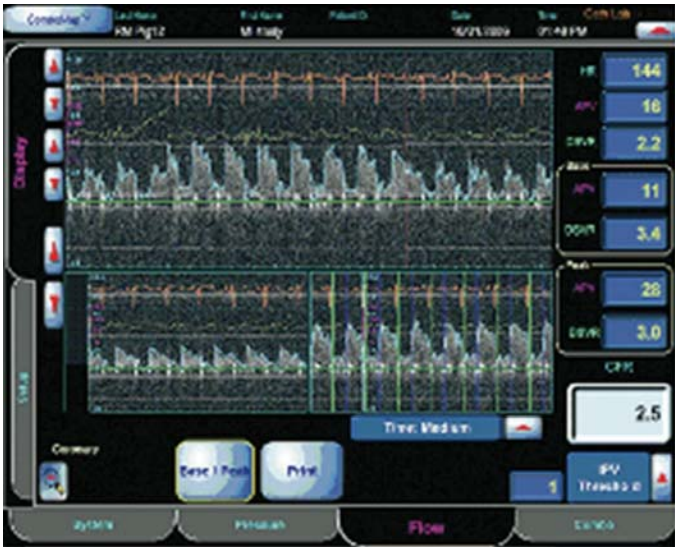


FIGURE 15: Coronary flow reserve. Top panel displays real-time doppler of coronary flow of the left anterior descending coronary artery. The bottom left panel demonstrates doppler at baseline and the bottom right panel is peak coronary doppler flow at maximal hyperemia during adenosine administration. The calculated coronary flow reserve is 2.5, with no significant physiologic impairment to coronary flow. (*Source:* Boyle, et al. Am J Cardiol. 2008;102:980-7, with permission)

such as tachycardia. Since CFR reflects both epicardial and microvascular flow, one must be aware of limitations with this technique in assessing the significance of coronary stenosis.

INDEX OF MICROCIRCULATORY RESISTANCE

Assessment of microcirculation is best performed by measuring the Index of microvascular resistance (IMR). This may be important in symptomatic patients with risk factors for epicardial coronary artery disease and yet no angiographic evidence of significant epicardial disease. Similar to FFR, IMR is performed by measuring the pressure distal to the coronary stenosis with a pressure sensor wire. A coronary thermodilution curve is generated using a pressor sensory wire with proximal and distal thermistor. The mean transit time is measured from the coronary thermodilution curve and the inverse of mean transit time is a surrogate of absolute flow. The product of the pressure distal to a coronary stenosis and the mean transit time at maximal hyperemia defines IMR:

$$\text{Resistance} = \frac{\Delta \text{ Pressure and Flow} \approx 1}{\text{Flow mean transit time}}$$

$$\text{IMR} = \frac{\text{Mean pressure distal to stenosis} - \text{Right atrial pressure}}{1/\text{Mean transit time}}$$

Using the assumption that right atrial pressure is neglible:

$$\text{IMR (mm Hg•s)} = \text{Mean transit time} \times \text{Pressure distal to stenosis}$$

Index of microcirculatory resistance (IMR) is measured at maximal hyperemia using a coronary vasodilator and reflects the resistance of the microcirculation, unaffected by the epicardial stenosis. In the presence of a stenosis or hemodynamic variations, both the pressure distal to the stenosis as well as the absolute coronary flow decrease, thus, the ratio of IMR will remain relatively unaffected.[30-32]

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Chapter 26

Cardiac Biopsy

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Chapter Outline

- History and Devices
- Techniques
- Safety and Complications
- Analysis of EMB Tissue
  - — Light Microscopy and Stains
  - — Cardiotropic Virus Detection
- Indications
- Disease States
  - — EMB in Cardiomyopathy
  - — EMB in Special Cardiac Disease States
- Cardiac Transplantation
- Guidelines

INTRODUCTION

The development and refinement of endomyocardial biopsy (EMB) has significantly advanced our understanding of many cardiac diseases which once confounded even the most astute clinicians. In fact, for several conditions, EMB is the only modality that provides a definitive diagnosis and, therefore, is the "gold standard" upon which other tests should be compared. The EMB has also helped to change the landscape of certain disease states. For example, EMB is partly responsible, in conjunction with the advent of immunosuppressive medications, for the dramatic reduction in mortality resulting from rejection in post heart transplant patients. Despite these benefits, there have been few, large, randomized controlled trials supporting the use of EMB in the clinical arena. In the face of our ever increasing knowledge about disease states, the clinician is faced not only with the onerous task of keeping pace but also making decisions about which diagnostic tools to employ. This chapter will attempt to highlight many of the salient features of EMB, including techniques, tissue processing as well as the characteristic pathological features for the most common diagnoses for which EMB is performed.

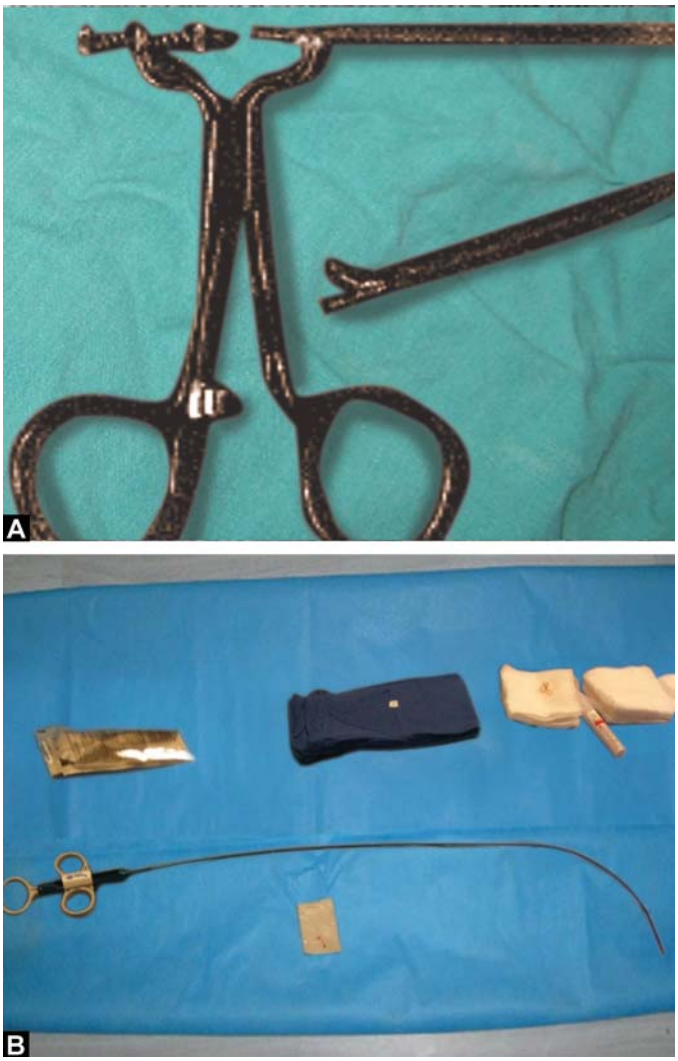
HISTORY AND DEVICES

The first transvenous EMB device was developed in Japan in 1962 and was called the Konno-Sakakibara bioptome (catheter-based biopsy system).[1] This device consisted of a 100 cm catheter shaft with two sharpened cusps at its tip. The catheter was introduced into the body by means of a cutdown of the saphenous or basilic vein (or the femoral or brachial artery) due to the large size of the catheter tip. The catheter was then advanced to the desired ventricle under fluoroscopic guidance and applied to the endocardial surface with the jaws closed. The catheter was then withdrawn a short distance, jaws opened, re-advanced into contact with the endocardium, jaws re-closed, and withdrawn. With the exception of the cutdown, a similar technique is employed today. In 1972, the Konno-Sakakibara bioptome was redesigned to work specifically for right ventricular biopsy by way of the right internal jugular vein and was called the Caves-Schultz-Stanford bioptome (Fig. 1A).[2,3] The device consists of a somewhat flexible coil shaft made of stainless steel and coated by clear plastic tubing. The tip of the catheter has two hemispheric cutting jaws with a combined diameter of 3.0 mm (9 French). One jaw is opened and closed via stainless steel wire running through the center of the bioptome shaft, while the other jaw remains stationary. The control wire is attached to a ratcheting surgical mosquito clamp by a pair of spring-loaded adjustable nuts that allow the operator to set the amount of force that is applied during opening and closing of the surgical clamp.[4]

Current bioptomes come in several lengths depending upon whether a right internal jugular vein approach (short bioptome) or a femoral vein approach (long bioptome) is employed (Fig. 1B). The catheters come in multiple diameters (French) in order to fit inside standard sheaths. At the end of the catheter is a set of jaws that have been specially designed to allow precise cutting of endomyocardial tissue with preservation of myocardial architecture for pathological examination.

TECHNIQUES

A transvenous approach is taken for right ventricular EMB. Either the femoral vein or the internal jugular vein (either right or left) is cannulated with an introducer sheath via the modified Seldinger technique (Fig. 2).[5] Electrocardiographic rhythm, blood pressure and pulse oximetry should be monitored in all patients undergoing EMB. Ultrasound guidance can facilitate identification of the vein of interest for purposes of cannulation and has been shown to reduce procedure time and complications.[6,7] In addition, in patients with normal or low right atrial pressure, elevating the patient's legs, using the Trendelenburg



FIGURES 1A AND B: (A) Stanford (Caves-Schulz) bioptome; (B) Current generation short, disposable bioptome for use through the internal jugular vein (*Source:* Grossman's cardiac catheterization, angiography and intervention by LWW,2000)

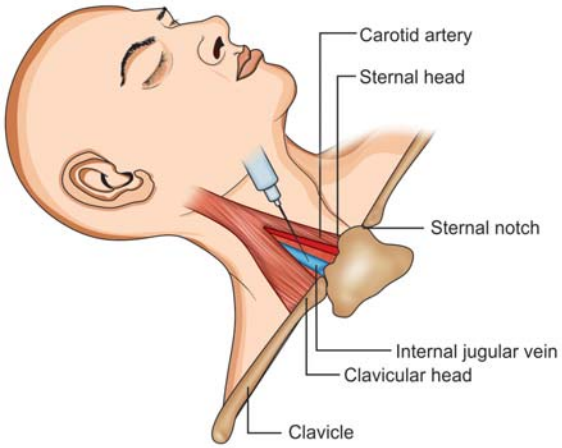
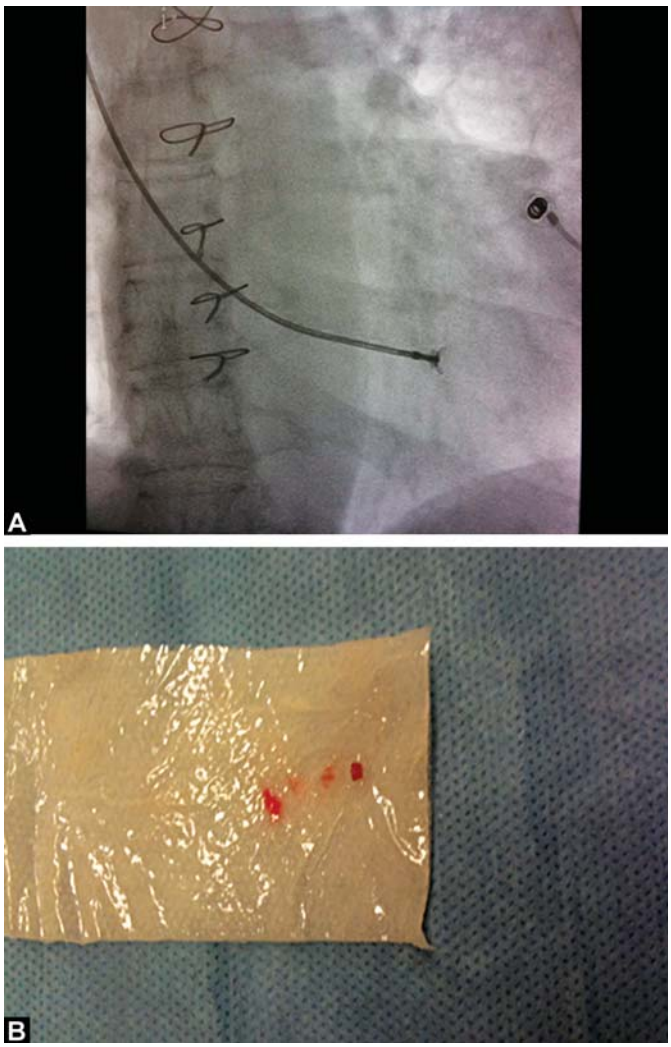


FIGURE 2: Regional anatomy for right internal jugular vein puncture. With the patient's head rotated to the left, the sternal notch, clavicle and the sternal and clavicular heads of the sternocleidomastoid muscle are identified. A skin nick is made between the two heads of the muscle, two fingerbreadths above the top of the clavicle, and the needle is inserted at an angle of 30–40° from vertical, and 20–30° right of sagittal. This approach leads to reliable puncture of the internal jugular vein and aims the needle away from the more medially located carotid artery (*Source:* Grossman's cardiac catheterization, angiography and intervention by LWW,2000)

(head-down) position, or having the patient perform a Valsalva maneuver all elevate central venous pressure (CVP) which distends the internal jugular vein and allows for easier cannulation. Once the internal jugular vein has been cannulated, a 40 cm J guidewire is advanced into the right atrium. Then a sheath (7–9 French) with a side-arm and back-bleed valve (Cordis Corporation) is advanced over the guidewire. The CVP is then recorded via the side arm before the biopsy.

Next, the bioptome is inserted into the sheath with the tip pointed toward the lateral wall of the right atrium and advanced to the right atrium under either echocardiographic or fluoroscopic guidance. At the level of the mid-right atrium, the bioptome is rotated anteriorly in a clockwise direction approximately 180 degrees and is advanced through the tricuspid valve apparatus toward the right ventricle. The bioptome is then advanced to the interventricular septum. The bioptome position in the right ventricle should be confirmed with fluoroscopy (30 degree right anterior oblique and 60 degree left anterior oblique views). The bioptome should appear to lie across the spine and below the upper margin of the left hemidiaphragm (Fig. 3A). The goal of this step is to take proper precaution to



FIGURES 3A AND B: (A) Fluoroscopic image of bioptome in the right anterior oblique projection demonstrating open jaws just prior to right ventricular biopsy; (B) Right ventricular endomyocardial biopsy tissue specimens displayed on moistened filter paper

avoid the thin, right ventricular free wall. Next, the jaws are opened and the bioptome is advanced to the right ventricular muscular septum. Proper localization of the bioptome is evidenced by lack of further advancement, the occurrence of premature ventricular contractions, and the transmission of ventricular impulses to the operator's hand. The jaws are then closed and allowed a brief delay to sever the tissue. The bioptome and enclosed sample are then slowly retracted all the way out of the sheath. Three to five separate biopsies should usually be obtained to account for sampling error. The samples are then placed in specific preservatives depending upon the diagnosis suspected. If a balloon-tipped pulmonary artery catheter was used to perform a right heart catheterization, such as during EMB for transplant rejection, it is our practice to advance the balloon-tipped pulmonary artery catheter to the right atrium for several minutes after completion of the EMB to ensure stable right atrial pressures and to screen for possible myocardial perforation which could lead to tamponade. Alternatively, repeat CVP measurement is obtained at conclusion of the biopsy through the side arm.

Left ventricular biopsy remains limited to individual cases in which the suspected disease is limited to the left ventricle.[8] The femoral artery is often used as the percutaneous access site for left ventricular biopsy.[9] In this approach, a preformed sheath is employed to maintain arterial patency. In addition, to avoid embolic events, the sheath must be maintained under constant pressurized infusion. Given the potential for serious consequences of left-sided embolization, aspirin or other antiplatelet agents are generally combined with heparin for left ventricular biopsy.

SAFETY AND COMPLICATIONS

Despite the invasive nature of the procedure and potential for severe complications, EMB is now considered a very safe technique. The EMB complications can be categorized as to those that occur in the acute setting and those that occur after a delayed period of time. Immediate periprocedural risks include perforation with pericardial tamponade, pneumothorax, pulmonary embolization, ventricular and supraventricular arrhythmias, heart block, recurrent laryngeal nerve paresis, damage to the tricuspid valve and creation of an arteriovenous fistula within the heart. Like any invasive procedure, degree of risk is heavily dependent upon operator's experience. In addition, baseline clinical features of the patient, access site and type of bioptome are also likely important. Delayed complications include access site bleeding, damage to the tricuspid valve, pericardial tamponade and deep vein thrombosis.

The precise risk of EMB is not known as the data are derived from several single-center experiences and registries. In one series of greater than 4,000 biopsies performed in transplantation and cardiomyopathy patients, complication rates were reported in less than 1%.[10] In addition, a worldwide survey of more than 6,000 cases of EMB reported a 1.17% complication rate with 28 perforations (0.42%) and 2 deaths (0.03%).[11]

Finally, a study by Deckers et al. from John's Hopkins hospital reported on complication rates in 546 consecutive biopsies in adults with cardiomyopathy.[12] There were 33 complications (6%) with 15 (2.7%) considered minor without sequelae and 18 (3.3%) serious with 2 (0.4%) deaths.

One of the most significant complications with EMB is cardiac perforation leading to tamponade. Several clinical features that have been associated with increased risk of perforation include: increased right ventricular systolic pressures, bleeding diathesis, recent receipt of heparin and right ventricular enlargement. Cardiac perforation should be suspected if the patient complains of chest pain with a biopsy pass, unexpected bradycardia or hypotension is encountered, or if the EMB samples float in 10% formalin (suggesting the presence of cardiac fat). In these circumstances, right atrial pressure, fluoroscopic appearance of the heart border and possibly bedside echocardiography should be used to monitor for hemopericardium. If confirmed, urgent pericardiocentesis should be performed. In most cases, in a patient with normal coagulation parameters, catheter drainage is sufficient to stabilize the patient. However, on occasion, it may be necessary to consult thoracic surgeons to evacuate the pericardial space. Of note, cardiac tamponade rarely occurs in patients after heart transplant or cardiac surgery as there is a layer of adhesive pericardium overlying the right ventricular free wall, although reported cases have occurred secondary to the pericardium being left open anteriorly.

Several additional approaches can be used to avoid EMB complications. In order to avoid pneumothoraces, a relatively high internal jugular vein approach should be employed which avoids the immediate supraclavicular location. Patients with pre-existing left bundle branch block can develop complete heart block when the catheter is placed into the right ventricle and pushes up against the interventricular septum. In this case, the catheter/bioptome should be withdrawn and, in most cases, the heart block will abate. However, in some patients, the heart block may persist and become permanent requiring temporary right ventricular pacing with eventual placement of a permanent pacemaker. Lidocaine injection into the jugular venous and carotid sheath can result in Horner's syndrome, vocal paresis and, occasionally, weakness of the diaphragm. These symptoms are usually transient and last only as long as it takes for the lidocaine to wear off.

ANALYSIS OF EMB TISSUE

The utility of EMB for diagnosis of suspected cardiac conditions is heavily dependent upon proper sampling technique, careful handling of the EMB sample and initial preparation of the sample in appropriate fixatives. In general, an attempt should be made to obtain samples from greater than 1 region of the right ventricular septum. In addition, between 5 and 10 samples of 1–2 mm^3 in size should be obtained to minimize sampling errors. Biopsy samples should be removed gently from the jaws of the bioptome with a fine needle (not forceps) and placed on moistened filter paper (Fig. 3B).[13,14] Next, the samples should be transferred to a container with 10% neutral buffered formalin for light microscopy or 4% glutaraldehyde for transmission electron microscopy.[14] Contraction band artifacts may occur due to the specimen being torn away from the beating heart resulting in myocyte hypercontraction. These artifacts are accentuated with cold fixatives, but can be minimized by using fixatives at room temperature.[15] The EMB samples can also be snap frozen in OCT embedding medium and stored at –80°F for molecular studies, immunohistochemistry or immunofluorescence.

In general, flash freezing is appropriate for culture, polymerase chain reaction (PCR) or reverse transcriptase PCR (rtPCR) to identify viruses, but is not well-suited for standard histological preparations due to the development of ice crystal artifacts.

Diagnostic yield of EMB is also largely dependent upon sampling error. Many diseases with cardiac involvement are heterogeneously distributed in the heart. For example, in one study by Chow et al., right ventricular EMB was performed on 14 autopsy/post-transplant hearts with confirmed myocarditis and found that 5 biopsy samples had a combined sensitivity of only 43–57%. Sensitivity increased to 80% when combining all 17 samples, a number that is not practical for routine clinical use.[16]

LIGHT MICROSCOPY AND STAINS

Once the EMB samples have been fixed and transported from the catheterization laboratory to the pathology laboratory, they are then embedded in paraffin and serial 4 μm thick sections are cut and sequentially numbered. The specimens are then stained with hematoxylin and eosin (H&E) as well as Movat or elastic trichrome stain to visualize collagen and elastic tissue. It is a common practice for many laboratories to routinely stain one slide for iron on men and all postmenopausal women to screen for hemochromatosis. In addition, Congo red staining may be performed to screen for amyloidosis.

CARDIOTROPIC VIRUS DETECTION

The EMB samples can also be screened for cardiotropic viruses. Identification of viral genomes from EMB samples has recently become more feasible due to the development of rapid, quantitative (qPCR) and qualitative (nested PCR) molecular techniques. Several studies have reported a high incidence of viral genome detection in the myocardium of patients with suspected myocarditis and dilated cardiomyopathy (DCM).[17,18] The most common viruses detected in the myocardium include: enteroviruses, adenoviruses, parvovirus B19, cytomegalovirus (CMV), influenza, respiratory syncytial virus, herpes simplex virus, Epstein-Barr virus, human herpes 6, HIV and hepatitis C. Given the exquisitely sensitive nature of PCR, samples must be carefully handled to avoid possible contamination and degradation. Pathogen-free biopsy devices and storage vials should be employed. In addition, new fixatives, such as RNAlater (Ambion, Austin, Texas), allow for PCR and rtPCR to be performed on samples transported on dry ice at room temperature without losing sensitivity compared to frozen tissue. Despite the ability to detect viruses at very low copy numbers, the true sensitivity of these techniques with EMB samples is not known. As a result, a positive PCR result is diagnostic, whereas a negative PCR result does not rule out the presence of virus. At this time, however, given the heterogeneity in methods and interpretation of results across centers, routine screening of EMB samples for viruses is not recommended outside of established centers with experience in viral genome analysis.

INDICATIONS

Reports in the literature regarding the utility of EMB for the diagnosis of cardiovascular conditions are limited to case series and cohorts. As a result, one of the most difficult decisions facing the clinician is determining under what circumstances performing an EMB would lead to a clinically meaningful diagnosis or change in therapy while taking into account the risk of harm from the procedure itself. Recognizing the need for a comprehensive review of the literature and a unified set of recommendations, the American Heart Association (AHA), the American College of Cardiology Foundation (ACCF) and the European Society of Cardiology (ESC) convened a multidisciplinary group of experts, and recently released a joint scientific statement.[19] In this statement, the authors review 14 clinical case scenarios where EMB might be considered and provide Class I–III recommendations along with levels of evidence (Levels A–C) to support these recommendations (Table 1). The two Class I recommendations (conditions for which there is evidence or there is general agreement that a given procedure is beneficial, useful and effective) as well as the one Class III recommendation (conditions for which there is evidence and/or general agreement that a procedure/treatment is not useful/effective and in some cases may be harmful) are reviewed here. For further details regarding the other 11 clinical scenarios, the reader is referred to the article by Cooper et al.[19]

The two clinical scenarios that received a Class I indication for EMB were:

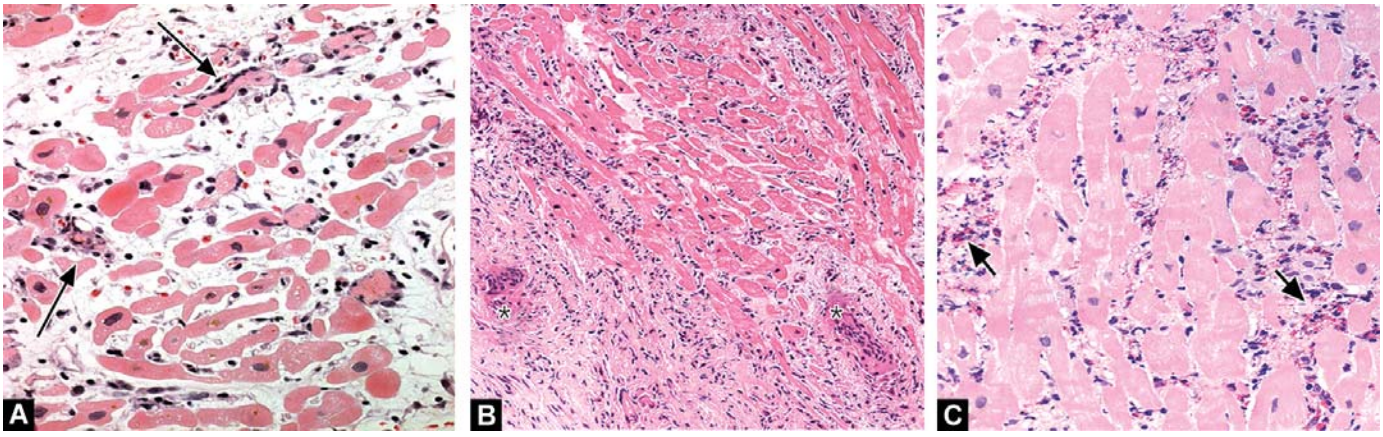
- In the setting of unexplained, new-onset heart failure of less than 2 weeks' duration associated with a normal-sized or dilated left ventricle in addition to hemodynamic compromise.
- In the setting of unexplained, new-onset heart failure of 2 weeks to 3 months duration associated with a dilated left ventricle and new ventricular arrhythmias, Mobitz type II second- or third-degree atrioventricular (AV) heart block, or failure to respond to usual care within 1–2 weeks.

The EMB should be performed in these two settings to identify three clinical entities: (1) lymphocytic myocarditis; (2) giant cell myocarditis (GCM) or (3) necrotizing eosinophilic myocarditis. Identification of these clinical entities is important both for prognostic as well as therapeutic purposes. Lymphocytic myocarditis is the most common type of myocarditis reported in the United States and Western Europe.[20] Adults and children presenting with severe left ventricular failure within two weeks of a distinct viral illness and have typical lymphocytic myocarditis on EMB have an excellent prognosis (Fig. 4A).[21,22] The left ventricular ejection fraction (EF) is often markedly depressed; however, the left ventricular volumes are generally normal.[23] Despite the benign long-term outcome in the acute setting, lymphocytic myocarditis often presents with cardiogenic shock requiring intravenous inotropic agents or mechanical assistance for circulatory support. Since lymphocytic myocarditis is still a relatively uncommon clinical entity, it is difficult to ascertain whether treatment with corticosteroids or intravenous immunoglobulin provides any significant clinical benefit. Necrotizing eosinophilic myocarditis is a rare condition that is characterized by an acute onset and rapid progression to hemodynamic compromise.[24] Histologically, there is a diffuse inflammatory infiltrate with predominant eosinophils associated with extensive myocyte necrosis (Fig. 4B). Therapy with a combination of immunosuppressive agents as well as biventricular assist device support has been associated with improved outcomes.[25]

TABLE 1

The role of endomyocardial biopsy in 14 clinical scenarios

Scenatio number	*Clinical scenario*	*Class of recommendation (I, IIa, IIb, III)*	*Level of evidence (A, B, C)*
1.	New-onset heart failure of < 2 weeks' duration associated with a normal-sized or dilated left ventricle and hemodynamic compromise	I	B
2.	New-onset heart failure of 2 weeks' to 3 months' duration associated with a dilated left ventricle and new ventricular arrhythmias, second- or third-degree heart block, or failure to respond to usual care within 1–2 weeks	I	B
3.	Heart failure of > 3 months' duration associated with a dilated left ventricle and new ventricular arrhythmias, second- or third-degree heart block, or failure to respond to usual care within 1–2 weeks	IIa	C
4.	Heart failure associated with a DCM of any duration associated with suspected allergic reaction and/or eosinophilia	IIa	C
5.	Heart failure associated with suspected anthracycline cardiomyopathy	IIa	C
6.	Heart failure associated with unexplained restrictive cardiomyopathy	IIa	C
7.	Suspected cardiac tumors	IIa	C
8.	Unexplained cardiomyopathy in children	IIa	C
9.	New-onset heart failure of 2 weeks' to 3 months' duration associated with a dilated left ventricle, without new ventricular arrhythmias or second- or third-degree heart block, that responds to usual care within 1–2 weeks	IIb	B
10.	Heart failure of > 3 months' duration assoicated with a dilated left ventricle, without new ventricular arrhythmias or second- or third-degree heart block, that responds to usual care within 1–2 weeks	IIb	C
11.	Heart failure associated with unexplained HCM	IIb	C
12.	Suspected ARVD/C	IIb	C
13.	Unexplained ventricular arrhythmias	IIb	C
14.	Unexplained atrial fibrillation	III	C



FIGURES 4A TO C: Myocarditis: (A) Lymphocytic myocarditis—sparse infiltrate of mononuclear cells is present in the interstitium surrounding individual damaged or dying myocytes (large arrows). (B) Giant cell myocarditis—there is extensive inflammation characterized by mononuclear cells and scattered giant cells (stars). The lower third of the field is comprised of granulation tissue due to extensive myocyte necrosis. (C) Hypersensitivity myocarditis—numerous interstitial eosinophils and very limited myocyte damage characterize the hypersensitivity reaction (small arrows). [H&E stains (400x magnification) (*Source:* Philip Ursell, UCSF pathology)]

The GCM, like necrotizing eosinophilic myocarditis and lymphocytic myocarditis, often presents with a fulminant picture. Both ventricular tachycardia (15%) and complete heart block (5%) can be complicating features of GCM. Presence of GCM in a patient with hemodynamic compromise should prompt consideration of biventricular mechanical circulatory device support as progressive right ventricular failure is often observed. However, most patients with GCM should be considered for early cardiac transplantation since this modality has been clearly shown to improve survival. The GCM is associated with a very high mortality; mean transplantation-free survival is only 5.5 months.[26] Therapy with cyclosporine has been shown to extend median transplantation-free survival to 12.3 months. Of note, GCM can recur in the transplanted heart

with a 20–25% frequency.[27] Greater consideration to use of EMB to rule out GCM should also be given to patients presenting with a coexisting history of thymoma or drug hypersensitivity as there has been an association with both entities.[28,29] The sensitivity of EMB for GCM is 80–85% in patients who subsequently die or undergo heart transplantation.[30] The characteristic histologic feature of GCM is myocyte necrosis with a mixed inflammatory infiltrate composed of lymphocytes, plasma cells, histiocytes, eosinophils and multinucleated giant cells (Fig. 4C). Differentiation between GCM and granulomatous myocarditis due to sarcoidosis can be difficult. Helpful features that may point to a diagnosis of GCM include myocyte necrosis, poorly formed granulomas and eosinophils.

The diagnosis of myocarditis by EMB can be confidently ascertained when there is a highly abnormal inflammatory infiltrate such as eosinophilic, granulomatous, or giant cell inflammation. However, one of the key limitations of this technique is sampling error. In about 40% of cases, false negative results occur.[20,31] Therefore, it is recommended that between five and ten biopsy samples be examined, and cut at multiple levels. In 1987, the Dallas criteria were established to help standardize the reporting and diagnosis of myocarditis (Table 2).[32] Initial EMB results are categorized as either myocarditis, borderline myocarditis or no myocarditis. In order to diagnose myocarditis, two criteria must be met: (1) inflammation and (2) myocyte necrosis.

The only Class III recommendation from the 2007 joint scientific statement for EMB was: EMB should not be performed in the setting of unexplained atrial fibrillation. The Writing Group based on this recommendation on the lack of

TABLE 2

Clinical scenarios for the diagnosis of myocarditis

Clinical scenario	*Duration of illness*	*Pathological correlates*	*Prognosis*	*Treatment*
Acute myocardial infarction-like syndrome with normal coronary arteries	Several hours or days	Active lymphocytic myocarditis or, rarely, necrotizing eosinophilic myocarditis or giant-cell myocarditis	Good if lymphocytic myocarditis is present on biopsy	Supportive
Heart failure with normal-sized or dilated left ventricle and hemodynamic compromise	Less than 2 weeks	Active lymphocytic myocarditis or, less commonly, necrotizing eosinophilic myocarditis or giant-cell myocarditis	Good in fulminant lymphocytic myocarditis, but acute care often requires inotropic or mechanical circulatory support	Supportive; possible use of corticosteroids or IVIG* in children
Heart failure with dilated left ventricle and new ventricular arrhythmias, high-degree heart block, or lack of response to usual care within 1–2 weeks	A few weeks or months	Giant-cell myocarditis, eosinophilic myocarditis, or lymphocytic myocarditis	Poor, high likelihood or death or need for cardiac transplantation if giant-cell myocarditis is found on biopsy	Variable therapy according to histopathological results
Heart failure with dilated left ventricle without new ventricular arrhythmias or high-degree heart block	A few weeks or months	Nonspecific changes most likely, with the presence of viral genomes in 25–35% of patients and of lymphocytic myocarditis (Dallas criteria) in about 10%	Good in the first several years, but a risk of late disease progression with heart failure and cardiomyopathy	Supportive; definition of genomic predictors of risk under investigation
Heart failure with eosinophilia	Any duration	Eosinophilic or hypersensitivity myocarditis, eosinophilic endomyocarditis	Poor	Supportive, including identification and treatment of underlying cause; possible use of corticosteroids for hypersensitivity myocarditis
Heart failure with dilated left ventricle and new ventricular arrhythmias, high-degree heart block, or lack of response to usual care in 1–2 weeks	More than several months	Cardiac sarcoidosis (idiopathic granulomatous myocarditis) or specific infection (e.g. *Trypanosoma cruzi* and *Borrelia burgdorfen);* nonspecific changes most likely	Increased risk of need for pacemaker or implantable cardioverter-defibrillator if sarcoidosis is confirmed on biopsy	Supportive; corticosteroids for biopsy-proven cardiac sarcoidosis
Heart failure with dilated left ventricle without new ventricular arrhythmias or high-degree heart block	More than several months	Nonspecific changes most likely; increased number of inflammatory cells shown by sensitive immunostaining in up to 40% of patients and the presence of viral genome in 25–35%	Depends on functional class ejection fraction and the presence or absence of inflammation and viral genomes on biopsy	Supportive; antiviral treatment and immunosuppression under investigation

*IVIG denotes intravenous immunoglobulin

significant evidence showing benefit of EMB in this setting. One small study was cited looking at EMB results in 14 "lone" atrial fibrillation patients unresponsive to traditional antiarrhythmic therapy.[33] In this study, all patients had some evidence of histologic abnormalities; however, 3 patients had EMB consistent with myocarditis and received steroid therapy with a reversion to sinus rhythm. Despite this apparent benefit of EMB diagnosis in lone atrial fibrillation, given the paucity of data, EMB was not felt to be appropriate in this setting.

DISEASE STATES

EMB IN CARDIOMYOPATHY

Dilated Cardiomyopathy

Dilated cardiomyopathy (DCM) is a common form of cardiomyopathy often observed in patients between the ages of 20 years and 60 years. Characteristic echocardiographic findings include 4-chamber dilatation with biventricular hypertrophy. Etiologies for DCM are numerous and include: end-stage hypertension, ischemic, valvular diseases, familial and secondary to specific heart muscle diseases. The EMB can be a useful adjunct to noninvasive modalities in defining the etiology of DCM. Often, EMB is more useful for excluding specific myocardial disorders than in diagnosing the etiology of DCM because it has nonspecific EMB findings such as myocyte hypertrophy and interstitial fibrosis (Fig. 5). In addition, the degree of interstitial fibrosis, myocyte diameters, and myofibril volume fraction have not been correlated with severity of clinical or hemodynamic data.[34,35] Other disorders that may be relevant to rule out in the patient with DCM include: iron deposition, amyloidosis, sarcoidosis, or lymphocytic myocarditis.

Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is the most common congenital cardiomyopathy observed with an incidence of 1:500 of the general population.[36] Heart failure and sudden cardiac death are both severe manifestations of the disease which can occur at any age. The diagnosis of HCM is made in the setting of a hypertrophied left ventricle with normal to reduced volumes in a patient without other systemic cardiac diseases that result in left ventricular wall thickening (e.g. aortic stenosis or long-standing hypertension). Echocardiography and cardiac magnetic resonance imaging (MRI) are the main modalities used to diagnose HCM and new genetic tests have become available to screen for common mutations known to lead to the HCM phenotype.

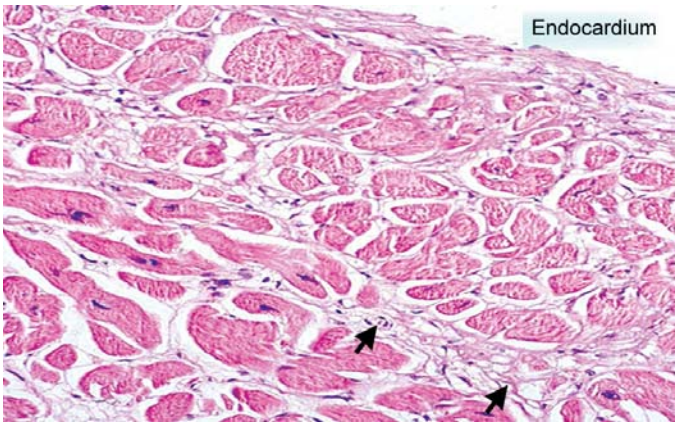


FIGURE 5: Dilated cardiomyopathy. In this subendocardial field, there is a delicate network of interstitial collagen (arrows) between hypertrophied myofibers; nonspecific histologic features of dilated cardiomyopathy [H&E stain (400x magnification) (*Source:* Philip Ursell, UCSF pathology)]

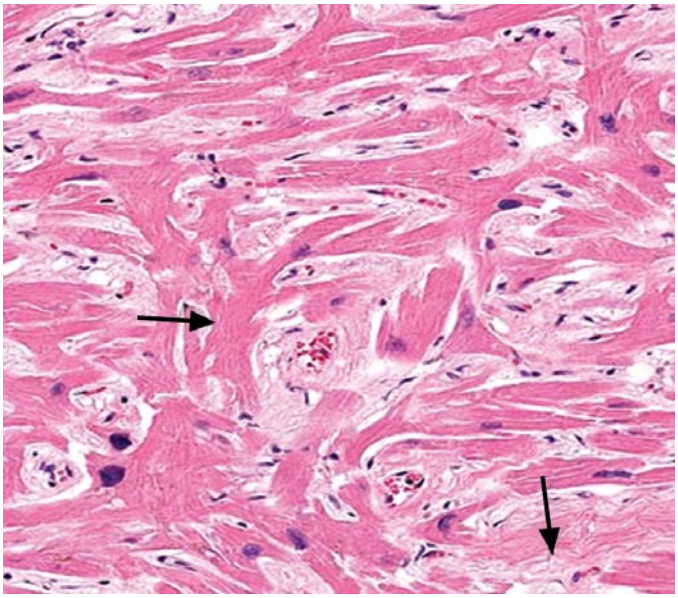


FIGURE 6: Hypertrophic cardiomyopathy. In the upper septum, disarray of hypertrophied myofibers and interstitial collagen (arrows) are hallmarks of hypertrophic cardiomyopathy [H&E stain (400x magnification). (*Source:* Philip Ursell, UCSF pathology)]

The most common finding on EMB for HCM is myocyte nuclear enlargement (hypertrophy) and interstitial fibrosis. The specificity of EMB for HCM is low as many other cardiomyopathies and secondary myocardial diseases, such as diabetes, hypertension, valvular diseases and ischemic heart disease, have similar histopathologic features. Myocyte disarray (Fig. 6) is also thought to be a hallmark of HCM, but unfortunately, this finding may not be seen in the EMB sample as HCM often lies deep within the interventricular septum and also may be patchy. Importantly, additional variants of HCM exist, such as the apical form, which would not be detected with right ventricular EMB. As a result, EMB for HCM is often reserved only to rule out other conditions that may mimic HCM such as amyloidosis. Amyloid stains, such as Congo red, should routinely be used on EMB samples if HCM is a clinical consideration. Finally, storage diseases, such as Pompe's or Fabry's disease,[37] may mimic HCM. Interestingly, up to 12% of female patients with late-onset HCM have Fabry's (alpha-galactosidase deficiency) disease which responds to enzyme replacement therapy.[38]

Restrictive Cardiomyopathy

Restrictive cardiomyopathy encompasses a heterogeneous group of diseases that are characterized by the presence of restricted ventricular filling or advanced diastolic dysfunction. These diseases include idiopathic restrictive cardiomyopathy, Loffler's

endocarditis, endomyocardial fibrosis and primary or secondary hypereosinophilic syndrome. Also in the differential include: amyloidosis, sarcoidosis, hemochromatosis and HCM with restrictive features. Early in these disease processes, the left ventricular volumes and systolic function are preserved, but there is evidence of atrial dilation and increased ventricular filling pressures.[39,40]

The restrictive cardiomyopathies can be divided into two groups based upon the presence or absence of eosinophilia. In the eosinophilic disorders, there is myocardial cell and microvascular damage thought to be due to the toxic metabolites (eosinophilic cationic protein and major basic protein) released from the infiltrating eosinophils. Early stages of these diseases are characterized by a necrotic stage which then progresses to a thrombotic stage with subsequent endomyocardial fibrosis.[41] The EMB can be useful for diagnostic purposes and reveals thrombus, eosinophils, myocyte necrosis and granulation-like tissue. In addition, EMB has been used to monitor response to steroid therapy.[42] In the non-eosinophilic disorders, EMB tends to be less useful as the findings are nonspecific and include myocyte hypertrophy and interstitial fibrosis.[40] In all cases where EMB samples are obtained for diagnosis of restrictive cardiomyopathies, amyloid stains should be utilized to rule out amyloidosis as this condition presents with similar hemodynamic findings.

Finally, in clinical cases where restrictive cardiomyopathy is being entertained as a diagnosis, the clinician should also consider a diagnosis of constrictive pericarditis. This is particularly important as pericardial surgery for constrictive pericarditis can be life-saving, and if a restrictive process is identified, the patient can be spared a pericardial biopsy. Generally, thickening or calcification of the pericardium should be visualized with either chest X-ray, MRI or CT. The EMB can help to differentiate between these two clinical entities as EMB samples from constrictive pericarditis reveals normal to slightly atrophic myocytes, whereas EMB samples from restrictive cardiomyopathy will reveal myocyte hypertrophy and interstitial fibrosis.[43]

Arrhythmogenic Right Ventricular Cardiomyopathy

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is an autonomic dominant cardiomyopathy affecting young adults that is characterized by fibrofatty replacement of the right ventricular myocardium. Clinical manifestations of ARVC include ventricular arrhythmias, right heart failure and sudden cardiac death. Recently, a mutation has been found in the gene coding for the protein plakophilin-2 which is thought to be critical for the pathogenesis of this disease.[44]

Guidelines have been established for the diagnosis of ARVC. These include characteristic findings on electrocardiogram, transthoracic echocardiographic, cardiac MRI, right ventricular angiograms and EMB.[45] Anatomically, the most involved areas of the myocardium form the 'triangle of dysplasia', between the right ventricular infundibulum, the apex and the diaphragmatic surface of the right ventricle.[46,47] Left ventricular involvement is also seen in up to 47% of cases.[48] The sensitivity of EMB for detecting ARVC by itself is low since the disease process is often patchy and in most cases does not involve the septum. Sensitivity is improved if the right ventricular free wall is biopsied, but many groups are reluctant to biopsy the right ventricular free wall due to its limited thickness and increased risk of perforation with resultant cardiac tamponade. In addition, the diagnosis of ARVC by EMB is complicated by the fact that mature adipose tissue can be seen in many normal hearts. Histomorphologic criteria have been proposed to improve specificity and include more than 3% fat, more than 40% fibrous tissue and fewer than 45% myocytes.[49] On microscopic examination, the areas of involvement demonstrate severe infiltration of the myocardium with mature fat cells and surrounding fibrosis.[47,50] Interestingly, myocarditis, both active and borderline, has been noted in EMB specimens of ARVC, but it is unclear whether this merely represents a reactive process or whether this is critical to the pathogenesis of the disease.[51] Finally, if the clinical suspicion for ARVC is high and the patient is symptomatic, all means should be employed to confirm the diagnosis as implantable cardioverter defibrillators or transplantation could be life-saving.

EMB IN SPECIAL CARDIAC DISEASE STATES

Sarcoidosis

Sarcoidosis is a multi-system, granulomatous disease of unknown etiology. A predominant feature of the disease is the presence of noncaseating granulomas affecting the lungs and lymph nodes as well as the heart, liver, spleen, skin, eyes and parotid glands. The disease usually presents in young and middle-aged adults between the ages of 20 years and 40 years, and can be a benign, incidentally discovered condition or a life-threatening disorder. The estimated prevalence of sarcoidosis with cardiac involvement is approximately 25% based upon several autopsy studies.[52,53] A common cardiac manifestation is congestive heart failure due to either direct infiltration of the myocardium, valvular regurgitation secondary to papillary muscle dysfunction or secondary right ventricular failure due to pulmonary hypertension with pulmonary involvement.[54] In addition, patients can present with varying conduction abnormalities due to granuloma involvement of virtually any aspect of the conduction system. Complete heart block is the most common presenting conduction abnormality (23–30%) and most frequently presents as syncope.[55]

The diagnosis of cardiac sarcoidosis is often difficult to establish especially in patients without evidence of sarcoid in other organs. Many patients with cardiac sarcoidosis are often given a diagnosis of idiopathic DCM. Several features that can support a diagnosis of cardiac sarcoidosis over idiopathic DCM include: higher incidence of advanced AV block, abnormal wall thickness, uneven wall motion abnormalities and perfusion defects preferentially affecting the anteroseptal and apical regions of the left ventricle. While having a high specificity for cardiac sarcoidosis, EMB has been estimated to have a low sensitivity (20–63%) largely due to the heterogeneous, patchy, and often basal distribution of myocardial involvement.[56,57] Therefore, EMB is generally not recommended for routine screening of cardiac involvement of sarcoidosis; however, in clinical situations where suspicion is high and other noninvasive modalities are inconclusive, EMB may prove to be diagnostic.

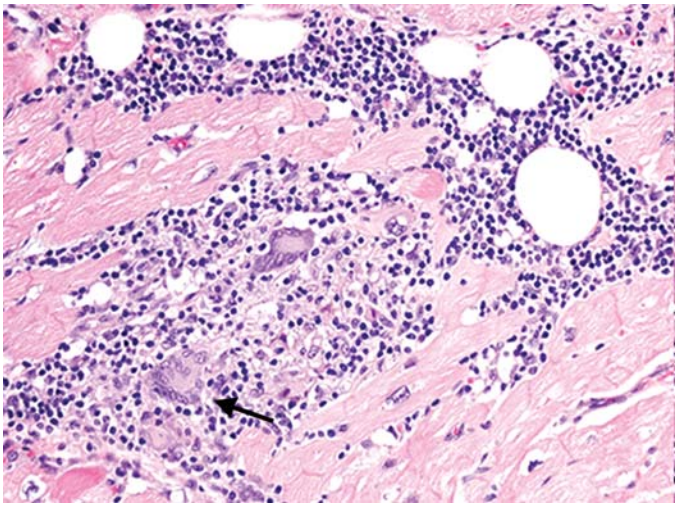


FIGURE 7: Cardiac sarcoidosis. In the central portion of the field, there are two myocardial granulomas characterized by clusters of mononuclear cells and giant cells (arrow) [H&E stain (400x magnification). (*Source:* Philip Ursell, UCSF pathology)]

The typical EMB findings include non-necrotizing granulomas which may also be associated with healed scars/fibrosis (Fig. 7). Of note, mycobacterial and fungal infections, hypersensitivity myocarditis and GCM may have overlapping features. In these instances, special stains and microbiological cultures may be useful. In Japan, where cardiac sarcoidosis has had an important clinical impact, the Ministry of Health and Welfare established specific guidelines for diagnosis based upon a combination of histological evidence, electrocardiographic, morphologic, scintigraphic or hemodynamic abnormalities (Table 3).[58] Unfortunately, these guidelines have not translated well to the international community. Finally, establishing a diagnosis of cardiac involvement with sarcoidosis is important as therapy with glucocorticoids, if initiated early, has been associated with improved five-year survival rates.[59]

Amyloidosis

Cardiac amyloidosis is classified by the protein precursor as primary, secondary (reactive), senile systemic, hereditary, isolated atrial and hemodialysis-associated. Patients with cardiac amyloidosis often present with clinical signs and symptoms of right heart failure including dyspnea and peripheral edema. One-important diagnostic clue to this diagnosis is observation of low voltage on electrocardiography despite significant left ventricular wall thickness on echocardiography. This set of findings has a high sensitivity (72–79%) and specificity (91–100%) for cardiac involvement.[60,61] In addition, cardiac MRI with gadolinium enhancement has begun to play a larger role in the noninvasive assessment of amyloidosis with cardiac involvement. Two recent studies illustrate the utility of this approach with varying patterns of late gadolinium enhancement.[62,63] In patients with a known diagnosis of amyloidosis on biopsy (either fat pad, rectal or renal) and echocardiographic and/or cardiac MRI findings consistent with amyloid deposition in the myocardium, EMB may not be necessary. The type of amyloid can be confirmed by specific tissue stains, serum and urine immunofixation electrophoresis or genetic analysis. However, in many cases where the diagnosis is suspected, but the non-invasive imaging is equivocal and biopsy of other organs is non-contributory, EMB can be particularly useful.

Histopathology of amyloidosis on EMB is characterized by homogeneous, eosinophilic deposition in the interstitium, vessels, and subendocardium as nodular deposits (Fig. 8). A

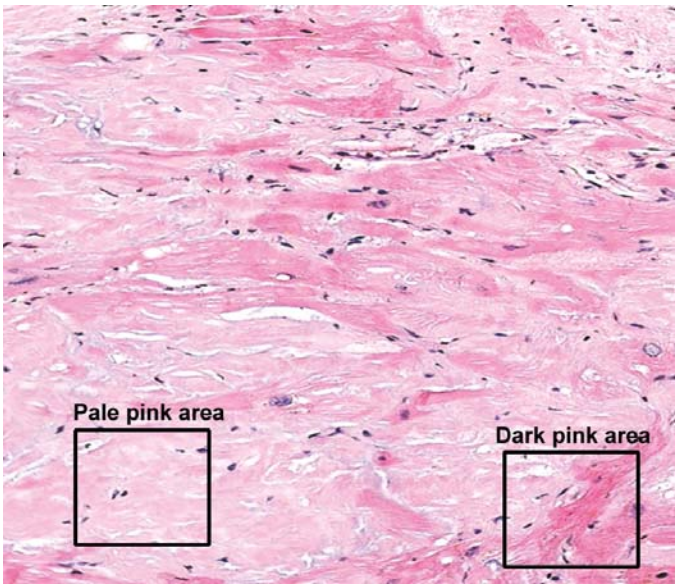


FIGURE 8: Cardiac amyloidosis. In this field there is abundant homogenous pale pink deposits of typical amyloid. The remaining viable myofibers (dark pink) are variably hypertrophied or atrophied [H&E stain (400x magnification). (*Source:* Philip Ursell, UCSF pathology)]

TABLE 3

Guidelines for diagnosing cardiac sarcoidosis (from the Japanese Ministry of Health and Welfare)

1. *Histologic diagnosis group*
   Cardiac sarcoidosis is confirmed when histologic analysis of operative or endomyocardial biopsy specimens demonstrates epithelioid granuloma without caseating granuloma

2. *Clinical diagnosis group*
   In patients with a histologic diagnosis of extracardiac sarcoidosis, cardiac sarcoidosis is suspected when item (a) and one or more of items (b) though (e) are present:
   - a. Complete right bundle branch block, left axis deviation, atrioventricular block, VT, premature ventricular contraction (≥ Lown 2), or abnormal Q or ST-T change on the ECG or ambulatory ECG
   - b. Abnormal wall motion, regional wall thinning, or dilatation of the left ventricle
   - c. Perfusion defect by thallium-201 myocardial scintigraphy or abnormal accumulation by gallium-67 or technetium-99m myocardial scintigraphy
   - d. Abnormal intracardiac pressure, low cardiac output or abnormal wall motion or depressed ejection fraction of the left ventricle
   - e. Interstitial fibrosis or cellular infiltration over moderate grade even if the findings are nonspecific

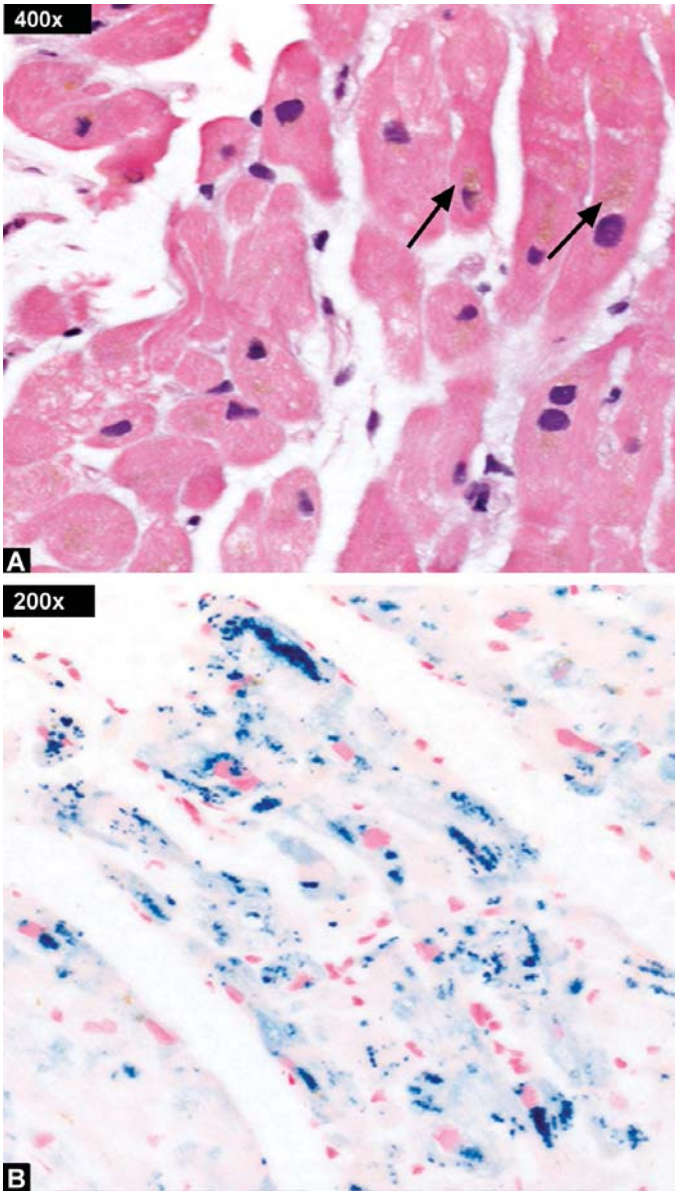
Congo red stain reveals apple-green birefringence under polarized light. In cases of early amyloid deposition with minimal cardiac involvement, Congo red staining may not have high enough sensitivity. In these cases, addition of Congo red fluorescence may enhance the sensitivity in making the diagnosis.[64] Once cardiac amyloidosis is confirmed by EMB, it is important to type the amyloid as prognosis and treatment differs among the various forms. Immunohistochemical and immunogold staining can be used to help differentiate the type of amyloid fibril. If the EMB sample stains positive for transthyretin, additional analysis should include isoelectric focusing of the serum to help distinguish between senile (wild type transthyretin) and familial (mutated transthyretin) amyloidosis.

Hemochromatosis

Hemochromatosis is one of the most common inherited metabolic disorders with an estimated prevalence in the general population of 1:200 to 1:400 depending upon the specific genotype or phenotype analyzed.[65–67] Hemochromatosis can be subdivided into a primary hereditary form involving a point mutation (C282Y) in the HFE (transferring-receptor binding protein) gene or secondary due to chronic iron overload in conditions such as thalassemia major.[68] A common feature of this disease is iron deposition in multiple organs including the liver, heart, pituitary, pancreas, joints and skin. With respect to cardiovascular manifestations, one analysis of multiple-cause mortality showed that patients with hemochromatosis are five times more likely to have a cardiomyopathy than those without hemochromatosis (Yang 1998). In addition, patients can develop heart block due to iron deposition in the AV node as well as a dilated and/or restrictive cardiomyopathy leading to death or cardiac transplantation.[69–72]

In suspected clinical cases, initial laboratory analysis including a serum ferritin, transferrin saturation, and HFE gene mutations can have good positive predictive value.[73] If the initial screen is positive, patients often undergo liver biopsy to determine if hepatic iron overload is present which would then prompt therapeutic phlebotomy. Screening for cardiac iron overload is indicated in patients with systemic manifestations of iron overload in conjunction with conduction abnormalities or signs/symptoms of congestive heart failure. The EMB has traditionally been the gold standard for demonstration of myocardial iron deposition. Iron is typically localized to the perinuclear region of myocytes (Figs 9A and B). As a result of the progressive hemosiderin accumulation within the myocytes, progressive interstitial fibrosis and myocyte necrosis occurs. Serial EMB has also been utilized to monitor response to therapy (chelation and/or phlebotomy), although iron can still remain in the heart even after the patient develops microcytic anemia which is an indicator of adequate treatment.[74] Of note, there is a potential for EMB sampling error as iron deposition localizes predominantly to the subepicardium early in the disease process.[69,75]

A new technique called cardiac MRI T2* has been validated across centers as an initial screen for cardiac hemochromatosis[76,77] and is decreasing the need for EMB to make the diagnosis. This technique is based on the fact that iron overload causes MRI signal loss in affected tissues because iron deposits become magnetized in the scanner leading to local irregularities in the magnetic field. The prognostic value of cardiac T2* was evaluated in a study of 652 thalassemia major patients who underwent 1,442 cardiac MRI scans at a single center in England.[78] The authors concluded that cardiac MRI T2* was a better predictor of high-risk heart failure and arrhythmia than serum ferritin and liver iron. While cardiac MRI T2* may eventually obviate the need for EMB to diagnose or monitor therapy in hemochromatosis, there remain a number of patients who are precluded from getting MRIs due to a history of an internal source of metal such as patients who have metallic valves, pacemaker/defibrillators, patent foramen ovale or atrial septal defect occluder devices, or aortic stents. In these cases,



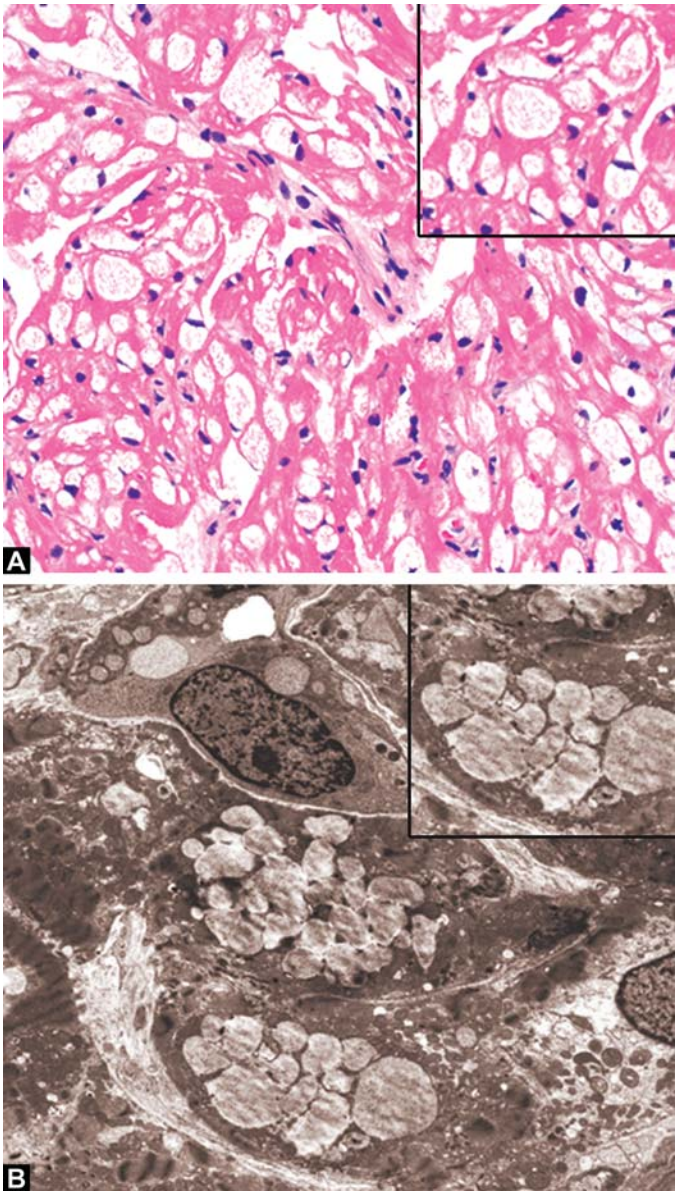
FIGURES 9A AND B: Hemochromatosis: (A) Multiple pigmented granules (arrows) are seen within myocytes consistent with iron [H&E stain (400x magnification)]. (B) A special stain discloses abundant bright blue iron in virtually every myofiber [Perl stain (200x magnification)]. (*Source:* Philip Ursell, UCSF pathology)

EMB remains a useful modality for both the diagnosis and follow-up of cardiac hemochromatosis.

Storage Diseases and Myopathy

Glycogen storage diseases are rare autosomal recessive diseases that are characterized by glycogen deposition in one or more tissues throughout the body. Type II (Pompe disease), type III (Cori disease), and type IV (Andersen disease) glycogen storage diseases can all involve the heart. Pompe's disease, a deficiency in the enzyme α-1,4-glucosidase, can present with significant morbidity related to cardiomegaly and congestive heart failure due to restrictive physiology. The particular enzyme defect, and hence diagnosis, is best performed on tissue cultures derived from leukocytes, liver cells, skin fibroblasts or even dried blood spots on filter paper.[79] Nevertheless, EMB can be helpful in making the diagnosis. Importantly, if a glycogen storage disease is suspected, the EMB sample should be fixed in alcohol in order to prevent the glycogen from dissolving in aqueous solutions. In Pompe's disease, there is deposition of morphologically normal glycogen with marked vacuolization of the myocytes (Figs 10A and B). Vacuolization of myocytes can also be seen in mitochondrial myopathies, carnitine deficiency, as well as Fabry's disease. In Fabry's disease, a deficiency of α-galactosidase A, EMB samples should be fixed in glutaraldehyde as electron microscopy reveals characteristic lysosomal lamellar bodies. Making a diagnosis of Fabry's disease can have important clinical implications as enzyme replacement therapy is now available.[80]

The EMB can also be helpful in making the diagnosis of inherited myopathies such as myotonic dystrophy, Becker muscular dystrophy and Duchenne muscular dystrophy. Genetic studies and peripheral skeletal muscle biopsies are first-line in the diagnostic algorithm; however, in cases where these modalities are unable to establish the diagnosis and the patient presents with congestive heart failure or arrhythmia, EMB may provide the only means of detecting cardiac involvement. The EMB samples in Becker and Duchenne muscular dystrophy have characteristic immunohistochemical staining patterns for dystrophin.[81,82] In addition, EMB samples from myotonic dystrophy also have characteristic electron microscopic abnormalities.[83]



FIGURES 10A AND B: Pompe's disease: (A) At high magnification, light microscopy discloses large empty appearing vacuoles (inset) in virtually every myofiber. A special stain for glycogen (not shown) was markedly positive [H&E stain (400x magnification)]. (B) Electron microscopy shows that the vacuoles are membrane bound aggregates of glycogen (inset) [Uranyl acetate and lead citrate (5000x magnification)]. (*Source:* Philip Ursell, UCSF pathology)

Drug Toxicity

Numerous chemotherapeutic drugs have been demonstrated to exert cardiotoxic effects. Anthracyclines, including daunorubicin and doxorubicin (adriamycin), are the best characterized of these agents and demonstrate dose-dependent cardiotoxic effects. Cardiotoxicity usually occurs within the first year of treatment, but delayed toxicity can also occur.[84,85] Several factors such as advanced age, prior mediastinal radiation, hypertension or preexisting cardiovascular disease have also been shown to predispose to subsequent anthracycline cardiotoxicity.[86] Newer chemotherapeutic agents, such as trastuzumab (Herceptin) for HER2/neu positive breast cancer, have also been shown to lead to cardiotoxicity, especially in the setting of prior anthracycline chemotherapy.[87] Screening for drug-induced cardiotoxicity is now commonly performed using noninvasive imaging modalities such as transthoracic echocardiography and radionuclide angiography (MUGA scan) focusing on left ventricular EF. A baseline scan is performed prior to the initiation of chemotherapy and scans are often performed every three months while on therapy.

Despite the ability of noninvasive means to detect myocardial dysfunction with chemotherapeutic agents, a tissue diagnosis made by EMB remains the gold standard.[88] Since chemotherapy-induced cardiotoxicity is best evaluated by electron microscopy, EMB samples should be specially processed. This includes analyzing both semi-thin and thin blocks of tissue.[88,89] While the primary lesion seen is myofibrillar loss, many of the changes seen can also be found in degenerative diseases such as DCM. Recognizing the need for a more comprehensive approach to detecting anthracycline

TABLE 4

Billingham anthracycline cardiotoxicity score

Grade	*Billingham scoring system (morphologic characteristics)*
0	Normal myocardial ultrastructural morphology
0.5	Not completely normal but no evidence of anthracycline-specific damage
1	Isolated myocytes affected and/or early myofibrillar loss; damage to < 5% of all cells
1.5	Changes similar to grade 1 except damage involves 6–15% of all cells
2	Clusters of myocytes affected by myofibrillar loss and/or vacuolization, with damage to 16–25% of all cells
2.5	Many myocytes (26–35% of all cells) affected by vacuolization and/or myofibrillar loss
3	Severe, diffuse myocyte damage (> 35% of all cells)

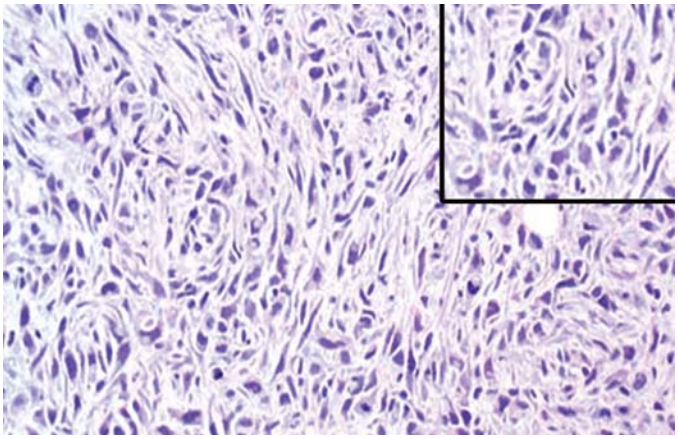


FIGURE 11: Anaplastic thyroid cancer. The entire tissue is comprised of poorly differentiated tumor (inset) consistent with anaplastic thyroid carcinoma [H&E stain of needle biopsy of right atrial mass (200x magnification)]. (*Source:* Philip Ursell, UCSF pathology)

cardiotoxicity, a grading scheme was developed in 1984 (Table 4) which takes into account the percentage of damage to myocardial cells.[89]

Neoplasms

Metastatic secondary tumors are the most common neoplasms affecting the heart and commonly infiltrate the pericardium. Renal cell carcinoma, lymphoma, leukemia, melanoma, breast cancer, lung cancer and anaplastic thyroid cancer can all metastasize to the heart (Fig. 11). Given the clinical necessity of obtaining a pathologic diagnosis to help direct treatment, transvenous biopsy plays a role in these settings. In addition, primary tumors (both benign and malignant) of the heart, such as atrial myoxoma, angiosarcoma, leiomyosarcoma and undifferentiated sarcoma, have been detected by right and left heart biopsy.[90–93] If a tumor is suspected, it is appropriate to fix and freeze some of the biopsy specimens for immunohistochemistry, molecular studies and electron microscopy. While a majority of cardiac biopsies of tumors are made by cardiothoracic surgeons, in certain cases, transesophageal echocardiography-guided transvenous biopsy may obviate the need for thoracotomy.

Cardiac Infections

Numerous systemic infections (viral, bacterial and protozoal) have been implicated in the pathogenesis of myocarditis. The role of EMB in these settings has been reviewed in the latest guideline statement from the ACC/AHA/ESC. Here it is worth mentioning several common infections with myocardial involvement and in which EMB may play a special role due to pathognomonic pathologic findings.

One of the leading causes of heart failure in South and Central America is infection with the tropical parasite *Trypanosoma cruzi* leading to Chagas disease. It is estimated that there are approximately 8–10 million infected people.[94] The disease is characterized by three phases: (1) an acute phase; (2) a latent phase and (3) a chronic phase. Cardiac involvement during the acute phase can be mild, but can also present with severe sequelae with a 3–5% mortality rate. The latent phase can last from up to 10–30 years and is often clinically silent. Eventually up to 30% of patients develop late manifestations, predominantly congestive heart failure, cardiac arrhythmias and sudden cardiac death. Historically, EMB has been widely performed in suspected Chagas cardiomyopathy and has led not only to a greater understanding of the pathophysiology, but also the clinical stages of the disease process.[95] *T. cruzi* parasites are rarely demonstrated in chronic Chagas cardiomyopathy, but are often demonstrated on histology in the acute phase. The PCR for *T. cruzi* DNA has been shown to be more sensitive and specific for detecting the organism.[96] In the acute phase, EMB histology can demonstrate myocarditis with inflammatory infiltrates around ruptured pseudocysts of parasites with associated myocyte necrosis and degeneration (Fig. 12).

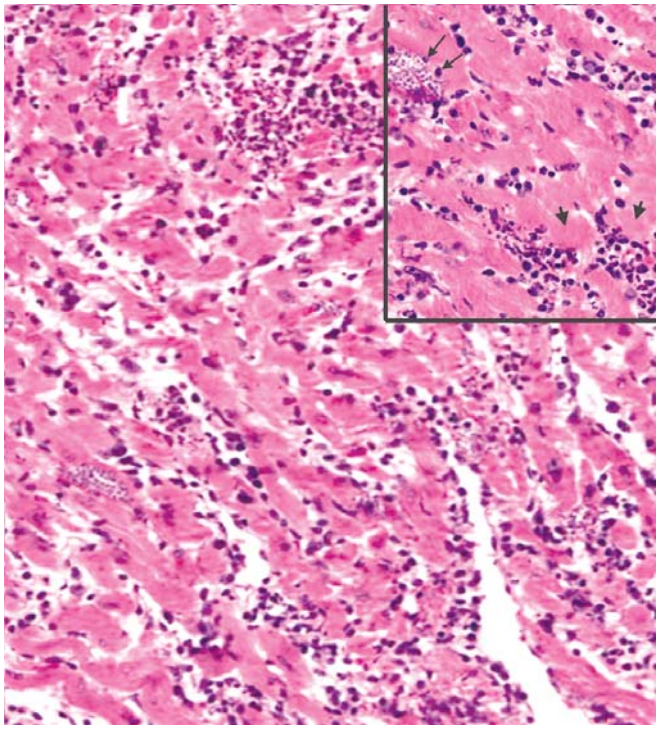


FIGURE 12: Chagas cardiomyopathy. Acute myocarditis with foci of myocytolytic necrosis and degeneration are seen with an intense inflammatory infiltrate around ruptured pseudocysts of parasite (short arrows), (in the inset). Intact intramyocyte parasite nest without inflammatory response (long arrows) (in the inset) [H&E staining]. (*Source:* Rossi et al. PLOS 2010)

Infectious complications, which can occur at any time after cardiac transplantation, remain a significant cause for concern among transplant physicians. The most common infections seen in the early post-transplant period include CMV and *Toxoplasma gondii*. Unlike bacterial and fungal infections which are often associated with predominantly neutrophilic inflammation, viral and protozoal infections can often mimic acute cellular rejection. In CMV infection and toxoplasmosis, the myocardium often contains a mixed inflammatory infiltrate with varying numbers of eosinophils. However, in the immunocompromised state, CMV inclusion bodies and *Toxoplasma* cysts can also be seen even in the absence of inflammation.

CARDIAC TRANSPLANTATION

Early experience with cardiac transplantation was limited by high rates of infection and allograft rejection. Before the advent of EMB, diagnosis of rejection relied upon noninvasive means such as electrocardiograms, echocardiography and nonspecific clinical signs/symptoms. As a result, identifying those patients who would benefit from rejection therapies had both low sensitivity and specificity. Over the past several decades there has been a remarkable improvement in outcomes for cardiac transplant patients driven largely by major advances in transplant immunology (such as the use of calcineurin inhibitors) as well as the widely accepted use of EMB to diagnose rejection.[97] Numerous studies have shown that EMB has both high sensitivity and specificity for detecting allograft dysfunction and is now the "gold standard" for monitoring of the cardiac allograft.[2] The EMB complication rates in experienced centers are low, and pathological diagnosis of rejection is more uniform secondary to newly established guidelines.[98,99]

In 2005, the International Society of Heart and Lung Transplantation (ISHLT) established criteria for defining and grading acute cardiac allograft rejection (Table 5).[99] In this classification scheme, grades 0–1 are considered low grade and often do not result in changes to therapy, particularly in asymptomatic individuals. Grade 2–3 lesions are significant and require augmentation of immunosuppressive therapy especially if there is evidence of allograft dysfunction. The histopathologic appearance/features of cellular and antibody-mediated rejection (AMR) are reviewed in Figures 13A to D. Confusion in grading may result from the presence of nodular infiltrates or "quilty" lesions which are thought to have a benign prognosis.[100,101]

Of note, false positive EMB results occur due to a number of histologic findings which may mimic grade 2 rejection. Specifically, this can occur due to biopsy sites being cut tangentially, identification of "quilty" lesions, ischemic injury, infection and post-transplant lymphoproliferative disorder. In addition, there are a number of patient cases of low-grade or no rejection who present with hemodynamic compromise.[102] Two explanations for these false negative EMB results have been posited. First, sampling error has been implicated as postmortem studies have confirmed that rejection and inflammatory lesions can be heterogeneous in nature and may be localized to the deep subendomyocardial regions not accessed by EMB. Second, acute AMR or humoral rejection may be the cause.

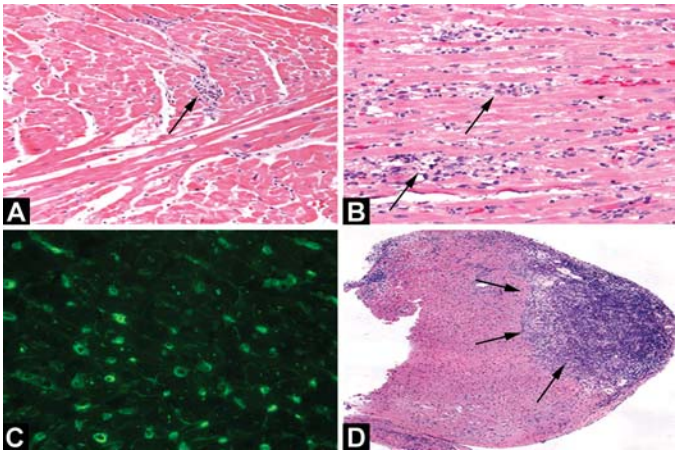
The AMR is thought to be responsible for a significant portion of chronic rejection and allograft vasculopathy. The recognition of AMR in the cardiac allograft has been facilitated by newer histological techniques. In particular, light microscopy and immunofluorescence demonstrate capillary endothelial swelling with capillary deposition of complement and immunoglobulin. These histological findings have been associated with a more aggressive clinical course and poorer responses to conventional anti-rejection therapies. As a result, the ISHLT recently revised their grading system to include assessments of AMR (Table 5).

While there is consensus regarding the necessity of EMB in allograft rejection surveillance, considerable variability still exists from center to center with regard to the frequency of biopsies required post-transplant. Most transplant centers utilize frequent EMB in the three month postoperative period (weekly for the first month, bi-weekly for the next two months, followed

TABLE 5

IHSLT grading of cellular and antibody mediated allograft rejection

Cellular	
Grade 0 R[a]	*No rejection*
Grade 1 R, mild	Interstitial and/or perivascular infiltrate with up to 1 focus or myocyte damage
Grade 2 R, moderate	Two or more foci of infiltrate with associated myocyte damage
Grade 3 R, severe	Diffuse infiltrate with multifocal myocyte damage ± edema, ± hemorrhage ± vasculitis
Antibody	
AMR 0	Negative for acute antibody-mediate rejection No histologic or immunopathologic features of AMR
AMR 1	Positive for AMR Histologic features of AMR Positive immunofluorescence or immunoperoxidase staining for AMR (positive CD 68, C4d)



FIGURES 13A TO D: Transplant rejection: (A) (1R)—Scattered perivascular and interstitial infiltrates of mononuclear cells are present (arrow). No myocyte damage is identified. (B) (3R)—Diffuse interstitial infiltrates of mononuclear cells with scattered areas of myocyte damage (arrows) characterize cellular 3R rejection. (C) Immunofluorescence methods demonstrate abundant vascular deposits of C4d characteristic of acute antibody mediated rejection. (D) A localized endocardial nodule comprised of dense mononuclear cells identifies a "Quilty" nodule. The inflammatory process has invaded into the underlying myocardium (arrows). There were no signs of rejection in this biopsy.

by every three months for the first year) as it is believed that the first three months represents the "critical window" for allograft rejection. The EMB frequency is also either maintained or decreased over time in relation to the incidence of rejection in preceding biopsies as well as the potency of the immunosuppressive regimen. Routine use of surveillance EMB beyond one year from transplant has been questioned by several studies. One retrospective study of more than 13,000 biopsies performed over an 8-year period found positive biopsies for rejection in 19% over the first 3 months, 7% by the end of the first year, and 4.7%, 4.5%, 2.2% and less than 1% for postoperative years 2 through 5 respectively.[103] In another study of over 1,000 biopsies performed 1–12 years after transplantation, 99.3% demonstrated a rejection grade of 0–1. Of the 0.6% of biopsies with a rejection grade of 2 or higher (7 biopsies), six were diagnosed with grade 2 rejection and only one biopsy was diagnosed as grade 3A. As a result, the authors concluded that the routine use of surveillance biopsy beyond one year after transplantation does not affect patient treatment and that a selective approach to biopsy should be employed after this time point.[104]

Despite the fact that EMB complication rates have declined significantly with the advent of newer bioptomes and increased operator experience, there remains a risk of serious complications, such as tricuspid valve dysfunction, pneumothorax and cardiac tamponade, not to mention the discomfort experienced by the patients themselves. As a result, there has been significant interest in developing strategies to reduce the number of biopsies without compromising care. Several new noninvasive approaches have been employed to detect allograft rejection including cardiac MRI, echocardiographic strain/strain rate analysis and serum blood tests identifying gene expression profiles consistent with rejection (AlloMap).[105–108] Two recent studies have highlighted the important clinical impact of molecular testing for transplant rejection. In a study by Starling et al.,[109] the amplification of 11 genes involved in cell-mediated rejection were analyzed from peripheral blood mononuclear cells of post heart transplant patients (AlloMap) by real-time PCR. An AlloMap score of less than 34 was found to have a 100% negative predictive value for diagnosis of moderate/severe allograft rejection. In addition, in a study by Pham et al.[110] from the IMAGE study group, 602 cardiac allograft recipients were randomized to be screened for cellular transplant rejection either by conventional route of right ventricular EMB or by gene expression profiling. The authors found no significant difference in the risk of serious adverse outcomes between the two approaches. The authors concluded that after six months from transplant, patients can be safely followed by gene expression profiling obviating the need for routine invasive EMB. Many of these new approaches are already being implemented in transplant centers around the world and it is likely that many more innovative approaches will reach the clinical arena in the near future.

SUMMARY

The EMB has led to a greater understanding of many cardiac diseases and continues to provide useful diagnostic information to the clinician. While recommendations about the utility of EMB are limited by the lack of large, randomized trials, there appears to be consensus regarding the use of EMB in the clinical scenario of the acute onset of decompensated heart failure of less than 3 months duration as well as in monitoring of cardiac allograft rejection. The EMB is also recognized to play an important role in the diagnostic algorithms of many other cardiac disease states, although its practical use should be evaluated in the context of the diseases being considered (i.e. it is important to rule out diseases or identify diseases with specific therapies that influence outcome). With the advent of newer techniques and improved bioptomes, complication rates have declined significantly. As a result, the clinical burden of proving benefit over risk has lessened considerably. Nevertheless, research is actively being pursued to identify new modalities (e.g. imaging, serum markers and genetic tests) that may ultimately lead to significantly fewer EMB procedures, reduced costs and more convenience for patients.

MODIFIED SUMMARIES OF GUIDELINES
AHA/ACC/ESC SCIENTIFIC STATEMENT. THE ROLE OF ENDOMYOCARDIAL BIOPSY IN THE MANAGEMENT OF CARDIOVASCULAR DISEASE. CIRCULATION. 2007;116:2216-33

Kanu Chatterjee

Class I: Conditions for which there is evidence or there is general agreement that a given procedure is beneficial, useful and effective.

Class II: Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment.

Class IIa: Conditions for which the weight of evidence/opinion is in favor of usefulness/efficacy.

Class IIb: Conditions for which usefulness/efficacy is less well established by evidence/opinion.

Class III: Conditions for which there is evidence and/or general agreement that a procedure/treatment is not useful and in some cases may be harmful.

THE LEVELS OF EVIDENCE

Level A (highest): Multiple randomized clinical trials.

Level B: (intermediate): Limited number of randomized trials, nonrandomized studies and registries.

Level C: Primarily expert consensus.

Class I

1. Unexplained, new-onset heart failure, 2 weeks duration with a normal or dilated left ventricle and hemodynamic compromise (level of evidence B).
2. Unexplained new-onset heart failure of 2 weeks to3 months' duration with a dilated left ventricle and new ventricular arrhythmias or advanced atrioventricular heart block or failure to respond to usual care in 1–2 weeks (level of evidence B).

Class IIa

1. Unexplained heart failure of greater than 3 months' duration with a dilated left ventricle and new ventricular arrhythmias or advanced atrio-ventricular heart block or failure to respond to usual care within 1–2 weeks. (level of evidence C).
2. Unexplained heart failure with a dilated cardiomyopathy of any duration and suspected allergic reaction and eosinophilia (level of evidence C).
3. Unexplained heart failure and suspected anthracycline cardiomyopathy (level of evidence C).
4. Heart failure with unexplained restrictive cardiomyopathy (level of evidence C).
5. With suspected (non-myxoma 0 cardiac tumors) (level of evidence C).
6. Unexplained cardiomyopathy in children (level of evidence C).

Class IIb

1. Unexplained new-onset heart failure of 2 weeks to 3 months' duration with a dilated left ventricle but without new ventricular arrhythmias or advanced atrioventricular heart block that responds to usual care within 1–2 weeks (level of evidence B).
2. Unexplained heart failure of greater than 3 months' duration with a dilated left ventricle without new ventricular arrhythmias or advanced atrioventricular heart block that responds to usual care within 1–2 weeks (level of evidence C).
3. Suspected arrhythmogenic right ventricular dysplasia/cardiomyopathy (level of evidence C).
4. Unexplained ventricular arrhythmias (level of evidence C).

Class III

Unexplained atrial fibrillation (level of evidence C).

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Chapter 27

Swan-Ganz Catheters: Clinical Applications

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Chapter Outline

- Historical Perspective and Evolution of Catheter Designs
- Placement of Balloon Flotation Catheters
- Normal Pressures and Waveforms
- Abnormal Pressures and Waveforms
- Clinical Applications
  - Cardiac Catheterization Laboratory
  - Acute Coronary Syndromes
  - Non-acute Coronary Syndrome
  - Chronic Heart Failure
  - Pulmonary Hypertension
- Indications for Pulmonary Artery Catheterization
- Complications
- Guidelines

INTRODUCTION

This was demonstrated, over eighty years ago, that pulmonary artery (PA) catheterization is feasible and may be useful in understanding cardiac hemodynamics in physiologic and pathologic conditions. However, before the introduction of the balloon flotation catheters (Swan-Ganz catheters),[1] PA catheterization outside the cardiac catheterization laboratory for bedside hemodynamic monitoring was not possible. With the availability of Swan-Ganz catheters, PA catheterization can be performed even in critically ill cardiac patients. In this chapter, indications and complications of PA catheterization with the use of balloon flotation catheters for hemodynamic monitoring have been discussed.

HISTORICAL PERSPECTIVE AND EVOLUTION OF CATHETER DESIGNS

In 1929, Dr. Warner Forsmann demonstrated that right heart catheterization in humans can be performed.[2] Interestingly, he catheterized himself and introduced the catheter to his right atrium. Drs. Andre Cournand and Dickinson Richards developed catheters that could be advanced into the pulmonary arteries, and they were able to study the pathophysiology of congenital and acquired heart diseases.[3] In 1956, Drs. Forsmann, Cournand and Richards were awarded the Nobel Prize in medicine (Fig. 1). Miniature diagnostic catheters were introduced in 1964.[4] Self-guiding and flow-directed right-heart catheters were developed to measure right heart pressures.[5,6] However, balloon flotation flow-directed catheters that can be placed at the bedside without fluoroscopy were developed and introduced in clinical practice by Drs. Jeremy Swan and William Ganz in 1970 (Fig. 2). The balloon flotation catheters were further developed to measure cardiac output by thermodilution technique.[7] The pacing electrodes were also incorporated for right atrial (RA) and right ventricular (RV) pacing.[8] The multipurpose catheters

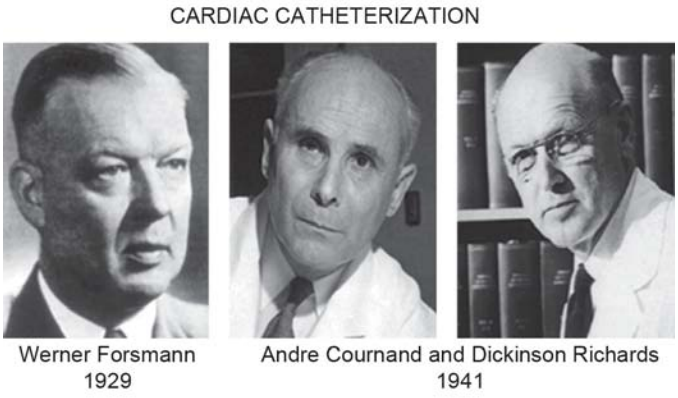


FIGURE 1: Drs. Forsmann, Cournand and Richards who developed pulmonary artery catheters and were awarded the Nobel Prize in medicine for their discoveries

that are often used in clinical practice are illustrated in Figure 3.

PLACEMENT OF BALLOON FLOTATION CATHETERS

In most instances the balloon flotation catheters can be placed at the bedside without the use of fluoroscopy. In patients with markedly dilated right atrium and right ventricle or with severe pulmonary hypertension, it is preferable to use fluoroscopy, which allows rapid placement of the catheters. Presently in most institutions, portable fluoroscopy units are available and are frequently used for placement of balloon flotation catheters.

Venous access is obtained by using one of multiple venous sites, the choice of which is determined by the preferences of the operator as well as clinical circumstances. The internal jugular or subclavian veins are the preferred route of entry due to proximity to the right heart. However, since direct pressure

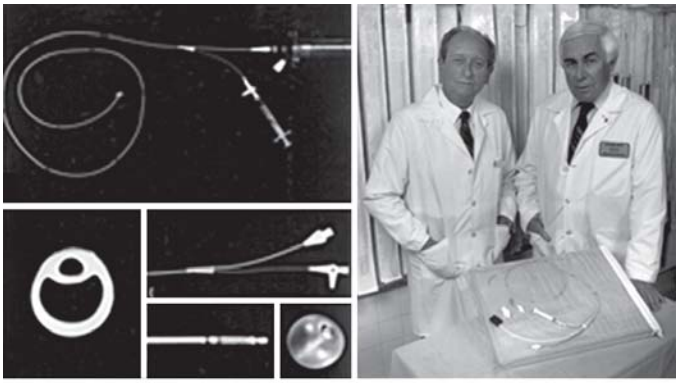


FIGURE 2: Drs. William Ganz and Jeremy Swan who developed balloon flotation catheter that can be used without fluoroscopy. The double-lumen catheter that was first introduced is also illustrated. Its placement with monitoring of hemodynamics is also illustrated. (Abbreviations: RA: Right atrial pressure; RV: Right ventricular pressure; PA: Pulmonary artery pressure; PCW: Pulmonary capillary wedge pressure)

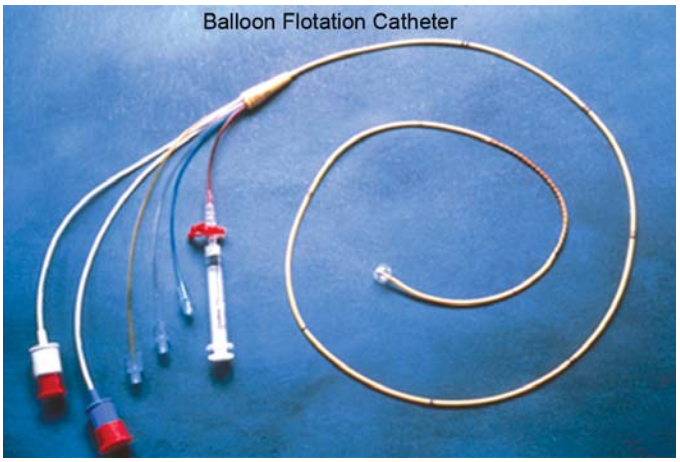


FIGURE 3: The multipurpose thermodilution triple-lumen catheters with pacing electrodes are illustrated

cannot be applied over the subclavian vein, this route should be avoided if the patient has a coagulopathy or is receiving anticoagulation therapy. The femoral vein is usually used during diagnostic catheterizations in the cardiac catheterization laboratories. For prolonged hemodynamic monitoring, the femoral vein approach should be avoided because there is a higher risk of infection. For hemodynamic monitoring for longer periods, internal jugular, subclavian or anticubital veins should be used.

Strict sterile conditions should be observed during insertion of the balloon flotation catheters, and the appropriate preparation of the skin is extremely important to minimize the risk of infection.

The catheter system must be appropriately zeroed to ambient air pressure. The catheter should be referenced, which is done by placing the air-fluid interface of the catheter (or the transducer) at a specific point to negate the effects of the length of the tubing and the fluid column.[9] The catheter is always advanced with the balloon inflated and withdrawn with the balloon deflated. The placement of the catheter is schematically illustrated in Figures 4A to D. After the catheter is in the right atrium and recognized by the RA pressure waveform, the catheter is advanced to the right ventricle. With the balloon inflated, the catheter is then advanced to the PA across the pulmonary valve. The catheter usually floats to the smaller PA branches and pulmonary capillary wedge pressure (PCWP) (PA occlusion pressure) is recognized. After deflation of the balloon, the PA pressure waveform is again recognized.

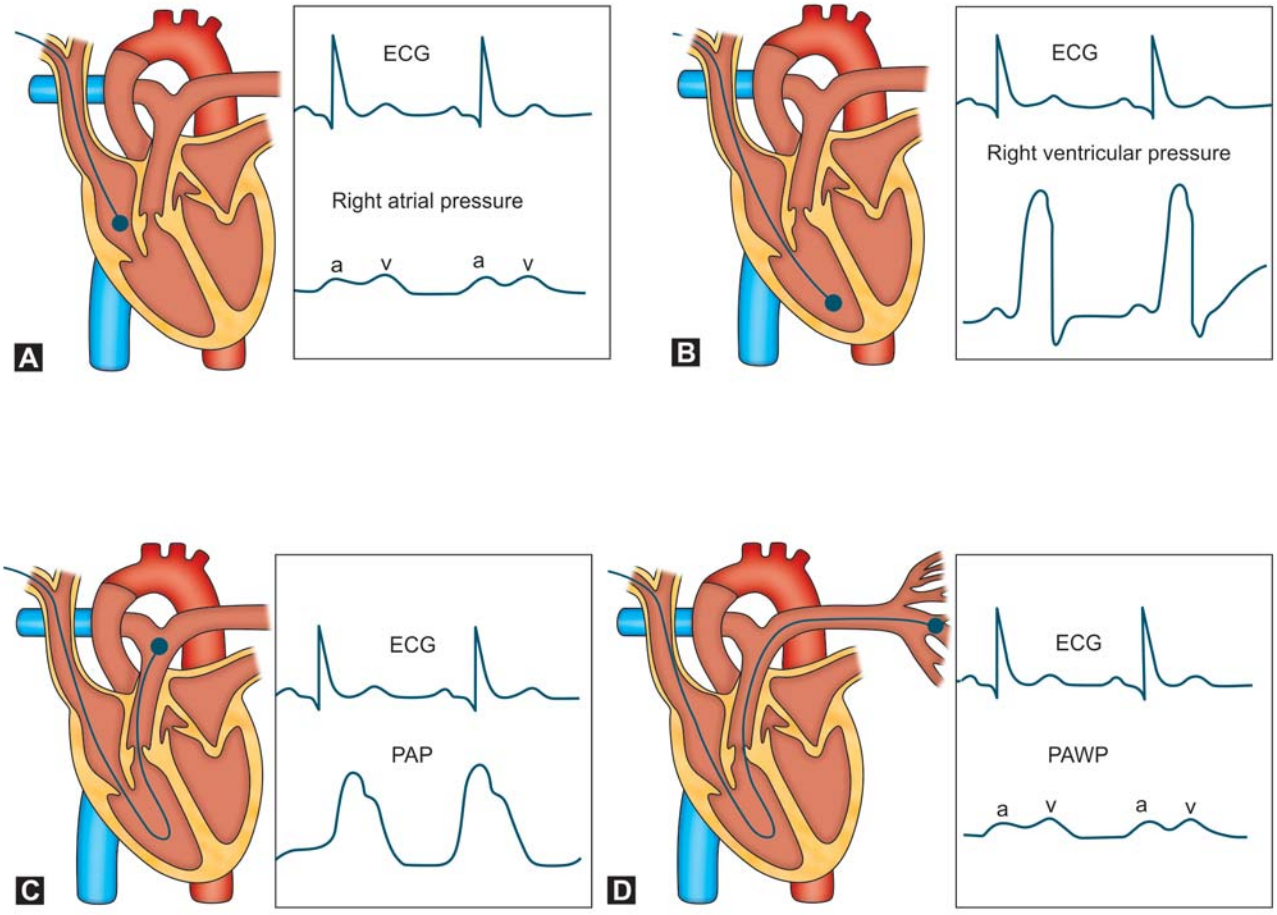
The PCWP (PA occlusion) is frequently used for indirect assessment of pulmonary venous and left atrial pressure. For the accurate measurement of PCWP, a continuous fluid column needs to be present between the distal tip of the catheter and the left atrium. The continuous fluid column is present when the pulmonary capillary pressure is higher than the surrounding alveolar pressure. If the alveolar pressure is much higher than the pulmonary capillary pressure, the capillaries collapse and a continuous fluid column between the distal tip of the catheter and the left atrium is no longer present. The measured PCWP in these locations does not reflect left atrial pressure. When there is partial obstruction of the capillaries due to increased alveolar pressure, an accurate assessment of left atrial pressure by measuring PCWP is also not possible.

Based on the relationship between pulmonary capillary blood flow, pulmonary capillary pressure and alveolar pressure, the lungs are divided into three physiologic zones.[10] Zone (1) is above the level of the left atrium where the alveolar pressure is much higher than the capillary pressure and there is compression of the capillaries. Zone (3) is located in the most dependent portion of the lung, below the level of the left atrium. In this zone, the pulmonary capillary pressure is higher than the alveolar pressure and there is a continuous fluid column between the distal tip of the catheter and the left atrium. If the catheter tip is placed in this zone, the measured PCWP reflects left atrial pressure. Whether the catheter tip is placed in Zone (3) or not can be verified by obtaining a lateral chest radiograph.

NORMAL PRESSURES AND WAVEFORMS

The normal range of RA pressure is 0–7 mm Hg, and of RV systolic pressure is 15–25 mm Hg. The mean pulmonary artery pressure (MPAP) is less than 18 mm Hg and mean PCWP is less than 15 mm Hg. The normal RV end-diastolic pressure ranges 0–8 mm Hg.

The RA pressure waveforms are characterized by two positive waves: (a) during RA systole and (b) at the end of RV rapid filling phase. There are two negative waves: (x) and (y) descents. The (x) descent is related to atrial relaxation, and (y) descent due to rapid ventricular filling. The RV pressure waveform is characterized by a sharp upstroke and a sharp down stroke during systole. During diastole, a rapid filling wave, diastasis, and atrial filling waves are recognized. The normal PA pressure waveform is characterized by a sharp upstroke and,



FIGURES 4A TO D: The schematic illustration of insertion of the balloon flotation catheter and the right atrial, right ventricular, pulmonary artery and pulmonary capillary wedge pressure waveforms are illustrated. The catheter is inserted into the right atrium (Panel A). In the right atrial pressure waveform there are two positive waveforms: "a" and "v." Then, the catheter is advanced to the right ventricle (Panel B). In the right ventricular pressure waveform, a rapid upstroke in systole is followed by the end-systolic dip. After the rapid filling phase, there is the phase of diastasis and atrial filling phase. Then, the catheter is advanced to the pulmonary artery (Panel C). The pulmonary artery pressure waveform is characterized by a rapid upstroke at the beginning of the ejection phase and the dicrotic notch and the dicrotic wave during the down stroke. The catheter is then advanced to a distal pulmonary artery branch to record the pulmonary capillary wedge pressure (Panel D). The pulmonary capillary wedge pressure waveform is similar to that of right atrial pressure waveform

during down stroke, by the dicrotic notch and the dicrotic wave. The PCWP waveforms are similar to those of RA pressure waveforms. The pressures, however, are higher than RA pressures.

During bedside hemodynamic monitoring, usually RA, PA and PCWPs and cardiac output are monitored. The RA pressure reflects RV diastolic pressure in absence of tricuspid valve obstruction. The RA pressure has a modest correlation with the PCWP in the absence of cardiopulmonary disease.[11] This correlation is further compromised in the presence of left ventricular dysfunction, valvular heart disease, coronary artery disease and pulmonary hypertension.[12,13]

The PCWP is frequently used to represent left ventricular preload. Left ventricular preload, however, is left ventricular end-diastolic volume. To assess left ventricular volume, it is preferable to perform transthoracic echocardiogram or other imaging techniques such as computerized cardiac tomography or cardiac magnetic resonance imaging.

Mean RA and mean PCWPs are used as right and left ventricular filling pressures respectively. It should be appreciated that the true ventricular filling pressures are transmural pressures.[14-16] The transmural pressure is the difference between ventricular distending pressure (diastolic pressure) and the pressures opposing filling (pericardial and mediastinal pressures). Normally the intrapericardial pressure is 0 and the mediastinal pressure is from –1 mm Hg to –3 mm Hg. Thus, in normal conditions, RA and PCWPs can be used to represent right and left ventricular filling pressures. However, when intrapericardial pressure is increased as in cardiac tamponade, RA and PCWPs cannot be used as right and left ventricular filling pressures. It should be appreciated that there is a close correlation between RA and pericardial pressures. The RA pressures are 2–5 mm Hg higher than the pericardial pressures. Thus, it is possible to use RA pressure for approximate estimation of pericardial pressure.

Normally there is a good correlation between PA end-diastolic and mean PCWPs.[17-19] Usually, the difference between PA end-diastolic and mean PCWP does not exceed 5 mm Hg. A greater difference indicates increased pulmonary vascular resistance (PVR).[20]

The PCWP is similar to mean left ventricular diastolic pressure in absence of mitral valve obstruction. However, left ventricular end-diastolic pressure is usually higher than the mean PCWP. In mitral stenosis, LA and PCWPs are higher than left ventricular diastolic pressure and thus, in these patients, PCWP cannot be used to represent left ventricular filling pressure.

The accurate determination of RA or PCWPs is difficult in ventilated patients, in patients with pulmonary diseases and in patients with sleep disordered breathing. There may be a wide swing in pressures during respiratory phases. It has been suggested that the pressure measurements should be done at end expiration. For practical purposes, one can use the mean of (mean wedge pressure) to approximate the left ventricular filling pressure.

In the presence of significant tricuspid regurgitation, the cardiac output measurements with the indicator dilution technique (whether with the thermodilution or by the dye dilution) can be erroneous. In these patients the cardiac output measurements may be more accurate with the use of Fick principle. However, it is difficult to use the Fick method during hemodynamic monitoring because frequent measurement of oxygen consumption is not yet possible. It is, however, reasonable to determine changes in PA (mixed venous) oxygen saturation to assess the trend in changes in cardiac output. An increase in the PA oxygen saturation suggests an increase in cardiac output and a decrease in oxygen saturation indicates a decrease in cardiac output.

The various hemodynamic indices can be measured to establish the diagnosis of the pathologic conditions.

The hemodynamic differential diagnosis of some of the commonly encountered clinical conditions with pre-shock or shock syndromes in the intensive care units are summarized in Table 1. In cardiogenic shock, whether complicating acute coronary syndromes or chronic systolic heart failure, PCWP is much higher than the RA pressure and the cardiac output and stroke volume are reduced. In cardiogenic shock complicating RV myocardial infarction, however, RA pressure is disproportionately higher than the PCWP. In these patients, PA pressure is normal. In cardiogenic shock resulting from severe chronic RV failure such as in patients with idiopathic pulmonary arterial hypertension, PA pressure and PVR are elevated.

In hypovolemic shock, both RA pressure and PCWP are low. The characteristic hemodynamic features of septic shock are abnormally low systemic vascular resistance (usually < 700 dynes/sec/cm-5) and high cardiac output and decreased mean arterial pressure. The RA pressure and PCWP are normal or lower than normal.

In septic shock, vascular paralysis and reduction in systemic vascular resistance is the primary pathologic mechanism. The increase in cardiac output results from unloading of the left ventricle. The syndrome of "pseudosepsis" is encountered in patients with chronic advanced systolic heart failure treated with vasodilators and angiotensin inhibitors. The hemodynamic features are relatively low systemic vascular resistance, normal cardiac output, and elevated PCWP and RA pressure. Frequently there is renal failure as well. In these patients temporary discontinuation of vasodilator therapy is required.

Cardiac tamponade is also associated with cardiogenic shock. The hemodynamic features are hypotension, low cardiac output, and elevated RA and PCWPs. The mean RA pressure and PCWP are also equal (equalization of diastolic pressures). There is significant pulsus paradoxus. It should be emphasized that the diagnosis of cardiac tamponade should not be made based on hemodynamic abnormalities. Transthoracic echocardiography is the investigation of choice for the diagnosis of cardiac tamponade. The hemodynamic abnormalities of adult respiratory distress syndrome (ARDS) are similar to those of septic shock. The systemic vascular resistance and mean arterial pressure are less than normal and RA pressure and PCWP are normal or less than normal. Cardiac output is usually normal but may be reduced.

ABNORMAL PRESSURES AND WAVEFORMS

A prominent (a) wave in RA pressure tracing indicates abnormally elevated RA pressure due to increased resistance to RA emptying during atrial systole. The increased resistance may be at the level of the tricuspid valve or distal to the tricuspid valve. The tricuspid valve obstruction is characterized by increased pressure gradient across the tricuspid valve. The more severe the tricuspid valve obstruction is, the higher is the pressure gradient. In tricuspid valve obstruction the (y) descent

TABLE 1

The hemodynamic features of a few clinical conditions that can be associated with shock are summarized

	CO L/minute	*MAP mm Hg*	*PCWP mm Hg*	*SVR Dynes/s/cm-5*	*PVR Dynes/s/cm-5*	*RAP mm Hg*
Cardiogenic shock	Low	Low	High	High or normal	Normal or high	Normal
Right ventricular infarction	Low	Low	Normal	High	Normal	High
Hypovolemic shock	Low	Low	Low	Normal	Normal	Low
Septic shock	High	Low	Low	Low	Low	low
Pseudosepsis	Normal	Low	High	Low	High	High
Cardiac tamponade	Low	Low	High	Normal	Normal	High
ARDS	Normal or low	Normal or low	Normal or high	Normal or low	Normal or low	Normal or high

(Abbreviations: CO: Cardiac output; PCWP: Pulmonary capillary wedge pressure; RAP: Right atrial pressure; SVR: Systemic vascular resistance; PVR: Pulmonary vascular resistance; ARDS: Adult respiratory disease syndrome; MAP: Mean arterial pressure)

is slower than normal. In adults, increased resistance to RA emptying is more often due to RV failure resulting from pressure overload or volume overload.

Another cause of a prominent (a) wave is a cannon wave. It results from atrial contraction when the tricuspid valve is closed. Cannon (a) waves may occur regularly or irregularly in abnormalities of atrioventricular conduction, ventricular tachycardia, atrioventricular nodal tachyarrhythmias and ventricular pacing.

The most common cause of an absent (a) wave is atrial fibrillation. An infrequent cause is (silent giant right atrium). A prominent (v) wave in the RA pressure waveform usually indicates tricuspid valve regurgitation. In severe tricuspid regurgitation, RA pressure waveform may appear like that of RV pressure waveform (Fig. 5). It is characterized by a prominent (v) wave followed by a sharp (y) descent. The steep "y" descent is also observed in constrictive pericarditis. A "dip and plateau" filling pattern is observed in constrictive pericarditis and in restrictive cardiomyopathy.

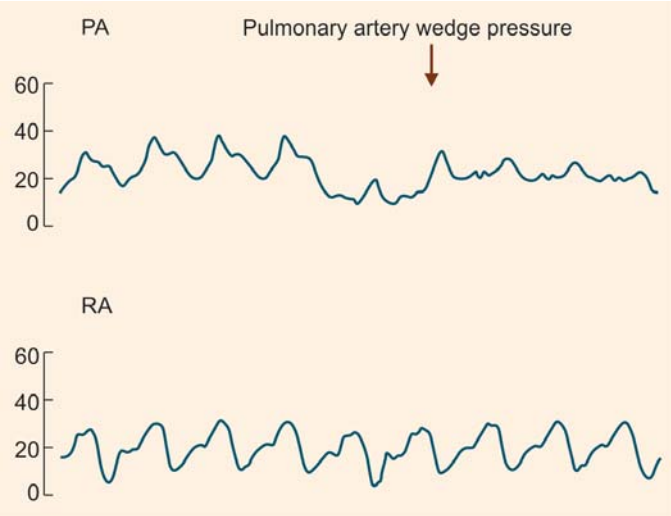


FIGURE 5: The right atrial pressure waveforms in severe tricuspid regurgitation are illustrated. There is a prominent "v" wave followed by a sharp "y" descent. The mean right atrial pressure and pulmonary capillary wedge pressure are also similar, illustrating equalization of diastolic pressures. (Abbreviations: PA: Pulmonary artery; RA: Right atrial)

CLINICAL APPLICATIONS

CARDIAC CATHETERIZATION LABORATORY

The balloon flotation catheters are most frequently used in the cardiac catheterization laboratory. The RA, RV, PA and PCWPs are determined routinely. Cardiac output and oxygen saturations in the different cardiac chambers are determined to assess presence of intracardiac and intrapulmonary shunts. For example, left to right shunt due to interventricular septal rupture complicating acute coronary syndromes can be diagnosed (Fig. 6). The oxygen saturation is higher in the PA than in the right atrium and the right ventricle. Severe acute or subacute mitral regurgitation can be diagnosed by analysis of PA and PCWP waveforms (Fig. 7). The PCWP waveform reveals a large tall peaked (v) wave. In the PA pressure waveform, there is a reflected (v) wave which occurs before the dicrotic notch.

Cardiac output is determined by thermodilution technique with the use of multipurpose balloon flotation catheters. Systemic and PVRs are calculated. The shunt calculations are also made whenever is indicated. In most cardiac catheterization laboratories and in the intensive care units, automated computerized systems are available to measure the hemodynamic indices.

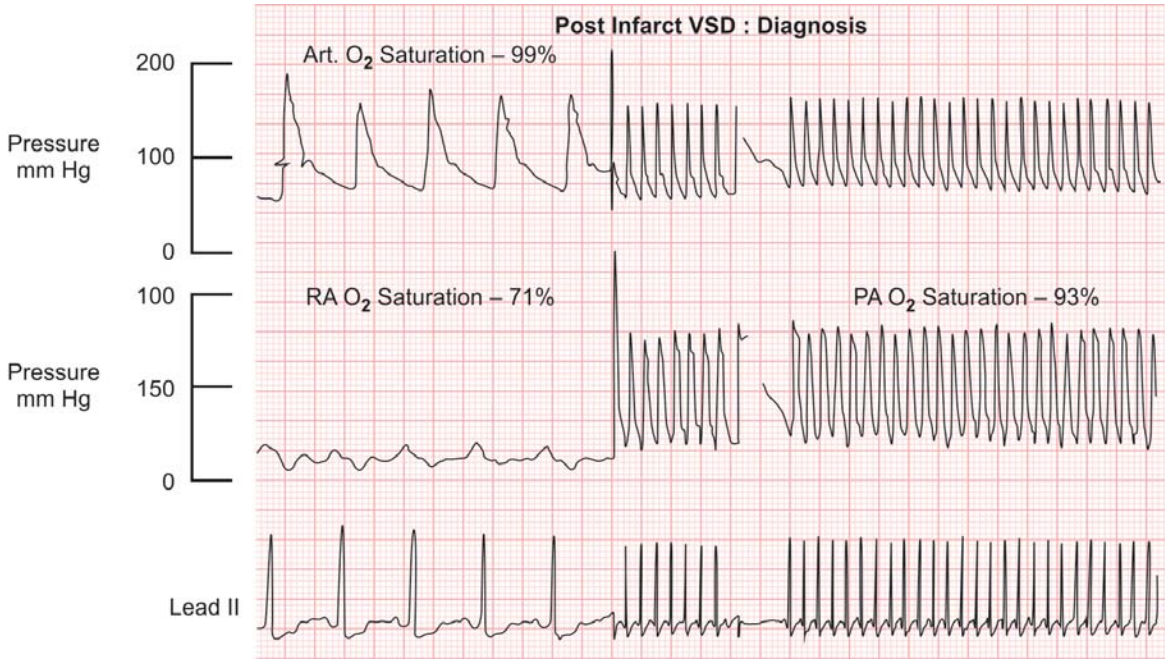


FIGURE 6: Diagnosis of severe left to right shunt due to ventricular septal rupture is illustrated. Pulmonary artery oxygen saturation is much higher than that in the right atrium. (Abbreviations: VSD: Ventricular septal defect; RA: Right atrial; PA: Pulmonary artery)

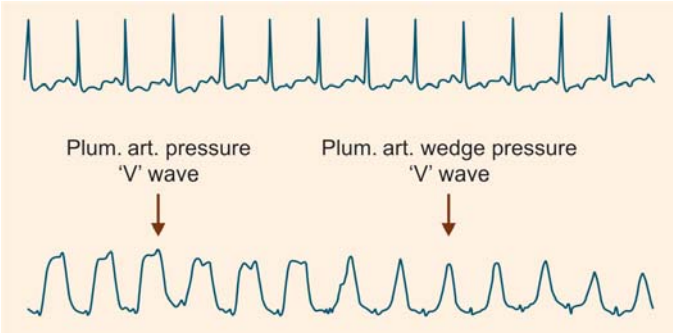


FIGURE 7: The pulmonary capillary wedge and pulmonary artery pressure waveforms in acute severe mitral regurgitation are illustrated. The pulmonary capillary wedge pressure waveform shows large tall peaked "v" waves. In the pulmonary artery pressure waveforms, there are reflected "v" waves which occur before the dicrotic notch

ACUTE CORONARY SYNDROMES

The treatment of ST-segment and non-ST segment elevation myocardial infarction consists of myocardial reperfusion therapy by either percutaneous coronary interventions or thrombolysis. Routine hemodynamic monitoring is not indicated in patients with acute coronary syndromes except in patients with cardiogenic shock.

Before the advent of echocardiography, determination of hemodynamics was employed for the diagnosis of complications of acute myocardial infarction such as severe mitral regurgitation and ventricular septal rupture. Severe mitral regurgitation is characterized by a large peaked "v" wave in the pulmonary capillary wedge pressure tracing. There is also a reflected "v" wave in the pulmonary artery pressure tracing.[7] In patients with ventricular septal rupture, there is a step up in oxygen saturation in the left ventricle and the oxygen saturation in the pulmonary artery is higher (Fig. 6). Severe right ventricular myocardial infarction can also be diagnosed by determination of hemodynamics (Fig. 8). Right atrial and right ventricular diastolic pressures are elevated. Mean right atrial and pulmonary capillary wedge pressures are equal (equalization of the diastolic pressures). The pulmonary artery pressure waveform is distorted.

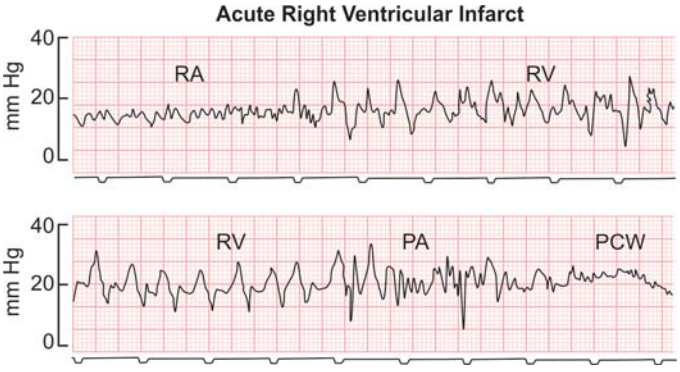


FIGURE 8: The hemodynamic features of acute right ventricular myocardial infarction. Right atrial (RA) and right ventricular (RV) end-diastolic pressures are elevated. The mean RA and pulmonary capillary wedge pressure (PCWP) are equal. There is also distortion of the pulmonary (PA) pressure waveform

TABLE 2

Pulmonary artery catheters: Hemodynamic subsets in acute myocardial infarction

Subset	*Signs*	*Cardiac index (L/min/m²)*	*PAWP (mm Hg)*
I	PC– HYP–	> 2.2	< 18
II	PC + HYP –	> 2.2	> 18
III	PC – HYP +	< 2.2	< 18
IV	PC + HYP +	< 2.2	> 18

(Abbreviations: PC: Pulmonary congestion; HYP: Hypoperfusion; PAWP: Pulmonary artery wedge pressure)

Before the introduction of current therapies, hemodynamic measurements were made to determine the hemodynamic subsets, and therapies were recommended based on these hemodynamic subsets.[21-23] Based on cardiac output and PCWP, four hemodynamic subsets were recognized (Table 2).

In the hemodynamic subset I, the cardiac index was greater than 2.2 L/min/m^2 with the PCWP less than 18 mm Hg. In these patients there were also no clinical signs of pulmonary congestion or hypoperfusion. In the subset II, the cardiac index was more than 2.2 L/min/m^2 and the PCWP was greater than 18 mm Hg. Clinically, these patients did not have evidence of hypoperfusion but had evidence of pulmonary congestion. In the patients in subset III, the cardiac index was less than 2.2 L/min/m^2 and also the PCWP less than 18 mm Hg (hypovolemic shock). Clinically, the patients in this subset had evidence of hypoperfusion but no evidence of pulmonary congestion. In the hemodynamic subset IV, the cardiac index was less than 2.2 L/min/m^2 and the PCWP greater than 18 mm Hg (cardiogenic shock). Clinically, in these patients there was evidence of hypoperfusion and pulmonary congestion.

Suggested therapies according to the hemodynamic subsets are summarized in Table 3.

In patients in subset I, no specific therapy was recommended. In subset II, diuretics were recommended. Diuretics are necessary to relieve pulmonary congestion following reperfusion therapy in patients with acute coronary syndromes. In subset III, fluid replacement treatments were recommended. Hypovolemic shock is an uncommon complication of acute myocardial infarction. Following reperfusion therapy by percutaneous coronary intervention, hypovolemic shock is

TABLE 3

Pulmonary artery catheters: Acute myocardial infarction. Suggested therapy according to hemodynamic subsets

Subset	*Therapy*
I	None
II	Volume expansion
III	Diuretics, vasodilators
IV	Vasodilators, IABP, vasopressors, inotropes

(Abbreviation: IABP: Intra-aortic balloon pump)

occasionally encountered due to excessive blood loss and in these patients fluid replacement treatments are necessary. In patients in subset IV, hemodynamic monitoring is useful after reperfusion treatments and recommended for management of cardiogenic shock complicating acute coronary syndromes.

The issue, however, is whether routine hemodynamic monitoring with the use of balloon flotation catheters is required for management of patients with acute coronary syndromes. That routine hemodynamic monitoring may be associated with increased mortality and morbidity has been reported. In 1987, Gore et al. reported that routine hemodynamic monitoring in patients with acute myocardial infarction was associated with higher in-hospital mortality even in the presence of congestive heart failure, hypotension, or both.[24] In patients with congestive heart failure, the mortality was 44.8% of those who had hemodynamic monitoring and 25.3% who did not. In patients with hypotension, it was 48.3% of those who had hemodynamic monitoring and 32.2% who did not. However, in patients with cardiogenic shock, it was 74.4% of those who had hemodynamic monitoring and 79.1% who did not. Thus, in patients with cardiogenic shock, the use of balloon flotation catheters was not associated with increased in-hospital mortality. In Gusto IIb and III randomized clinical trials, the hazard ratio for the 30-day mortality in patients without cardiogenic shock was 4.80 and in patients with cardiogenic shock it was 0.99.[25] Thus, PA catheterization is not recommended in patients with acute coronary syndromes without cardiogenic shock.

These studies suggest that routine PA catheterization is not indicated in the absence of cardiogenic shock. In patients with cardiogenic shock, however, either due to left ventricular or RV myocardial infarction hemodynamic monitoring is useful and recommended for appropriate management and assessment of response to therapy.

In patients with ventricular septal rupture or severe mitral regurgitation due to papillary muscle dysfunction, hemodynamic monitoring is useful to assess response to therapy. For example, in patients with severe mitral regurgitation, response to vasodilator therapy can be determined by hemodynamic monitoring (Fig. 9).[25] It should be emphasized, however, that for the diagnosis of the mechanical complications of acute coronary syndromes, determinations of hemodynamics are not indicated and transthoracic echocardiography should be performed for the diagnosis.

NON-ACUTE CORONARY SYNDROME

The balloon flotation catheter has been used in the high-risk patients in the medical and surgical intensive care units for the management of volume status, hypotension and shock. The PA catheterization has also been used to distinguish between hemodynamic and permeability pulmonary edema. The PA catheterization has been used in high-risk surgical patients for optimization of oxygen delivery by increasing cardiac output by pharmacologic agents and by maintaining adequate volume status with fluid therapy.[26] However, randomized clinical trials reported lack of any benefit with maximizing oxygen consumption by hemodynamic monitoring.[27]

In one randomized trial in intensive care units, 579 patients received PA catheterization and 522 patients did not. The hospital mortality was 68% in patients who received PA catheterization and 66% in those who did not receive catheterization.[28]

In another randomized trial in high-risk surgical patients, 997 patients received PA catheterization and 997 patients did not.[29] The hospital mortality was 7.8% in patients receiving PA catheterization and 7.7% who did not receive catheterization. The incidence of pulmonary embolism was 8% in patients who had PA catheterization and 0% in those not receiving catheterization. The results of these studies suggest that routine PA catheterization do not provide any survival benefit and can be associated with increased morbidity.

The balloon flotation catheter has been used for the management of patients with ARDS. It has been suggested that

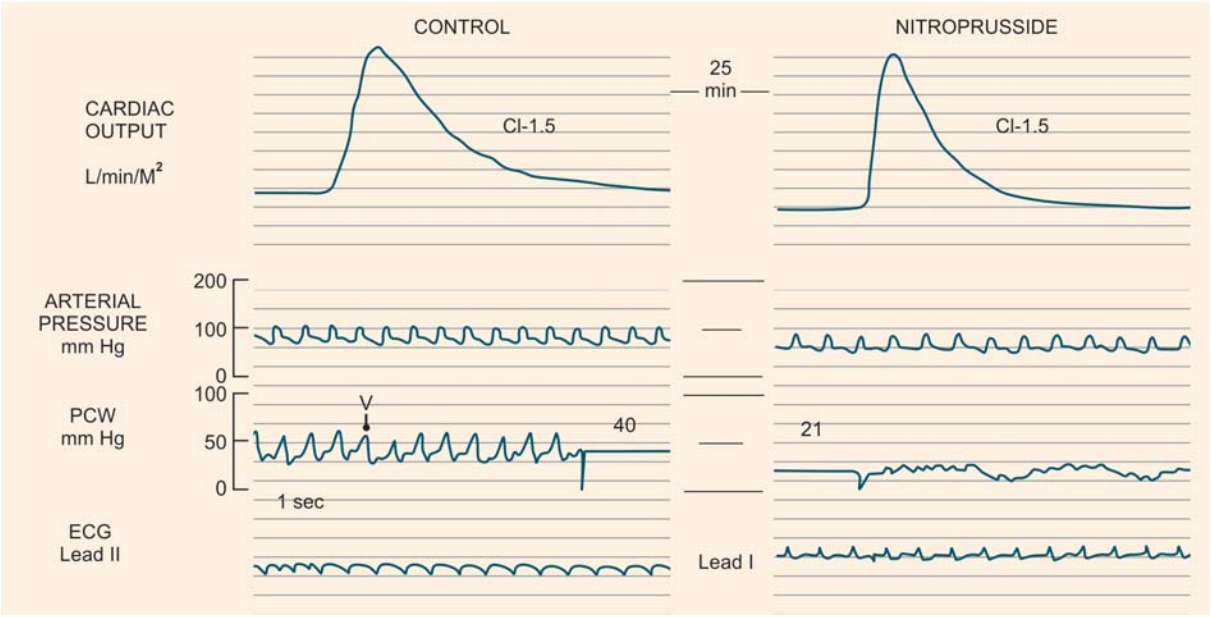


FIGURE 9: The hemodynamic response to vasodilator sodium nitroprusside in a patient with severe mitral regurgitation complicating acute myocardial infarction is illustrated. With nitroprusside, there was a marked decrease in the amplitude of the "v" wave along with an increase in cardiac output. (Abbreviations: PCW: Pulmonary capillary wedge; ECG: Electrocardiography)

monitoring of RA pressure and PCWP and cardiac output will facilitate maintenance of the volume status and regulation of vasopressors and inotropic agents. Indeed, some earlier randomized clinical trials have reported survival benefit of patients who received hemodynamic monitoring.[30]

However, in a large National Heart, Lung, and Blood Institute sponsored randomized trial, there was no benefit of PA catheterization. In this trial, 513 patients received PA catheterization and 488 patients received central venous monitoring. There were 37% of patients with shock in the PA catheterization group and 32% in the central venous monitoring group. The percentage of patients who received vasopressors was 36 in the PA group and 32 in the central venous catheter group. The 60-day mortality in patients receiving PA catheterization was 27.4% and 26.3% in patients receiving central venous monitoring. The ventilator-free and intensive care-free days were 13.2 and 12.0 days in patients who received PA catheterization respectively. In patients who received central venous catheterization, the ventilator-free and intensive care-free days were 13.5 and 12.5 days respectively. The complications rate, however, was higher in patients receiving PA catheterization (0.08%) than in patients receiving central venous catheterization (0.06%).

In this study it was concluded that "pulmonary artery catheterization (PAC) guided therapy did not improve survival or organ perfusion and complications were higher than central venous catheterization (CVC) guided therapy". Thus, there is no indication for routine use of PA catheters for hemodynamic monitoring during management of patients with acute respiratory distress syndrome.

CHRONIC HEART FAILURE

In patients with severe chronic systolic heart failure, hemodynamic subsets have been recognized not only to formulate therapy but also to assess prognosis. In patients with cardiac index of less than 2.2 L/min/m^2 and PCWP greater than 25 mm Hg, the prognosis was worse.[31,32] Systemic vascular resistance more than 1,800 dynes/sec/cm-5 and left ventricular stroke work index less than 45 gm/m^2 were also associated with worse prognosis. These hemodynamic findings suggest that severe chronic left ventricular failure with elevated left ventricular filling pressure and increased systemic vascular resistance indicate adverse prognosis. Based on these hemodynamic indices, the four subsets could be recognized similar to the subsets of acute coronary syndromes. The clinical findings were also incorporated in these hemodynamic subsets.

The hemodynamic subsets were also used for hemodynamic-tailored therapy.[33,34] It has been hypothesized that the determination of the hemodynamic subsets facilitates the use of aggressive diuretic, inotropic and vasoactive drugs. It has been reported that the reduction of PCWP to less than 18 mm Hg and the increase in cardiac index to greater than 2.2 L/min/m^2 improves the long-term prognosis of patients with advanced systolic heart failure.

The hemodynamic-tailored therapy was also reportedly reduced the hospital readmission rates, which is associated with a decrease in cost of therapy of patients with advanced chronic heart failure. The hemodynamic subsets were widely accepted by the heart failure specialists for the management of these patients. The PAC was regarded necessary for appropriate management of these patients. It should be appreciated that these studies were not randomized and were retrospective.

To assess the necessity and effectiveness of bedside hemodynamic monitoring by PAC with the use of balloon flotation catheters, a prospective randomized trial was performed.[35] The primary objective of this study was to determine whether hemodynamic monitoring is helpful for the management of patients with advanced systolic heart failure. Hemodynamic monitoring was compared to clinical assessment. The differences in mortality and number of days in hospital were compared. There was no difference in total and cardiovascular mortality and in the length of hospital stay between the patients who received PAC and patients managed by clinical assessment alone. The results of this study demonstrate that routine PA catheterization is not helpful in the management of patients with chronic advanced systolic heart failure.

It is apparent that routine PAC with the use of balloon flotation catheters is not helpful for the management of patients with acute coronary syndromes, high-risk surgical patients, patients with acute respiratory distress syndrome and patients with severe chronic heart failure (Fig. 10).[36] However, in individual critically ill patients, PAC is still necessary for appropriate management.

PULMONARY HYPERTENSION

The PAC is necessary to determine the cause of pulmonary arterial hypertension.[37] Bedside hemodynamic monitoring is also employed to assess response to therapy. Pulmonary hypertension is defined when the MPAP is greater than 25 mm Hg at rest or greater than 30 mm Hg with exercise.

PA pressure is the product of pulmonary blood flow (PBF) and PVR. In Table 4, the hemodynamic relationship between MPAP, PVR, PBF and mean pulmonary capillary wedge pressure (MPCWP) is illustrated.

The PA hypertension can be postcapillary, which is primarily due to increased pulmonary venous pressure. In postcapillary pulmonary hypertension, PA systolic/diastolic and mean pressures are higher than normal. PCWP is elevated. The PVR is normal. The difference between PA end diastolic pressure (PAEDP) and MPCWP is equal to or less than 5 mm Hg. The examples are mitral and aortic valve disease and primary left ventricular disease (Table 5). The precapillary pulmonary hypertension is primarily due to increased PVR. The PA systolic, diastolic and mean pressures are higher than normal and PVR

TABLE 4

Pulmonary hypertension hemodynamic determinants

1. MPAP = PBF × PVR
2. PVR = (MPAP – MPCWP)/PBF
3. MPAP = MPCWP = PVR × PBF
4. MPAP = (PVR × PBF) + MPCWP

(Abbreviations: MPAP: Mean pulmonary artery pressure; PBF: Pulmonary blood flow; PVR: Pulmonary vascular resistance; MPCWP: Mean pulmonarry capillary wedge pressure)

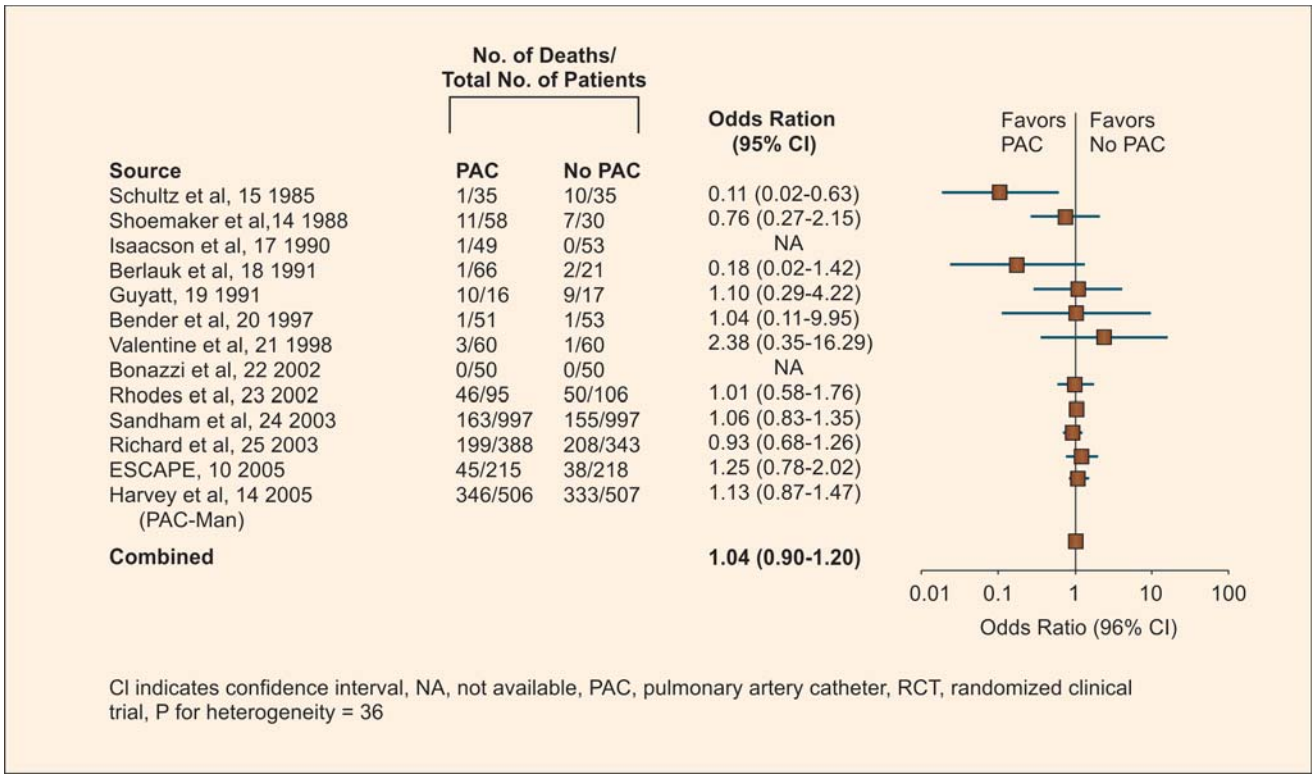


FIGURE 10: The results of a meta-analysis for the use of pulmonary artery catheters (PAC) in intensive care units. There was no benefit from the routine use of pulmonary artery catheters. (*Source:* Reproduced with permission from reference 36)

is increased. The PAEDP is significantly higher than MPCWP. The examples are "idiopathic pulmonary hypertension", collagen vascular disease, and congenital heart diseases (Table 6). The mixed type of PA hypertension is defined when pulmonary arterial hypertension results from both increased pulmonary venous pressure and PVR. The systolic, diastolic and MPAPs are higher than normal. Both MPCWP and PVR are elevated. The PAEDP is higher than the MPCWP. The examples are mitral and aortic valve diseases and chronic primary left ventricular myocardial disease (Table 7).

A selective (left to right shunt) or non-selective (high-cardiac output) increase in PBF may be associated with pulmonary hypertension (Tables 7 and 8). The PA systolic, diastolic and mean pressures are higher than normal. The MPCWP is normal or increased .The PAEDP is equal to or higher than MPCWP. The PVR is normal or decreased.

TABLE 5

Hemodynamic classification of pulmonary arterial hypertension (postcapillary)

Postcapillary pulmonary hypertension

- SPAP, DPAP, MPAP are higher than normal
- PCWP is normal
- PVR is normal
- PAEDP is ≤ 5 mm Hg of MPCWP

Clinical

- Left ventricular systolic or diastolic failure
- Aortic and mitral valve disease
- Pulmonary veno occlusive disease (congenital or acquired)

(Abbreviation: DPAP: Diastolic pulmonary artery pressure)

TABLE 6

Hemodynamic classification of pulmonary arterial hypertension (precapillary)

Precapillary pulmonary hypertension

- SPAP, DPAP, MPAP are higher than normal
- MPCWP is normal
- PVR is elevated
- PAEDP is higher than MPCWP

Clinical

- Primary pulmonary hypertension (PPH)
- PH associated with collagen vascular disease
- Eisemenger syndrome, porto-pulmonary hypertension
- HIV, high altitude PH, thromboembolic PH, peripheral pulmonary arterial branch stenosis

TABLE 7

Hemodynamic classification of pulmonary arterial hypertension (mixed)

Mixed

- SPAP, DPAP, MPAP are higher than normal
- MPCWP is elevated
- PAEDP is modestly higher than MPCWP
- PVR is modestly elevated

Clinical

- Chronic LV systolic and diastolic failure
- Chronic aortic and mitral valve diseases

It is apparent that the PAC is necessary for the diagnosis of the various types of PA hypertension. In addition, determination of hemodynamics is useful to decide what therapy should be employed and also to assess response to therapy.

TABLE 8

Hemodynamic classification of pulmonary arterial hypertension: Selective or nonselective increase in pulmonary blood flow

- Selective or nonselective increase in pulmonary blood flow
  - — SPAP, DPAP, MPAP are higher than normal
  - — PBF is increased
  - — PVR is normal or increased
  - — PCWP is normal or increased
- Clinical
  - — Selective—left to right shunt
    ASD, VSD, PDA, AV fistula
  - — Nonselective
    High cardiac output (e.g. thyrotoxicosis, liver disease)

(Abbreviations: ASD: Atrial septal defect; VSD: Ventricular septal defect; PDA: Patent ductus arteriosus; AV: Ateriovenous)

INDICATIONS FOR PULMONARY ARTERY CATHETERIZATION

Although routine bedside hemodynamic monitoring with the use of balloon flotation catheters is not indicated in patients in cardiac or medical and surgical intensive care units, there are still many indications for its use. In the cardiac catheterization laboratory, it is routinely used during diagnostic catheterization. The potential indications for the use of balloon flotation catheters are summarized in Table 9.

In patients with cardiogenic shock complicating acute coronary syndromes, PAC is indicated. In patients with cardiogenic shock due to chronic severe systolic heart failure, hemodynamic monitoring is frequently required to determine appropriate therapeutic approach. In patients with discordant right and left ventricular failure, measurement of hemodynamics is extremely useful to determine the relative contributions of right and left ventricular function to the hemodynamic abnormalities. Hemodynamic monitoring is also recommended in patients requiring aggressive inotropic and vasoactive drug therapy.

For the differential diagnosis of sepsis and "pseudosepsis" determination of hemodynamics are essential.

Hemodynamic monitoring is useful in some patients with potentially reversible systolic heart failure such as with fulminant myocarditis or peripartum cardiomyopathy.

TABLE 9

The indications for the use of the Swan-Ganz catheters

- Routine application is not indicated even in high-risk cardiac or non-cardiac patients
- In patients with cardiogenic shock complicating acute coronary syndromes during supportive therapy
- In patients with cardiogenic shock due to severe chronic systolic heart failure
- In patients with discordant right and left ventricular function
- In patients with severe chronic systolic or diastolic heart failure requiring inotropic, vasoactive drugs
- For the differential diagnosis of sepsis and "pseudosepsis"
- In some patients with potentially reversible systolic heart failure such as fulminant myocarditis and peripartum cardiomyopathy
- For determination of the etiology of pulmonary artery hypertension and response to therapy
- For the cardiac transplantation work up

For the determination of the etiology of pulmonary arterial hypertension and response to therapy, PAC is indicated.

For the pre-cardiac transplant work-up, PAC is necessary. The effects of vasoactive drugs are assessed during hemodynamic monitoring particularly to determine the reversibility of elevated PVR. The indications for PAC with the use of Swan-Ganz catheters are summarized in Table 9).[38]

COMPLICATIONS

The incidence of serious complications of hemodynamic monitoring with the use of balloon flotation catheters is low.[37] Atrial and ventricular premature beats occur almost universally during the placement of balloon flotation catheter. Non-sustained atrial or ventricular tachycardia occurs less frequently. There is wide variability in the rate of occurrence of atrial and ventricular dysrhythmias. The incidence of ventricular premature beats is from 1% to 68%. The incidence of nonsustained ventricular tachycardia is from 1% to 53%. The sustained ventricular tachycardia is rare. In patients with pre-existing left bundle branch block, complete heart block may be precipitated during placement of the PA catheters due to irritation of the right bundle branch.

If there is evidence for the rupture of the balloon at the distal tip of the catheter, it should be replaced.

It is difficult to estimate the incidence of thromboembolic complications during hemodynamic monitoring. However, the longer the duration of monitoring, the higher is the incidence of thromboembolism. The incidence of pulmonary infarction is approximately 7%. It results from embolization of thrombi formed around the catheter.

The PA perforation is a rare but almost always a fatal complication of PAC with the use of balloon flotation catheters. The incidence is about 0.2%. Sudden hemoptysis of bright red blood is indication of PA perforation. Emergency surgery may be required to prevent the fatal outcome.

Endocardial lesions, including subendocardial hemorrhage, formation of sterile thrombus and infective endocarditis, are infrequent complications of PAC.

The incidence of sepsis is about 4%, and it is more frequent when prolonged hemodynamic monitoring is required. To reduce the risk of sepsis, the insertion of the catheter via femoral vein should be avoided.

The rare complications are Bernard-Horner syndrome, pneumoperitoneum, fracture of the catheter and inadvertent insertion to the carotid artery. Knotting of the balloon flotation catheter around the cardiac structures is infrequently encountered.

CONCLUSION

The feasibility of PAC was demonstrated almost a century ago. With the introduction of balloon flotation (Swan-Ganz) catheters, it has been used indiscriminately in cardiac, medical and surgical intensive care units which were associated with undesirable complications including death. Following a number of randomized clinical trials, the appropriate indications for PAC have been reasonably established. However, there are a number of indications for PAC in critically ill patients.

GUIDELINES
SUMMARY OF GUIDELINES RECOMMENDATIONS (MODIFIED)

(Source: Mueller H, Chatterjee K, Davis KB, et al. Present use of bedside right heart catheterization in patients with cardiac disease. J Am Coll Cardiol. 1998;32:840-64)

GRADING OF RECOMMENDATIONS

1. Conditions in which there is general agreement that right heart catheterization is indicated.
2. Conditions in which reasonable differences of opinion exist regarding right heart catheterization.
3. Conditions in which right heart catheterization is not warranted.
4. Conditions in which a relative contraindication to right heart catheterization exists.
5. Conditions in which an absolute contraindication to right heart catheterization exists.

RECOMMENDATIONS: HEART FAILURE

Conditions in which right heart catheterization is warranted:
1. For differentiation between hemodynamic and permeability pulmonary edema, and when a trial of diuretic and/or vasodilator therapy has failed to distinguish or associated with high risk.
2. For differentiation between cardiogenic and noncardiogenic shock and for guidance of pharmacologic and/or mechanical support.
3. For guidance of therapy in patients with concomitant manifestations of “forward” and “backward” heart failure.
4. For guidance of perioperative management in selected patients with decompensated heart failure undergoing intermediate or high-risk non-cardiac surgery.
5. For pre-heart transplant work up.

Conditions in which a relative contraindication to right heart catheterization exists:
1. Coagulopathy or anticoagulation therapy that can not be temporarily discontinued.
2. Recent implantation of permanent pacemaker or cardioverter-defibrillator.
3. Left bundle branch block.
4. Bioprosthetic tricuspid or pulmonic valve.

Conditions in which an absolute contraindication to right heart catheterization exists:
1. Right-sided endocarditis.
2. Mechanical tricuspid or pulmonic valve prosthesis.
3. Presence of thrombus or tumor in right heart chambers.
4. Terminal illness for which aggressive management is considered futile.

RECOMMENDATIONS: ACUTE CORONARY SYNDROME.

Conditions in which there is general agreement that right heart catheterization is warranted:
1. Differentiation between cardiogenic and hypovolemic shock.
2. Guidance of therapy of patients with cardiogenic shock with pharmacologic and/or mechanical support with or without reperfusion therapy.
3. During short-term treatments of complications such as mitral regurgitation and ventricular septal rupture.
4. During management of patients with right ventricular myocardial infarction with hypotension.
5. For guidance of therapy of patients with refractory pulmonary edema.

Conditions in which right heart catheterization is not warranted:
1. For guidance of management of patients with postinfarction angina.
2. For guidance of therapy of pulmonary edema responding to standard therapy.

Conditions in which an absolute contraindication to right heart catheterization exist:
1. Same as in heart failure.

RECOMMENDATIONS: PERIOPERATIVE USE IN CARDIAC SURGERY.

Conditions in which there is general agreement that right heart catheterization is warranted:
1. For the diagnosis of the causes of low cardiac output.
2. For differentiation of right and left ventricular dysfunction.
3. For guidance of management of patients with low cardiac output syndromes.

Conditions in which right heart catheterization is not warranted:
1. For routine management of uncomplicated cardiac surgical patients.
2. For assessment of prognosis of cardiac surgery.

Conditions in which an absolute contraindication to right heart catheterization exists:
Same as in "heart failure".

RECOMMENDATIONS: PULMONARY ARTERIAL HYPERTENSION.

Conditions in which there is general agreement that right heart catheterization is warranted:
1. For the differential diagnosis of "postcapillary," "precapillary" and "mixed" pulmonary hypertension.
2. For the diagnosis of severity of precapillary pulmonary arterial hypertension and the prognosis.
3. For the assessment of therapy in patients with precapillary pulmonary arterial hypertension.

Conditions in which right heart catheterization is not warranted:
None

Conditions in which a relative or absolute contraindication to right heart catheterization exists:
Same as in "heart failure".

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Chapter 28

Coronary Angiography and Catheter-based Coronary Intervention

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Chapter Outline

- Indications for Coronary Angiography
- Contraindications for Coronary Angiography
- Patient Preparation
- Sites and Techniques of Vascular Access
  - Femoral Artery Approach
  - Transradial Approach
  - Brachial Artery Approach
- Catheters for Coronary Angiography
  - Judkins-type Coronary Catheters
  - Amplatz-type Catheters
  - Multipurpose Catheter
- Catheters for Bypass Grafts
  - Transradial Specific Catheters
- Arterial Nomenclature and Extent of Disease
- Angiographic Projections
- Normal Coronary Anatomy
  - Left Main Coronary Artery
  - Left Anterior Descending Artery
  - Left Circumflex Artery
  - Right Coronary Artery
  - Right Dominant Coronary Circulation
  - Left Dominant Coronary Circulation
  - Co-dominant or Balanced Coronary Circulation
  - Coronary Collateral Circulation
- Congenital Anomalies of the Coronary Circulation
  - Anomalous Pulmonary Origin of the Coronary Arteries
  - Anomalous Coronary Artery from the Opposite Sinus
  - Coronary Artery Fistulae
  - Congenital Coronary Stenosis or Atresia
  - Myocardial Bridging
- General Principles for Coronary and/or Graft Cannulation
  - Left Main Coronary Artery Cannulation
  - Right Coronary Artery Cannulation
  - Coronary Bypass Graft Cannulation
  - Saphenous Vein Grafts
  - Internal Mammary Artery Grafts
  - Gastroepiploic Artery
  - Standardized Projection Acquisition
- The Fluoroscopic Imaging System
- Characteristics of Contrast Media
  - Contrast Media Reactions
- Contrast-induced Renal Failure
- Access Site Hemostasis
- Complications of Cardiac Catheterization
  - Access Site Complications
  - Other Complications
- Lesion Quantification
  - Quantitative Angiography
  - Lesion Complexity
  - Lesion Length
  - Ostial Lesions
  - Bifurcation Lesions
  - Angulated Lesions
- Degenerated Saphenous Vein Grafts
- Lesion Calcification
  - Thrombus
  - Total Occlusion
  - Coronary Perfusion
- Physiologic Assessment of Angiographically Indeterminate Coronary Lesions
  - Fractional Flow Reserve
- Clinical Use of Translesional Physiologic Measurements
- Non-atherosclerotic Coronary Artery Disease and Transplant Vasculopathy
  - Coronary Artery Spasm
  - Spontaneous Coronary Artery Dissection
  - Vasculitis
  - Transplant Vasculopathy
- Potential Errors in Interpretation of the Coronary Angiogram
  - Inadequate Vessel Opacification
  - Catheter-induced Spasm
  - Incomplete Study
  - Coronary Anomalies
  - Total Occlusion of a Coronary Artery
  - Eccentric Stenoses
  - Superimposition of Vessels
  - Microchannel Recanalization
- Percutaneous Coronary Intervention

- Pharmacotherapy for PCI
  - — Antiplatelet Therapy
- Parenteral Anticoagulant Therapy
  - — Heparin
  - — Enoxaparin
  - — Bivalirudin
- Equipment for Coronary Interventions
  - — Guide Catheters
  - — Guidewire
  - — Balloons
  - — Other Specialized Intracoronary Balloons
- Percutaneous Transluminal Coronary Angioplasty
- Coronary Stents
- Types of Stents
- Stent Deployment
- Adjunctive Coronary Interventional Devices
  - — Thrombectomy
  - — Rotational Coronary Atherectomy
  - — Directional Coronary Atherectomy
- Embolic Protection Devices for Venous Bypass Graft PCI
  - — Distal Embolic Filters
  - — Distal Occlusion Devices
  - — Proximal Occlusion Devices
- Clinical Outcomes
  - — DES versus BMS
- Procedural Success and Complications Related to Coronary Intervention
- Complications Specific to PCI
  - — Threatened or Acute Closure
  - — Perforation
  - — No-Reflow
  - — Acute Thrombotic Closure

INTRODUCTION

The first attempt to image the coronary arteries began in the late 1940s. In 1953, Seldinger first introduced a method of percutaneous arterial catheterization to study the coronary arteries.[1] However, this percutaneous approach was not initially widely adopted.In the late 1950s, Sones developed a safe and reliable method of selective coronary angiography using a brachial artery cut down approach to arterial access.[2] In the late 1960s, Amplatz et al.[3] and Judkins[4] developed modifications of catheters for selective coronary angiography while also employing the percutaneous method previously introduced by Seldinger. This combination and modification of previous approaches ushered in the beginning of the modern era of coronary angiography as we recognize it today.

Coronary angiography has subsequently become one of the most widely used invasive procedures in cardiovascular medicine and remains the gold standard for identifying the presence or absence of atherosclerotic coronary artery disease (CAD). It provides not only the most reliable anatomic information but also along with adjunctive invasive modalities; it can now provide the clinician with a more precise characterization of the extent of atherosclerotic disease burden. This greatly assists the practitioner in selection of the most appropriate form of therapy for a given patient. More than two million patients will undergo coronary angiography in the United States this year alone.

The methods used to perform coronary angiography have continued to improve substantially over time. Smaller (5–6 French) high-flow injection catheters have replaced larger (8 French) thick-walled catheters. The smaller sheath sizes and the introduction and development of radial artery access for coronary catheterization have allowed same-day outpatient coronary angiography, early ambulation and discharge. Complication rates associated with coronary angiography have decreased secondary to a better understanding of the peri-procedural management of patients undergoing cardiac catheterization.

This chapter discusses the indications for and techniques of coronary angiography, normal coronary anatomy, some pathological coronary variants, various pitfalls to avoid in the safe and successful performance of this procedure, and a brief introductory discussion of coronary intervention.

INDICATIONS FOR CORONARY ANGIOGRAPHY

The American College of Cardiology/American Heart Association (ACC/AHA) Task Force has established indications for coronary angiography in patients with known or suspected CAD (Table 1).[5]

Despite the recent advances in noninvasive imaging of the coronary arteries, coronary angiography remains the gold standard for the delineation of coronary arterial anatomy. Patients who have a clear indication for coronary angiography include: individuals with known or suspected CAD who have severe stable angina [Canadian Cardiovascular Society (CCS) class III or IV], individuals with less severe symptoms but an abnormal noninvasive test, or asymptomatic individuals who demonstrate “high-risk” criteria on noninvasive testing. Patients resuscitated from sudden cardiac death (SCD)—particularly those with residual ventricular arrhythmias—are also candidates for coronary angiography, given the favorable outcomes associated with revascularization in this patient population. In the absence of symptoms or signs of ischemia, the presence of coronary calcification on fluoroscopy or a high calcium score by ultrafast computed tomographic (CT) scanning alone are not indications for coronary angiography.

Patients with ST segment elevation myocardial infarction (STEMI) should undergo emergent coronary angiography with intent of primary coronary intervention. Diagnostic coronary angiography should also be undertaken in patients presenting in cardiogenic shock, who are candidates for revascularization in the setting of STEMI. Additionally, patients with non-ST segment elevation myocardial infarction (NSTEMI) or unstable angina benefit from early invasive treatment with urgent coronary angiography and coronary revascularization. Coronary

TABLE 1

Indications for coronary angiography

ACC/AHA guideline summary: Coronary angiography for risk stratification in patients with chronic stable angina
Class I: There is evidence and/or general agreement that coronary angiography should be performed to risk stratify patients with chronic stable angina in the following settings: • Disabling anginal symptoms [Canadian Cardiovascular Society (CCS) classes III and IV] despite medical therapy • High-risk criteria on noninvasive testing independent of the severity of angina • Survivors of sudden cardiac death or serious ventricular arrhythmia • Symptoms and signs of heart failure • Clinical features suggest that the patient has a high likelihood of severe coronary artery disease
Class IIa: The evidence or opinion is in favor of performing coronary angiography to risk stratify patients with chronic stable angina in the following settings: • Left ventricular ejection fraction less than 45%, CCS class I or II angina and evidence, on noninvasive testing, of ischemia that does not meet high-risk criteria • Noninvasive testing does not reveal adequate prognostic information *Class IIb: The evidence or opinion is less well established for performing coronary angiography to risk stratify patients with chronic stable angina in the following settings:* • Left ventricular ejection fraction greater than 45%, CCS class I or II angina and evidence, on noninvasive testing, of ischemia that does not meet high-risk criteria • CCS class III or IV angina that improves to class I or II with medical therapy • CCS class I or II angina but unacceptable side effects to adequate medical therapy
Class III: *There is evidence and/or general agreement that coronary angiography should not be performed to risk stratify patients with chronic stable angina in the following settings:* • CCS class I or II angina that responds to medical therapy and, on noninvasive testing, shows no evidence of ischemia • Patient preference to avoid revascularization
(*Source:* Gibbons RJ, Abrams J, Chatterjee K, et al. ACC/AHA 2002 guidelines update for the management of patients with chronic stable angina—summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients with Chronic Stable Angina). Circulation. 2003;107:149.)

angiography should also be considered in patients with myocardial infarction (MI) complicated by congestive heart failure (CHF), hemodynamic instability, frequent complex arrhythmias, cardiac arrest or severe mitral regurgitation. Patients with angina or provocable ischemia after MI should also undergo coronary angiography, as revascularization may reduce the risk of reinfarction in these patients. Furthermore, there is evidence to support an early invasive strategy in patients with repeated presentations for acute coronary syndrome despite therapy and without evidence for ongoing ischemia or high risk, especially if these patients have not had a previous coronary angiogram. However, coronary angiography is not recommended for the subset of patients who present with chest discomfort suggestive of unstable angina, but no objective signs of ischemia and with normal coronary angiogram during the past 5 years.[5]

Patients with chest pain of unclear etiology, particularly those with high-risk criteria on noninvasive cardiac testing, may benefit from coronary angiography to evaluate for the presence of significant CAD.[5] Patients who have undergone prior revascularization, especially recently, should undergo coronary angiography if there is recurrent angina or the suspicion of abrupt vessel closure.

Coronary angiography should be performed in patients before noncardiac surgery who demonstrate high-risk criteria on noninvasive testing, have angina unresponsive to medical therapy, develop unstable angina, or have equivocal noninvasive test results and are scheduled to undergo high-risk surgery. It is also recommended for patients prior to surgery for valvular heart disease or congenital heart disease—particularly those with cardiac risk factors—and in patients with infective endocarditis with evidence of coronary embolization.[5]

Finally, surveillance coronary angiography should be performed in patients after cardiac transplantation. These angiograms should be performed at specified intervals even in the absence of clinical symptoms, secondary to the often asymptomatic nature of allograft atherosclerosis. Coronary angiography is also an important assessment in potential donors for cardiac transplantation whose age or cardiac risk profile increases the likelihood of CAD.

CONTRAINDICATIONS FOR CORONARY ANGIOGRAPHY

With the exception of patient refusal, there are no absolute contraindications to coronary angiography. Significant relative contraindications include: ongoing stroke or cerebrovascular accident (CVA) within a month, recent head trauma, significant active bleeding, anemia with hemoglobin less than 8 mg/dl, uncontrolled systemic hypertension, digitalis toxicity, previous contrast reaction without pretreatment with corticosteroids, severe electrolyte imbalance, unexplained fever and untreated infection. Other disease states that are relative contraindications to coronary angiography include: acute renal failure, decompensated CHF, severe intrinsic or iatrogenic coagulopathy [International Normalized Ratio (INR greater than 2.0)]—unless transradial approach is performed, and active endocarditis. Given that the majority of these conditions are self-limited, deferral of coronary angiography until important comorbidities have been stabilized is generally preferred, unless there is evidence of ongoing myocardial necrosis. It is well recognized that coronary angiography performed under emergency conditions is associated with a higher risk of procedural complications. The risks and benefits of the procedure and alternative evaluation techniques—if potentially indicated—should always be carefully reviewed with the patient and family in all circumstances prior to coronary angiography, but especially in the presence of relative contraindications (Table 2).

PATIENT PREPARATION

The procedure should be explained to the patient in simple terms and informed consent to perform the procedure is then obtained. The operator should clearly explain the potential risks and benefits for cardiac catheterization to the patient and family. Patient information should be tailored to the specific individual and the associated clinical question to be addressed. Patients with diabetes mellitus, renal insufficiency or previous reported hypersensitivity to iodinated contrast media constitute groups

TABLE 2

Contraindications to cardiac catheterization

Absolute contraindications
- Inadequate equipment or catheterization facility
- Patient refusal

Relative contraindications
- Acute gastrointestinal bleeding or anemia
- Anticoagulation (or known uncontrolled bleeding diathesis)
- Electrolyte imbalance
- Infection or fever
- Medication intoxication (e.g. digitalis, phenothiazine)
- Pregnancy
- Recent cerebral vascular accident (> 1 mo)
- Renal failure
- Uncontrolled congestive heart failure, high blood pressure, arrhythmias
- Uncooperative patient

who need special consideration. For diabetic patients, insulin dosing should be adjusted to minimize the risk of periprocedural hypoglycemia. Patients with renal insufficiency should have interventions for renal function preservation following contrast administration. These should include: volume repletion with intravenous (IV) fluids before contrast administration, consideration of N-acetylcysteine administration and consideration of biplane angiography if available. At our institution, all patients with renal insufficiency receive N-acetylcysteine prior to coming to catheterization laboratory. IV fluid administration is also given to patients with renal insufficiency who are not volume overloaded before their procedure. When available, biplane angiography is performed in a select subset of patients at very high risk of clinically significant contrast nephropathy. Patients with known hypersensitivity to iodinated contrast should be premedicated using established protocols—usually including steroid and antihistamine medications—to reduce the risk of a reaction with contrast administration.

Once the patient arrives in the catheterization laboratory, the designated access site is prepped and the patient is given IV sedative medications to keep them comfortable through the procedure.

SITES AND TECHNIQUES OF VASCULAR ACCESS

The site of vascular access is determined by the anticipated pathologic and anatomic findings relevant to the patient. Documentation of any difficulties encountered during a previous procedure, especially of vascular access, should be reviewed. Prior to the procedure, assessment of all peripheral pulses is mandatory. If a transradial approach is being considered, an Allen's test should also be performed to confirm candidacy for this approach.

FEMORAL ARTERY APPROACH

Percutaneous femoral arterial catheterization remains the most widely used vascular access site for coronary angiography in the United States, although the use of radial arterial access is steadily increasing. In patients with claudication, chronic lower extremity arterial insufficiency, diminished or absent pulses, or bruits over the iliofemoral area, alternate entry sites should be considered. In order to reduce access site complications,

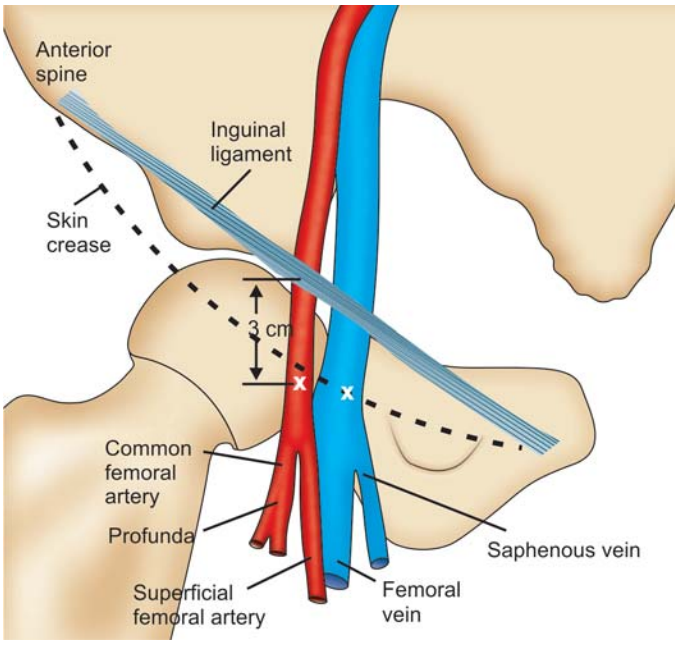


FIGURE 1: Femoral artery access site. Anatomy relevant to percutaneous catheterization of the femoral artery (FA) and vein. The right FA vein passes underneath the inguinal ligament, which connects the anterior-superior iliac spine and pubic tubercle. The arterial skin nick (indicated by X) should be placed approximately 1-1/2–2 fingerbreadths (3 cm) below the inguinal ligament and directly over the FA pulsation. (*Source:* Baim DS, Grossman W. Percutaneous approach including transseptal and apical puncture. In: Baim DS, Grossman W (Eds). Grossman's Cardiac Catheterization, Angiography, and Intervention, 6th edition. Baltimore: Lippincott, Williams and Wilkins; 2000.)

obtaining access to the common femoral artery below the inguinal ligament is strongly recommended. The common femoral artery passes underneath the inguinal ligament, which connects the anterior-superior iliac spine and pubic tubercle. Palpation of the femoral pulse and the previously mentioned anatomical landmarks is the first step in obtaining arterial access. Before the puncture, fluoroscopy of the tip of a metal clamp placed near the medial edge of the middle of the head of the femur is often performed. This step is done to enhance the likelihood of puncturing the common femoral artery, while remaining below the inguinal ligament. This location in the middle of the femoral head is typically the location of the common femoral artery in most patients, although there is certainly anatomic variation (Fig. 1). Adequate local anesthesia should be administered. A skin nick is then placed approximately 1-1/2–2 fingerbreadths (3 cm) below the inguinal ligament and directly over the femoral artery pulsation. Palpation identifies the middle of the artery and the needle is advanced at a 30–45° angle to the vessel, preferably puncturing only the front wall. Once brisk arterial flow through the needle is established, the guidewire is advanced through the needle to the descending aorta. The guidewire should pass freely without any resistance. If any resistance to passage of the wire is encountered, the operator should stop immediately and use fluoroscopy to visualize advancement of the wire. If the wire has not yet exited the needle tip, the wire should be removed to confirm pulsatile flow through the needle before attempting to readvance the wire, as there is concern of subintimal or extravascular passage of

the wire. If pulsatile flow through the needle is not apparent after removing the wire, then the needle is repositioned until arterial backflow is reestablished and the wire passes without resistance. Once the wire is successfully placed into the descending aorta to the level of the diaphragm, the needle is then exchanged for a valved sheath, which is usually 4–6 French in size for femoral access diagnostic procedures.

TRANSRADIAL APPROACH

The radial artery approach has several distinct advantages[6,7] and is becoming more commonly used for coronary angiography. The superficial location of the radial artery makes it easily accessible in most patients. There is dual blood supply to the hand via the radial and the ulnar arteries which decreases the potential of any meaningful clinical sequelae in the case of a procedural related radial artery occlusion. Patient comfort is enhanced as there is no need for flat bedrest after a transradial procedure. Also, radial artery access provides the most secure hemostasis in the fully anticoagulated patient. Patients with a palpable radial pulse and a normal Allen's test are generally candidates for the transradial approach, although there are some contraindications including: abnormal Allen's test, known upper extremity vascular disease including Reynaud's Disease, need for intra-aortic balloon pump or other left ventricular (LV) assist devices, patient refusal, planned or existing dialysis AV fistula or planned use of radial artery for bypass conduit. In appropriately selected patients, the ideal point to access the radial artery is just proximal to the styloid process of the radius. This is usually about 2–3 cm above the flexor crease (Fig. 2). A small amount of local anesthesia is given to the area. The radial artery can be accessed with two different techniques. In the first, the radial pulse is palpated at the site indicated previously. Then, a short (2.5 cm) 21-gauge needle is advanced into the radial artery at a 30–40°angle. Once pulsatile flow is obtained, a 0.021 inch diameter guidewire is advanced in the radial artery. A hydrophilic coated sheath (typically 5 French) is advanced into the radial artery—no skin nick is usually needed. As soon as the sheath is placed, intra-arterial administration of spasmolytic cocktail is given to prevent radial artery spasm. This spasmolytic cocktail typically contains a calcium channel blocker and nitroglycerin. Heparin is also always given during transradial catheterization as this is known to decrease the chance of procedural related radial artery occlusion. Although usually asymptomatic and without clinical sequelae in appropriately selected patients, radial artery occlusion may preclude access for future procedures.

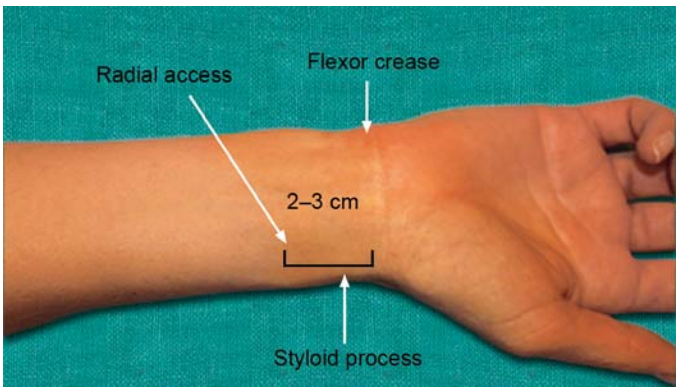


FIGURE 2: Ideal radial artery access site: just proximal to the styloid process (usually 2–3 cm from the flexor crease)

The second technique for obtaining radial arterial access involves the use of an IV catheter to puncture the radial artery instead of a bare needle. Once a backflow of blood is noted in the hub of the IV catheter, the catheter is advanced to also puncture the posterior wall of the vessel. The needle is then removed and the plastic cannula is slowly withdrawn until pulsatile flow is obtained. Then a guidewire (0.021–0.025 inch) is advanced into the radial artery and the IV catheter is then exchanged for the sheath and spasmolytic cocktail and heparin are given.

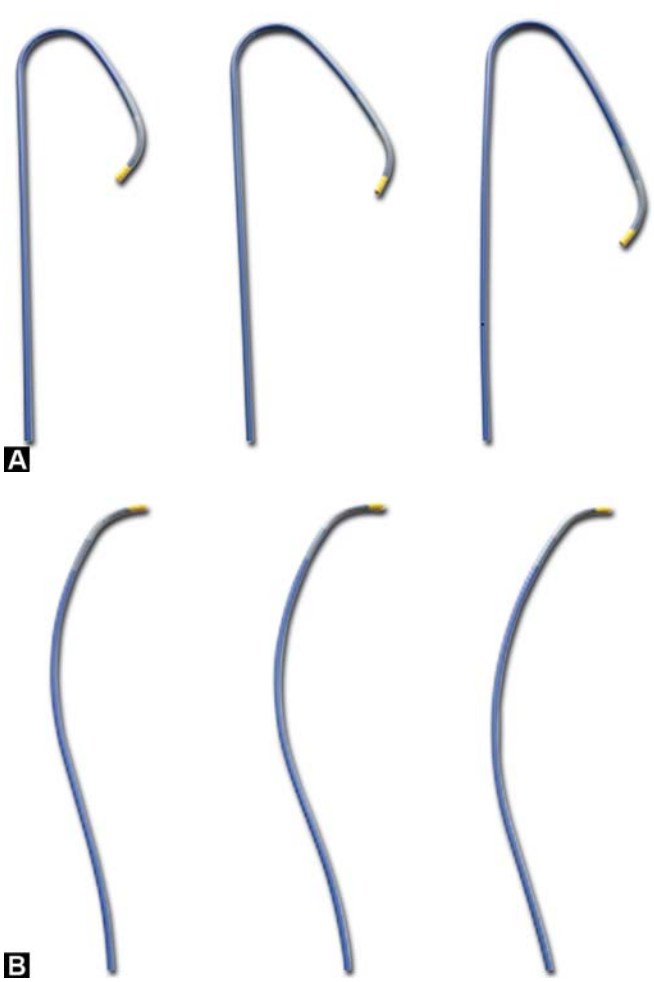
Both of these techniques are accepted methods of obtaining radial artery access for performing coronary angiography. An important difference to note between femoral and radial access is that the radial artery is much more prone to spasm which can affect the successful performance of the procedure. It is vital to give spasmolytic medications (usually consisting of a calcium channel blocker and nitroglycerin) into the sheath on initial insertion as well as with any necessary catheter exchange, as prevention of spasm is usually more effective than attempting to treat it once it occurs. Young or female patients (those with smaller radial arteries) are more likely to have spasm of the radial artery. In addition to spasmolytic medications, adequate patient sedation helps in reducing radial artery spasm.

BRACHIAL ARTERY APPROACH

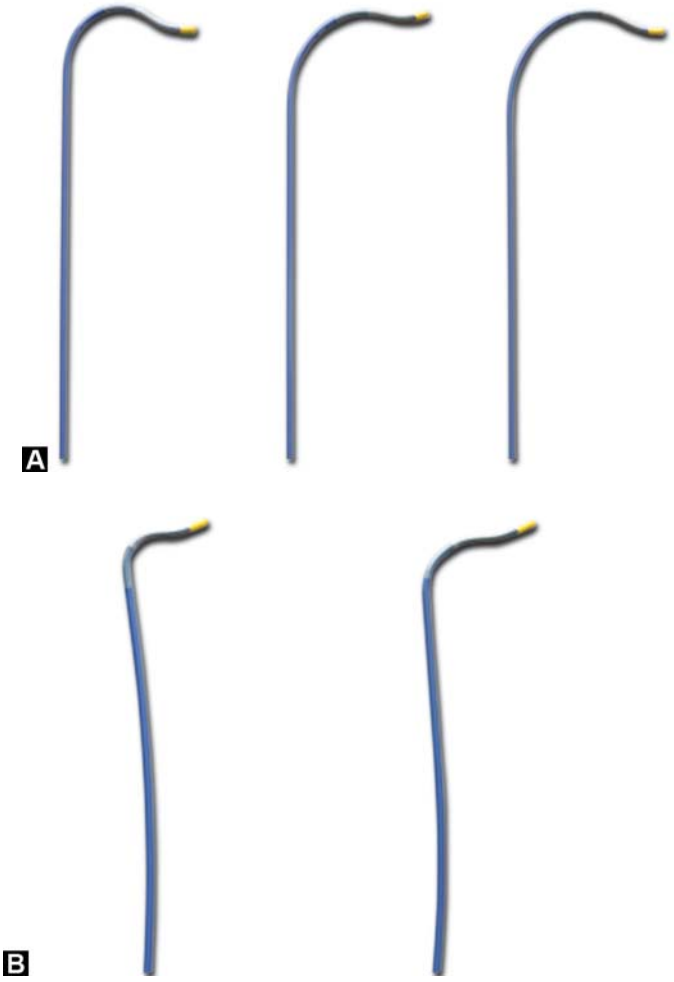
With the recent development and increase in the use of transradial catheterization, the brachial approach for catheterization has become less commonly used. There are more access site complications (bleeding, pseudoaneurysm, etc.) with brachial access compared to radial access. Accessing the brachial artery removes the advantage of dual blood supply to the hand that exists with radial access. However, when needed, the brachial approach is still a viable option for coronary angiography. For example, if femoral access is technically not possible and larger sheaths than can be accommodated by the radial artery are needed, brachial access may be indicated. In the past, brachial arterial access for coronary angiography was performed primarily with a cutdown approach. However, this technique has largely fallen out of favor in the performance of coronary angiography. Currently, when brachial access is used for coronary angiography, access is gained percutaneously, often with a 21G needle and 0.021 inch guidewire. The brachial artery is typically accessed 2–3 cm above the antecubital fossa, where the vessel is still relatively superficial. Accessing the vessel more proximal than this typically increases the risk of access difficulty and complications as the vessel is generally deeper in this area. There can be spasm of the brachial artery, but this is much less common than is observed with the radial artery. If encountered, it can be treated with spasmolytic medications including calcium channel blockers and/or nitrates.

CATHETERS FOR CORONARY ANGIOGRAPHY

Numerous shapes and sizes of catheters are available to the angiographer. Routinely used catheters that are preshaped for normal anatomy are available for both the radial and the femoral



FIGURES 3A AND B: (A) Judkins left 4,5,6 catheters (left to right); (B) Judkins right 3.5,4,5 catheters (left to right). (*Source:* Boston Scientific.)



FIGURES 4A AND B: (A) Amplatz left 1,2,3 catheters (left to right); (B) Amplatz right 1,2 catheters (left to right). (*Source:* Boston Scientific.)

approaches. There is an additional array of shapes and sizes to aid the operator with the various coronary artery anatomical variations that are encountered (Figs 3 and 4). Regardless of access site, all catheters should be advanced into the ascending aorta over a wire. The wire is then removed; the catheter is aspirated and then flushed with heparinized saline and connected to either a coronary manifold or power injector system. There are many different types of catheters that are used to perform coronary and bypass graft angiography. We have described and illustrated some of the most commonly used catheters; however, there are certainly many other less commonly used catheters that have not be discussed here.

JUDKINS-TYPE CORONARY CATHETERS

The Judkins catheters have unique preshaped curves and end-hole tips. The Judkins left coronary catheter has a double curve. The length of the segment between the primary and the secondary curve determines the size of the catheter (i.e. 3.5, 4.0, 5.0 or 6.0 cm) (Figs 3A and B). The proper size of the left Judkins catheter is selected depending on the length and width of the ascending aorta. The ingenious design of the left Judkins catheter permits cannulation of the left coronary artery most often without any major catheter manipulation except the slow advancement of the catheter under fluoroscopic guidance. With advancement, the catheter tip usually follows the ascending aortic border and falls into the left main coronary ostium. A Judkins left 4.0 catheter is generally appropriate for most adult patients with a presumed normal sized ascending aorta. When catheter size is appropriate, the catheter tip is aligned with the long axis of the left main coronary trunk in a coaxial fashion. At times, it may be necessary to upsize or downsize the catheter in order to obtain a coaxial position. This will allow the best opacification of the vessels and lessen the chance of a complication from injecting through a malpositioned catheter. If the catheter tip is pointed too superior, then a larger size catheter should be chosen. On the contrary, if the catheter tip is pointing below the level of the left main, then a shorter catheter may be needed. The Judkins left catheter is not only best suited for use from the femoral or left upper extremity approach but can also be helpful from the right upper extremity approach in selected cases.

The Judkins right coronary catheter is commonly used to cannulate the right coronary artery (RCA). It is sized by the length of the secondary curve (3.5, 4.0 and 5.0 cm sizes).

The 4.0 cm catheter is adequate for most cases and rarely is another size required—unlike with the Judkins left catheter. Also unlike the Judkins left catheter, the Judkins right catheter requires manipulation beyond just advancement in order to engage the coronary vessel. This catheter is advanced into the ascending aorta [usually in the left anterior oblique (LAO) projection] down to the level of the aortic valve. The catheter is then slightly withdrawn and torqued in a clockwise fashion to gently rotate the catheter into the right coronary sinus toward the right coronary ostium. A common error in attempting RCA cannulation is excessive rotation of the catheter. This results in an abrupt jumping of the catheter and often a very deep cannulation of the vessel. When this occurs, there is often pressure damping requiring additional manipulation of the catheter before safe performance of angiograms can be accomplished. Coronary spasm or even dissection can also result from this suboptimal method of cannulation. The Judkins right catheter is suited for use from the femoral approach as well as either upper extremity approach.

AMPLATZ-TYPE CATHETERS

The left Amplatz-type catheter is a preshaped half circle with the tip extending perpendicular to the curve. Amplatz catheter sizes (left 1, 2 and 3 and right 1 and 2) indicate the diameter of the tip's curve (Figs 4A and B). In the LAO projection, the Amplatz left catheter is advanced into the left coronary sinus. Further advancement of the catheter causes the tip to move upward and toward the left main ostium. Engagement of the left main ostium often requires additional rotational maneuvering of the catheter. After completion of the angiograms, it is most often necessary to advance the Amplatz left catheter slightly in order to safely disengage the catheter tip from the left main ostium. If the catheter is initially withdrawn instead of initially being slightly advanced, the tip often moves downward and deeper into the left main, potentially causing trauma to the vessel. An Amplatz left catheter is generally more challenging to manipulate compared to a Judkins left catheter and as a result its usage is less common. Unlike the Judkins left catheter, the Amplatz left catheter can also be used to cannulate the RCA, especially in the case of a high and/or anterior takeoff of the RCA.

The Amplatz right catheter has a much smaller but similar hook-shaped curve with a slightly downgoing tip. This catheter is advanced into the right coronary cusp. Then, like with a Judkins right catheter, it is advanced further to the level of the aortic valve, then slowly withdrawn and rotated in a clockwise direction to cannulate the RCA. Unlike the Amplatz left catheter, this catheter may be safely pulled or rotated out of the coronary artery upon completion of the angiograms.

MULTIPURPOSE CATHETER

This catheter is a gently curved catheter with an end hole and two side holes which are positioned close to the tapered tip. The multipurpose catheter can be used for both left and right coronary cannulation and theoretically for left ventriculography, although performance of left ventriculography is most safely and effectively performed with a pigtail catheter. This catheter is used much less frequently since the development of the many preshaped catheters that are generally easier to manipulate.

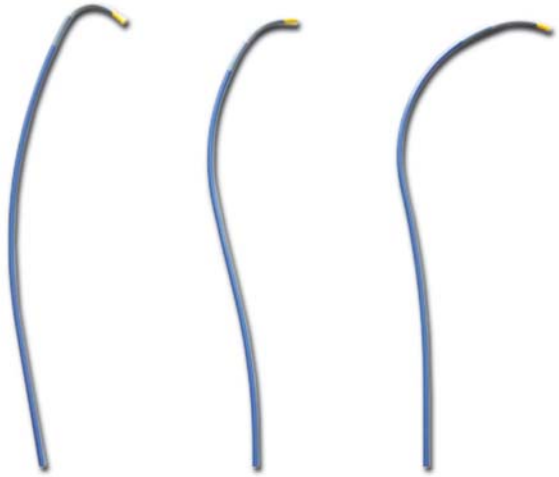


FIGURE 5: IMA, right and left bypass catheters. (*Source:* Boston Scientific.)

CATHETERS FOR BYPASS GRAFTS

Many of the bypass grafts that originate from the aorta (vein, radial or other arterial conduit) can be engaged with either a Judkins right catheter or an Amplatz right catheter. There are also dedicated bypass graft catheters that sometimes need to be used when one is unable to cannulate grafts with the Judkins or Amplatz shapes (Fig. 5). The right coronary bypass catheter is somewhat similar to a right Judkins catheter but has a wider, more open primary curve. This allows more reach that is typically needed for cannulation of the cranially and more rightward location of the bypass grafts to the right coronary and its branches. The left bypass graft catheter is also somewhat similar to the Judkins right catheter, but has a smaller secondary curve. This allows easier cannulation of grafts to the left coronary system, which usually are placed higher and more anterior than grafts to the right coronary system. The internal mammary artery (IMA) catheter has a hook-shaped tip that facilitates the engagement of pedicled IMA grafts. Cannulation of the IMA grafts first requires engagement of the brachiocephalic artery (in the case of a right internal mammary graft) or the left subclavian artery (in the case of a left internal mammary graft).Once this has been accomplished, the IMA catheter is used to engage the IMA. The technique for IMA graft cannulation has been discussed later in more detail.

TRANSRADIAL SPECIFIC CATHETERS

With the increasing use of radial arterial access for coronary angiography, diagnostic coronary catheters with unique shapes have been and continue to be developed for transradial use (Fig. 6). Although there are different shapes, all of the catheters developed for use from the transradial approach are intended to be used to perform a complete coronary angiogram with one catheter. Many of the catheters have a hydrophilic coating to help minimize radial artery spasm. Some of the most commonly used catheters are shown (Fig. 6) and include the Tiger and Jacky shapes. More transradial specific catheter shapes currently exist (Barbeau is another) and as transradial catheterization continues to increase in use, likely more new diagnostic and guide catheter shapes will be developed. Generally, transradial operators begin with one of the more common radial specific

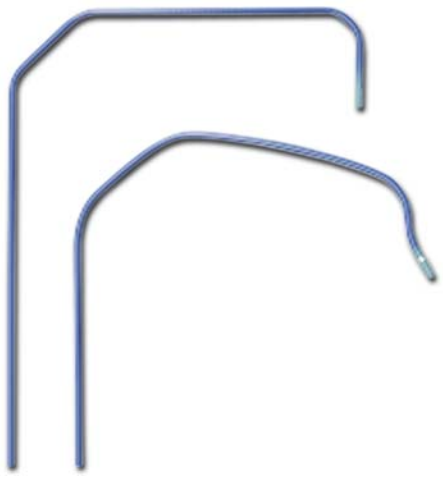


FIGURE 6: Tiger and Jacky catheters (left to right). (*Source:* Terumo)

catheters and are usually able to complete the diagnostic angiogram with one catheter. However, even if they are unable to complete all of the needed angiograms with one catheter, manipulation of that catheter usually helps to at least identify the origin of the vessel that cannot be selectively engaged, which facilitates the choice of an alternative catheter that will then likely engage the vessel. Sometimes this is another radial specific catheter, but at other times a catheter that is more typically used with femoral access procedures may be more appropriate.

ARTERIAL NOMENCLATURE AND EXTENT OF DISEASE

The major epicardial vessels and their second- and third-order branches can be visualized using coronary angiography. The network of smaller intramyocardial branches is generally not seen secondary to their size, cardiac motion and limitations in resolution of angiographic systems. These fourth-order and higher "resistance" vessels play a major role in autoregulation of coronary blood flow. Although we cannot visualize these vessels with angiography, they may limit myocardial perfusion during stress and can contribute to ischemia in patients with LV hypertrophy or systemic hypertension. Coronary perfusion in these smaller branch vessels can be quantitatively assessed using the myocardial blush score which has important prognostic significance in patients with STEMI and those undergoing percutaneous coronary intervention (PCI).[8]

The Coronary Artery Surgery Study (CASS) investigators established the nomenclature most commonly used to describe the coronary anatomy, defining 27 segments in three major coronary arteries (Table 3, Fig. 7). The Bypass Angioplasty Revascularization Investigators (BARI) modified these criteria with the addition of two segments for the ramus intermedius and addition of the third diagonal branch. In this system, the major coronary arteries include: the left main coronary artery (LMCA), the left anterior descending artery (LADA), left circumflex artery (LCX) and RCA. These are described as being a part of a right-dominant, co-dominant or left-dominant circulation. Dominance is determined by which coronary vessel

TABLE 3

Classification system for coronary segments

Number	*Map location*	*Number*	*Map location*	*Number*	*Map location*
Right coronary artery		Left main coronary artery		Left circumflex artery	
1	Proximal RCA	11	Left main coronary artery	18	Proximal LCX artery
2	Mid RCA	Left anterior descending artery		19	Distal LCX artery
3	Distal RCA	12	Proximal LADA	20	1st obtuse marginal
4	Right posterior descending branch	13	Mid LADA	21	2nd obtuse marginal
5	Right posterior atrioventricular	14	Distal LADA	22	Third obtuse marginal
6	First right posterolateral	15	1st diagonal	23	LCX atrioventricular groove
7	Second right posterolateral	16	2nd diagonal	24	1st left posterolateral branch
8	Third right posterolateral	17	LADA septal perforator	25	2nd left posterolateral branch
9	Posterior descending septals	29	3rd diagonal	26	3rd left posterolateral branch
10	Acute marginal segment	27	Left posterior descending branch		
		28	Ramus intermedium branch		

(Abbreviations: LADA: Left anterior descending artery; LCX: Left circumflex artery; RCA: Right coronary artery). (*Source:* CASS Principal Investigators and their Associates: Coronary Artery Surgery Study (CASS): A randomized trial of coronary artery surgery: Survival data. Circulation. 1983.68:939)

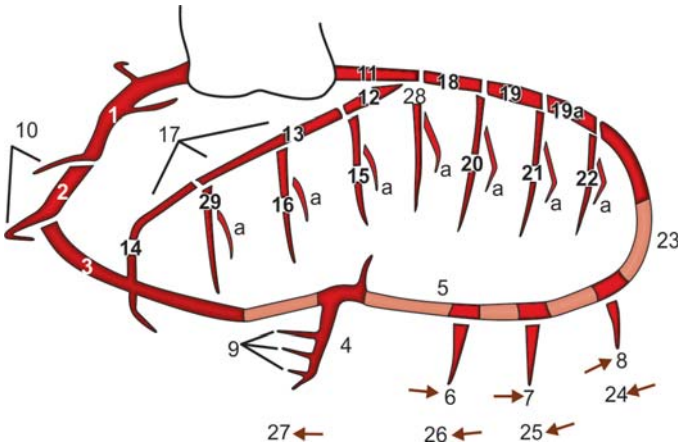
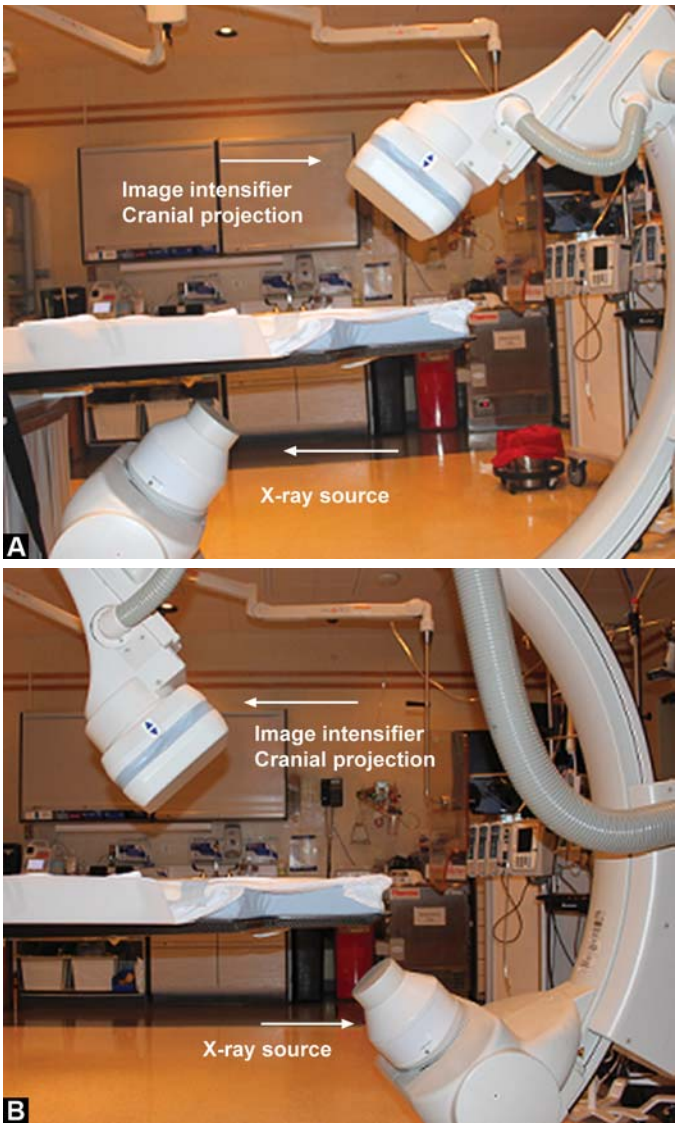


FIGURE 7: The coronary artery map used by the BARI investigators. The map is derived from that used in CASS with the addition of branch segments for the diagonal, marginal and ramus vessels



FIGURES 8A AND B: Geometry of angulated views. Head of the patient would be placed to the right (in these pictures). Cranial projection (A) and caudal projection (B)

gives rise to the posterior descending artery (PDA)—the RCA in right dominant circulation, and the lcx in a left dominant circulation. Obstructive CAD is defined as a more than 50% diameter stenosis in one or more of these vessels, although it is clear that stenoses of less than 50% do have prognostic implications because these lesions are most susceptible to plaque rupture and resulting acute MI. Subcritical stenoses of less than 50% are best characterized as nonobstructive CAD. Obstructive CAD is further classified as one, two or three-vessel disease.

In CASS, the major determinants of 6-year outcome included the number of diseased vessels, the number of diseased proximal segments and the global LV function. These three factors accounted for 80% of the prognostic information from the CASS study.

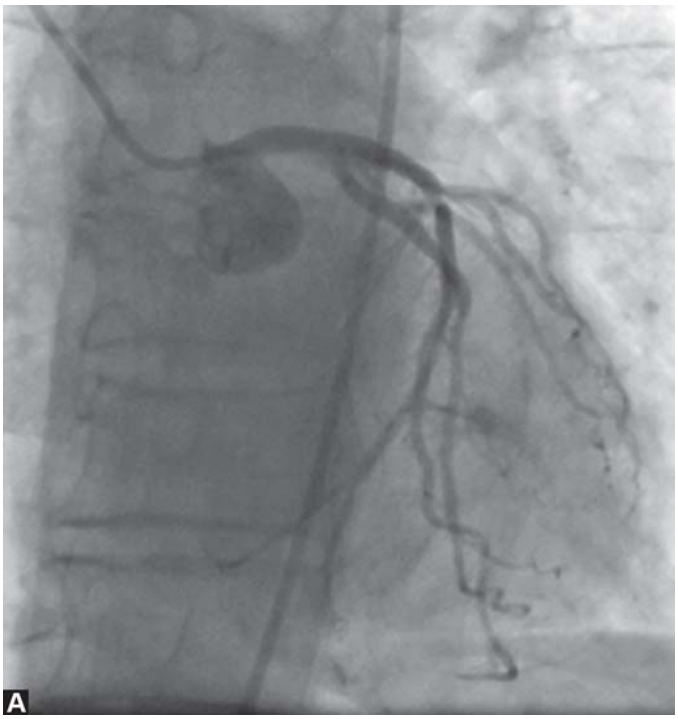
ANGIOGRAPHIC PROJECTIONS

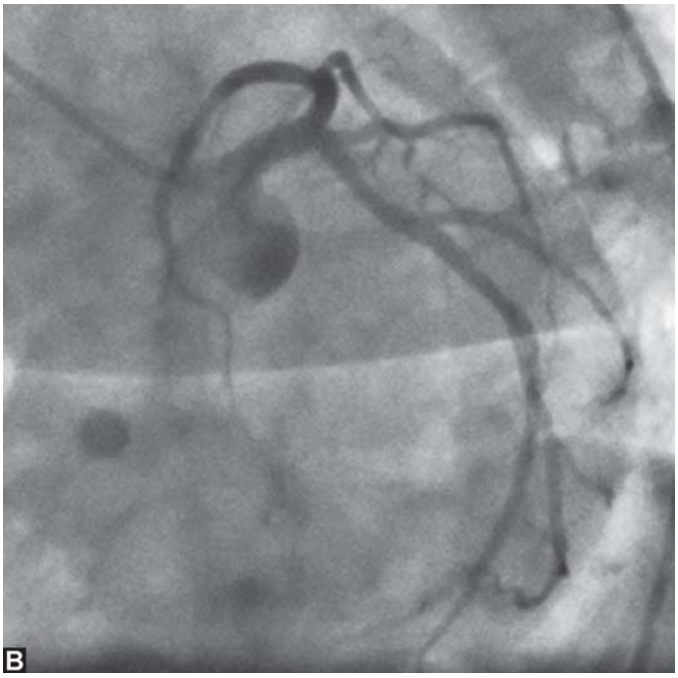
The major coronary arteries traverse the interventricular and atrioventricular (AV) grooves, aligned with the long and short axes of the heart, respectively. Since the heart is oriented obliquely in the thoracic cavity, the coronary circulation is generally visualized in the right anterior oblique (RAO) and LAO projections to furnish true posteroanterior and lateral views of the heart. However, without sagittal angulations, these views are limited by vessel foreshortening and superimposition of branches. Simultaneous rotation of the X-ray beam in the sagittal plane provides a better view of the major coronary arteries and their branches. A simple nomenclature has evolved for the description of these sagittal views, which characterizes the relationship between the image intensifier and the patient. Assuming that the X-ray tube is under the table and the image intensifier is over the table, the projection is referred to as the "cranial" view if the image intensifier is tilted toward the head of the patient (Figs 8A and B). The projection is referred to as the "caudal" view if the image intensifier is tilted down toward the feet of the patient. It is difficult to predict which angulated views will be most useful for any particular patient because the "optimal" angiographic projection depends largely on body habitus, variation in the coronary anatomy, location of the lesion and position of the heart within the chest. It is recommended that the coronary arteries be visualized in both the LAO and RAO projections using both cranial and caudal angulation with all segments of the vessels visualized in at least two preferably orthogonal views.

NORMAL CORONARY ANATOMY

LEFT MAIN CORONARY ARTERY

The left main coronary artery (LMCA) arises from the superior portion of the left aortic sinus, just below the sinotubular ridge of the aorta, which defines the border separating the left sinus of Valsalva from the smooth (tubular) portion of the aorta. The LMCA ranges 3–6 mm in diameter and may be up to 10–15 mm in length. The LMCA courses behind the right ventricular outflow tract and usually bifurcates into the LAD artery and LCX artery. In some patients, the LMCA trifurcates into the LAD, LCX and Ramus intermedius. When present, the ramus intermedius arises from the LMCA, between the LAD and LCX arteries and is somewhat analogous to either a diagonal branch





FIGURES 9A AND B: (A) Left main in LAO projection; (B) Left main in LAO caudal projection

or an obtuse marginal branch in the territory it serves, depending on its anterior or posterior course along the lateral aspect of the left ventricle. The ramus is often best visualized in the same views as used for proximally oriented diagonal or marginal branches, namely: AP, LAO and/or RAO with steep caudal angulation to see the origin, with progressively less caudal angulation needed to visualize the mid and distal vessel. Rarely, the LMCA is absent, and there are separate ostia of the LAD and lcx arteries. The ostium of the LMCA is often best visualized in a shallow LAO projection (20–30°) sometimes with slight (0–20°) caudal angulation. The distal LMCA is often best seen in the RAO or LAO caudal views. The LMCA should always

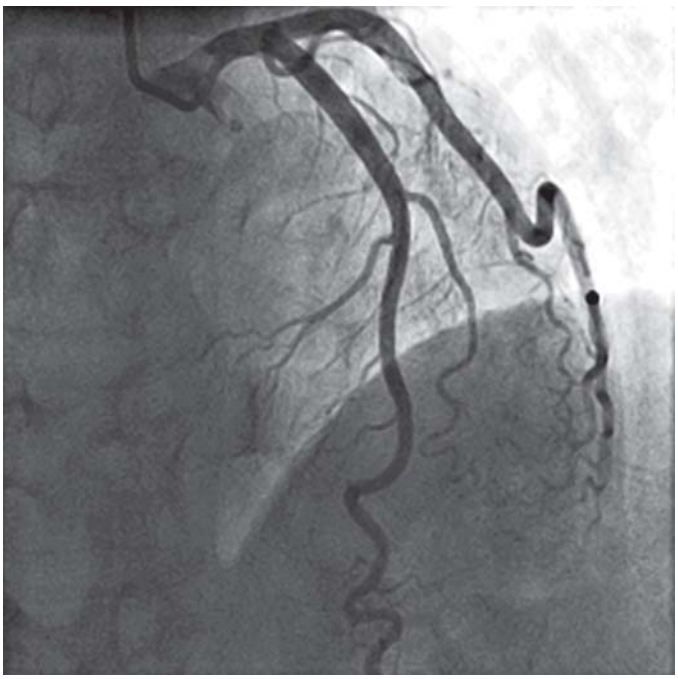


FIGURE 10: Anteroposterior cranial projection of left anterior descending

be viewed in several projections to exclude LMCA stenosis (Figs 9A and B).

LEFT ANTERIOR DESCENDING ARTERY

The LAD courses along the epicardial surface of the anterior interventricular groove toward the cardiac apex. In the RAO projection, it extends along the anterior aspect of the heart; in the LAO projection, it passes down the cardiac midline, between the right and left ventricles (Fig. 10).

Generally the best angiographic projections for viewing the entire course of the LAD are the cranially angulated AP, LAO and RAO views. The LAO cranial view displays the mid-portion of the LAD and separates the diagonal and septal branches. The proximal LAD is often somewhat foreshortened in the LAO cranial view. The AP cranial view displays the proximal, middle and distal segment of the LAD and also allows separation of the diagonal branches superiorly and the septal branches inferiorly. In some patients, a RAO cranial angulation is needed in addition to the AP cranial to further separate the origins of the branches. The LAO caudal view displays the origin of the LAD in a horizontally oriented heart and the AP or shallow RAO with deep caudal angulation visualizes the proximal LAD as it arises from the LMCA, as well as the origins of diagonal branches with proximal origins off of the LAD. A flat RAO is not often a standard view taken of the LAD, but can be very useful for visualizing the mid to distal LAD and its apical termination when additional views of this segment of the vessel are required.

The major branches of the LAD are the septal and diagonal branches. The septal branches arise from the LAD at approximately 90° angles and pass into the interventricular septum, varying in size, number and distribution. In some cases there is a large first septal branch that is vertically oriented and divides into a number of secondary branches that spread

throughout the septum. In other cases, a more horizontally oriented, large first septal branch is present that passes parallel to the LAD itself within the myocardium. In still other cases, a number of septal arteries are roughly comparable in size. These septal branches interconnect with similar septal branches passing upward from the posterior descending branch of the RCA to produce a network of potential collateral channels. The interventricular septum is the most densely vascularized area of the heart.

The diagonal branches of the LAD extend to the anterolateral aspect of the heart. Although virtually all patients have a single LAD in the anterior interventricular groove, there is wide variability in the number and size of diagonal branches. Most patients (90%) have one to three diagonal branches. Acquired atherosclerotic occlusion of the diagonal branches should be suspected if no diagonal branches are seen, particularly if there are unexplained wall motion abnormalities of the anterolateral left ventricle. Visualization of the origins of the diagonal branches often requires steep LAO (40–45°) and cranial (30–40°) angulated views, but can often be seen in the AP or RAO cranial views as well. The origins of diagonal branches with a rather proximal takeoff are often best visualized in LAO, AP or RAO projections, but with steep caudal angulation (35–45°).

In most patients, the LAD courses around the LV apex and terminates along the diaphragmatic aspect of the left ventricle. In the remaining patients, the LAD fails to reach the diaphragmatic aspect of the left ventricle, terminating instead either at or before the cardiac apex. In this circumstance, the PDA of the RCA or LCX is larger and longer than usual and supplies the apical portion of the ventricle.

In patients with no LMCA (i.e. separate ostia for the LAD and LCX), the LAD generally has a more anterior origin than the LCX. The LAD can be engaged with the Judkins left catheter in this setting with a slight counterclockwise rotation on withdrawal of the catheter and then gentle clockwise rotation on readvancement. This maneuver generally rotates the secondary bend of the catheter to a posterior position in the aorta and turns the primary bend and tip of the catheter to an anterior position. The opposite maneuver may be used to engage the LCX selectively in the setting of separate LAD and LCX ostia. Sometimes a single Judkins left catheter can be used to engage both of these vessels individually, but at other times, two different catheters are required. In this case, the larger sized Judkins left catheter will usually selectively engage the downward coursing LCX, and the shorter Judkins left catheter is used to engage the more anteriorly and superiorly located LAD.

LEFT CIRCUMFLEX ARTERY

The LCX artery originates from the LMCA and courses within the posterior (left) AV groove toward the inferior interventricular groove (Fig. 11). The LCX artery is the dominant vessel in approximately 15% of patients, supplying the left PDA from the distal continuation of the LCX. In right dominant systems, the distal LCX varies in size and length, depending on the number of posterolateral branches supplied by the distal RCA. The LCX usually gives off one to three large obtuse marginal branches as it passes down the AV groove. These are the principal branches of the LCX that supply the lateral free wall of the left ventricle. Beyond the origins of the obtuse marginal branches, the distal LCX tends to be small in most patients with a right dominant system.



FIGURE 11: Left circumflex in RAO caudal view

The RAO caudal and LAO caudal projections are best for visualizing the proximal and middle LCX and obtuse marginal branches. The AP (or shallow RAO/LAO) caudal projections also show the origins of the obtuse marginal branches. More severe rightward angulation often superimposes the origins of the obtuse marginal branches on the LCX. If the LCA is dominant, the optimal projection for the left PDA is the LAO cranial view. The LCX artery also gives rise to one or two left atrial circumflex branches. These branches supply the lateral and posterior aspects of the left atrium.

RIGHT CORONARY ARTERY

The RCA originates from the right aortic sinus somewhat inferior to the origin of the LCA (Fig. 12). It passes along the right AV groove toward the crux—a point on the diaphragmatic surface of the heart where the anterior AV groove, the posterior AV groove and the inferior interventricular groove coalesce. The first branch of the RCA is generally the conus artery, which arises at the right coronary ostium or within the first few millimeters of the RCA in about 50% of patients. In the remaining patients, the conus artery arises from a separate ostium in the right aortic sinus just above the right coronary ostium. The second branch of the RCA is usually the sinoatrial node artery. It has been found that this vessel arises from the RCA in just under 60% of patients, from the lcx artery in just under 40% and from both arteries in the remaining cases. The midportion of the RCA usually gives rise to one or several medium-sized acute marginal branches. These branches supply the anterior wall of the right ventricle and may provide collateral circulation in patients with LAD occlusion. The RCA terminates

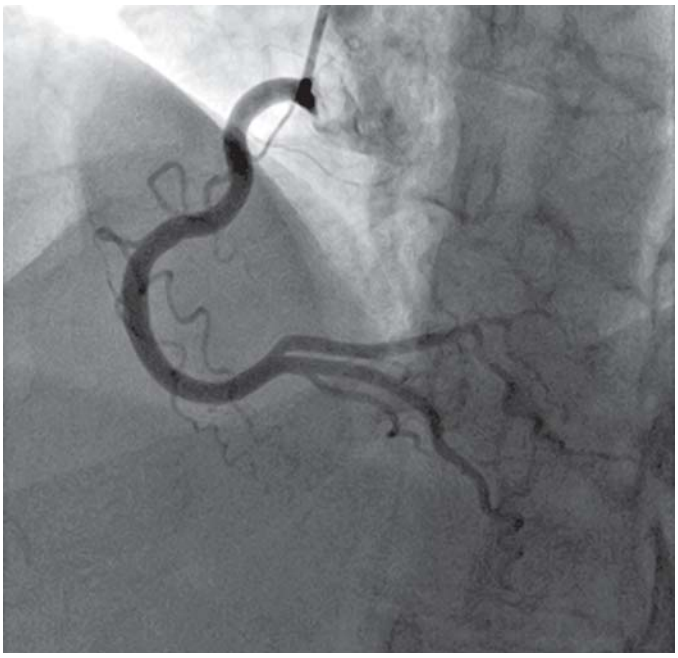


FIGURE 12: Right coronary artery in LAO cranial projection displaying the bifurcation

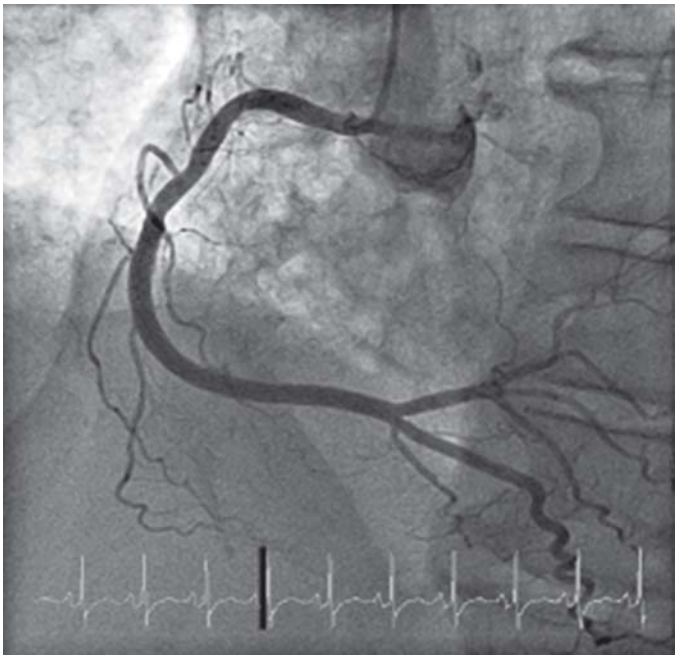


FIGURE 13: Right dominant circulation, PDA is seen coming of the RCA

in an RPDA (in right dominant circulation) and one or more right posterolateral branches.

Because the RCA traverses both the AV and the interventricular grooves, multiple angiographic projections are needed to visualize each segment of the RCA. The ostium of the RCA is best evaluated in the LAO views, with or without cranial or caudal angulation. The left lateral view is also useful for visualizing the ostium of the RCA in difficult cases. The ostium is identified by the reflux of contrast material from the RCA that also delineates the aortic root with swirling of contrast in the region of the ostium. The proximal RCA is generally evaluated in the flat LAO or LAO cranial projections but is markedly foreshortened in the RAO projections. The mid-portion of the RCA is best seen in the flat LAO, LAO cranial and flat RAO projections. The origin of the PDA and the posterolateral branches are best evaluated in the LAO cranial or AP cranial views, whereas the mid-portion of the PDA can be shown in the AP cranial or RAO projection.

RIGHT DOMINANT CORONARY CIRCULATION

The RCA is dominant in about 82–84% of patients, supplying the PDA and at least one posterolateral branch (Fig. 13). The PDA courses in the inferior interventricular groove and gives rise to a number of small inferior septal branches. These septal branches extend upward to supply the lower portion of the interventricular septum and interdigitate with superior septal branches extending down from the LAD artery. After giving rise to the PDA, the dominant RCA continues beyond the crux cordis (the junction of the AV and interventricular grooves) as the right posterior AV branch along the distal portion of the posterior (left) AV groove. This vessel then terminates in one or several posterolateral branches that supply the diaphragmatic surface of the left ventricle. There are significant anatomical variations in the origin of the PDA in a right dominant system. These variations include partial supply of the PDA territory by acute marginal branches, double PDA and early origin of the PDA proximal to the crux. In patients with right dominance, the LCX continues in the AV groove, but generally becomes rather small after it gives off a variable number of obtuse marginal and perhaps a posterolateral branch.

LEFT DOMINANT CORONARY CIRCULATION

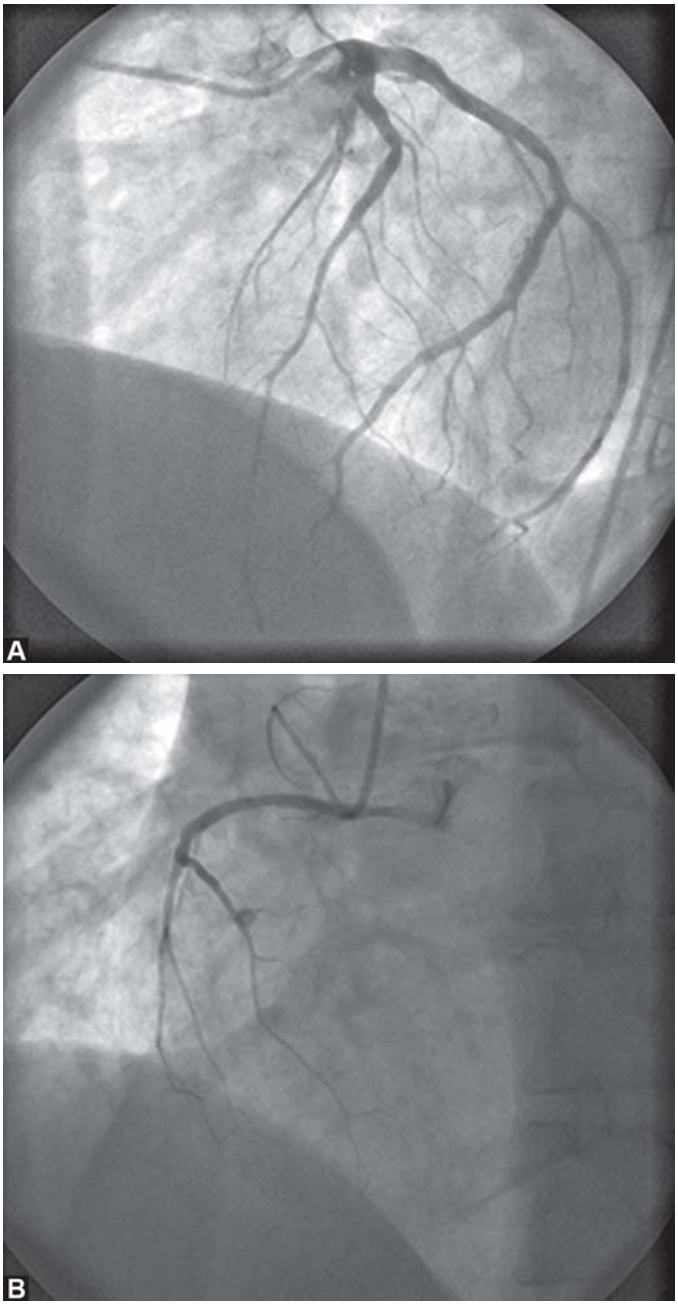
The LCX is dominant in about 12 to 14% of patients. In these patients, the LCX artery continues in the AV groove giving off both obtuse marginal as well as posterolateral branches through its course. The LCX then extends into the posterior interventricular groove and terminates as the left PDA. In these cases, the RCA is very small, terminates well before reaching the crux and does not supply any blood to the LV myocardium (Figs 14A and B).

CO-DOMINANT OR BALANCED CORONARY CIRCULATION

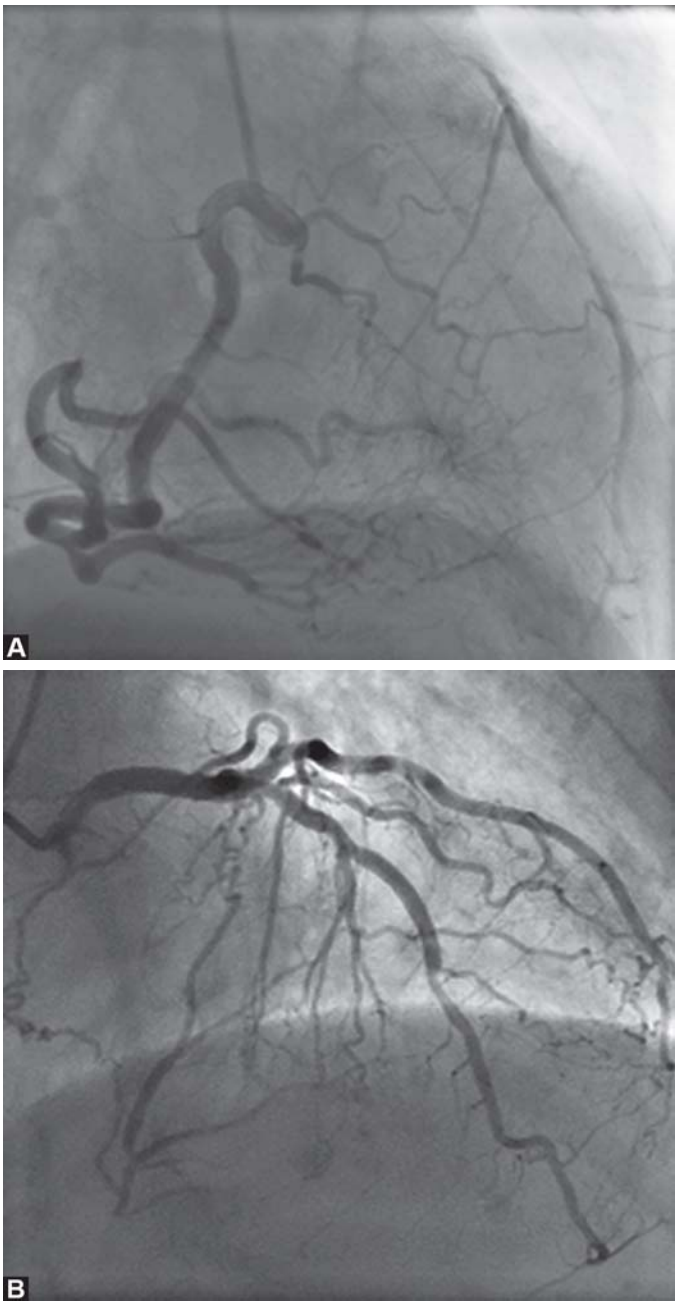
The remaining approximately 4% of patients have a co-dominant or balanced circulation. This is characterized by an RCA that gives rise to the PDA, but not to any posterolateral branches. In a balanced circulation, the LCX artery does not give rise to the PDA, but does provide essentially all of the posterolateral branches.

CORONARY COLLATERAL CIRCULATION

Networks of small anastomotic branches interconnect the major coronary arteries and serve as precursors for the collateral circulation that maintains myocardial perfusion in the presence of severe proximal atherosclerotic narrowings.[9] Collateral channels may not be seen in patients with normal or mildly diseased coronary arteries because of their small (< 200 mm) caliber. But, as CAD progresses and becomes more severe (> 90% stenosis), a pressure gradient is generated between the



FIGURES 14A AND B: (A) Left dominant system. PDA originates from LCX; (B) RCA as non-dominant vessel in same patient



FIGURES 15A AND B: (A) LAD filling via collaterals from RCA; (B) RCA filling via collaterals from LAD

anastomotic channels and the distal vessel that is hypoperfused.[10] The trans-stenosis pressure gradient facilitates blood flow through the anastomotic channels, which progressively dilate and eventually become visible with angiography as collateral vessels (Figs 15A and B).

The visible collateral channels arise either from the contralateral coronary artery, or from the ipsilateral coronary artery through intracoronary collateral channels, or through "bridging" channels that have a serpiginous course from the proximal coronary artery to the coronary artery distal to the occlusion. These collaterals may provide up to 50% of anterograde coronary flow in chronic total occlusions. This in turn may allow the development of a "protected" region of myocardial perfusion that does not develop ischemia during times of increased myocardial oxygen demands. Recruitment of collateral channels typically occurs over time with the gradual progression of atherosclerotic disease, but may also occur relatively quickly in patients who develop an acute STEMI caused by a sudden thrombotic occlusion. Other factors that affect collateral development are: patency of the arteries supplying the collateral, and the size and vascular resistance of the segment distal to the stenosis.

CONGENITAL ANOMALIES OF THE CORONARY CIRCULATION

Coronary anomalies may occur in 1–5% of patients undergoing coronary angiography, depending on the threshold for defining an anatomical variant (Table 4).[11,12]

The major reason for appropriately identifying and classifying coronary anomalies is to determine their propensity to

TABLE 4

Incidence of coronary anomalies among 1950 angiograms

Variable	*Number*	*Percent*
Coronary anomalies	110	5.64
Split RCA	24	1.23
Ectopic RCA (right cusp)	22	1.13
Ectopic RCA (left cusp)	18	0.92
Fistulas	17	0.87
Absent left main coronary artery	13	0.67
LCX artery arising from right cusp	13	0.67
LCA arising from right cusp	3	0.15
Low origin of RCA	2	0.1
Other anomalies	3	0.15

(*Source:* Angelini P (Ed). Coronary Artery Anomalies: A Comprehensive Approach. Philadelphia: Lippincott Williams and Wilkins; 1999. p. 42.)

develop fixed or dynamic myocardial ischemia and SCD, particularly in young and otherwise healthy individuals.[13] Documentation of precise ischemia risk for some of these anomalies using conventional exercise stress testing or intravascular Doppler flow studies is poorly predictive and may fail to detect significant anatomic abnormalities.[12,14,15] Accordingly, coronary artery anomalies are divided into those that cause and those that do not cause myocardial ischemia (Table 5).[12]

ANOMALOUS PULMONARY ORIGIN OF THE CORONARY ARTERIES

This syndrome is characterized by the origin of the coronary artery arising from the pulmonary artery. The most common variant is an anomalous origin of the LCA from the pulmonary artery (ALCAPA). Single vessel origins of the RCA, LCX coronary artery or LAD artery from the pulmonary artery have also been reported however.[15] Untreated and in the absence of an adequate collateral network, most infants (95%) with anomalous pulmonary origin of the coronary arteries (APOCA) die within the first year. In the presence of an extensive collateral network, patients may survive into adulthood. Aortography typically shows a large RCA with absence of a left coronary ostium in the left aortic sinus. During the late phase of the aortogram, patulous LAD and LCX branches fill by means of collateral circulation from RCA branches. Still later in the filming sequence, retrograde flow from the LAD and lcx arteries opacifies the LMCA and its origin from the main pulmonary artery.[15] Once detected, coronary artery bypass surgery is recommended because of the high incidence of sudden death, cardiomyopathy and arrhythmias associated with APOCA.

TABLE 5

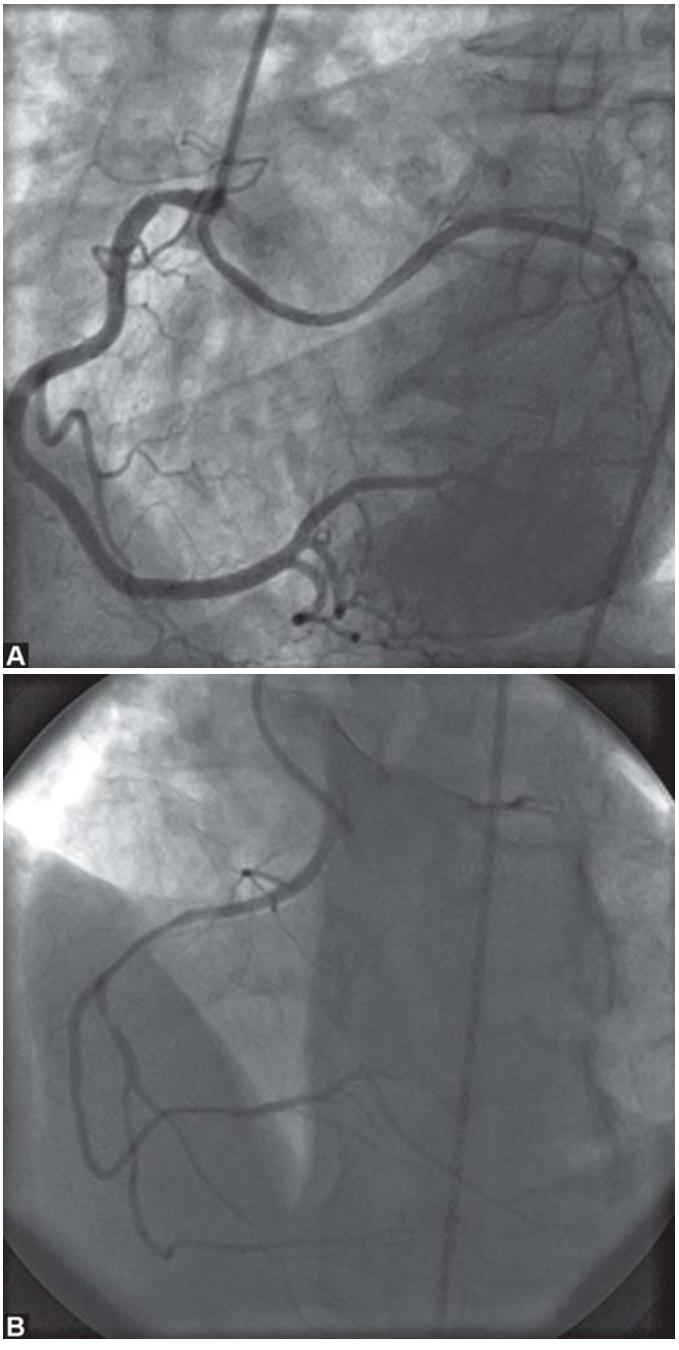
Ischemia occurring in coronary anomalies

Type of ischemia	*Coronary anomaly*
No ischemia	Majority of anomalies (split RCA, ectopic RCA from right cusp, ectopic RCA from left cusp)
Episodic ischemia	Anomalous origin of a coronary artery from the opposite sinus (ACAOS); coronary artery fistulas; myocardial bridge
Obligatory ischemia	Anomalous left coronary artery from the pulmonary artery (ALCAPA); coronary ostial atresia or severe stenosis

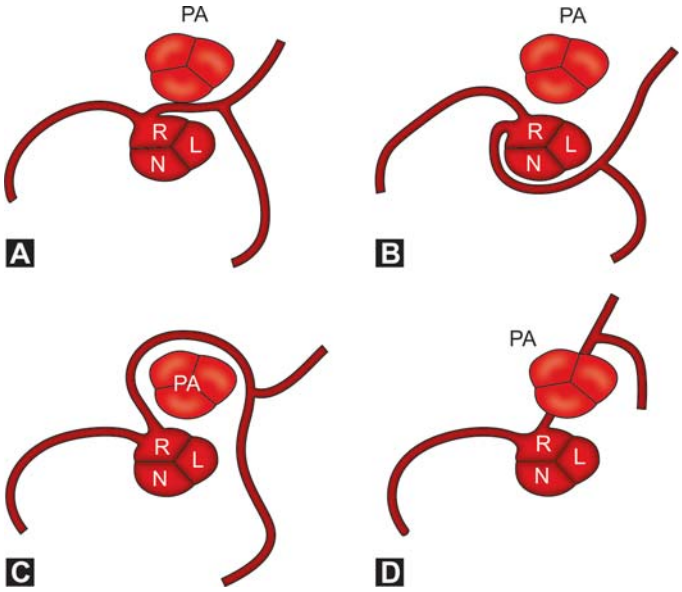
(Abbreviations: RCA: Right coronary artery; ACAOS: Anomalous origin of a coronary artery from the opposite sinus; ALCAPA: Anomalous left coronary artery from the pulmonary artery). (*Source:* Angelini P (Ed). Coronary Artery Anomalies: A Comprehensive Approach. Philadelphia; Lippincott Williams and Wilkins: 1999. p. 42)

ANOMALOUS CORONARY ARTERY FROM THE OPPOSITE SINUS

Origin of the LCA from the proximal RCA or the right aortic sinus with subsequent passage between the aorta and the right ventricular outflow tract has been associated with sudden death during or shortly after exercise in young persons (Figs 16A and B).[15,16] The increased risk of sudden death may be due to



FIGURES 16A AND B: (A) Anomalous circumflex from right cusp; (B) Anomalous origin of RCA from left cusp



FIGURES 17A TO D: Four possible pathways of the anomalous left coronary artery arising from the right coronary sinus (R): (A) interarterial, between the aorta and the pulmonary artery (PA); (B) retroaortic; (C) prepulmonic; (D) septal, beneath the right ventricular outflow tract

a slit-like ostium, a bend with acute takeoff angles of the aberrant coronary arteries, or arterial compression between the pulmonary trunk and aorta when there is increased blood flow through these vessels with exercise and stress. Origin of the RCA from the LCA or left aortic sinus with passage between the aorta and the right ventricular outflow tract is also associated with myocardial ischemia and sudden death.[16,17] In rare cases of anomalous origin of the LCA from the right sinus, myocardial ischemia may occur even if the LCA passes anterior to the right ventricular outflow tract or posterior to the aorta (i.e. not through a tunnel between the two great vessels). Although coronary bypass surgery has been the traditional revascularization approach in patients with anomalous coronary artery from the opposite sinus(ACAOS), coronary stenting has also been reported with acceptable medium-term success.[18]

The course of the anomalous coronary arteries can be assessed by angiography. Usually the RAO view is most helpful. The four common courses for the anomalous LCA arising from the right sinus of Valsalva include a septal, anterior, interarterial or posterior course (Figs 17A to D).[19] The posterior course of the anomalous LCA arising from the right sinus of Valsalva is similar to the course of the anomalous LCX artery arising from the right sinus of Valsalva, whereas the common interarterial course of the anomalous RCA from the left sinus of Valsalva is similar to the interarterial course of the anomalous LCA arising from the right sinus of Valsalva.

Although angiography is useful for establishing the presence of anomalous coronary arteries, CT angiography is a very important adjunctive diagnostic tool for establishing the course of the vessels and relationship to the great vessels.[19,20] If a coronary anomaly is identified during coronary angiography, it may in fact be most prudent to obtain a coronary CT angiogram to best delineate the course of the coronary arteries and their relationship to the great vessels.

CORONARY ARTERY FISTULAE

A coronary artery fistula is defined as an abnormal communication between a coronary artery and a cardiac chamber or major vessel, such as the vena cava, right or left ventricle, pulmonary vein or pulmonary artery.[21,22] Congenital fistulae arise from the RCA or its branches in about one-half of the cases, and drainage generally occurs into the right ventricle, right atrium or pulmonary arteries. Coronary artery fistulas terminating in the left ventricle are uncommon (3%).[21] Coronary angiography is the best method for demonstrating these fistulae. Acquired coronary fistulae may develop in heart transplant patients who have had multiple endomyocardial biopsies of the right ventricular septum. Over time, coronary fistulae may develop from the septal arteries to the right ventricle. These coronary fistulae are usually small and not clinically significant, but are not unusual to observe with routine coronary angiography in this subset of patients.

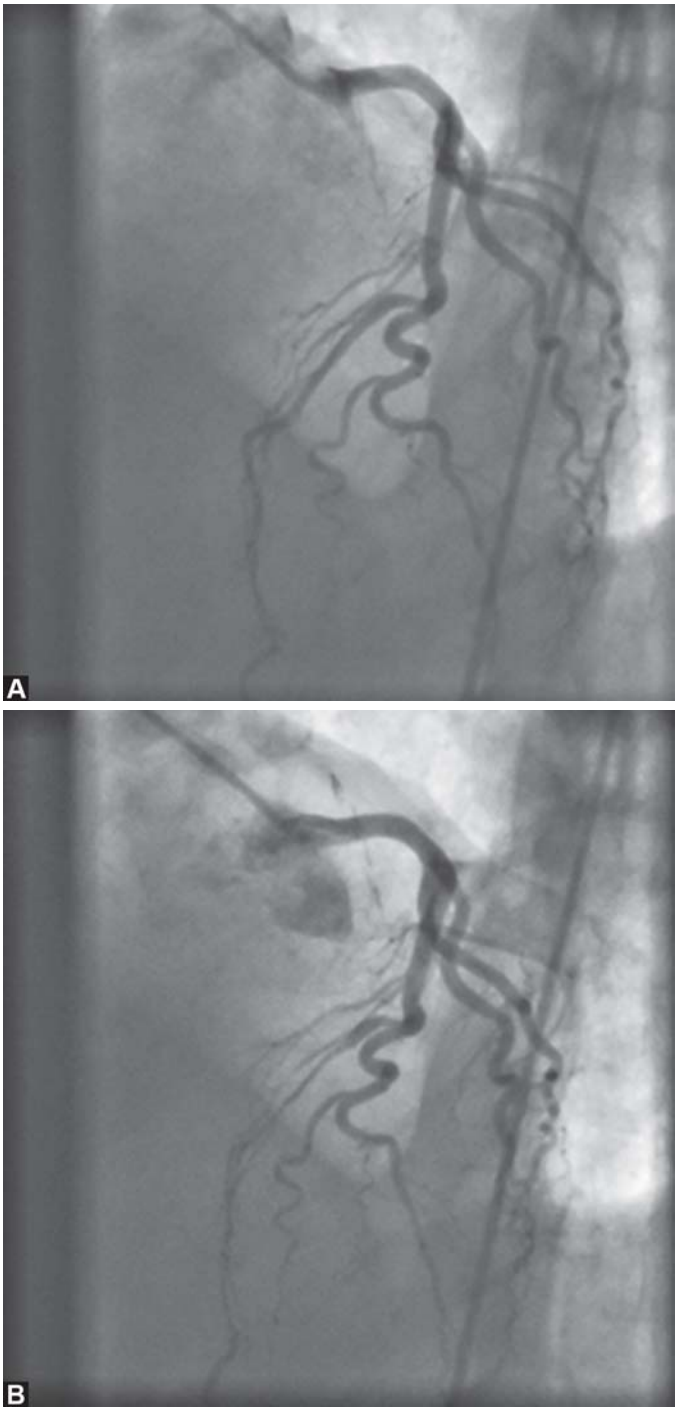
The clinical presentation associated with a coronary artery fistula is dependent on the type of fistula, shunt volume, site of the shunt and presence of other cardiac comorbidities. Dyspnea on exertion, fatigue, CHF, pulmonary hypertension, bacterial endocarditis and arrhythmias are common presentations in symptomatic patients. Myocardial ischemia may also occur, but the mechanism remains speculative.[21] More than half of these patients are asymptomatic and the fistula is incidentally detected while performing angiography for unrelated reasons. Symptomatic patients or those with severe shunts may be treated with surgical closure, although some reports of percutaneous closure with coil embolization have had promising results.

CONGENITAL CORONARY STENOSIS OR ATRESIA

Congenital stenosis or atresia of a coronary artery can occur as an isolated lesion or in association with other congenital diseases, such as calcific coronary sclerosis, supravalvular aortic stenosis, homocystinuria, Friedreich's ataxia, Hurler syndrome, progeria and Rubella syndrome. In these cases, the atretic vessel usually fills by means of collateral circulation from the contralateral side.

MYOCARDIAL BRIDGING

The three major coronary arteries generally course along the epicardial surface of the heart. On occasion, short segments of a coronary artery may descend into the myocardium for a variable distance. This abnormality, termed myocardial bridging, occurs in 5–12% of patients and is usually confined to the LAD (Figs 18A and B).[23] Because a "bridge" of myocardial fibers passes over the involved segment of the LAD, each systolic contraction of these fibers can cause narrowing of the artery. Myocardial bridging has a characteristic appearance on angiography with the bridged segment of normal caliber during diastole but abruptly narrowed with each systole. Although bridging is not thought to have any hemodynamic significance in most cases, myocardial bridging has been associated with angina, arrhythmia, depressed LV function, myocardial stunning, early death after cardiac transplantation and sudden death.[23,24]



FIGURES 18A AND B: Myocardial bridge in the mid LAD in diastole (A) and systole (B)

GENERAL PRINCIPLES FOR CORONARY AND/OR GRAFT CANNULATION

Coronary cannulation is typically performed using an approximate 30° LAO projection. Pressure is constantly transduced from the tip of the catheter throughout the procedure to monitor for pressure damping or ventricularization. Either of these phenomena may indicate a severe stenosis with wedging of the catheter into the stenosis, or that the catheter tip is positioned against the coronary vessel wall. Injection of contrast when there is damping or ventricularization of the pressure waveform should be avoided as the incidence of coronary dissection or ventricular arrhythmia is clearly increased in this situation. When pressure damping is present, care should be taken to adjust the position of the catheter until it is resolved before performing contrast injections. In the case of the RCA, dampening could also signify selective engagement of the conus branch. Whenever pressure waveform damping is present, the catheter should be repositioned until a normal waveform appears or nonselective injections performed to assess the possibility of an ostial stenosis or other anatomical reason for the pressure damping. Subsequently, a smaller French or different shape catheter may be considered to safely perform the angiogram. The basic principles regarding pressure waveform ventricularization or damping briefly described above apply to the cannulation and angiography of all coronary vessels and bypass grafts.

LEFT MAIN CORONARY ARTERY CANNULATION

As previously noted, the Judkins left 4.0 coronary catheter is used most often to engage the LMCA in femoral access procedures, with a gentle advancement under fluoroscopic guidance. However, if the Judkins left catheter begins to turn out of profile (so that one or both curves of the catheter are no longer visualized en face), it can be rotated clockwise very slightly and advanced slowly to enter the left sinus of Valsalva, permitting the catheter tip to engage the ostium of the LMCA. If the ascending aorta is dilated, advancement of the Judkins left 4.0 coronary catheter may result in the formation of an acute secondary angle of the catheter, pointing the tip of the catheter upward, away from the left coronary ostium. Further advancement of the Judkins left catheter in this position should be avoided because the catheter will then prolapse on itself and become folded in the ascending aortic arch. In the event this does occur, a guidewire should be temporarily reinserted into the catheter to straighten the secondary bend and permit the catheter to be advanced to the left sinus of Valsalva. If the ascending aorta is significantly dilated, the Judkins left 4.0 catheter should be exchanged for a larger size (e.g. Judkins left 4.5, 5.0 or 6.0). If the tip of the Judkins left catheter advances beyond the ostium of the LMCA without engagement, the primary bend of the catheter can sometimes be reshaped within the patient's body by further careful advancement to the aortic valve to gently bend the catheter tip. Then, the catheter is withdrawn to the level of the LMCA. This maneuver, along with gentle clockwise or counterclockwise rotation, frequently permits selective engagement of the LMCA when the initial attempt has failed. If the LMCA is still not cannulated and the catheter tip remains below the origin of the LMCA, a shorter Judkins left catheter can be used to allow coaxial engagement of the LMCA.

Use of an Amplatz left catheter to cannulate the LMCA generally requires more catheter manipulation than with the Judkins left catheter. When using an Amplatz left catheter, the broad secondary curve of the catheter is positioned so that it rests on the right aortic cusp with its tip pointing toward the left aortic cusp. Alternating advancement and withdrawal of the catheter with slight clockwise rotation allows the catheter tip to advance slowly and superiorly along the left sinus of Valsalva to enter the left coronary ostium. When the tip enters the ostium,

the position of the catheter can usually be stabilized with slight withdrawal of the catheter. After the left coronary ostium has been cannulated, the pressure at the tip of the catheter should be checked immediately to ensure that there is no damping or ventricularization of the pressure contour. If the pressure measured at the catheter tip is normal, left coronary angiography is then performed using standard techniques. To remove the Amplatz left catheter from the coronary artery, the catheter should be advanced slightly to disengage the catheter tip superiorly from the coronary ostium. Simply withdrawing the Amplatz left catheter often results in deep seating of the catheter tip within the coronary artery—which should be avoided, as that could potentially result in catheter-induced arterial dissection.

RIGHT CORONARY ARTERY CANNULATION

As with the LMCA, cannulation of the RCA is also generally performed in the LAO view but requires different maneuvers than those for cannulation of the LMCA. Whereas the Judkins left catheter naturally seeks the ostium of the LMCA, the Judkins right or Amplatz right catheters that are typically used to engage the RCA must be rotated to engage the vessel. This is usually accomplished by first advancing the catheter into the right coronary sinus to the level of the aortic valve. The catheter is then slowly withdrawn slightly and rotated clockwise to turn the tip of the catheter toward the RCA ostium. The catheter is gently rotated until a further rightward and sometimes a slight downward movement of the catheter tip is noted. This typically signifies entry of the catheter into the right coronary ostium. If the ostium of the RCA is not easily located, the most common reason is that the ostium has a more superior and leftward origin than anticipated. Nonselective contrast injections in the right sinus of Valsalva may reveal the site of the origin of the RCA and allow successful cannulation, or selection of a different catheter (sometimes as Amplatz left catheter is helpful in this case) to accomplish this. An Amplatz left catheter can also be used to cannulate the RCA when it is in a more conventional location as well. Positioning an Amplatz left catheter in the ostium of the RCA requires a technique similar to that used with the Judkins right catheter. However, the Amplatz left catheter often engages the RCA rather deeply, increasing the risk of catheter induced dissection. So, the use of an Amplatz left catheter to engage the RCA is usually reserved for cases where the RCA ostium is not in the usual location. As in removing this catheter from the left coronary artery, removal of the Amplatz left catheter from the RCA can be achieved by slight clockwise or counterclockwise rotation and gentle advancement to disengage the catheter tip from the ostium. Initial withdrawal of the Amplatz left catheter usually leads to deep seating of the catheter into the coronary vessel and should be avoided.

An abnormal pressure tracing showing damping or ventricularization may suggest the presence of an ostial stenosis or spasm, selective engagement of the conus branch, or deep intubation of the RCA. If an abnormal pressure tracing has been encountered, injections should not be performed until this situation is rectified. In the case of pressure damping in the RCA specifically, the catheter tip should initially be gently rotated counterclockwise and sometimes withdrawn slightly in an effort to free the tip of the catheter from the vessel wall. If persistent damping occurs, the catheter should be withdrawn until it is disengaged and the pressure waveform normalizes. Attempts to re-engage the vessel can be made, but if dampening with engagement persists, a nonselective cusp injection should be performed to help assess the etiology of the damping. Sometimes this will reveal the reason and appropriate changes can be made to safely perform the angiogram including different positioning of the catheter, use of a different shaped catheter or use of a smaller French size catheter. If selective engagement of the conus branch is determined to be the etiology of the pressure damping, sometimes the catheter can be further rotated in a clockwise manner to free the catheter from the conus and engage the RCA. However, if this is not successful, the catheter should be disengaged and further attempts to successfully engage the RCA be made. If the pressure tracing is normal on initial entry into the RCA, the vessel should be imaged in at least two, preferably three projections. The initial injection should be gentle because of the possibility that forceful injection through a catheter whose tip is immediately adjacent to the vessel wall may also lead to dissection of the coronary artery, particularly when the catheter engagement is not coaxial. Coronary spasm of the proximal or ostial RCA may also occur as a result of catheter intubation. When an ostial stenosis of the RCA is seen, intracoronary nitroglycerin or calcium channel antagonists should be administered to eliminate the possibility of catheter-induced spasm as a cause of the coronary artery narrowing.

CORONARY BYPASS GRAFT CANNULATION

Selective cannulation of bypass grafts is generally more challenging than cannulation of the native coronary arteries because the locations of graft origins are more variable, even when surgical clips or graft markers are present to assist with graft location. Knowledge of the number, course and type of bypass grafts obtained from the operative report is invaluable for the identification of the bypass grafts during coronary bypass graft angiography.

SAPHENOUS VEIN GRAFTS

Saphenous vein grafts (SVGs) from the aorta to the distal RCA or PDA generally originate from the right anterolateral aspect of the aorta approximately 5 cm superior to the sinotubular ridge. SVGs to the LAD artery (or diagonal branches) originate from the anterior portion of the aorta about 7 cm superior to the sinotubular ridge. SVGs to the obtuse marginal branches arise from the left anterolateral aspect of the aorta approximately 9–10 cm superior to the sinotubular ridge. In most patients, all SVGs can be engaged with a single catheter, such as a Judkins right 4.0 or a modified Amplatz right 1. Other catheters useful for engaging SVGs include the right and left bypass graft catheters (Fig. 5). Amplatz left catheters can occasionally be useful for superiorly oriented SVGs. A multipurpose catheter may very occasionally be useful for the cannulation of an SVG to the RCA or one of its branches that has a particularly downgoing origin and was not able to be successfully cannulated with one of the aforementioned catheters.

Viewed in the LAO projection, the Judkins or Amplatz right catheters rotate anteriorly from the leftward position as the catheter is rotated in a clockwise direction. Steady advancement and withdrawal of the catheter tip in the ascending aorta (approximately 5–10 cm above the sinotubular ridge) with varying degrees of rotation usually results in cannulation of an SVG. A well-circumscribed "stump" is almost always present if the SVG is occluded at the origin. Each patent SVG or "stump" (occluded SVG) should be viewed in nearly orthogonal views. The relation between the origin of the SVGs and the surgical clips or graft markers may help to confirm whether all targeted SVGs have been visualized. However, knowing which grafts are present (by review of operative report and/or previous angiogram when available) is a much more reliable method. Additionally, if this previous data is not present, being sure that all vascular territories have been accounted for on the current study is another important element in helping to confirm that all grafts have been visualized. If a patent SVG or a stump cannot be located, it may be necessary to perform an ascending aortogram in an attempt to visualize all SVGs and their course to the coronary arteries. If a graft is noted to be patent on the aortogram, then further attempts to selectively cannulate the graft should be performed, perhaps with a different catheter if needed.

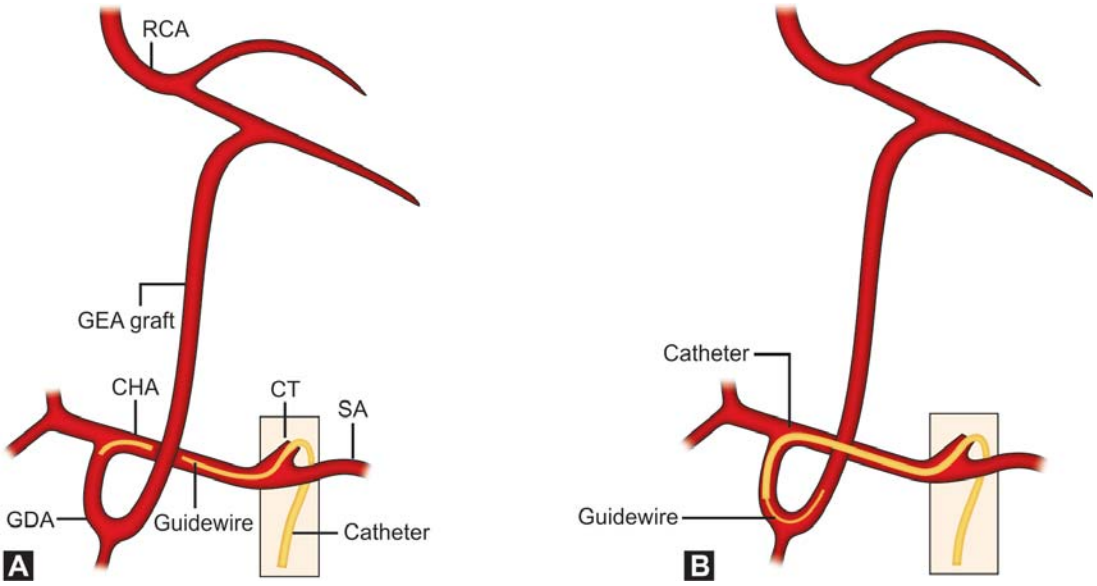
The goal of SVG angiography is to image and assess the origin of the SVG, its entire course (body of the graft) and the distal insertion site at the anastomosis between the bypass graft and the native coronary vessel. The origin of the SVG is best evaluated by achieving a coaxial engagement of the catheter tip with the origin of the SVG. The mid-portion (body) of the SVG should be evaluated with complete contrast filling of the SVG, as inadequate opacification may produce an angiogram suggestive of obstructive defects. SVGs, as all veins, have valves which should not be interpreted as being pathologic narrowings. It is critical to assess the SVG insertion or anastomotic site in full profile without overlap of the distal SVG or the native vessel. This can sometimes be challenging, but is a very important aspect of performing a diagnostically adequate angiogram. Angiographic assessment of the native vessels beyond SVG anastomotic sites generally requires views that are conventionally used for the native vessels themselves. Sequential grafts are those that supply two different epicardial branches in a side-to-side fashion (for the more proximal epicardial artery) and terminating in an end-to-side anastomosis (for the more distal epicardial artery). A "Y" graft is one in which there is a proximal anastomosis in an end-to-side fashion to another saphenous vein or arterial graft with two distal end-to-side anastomoses to the two epicardial vessels from these two grafts. Visualization of all segments and anastamoses of each of these types of grafts is imperative and may take several different projections of each graft to accomplish.

INTERNAL MAMMARY ARTERY GRAFTS

The left IMA usually arises inferiorly from the left subclavian artery at a variable distance from the origin of the subclavian. The origin of the IMA is however typically located near, but inferior to the origin of the thyrocervical trunk. Cannulation of the left IMA is usually performed with an IMA catheter (Fig. 5). Usually in the LAO projection, the catheter is advanced over a wire into the aortic arch to an area near the junction of the ascending aorta and the transverse portion of the aortic arch. The catheter is then slowly withdrawn and rotated counter-clockwise to turn the tip in a cranial direction, allowing entry into the left subclavian artery. Once the left subclavian artery is engaged, a guidewire is advanced into the left subclavian artery under fluoroscopic guidance. The catheter is then advanced into the subclavian artery over the wire to a point distal to the expected origin of the left IMA. IMA cannulation is performed typically in the AP projection by withdrawing and slightly rotating the catheter counterclockwise to bring the tip anteriorly. Successful cannulation of the IMA is usually noted with a slight drop of the catheter tip in a downward and slightly anterior direction.

The right IMA is also typically cannulated with the IMA catheter. The brachiocephalic artery is entered in the LAO projection in a manner similar to how the left subclavian is entered in the case of a left IMA. However, the brachiocephalic artery tends to be more tortuous than the left subclavian. Additionally, the right common carotid artery origin is off the brachiocephalic artery, so care should be taken to avoid inadvertently advancing the guidewire into the right common carotid artery. When the guidewire is successfully positioned in the distal right subclavian artery, the IMA catheter is advanced over the wire to a point distal to the expected origin of the right IMA. The catheter is then gently withdrawn and rotated to cannulate the right IMA, similar to the method used with the left IMA.

Unlike SVGs, the IMA itself is generally less affected by atherosclerotic disease. As with all graft studies, angiograms of the IMA graft should assess all portions of the graft completely—the origin, the body and the anastomosis. This can generally be accomplished with a flat LAO, flat RAO and one cranially angulated view, typically an AP cranial view. It is important to keep in mind that visualization of the native vessel after the graft insertion site is also of importance. So, using views that one would typically use for native coronary angiography of that vessel is often a good starting point in performing coronary graft angiography. Although the LAO cranial view may be limited in its ability to demonstrate the anastomosis of the LIMA and the LAD because of vessel overlap, it may be a very good view to visualize the body of the graft and the native LAD and diagonal branches. An additional view that is sometimes helpful is assessing a "difficult to see" LIMA to LAD anastomosis is a left lateral projection, with the patient's arms placed above his or her head. In cases where there is a potential need for a repeat sternotomy (e.g. the patient had a previous bypass surgery and now needs a valve surgery), it is helpful to also obtain an AP angiogram of the IMA grafts so that their location with respect to the sternum is known to limit the chance of damage to the graft during the next sternotomy. The risk of catheter-induced dissection of the origin of the IMA can be reduced by careful manipulation of the catheter tip and avoidance of forceful advancement of the catheter in the subclavian artery without the protection of the guidewire. If the IMA cannot be selectively engaged because of tortuosity of the subclavian artery, nonselective angiography is sometimes adequate and can be enhanced by placing a blood pressure cuff on the ipsilateral arm and inflating it to a pressure



FIGURES 19A AND B: Catheterization of the right gastroepiploic artery (GEA) graft. The celiac trunk (CT) is selectively engaged with a cobra catheter, and a guidewire is gently advanced to the gastroduodenal artery (GDA) and the GEA. The catheter is advanced over the guidewire for selective arteriography of the GEA graft. (Abbreviations: CHA: Common hepatic artery; RCA: Right coronary artery; SA: Splenic artery). (*Source:* Bonow RO. Braunwald's Heart Disease—A Textbook of Cardiovascular Medicine, 9th edition.)

above systolic arterial pressure before the nonselective injection is performed. Alternatively, if nonselective angiography does not result in an adequate angiogram, the ipsilateral radial or brachial artery may need to be accessed to facilitate selective IMA engagement. IMA spasm is not uncommon and should be treated with intra-arterial nitrates or calcium channel blockers. Before performing IMA injections, the patient should be warned that they may feel chest warmth or discomfort with contrast injection due to injection into small IMA branches supplying the chest wall.

GASTROEPIPLOIC ARTERY

The right gastroepiploic artery (GEA) is the largest terminal artery of the gastroduodenal artery and was briefly used as an alternative in situ arterial conduit to the PDA in patients undergoing CABG. Use of this arterial conduit has largely been abandoned, but there is an occasional patient who may still have this type of graft so it will be briefly discussed here. The gastroduodenal artery arises from the common hepatic artery in 75% of cases, but it may also arise from the right or left hepatic artery or the celiac trunk. Catheterization of the right GEA is carried out by first entering the common hepatic artery, usually with a cobra catheter (Figs 19A and B). A torquable, hydrophilic-coated guidewire is then advanced to the gastroduodenal artery and then to the right GEA. The cobra catheter is then exchanged for a multipurpose or Judkins right coronary catheter, which then permits selective angiography of the right GEA.

STANDARDIZED PROJECTION ACQUISITION

General recommendations can be made for a sequence of angiographic image acquisition that is applicable to most patients. However, tailored views are often needed to accommodate individual variations in anatomy. As a general rule, each coronary artery should be visualized with number of (at least two) different projections that minimize vessel foreshortening and overlap. An LAO view (sometimes with shallow caudal angulation) is often performed first to evaluate the possibility of ostial LMCA disease. Other important views include the LAO cranial view to evaluate the middle and distal LAD. The LAO cranial view should have sufficient leftward positioning of the image intensifier to allow separation of the LAD, diagonal and septal branches, and enough cranial angulation to minimize foreshortening of the LAD. An LAO caudal view should be performed to clearly evaluate the distal LMCA and ostia of the LAD and LCX. The RAO caudal view best assesses the LCX and marginal branches. The distal LMCA and ostial LAD are often also well visualized in this view. A shallow RAO or AP cranial view should be obtained to evaluate the mid and distal portions of the LAD. A general sequence of views to obtain for the left coronary system may be: flat LAO, RAO caudal, AP (or slight RAO) cranial, LAO cranial and LAO caudal. The RCA should be visualized in at least two views, possibly three. A flat LAO view is useful to visualize the ostium and mid-portion of the RCA with separation of the RCA and its right ventricular branches. An LAO cranial view usually demonstrates most of the course of the RCA, but specifically visualizes the distal bifurcation of a dominant RCA into the PDA and posterolateral branches. Occasionally, a more AP cranial view is needed to assess the distal bifurcation. A flat RAO view demonstrates the mid-RCA and proximal, middle and distal termination of the PDA. A general sequence for RCA angiography may include: flat LAO, LAO cranial and then flat RAO. It cannot be overstated, that with all angiographic studies, individual

TABLE 6

Angiographic views

Vessel segment	*Angiographic view*	*Comments*
Left main	• AP projection with slight caudal angulation • LAO caudal view • RAO caudal	• Left main should be visualized in multiple projections • LAO cranial and RAO cranial views are sometimes helpful in visualization of body and distal left main
Left anterior descending	• LAO cranial • AP cranial • RAO cranial	• RAO cranial views display proximal, mid and distal segments. It also separates diagonal branches superiorly and septal inferiorly • LAO caudal for origin of lad • AP cranial views to see the proximal and mid segments • AP cranial for also the ostium of lad • Lateral projections for mid LAD and also for bifurcating disease of lad and diagonal branch
Left circumflex	• RAO caudal • AP caudal • LAO caudal (spider view)	• RAO and LAO caudal views are best to visualize proximal and mid segments along with the marginals • For left dominant system LAO cranial for left PDA branch
Right coronary artery	• LAO • LAO or AP cranial • RAO	• Ostium is best seen in LAO or LAO with caudal angulation • RAO is good view for mid segment of RCA • Distal bifurcation is best visualized with LAO cranial projection • RAO is helpful for coaxial cannulation • Left lateral is sometimes helpful for mid segment

variations may be necessary to view all of the needed segments of the coronary arteries in a given patient. It is incumbent upon the angiographer to ensure that a complete study is performed (Table 6).

THE FLUOROSCOPIC IMAGING SYSTEM

The basic principle of radiographic coronary imaging is that radiation produced by the X-ray tube is attenuated as it passes through the body. This attenuation of the X-ray is detected by the image intensifier (Fig. 20). Iodinated contrast medium is injected into the coronary arteries which enhances the absorption of the X-rays and produces a sharp contrast with the surrounding cardiac tissues. The X-ray shadow is then converted into a visible light image by the image intensifier and displayed on fluoroscopic monitors. Previously, these images were then stored on 35 mm cinefilm. However, storage of images digitally has now replaced 35 mm cinefilm for coronary angiography because of its versatility with respect to image transfer, low-cost acquisition and storage, and capability for image enhancement after image acquisition. More recently, direct digital imaging systems have eliminated the need for analog to digital converters which were previously required with conventional image intensifiers. This has all been accomplished without compromise of the image integrity[25] and has resulted in significantly reduced radiation exposure while enhancing image quality.

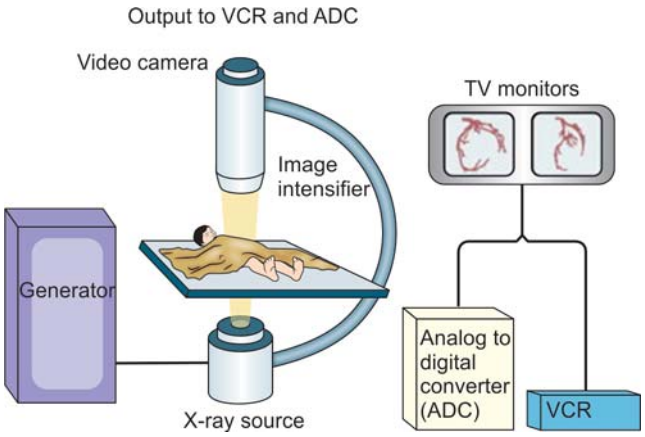


FIGURE 20: Cineangiographic equipment. The major components include: a generator, X-ray tube, image intensifier attached to a positioner such as a C-arm, optical system, video camera, videocassette recorder (VCR), analog to digital converter (ADC) and television monitors

Passage of catheters and acquisition of angiographic images requires a high-resolution image-intensifier system with digital cineangiographic capabilities. The components are mounted on a U or C arm (which acts as a support) with the X-ray tube beneath the patient and the image intensifier above. Rotation of the arm allows viewing over a wide range of angles and positions. Some laboratories have two support systems perpendicular to one another (biplane) and use a double monitoring system, providing simultaneous angiography from two different angles (Fig. 18 Biplane). This is particularly helpful in patients with renal insufficiency as less contrast will generally be delivered for a complete study when two images are obtained with each contrast injection.

The operators stand on the patient's right side facing the fluoroscopic and hemodynamic monitors. The image intensifier is positioned over the patient's left shoulder to produce an LAO cranially angulated view of the heart. The image intensifier can be rotated to other positions e.g. caudal or RAO as well to visualize the cardiac structures from any angle. During catheterization, it is necessary to monitor and record electrocardiographic and hemodynamic data—particularly pressure waveforms.

CHARACTERISTICS OF CONTRAST MEDIA

All types of contrast media contain three iodine molecules attached to a fully substituted benzene ring. The fourth position in the standard ionic agent is taken up by sodium or

methylglucamine as a cation; the remaining two positions of the benzene ring have side chains of diatrizoate, metrizoate, or iothalamate. All contrast media is excreted predominantly (99%) by glomerular filtration with about 1% excreted by the biliary system. The normal half-time of excretion is 20 minutes. The vasodilator effect and transient decrease in systemic vascular resistance are directly related to the degree of osmolality of the contrast medium used. Transient hypervolemia and depressed contractility are related to both osmolality and ionic charge and in part responsible for the elevation of left atrial and LV end-diastolic pressure after contrast injection. To reduce the osmotic effects of contrast medium, the number of dissolved particles must be decreased or the molal concentration of iodine per particle must be increased. New-generation, nonionic, monomeric and ionic dimeric contrast agents have approximately the same viscosity and iodine concentration but have only one-half or less of the osmolality of the ionic agents.[26] The advantages of the nonionic, low-osmolar agents include less hemodynamic loading, patient discomfort, binding of ionic calcium, depression of myocardial function and blood pressure, and possibly fewer anaphylactoid reactions.[27,28] Currently, nonionic, low-osmolar agents are preferred in all patients, but especially in adults with poor LV function; patients with renal disease, especially those with diabetes; and patients with a history of serious reaction to contrast media or with multiple allergies. Table 7 provides a summary of commonly used contrast agents for coronary and LV angiographic studies.

CONTRAST MEDIA REACTIONS

There are three types of contrast allergies: (1) minor cutaneous and mucosal manifestations; (2) smooth muscle and minor anaphylactoid responses and (3) major cardiovascular and anaphylactoid responses. Major reactions involving laryngeal or pulmonary edema often are accompanied by minor or less severe reactions. Nonionic contrast media has replaced ionic contrast media for most patients to minimize the chance of allergic or other adverse contrast reactions.[29,30] Patients reporting allergic reactions to contrast media should be premedicated typically with a steroid and diphenhydramine before the procedure. The premedication protocol for different laboratories may vary slightly, but common dosages include 60 mg prednisone the night before and 60 mg of prednisone the morning of the catheterization. Additionally, diphenhydramine 50 mg should be given on call to the catheterization lab. Premedication may not prevent the occurrence of adverse reactions completely. Additional routine treatment of patients with prior allergic reactions with an H_2 blocker (e.g. cimetidine) does not appear to have any additional benefit, so this practice has fallen out of favor. Patients with known prior anaphylactoid reactions to contrast dye should be pretreated with steroids and an H_1 blocker (e.g. diphenhydramine). Table 8 lists the adverse reactions associated with radiocontrast materials.

CONTRAST-INDUCED RENAL FAILURE

Patients with diabetes, renal insufficiency or volume depletion from any cause are at risk for contrast-induced nephropathy (CIN).[29,30] Advanced preparations to limit the chance of CIN include volume repletion (IV fluid administration, holding diuretics) and maintenance of large-volume urine flow (> 200 ml/h). Patients at risk for CIN should be volume replete before contrast is administered. Following the contrast study, IV fluids should be liberally continued unless intravascular volume overload is a problem. A decreased urine output after the procedure that is unresponsive to increased IV fluids and/or diuretics indicates that significant renal injury is probable. Consultation with a nephrologist is often helpful in these cases. All types of contrast agents (ionic, nonionic or low-osmolar) are associated with a similar incidence of CIN.

ACCESS SITE HEMOSTASIS

After the catheterization procedure has been completed and the catheters removed, the sheath is flushed. If heparin has been given, an activated clotting time (ACT) is obtained for femoral or brachial access procedures. The sheath is removed when the ACT is below a level specified by each institutional protocol—typically below 150–180 seconds. To remove the femoral arterial sheath, gentle pressure is applied proximal to the puncture site while the sheath is removed, taking care not to crush the sheath and/or strip clot into the distal artery. Once the sheath is removed, firm downward pressure is then applied just proximal

TABLE 7

Commonly used iodinated contrast agents in cardiac angiography

Product category	*Proprietary name*	*Genetic constituent*	*Ratio of iodine to osmotically active particles*	*Calcium chelation*	*Anticoagulation effect*	*Osmolality*
High-osmolar, ionic	Renografin-76	Diatrizoate and citrate	1.5	(+)	(+++)	1940
High-osmolar, ionic	Hypaque-76	Diatrizoate only	1.5	(–)	(+++)	1690
Low-osmolar, ionic	Hexabrix	Ioxaglate	3.0	(–)	(+++)	600
Low-osmolar, nonionic	Isovue	Iopamidol	3.0	(–)	(+)	790
Low-osmolar, nonionic	Omnipaque	Iohexol	3.0	(–)	(+)	844
Low-osmolar, nonionic	Optiray	Ioversol	3.0	(–)	(+)	702
Low-osmolar, nonionic	Visipaque	Iodinaol	3.0	(–)	(+)	290

(+), present; (+++), strongly present; (–), absent
(*Source:* Modified from Peterson KL, Nicod P. Cardiac Catheterization: Methods, Diagnosis, and Therapy. Philadelphia: Saunders; 1997.)

TABLE 8

Reactions associated with contrast media

Allergic (anaphylactoid) reactions
Grade I: Single episode of emesis, nausea, sneezing or vertigo
Grade II: Hives; multiple episodes of emesis, fevers or chills
Grade III: Clinical shock, bronchospasm, laryngospasm or edema, loss of consciousness, hypotension, hypertension, cardiac arrhythmia, angioedema or pulmonary edema
Cardiovascular toxicity
Electrophysiologic
Bradycardia (asystole, heart block)
Tachycardia (sinus, ventricular)
Ventricular fibrillation
Hemodynamic
Hypotension (cardiac depression, vasodilation)
Heart failure (cardiac depression, increased intravascular volume)
Nephrotoxicity
Discomfort
Nausea, vomiting
Heat and flushing
Hyperthyroidism

TABLE 9

Advantages or disadvantages of vascular closure devices

Device	*Mechanism*	*Advantages and limitations*
• Angioseal	• Collagen seal	• Secure hemostasis • Anchor may catch on side branch
• Duett	• Collagen-thrombin	• Stronger collagen-thrombin seal • Intra-arterial injection of collagen-thrombin
• Perclose	• Sutures	• Secure hemostasis of suture • Device failure may require surgical repair
• Vasoseal	• Collagen plug	• No intra-arterial components • Positioning wire may catch on side branch
• Starclose	• Nitinol Clip	• No intra-arterial material • Secure hemostasis of clip

(*Source:* Adapted and modified from Hurst's The Heart, 12 edition.)

to the arteriotomy for 15–30 minutes, with gradual reduction in pressure after the initial 10–15 minutes. After manual hemostasis is achieved, a small adhesive bandage is used to cover the wound. Large pressure dressings tend to obscure the puncture site (thus limiting ongoing site assessment) and are generally ineffective to prevent rebleeding so are best avoided in most cases. Depending on the sheath size, bedrest is required for typically 4–6 hours after sheath removal. Additional methods to secure postprocedure arterial hemostasis include external hemostasis pads, mechanical pressure clamps and vascular closure devices. A variety of vascular closure devices are currently available.[31-33] These devices do reduce the time to obtain hemostasis and allow earlier ambulation. They may be particularly helpful in anticoagulated patients, patients with back pain or an inability to lie flat. The advantages and disadvantages of closure devices are summarized in Table 9. All vascular closure devices should be used with caution in patients with peripheral arterial disease.

The brachial sheath is removed in relatively the same manner as a femoral sheath. There are however no mechanical pressure clamp devices or closure devices for use with brachial access. These lines are typically all manually pulled. After hemostasis is obtained, it is recommended that the arm be kept straight for several hours. Often an arm board is placed to help the patient refrain from bending or otherwise using the procedural arm during this time.With transradial catheterization, sheath removal is always done at the end of the procedure, regardless of anticoagulation status. There are various devices used to apply pressure on the radial artery site, but the most effective devices are able to isolate the pressure to the radial artery while not compromising flow in the ulnar artery. One commonly used device is a bracelet which has a small inflatable pillow on the inner portion of the bracelet which is placed over the radial artery. The bracelet is placed around the wrist just proximal to the puncture site. Once the bracelet is secured in place, the sheath is gently withdrawn and the "pillow" (on the underside of the bracelet). Positioned over the radial artery is simultaneously inflated with air to obtain hemostasis. The air is gently released until there is slight bleeding from the site and then a small amount of air is reinjected into the "pillow" of the hemostatic device with the goal of providing hemostasis of the vessel but continued patency of the artery as determined by presence of the radial pulse distal to the device, but no visible bleeding. Deflation of air from the device and subsequent removal of the bracelet are usually accomplished within 1–2 hours after a diagnostic procedure.

COMPLICATIONS OF CARDIAC CATHETERIZATION

The cumulative incidence of the major risks of stroke, death and MI is approximately 0.1%. The minor risks of vascular injury, allergic reaction, bleeding, hematoma and infection range from 0.04% to 5% (Table 10). For diagnostic catheterization,

TABLE 10

Complications and risk for cardiac catheterization [SCAI Registry (%)]

Mortality	0.11
Myocardial infarction	0.05
Cerebrovascular accident	0.07
Arrhythmias	0.38
Vascular complications	0.43
Contrast reaction	0.37
Hemodynamic complications	0.26
Perforation of heart chamber	0.03
Other complications	0.28
Total of major complications	1.70

(*Source:* Adapted from Scanlon P, Faxon D, Audet A, et al. ACC/AHA guidelines for coronary angiography. J Am Coll Cardiol.1999;33:1756.)

TABLE 11

Patients at increased risk for complications after coronary angiography

Increased General Medical Risk
• Age greater than 70 years
• Complex congenital heart disease
• Morbid obesity
• General debility or cachexia
• Uncontrolled glucose levels
• Arterial oxygen desaturation
• Severe chronic obstructive lung disease
• Renal insufficiency with creatinine greater than 1.5 mg/dl
• Increased Cardiac Risk
• Three-vessel coronary artery disease
• Left main coronary artery disease
• Functional NYHA class IV (CHF)
• Significant mitral or aortic valve disease or mechanical valve prosthesis
• Ejection fraction less than 35%
• High-risk exercise treadmill testing (hypotension or severe ischemia)
• Pulmonary hypertension
• Pulmonary artery wedge pressure greater than 25 mm Hg
• Increased Vascular Risk
• Anticoagulation or bleeding diathesis
• Uncontrolled systemic hypertension
• Severe peripheral vascular disease
• Recent stroke
(*Source:* Scanlon P, Faxon D, Audet A, et al. ACC/AHA guidelines for coronary angiography. J Am Coll Cardiol.1999;33:1756.)

analysis of the complications in more than 200,000 patients indicates the incidence of risks as follows: death less than 0.2%; MI less than 0.05%, stroke less than 0.07%, serious ventricular arrhythmia less than 0.5% and major vascular complications (thrombosis, bleeding requiring transfusion or pseudoaneurysm) less than 1%.[34-38] Vascular complications are more frequent when the femoral or brachial approaches are used as compared to the transradial approach. The incidence of death during coronary angiography is higher in the presence of LMCA disease (0.55%), with LVEF less than 30% (0.30%) and with New York Heart Association functional Class IV disease (0.29%). Patients at increased risk for complications of cardiac catheterization are shown in Table 11.

ACCESS SITE COMPLICATIONS

The most common complication noted with femoral access catheterization is hemorrhage and local hematoma formation. These complications occur more frequently with increasing size of the access sheath, concomitant venous access, increased amounts of anticoagulation, female patients, obesity and also low body weight. Other possible access site complications (in order of decreasing frequency) include retroperitoneal hematoma, pseudoaneurysm, arteriovenous (AV) fistula and arterial thrombosis.[37] The frequency of access site complications is increased in obese patients, during high-risk procedures, in critically ill elderly patients with extensive atheromatous disease, in patients receiving anticoagulation therapies and with concomitant interventional procedures. A retroperitoneal hematoma should be suspected in patients with hypotension, tachycardia, pallor, a falling hematocrit postcatheterization, lower abdominal or back pain, or neurologic changes in the procedural extremity. This complication is associated with high femoral arterial puncture and full anticoagulation.[34] Retroperitoneal hemorrhage can cause significant morbidity and even mortality, especially if not promptly recognized. Pseudoaneurysm is a complication more often associated with low femoral arterial puncture, usually below the head of the femur. This complication should be suspected in a patient with swelling at the access site and especially if there is a bruit present. The risk of pseudoaneurysm formation is higher with concomitant anticoagulation. Pseudoaneurysm can most often easily be identified with ultrasound imaging. Manual compression of the expansile growing mass guided by Doppler ultrasound with or without thrombin or collagen injection is an acceptable therapy for femoral pseudoaneurysm.[35,37] The more common treatment currently in use is ultrasound guided thrombin injection of the pseudoaneurysm. Larger pseudoaneurysms, or those not favorable for thrombin injection based on anatomic issues, may require surgical treatment.

OTHER COMPLICATIONS

Embolic stroke is a rare complication of diagnostic coronary angiography but, when it occurs, it can be devastating. Embolic stroke more commonly occurs in patients with significant aortic atheroma. Careful attention to aspiration and flushing of catheters is imperative in all procedures. Giving heparin for longer duration procedures (such as bypass graft procedures, aortic valve assessment) or in patients at higher risk for stroke should be considered. Catheter induced coronary artery dissection is an infrequent but important complication to be aware of. When it occurs, urgent or even emergent therapy may be needed in the form of PCI or sometimes even bypass surgery in the case of a left main dissection or inability to successfully percutaneously treat a catheter induced RCA dissection. This complication can often be avoided with proper coaxial positioning of catheters, avoiding abrupt or deep engagement of vessels, refraining from injecting when a dampened waveform is present and generally not injecting with excessive force. However, there are certainly times where, despite using appropriate technique and caution, this complication can still occur, especially in vessels with atherosclerotic disease. Air embolus is a rare (0.1%) complication during diagnostic coronary angiography and is generally preventable with meticulous attention to elimination of air within the manifold system. If an air embolus does occur, 100% oxygen should be administered, which theoretically allows resorption of smaller amounts of air within 2–4 minutes. Prompt and aggressive supportive care is sometimes necessary depending on the size and the location of the air embolus. Distal cholesterol embolization is also relatively uncommon, but is more common during procedures in patients with significant peripheral arterial disease. Nerve pain after diagnostic catheterization is infrequent, but can occur as a result of local anesthesia given during the procedure as well as the location of the sheath near a superficial nerve causing local irritation of the nerve. This condition generally resolves spontaneously over time. Although lactic acidosis may develop after coronary angiography in diabetic

patients taking metformin, this complication is very rare and has been essentially eliminated with the practice of metformin discontinuation immediately before coronary angiography and not restarting the medication until renal function has been documented to be in the normal range postprocedure.With the expanded use of complex PCI, patients may now return for multiple procedures over their lifetime which can subject them to the risk of cumulative radiation injury.[39,40] An average PCI procedure imparts 150 times the radiation exposure received with a single chest X-ray and 6 times the annual radiation received by background environmental radiation.[39,40] Skin related radiation injury is more often related to a single long exposure with limited movement of the X-ray tube during the procedure. Reports of radiodermatitis related to prolonged X-ray exposure have led to the recommendation that patients who receive fluoroscopy for more than 60 minutes be counseled about the delayed effects of radiation injury to the skin, although proportionately significantly more radiation is received with digital cineangiography than with fluoroscopy alone. Radiation-induced skin lesions are generally identified by their location in the region of the body that was imaged and are manifest by an acute erythema, delayed pigmented telangiectasia and indurated or ulcerated plaques. The risk of causing radiation induced skin injury can be minimized with meticulous attention to limiting the amount of fluoroscopy and digital cineangiographic exposure during the case. In very complex procedures where increased amounts of X-ray exposure are difficult to control, care should be taken to use multiple different angles to reduce the exposure of one certain area of the body to the X-ray.

LESION QUANTIFICATION

QUANTITATIVE ANGIOGRAPHY

Although visual estimations of coronary stenosis severity are used by virtually all clinicians to guide clinical practice, "eyeball" estimates of percent diameter stenosis are limited by substantial observer variability and bias. However, more reliable and objective quantitative coronary measurements have had limited clinical use in the assessment of intermediate coronary lesions (40–70%), having been largely supplanted by physiological measures of stenosis significance, most often fractional flow reserve (FFR). Quantitative coronary angiography was initially performed by Greg Brown and his colleagues at the University of Washington nearly 30 years ago. Using hand-drawn arterial contours, reference vessel and minimal lumen diameters were measured and were used to evaluate the effect of pharmacological intervention for a number of angiographic plaque regression studies. These initial quantitative angiographic methods were time consuming and cumbersome and have now been largely replaced with computer-assisted methods for automated arterial contour detection.Quantitative angiographic analysis is divided into several distinct processes, including film digitization (when needed), image calibration and arterial contour detection.[25] The contrast-filled diagnostic or guiding catheter can be used as a scaling device for determining absolute vessel dimensions, yielding a calibration factor in millimeters per pixel. Catheter and arterial contours are obtained by drawing a center line through the segment of interest. Linear density profiles are then constructed by the computer perpendicular to the center line, and a weighted average of the first and second derivative function is used to define the catheter or arterial edges. Individual edge points are then connected using an automated algorithm, and outliers are discarded and the edges are smoothed. The automated algorithm is then applied to a selected arterial segment, and absolute coronary dimensions and percent diameter stenosis are obtained.

LESION COMPLEXITY

Heterogeneity of the composition, distribution and location of atherosclerotic plaque within the native coronary artery results in unique patterns of stenosis morphology in patients with CAD. These patterns have been used to identify risk factors for procedural outcome and complications after PCI and to assess the risk for recurrent events in patients who present with an acute coronary syndrome.[41] Criteria established by a joint ACC/AHA task force suggested that procedure success and complication rates were related to a number of different lesion characteristics (Table 12). Over the decade following the publication of these criteria, the most complex lesion morphologies (i.e. "type C" lesions) remain associated with reduced procedural success in patients with ischemic CAD. This is despite substantial improvements in the techniques used for coronary intervention over this same time period.

TABLE 12

Characteristics of type A, B and C coronary lesions

Type A lesions (high success, > 85%; low risk)	
Discrete (< 10 mm)	Little or no calcium
Concentric	Less than totally occlusive
Readily accessible	Not ostial in locations
Non-angulated segment, < 45°	No major side branch involvement
Smooth contour	Absence of thrombus
Type B lesions (moderate success, 60–85%; moderate risk)	
Tubular (10–20 mm length)	Moderate to heavy calcification
Eccentric	Total occlusions < 3 months old
Moderate tortuosity of proximal segment	Ostial in location
Moderately angulated segment, ≥ 45°, < 90°	Bifurcation lesion requiring double guidewire
Irregular contour	Some thrombus present
Type C lesions (low success, < 60%; high risk)	
Diffuse (> 2 cm length)	Total occlusion > 3 months old
Excessive tortuosity of proximal segment	Inability to protect major side branches
Extremely angulated segments, ≥ 90°	Degenerated vein grafts with friable lesions

(*Source:* Ryan TJ, Bauman WB, Kennedy JW, et al. Guidelines for percutaneous coronary angioplasty. A report of the American Heart Association/American College of Cardiology Task Force on Assessment of Diagnostic and Therapeutic Cardiovascular Procedures (Subcommittee on Percutaneous Transluminal Coronary Angioplasty). Circulation.1993;88:2987.)

The predictive value of two other risk scores has been compared to the ACC/AHA lesion complexity score.[42,43] The Society for Cardiac Angiography and Interventions (SCAI) risk score used an ordinal ranking of two composite criteria (vessel patency and complex morphology) to classify lesions into four groups: (1) non-type C–patent; (2) type C–patent; (3) non-type C–occluded and (4) Type C–occluded.[42] For correctly classifying lesion success, the ACC/AHA classification had a C-statistic of 0.69; the modified ACC/AHA system had a C-statistic of 0.71; and the SCAI classification had a C-statistic of 0.75. The Mayo Clinic Risk Score added the integer scores for the presence of eight morphological variables and provided a better risk stratification than the ACC/AHA lesion classification for the predicting of cardiovascular complications, whereas the ACC/AHA lesion classification was a better system for identifying angiographic success of PCI.[43]

LESION LENGTH

Lesion length may be measured using a number of methods, including measurement of the "shoulder-to-shoulder" extent of atherosclerosis narrowed by more than 20%, quantifying the lesion length more than 50% narrowed, and estimating the distance between the proximal and the distal angiographically "normal" segment. The last method is used most commonly in clinical practice and provides a longer length than more quantitative methods. Diffuse (> 20 mm) lesions are associated with reduced procedural success with drug-eluting stents, primarily related to large degrees of late lumen loss and more extensive underlying atherosclerosis.[44]

OSTIAL LESIONS

Ostial lesions are defined as those arising within 3 mm of the origin of a vessel or branch and can be further characterized into aorto-ostial and non-aorto-ostial. Aorto-ostial lesions are often fibrocalcific and rigid, sometimes requiring additional ablative devices—such as rotational atherectomy (RA) in the presence of extensive calcification—in order to obtain adequate stent expansion. Positioning of the proximal portion of the stent in the aorto-ostial location so that no more than 1 mm of stent extends into the aorta requires meticulous care. Ostial stenoses that do not involve the aorta may also be more elastic and fibrotic than non-ostial lesions but also require the additional principles for treatment as bifurcation lesions.

BIFURCATION LESIONS

The optimal strategic approach for bifurcation lesions remains controversial. The risk for side branch occlusion during PCI relates to the relative size of the parent and branch vessel, the location of the disease in the parent vessel and the stenosis severity in the origin of the side branch. In general, placement of one stent in the larger vessel (usually the parent) is preferable to stent placement in both the parent vessel and the side branch.

ANGULATED LESIONS

Vessel angulations should be measured in the projection with the least amount of foreshortening at the site of maximum stenosis. Balloon angioplasty of angulated lesions increases the risk for dissections, although with the advent of coronary stenting, this is now most often readily treated. If a stent is placed in a highly angulated lesion, there is subsequent straightening of the vessel that may predispose to late stent strut fracture, although this is a largely theoretic risk.

DEGENERATED SAPHENOUS VEIN GRAFTS

A serial angiographic study in patients undergoing coronary bypass surgery showed that 25% of SVGs occlude within the first year after coronary bypass surgery.[45] Drug-eluting stents may reduce the restenosis rate and resulting need for PCI, in SVGs[46] but only embolic protection devices (EPD) have reduced procedural complications during SVG PCI. A study that evaluated the extent of graft degeneration and estimated volume of plaque in the target lesion found that the independent correlates of increased 30-day major adverse cardiac event rates were more extensive vein graft degeneration ($p = 0.0001$) and bulkier lesions (larger estimated plaque volume, $p = 0.0005$).[47]

LESION CALCIFICATION

Coronary artery calcium is an important marker for coronary atherosclerosis. Conventional angiography is moderately sensitive for the detection of extensive lesion calcification, but is less sensitive for detecting the presence of milder degrees of lesion calcification. Severely calcified lesions tend to be more rigid and difficult to dilate with a balloon than noncalcified lesions. In heavily calcified lesions, RA may be useful before stenting to ensure both stent delivery and more importantly, complete stent expansion.

THROMBUS

Conventional angiography is a relatively insensitive method for detecting coronary thrombus. However, its presence is associated with a higher risk of procedural complications, primarily relating to embolization of thrombotic debris into the distal circulation. Large intracoronary thrombi are most often noted as intraluminal filling defects during angiography in STEMI and may be treated with a combination of pharmacological agents (e.g. glycoprotein IIb/IIIa inhibitors) and mechanical devices (e.g. rheolytic thrombectomy, manual aspiration catheters).

TOTAL OCCLUSION

Total coronary vessel occlusion is identified as an abrupt termination of an epicardial vessel. Anterograde and retrograde collaterals may be present and are helpful in quantifying the length of the totally occluded segment. The success rate of passage of a coronary guidewire across the occlusion depends on the occlusion duration and on certain lesion morphological features. The following are lesion features that decrease the chance of procedural success: the presence of bridging collaterals, occlusion length greater than 15 mm, branches that originate at or near the occlusion point and the absence of an angiographic "beak" at the occlusion site. Newer guidewires and improved operator experience have improved procedural success rates, although the presence of a total l occlusion remains one of the major reasons for referring patients for coronary bypass surgery.

TABLE 13

Thrombolysis in myocardial infarction (TIMI) flow

Grade 3 (complete reperfusion)	Anterograde flow into the terminal coronary artery segment through a stenosis is as prompt as anterograde flow into a comparable segment proximal to the stenosis. Contrast material clears as rapidly from the distal segment as from an uninvolved, more proximal segment
Grade 2 (partial reperfusion)	Contrast material flows through the stenosis to opacify the terminal artery segment. However, contrast material enters the terminal segment perceptibly more slowly than more proximal segments
	Alternatively, contrast material clears from a segment distal to a stenosis noticeably more slowly than from a comparable segment not preceded by a significant stenosis
Grade 1 (penetration with minimal artery perfusion)	A small amount of contrast material flows through the stenosis but fails to opacify fully the epicardial vessel
Grade 0 (no perfusion)	No contrast flow through the stenosis

(*Source:* Modified from Sheehan F, Braunwald E, Canner P, et al. The effect of IV thrombolytic therapy on LV function: a report on the tissue-type plasminogen activator and streptokinase from the thrombolysis in myocardial infarction (TIMI) phase 1 trial. Circulation.1989;72:817.)

CORONARY PERFUSION

Perfusion distal to a coronary stenosis can occur anterograde by means of the native vessel, retrograde through collaterals, or through a coronary bypass graft. The rate of anterograde coronary flow is influenced by both the severity and complexity of the stenosis and the status of the microvasculature. The Thrombolysis in Myocardial Infarction (TIMI) study group established criteria to assess the degree of anterograde coronary perfusion in patients with acute MI and found that complete restoration of anterograde perfusion to TIMI 3 flow was associated with the lowest mortality rate (Table 13).

PHYSIOLOGIC ASSESSMENT OF ANGIOGRAPHICALLY INDETERMINATE CORONARY LESIONS

FRACTIONAL FLOW RESERVE

Coronary artery physiologic data can be used to facilitate clinical decisions regarding revascularization in the catheterization laboratory. Angiography alone cannot always determine the clinical or physiologic importance of a coronary stenosis that narrows the vessel by between 40% and 70% of its normal diameter.[48,49] In order to overcome this limitation, physiologic testing is often performed before making a recommendation for revascularization. Guidewires with a pressures sensor have been developed that can safely be used[50] to permit pressure measurement distal to a coronary stenosis. Some of these guidewires can measure both pressure and flow velocity. Translesional pressure at maximal hyperemia is measured. Maximal hyperemia is induced by IV (140 mcg/kg/min) or intracoronary (30–60 mcg bolus) adenosine. FFR is the ratio of the pressure distal to a coronary stenosis and pressure proximal to the stenosis. It is a pressure-derived estimate of the percent of normal coronary blood flow that would be available to the myocardium. A normal value is 1, while values less than 0.80 are associated with provocable ischemia on myocardial perfusion imaging.

CLINICAL USE OF TRANSLESIONAL PHYSIOLOGIC MEASUREMENTS

Intermediate coronary stenosis, defined as a 40–70% diameter narrowing, is encountered in almost 50% of patients undergoing coronary angiography. FFR measurements parallel noninvasive stress testing results and can identify hemodynamically significant lesions, thereby assisting in immediate decision-making regarding revascularization at the time the diagnostic angiogram. A high degree of correlation between the noninvasive stress testing and the FFR measurement has been found in analyses of patients with stable angina[51-53] non-ST elevation acute coronary syndrome[54] and chest pain of uncertain origin.[55]The FFR is useful for critical decision-making regarding stenting in patients with single or multivessel disease.[56-58] In patients with intermediate lesions, translesional hemodynamic data can be easily acquired. If the FFR is normal, intervention can be safely deferred.[57,59-61]Patients with CAD often have multiple sequential stenoses. It is important to objectively select the most appropriate of several stenoses to be treated. Coronary artery pressure measurements for calculation of FFR of each stenosis can be made by a pull-back pressure recording at maximal hyperemia.[62] In vessels with diffuse disease and long lesions (not uncommon in diabetic patients) FFR measurements can be useful in decision-making regarding the optimal location for PCI within a given artery, or perhaps to recommend CABG as an alternative to PCI. The practice of attempting complete or near complete revascularization in the catheterization laboratory for patients with symptomatic CAD has become more frequent. However, this approach has not been shown to be associated with better outcomes. Attempts to identify which arteries need to be revascularized have been made using both invasive and noninvasive techniques to assess for myocardial ischemia. Noninvasive assessment of myocardial ischemia with myocardial perfusion imaging may not accurately identify the severity of any given lesion in the setting of multivessel disease. However, FFR measurements can identify the clinical severity of individual lesions in patients with multivessel disease[53] thus helping to direct the most appropriate revascularization strategy.[58] The clinical significance of an ostial stenosis can also be further evaluated with FFR, which may be especially beneficial in patients with ostial left main disease.[63,64] Assessment of the physiologic significance of individual coronary stenosis is not only an economically viable strategy, but it also favorably modifies outcomes for patients.[54,59,65]

Historically, improvement in physiology after balloon angioplasty has been poorly correlated to both angiographic results and clinical outcomes because of the inherent limitations of the angiogram. Stenting has replaced balloon angioplasty as

the mainstay for the percutaneous treatment of CAD. Unlike with percutaneous transluminal coronary angioplasty (PTCA), coronary pressure measurements after stenting can be used to predict adverse cardiac events.[66]

NON-ATHEROSCLEROTIC CORONARY ARTERY DISEASE AND TRANSPLANT VASCULOPATHY

CORONARY ARTERY SPASM

Coronary artery spasm is defined as a dynamic and reversible stenosis of an epicardial coronary artery caused by focal constriction of the smooth muscle cells within the arterial wall. Initially described by Prinzmetal and his colleagues ("Prinzmetal" or "variant" angina) in 1959, this form of angina was not provoked by the usual factors such as exercise, emotional upset, cold or ingestion of a meal. Coronary artery spasm is more commonly invoked by cigarette smoking, cocaine use, alcohol, intracoronary radiation and administration of catecholamines during general anesthesia. It is characterized by chest discomfort associated with ST elevations on ECG. Although the ST segment elevation is often striking with coronary spasm, the ST elevations rapidly revert to normal when the pain disappears spontaneously or is terminated by the administration of nitroglycerin. Coronary artery spasm may be accompanied by AV block, ventricular ectopy, ventricular tachycardia or ventricular fibrillation. MI and death are rare manifestations of coronary artery spasm. Coronary artery spasm can also be superimposed on an intramyocardial bridge.[24]

Coronary angiography is useful in patients with suspected coronary artery spasm to exclude the presence of concomitant atherosclerotic CAD and to document an episode of coronary artery spasm using provocative IV medications. Three provocative tests can be performed to detect the presence of coronary artery spasm. IV ergonovine maleate can elicit two types of responses. A diffuse coronary vasoconstriction that occurs in all the epicardial arteries is a physiological response to ergonovine and is not diagnostic of coronary artery spasm. The second response to ergonovine is a focal, occlusive spasm of the epicardial artery that is associated with chest pain and ST segment elevation on ECG. This is diagnostic of coronary spasm. Nitroglycerin should be administered directly into the coronary artery to relieve the coronary spasm. A second provocative test is the use of IV acetylcholine. Although it is more sensitive than ergonovine, it may be less specific because of the positive response in patients with atherosclerotic CAD. The final provocative test is hyperventilation during coronary angiography, which is less sensitive but highly specific for the presence of coronary artery spasm.

In the absence of a positive stimulation test, the diagnosis of coronary artery spasm must rely instead on clinical features and response to treatment with nitrates and calcium channel blockers. Sole therapy with beta blockers should be avoided because it can increase the occurrence and severity of coronary artery spasm.

SPONTANEOUS CORONARY ARTERY DISSECTION

Spontaneous coronary artery dissection is a rare cause of acute MI that is more common in younger patients and in women.[67] SCD is often the first manifestation[68] and the majority of cases have been diagnosed at autopsy.[68] However, the entire spectrum of acute coronary syndromes may be seen.[68]The etiology of spontaneous coronary dissection is not known. Most patients presenting with this entity do not have risk factors for atherosclerotic CAD. Histologically, an inflammatory reaction in the adventitia has been described, suggestive of periarteritis. However, this inflammatory response may be reactive rather than causative.[68]In women, the risk of spontaneous coronary dissection appears to be increased during the peripartum period.[68-70,] It has been suggested that the association between coronary dissection and pregnancy may be a consequence of increased hemodynamic stress or of hormonal effects on the arterial wall.[68]

VASCULITIS

Kawasaki disease (KD) is a vasculitis of infancy and early childhood. The typical presentation is an acute febrile illness in children under the age of five; the incidence is higher in Asian and Asian-American populations than in other groups. The etiology of KD is unknown, although an inflammatory response precipitated by an infectious agent is suggested by some epidemiologic data. The most important complication of KD is coronary vasculitis, leading to coronary aneurysm formation in 20–25% of untreated patients during the acute stage of the disease. Nearly half of acute aneurysms regress, but approximately 20% lead to the development of coronary stenosis in the long term. Patients can present with MI or SCD.

While patients with known KD are followed for the development of coronary artery stenoses, some patients who were not previously diagnosed are recognized only after presenting with sequelae of CAD, including MI, heart failure and SCD.[71,72] Thus, young patients with MI should be asked about a possible childhood history of KD.

TRANSPLANT VASCULOPATHY

The incidence of angiographic allograft coronary vasculopathy is approximately 7% at 1 year. Long-term incidence of allograft coronary vasculopathy is about 32% at 5 years and 53% at 10 years.[73] Risk is slightly greater in patients transplanted because of ischemic heart disease compared to those with nonischemic heart disease.[73] Additional risk factors for transplant vasculopathy are: donor age (curvilinear), recipient age (inverse), gender (male donor), donor hypertension and number of HLA-DR mismatches. Higher transplant center volume was unexpectedly found to be associated with increased risk of vasculopathy. This may be due to higher volume centers either accepting more diverse donors or more aggressive screening for vasculopathy over time.

The diagnosis of transplant vasculopathy is often difficult to establish based upon clinical evaluation alone. Cardiac transplant recipients have both afferently and efferently denervated hearts. Although there is evidence for some reinnervation in select patients by 5 years after transplantation, the degree of reinnervation is generally incomplete.[74,75] As a result, patients with transplant vasculopathy seldom experience the classic symptom of angina pectoris. Silent MI, sudden death and progressive heart failure are common presentations of

transplant vasculopathy. Symptoms associated with exertion such as dyspnea, diaphoresis, gastrointestinal distress, presyncope or syncope, are often infrequent, atypical and may be misleading.[76]Thus, to improve long-term outcomes, early diagnosis is essential. Serial screening studies are the preferred approach for detection of vasculopathy in this population.

Prospective coronary angiography is used to establish the diagnosis of transplant coronary vasculopathy. At some centers, coronary angiography is performed prior to discharge after transplantation (as a baseline) and at most centers it is performed annually starting at 1 year postoperatively. Coronary angiography yields important prognostic information, as the absence of angiographic coronary disease was a significant predictor of survival without adverse cardiac events.[77]

Although coronary angiography is the gold standard for the diagnosis of nontransplant atherosclerosis, it is less sensitive in detecting transplant vasculopathy. This is due to the often diffuse and concentric nature of this form of coronary disease. As a result, many patients who develop clinical events that are presumably due to transplant vasculopathy do not have angiographically significant disease.[78,79]

Due to these limitations, adjuncts to angiography have been sought that might improve the detection of early transplant vasculopathy. These include the TIMI frame count, Doppler measurement of coronary flow reserve and, in some centers, intravascular ultrasound imaging.

POTENTIAL ERRORS IN INTERPRETATION OF THE CORONARY ANGIOGRAM

Errors in image acquisition and interpretation of the coronary angiogram can have a profound impact on management strategies in patients with ischemic CAD, particularly when there is disagreement between angiographic, physiological and clinical findings. Attention to factors that affect angiographic image quality at the time of image acquisition will improve the ultimate course selected for patients who undergo angiography.

INADEQUATE VESSEL OPACIFICATION

Inadequate filling of the coronary artery with contrast medium results in incomplete vessel opacification or "streaming" of contrast. When this occurs, there may be an overestimation of the severity of a stenosis within the vessel. Some common causes of inadequate vessel opacification include: suboptimal position of the diagnostic catheter (i.e. not coaxial with the coronary ostium), inadequate force of contrast injection and competition from increased native coronary blood flow in cases of very large coronary vessels or high cardiac output states. Inadequate filling of the coronary vessels with contrast can often be overcome by various techniques (depending on the cause of the underfilling) including: coaxial catheter engagement (this may involve changing the catheter), a more forceful contrast agent injection (as long as catheter tip position and pressure recording confirm the safety of such a maneuver), upsizing catheter diameter or use of a guide catheter for diagnostic angiograms. In cases of absent or very short left main, selective injection of contrast medium into the LCX artery (or LAD) may give the impression of severe disease of even total occlusion of the LAD (or LCX). This situation must be recognized and care taken to repeat the angiograms with adequate filling of both vessels.

CATHETER INDUCED SPASM

Catheter induced spasm is a relatively common occurrence during coronary angiography and important to recognize. It is more common with engagement of the RCA but can certainly also occur in the left main as well as in bypass grafts—especially free radial artery and IMA bypass grafts. Catheter induced spasm is characterized by a focal stenosis which is typically seen at or near the tip of the catheter. This often results in dampening of the pressure waveform and the need to adjust the catheter until the waveform normalizes before injecting. Often, even after adjusting the catheter until the waveform has normalized, there will appear to be a stenosis in the vessel. It is very important to give intracoronary nitroglycerin and repeat the angiogram to confirm that there is not an atherosclerotic stenosis at that site, but rather that there was coronary spasm that has been relieved with nitrates. Other maneuvers to consider in this assessment are performing a nonselective injection to assess the ostium or using a smaller French size catheter. Failure to recognize catheter induced spasm could result in the erroneous interpretation of an obstructive atherosclerotic stenosis and a subsequent unnecessary recommendation for revascularization.

INCOMPLETE STUDY

A study is considered incomplete when an inadequate number of angiographic images are taken. There is no standard number of views that should be taken, but it is critical to completely define the coronary anatomy and account for all vascular territories. This can certainly be more challenging in cases of chronically occluded vessels, after bypass surgery, or with coronary anomalies. When previous angiograms are available for review, they should be reviewed before the current procedure to ensure that all necessary angiograms have been obtained. If no previous angiogram is available and not all vascular territories are accounted for then further investigation is warranted. In procedures performed after a bypass surgery when bypass grafts are not initially able to be selectively engaged and there is no filling seen (either antegrade or by collaterals) of the vessel that was reported to be bypassed, performance of an ascending aortogram to confirm the number of grafts patent from the aorta is indicated. If additional grafts are then visualized, further attempts to selectively cannulate the grafts can be made. In cases where patients have not had previous bypass surgery but not all vascular territories are accounted for in the obtained angiograms, coronary anomaly should be suspected and investigated as described below.

CORONARY ANOMALIES

Coronary anomalies are rare but important to recognize. When unrecognized, the erroneous conclusion that a coronary vessel occlusion is present can occur. For example, if there is no LCX apparent with initial injection of the left main and there is no collateral filling of the vessel, a nonselective injection of the left coronary cusp can be performed to exclude separate LAD and LCX ostia. If there are separate ostia, then these vessels

can be selectively engaged and a complete angiogram obtained. If this is not the case, than suspicion of an anomalous LCX off the proximal RCA or right coronary cusp can be suspected and investigated accordingly. Additionally, if on attempted engagement of the RCA, there is no apparent ostium in the right coronary cusp on nonselective injection, suspicion of an anomalous RCA (often with a high and leftward takeoff from the aorta) should be raised. Switching catheters and interrogating the aorta in the suspected area often results in successful cannulation of the RCA. If cannulation is still not successful, then aortography can be performed to further evaluate the RCA origin. These are some of the most commonly seen coronary anomalies with a few ideas on how to avoid performing an incomplete angiogram when they are present. Certainly there are many other anomalous coronary artery possibilities that may occur which all cannot be described here. The important concept to take away is to be aware of the possibility of coronary anomaly when all vascular territories are not accounted for while performing a coronary angiogram and be vigilant in making a full assessment. This may include recommending coronary CT angiography in some cases.

TOTAL OCCLUSION OF A CORONARY ARTERY

Total occlusion of a coronary vessel can sometimes be difficult to identify, particularly when there is a "flush" occlusion at the origin making identification of the origin very difficult. This can be especially challenging in the case of a flush occlusion of the RCA. It is important for the angiographer to make sure that all vascular territories are accounted for in the angiograms that have been obtained. If there seems to be a portion of the myocardium that does not have a clearly visible epicardial vascular supply, careful attention should be directed to the possibility of faint collateral filling of an occluded vessel in that area.

ECCENTRIC STENOSES

Coronary atherosclerosis is a ubiquitous process that leads to asymmetrical plaque distribution within the coronary artery. Although most segments of the artery wall are involved in the atherosclerotic process, eccentric lesions may appear non-obstructive in one angiographic view, while quite severe in another. This phenomenon reinforces the importance of obtaining multiple (at least two orthogonal) views of each coronary artery. If there is still question about the severity of an eccentric stenosis, then further evaluation [noninvasive physiologic assessment, pressure wire assessment or intravascular ultrasound (IVUS)] can be recommended and completed.

SUPERIMPOSITION OF VESSELS

Superimposition of the left and the right coronary arteries with their respective branches can result in failure to detect significant stenoses or even total occlusions. Overlap of vessels can occur in any area during a coronary angiogram, but it is especially important to adequately evaluate the distal left main, LAD ostium, LCX ostium and ramus intermedius origin (when present) without superimposition of branches. Other areas that may be more difficult to image can include the LAD and parallel diagonal branches, the origins of obtuse marginal branches of the LCX, and the distal bifurcation of the RCA into the RPDA and RPLA. It is important to obtain sufficient angulations to clearly visualize these areas. Typical views used for visualization of these various areas were discussed earlier, but in some cases there will need to be further adjustments made based on individual anatomical considerations.

MICROCHANNEL RECANALIZATION

It is sometimes difficult to differentiate very severe (> 90%) coronary stenoses (with an anterograde lumen) from total coronary occlusions (with no anterograde lumen) that have been recanalized with microchannels and bridging collaterals. Pathological studies suggest that approximately one-third of totally occluded coronary arteries ultimately recanalize, resulting in the development of multiple tortuous channels that are quite small and close to one another, creating the impression on angiography of a single, slightly irregular channel. As angiography lacks sufficient spatial resolution to demonstrate this degree of detail in most patients with recanalized total occlusions, wire crossing may not be possible in some cases unless advanced wire techniques are used.

PERCUTANEOUS CORONARY INTERVENTION

The term "angina pectoris" was introduced by Heberden in 1772 to describe a syndrome characterized by a sensation of "strangling and anxiety" in the chest. This was attributed to myocardial ischemia arising from increased myocardial oxygen consumption due to obstructive CAD. Treatment of this syndrome was initially done with coronary artery bypass surgery, first introduced in 1968. In 1977, the first PTCA was performed by Andreas Gruentzig.

The early percutaneous revascularization procedures used cumbersome equipment, which limited the success and use of these procedures. Guide catheters were large and could easily traumatize the vessel. There were no guidewires, and balloon catheters were large with low burst pressures. As a result, the procedure was limited to patients with refractory angina, good LV function, and a discrete, proximal and non-calcific lesion in a single major coronary artery. Additional requirements were that there were no involvement of major side branches or significant angulations at the lesion site. Due to these limitations, percutaneous treatment was considered feasible in only 10% of all patients needing revascularization.

The next several decades saw significant advancements and refinement of guide catheters and guidewire technology. Balloon catheters were also improved, with slimmer crossing profiles and increased tolerance to high inflation pressures. Coronary stents were developed which greatly improved the overall success of percutaneous coronary interventions (PCIs) and significantly reduced the risk of abrupt vessel closure after angioplasty. As equipment improved, experience increased and adjunctive pharmacological therapies were better understood, more complex lesions were treated in both elective and acute situations. Although femoral access has been and currently continues to be the favored approach by most for the performance of PCI, the radial artery is an increasingly attractive

alternative access site. The radial artery access site is becoming more practical as the development of coronary interventional equipment (specifically radial specific guide shapes, lower profiles of balloons and stents) allows many PCI procedures to be able to be successfully completed with either 5 or 6 French systems.

Today, PCI encompasses a broad array of procedures including angioplasty, stenting and various "niche" devices which all together allow the performance of safe and effective percutaneous revascularization in many different clinical situations (Table 14).

PHARMACOTHERAPY FOR PCI

Treatment with antiplatelet and anticoagulant medications is a requirement for the safe and successful performance of any PCI. Some of the most commonly used medications during PCI are described below.

ANTIPLATELET THERAPY

Aspirin

Aspirin irreversibly inhibits cyclooxygenase and thus blocks the synthesis of thromboxane A_2, a vasoconstricting agent that promotes platelet aggregation. Aspirin substantially reduces periprocedural MI caused by thrombotic occlusions compared with placebo and has been established as a standard for all patients undergoing PCI. The inhibitory effect of aspirin occurs within 60 minutes, and its effect on platelets lasts for up to 7 days after discontinuation. Although the minimum effective aspirin dosage in the setting of PCI remains uncertain, patients taking daily aspirin should receive 75–325 mg aspirin before PCI. Patients not already taking daily long-term aspirin therapy should be given 300–325 mg of aspirin at least 2 hours and preferably 24 hours before PCI is performed.

Thienopyridines

Dual antiplatelet therapy with aspirin and a thienopyridine is required in any PCI that includes stenting. The indicated duration of dual antiplatelet therapy specifically related to stenting varies, depending on if bare metal or drug-eluting stents are used. Dual antiplatelet therapy is needed for at least 1 month with bare metal stent placement and for at least 1 year if a drug-eluting stent is placed. The initial thienopyridine developed and used was ticlopidine. It has been largely replaced by newer generations of thienopyridines that are described below as these newer medications have more favorable side effect profiles.

Clopidogrel inhibits platelet activation by irreversibly blocking the ADP (P_2Y_{12}) receptor. It has better tolerability, fewer side effects, and is at least as effective as ticlopidine. Along with aspirin, clopidogrel is routinely administered prior to stent implantation. Recent evidence also supports its use in non-stent PCI.[80,81] An initial clopidogrel dose of 600 mg is needed to produce potent inhibition of ADP-induced platelet aggregation within 2 hours.[82-84] A 300 mg loading dose can be used when longer pretreatment is possible and has been shown to produce maximal platelet inhibition within 24 hours with substantial inhibition at 15 hours.[85] Following PCI, long-term (1 year) clopidogrel use is associated with a 27% relative reduction in adverse ischemic events ($p = 0.02$) compared to 4 weeks of therapy.[86] These findings extended and amplified the similar findings of the PCI-CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events) trial.[81] Major bleeding was not significantly increased at 1 year, and clopidogrel therapy for 1 year was found to be cost-effective. Recent reports suggest that inadequate inhibition of platelet aggregation may occur in patients with higher body mass index and that insensitivity to clopidogrel is more common than previously thought. Both factors may contribute to periprocedural ischemic complications and stent thrombosis. Depending on the definition used, 10–15% of patients undergoing PCI are resistant to aspirin, and 25% are resistant to clopidogrel. In addition, about half of aspirin-resistant patients have a lower response to clopidogrel, placing them at higher risk of periprocedural myonecrosis and stent thrombosis.[87-89] However, reliable, standardized, bedside measures of resistance to dual antiplatelet therapy are not currently available.

Prasugrel is a more potent P_2Y_{12} ADP receptor inhibitor that has a more rapid onset of action and higher levels of platelet inhibition than higher dose clopidogrel.[90] In a study of 13,608 patients with moderate- to high-risk acute coronary syndromes undergoing scheduled PCI and randomly assigned to receive prasugrel (60 mg loading dose and 10 mg daily maintenance dose) or clopidogrel (300 mg loading dose and 75 mg daily maintenance dose) for 6–15 months, the primary efficacy endpoint, a composite of death from cardiovascular causes, nonfatal MI, or nonfatal stroke, occurred in 12.1% of patients receiving clopidogrel and 9.9% of patients receiving prasugrel ($P < 0.001$).[91] There were also significant reductions in the prasugrel group in the rates of MI (9.7% for clopidogrel vs 7.4% for prasugrel; $P < 0.001$), urgent target vessel revascularization (3.7% vs 2.5%; $P < 0.001$) and stent thrombosis (2.4% vs 1.1%; $P < 0.001$).[91] However, major bleeding was observed in 2.4% of patients receiving prasugrel and in 1.8% of patients receiving clopidogrel ($P = 0.03$), with more frequent rates of life-threatening bleeding in the prasugrel group (1.4% vs 0.9% with clopidogrel; $P = 0.01$), including fatal bleeding (0.4% vs 0.1% respectively; $P = 0.002$). Among persons treated with clopidogrel, carriers of reduced-function CYP_2C_{19} alleles had significantly lower levels of active metabolite, diminished platelet inhibition and higher rates of adverse cardiovascular events.[92] However, a similar relationship was not found in patients treated with prasugrel. Further research will be necessary to determine if measurement of point-of-care platelet assays of genetic polymorphisms can help in allocating therapy. In patients with an acute coronary syndrome undergoing PCI who are at low bleeding risk and have not had a previous stroke, prasugrel 60 mg loading dose should be given as soon as possible after definition of the coronary anatomy and continued for the appropriate course after stent placement, depending on the type of stent used.

Ticagrelor is a reversible oral P_2Y_{12} receptor antagonist which provides faster, greater and more consistent ADP-receptor inhibition than clopidogrel.[93] In a multicenter, double-blind trial of 18,624 patients presenting with an acute coronary syndrome with or without ST segment elevation, random assignment was made to treatment with ticagrelor (180 mg loading dose, 90 mg

TABLE 14

Indications for PCI

Common indications for percutaneous coronary interventions according to patient presentation:[1,2]

Patients with asymptomatic ischemia or CCS class I or II angina

Class IIa

PCI is reasonable in patients with 1 or more significant lesions in 1 or 2 coronary arteries suitable for PCI. The vessels intended to be treated must subtend a moderate to large area of viable myocardium or be associated with a moderate to severe degree of ischemia on noninvasive testing. It is also indicated in patients with recurrent stenosis after PCI with large area of viable myocardium. PCI can also be offered to patients with significant left main disease (> 50%), who are not eligible for CABG

Class IIb

(1) The effectiveness of PCI for patients with asymptomatic ischemia or CCS class I or II angina who have 2- or 3-vessel disease with significant proximal LAD CAD who are otherwise eligible for CABG with 1 arterial conduit and who have treated diabetes or abnormal LV function is not well established. However it can be considered in patients with non-proximal LAD disease in a vessel that serves a moderate area of viable myocardium with demonstrable ischemia on testing

Class III

PCI is generally not recommended in patients with asymptomatic ischemia or CCS class I or II angina who do not meet the criteria as listed under the class II recommendations or who have 1 or more of the following:

1. Only a small area of viable myocardium at risk
2. No objective evidence of ischemia
3. Lesions that have a low likelihood of successful dilatation
4. Mild symptoms those are unlikely to be due to myocardial ischemia
5. Factors associated with increased risk of morbidity or mortality
6. Left main disease and eligibility for CABG
7. Insignificant disease (< 50% coronary stenosis)

Patients with CCS class III angina

Class IIa

1. It is reasonable that PCI be performed in patients with CCS class III angina and single-vessel or multivessel CAD who are undergoing medical therapy and who have 1 or more significant lesions in 1 or more coronary arteries suitable for PCI with a high likelihood of success and low risk of morbidity or mortality
2. It is reasonable that PCI be performed in patients with CCS class III angina with single-vessel or multivessel CAD who are undergoing medical therapy with focal saphenous vein graft lesions or multiple stenoses who are poor candidates for reoperative surgery
3. Use of PCI is reasonable in patients with CCS class III angina with significant left main CAD (> 50% diameter stenosis) who are candidates for revascularization but are not eligible for CABG

Class IIb

1. PCI may be considered in patients with CCS class III angina with single-vessel or multivessel CAD who are undergoing medical therapy and who have 1 or more lesions to be dilated with a reduced likelihood of success
2. PCI may be considered in patients with CCS class III angina and no evidence of ischemia on noninvasive testing or who are undergoing medical therapy and have 2- or 3-vessel CAD with significant proximal LAD CAD and treated diabetes or abnormal LV function

Class III

PCI is not recommended for patients with CCS class III angina with single-vessel or multivessel CAD, no evidence of myocardial injury or ischemia on objective testing, and no trial of medical therapy, or who have 1 of the following:

1. Only a small area of myocardium at risk
2. All lesions or the culprit lesion to be dilated with morphology that conveys a low likelihood of success
3. A high risk of procedure-related morbidity or mortality
4. Insignificant disease (< 50% coronary stenosis)
5. Significant left main CAD and candidacy for CABG

Patients with UA or NSTEMI

Class I

An early invasive PCI strategy is indicated for patients with UA or NSTEMI who have no serious comorbidity and coronary lesions amenable to PCI. Patients must have any of the following high-risk features:

1. Recurrent ischemia despite intensive anti-ischemic therapy
2. Elevated troponin level
3. New ST segment depression
4. HF symptoms or new or worsening mitral regurgitation
5. Depressed LV systolic function
6. Hemodynamic instability
7. Sustained ventricular tachycardia
8. PCI within 6 months
9. Prior CABG

Class IIa

1. It is reasonable that PCI be performed in patients with UA or NSTEMI and single-vessel or multivessel CAD who are undergoing medical therapy with focal saphenous vein graft lesions or multiple stenoses who are poor candidates for reoperative surgery
2. In the absence of high-risk features associated with UA or NSTEMI, it is reasonable to perform PCI in patients with amenable lesions and no contraindication for PCI with either an early invasive or early conservative strategy
3. Use of PCI is reasonable in patients with UA or NSTEMI with significant left main CAD (> 50% diameter stenosis) who are candidates for revascularization but are not eligible for CABG

Contd...

contd...

Class IIb

1. In the absence of high-risk features associated with UA or NSTEMI, PCI may be considered in patients with single-vessel or multivessel CAD who are undergoing medical therapy and who have 1 or more lesions to be dilated with reduced likelihood of success
2. PCI may be considered in patients with UA or NSTEMI who are undergoing medical therapy who have 2- or 3-vessel disease, significant proximal LAD CAD, and treated diabetes or abnormal LV function

Class III

In the absence of high-risk features associated with UA or NSTEMI, PCI is not recommended for patients with UA or NSTEMI who have single-vessel or multivessel CAD and no trial of medical therapy, or who have 1 or more of the following:

1. Only a small area of myocardium at risk
2. All lesions or the culprit lesion to be dilated with morphology that conveys a low likelihood of success
3. A high risk of procedure-related morbidity or mortality
4. Insignificant disease (< 50% coronary stenosis)
5. Significant left main CAD and candidacy for CABG

STEMI

Class I

General considerations:

1. If immediately available, primary PCI should be performed in patients with STEMI who can undergo PCI of the infarct artery within 12 hours of symptom onset, if performed in a timely fashion (balloon inflation goal within 90 minutes of presentation)

Specific considerations:

2. Primary PCI should be performed for patients less than 75 years old with ST elevation or presumably new left bundle-branch block who develop shock within 36 hours of MI and are suitable for revascularization that can be performed within 18 hours of shock, unless further support is futile because of the patient's wishes or contraindications/unsuitability for further invasive care
3. Primary PCI should be performed in patients with severe congestive heart failure and/or pulmonary edema (Killip class 3) and onset of symptoms within 12 hours

Class IIa

1. Primary PCI is reasonable for selected patients 75 years or older with ST elevation or left bundle-branch block or who develop shock within 36 hours of MI and are suitable for revascularization that can be performed within 18 hours of shock. Patients with good prior functional status who are suitable for revascularization and agree to invasive care may be selected for such an invasive strategy
2. It is reasonable to perform primary PCI for patients with onset of symptoms within the prior 12–24 hours and 1 or more of the following:
   A. Severe congestive heart failure
   B. Hemodynamic or electrical instability
   C. Evidence of persistent ischemia

Class III

1. Elective PCI should not be performed in a noninfarct related artery at the time of primary PCI of the infarct related artery in patients without hemodynamic compromise
2. Primary PCI should not be performed in asymptomatic patients more than 12 hours after onset of STEMI who are hemodynamically and electrically stable

PCI after successful fibrinolysis or for patients not undergoing primary reperfusion

Class I

1. In patients whose anatomy is suitable, PCI should be performed when there is objective evidence of recurrent MI
2. In patients whose anatomy is suitable, PCI should be performed for moderate or severe spontaneous or provocable myocardial ischemia during recovery from STEMI
3. In patients whose anatomy is suitable, PCI should be performed for cardiogenic shock or hemodynamic instability

Class IIa

1. It is reasonable to perform routine PCI in patients with LV ejection fraction less than or equal to 40%, HF, or serious ventricular arrhythmias
2. It is reasonable to perform PCI when there is documented clinical heart failure during the acute episode, even though subsequent evaluation shows preserved LV function

Class IIb

PCI might be considered as part of an invasive strategy after fibrinolytic therapy

Percutaneous intervention in patients with prior coronary bypass surgery

Class I

1. When technically feasible, PCI should be performed in patients with early ischemia (usually within 30 days) after CABG
2. It is recommended that embolic protection devices (EPD) be used when technically feasible in patients undergoing PCI to saphenous vein grafts

Class IIa

1. PCI is reasonable in patients with ischemia that occurs 1–3 years after CABG and who have preserved LV function with discrete lesions in graft conduits
2. PCI is reasonable in patients with disabling angina secondary to new disease in a native coronary circulation after CABG
3. PCI is reasonable in patients with diseased vein grafts more than 3 years after CABG
4. PCI is reasonable when technically feasible in patients with a patent left internal mammary artery graft who have clinically significant obstructions in other vessels

Class III

1. PCI is not recommended in patients with prior CABG for chronic total vein graft occlusions
2. PCI is not recommended in patients who have multiple target lesions with prior CABG and who have multivessel disease, failure of multiple SVGs and impaired LV function unless repeat CABG poses excessive risk due to severe comorbid conditions

(*Source:* Modified from: King SB, Smith SC, Hirshfeld JW, et al. 2007 focused update of the ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention. Circulation. 2008;117:261; and Modified from: Kushner FG, Hand M, Smith SC, et al. 2009 focused updates: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction. Circulation. 2009;120:2271.)

twice daily thereafter) or clopidogrel (300–600 mg loading dose, 75 mg daily thereafter) for 12 months. The primary endpoint, a composite of death from vascular causes, MI or stroke at 12 months, occurred in 9.8% of patients receiving ticagrelor and 11.7% of those receiving clopidogrel (hazard ratio, 0.84; $P < 0.001$).[94] There was also a significant reduction in MI alone (5.8% in the ticagrelor group vs 6.9% in the clopidogrel group; $P = 0.005$) and death from vascular causes (4.0% vs 5.1%; $P = 0.001$) [No significant difference in the overall rates of major bleeding was found between the ticagrelor and clopidogrel groups (11.6% and 11.2% respectively; $P = 0.43$), but ticagrelor was associated with a higher rate of major bleeding not related to CABG (4.5% vs 3.8%, $P = 0.03$)[94]].

Current evidence suggests that in the absence of risk factors for bleeding, dual antiplatelet therapy should be continued for at least 1 month after BMS placement and for 1 year after drug-eluting stents (DES) placement. Prolonged thienopyridine therapy not only reduces late stent thrombosis but also reduces the risk of MI by potentially reducing embolus of thrombi that complicate plaques remote from the initial intervention. Indefinite aspirin and clopidogrel therapy is recommended in patients previously receiving brachytherapy and in those patients in whom stent thrombosis may be catastrophic, such as patients with unprotected left main artery stenting, or those with stenting of the "last remaining vessel". Finally, the heightened risk of stent thrombosis associated with premature discontinuation of dual antiplatelet therapy, especially in the setting of preparation for noncardiac surgery, deserves special consideration when choosing the stent type to implant at the time of PCI.

IIb/IIIa Platelet Receptor Inhibitors

Thrombin and collagen are potent platelet agonists that can cause ADP and serotonin release and activate glycoprotein (GP) IIb/IIIa fibrinogen receptors on the platelet surface. Functionally, active GP IIb/IIIa serves in the "final common pathway" of platelet aggregation by binding fibrinogen and other adhesive proteins that bridge adjacent platelets. There are currently three GP IIb/IIIa inhibitors approved for clinical use. Studies supporting the use of these agents during PCI were performed before the widespread use of dual antiplatelet therapy; henceforth, the routine use of these agents in current practice of interventional cardiology continues to be reevaluated.

The first such agent approved by the FDA was abciximab (reopro, Centocor, Malvern, PA), a monoclonal antibody. Abciximab was shown to reduce ischemic complications and late clinical events in high-risk angioplasty.[95] The other IIb/IIIa receptor inhibitors approved by the FDA include: eptifibitide (Integrilin, COR Therapeutics, San Francisco, CA) a peptide and tirofiban (Aggrastat, Merck, White House Station, NJ) a small nonpeptide molecule. These are both competitive inhibitors. Each of these agents reduces a composite end point of death or nonfatal MI in the setting of coronary intervention and in acute coronary syndromes.[96] Furthermore, in the EPIC trial, a subgroup of 555 patients with acute coronary syndromes treated with bolus abciximab and infusion had a significant reduction in mortality at 3 years.[97] A meta-analysis of 19 randomized trials of IIb/IIIa agents (20,137 patients) during PCI reported a significant and sustained decrease (20–30%) in the risk of death.[98] The GP IIb/IIa inhibitors have demonstrated benefit in improving clinical outcomes within the first 30 days after PCI, primarily by reducing ischemic complications, including periprocedural MI and recurrent ischemia. They are particularly useful in patients with troponin-positive acute coronary syndromes[99] but have no consistent effect on reducing late restenosis. Although GP IIb/IIIa inhibitors differ in their structure, reversibility and duration, there is no difference between their clinical effects in patients undergoing primary PCI.[100,101] Bleeding is the major risk of GP IIb/IIIa inhibitors and a downward adjustment of the unfractionated heparin dose has been recommended. GP IIb/IIIa inhibitors are recommended in patients with NSTEMI and unstable angina who are not pretreated with clopidogrel and it is reasonable to administer them to patients who have a troponin-positive acute coronary syndrome who have also been pretreated with clopidogrel. Although GP IIb/IIIa inhibitors are recommended in selected patients at the time of PCI, the value of GP IIb/IIIa inhibitors as part of a routine preparatory strategy in patients with STEMI before their transport to the catheterization laboratory is not routinely recommended on the basis of the results of three studies that failed to show benefit of GP IIb/IIIa inhibitors in patients who were pretreated with oral dual antiplatelet therapy.[102-104]

The decision to use a IIb/IIIa platelet receptor in the era of high-dose clopidogrel pretreatment is complex and requires an assessment of the patient's risk of bleeding and ischemic complications with or without these agents. The patient who cannot receive the acute benefit of clopidogrel therapy due to allergy or intolerance should receive a IIb/IIIa receptor, a class I indication in the ACC Guideline statement. Based upon current evidence, it appears that IIb/IIIa receptor inhibitors are more effective in patients with refractory unstable angina, complex anatomy, slow flow on angiogram and troponin positive acute coronary syndromes.[105]

PARENTERAL ANTICOAGULANT THERAPY

Intravenous anticoagulation is always given during PCI to prevent thrombosis during the procedure. This practice was historically initiated because of the central role of thrombin in arterial thrombosis. Anticoagulation is used in conjunction with antiplatelet therapy for PCI. There are a few options of different agents to use for anticoagulation during PCI.

HEPARIN

For PCI, heparin monitoring is usually performed via the ACT, since the partial thromboplastin time (PTT) becomes prolonged at the heparin concentrations used in these procedures.[106] Initial studies of PCI indicated that unfractionated heparin should be administered to achieve an ACT of 250–350 seconds in patients undergoing PCI.[107] Similarly, the most recent American College of Cardiology/American Heart Association/Society for Cardiovascular Angiography and Intervention guideline update for PCI also recommends that intravenous, unfractionated heparin (UFH) should be given using a weight-adjusted bolus of 70–100 IU/kg to achieve an ACT between 250 and 350 seconds, in patients who do not receive a GP IIb/IIIa inhibitor.

Further heparin boluses are given if the goal ACT is not achieved. However, when a GP IIb/IIIa inhibitor is used, the heparin bolus should be reduced to 50–70 units/kg. In such patients, an ACT of 200–250 seconds appears to be safe and effective and is the current practice during PCI.[41]

Careful monitoring of the ACT is important because some patients have persistent thrombin activity despite heparin therapy, as documented by an elevation in fibrinopeptide A (FPA), a marker of thrombin activity. Increased FPA levels have been noted in patients with intracoronary thrombus, abrupt closure, postprocedural non-ST segment elevation MI and clinically unsuccessful procedures.[108]

Postprocedural heparin is not recommended in patients with an uncomplicated procedure. There is no evidence that prolonged use of postprocedural heparin or low-molecular weight heparin prevents stent thrombosis or restenosis, and postprocedural heparin is associated with increased bleeding and vascular complications.

ENOXAPARIN

Although seemingly safe and as effective as unfractionated heparin,[109,110] the clinical role of low molecular weight heparin remains uncertain as a routine strategy for PCI. It seems reasonable to continue enoxaparin rather than switching to unfractionated heparin once it has been initiated, but it must be re-dosed at the time of the PCI in most cases. It is important to note that ACT cannot be used to monitor anticoagulation status with enoxaparin use, as the ACT is not an accurate reflection of the anticoagulation status with use of this medication.

BIVALIRUDIN

Bivalirudin is a specific direct thrombin inhibitor. The REPLACE-2, ISAR-REACT-3 and ACUITY trials evaluated the efficacy and safety of bivalirudinas an alternative to unfractionated heparin with or without GP IIb/IIIa inhibitors in patients across a broad spectrum of illness severity. Most patients in the study were given a loading dose of clopidogrel (either 300 or 600 mg) at least 2 hours before the procedure. These trials showed that bivalirudin is statistically non-inferior to unfractionated heparin for the prevention of ischemic complications in patients undergoing PCI with stenting. Importantly, the overall rates of protocol-defined major bleeding were significantly lower with bivalirudin in all patients. In patients with renal insufficiency, specifically bivalirudin, was found to have a lower rate of both ischemic and bleeding complications.[111] Additionally, bivalirudin is one of the alternatives in patients with known or suspected heparin-induced thrombocytopenia who require PCI. One potential disadvantage of bivalirudin is its increased cost compared to unfractionated heparin. Although, reduction of bleeding complications may certainly balance out this initial increased cost. One last thing to keep in mind about bivalirudin is that there is no reversing agent for its anticoagulant effect. This is in contrast to unfractionated heparin as its effect can be reversed with administration of protamine. It should be noted, however, that this would only be required in the extremely rare case of a PCI with a complication that requires reversal of anticoagulation.

EQUIPMENT FOR CORONARY INTERVENTIONS

Appropriate selection and use of equipment is critical in the safe and successful performance of coronary intervention. Needless to say, performance of coronary intervention entails a thorough understanding of coronary anatomy and lesion characterization. The first step to performing a successful coronary intervention is performing an adequate diagnostic coronary angiogram to best define the area to be treated. Once this has been completed, a plan for intervention can be formulated and consideration can be given to equipment selection.

GUIDE CATHETERS

An optimal guide provides a stable platform for the operator to deliver devices to the diseased segment of the coronary artery. The guide catheter is primarily selected according to the size of the ascending aorta and the coronary vessel to be cannulated. Additional factors in guide selection may be anatomically based as extremely tortuous and/or calcified vessels may require a more supportive guide catheter to best ensure a successful intervention. The guide size (French) selection may also be influenced by the intended treatment of the chosen lesion. For example, interventions requiring athrectomy or simultaneous balloon or stent inflations will require a larger lumen guide catheter. Compared to diagnostic catheters, guides have a stiffer shaft because of reinforced construction and also have a larger internal diameter for a given French size. Guide catheters that are coaxially engaged provide the best support and best minimize the risk of guide catheter trauma to the vessel.

Passive guide support is provided by the inherent design and shape of the guide as well as the stiffness from the manufactured material. Active support is typically achieved by either guide manipulation into a configuration conforming to the aortic wall, or by sub-selective intubation with deep engagement in to the coronary vessel.[34] Sometimes this is necessary, but these types of aggressive guide manipulations do increase the risk of trauma to the vessel. It cannot be overstated that coaxial guide alignment with the coronary ostium is more important than the active or passive support. This coaxial alignment allows the operator the best support both to deliver equipment, as well as to allow for optimal contrast opacification to aid in proper positioning of equipment in the vessel.

The most commonly used guides are Judkins, Amplatz and Extra back up type guides. Others that have a niche in various clinical situations include IMA guide for IMA interventions and left and right bypass graft guide catheters. Additionally, there are transradial specific guide catheter shapes that are available for procedures performed from radial artery access. Standard safety measures for guide manipulations include and are listed in Table 15.

GUIDEWIRE

The wire manipulation is one of the most important aspects of PCI. Proper intraluminal advancement of the guidewire through the lesion and into the distal vessel is necessary for the safe delivery of various diagnostic and therapeutic devices while

TABLE 15

Standard safety measures for guide manipulations

- Vigorous aspiration of guide after it is inserted into the ascending aorta
- Generous bleed back and introduction of devices into the Y adaptor on the flush
- Flush frequently to avoid blood stagnation and thrombus formation
- Constantly watch the tip of guide while advancing or retrieving devices
- Pressure monitoring for dampening to avoid trauma to the vessel by inadvertent deep engagement

maintaining secure access to vessel lumen. The ability to negotiate the coronary arterial tree and to deliver the various devices to the diseased site to be treated depends somewhat on individual anatomy and makes guidewire selection variable. Important considerations in appropriate guidewire selection include: torque response, tip flexibility, pushability, stiffness and support for the delivery of devices. Angiographic characteristics of the lesion to be treated should also be considered in the selection of a coronary guidewire for PCI, as individual anatomical variations and lesion characteristics may make a certain wire more appropriate for the given PCI. Some "niche" devices, such as the athrectomy device, have dedicated wires that must be used with that specific device. Based on these requirements, the lesion and vessel characteristics noted above and, from experience in daily clinical practice, various guidewires are chosen for use by the operator.

BALLOONS

General Use Balloons

Balloons for use in PCI are delivered to the lesion over a coronary guidewire and inflated with a device that measures the inflation pressure. There are different types of balloons with the most widely used balloons falling into two basic categories: compliant and non-compliant. Compliant balloons are generally more flexible and therefore more deliverable. When inflated, they do increase in size more significantly with increased pressures. A non-compliant balloon differs in that is somewhat less flexible and less deliverable, but it is able to be inflated to higher pressures with less growth of the balloon diameter. Generally, compliant balloons are used for initial dilation of a lesion before stenting (when needed), but non-compliant balloons may be used for initial lesion dilation if there is concern that a lesion may be difficult to dilate (significant calcification in the lesion). Non-compliant balloons are generally used for further dilating stents after they have been placed, or for dilation of lesions that are more difficult to dilate as noted above.

OTHER SPECIALIZED INTRACORONARY BALLOONS

Cutting Balloon

A cutting balloon is a specialized angioplasty balloon that has several longitudinal atherotomes along its length. With balloon inflation, the atherotomes score the plaque to allow successful dilation of the lesion. They are generally a more difficult device to deliver, as they are stiffer than conventional balloons and are currently relegated to a niche indication use. Cutting balloons can be useful in the treatment of lesions that have not dilated with conventional balloons. These are often in-stent restenosis lesions or lesions in ostial locations.

Perfusion Balloon Catheter

The perfusion balloon catheter has small holes in the shaft both proximal and distal to the balloon itself. This allows continued distal perfusion of the artery while the balloon is inflated. Perfusion balloons were initially used in patients who were unable to tolerate the prolonged balloon inflations that were sometimes used during angioplasty when it was the only available coronary intervention. However, in modern day practice, the widespread use of stenting has allowed the practice of prolonged balloon inflations to be very limited today. Perfusion balloons do still have a niche application of being used to help stabilize patients with coronary perforation. This balloon can be inflated at the site of the perforation to help seal it, but still allow perfusion distal to the perforation site via the distal lumen of the balloon catheter.

PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY

Percutaneous transluminal coronary angioplasty (PTCA) expands the coronary lumen by stretching and tearing the atherosclerotic plaque and vessel wall and, to a lesser extent, by redistributing atherosclerotic plaque along its longitudinal axis. Elastic recoil of the stretched vessel wall generally leaves a 30–35% residual diameter stenosis, and the vessel expansion can result in propagating coronary dissections, leading to abrupt vessel closure in 5–8% of patients.

PTCA was the first and only initial technique of PCI and was indeed a great accomplishment. Due to significant technological advances (stent development primarily) and the increased rates of abrupt vessel closure and restenosis with PTCA alone compared to stenting that has been demonstrated, "stand alone" PTCA has a limited role in PCI today. However, the basis of this technique remains the mainstay of PCI today, as the deployment of all stents is accomplished through the inflation of a balloon.

Some situations where angioplasty alone still does have a role in current PCI are: the "bailout" treatment of the origins of branch vessels that are covered by a stent in the parent vessel, focal in-stent restenosis lesions and the treatment of vessels that are of too small caliber to stent.

CORONARY STENTS

PTCA was associated with two major limitations: acute (during the procedure) or subacute (after the procedure and within 30 days) vessel closure and late (4–8 months postprocedure) restenosis. The development and use of intracoronary stents and the enhanced use of various antithrombotic therapies have resulted in significant reductions in both of these complications.[112-115]

Due to these advantages, stenting is now performed in the majority of PCIs. Despite substantial improvements in early and late outcomes with bare metal stenting compared to PTCA,

restenosis of these stents can occur in the months to years after bare metal stenting. Further improvements in stent designs and more importantly, the development of drug-eluting stents, have further reduced restenosis rates. These advances in stenting technology are responsible for a further increase in stent utilization in PCI, relegating non-stenting PCI techniques to niche applications.

Intracoronary stents are increasingly used in patients with a previous MI, older patients and in those who have more extensive and more complex coronary lesions. Despite these more challenging subsets of patients, the overall success rate of PCI has actually increased. Despite this, the rates of emergent CABG, in-hospital ST segment elevation MI (STEMI) and mortality associated with PCI have all fallen.[116]

TYPES OF STENTS

There are many different types of intracoronary stents. They can generally be considered according to metal composition, open versus closed cell design, and whether or not they are capable of eluting drugs for local delivery.

Currently available intracoronary stents are generally composed of either stainless steel or a cobalt-chromium alloy. In general, cobalt-chromium stents tend to be more flexible, while the stainless steel designs may offer greater radial strength for bulky lesions or those involving the more fibro-muscular aorto-ostial locations. In general, modern stent designs make either of these stent types acceptable for use in virtually all cases.

Historically, the initial coil design of intracoronary stents was associated with poor radial strength and increased restenosis. Given these limitations, this design was abandoned. Currently available stents have a tubular configuration with either a closed or open cell design. Closed cell designs (in which each ring is interconnected) are slightly less flexible than open cell, but may provide more support. Today, most commercially available stents employ an open cell design. Additionally, thinner struts appear to reduce vessel injury. Given this, most stents have been designed with reduced strut thickness.

A more detailed discussion of the clinical use of bare metal and drug-eluting stents will follow further below.

STENT DEPLOYMENT

Today, intracoronary stents come premounted on a compliant balloon are delivered through a coronary guide catheter over a guidewire to the lesion and deployed by inflation of the balloon. Optimal stenting is performed in a way that reduces the minimal residual luminal stenosis to as small as possible. Attainment of a large luminal diameter minimizes the risk of both stent thrombosis and restenosis.[114,116] Suboptimal luminal dilation with stent deployment is generally due to inadequate balloon expansion and elastic recoil of the vessel. Both of these issues are related in part to plaque characteristics (lesion is resistant to dilation), as well as stent design.[117] Suboptimal stent dilation is associated with increases in the periprocedural incidence of non-ST elevation MI, overall 30 day mortality and clinical restenosis. Clinical restenosis specifically was associated with a smaller final lumen diameter and the use of multiple stents in a given procedure.[118]

Given the current availability of low profile stent delivery systems, many stenting procedures are completed with a direct stenting technique where the first intervention to the lesion is the placement of the stent. A number of randomized clinical trials have compared direct stenting to stenting after balloon dilation.[119-122] The major outcomes were similar, including procedural success. Based on these studies, the settings in which direct stenting can be considered include: vessel greater than or equal to 2.5 mm in diameter, absence of severe coronary calcification, absence of significant angulation (bend > 45°) and absence of occlusions and bifurcations lesions.

This being said, a lesion should always be dilated with a balloon before stent deployment is attempted if there is any concern that the lesion may not dilate optimally with initial stent deployment. Significant lesion calcification and the fibrotic, sometimes resistant plaque in cases of restenosis are situations where lesion predilation should be strongly considered. Balloon dilation of a lesion before stent deployment is virtually always done in situations where the vessel distal to the lesion is not initially visualized (during MI or with chronic vessel occlusion PCI). If a lesion is significantly calcified and not able to be dilated with a conventional balloon, cutting balloon angioplasty or RA can be considered so that the lesion can be dilated and optimal stent deployment can be achieved.

In addition to angiography, other modalities can be used to assess optimal stent deployment. The IVUS can be used to assess whether or not a stent has been optimally deployed and, if not, the stent can be further dilated to accomplish this.[123] Additionally, FFR measurement can be performed after stent deployment to assess the effectiveness of the stent placement. The prognostic information of the FFR has been demonstrated in several studies.[66,124] At a normal FFR, (> 0.95) adverse events are known to be significantly reduced.

ADJUNCTIVE CORONARY INTERVENTIONAL DEVICES

THROMBECTOMY

Visualization of thrombus by angiography is associated with increased risk of distal embolization and the no reflow phenomenon. The angiojet rheolytic thrombectomy catheter (Possis Medical, Inc., Minneapolis, MN) was introduced as a dedicated device for thrombus removal through the dissolution and aspiration of the thrombus. High-speed saline jets within the tip of the catheter create intense local suction by the Venturi effect. This results in pulling surrounding blood, thrombus and saline into the lumen of the catheter opening, propelling the debris proximally through the catheter lumen. Rheolytic thrombectomy was superior to a prolonged intraluminal urokinase infusion in patients with large thrombus burden, but its routine use in patients with STEMI was not associated with improvement in infarct size by single-photon emission computed tomography (SPECT) imaging and may have caused more complications.[125] Rheolytic thrombectomy is still useful and likely beneficial in clinical practice, however, with careful limited selection of some patients with a large angiographic thrombus burden in a native vessel or SVG. Bradyarrhythmias are common and prophylactic placement of a temporary pacemaker is recommended.

Newer lower profile manual aspiration catheters have been developed as an alternative to rheolytic thrombectomy in patients with thrombus-containing lesions. In a multicenter study of 1,071 patients with STEMI who were randomly assigned to the thrombus-aspiration group or the conventional-PCI group, a myocardial blush grade of 0 or 1 occurred in 17.1% of the patients in the thrombus-aspiration group and in 26.3% of those in the conventional-PCI group ($P < 0.001$).[125] At 30 days, the rate of death in patients with a myocardial blush grade of 0 or 1, 2 and 3 was 5.2%, 2.9% and 1.0% respectively ($P = 0.003$), and the rate of adverse events was 14.1%, 8.8% and 4.2% respectively ($P < 0.001$).[126] Meta-analysis of the data suggests that simple manual thrombus aspiration before PCI reduces mortality in patients with STEMI undergoing primary PCI.[127] Bradyarrhythmias are common, and prophylactic placement of a temporary pacemaker is recommended.

ROTATIONAL CORONARY ATHERECTOMY

Atherectomy refers to removal of the obstructing atherosclerotic plaque. It diminishes plaque volume by abrasion, as opposed to fracturing plaque radially.[128] The physical principal governing RA is known as differential cutting. Differential cutting results in the destruction of inelastic material, such as atherosclerotic, calcified and fibrotic plaques, while sparing normal elastic tissue. It favorably modifies vessel wall compliance and is particularly useful in treatment of calcified lesions.[128,130] The RA system consists of four main components (Boston Scientific, Natick, MA): guidewire, advancer, diamond coated burr catheter and control console system. Burrs are available from 1.25 mm to 2.5 mm in diameter. Selection of burr size should not exceed a burr or artery diameter ratio of 0.70.[129-131] Aggressive advancement of the burr should also be avoided because of higher rates of complication including dissection, slow or no reflow and perforation. Most RA is currently performed as an adjunct to either angioplasty or stenting in order to either debulk or modify plaque, usually in order to facilitate delivery and appropriate expansion of stents within the lesion. However, it should be noted that RA did not lower rates of restenosis in randomized trials.[132-134]

Contraindications to RA include: patients with occlusions in which a guidewire cannot cross the lesion, the presence of thrombus, or extensive vessel dissection. Extreme caution must also be given to patients with lesion lengths greater than 25 mm, angina at rest, poor distal run off and severe LV dysfunction (LVEF < 30%) as these patients are at increased risk for ischemic complications.[135] Patients generally should receive a prophylactic temporary pacemaker due to increased risk of bradycardia and heart block associated with this procedure.

DIRECTIONAL CORONARY ATHERECTOMY

Directional coronary atherectomy (DCA) uses a rotating cup shaped blade within a windowed cylinder to directionally excise atheroma. By physically removing plaque from coronary lumen, it was hoped that it would achieve larger coronary lumen diameters and result in lower restenosis rates. Clinical trials have showed that effective use of DCA produced only a modest reduction in restenosis compared to balloon angioplasty alone. In current practice DCA is used in less than 1% of patients. Occasionally DCA may be useful when pathological sample of atheroma is of interest.[135] It could also be used to treat noncalcified bifurcation lesion involving a large branch or in the ostium of LAD artery. However, this modality has largely fallen out of favor and is used only very infrequently.

EMBOLIC PROTECTION DEVICES FOR VENOUS BYPASS GRAFT PCI

Sabor et al. drew attention to the importance of microembolization during PCI when they studied 32 patients who died within 3 weeks, noting that more than 80% had histologic evidence of microembolization.[137] Subsequently, there has been increasing awareness of the importance of embolization in atherosclerotic vascular disease, particularly during PCI in patients with acute coronary syndrome and SVG lesions.[138] A variety of occlusion—aspiration and filter-based strategies—have evolved for embolic protection during SVG interventions. The advent of EPD has reduced the risk of postprocedural adverse events after SVG PCI. Embolic protection for SVG PCI now constitutes a class I indication in the PCI guidelines.

Despite their potential benefit in preventing thromboembolization in patients with STEMI, none of the EPD has reduced MI size with primary intervention, possibly relating to the high profile of the devices. There has been limited application of embolic protection in native vessel PCI.

The EPD fall into three broad categories: distal occlusion devices, distal embolic filters and proximal occlusion devices.

DISTAL EMBOLIC FILTERS

Distal filters devices are advanced across the target lesion over a standard coronary wire in their smaller collapsed state and a retaining sheath is withdrawn, allowing the filter to open and to expand against the vessel wall. The filter then remains in place to catch any embolic material larger than the filter pore size (usually 120–150 micron pores) that is liberated during intervention. At the end of the intervention, the filter is collapsed by use of a special retrieval sheath and the filter containing the captured embolic material is removed from the body. This type of device has the advantages of maintaining anterograde flow during the procedure and allowing intermittent injection of contrast material to visualize underlying anatomy during stent deployment. However, it has the potential disadvantage of allowing the component of debris with a diameter less than the filter pore size to pass through. Newer filter devices with reduced crossing profiles and more efficient capture of embolic debris continue to be developed.

DISTAL OCCLUSION DEVICES

The GuardWire (Medtronic Vascular, Santa Rosa, CA) is a low-pressure balloon mounted on a hollow guidewire shaft. The device is passed across the target lesion and the balloon is gently inflated to occlude flow. The PCI is then performed and the debris liberated by intervention remains trapped in the stagnant column of blood. This debris is then aspirated with a specially designed catheter before the occlusion balloon is deflated to restore anterograde flow. Compared with SVG intervention without a distal occlusion device, the use of the guardwire

reduced 30-day major adverse clinical events and no-reflow.[139] The major disadvantage of this device is that blood flow is stopped during SVG intervention while the balloon is inflated, creating an obligatory period of ischemia.

PROXIMAL OCCLUSION DEVICES

The third type of EPD occludes flow into the vessel with a balloon in the proximal part of the graft. Two proximal occlusion devices are currently in use: (1) the Proxies catheter (St. Jude Medical) and (2) the Kerberos embolic protection system (Kerberos, Sunnyvale, CA). With such inflow occlusion, retrograde flow generated by distal collaterals or infusion through a "rinsing" catheter can propel any liberated debris back into the lumen of the guiding catheter. These approaches have the potential advantage of providing embolic protection even before the first wire crosses the target lesion.[140]

CLINICAL OUTCOMES

The PCI refers to both nonstenting procedures and stent intervention. We will now discuss the evolution of PCI over the years with the focus of the discussion on clinical outcomes related to the use of bare metal and drug-eluting stents.

Progressive improvements in technology and innovations in delivery systems have led to catheter based therapy as a safe and viable alternative to coronary artery bypass graft surgery (CABG) for revascularization. The Angioplasty Compared to Medical Therapy Evaluation (ACME) trial, involving 212 patients with single-vessel disease and abnormal stress tests, revealed greater freedom from angina in the angioplasty group at 6 months (64% vs 46%) as well as better treadmill performance. There was no difference in death or MI.[141] Angina relief and treadmill performance were significantly better in the PTCA patients, but complications also were more frequent as demonstrated by RITA-2.[142] Meta-analyses of eight randomized published trials comparing PTCA and CABG reported no difference in mortality or MI at 1 year after angioplasty or CABG, but 18% of the angioplasty patients had required bypass surgery and 20% had an additional angioplasty, a significantly higher rate of repeat revascularization than in the surgery group.[143,144]

However, catheter based therapies were associated with angiographic restenosis rate of almost 40% at 6 months after PTCA alone. More than half of these patients had recurrent ischemic symptoms, most often progressive effort angina. Thus, 20–30% of patients required clinically driven repeat target lesion revascularization within the first year after PTCA. After this period, restenosis is uncommon as recurrent ischemia after 1 year is most often due to a new or progressive lesion.[145-146]

In current day practice, stand-alone balloon angioplasty is rarely used other than for very small (< 2.25 mm) vessels, or in the "bailout" of branch vessels that are jailed by a parent vessel stent. However, balloon angioplasty remains integral to PCI for predilation of lesions before stent placement, deployment of coronary stents and further expansion of stents after deployment. It also continues to have a role in treatment of some in-stent restenosis.

The introduction of bare metal stents (BMS) produced a significant improvement in the durability of balloon angioplasty. Bare metal stenting produced better short-term results with less residual stenosis, elimination of dissection and lower rates of in-hospital CABG and MI. Additionally, the rate of angiographic restenosis fell to 20–30% and the rate of target lesion revascularization fell to 10–15%.[115,117,147,148] As with PTCA, clinical restenosis—when it occurs—typically happens within the first year. After this time, recurrent ischemia is much more likely to be due to new or progressive disease rather than restenosis.[148]

Although BMS clearly improved clinical outcomes and restenosis rates as compared to PTCA, there was still a significant amount of clinical restenosis of BMS. The DES were then developed in an effort to further reduce both the rate of restenosis and the need for target lesion revascularization. Late lumen loss and restenosis after nonstent interventions are caused by a combination of acute recoil, negative remodeling of the treated segment and local neointimal hyperplasia. In contrast, late lumen loss after stenting is due primarily to in-stent neointimal hyperplasia. The restenosis benefit of DES compared to BMS results from inhibition of in-stent neointimal hyperplasia.[149] A DES consists of a standard metallic stent platform, a polymer coating and an anti-restenotic drug (sirolimus, everolimus,paclitaxel, etc.). That reduces the local proliferative healing response to stent placement.The drug is mixed within the polymer that coats the stent and is released over a designated period of time which can vary from as short as days to as long as 1 year after implantation of the stent. Drug-eluting stents have indeed yielded a marked reduction in the incidence of restenosis and target lesion revascularization when compared to BMS.[150] "Real world" experience also shows a marked reduction in repeat revascularization, although restenosis rates were somewhat higher in more complex anatomical lesion subsets such as small vessels, long lesions and bifurcations.[151]

Based upon the marked reductions in restenosis and target lesion revascularization, DES have been used in most PCIs in the United States (71% in a report of usage in 2004 and 94% in a report of usage in 2005).[152,153] Although all currently approved DES have the same general components, they differ with respect to the stent platform, polymer and antirestenotic drug type. Thus, differences may be observed with respect to deliverability (ease of placement), efficacy (prevention of restenosis) and safety (rates of stent thrombosis and MI).

The first two DES to be approved in the United States were the sirolimus-eluting stent (SES) in 2003 and paclitaxel-eluting stent (PES) in 2004. They are now often referred to as "first generation" DES. In 2008, the zotarolimus-eluting stent and the everolimus-eluting stent were approved for use and they are referred to as "second generation" DES. The newer DES have a stent platform of a cobalt-chromium alloy and are thinner and more flexible than the first generation DES. Second generation DES are potentially more biocompatible than first generation DES, as they may generate less inflammatory response and have more rapid vessel endothelialization.[154]

DES VERSUS BMS

The United States Food and Drug Administration initially approved both SES and PES for patients who have newly diagnosed, previously untreated, single native coronary lesions that were less than 28–30 mm in length in a vessel with a

diameter between 2.5 mm and 3.75 mm. Use of DES in patients with these characteristics was considered "on-label". Off-label use was defined as patients with complex anatomy (e.g. multilesion PCI, vessels outside the 2.5–3.75 mm range, lesions longer than 30 mm, ostial lesions, restenotic lesions, lesions of the left main, total occlusions and bifurcation lesions) and those with SVG lesions.

Multiple individual randomized trials and two large PCI registry data bases provide strong evidence of benefit (reduction in target lesion revascularization) with the use of DES compared to BMS. Benefit was noted both with "on label" and "off label" use of DES. A 2007 meta-analysis included 38 randomized trials involving over 18,000 patients with on-label indications.[149] The three largest were SIRIUS, TAXUS IV and TAXUS V, and the duration of follow-up was 1–4 years. The principal finding was that there was a significant reduction in target lesion revascularization with both SES and PES compared to BMS (odds ratios 0.30 and 0.42, 95% CI 0.24–0.37 and 0.33–0.53 respectively). There was no difference in overall mortality among the three groups (hazard ratio 1.00 for SES and 1.03 for PES compared to BMS). The greatest benefit was found in the subsets of patients who are at the highest risk for restenosis (diabetics, vessel diameter < 3 mm and lesion length > 20 mm).[154-157]

In reports from different large registries in the United States, the proportion of DES procedures performed with off-label use has been steadily increasing.[158] This is mainly due to lower rate of target vessel revascularization.[156]

For patients with off-label indications for DES, a thorough attempt to weigh the relative risks and benefits of restenosis protection, late stent thrombosis and prolonged dual antiplatelet therapy must be made. Alternative therapies including medical management, bare metal stenting, or CABG must be considered in these decisions and individualized to each patient.

Regarding efficacy of individual drug eluting stents, lower rates of clinical restenosis have been noted with SES compared to PES.[159,160]

Data from randomized trials directly comparing sirolimus and paclitaxel stents have generally shown significantly lower rates of angiographic restenosis and less late lumen loss with the sirolimus stent. However, differences in target lesion revascularization have been variable and often not statistically significant. Importantly, there was no significant difference in the composite end point of death or MI.[161] In the diabetic population, the benefit of SES over PES is less clear. This being said, the data must be interpreted with caution given the known limitations of meta-analyses. In contrast to the evidence from randomized trials, two large registries (T-SEARCH and STENT) found no significant difference between PES and SES in the rates of target vessel revascularization.[162,163]

There is, however, growing evidence to support the superiority of the sirolimus stent compared to the paclitaxel stent for reducing angiographic late lumen loss and angiographic restenosis. The advantage of the sirolimus stent also extends to lower rates of target vessel revascularization in complex lesion subsets. Utilization of the paclitaxel stent, however, is acceptable given that the outcomes are superior to BMS and several studies have observed similar outcomes in unselected patients treated with either sirolimus or paclitaxel stents at the discretion of the operator.[164]

Although restenosis rates have been significantly reduced with DES, it still does occur. The DES restenosis is often felt to be a consequence of balloon barotrauma to the artery in areas not covered by the stent, gaps in stent coverage, inadequate stent expansion, or the inability of the drug to limit neointimal hyperplasia.[165-168] In the SIRIUS trial, restenosis in the target lesion vessel segment (includes the stent and area 5 mm proximal and distal to the stent) occurred more frequently than restenosis within the stent among patients receiving a SES (8.9% vs 3.2%).[169] This further reinforces the importance of optimal stenting techniques to take advantage of the decreased restenosis benefit of DES demonstrated in the clinical trials. Diabetes, ostial lesions, stented length of greater than 36 mm, reference vessel diameter less than 2.17 and treatment of in-stent restenosis have been identified to be predictors of restenosis.[170]

It is important to understand the long-term safety of DES in comparison to BMS. Clinical events including development of late stent thrombosis, mortality, MI, impairment of coronary collateral function and hypersensitivity reactions must be considered. Available data demonstrates similar risks of death and MI after DES or BMS when used for either on-label or broader "real world" experience. Nevertheless, it is possible that there is a small but increased risk for very late stent thrombosis after DES (compared to BMS) that appears to be counterbalanced by a reduction in the risks associated with restenosis and repeat revascularization.[171,172] Large observational studies have found no difference in combined endpoints of death, MI or individual endpoint of mortality during mean follow-up of about 3 years.[173-175] More importantly, in a retrospective cohort of 76,525 Medicare (United States) beneficiaries, receipt of a DES was associated with a significantly lower adjusted mortality compared with either historical (hazard ratio 0.79, 95% CI 0.77–0.81) or contemporary controls (hazard ratio 0.83, 95% CI 0.82–0.86).[176]

The decision to use either a BMS or DES needs to balance the relative advantages and disadvantages of each type of stent. Restenosis and stent thrombosis are the two most important factors to consider. As noted above, DES are associated with less restenosis and lower rates of target lesion revascularization, but a greater risk of late or very late stent thrombosis, particularly after clopidogrel is discontinued. Circumstances in which implantation of a BMS is most appropriate are listed in Table 16.

In view of the potentially life-threatening consequences of stent thrombosis, the interventional cardiologist must evaluate the patient's ability to comply with a recommendation for continuous, long-term (at least 1 year) dual antiplatelet therapy

TABLE 16

Bare metal stent implantation recommended (when stenting indicated)

- When compliance of dual antiplatelet therapy is a question
- Patients with high risk of bleeding
- Patients who need long-term anticoagulation with Coumadin
- Use of larger stent size > 3.5, especially with shorter lesion length
- Patients who are preoperative for noncardiac surgery

as well as their potential for having to discontinue dual antiplatelet therapy for other reasons, prior to deciding to place a DES. The DES is perhaps preferred over BMS for patients with complex anatomy (e.g. multilesion PCI, small vessels, lesions longer than 30 mm, ostial lesions, restenotic lesions, lesions of the left main, total occlusions and bifurcation lesions). For patients with SVG stenosis, the current evidence appears to favor DES over BMS.[177]

PROCEDURAL SUCCESS AND COMPLICATIONS RELATED TO CORONARY INTERVENTION

Procedural success after PCI is measured both in terms of the angiographic success in treating the diseased vessel as well as in the complication rates related to the performance of the procedure. Complications during coronary interventions can be considered as those that are common to the complications that occur with diagnostic coronary angiography (as discussed previously), or those that occur specifically as a result of the coronary intervention. This section will focus primarily on those complications that are specifically related to the performance of PCI. Anatomic (or angiographic) success after PCI is defined as the attainment of a residual diameter stenosis of less than 50% after PTCA or less than 20% after stenting.[178] A number of clinical, angiographic and technical variables predict the risk of procedural failure and complications in patients undergoing PCI. Major complications include death, MI or stroke; minor complications include transient ischemic attacks, vascular access site complications, CIN and a host of angiographic complications (Table 17).[178]

COMPLICATIONS SPECIFIC TO PCI

Some of the most common mechanical complications of coronary intervention include: acute or threatened vessel closure, coronary perforation and no-reflow. These events can cause prolonged ischemia, hemodynamic collapse and death. Prompt recognition and treatment of these complications can significantly reduce adverse patient outcomes.

TABLE 17

Variables associated with early failure and complications after percutaneous coronary intervention

Clinical variables
- Women
- Advanced age
- Diabetes mellitus
- Unstable or Canadian Cardiovascular Society (CCS) Class IV angina
- Congestive heart failure
- Cardiogenic shock
- Renal insufficiency
- Preprocedural instability requiring intra-aortic balloon pump support
- Preprocedural elevation of C-reactive protein
- Multivessel coronary artery disease

Anatomic variables
- Multivessel CAD
- Left main disease
- Thrombus
- SVG intervention
- ACC/AHA type B2 and C lesion morphology
- Chronic total coronary occlusion
- Large area of myocardium at risk
- PCI of vessel supplying collaterals to a large artery

Procedural factors
- A higher final percentage diameter stenosis
- Smaller minimal lumen diameter
- Presence of a residual dissection or trans-stenotic pressure gradient

THREATENED OR ACUTE CLOSURE

Threatened closure is defined as a more then 50% narrowing of an artery during a coronary intervention procedure with evidence of active ischemia. Major causes of acute or threatened closure include: coronary dissection, coronary spasm, distal embolization and thrombus formation with coronary dissection being the most common of these.

Excessive iatrogenic plaque fracturing from balloon inflation or device manipulation with subsequent separation of the layers of the vessel wall can lead to threatened or abrupt vessel closure. The National Heart Lung and Blood Institute (NHLBI) classification of coronary dissection is shown in Table 18.[179]

Other things to consider when there is concern for a coronary dissection during PCI include: streaming of contrast related to inadequate contrast injection, vessel straightening artifact (often related to the coronary guidewire) or overlap of branches (often very small branches) in the area of concern. Some maneuvers that can be completed in this assessment are: giving intracoronary nitroglycerin, obtaining angiograms with multiple different angles to best eliminate vessel overlap, withdrawing the guidewire so that the floppy portion of the wire is across the area of concern and repeating the angiogram. Generally, dissections of Grade C or worse are readily identified with angiography. However, sometimes dissections of Type A or B are more difficult to confirm. It is important for the operator to carefully assess all of these possibilities with angiography and if there is still a question, IVUS can be used to further clarify.

The major predictors of outcome related to coronary dissection include: the length of compromised vessel, the extent of the area of myocardium jeopardized and the integrity of antegrade flow. Minor dissections which are non-flow limiting are usually well tolerated and generally do not always require further treatment, but this decision also depends on the extent of myocardium at risk and other clinical considerations. However, any flow limiting dissection should be stented whenever possible in order to prevent abrupt vessel closure.

Most cases of abrupt vessel closure occur within minutes of the final balloon inflation, but subacute vessel closure after PCI can occur up to hours later in 0.5–1.0% of cases, typically as the antithrombotic therapy used during the procedure wears off.[180,181] Stents can reverse abrupt closure in more than 90% of cases overall and certainly in an even higher percentage of

TABLE 18

National Heart Lung and Blood Institute (NHLBI) classification of coronary dissection

- Type A: Luminal haziness
- Type B: Linear dissection
- Type C: Extraluminal contrast staining
- Type D: Spiral dissection
- Type E: Dissection with reduced flow
- Type F: Dissection with total occlusion

TABLE 19

Risk factors for coronary perforation during PCI

Over sizing of the angioplasty balloon (balloon to artery ratio > 1.2)
• High pressure balloon inflations outside stented segments
• Stenting of small or tapering vessel
• Stenting of lesions that are re-crossed after dissection or abrupt closure
• Treatment of chronic total occlusions
• Atherectomy device use—especially in angulated lesions

cases when the closure is related to a previously untreated dissection.

PERFORATION

Perforation or frank rupture of coronary arteries resulting from the guidewire, atherectomy devices, or balloons occurs in 0.2–0.6% of patients undergoing PTCA, with guidewire coronary artery perforation being the most common.[182,183] The incidence is higher with the use of atherectomy devices to ablate tissue for certain complex lesions.[182,183] The use of newer devices and more aggressive attempts to cross chronic total occlusions (with the use of stiffer coronary guidewires) harbor an increased risk for coronary artery perforation during PCI. The consequences of coronary perforation in the setting of the anticoagulation needed during PCI can cause significant morbidity and mortality (Table 19).

Coronary artery perforation in the stent era (at the site of the lesion) is a rare but potentially catastrophic complication. It may occur during stent deployment—particularly if the stent is oversized—if the lesion is very resistant to dilation (calcified lesions) and if extremely high deployment pressures are used. The degree of perforation varies from barely perceptible to severe. There is a classification scheme based upon angiographic appearance of the perforation.

- Class I: Intramural crater without extravasation
- Class II: Pericardial or myocardial blushing (staining)
- Class III: Perforation greater than or equal to 1 mm in diameter with visible contrast extravasation.

The incidence of complications varies with the severity of the perforation. For classes I, II and III perforations, the respective values were 0%, 14% and 50% for MI and 8%, 13% and 63% for cardiac tamponade. Emergency cardiac surgery with or without coronary bypass may be required.[182] The indications for emergency surgery are continued bleeding and/or hemodynamic compromise unrelieved by pericardiocentesis.

Serious perforations require immediate treatment in the cath lab, even if definitive surgical intervention is later needed. Rapid filling of the pericardial space secondary to coronary perforation in the setting of anticoagulation may very quickly lead to cardiac tamponade. Prompt recognition and treatment of tamponade with immediate pericardiocentesis is necessary to prevent a potentially catastrophic event.

When coronary perforation occurs, prompt recognition of the perforation is imperative to its successful treatment. An initial strategy is to inflate a balloon at the site of the perforation. Occasionally, this can seal the perforation, but, if not, further bleeding into the pericardium can be temporarily halted to provide some time (before development of pericardial tamponade) for other maneuvers. Next, reversal of anticoagulation should be considered when possible. Protamine is specific antagonist of heparin and should be administered promptly. It should be recognized that there is no similar reversal agent for bivalirudin. The infusion should be discontinued and the anticoagulant effect will wear off, but this may take up to 2 hours. If the perforation is not sealed with simple balloon inflation and reversal of anticoagulation, the placement of a covered stent should be considered.

Significant distal perforations of small branches by guidewires should be initially managed with balloon inflation as far distal in the vessel as is possible, reversal of anticoagulation and pericardiocentesis if needed. If the perforation persists despite this, coil embolization of the distal vessel may be considered. It should be recognized that this maneuver will likely be successful in stopping the bleeding, but will result in total occlusion of that arterial segment.

NO-REFLOW

No-reflow is defined as stagnant column of contrast agent in the vessel being treated without an identifiable mechanical obstruction. The cause is mainly embolization of atheromatous material and is aggravated by microembolization of platelet rich thrombi that release vasoactive agents leading to intense arteriolar spasm.[184] The incidence is about 2% with plain balloon angioplasty, 7% with use of RA and almost 40% for interventions involving degenerated SVGs. When no-reflow is suspected, it is important to ensure that there is not a mechanical obstruction that is causing the poor flow (dissection, incomplete treatment of the lesion, etc.). If no mechanical obstruction is identified, then no-reflow is the likely problem. Management includes intracoronary administration of various medications which may include: nitroglycerin, nipride, verapamil or adenosine. Use of EPD for interventions involving SVGs should always be considered to help reduce the severity of no reflow in these procedures.

ACUTE THROMBOTIC CLOSURE

Intracoronary thrombus is recognized angiographically as a progressively enlarging intraluminal lucency surrounded by contrast agent. Uncontrolled platelet aggregation along with superimposed spasm both play major roles in the formation of thrombus. An initial assessment to make when thrombus forms during PCI is to confirm that anticoagulation therapy is adequate and promptly correct it if needed. Generally, the risk for acute intraluminal thrombus formation during PCI is relatively low in stable angina patients. However, in patients presenting with acute coronary syndrome, lesions with visible thrombus before treatment begins, long and diffuse disease segments, or in degenerated vein grafts, the risk of thrombotic occlusion is high.[185] After stenting, acute closure due to subacute thrombosis may happen if there is incomplete apposition of stent struts with vessel wall or unrecognized obstruction proximal or distal to stent. This can generally be avoided with high pressure deployment of appropriately sized stents and adequate treatment of the entire diseased segment (Table 20).

TABLE 20

Variables associated with stent thrombosis

Anatomic variables
- Long lesions
- Smaller vessels
- Multivessel disease
- Acute myocardial infarction
- Bifurcation lesions

Procedural factors
- Stent underexpansion
- Incomplete wall apposition
- Residual inflow and outflow disease
- Margin dissections
- Crush technique
- Overlapping stent
- Polymer materials

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Section 4

ELECTROPHYSIOLOGY

Chapter 29

Arrhythmia Mechanisms

Mark Anderson

Chapter Outline

- Arrhythmia Initiation
  - — Molecular and Cellular Mechanisms
  - — Action Potentials Require Orchestrated Ion Channel Opening and Inactivation
  - — Action Potential Physiology is a Consequence of Ion Channel and Cellular Properties
  - — Action Potentials are Designed for Automaticity and to Initiate Contraction
  - — Action Potential Physiology is Reflected by the Surface Electrocardiogram
  - — Afterdepolarizations and Triggered Arrhythmias
  - — Proarrhythmic Substrates
  - — Proarrhythmic Triggers and Substrates are Promoted in Failing Hearts

INTRODUCTION

Arrhythmias require initiating conditions and a hospitable substrate for perpetuation. Triggers and substrates are often considered as unrelated or independent events. However, new findings suggest that triggers and substrates may be connected, particularly in structural heart disease, by hyperactivity of signaling molecules, intracellular Ca^{2+} and reactive oxygen species (ROS).[1] There is now a body of evidence to support a view that the increased ROS and disturbed intracellular Ca^{2+} homeostasis that mark structural heart disease contribute to arrhythmia initiation, while actively promoting a proarrhythmic substrate. Ion channels are the fundamental effectors that determine membrane currents and arrhythmias, but ion channels are regulated by multiple factors in myocardium, including intracellular Ca^{2+}, phosphorylation and ROS. These same factors participate in responses to common forms of myocardial injury, including ischemia and infarction, which lead to proarrhythmic adaptations in myocardium. This chapter will briefly review ion channel biology, genetic diseases of ion channels, and cellular and tissue arrhythmia mechanisms in an effort to present a broad, but comprehensible, approach to understanding arrhythmia mechanisms.

At a basic level, much of our understanding is due to studies in reduced systems (e.g. isolated heart muscle cells or non-cardiac cells heterologously expressing ion channel proteins) and animal models. However, many key arrhythmia mechanisms, including afterdepolarizations[2,3] and reentry[4] have been identified in patients. In fact, clinical studies and therapies, particularly ablation of focal and reentrant arrhythmias have provided strong evidence for fundamental concepts first formulated from analysis of animal studies. However, not all basic knowledge supporting discussion in this chapter has been translated to and validated in patients.

ARRHYTHMIA INITIATION

MOLECULAR AND CELLULAR MECHANISMS

Ion channels and exchangers are the fundamental units directing physiological and pathological membrane excitability and conduction.

Equation 1:

$$E = \frac{RT}{zF} \ln \frac{[\text{ion outside cell}]}{[\text{ion inside cell}]} = 2.303 \frac{RT}{zF} \log_{10} \frac{[\text{ion outside cell}]}{[\text{ion inside cell}]}$$

Nernst Equation E-equilibrium potential or Nernst potential is the cell membrane potential that is necessary to oppose the diffusion of an ion across the cell membrane as motivated by the concentration gradient of each ion (R—universal gas constant; T—temperature in degrees Kelvin; z—valence: F—Faraday's constant). At 25°C, RT/F = 25.693 mV.

Selective membrane permeability coupled with active pumps (ATPases) allow for an electrochemical gradient across cell membranes. The Nernst equation[5] is a powerful, but simplified (i.e. relies exclusively on two ions), description of a half cell that predicts how ionic gradients determine cell membrane potential. The maintenance of Na^+ and K^+ gradients under conditions of selective membrane permeability requires a Na^+ and K^+ 'pump'—the Na^+/K^+ ATPase. The Na^+/K^+ pump transports extracellular Na^+ $[Na^+]_o$ and intracellular K^+ $[K^+]_i$ against their concentration gradients, a process that requires energy input from ATP hydrolysis. The Na^+/K^+ ATPase is required to maintain physiological $[Na^+]_o$ (~ 145 mM), $[K^+]_o$ (~ 4 mM) and $[Na^+]_i$ (~ 10 mM), $[K^+]_i$ (~ 140 mM) in the face of the tendency of these gradients to dissipate with repetitive opening of Na^+ and K^+ channel proteins. Under resting conditions myocardial cell membrane potentials approximate

the equilibrium potential for K^+, ~ –90 mV, where the cytosolic side of the membrane is negative and the extracellular side of the membrane is positive, because the cell membrane permeability is greatest for K^+ under resting conditions. The resting membrane permeability to K^+ occurs because a particular ion channel, the inward rectifier, opens at the negative potentials present in resting membranes.

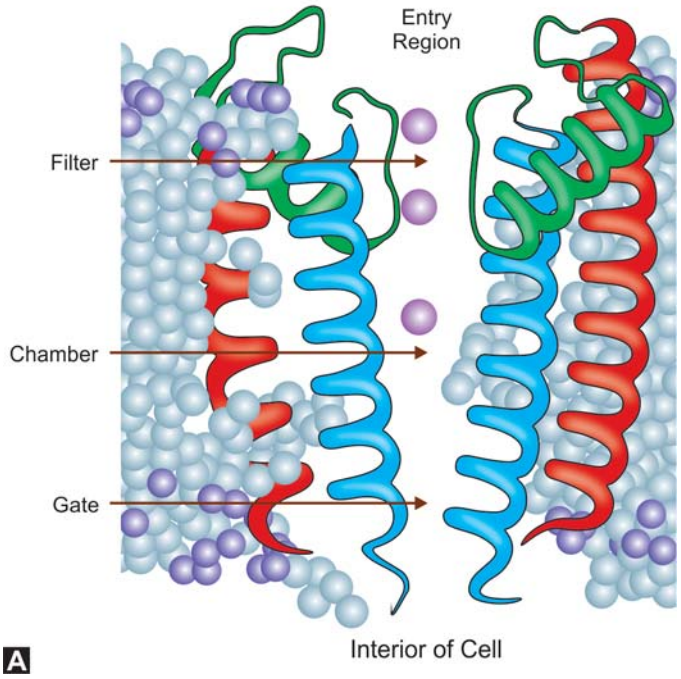
Equation 2:

$$E_{eq,K^+} = \frac{RT}{zF} \ln \frac{[K^+]_o}{[K^+]_i},$$

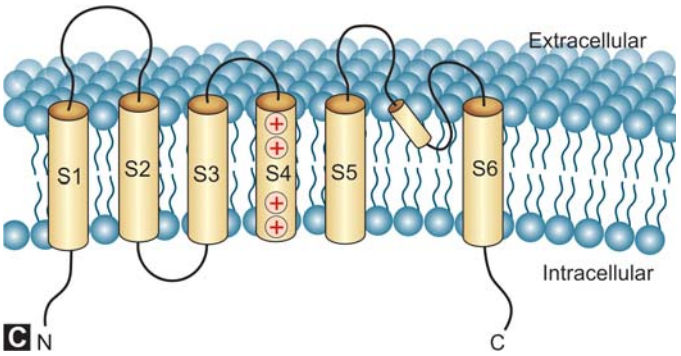
Nernst Equation for K^+.

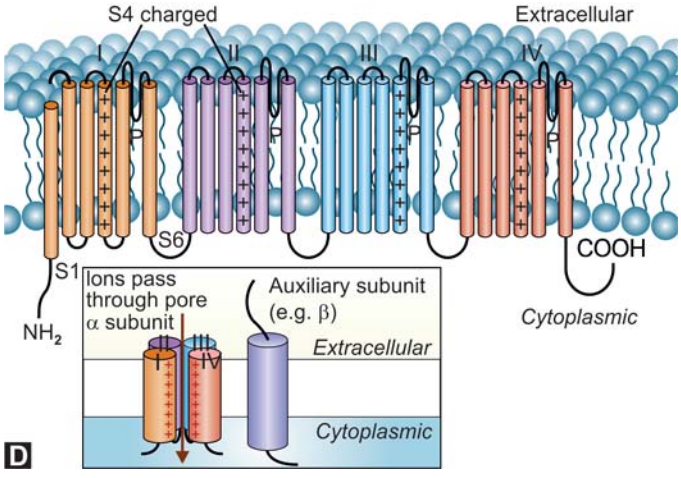
The resting membrane potential is highly dependent upon $[K^+]_o$ and the resting membrane potential determines membrane excitability in part because voltage-gated Na^+ channels (mostly $Na_V1.5$) begin to inactivate at membrane potentials more positive than –100 mV. At 37 °C (~ 310 °K) the equilibrium potential for K^+ (Eeq, K^+) is –91 mV for $[K^+]_o$ = 4.5 mM and $[K^+]_i$ = 140 mM. If the $[K^+]_o$ is reduced to 2.5 mM the Eeq, K^+ is –107.5 mV (and more $Na_V1.5$ channels are available to activate), and if the $[K^+]_o$ = 6.5 mM, the Eeq, K^+ is –82 mV (with reduced $Na_V1.5$ channel availability). Thus, the Nernst equation provides quantitative insight into the importance of K^+ homeostasis for normal cardiac electrophysiology.

Ion channels are protein complexes embedded in cell membranes (Figs 1A to D). All ion channels consist of a pore forming α subunit (Figs 1A to C). Some α subunits (e.g. K^+ channels) aggregate with identical or similar α subunits to form a cell membrane spanning pore. This pore is the conductance pathway that allows individual ions to cross lipid bilayer membranes with high throughput. Ion channels are configured for relative ion selectivity. The specific amino acids lining the pore create a 'filter' that selects ionic species for conductance









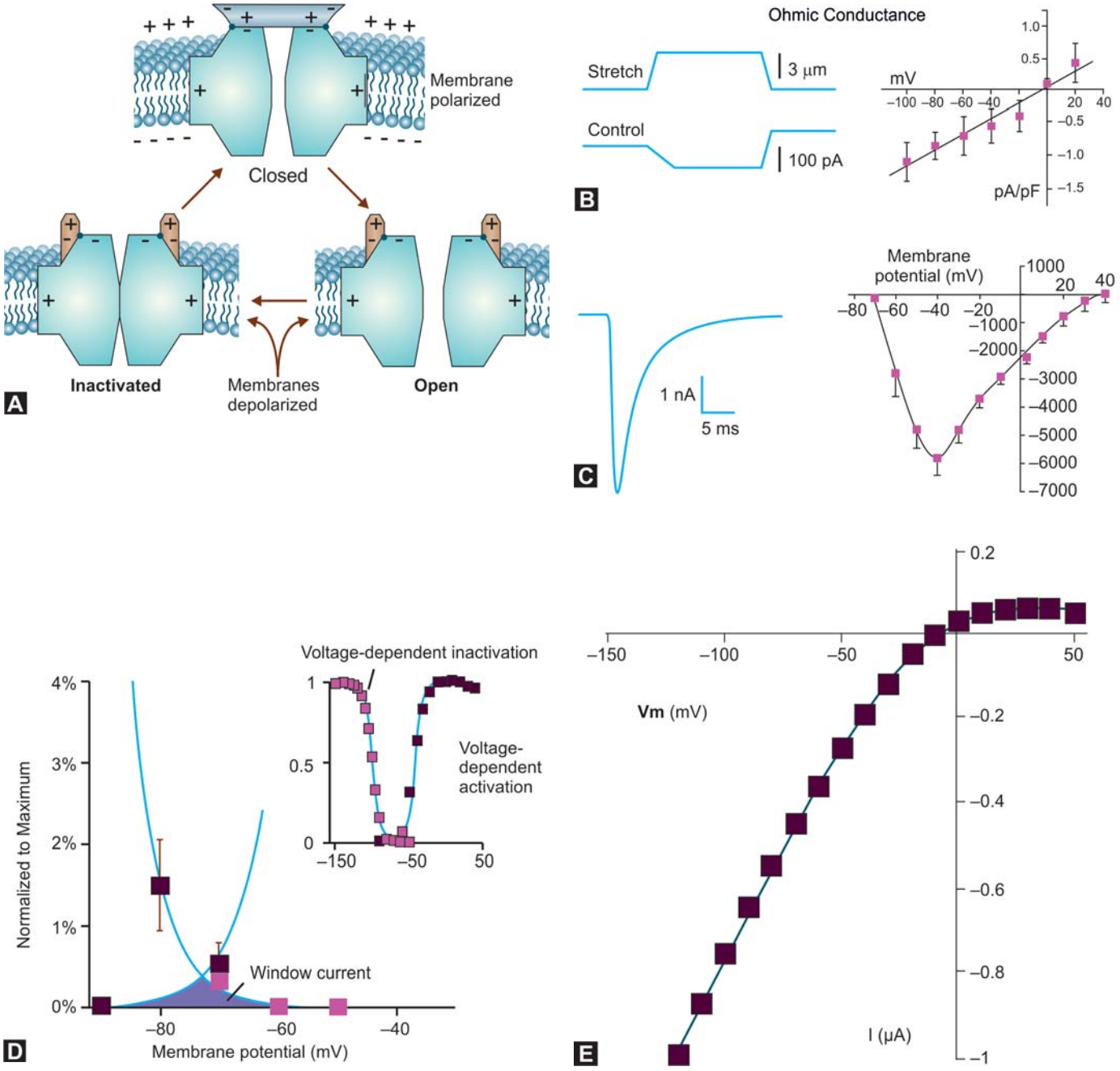
FIGURES 1A TO D: Ion channels are proteins that form a conductance pore through bilayer lipid cell membranes. (A) A ribbon diagram representation of the pore forming α subunit for a bacterial voltage-gated K^+ channel viewed from the side. (B) Ribbon diagram of a voltage-gated K^+ channel viewed from above. This view shows the fourfold symmetry of α subunit proteins that assemble to form a conductance pore for K^+ (center). (C) Schematic representation of a voltage-gated K^+ channel α subunit showing the voltage sensor (S4) and the pore (P) loop between S5 and S6. (D) A schematic representation of a voltage-gated Na^+ or Ca^{2+} channel that is similar to four concatenated K^+ channel α subunits

based on ionic size and charge. In solution ions are effectively larger due to a sphere of hydration that is a result of charge-associated water molecules. The selectivity filter in ion channels may remove water (dehydrate) from permeant ions as a requirement for passage through the conductance pore. Other α subunits are formed from a single large protein (e.g. Na^+ and Ca^{2+} channels). Ion channels open and close in response to a blend of various stimuli. In contracting atrial and ventricular myocardium and in specialized pacemaking [sinoatrial node (SAN)] and conduction tissue (atrioventricular node and His-Purkinje system) the most important and best understood ion channels are primarily opened by changes in membrane potential. These so-called 'voltage-gated ion channels' all contain a cell membrane spanning domain enriched in charged amino acids that act as a membrane voltage sensor (Figs 1C and D). The voltage sensor moves in response to changes in the membrane potential, and these movements are allosterically coupled to the pore domain. Voltage-gated ion channels open and close in response to a change in membrane potential, but also inactivate. Inactivation appears to be the result of various protein conformations that hinder the availability of the pore domain to open in response to a voltage stimulus, before the ion channel is 'reset' by recovering from the state of inactivation. Importantly, voltage-gated ion channels respond to additional factors, including amino acid phosphorylation and oxidation, which influence the probability of ion channels to open (Fig. 2A).

The voltage dependence of ionic current carried by voltage-dependent ion channels and exchangers is often presented as a current-voltage (I-V) relationship (Figs 2B and C). The I-V relationship is obtained in voltage-clamped cells or tissue, typically under conditions designed to isolate individual currents (e.g. by controlling the ionic constituents in the intracellular and extracellular solutions, addition of antagonist drugs or pore blocking ions, or by heterologous expression of individual ionic channels in non-excitable cells by gene transfection). The I-V relationships can reveal important ion channel behaviors such as the voltage dependence of activation and inactivation, ion selectivity, rectification and conductance. Voltage-gated ion channels activate and inactivate over a range of membrane potentials. In some cases, the voltage-range of activation and inactivation permits a 'window current' where ion channels can reactivate (Fig. 2D). An important window for voltage-gated Ca^{2+} channel (Ca_V1) currents (I_{Ca}) occurs during the membrane potentials present during the AP plateau. Excessive Ca_V1 window currents are a cause of triggered arrhythmias. Many ion channels (e.g. Na_V, K_V and Ca_V) have a very high selectivity for their namesake ions under physiological conditions. For example, K^+ channels are greater than 1,000 times more likely to conduct K^+ compared to Na^+. A simple, Ohmic, I-V relationship is linear with the line crossing through the zero point (Fig. 2B). However, the I-V relationship of most ion channels in heart is complex, and curvilinear (Fig. 2C). The point of current reversal, or equilibrium potential (mV), can be calculated by the Nernst equation: ~ +60 for Na^+, ~ –98 for K^+ and ~ +130 for Ca^{2+} under physiological conditions. The I-V relationship is influenced by the electrochemical gradient, which determines where a current transitions from inward to outward (as referenced to the cell membrane and cytoplasm). Convention holds that inward currents are negative and outward currents are positive. The I-V relationship is also affected by a property of some ion channels called rectification. Rectification is the tendency of a current to conduct preferentially inwardly or outwardly. A prominent example is the inwardly rectifying K^+ current (I_{K1}) that is crucial for determining resting membrane potential in myocardium. I_{K1} exhibits a pronounced inward rectification that is most evident at very negative membrane potentials. However, the physiologically relevant outward current is relatively small and is present near the resting membrane potential (Fig. 2E). Ion channel current is determined by gating properties, including opening probability, conductance, rectification, the electrochemical gradient of a particular ion and ion selectivity. Some ion channels may assume more than a single conductance (i.e. a subconductance state). The Ca^{2+}-gated ryanodine receptor Ca^{2+} channel has multiple subconductance states. Ion channel activity is also regulated by ions (e.g. Ca^{2+} and H^+), oxidation and phosphorylation.

Ion channel α subunits do not exist or operate in isolation. Accessory subunit proteins, often labeled as β, δ and γ, comprise the ion channel macromolecular complex. These accessory subunits may serve as chaperones to increase expression of α subunit proteins on the cell membrane. Accessory subunits are also targets for regulatory proteins, such as kinases and phosphatases, and may influence the probability of α subunits to open in response to a voltage stimulus. Ion channel macromolecular complexes require precise localization in the cellular ultrastructure to function properly. For example, voltage-gated Ca^{2+} channels, Ca_V1, are enriched in T-tubular membranes across from intracellular Ca^{2+} channels called ryanodine receptors (RyR2) that control Ca^{2+} release from the sarcoplasmic reticulum (SR) (Fig. 3).[6,7] Distortion of the relationship of Ca_V1 and RyR channels occurs in heart failure and contributes to loss of normal intracellular Ca^{2+} homeostasis, mechanical dysfunction and promotes arrhythmia-initiating afterdepolarizations.[8] Cytoskeletal proteins also contribute to ion channel disposition and localization, and cytoskeletal diseases, such as the ankyrin syndromes,[9,10] cause arrhythmias and other pathological phenotypes in excitable cells in brain and pancreas.

The current view of ion channel structure and function arose using three fundamental investigational approaches. The first was a combination of voltage clamp and mathematical modeling. Voltage clamp uses an operational amplifier with feedback control to 'clamp' a cell membrane at a command potential. By controlling cell membrane potential and the concentration of ions in the cell interior and exterior, it was possible to study individual macroscopic currents that arose from all the ion channels of a particular type operating together on the cell membrane. Originally, voltage clamp studies were focused on very large excitable cells, such as the squid giant axon, which were amenable to early techniques such as Vaseline gap and intracellular electrodes. Hodgkin and Huxley used data obtained in squid axon to develop a model of ion channel physiology that postulated 'gates' for activation and inactivation.[11] Their studies provided a conceptual and quantitative framework for understanding ion channels that has endured, albeit with modifications, into the modern era. In 1981, Hammell et al. published the first description of voltage clamp studies using the patch clamp technique (Figs 4A to D).[12] Cardiac myocytes



FIGURES 2A TO E: Ion channel gating is the process that determines the probability of an α subunit being available to conduct ionic current. (A) A schematic representation of basic gating states: open; closed and inactivated for a voltage-gated ion channel. (B) Examples of a non-rectifying, stretch-activated ionic current (left). The current, normalized to membrane surface area, (pA/pF)-voltage (mV) relationship for this current shows an Ohmic conductance that is linear and passes through zero. (C) The left panel shows an example of a voltage-gated Na^+ current that activates rapidly (inward deflection) and then rapidly inactivates (resolution of the inward current back to baseline within a few milliseconds). The right panel shows the parabolic current-voltage relationship that is characteristic of voltage-gated Na^+ current in myocardium. (D) An example of a 'window current' for voltage-gated Na^+ channels. The shaded overlap between the voltage-dependent loss of Na^+ channel availability to open (inactivation, pink boxes) and voltage-dependent Na^+ channel activation (purple boxes) is the window current. (E) An example of a current-voltage relationship for an inwardly rectifying K^+ channel current (I_{K1})

were the subject of one of the first studies using patch clamp that described currents flowing through individual ion channels.[13] Patch clamp allowed for high resistance, giga-Ohm, seals between a glass microelectrode and the cell membrane. This high resistance seal allowed resolution of the extremely small currents associated with individual ion channels (in the pico-Ampere range for Ca_V). Patch clamp used in the whole cell mode allowed investigators to measure macroscopic currents in single cells grown in culture or isolated from tissue, and to control intracellular contents by dialysis of an investigator-selected solution. Modern molecular biology techniques of gene cloning and expression were developed after voltage clamp.[14] Expression of wild type and mutant ion channels studied in non-native and native cells allowed investigators to determine the

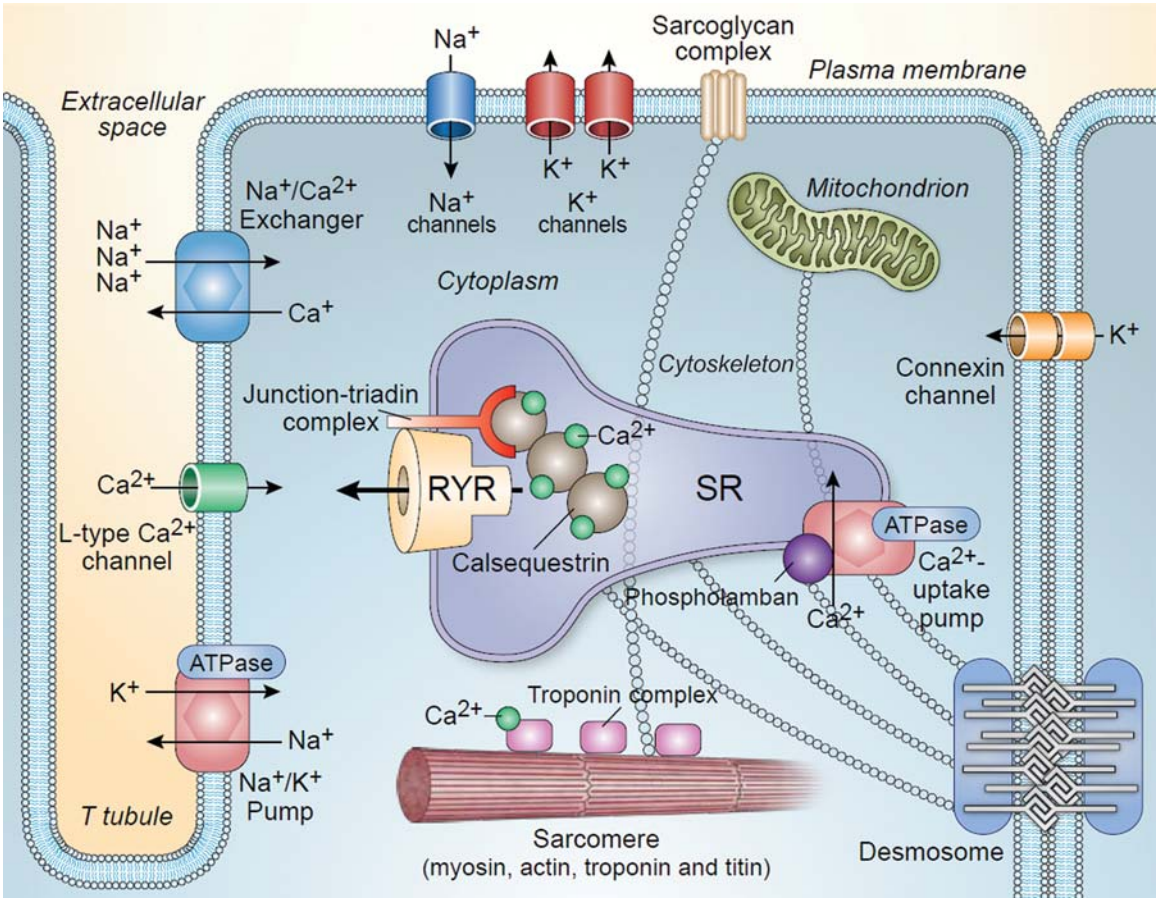


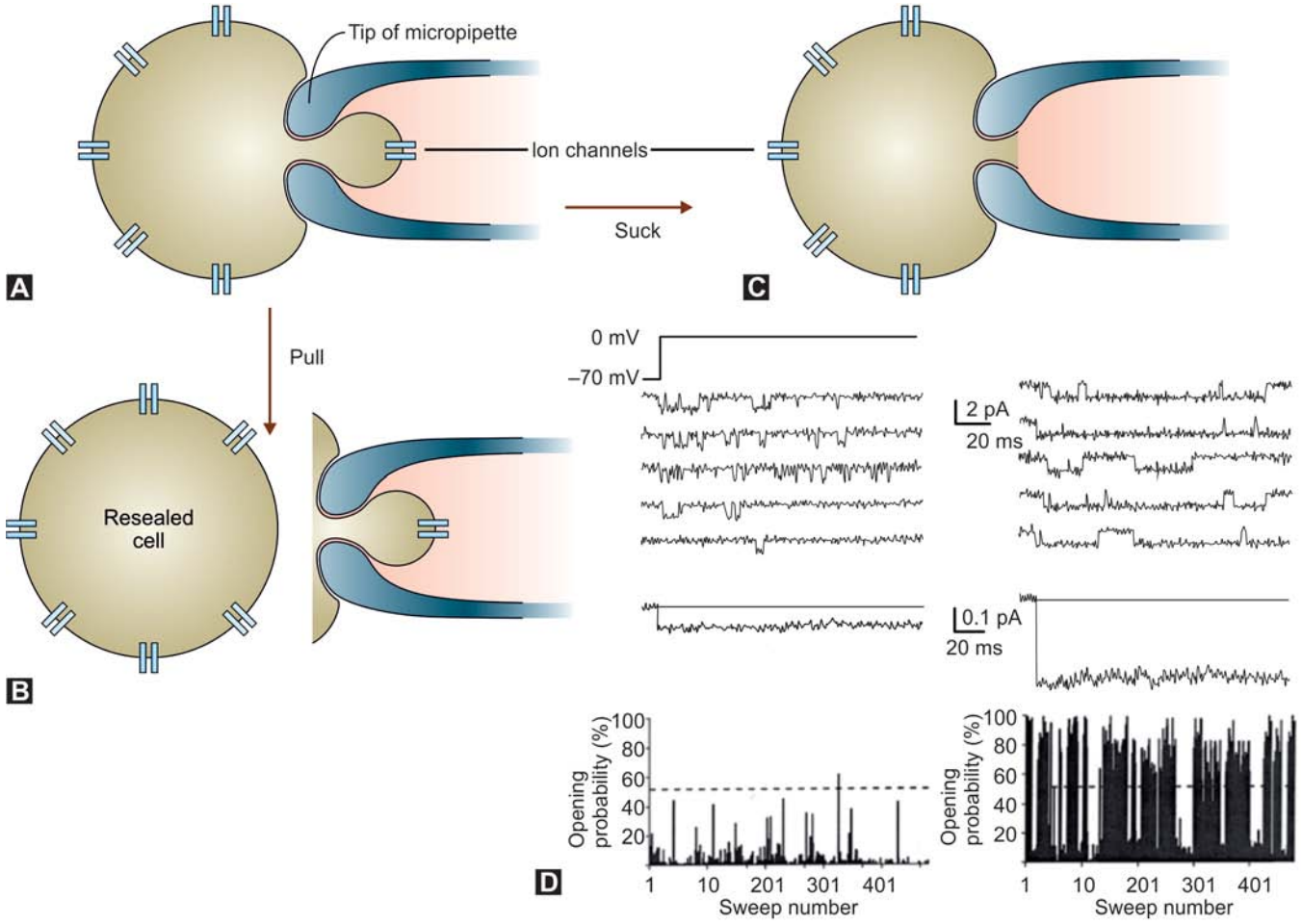
FIGURE 3: Myocardial cells are designed for excitation-contraction coupling, the process whereby action potentials generate inward Ca^{2+} current that triggers myofilament-activating Ca^{2+} release from ryanodine receptors (RyR) on the sarcoplasmic reticulum (SR) to cause contraction. The cell membrane ultrastructure formed by T tubules allows Ca^{2+} channels and RyR to face one another across a narrow (~ 10 nm) cytoplasmic space

biophysical purpose of various ion channel domains such as the voltage sensor.[15] These 'structure-function' studies provided highly detailed information that led to more complete understanding of ion channel molecular physiology in health and disease. Because ion channel proteins are expressed in cells at relatively low copy number, have prominent lipophilic regions (that allow for membrane insertion) and are large, they are difficult to crystallize. However, the MacKinnon laboratory overcame many of these obstacles by over-expressing bacterial K^+ channels,[16,17] which have served as a structural model for many of the voltage-gated cation channels present in heart. The combination of voltage clamp, molecular biology and high resolution structural information form the modern tool kit for understanding cardiac ion channels.

Ion channels are not the only source of ionic membrane currents. In myocardium, the Na^+/Ca^{2+} exchanger is the predominant mechanism for removing Ca^{2+} from the cytoplasm to the extracellular space. The Na^+/Ca^{2+} exchanger transfers a Ca^{2+} for $3Na^+$ (forward exchange mode). Because there is a single net positive charge moved to exchange a Ca^{2+} ion from the cytoplasm to the extracellular space, the Na^+/Ca^{2+} exchanger produces a small inward Na^+ current in forward mode. Although the Na^+/Ca^{2+} exchanger does not directly require ATP, the Na^+ gradient necessary for forward mode exchange depends upon the ATP-requiring Na^+/K^+ ATPase. The Na^+/K^+ ATPase and a sarcolemmal Ca^{2+} ATPase produce small, but measurable currents. The Na^+/Ca^{2+} exchanger current, although small in magnitude compared to Na_V or Ca_V channel currents, contributes to AP duration. It is essential for the direct myocardial inotropic actions of digitalis glycosides, which inhibit the Na^+/K^+ ATPase leading to accumulation of $[Na^+]_i$ and consequent increase in $[Ca^{2+}]_i$, because the gradient for Ca^{2+} extrusion by Na^+/Ca^{2+} exchanger is less favorable than when $[Na^+]_i$ is lower. The Na^+/Ca^{2+} exchanger is a source of inward currents for arrhythmia triggering afterdepolarizations, as will be discussed below.

ACTION POTENTIALS REQUIRE ORCHESTRATED ION CHANNEL OPENING AND INACTIVATION

Action potentials are the fundamental unit of membrane excitability (Fig. 5). In most myocardial cells action potentials are initiated by opening of voltage-gated Na^+ channels, $Na_V1.5$. The inward $Na_V1.5$ current (I_{Na}) depolarizes atrial and ventricular myocytes in a few milliseconds. The brevity of I_{Na} is due to the rapidity of the inactivation process, which competes with activation to modulate the peak current. The membrane potential depolarizes (becomes more positive) from the negative resting potential (~ –80 mV) to approach the reversal potential for Na^+, estimated by the Nernst equation (~ +50 mV). Specialized myocytes that are dedicated more to automaticity (i.e. SAN) and conduction (i.e. the atrioventricular node) than contraction rely on I_{Ca} for their (phase 0) action potential



FIGURES 4A TO D: Patch clamp is a flexible approach to voltage clamp single cells or cell membrane patches. The high resistance seals (giga Ohm) between the glass micro-pipette and the cell membrane allow for resolution of very small (pA) currents. (A) On cell configuration for recording a subset of ion channels on a cell membrane. (B) Excised membrane patch for recording a subset of ion channels on a cell membrane under conditions where the cytoplasmic constituents can be easily manipulated. (C) Whole cell mode configuration for recording all the ion channels on a cell membrane and where the pipette solution can be dialyzed into the cell. (D) Examples of single Ca^{2+} channel recordings ($Ca_V1.2$) using excised cell membrane patches (as in panel B) at baseline (left panels) and after application of calmodulin kinase II to the cytoplasmic face of the membrane. The top panels show ionic currents from single $Ca_V1.2$ channels in response to a voltage clamp command from –70 to 0 mV. The downward deflections indicate channel openings. The middle tracing is an ensemble current averaged from multiple 'sweeps', as shown in the top five tracings. The bottom panels show a diary plot that indicates the opening probability of the single channel in the recording for each sweep. Panel D is adapted from Dzhura et al. 2000

upstroke. Membrane depolarization activates a combination of voltage-gated ion channels, but the most prominent are depolarizing inward $Ca_V1.2/1.3$ currents (I_{Ca}) and several distinct, but structurally related repolarizing inward K^+ channel (K_Vx) currents (I_K). The interplay between I_{Ca} and I_K largely determines the duration of the myocardial action potentials, which last hundreds of milliseconds. Atrial and ventricular myocardial action potentials have different shapes and electrophysiological properties. In fact, there are important heterogeneities in action potential configuration within the atrium and ventricle. The ventricular endocardium, mid-myocardium and epicardium show prominent differences in action potential configuration, due to variability in expression of repolarizing K^+ currents (Fig. 6). While the physiological benefit of action potential heterogeneity is unknown, the heterogeneities are affected by K^+ channel antagonist drugs and by electrical remodeling during heart failure, where expression of various repolarizing K^+ channels is reduced.[18] In addition to voltage-gated ion channels and exchangers, there is an increasing recognition that other non-voltage-gated ion channels contribute to action potential configuration. A more complete discussion of these channels is reviewed elsewhere.[19,20]

ACTION POTENTIAL PHYSIOLOGY IS A CONSEQUENCE OF ION CHANNEL AND CELLULAR PROPERTIES

Myocardial action potentials are distinguished from action potentials in other excitable tissues by their extreme length, lasting up to hundreds of milliseconds. In contrast, action potentials in most neurons last only a few milliseconds. Cardiac action potentials are often described in phases (Fig. 5). Phase 0 marks the abrupt depolarization from the resting potential and is attributable to $Na_V1.5$ current in most myocardial cells. Cardiac action potentials are long because of their plateau. The action potential plateau occurs because of a fine balance, mostly

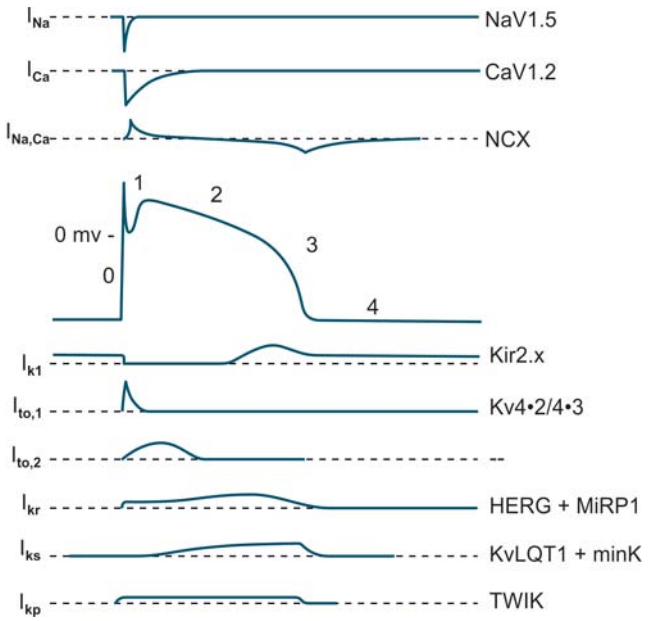


FIGURE 5: The action potential duration and configuration is shaped by the interplay between inward and outward-going ionic currents. The top two tracings represent $Na_V1.5$ and $Ca_V1.2$ inward currents that initiate and sustain action potential depolarization. The third tracing from the top is the Na^+/Ca^{2+} exchanger (NCX) that can produce inward (forward mode) and outward (reverse mode) currents at various action potential phases. The ventricular action potential is labeled by phase (0–4). The lower six tracings represent some of the K^+ currents that contribute to action potential repolarization

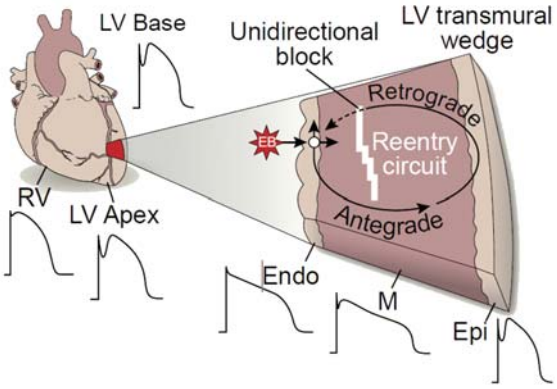


FIGURE 6: Ventricular action potentials are heterogenous and vary between base and apex and across the myocardium from endocardium to epicardium. M cells in the mid-myocardium have characteristically long action potentials with a reduced phase 1. Structural defects, such as scar tissue, can serve as a structural barrier that supports a reentry circuit for arrhythmias. Exaggeration of action potential heterogeneities, by genetic disease or acquired disease, can also support a reentry circuit, even in the absence of scar

between depolarizing inward Ca_V current, a small persistent (slowly inactivating) component of $Na_V1.5$ current, and activation of repolarizing K^+ currents. The initial plateau is referred to as phase 2, while the later plateau is referred to as phase 3. In electrically healthy myocardium phase 3 is the period of repolarization to resting membrane potential (phase 4). Phase 3 occurs as inward currents inactivate and repolarizing currents become preeminent. Phase 1 occurs immediately after peak membrane potential depolarization (i.e. the end of phase 0) and where prominent (e.g. ventricular epicardium) is marked by a 'notch' that is due to a combination of K_V channel currents that support a transient inward current (I_{to}) and a more rapid repolarizing K^+ current (the ultrarapid transient outward current, I_{Kur}). The initial component of the action potential plateau (phase 2) is marked by high membrane resistance (R), so small increases in net inward current lead to prominent positive increases in membrane voltage, according to Ohm's law ($V = I \times R$). In automatic cells phase 4 is not stable, but instead consists of an increasing positive membrane potential in late diastole that leads to activation of Ca_V channel currents to initiate phase 1 AP depolarization. Thus, a rich diversity of ion channels contributes to various AP configurations. These AP configurations are matched to the purpose of particular myocardial cells (e.g. pacing or contraction), but in disease AP parameters are directly relevant to arrhythmia initiation and perpetuation.

Action potentials can be repetitively initiated in atrial and ventricular myocardium within the time constraints of the tissue refractory period (Figs 7A and B). The refractory period is determined in large part by the duration of the cardiac action potential. Action potentials are initiated by positive (inward) current sufficient to depolarize the membrane potential to the threshold for activation of $Na_V1.5$ in contracting myocardium or Ca_V1 in specialized conduction tissue. During phase 2 of the action potential plateau myocardial cells are absolutely refractory, meaning that no amount of inward current is adequate to elicit an action potential. Later in the course of action potential repolarization (phase 3) an action potential can be stimulated, but only by a larger inward current than would be necessary after completion of action potential repolarization. Tissue where an action potential can only be stimulated by a supranormal current is said to be relatively refractory. Under physiological conditions action potentials shorten in response to shorter stimulation intervals (i.e. faster rates), due to a process called restitution (Fig. 7C). Action potential restitution occurs, in part, because rapid simulation enhances net outward repolarizing current. Action potential restitution is impaired in genetic long QT syndromes (LQTS), where repolarizing currents are defective, or in common forms of heart failure where reduction in repolarizing currents is a signature event in the proarrhythmic electrical remodeling process. Tissue refractoriness can persist after action potential repolarization under conditions of reduced availability of inward currents responsible for phase 0 depolarization (i.e. $Na_V1.5$ in contracting myocardium and $Ca_V1.2$ and $Ca_V1.3$ in specialized conduction tissue). Various factors contribute to availability of these channels to open, including cell membrane potential (e.g. fewer Na_V and Ca_V channels are available to open at depolarized potentials because membrane depolarization favors inactivation), oxidation, pH, $[Ca^{2+}]_i$, ischemia and autonomic tone. Thus, cell membrane excitability depends on multiple input variables that ultimately converge on ion channels and APs.

The rate that APs are conducted across myocardium (i.e. the conduction velocity) is determined by two principle factors. The first are determined by inputs that affect phase 0: availability of Na_V currents in contracting myocardium and Ca_V currents in specialized conducting and automatic tissue. The second is the



FIGURES 7A TO C: Tissue refractoriness to excitation is determined by action potential repolarization and reflected in the surface ECG. (A) A schematic ECG tracing. (B) The surface ECG is a reflection of many action potentials. Myocardial tissue is absolutely refractory to repeat stimulation (dark bars) until late in repolarization. Tissue is potentially excitable prior to completion of repolarization, but initiation of excitation requires a supranormal depolarizing current, a state of relative refractoriness (light bars). (C) Action potential restitution is revealed by a premature stimulus (S2) deployed over a range of coupling intervals

efficacy of electrical coupling between myocardial cells. Myocardial cells are electrically coupled by connexin hemichannels that cooperate to form a conductance pore between adjacent cells. The predominant connexin (Cx) type is specific to atrium, ventricle and specialized conduction tissue. Cx 40 and 43 are the major forms in atrium, Cx 43 is the major form in ventricle and Cx 45 is the major form in sinus node, AV node and His-Purkinje cells. Longitudinal intercellular coupling is favored in ventricular myocardium, based on the greater density of Cx 43, compared to side-to-side connections. Conduction velocity is more rapid in the longitudinal direction, due to the greater density of Cx 43 and because $Na_V1.5$ is enriched at the longitudinal junctions, analogous to Nodes of Ranvier in neurons.[21] Like voltage-gated ion channels, Cxs are part of a substantial macromolecular complex that influences intercellular conduction. Altered Cx behavior, localization and expression[22] contributes to conduction velocity dispersion and slowing that are critical components of the proarrhythmic substrate in rare genetic diseases and common forms of structural heart disease.

ACTION POTENTIALS ARE DESIGNED FOR AUTOMATICITY AND TO INITIATE CONTRACTION

Myocardial action potentials are committed to the major tasks of myocardium: rhythmic, repetitive beating and mechanical work that propels blood through the circulatory system. Sinoatrial node (SAN) action potentials have a specialized, late diastolic component or phase 4 where membrane depolarization leads to activation of Ca_V channel currents to drive phase 0 depolarization. The slope of phase 4 is the membrane potential mechanism for increasing (steeper slope) or decreasing (shallower slope) heart rate (Fig. 8). In healthy hearts, the activity of phase 4 is largely confined to the SAN, where the steady increase in net inward current during late diastolic depolarization is augmented by β adrenergic receptor stimulation

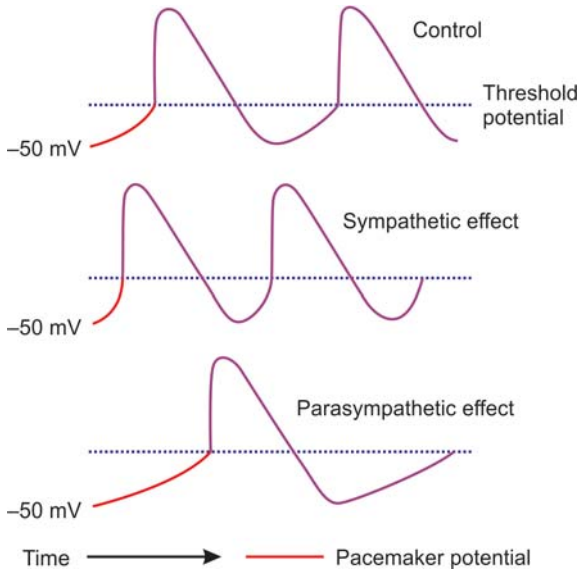


FIGURE 8: The cell membrane potential for determining heart rate in sinoatrial nodal cells is set by the steepness of phase 4 (pacemaker) potential. Steeper phase 4 allows the membrane potential to reach the threshold for action potential initiation more rapidly than shallow phase 4 depolarization

and reduced by muscarinic receptor stimulation. Multiple currents likely contribute to physiological phase 4 depolarization in SAN, but recent evidence suggests that two currents play a critical role in physiological pacing. The classical 'pacemaker' current is a Na^+/K^+ selective cation current carried by an *HCN4* gene encoded channel. The *HCN4* current, also called the funny current (I_f) is enhanced by cyclic AMP, which confers increased activity (and steeper phase 4) with α adrenergic receptor agonist stimulation.[23,24] More recent understanding of physiological automaticity in SAN cells suggests that SR Ca^{2+} release enhances inward Na^+/Ca^{2+} exchanger current. The relationship between spontaneous SAN cell SR Ca^{2+} release and inward Na^+/Ca^{2+} exchanger current that contributes to phase 4 depolarization has been called a 'Ca^{2+} clock mechanism' of pacing.[25] The Ca^{2+} clock is responsive to α adrenergic receptor agonist stimulation because cellular Ca^{2+} entry by Ca_V1 currents and SR Ca^{2+} release are both increased by catecholamines. The Ca^{2+} clock concept has important and interesting implications, because it identifies proteins and subcellular systems designed for excitation-contraction coupling in mechanically purposed atrial and ventricular myocardium as serving a dual purpose as a mechanism for automaticity—excitation-excitation coupling. While the Ca^{2+} clock appears to contribute to the normal physiology of SAN cells, SR Ca^{2+} leak and increased inward Na^+/Ca^{2+} exchanger current is known to induce DADs and trigger arrhythmias in atrial and ventricular myocardium under conditions of pathological stress. Thus, physiological automaticity resembles pathological triggering, suggesting that so-called 'triggered' arrhythmias are a natural consequence of excitation-contraction coupling. In my opinion, the similarities between automaticity and triggering suggest that bright line distinctions between these concepts are no longer warranted or appropriate.

The AP plateau is unique to cardiac muscle because cardiac muscle relies on a specific mode of excitation-contraction coupling called Ca^{2+}-induced Ca^{2+} release (CICR, Fig. 3).[26] The AP plateau is the membrane potential substrate for grading Ca^{2+} entry by voltage-gated Ca^{2+} channels. CICR is initiated by a Ca^{2+} current trigger, mostly through $Ca_V1.2$ in ventricular myocardium, and $Ca_V1.2$ and $Ca_V1.3$ in atrial myocardium. Ca_V channels are arrayed in close juxtaposition to RyRs and the Ca_V current triggers RyR opening. Ryanodine receptor (RyR) opening results in a release of myofilament-activating Ca^{2+} from the SR lumen into the cytoplasm in the vicinity of myofilaments. Ca^{2+} triggers myofilament crossbridge formation that causes myocardial contraction. Systole requires energy, in part, due to the ATP cost of sequestering Ca^{2+} into the SR. Like systole, diastole is an energy requiring process that is initiated when the SR bound Ca^{2+} ATPase pumps (SERCa 2a: sarcoplasmic endoplasmic reticulum Ca^{2+} ATPase type 2a) sequester Ca^{2+} from the cytoplasm into the SR lumen, allowing release of myofilament crossbridge formation and myocardial relaxation. SR Ca^{2+} release occurs in a highly structured subcellular domain, resulting in very high local $[Ca^{2+}]_i$. SR Ca^{2+} affects myocardial ion channels, particularly Ca_V1 and the Na^+/Ca^{2+} exchanger. The actions at Ca_V1 currents are complex, and include conflicting processes called facilitation (peak current is increased and inactivation is reduced) and Ca^{2+} dependent inactivation (peak current is reduced and inactivation is increased). These processes are labile and may have marked influence on the shape, duration and stability of the AP plateau. In our opinion, the best available evidence suggests that Ca_V1 channel current facilitation is due to phosphorylation of a specific residue on the Ca_V1 β subunit by the multifunctional Ca^{2+} and calmodulin-dependent protein kinase II (CaMKII).[27] Ca_V1 channels current facilitation occurs because Ca_V1 channels enter a highly active gating mode after CaMKII phosphorylation where the probability of channel opening rises significantly above baseline.[28] CaMKII actions on Ca_V1 channels cause proarrhythmic afterdepolarizations and arrhythmias.[29-31]

ACTION POTENTIAL PHYSIOLOGY IS REFLECTED BY THE SURFACE ELECTROCARDIOGRAM

The electrocardiogram (ECG) is one of the most commonly ordered medical tests in most hospitals. The ECG is a surface report on myocardial electrical activity. Although multiple factors influence ECG parameters, the basic intervals (PR, QRS, QT) reflect ion channel-directed AP parameters (Figs 7A to C). The PR interval is the duration required for an electrical impulse to conduct from the point of 'break out' near the SAN, through atrial myocardium and AVN to the ventricle. In healthy myocardium, this interval will be dominated by the slowest conducting segment, which is in the AVN. In diseased myocardium, impaired atrial and His-Purkinje conduction may contribute to PR prolongation. The QRS interval reflects the speed of conduction and depolarization through the right and left ventricles. The QRS interval can be prolonged by Na_V or Cx gene defects or antagonist drugs, injury or disease in the His-Purkinje system or myocardial injury, including myocardial ischemia, infarction and scar. The QT interval corresponds to ventricular repolarization. Ventricular repolarization is complex, due to the physiological variation in repolarizing ionic currents in endocardium, mid-myocardium and epicardium, as well as between the ventricular apex and base. QT interval prolongation can occur in long QT syndromes that are due to intrinsic defects in repolarizing ionic currents or their cellular localization (LQTS). Ion channel antagonist drugs are the most common reason for QT interval prolongation. Importantly, a wide variety of drugs are antagonists of the hERG (human ether-a-go-go related gene)[32,33] or *KCNH2* encoded $K_V11.1$ K^+ channel α subunit protein that conducts the rapid delayed rectifier current (I_{Kr}).[34] Rectifier current antagonist properties are a major obstacle for drug development because of the link between QT prolongation, Torsade de Pointes ventricular arrhythmia and sudden death.[35] Diseases of ion channel encoding genes that alter membrane repolarization (Table 1) can result in AP and QT interval lengthening (Long QT syndromes) or AP and QT interval shortening (Short QT syndromes).[36] Failing myocardium from a variety of causes (e.g. myocardial infarction, valvular disease, genetic disease) undergoes a proarrhythmic electrical remodeling process where repolarizing K^+ currents are reduced resulting in AP and QT interval prolongation.[18] Understanding basic electrophysiological principles constitutes the foundation for understanding arrhythmia mechanisms and for interpreting ECGs.

TABLE 1

A compilation of genetic arrhythmia syndromes due to mutation in ion channel proteins

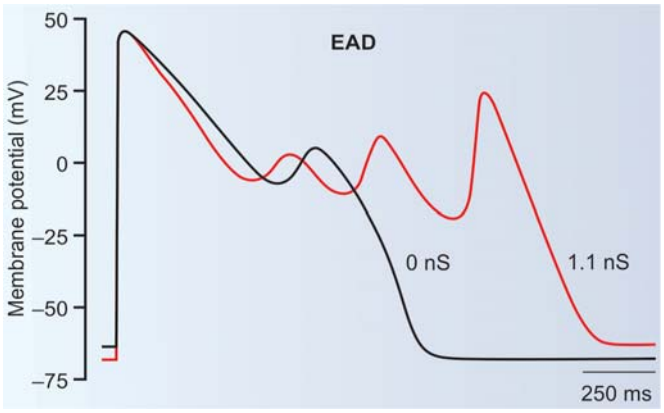
	Rhythm	*Inheritance*	*Locus*	*Ion channel*	*Gene*
Long QT syndrome (RW)	TdP	AD			
LQT1			11p15	I_{Ks}	*KCNQ1, KvLQT1*
LQT2			7q35	I_{Kr}	*KCNH2, HERG*
LQT3			3p21	I_{Na}	*SCN5A, $Na_v1.5$*
LQT4			4q25		*ANKB, ANK2*
LQT5			21q22	I_{Ks}	*KCNE1, minK*
LQT6			21q22	I_{Kr}	*KCNE2, MiRP1*
LQT7 (Andersen-Tawil syndrome)			17q23	I_{K1}	*KCNJ2, Kir 2.1*
LQT8 (Timothy syndrome)			6q8A	I_{Ca}	*CACNA1C, $Ca_v1.2$*
LQT9			3p25	I_{Na}	*CAV3, caveolin-3*
LQT10			11q23.3	I_{Na}	*SCN4B, Na_vb4*
Long QT syndrome (JLN)	TdP	AR	11p15	I_{Ks}	*KCNQ1, KvLQT1*
			21q22	I_{Ks}	*KCNE1, minK*
Brugada syndrome					
BrS1	PVT	AD	3p21	I_{Na}	*SCN5A, $Na_v1.5$*
BrS2	PVT	AD	3p24	I_{Na}	*GPD1L*
BrS3	PVT	AD	12p13.3	I_{Ca}	*CACNA1C, $Ca_v1.2$*
BrS4	PVT	AD	10p12.33	I_{Ca}	*CACNB2b, $Ca_v\beta_{2b}$*
Short QT syndrome					
SQT1	VT/VF	AD	7q35	I_{Kr}	*KCNH2, HERG*
SQT2			11p15	I_{Ks}	*KCNQ1, KvLQT1*
SQT3		AD	17q23.1–24.2	I_{K1}	*KCNJ2, Kir2.1*
SQT4			12p13.3	I_{Ca}	*CACNA1C, $Ca_v1.2$*
SQT5		AD	10p12.33	I_{Ca}	*CACNB2b, $Ca_v\beta_{2b}$*
Catecholaminergic VT					
CPVT1	VT	AD	1q42–43		*RyR2*
CPVT2	VT	AR	1p13–21		*CASQ2*

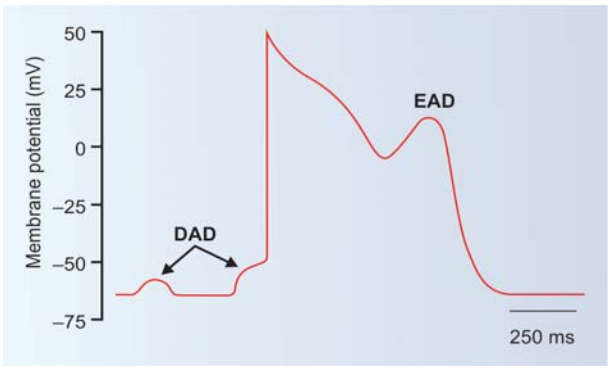
(Abbreviations: AD: Autosomal dominant; AR: Autosomal recessive; JLN: Jervell and Lange-Nielsen; RW: Romano-Ward; TdP: Torsade de pointes; VF: Ventricular fibrillation; VT: Ventricular tachycardia; PVT: Polymorphic VT; I_{Ks}: Slowly activating delayed rectifier current; I_{Kr}: Rapidly activating delayed rectifier current; I_{Na}: Na^+ channel current; I_{K1}: Inward rectifier current; I_{Ca}: Ca^{2+} channel current; GPDIL: Glycerol-3-phosphate dehydrogenase 1-like gene; RyR2: Ryanodine receptor 2 gene; CASQ2: Calsequestrin 2 gene. (*Source:* Antzelevitch 2007)

AFTERDEPOLARIZATIONS AND TRIGGERED ARRHYTHMIAS

Afterdepolarizations are arrhythmia-initiating oscillations in cell membrane potential. Early afterdepolarizations (EADs) occur during the plateau phases (2 and 3) of AP repolarization. Delayed afterdepolarizations (DADs) occur after AP repolarization, during phase 4 (Figs 9A and B). EADs and DADs can trigger an arrhythmia by propagating to adjacent tissue under favorable source-sink conditions. In theory, EAD and DADs can emerge from an essentially limitless set of conditions, sharing a common requirement that net inward current is enhanced to initiate a depolarizing oscillation in membrane potential. EADs and DADs of sufficient magnitude depolarize the cell membrane to reach the threshold for activation of Na_V and/or Ca_V channel currents to initiate AP phase 0. EADs and DADs that occur at the same time in a sufficient number of cells can lead to a premature AP. One or more premature APs can trigger an arrhythmia by engaging a proarrhythmic substrate supporting reentry. Although there are many potential scenarios for increasing net inward current to initiate EADs or DADs, there is an emerging body of experimental evidence that a common pathway for promoting EADs is reactivation of Ca_V channel currents, while a common pathway favoring DADs is loss of synchronous SR Ca^{2+} release leading to inward Na^+/Ca^{2+} exchanger current. Thus, both EADs and DADs can be thought to arise as a consequence of corruption of key components of CICR.

EADs and DADs are hypothesized to initiate life-threatening arrhythmias in long QT syndromes, catecholaminergic polymorphic VT, atrial fibrillation, and ventricular arrhythmias in heart failure. Long QT syndromes are mostly the result of dominant or dominant negative mutations that cause a defect in depolarization that results in AP prolongation (Table 1),





FIGURES 9A AND B: Afterdepolarizations are arrhythmia-triggering oscillations in cell membrane potential. (A) Early afterdepolarizations (EADs) occur during action potential repolarization. (B) Delayed afterdepolarizations (DADs) occur after action potential repolarization

secondary increases in Ca_V1 current and afterdepolarizations. CaMKII is activated in atrial fibrillation[37,38] and during AP prolongation,[39] due to enhanced Ca^{2+} entry, and is thought to promote arrhythmias by enhancing Ca_V1 current facilitation,[29] the non-inactivating component of $Na_V1.5$[40] and SR Ca^{2+} leak[41] in animal and cellular models. CaMKII inhibition can suppress afterdepolarizations[29,30,39] and arrhythmias[31] without AP or QT interval shortening, suggesting that CaMKII contributes to a critical proarrhythmic connection between AP prolongation and afterdepolarizations. EADs and DADs are also implicated in arrhythmogenesis in heart failure, due to a proarrhythmic electrical remodeling process where K^+ current expression is reduced—leading to AP prolongation and increased activity and expression of CaMKII in failing myocardium.[42] CaMKII activity and/or expression are increased in failing myocardium from animal models and from patients.[43] Thus, emerging concepts suggest that afterdepolarizations and excessive CaMKII activity constitute a unified mechanism for arrhythmia triggering in genetic and structural forms of heart disease.[1,44,45] CaMKII may contribute to other competing concepts favoring afterdepolarizations, including RyR2 Ca^{2+} leak due to ROS[46] and hyperphosphorylation by protein kinase A.[47]

PROARRHYTHMIC SUBSTRATES

Cardiac arrhythmias are often initiated by afterdepolarizations, but sustained by a mechanism called reentry (Fig. 10). Reentry can occur over a large tissue domain (e.g. typical atrial flutter, bundle branch reentry ventricular tachycardia, the atrioventricular reciprocating tachycardia), or in a small volume of tissue (e.g. atrioventricular nodal tachycardia, fasicular ventricular tachycardia). Processes that lead to myocardial scar formation, such as myocardial infarction, can favor reentry by producing regions of slowed conduction.[4] Reentry can be supported by an anatomically defined pathway involving scar, specialized conduction tissue, or both. However, functional reentry can occur in structurally normal tissue due to exaggerated electrical inhomogeneities of activation[48,49] or repolarization. Physiological electrical heterogeneity is exaggerated by proarrhythmic drugs, and in animal models of mycoardial hypertrophy.[50] Enhanced dispersion of repolarization is thought to support a voltage gradient that constitutes a functional

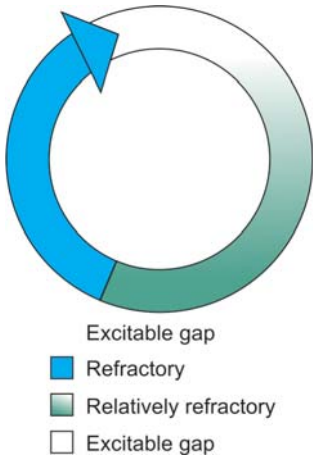


FIGURE 10: A simplified reentrant circuit with core components indicated by color coding

reentrant circuit. Reduced I_{Na}, as occurs in the Brugada Syndrome, can also induce a functional reentrant circuit by unmasking enhanced transient outward K^+ current in AP phase 1.[51] In cases of structural heart disease where scar and fibrosis contribute to anatomical reentrant pathways, the exaggeration of heterogeneity of repolarization may also contribute to creation of a sustainable arrhythmia circuit. It is likely that failing human hearts exhibit focal and reentrant arrhythmias,[52,53] with the caveat that an apparent arrhythmia focus could be a 'microreentrant' circuit. Programmed electrical stimulation (discussed in another chapter) can be used to distinguish between reentry and focal arrhythmia mechanisms.

PROARRHYTHMIC TRIGGERS AND SUBSTRATES ARE PROMOTED IN FAILING HEARTS

Although afterdepolarizations and reentry are distinct entities, there is a growing appreciation that common biological factors can promote development of proarrhythmic triggers and substrates in heart failure. CaMKII has emerged as a signal that drives structural and electrical components of myocardial injury, providing a molecular rationale to explain why failing hearts are prone to arrhythmias. While it is likely that many signaling

molecules participate in promoting afterdepolarizations and proarrhythmic tissue substrates, this concept is best developed for CaMKII. Failing myocardium is consistently marked by AP prolongation, loss of normal intracellular Ca^{2+} homeostasis, increased ROS and increased expression of CaMKII. These factors favor EADs because the prolonged AP plateau occurs over a membrane potential window permissive for $Ca_V1.2$ opening.[54,55,56] CaMKII is activated by Ca^{2+} bound calmodulin and by ROS,[57] and CaMKII mediated phosphorylation leads to high $Ca_V1.2$ activity (so-called mode 2 gating)[28] and afterdepolarizations.[29,31,58] CaMKII actions at a specific site on a $Ca_V1.2$ β subunit (Thr 498)[27] lead to increased cellular Ca^{2+} entry and increased SR Ca^{2+} filling.[29] CaMKII also phosphorylates RyR2 (at Ser 2814)[59] leading to increased RyR2 opening, SR Ca^{2+} leak and afterdepolarizations that promote ventricular arrhythmia in failing hearts.[41] A similar mechanism may also favor atrial fibrillation.[38] RyR2 Ca^{2+} leak can trigger inward Na^+/Ca^{2+} exchanger current[60] that promotes DADs and phase 3 EADs. CaMKII activity at key Ca^{2+} homeostatic proteins ($Ca_V1.2$ and RyR2) promotes loss of normal intracellular Ca^{2+} homeostasis, which may reduce the efficacy of CICR resulting in reduced mechanical performance.[61]

After myocardial infarction the borderzone tissue between non-living scar and normal myocytes serves as a substrate for reentry. Surviving borderzone tissue undergoes electrical remodeling marked by reduced $Na_V1.5$ expression that is due, at least in part, to reduction in ion channel-targeting ankyrin G expression. [21] Loss of $Na_V1.5$ current contributes to conduction slowing. In addition, borderzone tissue is enriched in ROS and ROS activated CaMKII is increased in the MI borderzone,[62] where it may contribute to conduction slowing by effects, at least in part, on Na_V channels.[63] CaMKII activation contributes to scar formation by increasing myocardial death in response to ischemic injury.[64] The pro-survival effects of CaMKII inhibition are likely multifactorial, and have been mapped to $Ca_V1.2$,[29,65] SR Ca^{2+},[64] and mitochondria.[65,66] CaMKII activation after MI results in activation of inflammatory signaling by increased nuclear factor for κB (NF-κB) transcription.[67] Thus, understanding CaMKII signaling provides insight into how a properly positioned nodal signal can produce the twin phenotypes of heart failure and arrhythmias. CaMKII resides at an intersection of the β adrenergic receptor and angiotensin II signaling pathways,[57] both of which are extensively therapeutically validated to improve heart failure symptoms and reduce sudden death after MI. Improved understanding of cellular signaling important for arrhythmias has the potential to lead to more effective and novel non-invasive antiarrhythmic treatments.

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Chapter 30

Antiarrhythmic Drugs

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Chapter Outline

- Arrhythmia Mechanisms and Antiarrhythmic Drugs
- Indications for Antiarrhythmic Drug Therapy
- Proarrhythmia
- Classification Scheme
- Vaughan-Williams Classification
  - — Class I Antiarrhythmic Drugs: Sodium Channel Blockers
  - — Class II Antiarrhythmic Drugs: Beta-Adrenoceptor Blockers
  - — Class III Antiarrhythmic Drugs: Drugs that Prolong Repolarization
  - — Class IV Antiarrhythmic Drugs: Calcium Channel Antagonists
- Miscellaneous Drugs
  - — Adenosine
- Newer Drugs
  - — Tedisamil
  - — Vernakalant
  - — Ivabradine
  - — Ranolazine
- Emerging Antiarrhythmic Drugs
- Antiarrhythmic Drug Selection in Atrial Fibrillation
- Out-patient versus in-Hospital Initiation for Antiarrhythmic Drug Therapy
- Antiarrhythmic Drugs in Pregnancy and Lactation
- Comparing Antiarrhythmic Drugs to Implantable Cardioverter Defibrillators in Patients at Risk of Arrhythmic Death
- Antiarrhythmic Drug-device Interactions

INTRODUCTION

Antiarrhythmic drugs (AADs) were developed to suppress cardiac arrhythmias, and therefore improve survival, symptoms and morbidity. Much of the original data were based on studies performed on cellular preparations and in vivo animal models. Despite a surfeit of supporting data demonstrating that AADs can have potent impact on various cardiac ion channels and receptors to affect arrhythmias, the lofty goal of improving survival and outcomes in patients with cardiovascular disease and arrhythmias have been less than anticipated based on results from large long-term randomized controlled clinical trials.

The AAD therapy has undergone constant evolution as new therapies have emerged and the risk benefit profile of these drugs on major clinical endpoints is better understood. The AAD therapy continues to have a critical role in the management of patients with cardiac arrhythmias, but its place is now better appreciated and understood in light of other advancements including radiofrequency catheter ablation and implantable devices. The role has transformed, as it is now realized that AADs are often not perfectly effective under all circumstances and there is risk for proarrhythmia. Many older AADs, considered the staple of arrhythmia management for years, have begun to disappear with the emergence of several purportedly safer and potentially more effective therapies.

The history of AAD therapy can be best described as a somewhat sobering transition from “panacea” to “Pandora’s box”. Currently, AADs, for the most part, are used as an adjunct to therapies that target and cure the rhythm like catheter ablation or those directed against the underlying structural heart disease. This role reversal has resulted from superior efficacy of newer therapies, as well as concerns over the safety and effectiveness of AADs.

Perhaps the biggest concern, notwithstanding mediocre efficacy, is the proarrhythmic, as well as systemic, side effects of AADs. Proarrhythmia may have contributed to the lack of benefit from AADs on hard clinical endpoints. The AADs are among the most complex to prescribe and monitor. Now, with a better understanding of the risks and benefits, AADs are used in a much more regulated and rigorous fashion. Several drugs disappearing from the scenery include quinidine, procainamide, phenytoin, tocainide and bretylium. Others (mexiletine and disopyramide) are used infrequently. Now, there is a better understanding of the proarrhythmic and toxic effects of these AADs. Even though guidelines are developed for their use, AADs is still often used indiscriminately without careful observation for adverse effects. AADs are available, being used and being developed. Proper and effective AAD therapy continues to play an important role to treat symptomatic and potentially life-threatening arrhythmias. The drugs are used to treat a wide variety of sustained and nonsustained atrial and ventricular tachyarrhythmias, as well as atrial and ventricular ectopy. As these drugs play an important role to treat a wide variety of arrhythmias, clinicians who use these drugs must be

familiar with their indications, pharmacology, mechanisms of action, dosing, adverse effects, proarrhythmic effects and interactions with other drugs.

This chapter describes the classification schema, as well as clinical pharmacology, adverse effects and interactions of individual drugs. We will also focus on the clinical applicability of the individual agents based on available clinical data. A small section at the end of the chapter focuses on emerging and investigational AADs.

ARRHYTHMIA MECHANISMS AND ANTIARRHYTHMIC DRUGS

Cardiac tachyarrhythmias are due to several well understood mechanisms including various forms of reentry, triggered activity and automaticity. The AADs can affect cardiac ionic channels and receptors to affect properties that alter the chance of initiation, perpetuation and termination of tachyarrhythmias. The AADs can affect cardiac excitability, conduction and refractoriness. The AADs, depending on the type, can block the sodium channel and, therefore, slow down conduction in the myocardium by reducing the electrical gradient of cellular activation (Vmax, rate of rise of phase 0 of the action potential) to reduce the presence of reentrant ventricular and supraventricular arrhythmias. The AADs can also suppress spontaneous depolarization of cells leading to decreased automaticity. Many of the AADs are specific for certain cardiac tissue such as atrial, AV nodal or ventricular myocardium. Some AADs affect myocardial repolarization by affecting several potassium channels. Other AADs block calcium channels to affect other forms of reentry triggered activity, as well as automaticity dependent on the tissue and the mechanism of the arrhythmia. Some newer AADs also can affect cell-to-cell communications or work by other novel mechanisms.

INDICATIONS FOR ANTIARRHYTHMIC DRUG THERAPY

The AADs are now mainly used to treat atrial tachyarrhythmias, particularly atrial fibrillation (AF).[1] While mortality outcome with regard to rhythm control with an AAD is not superior to rate control,[2] symptom reduction and improvement in quality of life can be superior in select patients who have AF and atrial flutter. The AADs are used to treat other supraventricular tachyarrhythmias including AV node reentry, sinoatrial reentry, AV reentry tachycardia and atrial tachycardias. Occasionally, AADs are used to suppress ventricular and atrial ectopy including nonsustained and even sustained ventricular tachycardia (VT) but their use is balanced by potential adverse effects. The AADs can be used as primary therapy for patients with idiopathic VT but for patients with underlying structural heart disease and VT, AADs are not generally recommended as primary therapy unless there are specific reasons to do so in lieu of ablation therapy and/or implantable devices. The reason for this is that the proarrhythmic effects of the drugs can exceed the benefits.

PROARRHYTHMIA

The AADs suppress, and otherwise treat, arrhythmias but they can also create new ones. In some instances, this is simply an increase in the amount of atrial or ventricular ectopy but in the worst case scenario, it can lead to ventricular fibrillation and sudden cardiac death. The proarrhythmic effects of the AADs are drug and patient specific but include the following potentially important problems:

- Sinus bradycardia
- Atrioventricular block
- Increased ventricular or atrial ectopy
- VT (monomorphic and polymorphic), including torsades de pointes related to QT interval prolongation (Fig. 1)
- Ventricular fibrillation
- Slowing of atrial tachyarrhythmias allowing one-to-one AV conduction when this was not present before the drug.

In some instances, based on the drug and the patient, a proarrhythmic response can be identified or predicted. For some drugs, starting the drug in the hospital to observe for developing proarrhythmia or the presence of QT interval prolongation that could predict proarrhythmia is effective. In other instances, this is not helpful, and only long-term monitoring can determine proarrhythmia. In some instances, it is difficult to determine if a cardiac arrest on a drug is due to drug proarrhythmia or due to lack of efficacy.

CLASSIFICATION SCHEME

The Vaughan-Williams classification, the most commonly used and by far the most clinically relevant, classifies the drugs based on their most prominent electrophysiological action[3] (Table 1). The more complex "Sicilian Gambit" scheme classifies AADs based on their cellular mechanism of action and is mostly utilized for research purposes and drug development[4] (Fig. 2). While the Sicilian Gambit held up hope for defining the potential mechanisms of AADs better, its role has all but disappeared. There are problems with both classifications. In fact, our understanding of the mechanisms of action of AADs is at best questionable, as much of the data are from animal models and isolated muscle preparations rather than from clinical assessment. Drugs can have a multiplicity of effects by themselves and by their active metabolites that do not fit neatly into one specific classification scheme.

VAUGHAN-WILLIAMS CLASSIFICATION

Class I: Sodium channel blockers:

Class IA, e.g. quinidine, procainamide, disopyramide

Class IB, e.g. lidocaine, mexiletine, phenytoin

Class IC, e.g. flecainide, propafenone

Class II: Sympathetic antagonists—beta-blockers

Class III: Prolong repolarization, e.g. sotalol, amiodarone, dofetilide, ibutilide, dronedarone, azimilide

Class IV: Calcium channel antagonists

The dosing, common uses and adverse effects of the orally available AADs are shown in Table 2. Table 3 describes the major drug interactions of AADs.

CLASS I ANTIARRHYTHMIC DRUGS: SODIUM CHANNEL BLOCKERS

The class I antiarrhythmic drugs primarily act by slowing conductance of sodium (Na^+) across the cell membrane. These



FIGURE 1: An example of sotalol-induced QTc prolongation resulting in torsades de pointes. This patient had a recent increase in his diuretic dosage and was hypokalemic at the time of presentation

TABLE 1

The Vaughan-Williams classification of antiarrhythmic drugs

Class	*Drug*	*Ion channel effect*	*Electrophysiological effect*
I		Block inward Na^+ channel and outward K^+ channels	
IA	Quinidine Procainamide Disopyramide		Slow conduction velocity (predominant effect) and increase refractoriness
IB	Lidocaine Mexiletine		Shorten APD, especially in depolarized cells
IC	Flecainide Propafenone		Marked conduction slowing (minimal effect on refractoriness)
II	Beta-blockers	Beta-adrenoceptor blockade	Sympatholytic effect
III	Sotalol	Block Ikr and beta-receptors	Prolong refractoriness and APD
	Amiodarone	Blocks multiple potassium channels, Na^+ channels, Ca^{++} channels, beta-receptors	Prolong refractoriness and APD
	Dronedarone	Blocks multiple potassium channels, Na^+ channels, Ca^{++} channels, beta-receptors	Prolong refractoriness and APD
	Ibutilide	Blocks Ikr and late Na^+ current	Prolong refractoriness and APD
	Dofetilide	Blocks Ikr	Prolong refractoriness and APD
	Azimilide	Blocks Ikr and Iks	Prolong refractoriness and APD
IV	Calcium channel blockers	Blocks Ca^{++} channels	Negative chronotropic and inotropic effects

(Abbreviations: APD: Action potential duration; IKr: Rapid rectifier current; IKs: Delayed rectifier current)

drugs, therefore, interfere with the depolarization phase of the cardiac action potential ("phase 0") and also decrease responsiveness to excitation (reduction in $\dot{V}_{max}$). The magnitude of Na^+ channel blockade is determined by specific cardiac tissue, specific drug properties, heart rate, autonomic (parasympathetic and sympathetic) activation, ischemic state and the state of depolarization, among others.

Based on the mechanisms by which these drugs act to block the sodium channel, as well as their effects on other channels, can alter refractoriness. Class I drugs are further classified into IA (quinidine, procainamide and disopyramide), IB (mexiletine, lidocaine), and IC (flecainide, propafenone).[5] Depending on the type, class I drugs can block sodium channels (class IC drugs) or alter the ability of the sodium channel to conduct; the effect on the channel can be short or prolonged.

Sodium channels normally transition through three distinct conformational states during the action potential: (1) open, (2) closed and (3) inactivated.[6] Only open channels conduct sodium current. Sodium channel blockers interact with open, as well as inactivated channel states, but not usually with closed channels. Thus, sodium channel blockade depends on the conformational state of the channel and blockade is phasic. The extent of sodium channel block can be increased by reducing the recovery rate of the sodium channel. This can happen in disease states, such as ischemia, or can be the property of a particular drug. For example, the class IC drugs, which unbind "very slowly" from sodium channels, are the most potent sodium channel blockers. Class I AADs exhibit use dependence. Tachycardia increases the number of sodium channels in the open and inactivated states. Since sodium channel blockers have greater affinity for the open and inactivated channels, when compared to closed

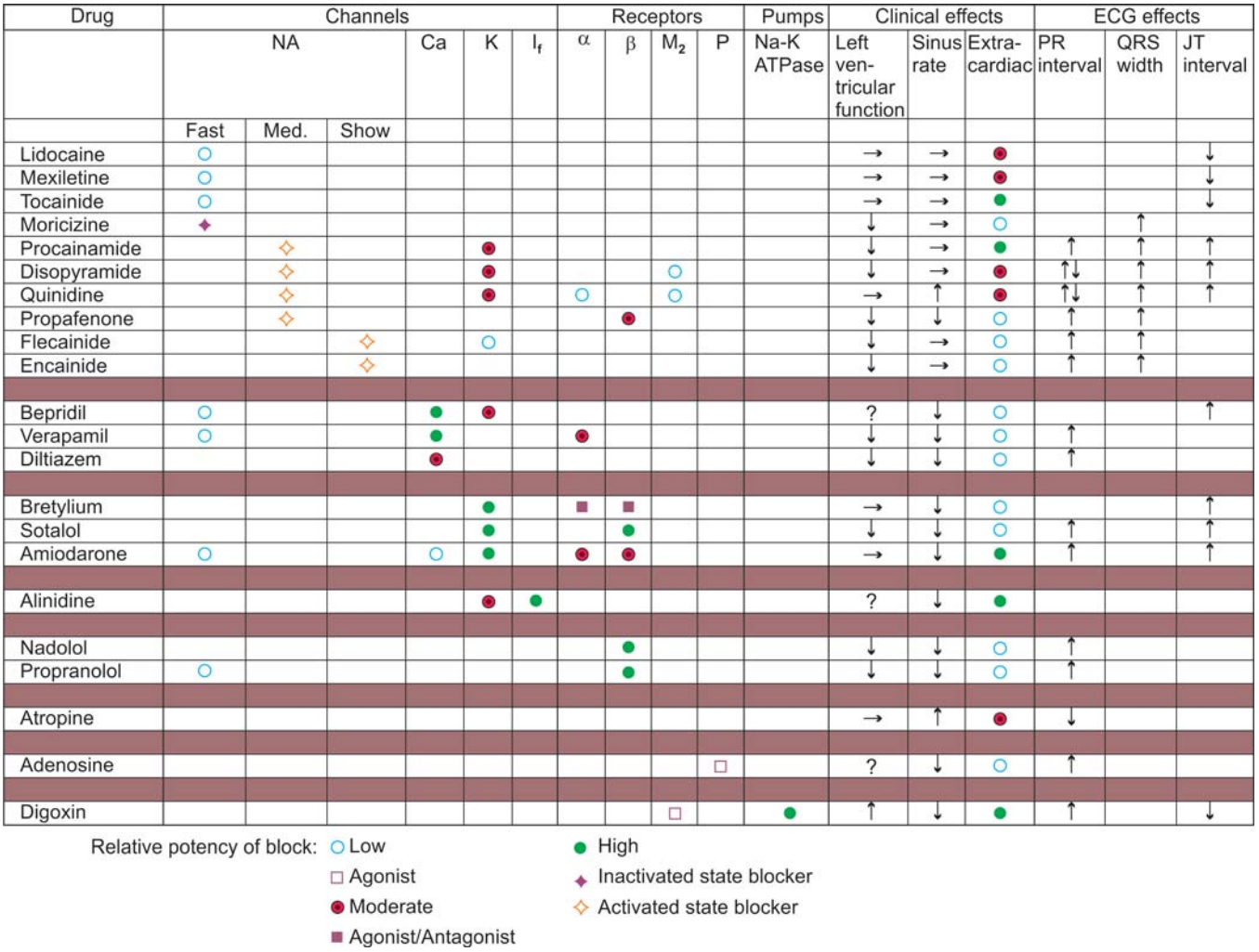


FIGURE 2: The Sicilian Gambit scheme for classifying antiarrhythmic drugs. [*Source:* Task Force of the Working Group on Arrhythmias of the European Society of Cardiology. Circulation. 1991;84:1831-51 (Reference 4)]

channels, the extent of sodium channel blockade and consequently, conduction slowing, is greater during faster heart rates. This phenomenon is called use dependence.

Class IA drugs (quinidine, procainamide, disopyramide) slow conduction in atrial and ventricular myocardium and have a moderate effect on slowing myocardial conduction by moderate effect on phase 0 ($\dot{V}_{max}$) but they also have other effects. These drugs prolong repolarization by their effects on potassium channels. Disopyramide, in particular, can have an anticholinergic effect. Additionally, these drugs have vasodilatory (intravenous procainamide and quinidine), negative inotropic (disopyramide) and vagolytic (quinidine and disopyramide effects).

Quinidine, disopyramide and procainamide have active metabolites (3-hydroxyquinidine, mono-N-dealkylated disopyramide and N-acetylprocainamide respectively). These drug and metabolites can be toxic by several mechanisms. In particular, they are known to prolong action potential duration in the ventricle causing QT prolongation and torsades de pointes. These drugs can have multiple adverse side effects including negative inotropic effects (disopyramide), anticholinergic effects (disopyramide), hypotensive effects (intravenous procainamide and quinidine), autoimmune effects (procainamide in particular), agranulocytosis (disopyramide and procainamide), thrombocytopenia (quinidine) and neurological side effects with nightmares (procainamide).

Due to a wide range of side effects that cause serious problems and require termination of the drug, these drugs are used rarely as the toxicity limits their utility. Furthermore, they are not necessarily the most effective AADs to suppress atrial or ventricular arrhythmias. Due to their toxicity, they have not been well tested in controlled clinical trials, but meta-analyses[7] and other observational data would suggest that their use is limited for both atrial and ventricular arrhythmias and, therefore, these drugs have become phased out for routine use in patients. Nevertheless, there may still be a role for the use of disopyramide in particular to treat some forms of AF, particularly those suspected to be due to vagal activation.

Class IA Antiarrhythmic Drugs

Quinidine: Quinidine not only blocks the rapid sodium current but also affects rapid (IKr) and slow (IKs) components of the delayed-rectifier potassium current, the inward-rectifier potassium current (IKI), the ATP-sensitive potassium channel (IKATP) and transient outward current (Ito). With regard to Ito, the effect is different from the other class IA AADs.

TABLE 2

Dosing, uses and side effects of orally available antiarrhythmic drugs

Class	*Drug*	*Maintenance oral dosing*	*Side effects*	*Uses*
IA	Quinidine	300–600 mg every 6 hours	• Nausea, vomiting, diarrhea, anorexia, abdominal pain • Tinnitus, hearing loss, visual disturbance, confusion (cinchonism) • Thrombocytopenia, hemolytic anemia, anaphylaxis • Hypotension, QRS prolongation, syncope, torsades de pointes, QT prolongation	• PVCs • Sustained VT and VF • Short QT syndrome • Brugada syndrome • AF • Atrial flutter
	Procainamide	250–1,000 mg every 4–6 hours (no longer available)	• Rash, myalgia, vasculitis, Raynaud • Fever, agranulocytosis • Hypotension, bradycardia, QT prolongation, torsades de pointes • Drug-induced lupus	• Sustained VT • Unmasking Brugada syndrome • AF in WPW
	Disopyramide	100–200 mg every 6 hours	• Urinary retention, constipation, glaucoma, xerostomia • QT prolongation, torsades de pointes • Reduced ventricular contractility	• PVCs • VT • Hypertrophic CMP • AF
IB	Mexiletine	200–300 mg every 8 hours	• Tremor, dysarthria, dizziness, diplopia, nystagmus, anxiety • Nausea, vomiting, dyspepsia • Hypotension, bradycardia	• VT and VF • Reduction of ICD shocks
IC	Flecainide	100–200 mg two times daily	• Negative inotropy, AV block, bradycardia • Decreases pacing threshold • Confusion, irritability	• Paroxysmal AF • SVTs • VT • PVCs unmasking Brugada syndrome
	Propafenone	150–300 mg every 8 hours	• Dizziness, blurred vision • Bronchospasm • AV block, bradycardia, heart failure exacerbation • Decreases pacing threshold	• Paroxysmal AF • SVTs • VT • PVCs
II	Beta-blocker	Beta-blocker specific	• Hypotension, bradycardia, heart block, heart failure exacerbation • Bronchospasm • Depression • Impairment of sexual function	• Atrial arrhythmias • Rate control in AF • SVTs • PVCs • VT • VF
III	Amiodarone	1,200–1,800 mg daily for the first 7–10 days, then taper gradually to 200–400 mg daily	• Pulmonary fibrosis • Abnormal liver function tests • Hyperthyroidism or hypothyroidism • Bradycardia, heart failure exacerbation • Tremor, paresthesia • Photosensitivity • Corneal deposits	• VT • VF • Reduction of ICD shocks • AF • Atrial flutter • AF in WPW • Other SVTs
	Sotalol	80–160 mg every 12 hours	• Bradycardia, torsades de pointes	• Sustained VT/VF • VT in ARVD • Reduction of ICD shocks • AF • Atrial flutter
	Dofetilide	250–500 mcg twice daily	• Torsade de pointes	• AF
	Dronedarone	400 mg twice daily	• Gastrointestinal side effects	• To reduce the risk of cardiovascular hospitalization in patients with non-permanent AF and associated cardiac risk factors • Rhythm control in AF
IV	Calcium channel blocker (Verapamil)	80–160 mg every 8 hours	• Hypotension, bradycardia, AV block	• Idiopathic VT • PVCs • Rate control in AF • SVTs

(Abbreviations: AF: Atrial fibrillation; CMP: Cardiomyopathy; ICD: Implantable cardioverter defibrillator; PVCs: Premature ventricular contractions; SVTs: Supraventricular tachycardias; VF: Ventricular fibrillation; VT: Ventricular tachycardia; WPW: Wolff-Parkinson-White syndrome)

TABLE 3

Major drug interactions of antiarrhythmic drugs

Drug	*Interacting drug*	*Interaction*
Quinidine	Phenytoin	↓ Quinidine levels
	Phenobarbital	↓ Quinidine levels
	Rifampin	↓ Quinidine levels
	Ketoconazole	↑ Quinidine levels
	Verapamil	↑ Quinidine levels
	Propafenone	↑ Propafenone level
	Beta-blockers	↑ Beta-blockade
	Digoxin	↑ Digoxin concentration
Mexiletine	Phenytoin	↓ Mexiletine levels
	Phenobarbital	↓ Mexiletine levels
	Rifampin	↓ Mexiletine levels
	Ketoconazole	↑ Mexiletine levels
	Isoniazid	↑ Mexiletine levels
	Theophylline	↑ Theophylline levels
Flecainide	Digoxin	↑ Digoxin levels
	Amiodarone	↑ Flecainide levels
	Quinidine	↑ Flecainide levels
Propafenone	Digoxin	↑ Digoxin levels
	Warfarin	↓ Warfarin clearance
	Cyclosporine	↑ Cyclosporine levels
	Quinidine	↑ Propafenone levels
Amiodarone	Digoxin	↑ Digoxin effect
	Warfarin	↑ Warfarin effect
	QT prolonging drugs	↑ Risk of torsades de pointes
	Beta-blockers	Bradycardia and AV block
	Diltiazem and Verapamil	Hypotension and Bradycardia ↑ cyclosporine concentration
	Anesthetic drugs	
	Cyclosporine	
Sotalol	QT prolonging drugs	↑ Risk of torsades de pointes
Dofetilide	QT prolonging drugs	
Dronedarone		
Beta-blockers	Quinidine	↑ Beta-blockade
	Amiodarone, Digoxin,	Bradycardia
	Diltiazem, Verapamil	
Calcium channel blockers (Verapamil)	Digoxin	↑ Digoxin levels

The Ito blockade is purported to reduce the disparity of repolarization in the right ventricular outflow tract and thereby attenuate anterior precordial ST-segment elevation in the Brugada syndrome. Quinidine has been shown to reduce inducibility of ventricular arrhythmias, as well as suppress electrical storm in small studies of Brugada syndrome patients.[8,9] Thus, quinidine has been proposed as an adjunct, but not an alternative, to implantable cardioverter defibrillator (ICD) therapy in high-risk patients with Brugada syndrome.[10] Otherwise, quinidine is rarely used due to its proarrhythmic effects and its adverse effects.

Diarrhea is common; thrombocytopenia can occur or tinnitus is possible. Quinidine can cause idiosyncratic QT prolongation and torsades de pointes. There is a potential interaction between digoxin and quinidine such that quinidine will increase and even double the digoxin levels. The dose of quinidine is generally 200–400 mg every six hours but can be used in a long-acting preparation that is difficult to obtain.

Procainamide: Similar to quinidine, the adverse effects, as well as the proarrhythmic effects, outweigh the potential benefits in many cases and therefore, this drug is rarely used. It is hardly available other than in the intravenous form. Nausea, lupus-like syndrome (positive antinuclear antibodies with antihistone antibodies) and agranulocytosis, along with proarrhythmia, are some of the reasons for not using this drug. Intravenous procainamide is very useful in the acute management of supraventricular tachycardias, in particular, rapidly conducted AF and atrial flutter in patients with Wolff-Parkinson-White syndrome. Procainamide can help to facilitate pace termination of atrial arrhythmias.[11] Procainamide can cause torsades de pointes mainly due to its active class III metabolite, N-acetylprocainamide.[12]

Disopyramide: Disopyramide is still available but used rarely. The primary use of disopyramide is in patients with hypertrophic cardiomyopathy and left ventricular outflow tract obstruction, and to treat AF. A multi-center study showed that disopyramide can be an effective therapy in symptomatic hypertrophic obstructive cardiomyopathy, with 66% of patients remaining asymptomatic at 3 years with a 50% reduction in outflow gradient. Although disopyramide did not show any mortality benefit in hypertrophic cardiomyopathy, it should nevertheless be considered before invasive options such as surgical myectomy.[13]

Long-term use of disopyramide, however, is limited due to its severe anticholinergic effects, including constipation and dry mouth, as well as urinary retention (as it is about 10% as potent as atropine) and cannot be used in patients with a history of ventricular dysfunction, congestive heart failure or for men with enlarged prostate. Disopyramide is usually used in a long-acting preparation. The dosing is between 400 mg and 600 mg a day in divided doses. Disopyramide can have a marked negative inotropic effect in patients with heart failure and is contraindicated under such circumstances. It can lengthen QT interval and cause torsades de pointes.

Class IB Antiarrhythmic Drugs

Lidocaine and mexiletine are the only currently available and utilized class IB drugs. As a group, class IB drugs block sodium channels in both activated and inactivated states, but do not delay channel recovery. They affect conduction in ventricular myocardium and have little, if any, effect on atrial myocardium or on AV conduction. This results in shortening of action potential duration and refractoriness. Lidocaine may affect ischemic myocardium preferentially. Their efficacy is increased at high heart rates and also in depolarized tissues, which makes them effective in treatment of ventricular arrhythmias in the ischemic myocardium.

Lidocaine: Lidocaine is useful to treat patients who have had recurrent VT or ventricular fibrillation.[14] It does not appear to be effective or beneficial as a prophylactic drug for patients

who have had myocardial infarction.[15-17] It has negligible effects on atrial electrophysiology. Lidocaine can suppress conduction, preferentially in ischemic myocardium and does not prolong the QT interval. The purported effect is to prevent reentrant arrhythmias, but it can also suppress automatic and escape rhythms.

Lidocaine dosing can be complex. It undergoes extensive first-pass metabolism in the liver and so can only be administered parenterally. Given rapid initial distribution (half-life of 8 minutes), lidocaine should be administered with multiple loading doses, followed by a maintenance infusion to maintain levels in therapeutic range. The drug has two active metabolites, monoethylglycinexylidide and glycinexylidide. Up to 70% of the drug is protein bound and this number increases in the acute phase of a myocardial infarction when alpha-1-acid glycoprotein increases (as such, over long time periods, lidocaine levels can increase despite a relatively short half-life). In congestive heart failure, where the volume of distribution is reduced, lidocaine achieves higher than normal initial concentration and so the initial dose should be reduced to avoid toxicity. Lidocaine is actively bound to alpha-1-acid glycoprotein, whose levels are increased in heart failure, and perhaps after myocardial infarction thereby decreasing drug availability.

Lidocaine has an elimination half-life of about 2 hours and steady state is reached in 4–5 half lives. Steady state concentration for lidocaine is determined by liver blood flow[18] and is reduced in both heart failure and liver disease. Thus, maintenance dosage of lidocaine should be reduced in both conditions. Renal dysfunction has no impact on lidocaine metabolism.

Lidocaine is most commonly used for acute suppression of potentially life-threatening ventricular arrhythmias (although little data support its role as a drug that improves survival). Lidocaine administration in this setting is based more on anecdotal experience than real data. Lidocaine is frequently ineffective, has a narrow therapeutic range and is frequently associated with neurological toxicity. There are no randomized controlled trials demonstrating benefits of lidocaine. Lidocaine has little effect on atrial tissue and has no value in treating supraventricular tachycardias. The effect of lidocaine in treating arrhythmias in Wolff-Parkinson-White syndrome is controversial[19] and other drugs, including procainamide, ibutilide or amiodarone, are preferred.

Lidocaine is usually administered as a loading dose followed by a maintenance infusion. A commonly used loading regimen is one suggested by Wyman et al., where an initial bolus of 75 mg is given, followed by 50 mg given every 5 minutes repeated three times, for a total loading dose of 225 mg.[20] This regimen usually achieves and maintains plasma concentrations in the therapeutic range of 1.5–5 mcg/ml. This is followed by a maintenance infusion at 1–4 mg/min. It should be noted that wide inter-individual variability in peak plasma concentration exists and, therefore, patients should be closely monitored for evidence of toxicity during loading. Lidocaine has little therapeutic effect at plasma concentrations below 1.5 mcg/ml, and the risk of toxicity increases above 5 mcg/ml.

Symptoms of central nervous system are the most frequent side effects associated with lidocaine administration. Symptoms include paresthesias, perioral numbness, drowsiness, diplopia, dysarthria, confusion and hallucinations. Nystagmus can be an early sign of neurological toxicity. Toxic levels can result in seizures and coma. In patients with known infranodal conduction abnormalities, lidocaine may worsen conduction and should be administered cautiously. Metoprolol, propranolol and cimetidine can reduce hepatic blood flow, decrease lidocaine clearance and can potentially result in lidocaine toxicity when administered concomitantly.[21,22]

Mexiletine: Mexiletine is an orally active congener of lidocaine. Mexiletine, like lidocaine, does not suppress AV conduction and has little effect on hemodynamics and ventricular function.[23] Like lidocaine, mexiletine has little effect on atrial electrophysiology. Mexiletine is almost completely absorbed orally, is primarily metabolized (90%) in the liver by the CYP2D6 system to inactive metabolites and is excreted in urine. Mexiletine has a plasma half-life of 9–12 hours. Intravenous mexiletine is not available in the United States.

Mexiletine is primarily used to suppress ventricular arrhythmias and ICD shocks in patients with structural heart disease, either as monotherapy or in combination with another AAD, such as amiodarone or, in years past, quinidine. Effectiveness of mexiletine in this setting varies widely and ranges from 6% to 60%, with majority of studies suggesting a success rate around 20%[24] depending on the condition and the type of ventricular arrhythmia being suppressed. It alone does not improve survival in a controlled trial of high-risk patients.[25] Mexiletine does not prolong and may even shorten the QT interval and can therefore be useful to suppress arrhythmias for patients with the congenital long QT syndrome type III and those with history of drug-induced torsades de pointes.[26]

Mexiletine is usually initiated at a dose of 150 mg every 8 hours. The dose can be increased at 2–3 day intervals until arrhythmia suppression or intolerable side effects develop. Suggested maximum maintenance dose is 300 mg every 6–8 hours. Patients with renal failure should be initiated at a lower dose. Dosage adjustment is also advised in patients with hepatic failure and congestive heart failure, as they impair liver blood flow and prolong elimination half-life of mexiletine.

The most common adverse events with mexiletine are gastrointestinal and neurologic. Tremor, nausea and vomiting are common; dizziness, confusion, blurred vision and ataxia are also seen. Mexiletine-induced tremor may respond to beta-blockers. Thrombocytopenia occurs infrequently.[27] Neurologic side effects are dose-dependent. Severe bradycardia and abnormal sinus node recovery times, with mexiletine have been reported in patients with otherwise or symptomatic sinus node dysfunction.

The major drug interactions of mexiletine are listed in Table 3. Inducers and inhibitors of the CYP2D6 system can influence mexiletine metabolism and can affect effectiveness and/or toxicity. Mexiletine decreases theophylline clearance and increases plasma theophylline concentrations.[28] Digoxin and warfarin levels are unaffected by mexiletine.

Class IC Antiarrhythmic Drugs

The currently available class IC drugs, flecainide and propafenone, are potent sodium channel blockers and cause marked conduction slowing in cardiac tissues without exerting any effects on refractoriness. Their sodium channel blocking effects are exaggerated at high heart rates (use dependency) and

in depolarized tissues. At therapeutic doses, class IC drugs prolong the PR and QRS intervals without having significant effects on the QTc interval. Class IC drugs also exert negative inotropic effects and can worsen heart failure in patients with left ventricular dysfunction. The use of these drugs is not recommended in patients who have ventricular dysfunction, who have marked left ventricular hypertrophy or who have ischemic heart disease.[29]

Flecainide: Oral flecainide is 90–95% bioavailable and is predominantly metabolized in the liver by CYP2D6 to inactive metabolites. Flecainide is also eliminated to some extent by the kidneys and because of this, genetic variations in CYP2D6 does not seem to significantly affect pharmacological actions of flecainide. Flecainide is eliminated slowly with a half-life of 16–20 hours.

Flecainide is highly effective in suppressing a variety of ventricular and supraventricular tachycardias.[30] It is one of the most potent drugs to suppress ventricular ectopy.[29] At the present time, flecainide is commonly used for restoration and maintenance of sinus rhythm in patients with paroxysmal AF and no structural heart disease. It can be used for maintenance therapy or as a "pill-in-the-pocket" drug for AF termination.[31,32] Flecainide is also effective for suppression of idiopathic ventricular arrhythmias of right and left ventricular outflow tract origin,[33] as well as to treat supraventricular tachycardias in patients with Wolff-Parkinson-White syndrome.

Recently, flecainide has been found to be effective in suppression of catecholaminergic polymorphic VT, which is an inherited, potentially lethal arrhythmic syndrome resulting from mutations in the ryanodine and calsequestrin receptors, causing abnormal calcium handling. Flecainide was found to completely suppress adrenergically mediated polymorphic VT in a mouse model of catecholaminergic polymorphic VT, as well as in two patients with drug-refractory catecholaminergic polymorphic VT. Flecainide was shown in the mouse model to have direct inhibitory effect on the defective ryanodine receptor-mediated calcium release.[34] Flecainide may also be beneficial for patients with long QT interval syndrome type III with a specific SCN5A (D1790G) mutation.[35]

Based on results of the Cardiac Arrhythmia Suppression Trial I (CAST I), although flecainide suppressed premature ventricular contractions (PVCs) in post-myocardial infarction patients, it increased mortality compared with placebo. The same was true of another now obsolete class IC AAD—encainide.[29] Additionally, moricizine, another class I AAD, was shown to have an early proarrhythmic effect during the loading phase in the CAST II trial, even though it did not have any long-term adverse effects compared with placebo.[36] Based on these and other similar data, class IC drugs are contraindicated in patients with advanced structural heart disease and those at risk to develop myocardial ischemia.

Oral flecainide is usually initiated at a dose of 50–100 mg twice daily and can be titrated to a maximum recommended dose of 300 mg daily. At efficacious doses, QRS widening of up to 25% is seen and this is usually evaluated by exercise treadmill testing at high heart rates.[37] A one-time dose of 300 mg or 600 mg flecainide is used when employed as a "pill-in-the-pocket" dosing.[38] To reduce the incidence of adverse effects, flecainide therapy should start with a low dosage that is maintained until steady state has been reached (at least 4 days) and altered relative to clinical response. Flecainide levels can be measured. There is little issue with regard to active metabolites. Caution should be exercised with initial dosing and up titration in patients with hepatic and renal dysfunction. Major drug interactions with flecainide are shown in Table 3.

Most common adverse effects of flecainide are dose-dependent and include headache, ataxia, and blurred vision. Flecainide can cause AF to convert to atrial flutter and, in the absence of AV blocking drugs, can result in rapid 1:1 AV conduction (often with aberrant conduction). In patients with depressed ventricular function, negative inotropic effects can precipitate heart failure.[39] In patients with pacemakers and ICDs, flecainide should be used with caution as it can significantly increase pacing and defibrillation thresholds.[40,41] There is a risk of incessant monomorphic VT in patients who have VT, but this is now uncommon as the drug is rarely, if ever, used under these circumstances. Flecainide is also contraindicated in patients with suspected sodium channelopathies, like Brugada syndrome, as it can worsen this condition (indeed, it has been used to bring out the classic ECG abnormality). Additionally, caution is needed for patients with advanced His-Purkinje conduction system disease as infra-Hisian block can ensue. Caution about using this drug in patients with substantial left ventricular hypertrophy is recommended in the current ACC/AHA/HRS AF guidelines.[31]

Propafenone: Propafenone, in addition to being a potent sodium channel blocker, has beta-adrenergic blocking (about one-thirtieth of the potency of propranolol) and calcium-channel blocking properties. The drug is structurally similar to propranolol and can have significant beta-blocking properties in patients who are slow metabolizers of propafenone.[42]

Propafenone is metabolized through the hepatic CYP2D6 pathway into 5-hydroxy propafenone and this process is largely genetically determined. Approximately 7% of the US population is deficient in CYP2D6, resulting in very slow conversion of propafenone to the active metabolites, 5-hydroxypropafenone and N-depropylpropafenone. The consequent accumulation of high concentrations of propafenone leads to significant beta-adrenoceptor antagonism in poor metabolizers.[43,44] The genetic phenotype, while determining the degree of beta-blockade, does not seem to significantly affect the antiarrhythmic effects of propafenone in most patients.

Propafenone is used to help in maintaining sinus rhythm in patients with paroxysmal or persistent AF who have no associated structural heart disease. It is usually administered in doses ranging from 150 mg to 300 mg every 8–12 hours (a long-acting preparation is available). Peak plasma concentrations are achieved in 1–3 hours following an oral dose. Propafenone increases the PR and QRS intervals on the surface electrocardiogram, but it does not prolong the QT interval. Propafenone can result in acceleration of the ventricular rate in AF if it is converted to a slow atrial flutter. Therefore, administration of an AV nodal blocking drug along with propafenone is recommended. Like flecainide, propafenone is contraindicated in patients with prior myocardial infarction, known ischemic heart disease, severe ventricular hypertrophy and history of sustained VT or severe structural heart disease.[31]

The most common side effects of propafenone are nausea, dizziness and metallic taste. Neurological side effects, like paresthesias and blurred vision, are dose-dependent and are more common in poor metabolizers. Enhanced beta-blockade resulting from poor metabolism can result in bronchospasm and asthma exacerbations. Sustained VT, as a proarrhythmic effect of sodium channel blockade, has been reported and tends to occur in patients with history of VT and underlying structural heart disease.

Propafenone decreases warfarin clearance by inhibition of CYP2C9, resulting in an increased anticoagulant effect. Propafenone markedly increases digoxin levels by decreasing non-renal clearance of digoxin. Quinidine, cimetidine and antidepressants, like fluoxetine and paroxetine, can all inhibit CYP2D6; thereby increasing propafenone levels. Levels of metoprolol[45] and propranolol, which are also metabolized by CYP2D6, are increased in the presence of propafenone.

CLASS II ANTIARRHYTHMIC DRUGS: BETA-ADRENOCEPTOR BLOCKERS

Beta-adrenergic blocking drugs are one of the most efficacious drugs used in clinical cardiology for a variety of purposes, including treatment of congestive heart failure and myocardial ischemia. Beta-blockers also have AAD properties and can reduce the risk of sudden cardiac death by a number of mechanisms, can reduce ventricular tachyarrhythmias in select patients, can inhibit AF, can prevent paroxysmal supraventricular tachyarrhythmias of various types and can have additive effects to other AADs. Additionally, beta-blockers can slow AV nodal conduction in patients with rapid atrial tachyarrhythmias including AF and atrial flutter.[46]

Specifically, beta-blockers can prevent catecholamine induced or modulated arrhythmias[47] that occur in catecholaminergic polymorphic VT, idiopathic exercise-induced VT, right ventricular outflow tract tachycardia and ventricular tachyarrhythmias due to the long QT interval syndrome; in particular, those patients with long QT interval syndrome type 1.[26]

Beta-blockers work by a variety of mechanisms. They can suppress automaticity and the triggers for atrial tachycardias, AF and ventricular fibrillation. They can also interfere with the reentry circuit in patients with AV node reentry and with AV reentry tachycardia (by facilitating blockade in the AV node).[48] Beta-blockers may facilitate the effects of class I AADs since their efficacy may be blunted under conditions of catecholamine excess. Additionally, recent data suggest that the combination of amiodarone and beta-blockers is most effective at preventing potentially life-threatening arrhythmias in an ICD population.[49] The mechanism by which this occurs is not completely known.

While a variety of beta-blockers are available for use, when it comes to arrhythmia management, it is important to have drug levels that persist throughout the day. Several beta-blockers do not do this when given on once-a-day basis; for example, atenolol. Specific beta-blockers may be effective for other reasons, including treatment of congestive heart failure and hypertension. When it comes to treating arrhythmias, although it is important to use a beta-blocker such that levels persist throughout the day. Sotalol is a beta-blocker, but it is actually a stereoisomer including d-sotalol and l-sotalol. While d-sotalol is a class III AAD; l-sotalol is a beta-blocker. When using sotalol at lower doses, the greatest effect is from the l-stereoisomer.

Some beta-blockers may have additional central nervous system effects and this effect may depend upon lipid solubility. Water-soluble and renally excreted beta-blockers, such as atenolol, rarely cross the blood-brain barrier, whereas lipid soluble beta-blockers, such as propranolol, cross the blood-brain barrier easily. It is likely that some of the benefits of beta-blockers are through central effects that are not well understood. Additionally, there are data to suggest that carvedilol may be more than just a beta-blocker as it can inhibit the rapid activating delayed-rectifier current, the L-type calcium current and the Ito, as well as the delayed-rectifier current (IKs).[50]

Beta-blockers can terminate specific acute arrhythmias, such as AF with rapid ventricular response rates that may occur in the period early after cardiac and non-cardiac surgery. In this particular case, as in other cases whereby AF is catecholamine mediated, beta-blockers can be modestly effective.[51] Additionally, AF can be treated by a beta-blocker in the setting of thyrotoxicosis.

CLASS III ANTIARRHYTHMIC DRUGS: DRUGS THAT PROLONG REPOLARIZATION

All clinically available class III drugs block the rapid component of the delayed-rectifier potassium channel (Ikr), resulting in an increase in action potential duration and refractoriness in various cardiac tissues, the hallmark of a class III AAD. With class III AADs, reverse use dependence can also occur. In this situation, the AAD effect is most pronounced during slow heart rates. The class III AADs (d-sotalol and N-acetylprocainamide—a metabolite of procainamide, but not amiodarone) demonstrate reverse use dependence. Quinidine can show reverse use dependence for the potassium channel, but use dependence for the sodium channel.

Sotalol

Sotalol is a class III AAD with beta-blocking properties. This combination results in sinus slowing, decrease in AV nodal conduction and increased refractoriness in atria, AV node, ventricle and accessory pathways. The dextro stereoisomer of sotalol (d-sotalol) is a pure class III AAD without beta-blocking properties.

Oral bioavailability of sotalol is close to 100%. Peak concentrations are seen in 2.5–4 hours following a dose. The drug has an elimination half-life of 12–16 hours and is excreted unchanged by the kidneys. Thus, drug accumulation results in the setting of renal insufficiency, increasing the risk of torsades de pointes and necessitating dose adjustment.

Sotalol is currently available in the United States only in the oral form. Usual starting dose of sotalol is 80 mg twice daily with gradual increase to 240–320 mg daily, provided the QTc is within accepted limits (< 500 msec). The following dosing algorithm is proposed in patients with renal insufficiency (Table 4A). No dose adjustment is needed in patients with hepatic disease.

Patients with heart failure and severe left ventricular dysfunction will fare poorly on this drug due to the substantial

TABLE 4A

Sotalol renal dosing algorithm

Creatinine clearance (measured by Cockcroft-Gault method) ml/min	*Dosing frequency*
> 60	Every 12 hours
30–60	Every 24 hours
10–30	Every 36–48 hours
< 10	Individualize

beta-blocking effects. Concern has been raised for those patients with marked left ventricular hypertrophy, as such patients have a preponderance of mid-myocardial cells and therefore can be at a greater risk for developing QT interval prolongation.

The combined class III and beta-blocking properties make sotalol effective for supraventricular and ventricular arrhythmias.[52] Sotalol is most commonly used as a rhythm control drug in AF and to suppress ventricular arrhythmias in ICD patients.

The Survival With Oral d-Sotalol (SWORD) trial evaluated the effect of d-sotalol, a pure class III drug and one that is no longer available, versus placebo on mortality in patients who had a myocardial infarction and a left ventricular ejection fraction less than or equal to 40%. The SWORD trial was stopped prematurely due to increased mortality in the d-sotalol arm which was primarily due to arrhythmic death.[53] In a multicenter, double-blind study of 1,456 patients with recent myocardial infarction randomized to d-sotalol and l-sotalol 320 mg once daily versus placebo, the mortality rate at 12-month follow-up was not significantly different between the two groups (8.9% in the sotalol group vs 7.3% in the placebo group), but the reinfarction rate was 41% lower in the sotalol group ($p < 0.05$). This beneficial effect was attributed to the beta-blocking properties of l-sotalol.[54]

In the Electrophysiologic Study Versus Electrocardiographic Monitoring (ESVEM) trial, a randomized, NIH-sponsored multicenter trial designed to determine the best method to guide drug therapy for patients who had malignant ventricular arrhythmias, sotalol was effective in 31% of the patients, which was the best among the different AADs tested.[55] It should be noted, however, that ESVEM did not test amiodarone or ICDs. Sotalol has been shown to be effective in an ICD population where, when compared to placebo, it significantly reduced the number of both appropriate and inappropriate ICD shocks.[56]

The Sotalol Amiodarone AF Efficacy Trial (SAFE-T) was a randomized, double-blind, placebo-controlled trial that compared sotalol versus amiodarone in restoration and maintenance of sinus rhythm in patients with persistent AF. A total of 665 patients were randomized to sotalol ($n = 261$), amiodarone ($n = 261$) and placebo ($n = 137$), and were monitored weekly for 1–4.5 years. The primary endpoint was time to recurrence of AF. Sotalol and amiodarone were equally efficacious in converting AF to sinus rhythm (24% in sotalol group vs 27% in amiodarone group) and both were superior to placebo. The median time to AF recurrence was 487 days in the amiodarone group when compared to 74 days in the sotalol group and 6 days in the placebo group. Amiodarone was clearly superior to sotalol and placebo for maintenance of sinus rhythm. Sotalol, however, was equally efficacious as amiodarone in maintaining sinus rhythm in the subgroup of patients with ischemic heart disease. Major adverse events were comparable among the three groups.[57]

The effects of sotalol, a class III AAD, can result in dose-dependent QTc prolongation and risk of torsades de pointes. At doses ranging from 160 mg/day to 240 mg/day, QTc prolongation of 10–40 ms was noted. Of particular concern is the situation where patients receive concomitant diuretics with frequent dose changes and inadequate potassium replacement. The overall incidence of torsades de pointes appears to be 2% and is more common in females, structural heart disease, and is exacerbated by hypokalemia and concomitant use of other AADs or QT-prolonging drugs. Careful dose titration and dose adjustment in renal insufficiency are essential to avoid risk of torsades de pointes. Typical adverse effects of beta-blockers such as bronchospasm, masking of hypoglycemia and rebound tachycardia, and hypertension on drug withdrawal may also be seen with sotalol. Concomitant use of sotalol with other QT-prolonging drugs increases the risk of torsades de pointes.

Dofetilide

Dofetilide is a potent and selective IKr blocker that prolongs action potential duration and refractoriness, more so in the atrium than in the ventricle.[58] Dofetilide does not exhibit any negative inotropic properties and has no effect on conduction velocity.

Oral bioavailability of dofetilide exceeds 90% and peak plasma concentrations are attained in 2–3 hours. The drug is partially metabolized by CYP3A4 to inactive metabolites and excreted predominantly (80%) in the urine with an elimination half-life of 8–10 hours. Drug elimination is reduced and accumulation results in renal failure, necessitating dosage adjustment and/or drug discontinuation. Medications that can induce or inhibit CYP3A4 metabolism can affect dofetilide concentrations and can potentially lead to adverse effects.[59]

Dofetilide is primarily used in the restoration and maintenance of sinus rhythm in AF, especially in patients with structural heart disease. The Danish Investigators of Arrhythmia and Mortality on Dofetilide trial (DIAMOND), which evaluated dofetilide versus placebo on all-cause mortality in 1,518 patients with symptomatic congestive heart failure and severe left ventricular dysfunction, showed no difference in all-cause mortality between the two arms. A significant decrease in the risk of heart failure hospitalization was observed in the dofetilide group. In patients with AF, dofetilide resulted in a 12% conversion rate to sinus rhythm compared to 1% in the placebo group ($p < 0.05$) and once sinus rhythm was restored, dofetilide was significantly more effective in maintaining sinus rhythm than placebo (HR 0.35; 95% confidence interval 0.22–0.57; $P < 0.001$). Twenty-five cases of torsades de pointes were reported in the dofetilide group (3.3%) as compared with none in the placebo group.[60]

The recommended dosage of dofetilide is 500 µg twice daily, but the dose varies based on renal function. Given the risk of torsades de pointes, physicians are required to receive special training prior to prescribing dofetilide. The drug has to be initiated in the hospital with continuous electrocardiographic

TABLE 4B

Dofetilide renal dosing algorithm

Creatinine clearance (measured by Cockcroft-Gault method) ml/min	*Dosing frequency*
> 60	500 mcg twice daily
40–60	250 mcg twice daily
20–39	125 mcg twice daily
< 20	Contraindicated
Hemodialysis	Contraindicated

monitoring for either 3 days or 12 hours after conversion to sinus rhythm, whichever is greater. Creatinine clearance needs to be measured (using the Cockcroft-Gault formula) prior to initiation. A 500 mcg twice daily dosing is initiated only in patients with creatinine clearance more than 60 ml/min. The renal dosing algorithm for dofetilide is shown in Table 4B. Once initiated, if the QTc at 2–3 hours following the first dose is more than 15% from baseline or more than 500 msec (> 550 msec for bundle branch block or intraventricular conduction delay), then the dose needs to be reduced. If the QTc is more than 500 msec (> 550 msec for bundle branch block or intraventricular conduction delay) at any time during doses 2–6, dofetilide needs to be discontinued and an alternative drug sought. Despite initial enthusiasm with regard to the use of the drug,[61] its use has been tempered by strict regulations regarding its use.

The major adverse effect of dofetilide is torsades de pointes. The incidence is dose-dependent and is also influenced by structural heart disease and concomitant usage of QT-prolonging medications.[60,62] The overall incidence, during maintenance therapy on 500 µg twice daily, is around 1.7%.[63] Verapamil, trimethoprim, thiazides, azole antifungals and cimetidine should be discontinued prior to dofetilide initiation as concomitant administration results in markedly elevated plasma concentrations of dofetilide and increases risk of torsades de pointes.[59] Inducers of CYP3A4, such as phenobarbital and rifampin, can enhance dofetilide metabolism and decrease its efficacy. Dofetilide does not interact with digoxin or warfarin.

Ibutilide

Ibutilide is a methane sulfonamide analog of sotalol that is a potent blocker of IKr, resulting in prolongation of action potential duration and refractoriness. In addition, ibutilide also activates the slow inward sodium current.[64] Ibutilide is only available for intravenous use and is currently approved for rapid conversion of recent-onset AF and atrial flutter.

The Ibutilide Repeat Dose Study was a multicenter trial that randomly assigned 266 patients with AF of atrial flutter of recent-onset (3–45 days) to ibutilide or matching placebo. Ibutilide was administered as two 10-minute infusions of 1 mg, separated by 10 minutes. The overall conversion rate was 47% with ibutilide versus 2% with placebo ($p < 0.0001$), with the drug being more efficacious in atrial flutter than AF (63% vs 31%; $p < 0.0001$). The mean time to conversion was 27 minutes postinfusion. Among patients who received ibutilide, 8.3% developed torsades de pointes during infusion.[65] Ibutilide has also been shown to be efficacious in conversion of AF in patients with Wolff-Parkinson-White syndrome.

Ibutilide is given as an intravenous infusion over 10 minutes. Recommended dose is 1 mg given over 10 minutes. A second 1 mg dose, separated from the first dose by 10 minutes, can be given if the atrial arrhythmia persists. The drug has a half-life of ~ 6 hours and is primarily metabolized by the liver. No dosage adjustments are recommended for hepatic or renal dysfunction.

The major side effect of ibutilide is QTc prolongation and torsades de pointes, which developed in 8.3% of patients in the Ibutilide Repeat Dose Study.[65] Due to this, it is essential that patients receiving ibutilide have continuous electrocardiographic monitoring for 4–6 hours following treatment, with skilled personnel and resuscitation equipment available and ready. Ibutilide should be avoided in patients with baseline QTc prolongation (> 440 msec), advanced structural heart disease, and electrolyte abnormalities such as hypokalemia or hypomagnesemia, given the higher risk of torsades de pointes in these situations.

The use of ibutilide for pharmacological conversion of AF or atrial flutter was never popular given modest efficacy, high risk of polymorphic VT, and the need for close monitoring following drug administration. Several studies have shown that concurrent administration of intravenous magnesium improves efficacy of ibutilide.[66-70] A better method to improve the safety and efficacy of ibutilide was addressed in a recent randomized trial. Fragakis, et al. randomly assigned patients with recent-onset AF with rapid ventricular rate to receive ibutilide alone or a combination of ibutilide and esmolol and showed that intravenous beta-blockade resulted in a significant improvement in conversion rate (67% for the combination vs 46% for ibutilide alone) with marked reduction in immediate recurrence of AF. The combination of ibutilide plus esmolol proved to be safer also (no cases of polymorphic VT in the combination group vs 6.5% in the ibutilide group).[71] This combination of ibutilide and esmolol, along with newer drugs like vernakalant, may result in an expanded role for pharmacological agents in the restoration of sinus rhythm in AF.[72]

Amiodarone

Amiodarone, a synthesized, iodinated benzofuran derivative, structurally similar to thyroxine, was identified with initial work with the ammi visnaga plant.[73] Although classified as a class III AAD, it is a complex and unique drug with properties spanning all four Vaughan-Williams classes. The exact mechanism responsible for its antiarrhythmic actions remains unclear. In animal studies, amiodarone has been shown to prolong action potential duration and refractoriness in the atria and the ventricles, the AV node, and Purkinje fibers.[74] Amiodarone also blocks inactivated sodium channels, slows phase 4 depolarization in sinus node, and delays AV nodal conduction.[75] Electrophysiological properties of amiodarone differ between intravenous and oral use. During intravenous use, amiodarone exhibits sodium and calcium channel blocking properties, has greater effect at higher heart rates and in depolarized tissue. This property makes it useful in treatment of ventricular arrhythmias in the setting of myocardial ischemia. Chronic oral therapy with amiodarone prolongs the PR and QT intervals on the surface electrocardiogram.

Amiodarone is highly lipid-soluble and has a large volume of distribution (20–200 l/kg).[76] Oral bioavailability is highly variable and it usually takes weeks before a steady state is reached, as it accumulates slowly in the adipose tissue. A dose of more than 10 g is usually needed to saturate the fat stores. Amiodarone is mostly metabolized to desethylamiodarone. Plasma half-life after intravenous administration ranges from 4.8 hours to 68.2 hours.[77] Elimination is slow and extremely variable with a half-life ranging from 13 days to 103 days. Dosage adjustment is not required in renal disease. Neither hemodialysis nor peritoneal dialysis removes amiodarone.

US Food and Drug Administration has currently approved amiodarone only for refractory, life-threatening ventricular arrhythmias, although the drug is widely used in the treatment of a variety of atrial and ventricular arrhythmias. Clinical data supporting the use of the amiodarone in ventricular arrhythmias is summarized below.

The European Myocardial Infarction Amiodarone Trial (EMIAT)[78] and Canadian Amiodarone Myocardial Infarction Arrhythmia Trial (CAMIAT)[79] were large randomized trials that evaluated the impact of amiodarone after myocardial infarction. In EMIAT, 1,486 post-myocardial infarction patients with a left ventricular ejection fraction less than 40% were randomly assigned to receive either amiodarone (n = 743; loading period followed by 200 mg/day), or matching placebo (n = 743). Presence of ventricular arrhythmia was not needed for inclusion. No difference in all-cause or cardiovascular death was seen after a median follow-up of 21 months. A 35% risk reduction ($p < 0.05$) in arrhythmic deaths was seen in the amiodarone group.[78]

In CAMIAT, 1,202 patients who were 6–45 days post-myocardial infarction and had a mean of at least 10 PVCs/hour were randomly assigned to amiodarone (n = 606) or placebo (n = 596) and followed for a mean of 1.8 years. Patients in the amiodarone group had a 48.5% reduction (p = 0.016) in the combined endpoint of resuscitation from ventricular fibrillation or arrhythmic death (3.3% in the amiodarone group vs 6.6% in the placebo group). There was no significant difference in all-cause mortality (p = 0.13) between the two groups.[79]

The EMIAT and CAMIAT showed that amiodarone given post-myocardial infarction can reduce arrhythmic death but did not improve total mortality. In a pooled post-hoc analysis of EMIAT and CAMIAT, the combination of amiodarone with a beta-blocker resulted in significant improvements in arrhythmic death or resuscitated cardiac arrest when compared to beta-blockers alone, amiodarone alone, or placebo. Non-significant reductions in total mortality were noted with the combination compared to those not receiving beta-blockers.[80]

Estudio Piloto Argentino de Muerte Sfibita y Amiodarone (EPAMSA), Grupo de Estudio de la Sobrevida en la Insuficiencia Cardiaca en Argentina (GESICA) and Congestive Heart Failure Survival Trial of Antiarrhythmic Therapy (CHF-STAT) were trials that evaluated the role of amiodarone in patients with congestive heart failure.[81-83] The EPAMSA randomized patients with a left ventricular ejection fraction less than or equal to 35% and asymptomatic ventricular arrhythmias to receive either amiodarone (n = 66) or no drug (n = 61). During a 12-month follow-up period, total mortality (10.6% vs 28.8%, p = 0.02) and sudden death (7% vs 20.4%, p = 0.04) were reduced in patients receiving amiodarone compared to placebo.[81]

The GESICA was a multicenter, randomized trial of 516 patients in Argentina with congestive heart failure and left ventricular systolic function less than or equal to 35% (39% with ischemic cardiomyopathy), but no history of symptomatic ventricular arrhythmias. The trial showed that patients receiving amiodarone had a 28% reduced risk of death and a 31% reduced risk of heart failure hospitalizations, when compared to placebo.[82]

The CHF-STAT, on the other hand, randomized 674 patients with congestive heart failure, a left ventricular ejection fraction less than or equal to 40%, and at least 10 PVCs/hour, to amiodarone (n = 336) or matching placebo (n = 338). Over a median follow-up of 45 months, amiodarone was associated with PVC suppression and improved left ventricular function. No difference in total mortality (p = 0.6) or sudden death (p = 0.43) was found between the two groups.[83] The reason for the difference in outcomes between GESICA and EPAMSA versus CHF-STAT has been attributed to the presence of a higher percentage of patients with ischemic cardiomyopathy in CHF-STAT. Drug discontinuation rate of amiodarone in these studies ranged from 20% to 40%.

A meta-analysis of 15 randomized controlled trials (n = 8,522) of amiodarone versus placebo for prevention of sudden cardiac death showed that amiodarone was associated with a 29% reduced risk of sudden cardiac death (7.1% vs 9.7%; OR 0.72, $p < 0.001$) and an 18% reduced risk of cardiovascular death (14.0% vs 16.3%; OR 0.82, p = 0.004). No significant difference in all-cause mortality was demonstrated. Patients who received amiodarone were more likely to have thyroid problems (OR 5.68; $p < 0.0001$), pulmonary toxicity (OR 1.97; p = 0.002), hepatotoxicity (OR 2.1; p = 0.015), or bradyarrhythmias (OR 1.78; p = 0.008) when compared to the control group.[84] The literature thus suggests that amiodarone is beneficial in treatment of ventricular arrhythmias in patients with cardiomyopathy and congestive heart failure. These findings also suggest that amiodarone is a reasonable option, albeit with risk for long-term side effects and no all-cause mortality benefit, for prevention of sudden cardiac death in patients who are not ICD candidates.

For most patients, however, the reason to use amiodarone to treat ventricular arrhythmias in patients with implantable devices is to suppress recurrent episodes of VT and ventricular fibrillation leading to ICD shocks. It is important to recognize that amiodarone can increase the threshold of energy necessary to defibrillate the patient and can slow the VT rates.[40]

Amiodarone is by far the most effective AAD to maintain sinus rhythm in patients with AF. The Canadian Trial of AF (CTAF) was a prospective, multicenter, randomized trial that randomly assigned 403 patients with at least one episode of AF in the past 6 months to receive amiodarone or either sotalol or propafenone. After a mean follow-up of 16 months, AF recurrence was noted in 35% of patients in the amiodarone group versus 63% in the sotalol or propafenone groups ($p < 0.001$). Adverse effects resulting in drug discontinuation was higher in the amiodarone group (18% vs 11% in the sotalol/propafenone group) but was not statistically significant (p = 0.06).[85]

The SAFE-T trial, which compared amiodarone against sotalol in the restoration and maintenance of sinus rhythm in patients with persistent AF, showed that amiodarone was equally efficacious as sotalol in restoring sinus rhythm but was vastly superior to sotalol in maintaining sinus rhythm. Major adverse events in the amiodarone group were comparable to placebo.[57] The relative safety of amiodarone when used in treatment of AF was illustrated in a Cochrane database review of 45 randomized controlled studies (n = 12,559) that evaluated the different AADs used for maintenance of sinus rhythm in AF. The effect on these drugs on mortality, thromboembolic events, and proarrhythmia were noted. The study found that class IA, class IC and class III drugs showed a significant reduction in AF recurrence (odds ratio 0.19–0.60, number needed to treat: 2–9) compared to placebo, but none improved mortality. Class IA drugs were associated with increased mortality and all drugs, except propafenone and amiodarone, increased the risk of proarrhythmia.[7]

Given huge volume of distribution, a loading dose regimen is essential to ensure onset of therapeutic action within a reasonable time frame. Loading can be done using intravenous or oral dosing. For outpatient initiation, we routinely employ a loading regimen (400 mg three to four times a day) that ensures a 10–15 g load within 7–10 days after initiation. Once the 10 g load is complete, the patient is switched to a maintenance dose of 200–400 mg a day. The loading dose is generally higher in those patients who have ventricular tachyarrhythmias and the long-term maintenance dose is higher as well. For patients with AF or other atrial arrhythmias, the maintenance dose can be as low as 100–200 mg a day with a load less than 10 g orally.

The manufacturer recommended and routinely used intravenous infusion regimen follows three phases over 24 hours: 150 mg over 10 minutes (with an additional bolus dose of 150 mg for patients with recurrent VT), followed by 1 mg/min over the next 6 hours, followed by 0.5 mg/min over next 18 hours. Infusion should preferably be through a central line to avoid risk of phlebitis. Intravenous amiodarone can result in hypotension and negative inotropy.

Amiodarone is well-tolerated in the long-term if close attention is paid to screen for and recognize adverse events.[86] Side effects are common and can range from 15% in the first year to 50% with long-term use. The majority of the side effects are extracardiac, with the most serious one being interstitial pneumonitis leading to pulmonary fibrosis.[87] This can be difficult to predict and challenging to diagnose.[87,88]

Amiodarone frequently affects thyroid function, but it can also cause hypersensitivity to the sun, cause skin color changes, have neurological effects (weakness, difficulty in walking especially in the elderly), effects on hepatic function and potentially optic neuritis. Corneal microdeposits are common but of little importance. Amiodarone can also cause sinus bradycardia and AV block.[86]

Amiodarone can increase serum levels of digoxin, quinidine, procainamide, flecainide, cyclosporine and warfarin. Although amiodarone can prolong QTc interval, risk of torsades de pointes is extremely rare, perhaps secondary to its multichannel blocking properties or to the uniformity by which it prolongs repolarization.

A comprehensive list of adverse reactions to amiodarone and their management is shown in Table 5. Fortunately, the majority of the adverse reactions can be easily managed and do not necessitate discontinuation of the drug. Adverse reactions to amiodarone depend, in part, on the dose and the duration of therapy. If long-term administration is considered, the lowest effective dose should be selected to minimize toxicity. Even then, regular and careful monitoring is essential to ensure patient safety. All patients at initiation of therapy should have a 12-lead electrocardiogram, chest X-ray, pulmonary function test (including DLCO), and laboratory evaluation for electrolytes and renal function, liver function, and thyroid function. An ophthalmological evaluation is recommended at baseline if there is visual impairment, and a follow-up evaluation should be done for new eye-related symptoms. Liver function and thyroid function tests are assessed every 6 months. An electrocardiogram and a chest X-ray should be repeated yearly. Follow-up pulmonary function tests should be done for new or unexplained dyspnea or if there are abnormalities in the chest X-ray compared to baseline.[86]

Amiodarone interferes with the clearance of many drugs, especially those that are highly protein bound. The major drug interactions of amiodarone are listed in Table 3. Of particular importance is the inhibition of warfarin and digoxin clearance by amiodarone, resulting in higher plasma levels of these drugs and necessitating dosage reduction or discontinuation. Warfarin dose should be reduced to half and digoxin should be discontinued if that particular patient is started on amiodarone.

Dronedarone

Dronedarone is structurally similar to amiodarone but lacks the iodine moiety. It has multichannel blocking properties similar to amiodarone but it is not as potent. Dronedarone was initially developed with the aim to reducing or eliminating amiodarone-induced toxicity while maintaining efficacy. For clinical purposes, dronedarone is classified as a Vaughan-Williams Class III AAD. Electrophysiological properties of dronedarone include inhibitory effects on the rapid delayed-rectifier, slow delayed-rectifier, acetylcholine-activated, and inward-rectifier potassium channels, inward sodium current, T-type and L-type calcium channels, and alpha-adrenoceptors and beta-adrenoceptors.[89,90] Dronedarone slows down sinus rate by suppression of sinus node automaticity and by changing the slope of phase 4 depolarization in the sinus node.[91] The drug also slows AV conduction, increase SAV nodal and ventricular effective refractory period, and has been shown to reduce VT and PVCs in ischemic animal models.[89,92]

Dronedarone has negligible proarrhythmic effect but has been shown to increase mortality in patients with acute heart failure.[93] Dronedarone is devoid of the many adverse effects and drug interactions associated with amiodarone. Pulmonary toxicity has not been reported with dronedarone. When compared to placebo, there was no significant difference in hyperthyroidism, hypothyroidism, neurological abnormalities, gastrointestinal and hepatic abnormalities with dronedarone. Similar to amiodarone, dronedarone causes mild increases in serum creatinine by inhibiting cation transport in the renal tubules. Glomerular filtration rate, however, is not affected.[94]

TABLE 5

Incidence, diagnosis, and management of major adverse reactions to amiodarone

Reaction	*Incidence (%)*	*Diagnosis*	*Management*
Pulmonary	2	Couth and/or dyspnea, especially with local or diffuse opacities on high-resolution CT scan and decrease in DLCO from baseline	Usually discontinue drug; corticosteroids may be considered in more severe cases; occasionally, can continue drug if levels high and abnormalities resolve; rarely, continue amiodarone with corticosteroid if no other option
Gastrointestinal tract	30 15–30 <3	Nausea, anorexia and constipation AST or ALT level greater than 2 times normal Hepatitis and cirrhosis	Symptoms may decrease with decrease in dose If hepatitis considered, exclude other causes Consider discontinuation, biopsy or both to determine whether cirrhosis is present
Thyroid	4–22 2–12	Hypothyroidism Hyperthyroidism	L-Thyroxine Corticosteroids, propylthiouracil or methimazole; may need thyroidectomy
Skin	<10 25–75	Blue discoloration Photosensitivity	Reassurance; decrease in dose Avoidance of prolonged sun exposure; sunblock; decrease in dose
Central nervous system	3–30	Ataxia, paresthesias, peripheral polyneuropathy, sleep disturbance, impaired memory and tremor	Often dose dependent, and may improve or resolve with dose adjustment
Ocular	<5 ≤1 >90	Halo vision, especially at night Optic neuropathy Photophobia, visual blurring and microdeposits	Corneal deposits the norm; if optic neuropathy occurs, discontinue Discontinue drug and consult an ophthalmologist
Heart	5 <1	Bradycardia and AV block Proarrhythmia	May need permanent cardiac pacing May need to discontinue the drug
Genitourinary	<1	Epididymitis and erectile dysfunction	Pain may resolve spontaneously

(Abbreviations: ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; DLCO: Diffusion capacity of carbone monoxide). [*Source:* Goldschlager N, Epstein AE, Naccarelli GV, et al. A practical guide for clinicians who treat patients with amiodarone: 2007. Heart Rhythm. 2007;4:1250-9 (Reference 86)]

Dronedarone is metabolized by the hepatic CYP3A4 system and in turn is also a moderate inhibitor of the CYP3A4 system and weak CYP2D6 and P-glycoprotein inhibitor. These properties result in increased effects of drugs like cyclosporine, digoxin and some statins when coadministered with dronedarone.[94] Unlike amiodarone, dronedarone does not have any drug interactions with warfarin.

A synopsis of the randomized clinical trials that evaluated the impact of dronedarone in AF and heart failure are shown in Table 6 and have been summarized in detail.[95] The European Trial in AF or Flutter Patients Receiving Dronedarone for the Maintenance of Sinus Rhythm (EURIDIS) and the American-Australian-African Trial with Dronedarone in AF or Flutter Patients for the Maintenance of Sinus Rhythm (ADONIS) compared dronedarone to placebo in maintaining sinus rhythm after conversion from atrial flutter or AF. The EURIDIS showed that at the end of 1 year of follow-up, 67% of patients on dronedarone had a recurrence of AF compared to 78% in the placebo group. In the ADONIS trial, 61% in the dronedarone group had recurrent AF compared to 73% in the placebo. Although significantly different from placebo, the high recurrence rate of AF with dronedarone cast doubts on its efficacy to maintain sinus rhythm.[96]

The DIONYSOS trial[97] [Randomized, Double-Blind TrIal to Evaluate the Efficacy and Safety of DrOnedarone (400 mg bid) Vs AmiodaroNe (600 mg qd for 28 daYS, then 200 mg qd Thereafter) for at least 6 months for the Maintenance of Sinus Rhythm in Patients with AF] directly compared dronedarone (400 mg twice daily) to amiodarone (600 mg every day for 28 days, then 200 mg every day thereafter) in restoration and maintenance of sinus rhythm in patients with AF. During a mean follow-up of 7 months, 64% of patients in the dronedarone arm had AF recurrence when compared to 42% in the amiodarone arm. Adverse event rates were high, but comparable between both drugs (39% with dronedarone vs 45% with amiodarone; HR 0.80, $p = 0.13$). There were fewer thyroid, neurological, skin, and eye-related adverse events with dronedarone except gastrointestinal side effects, which were higher in the dronedarone group. In summary, dronedarone was inferior to amiodarone in efficacy, but was more favorable than amiodarone in terms of safety.[97]

The Efficacy and Safety of Dronedarone for the Control of Ventricular Rate during AF (ERATO) study found dronedarone to be effective for ventricular rate control in patients with AF, both at rest and with exercise.[98]

The ATHENA (A Placebo-Controlled, Double-Blind, Parallel Arm Trial to Assess the Efficacy of Dronedarone 400 mg bid for the Prevention of Cardiovascular Hospitalization or Death from Any Cause in Patients with Atrial Fibrillation/Atrial Flutter) trial evaluated the effect of dronedarone in reducing a

TABLE 6

Summary of randomized clinical trials that assessed the efficacy and safety of dronedarone in patients with atrial fibrillation and heart failure

Clinical trial	*Patient profile*	*Number of patients*	*Intervention*	*Primary end point*	*Follow-up (months)*	*Results/Conclusions*
DAFNE	Persistent AF post-cardio-version	199	Dronedarone (400–800 mg twice daily) versus placebo	Time to first recurrence of AF	6	Use of dronedarone was associated with a longer median time to AF recurrence (60 days vs 5.3 days for dronedarone and placebo respectively, $p = 0.026$; 55% relative risk reduction, $p = 0.001$); likewise, patients receiving dronedarone, 400 mg orally twice daily, were more likely to maintain sinus rhythm compared with patients receiving placebo
EURIDIS and ADONIS	Paroxysmal AF	1,237	Dronedarone 400 mg twice daily versus placebo	Time to first recurrence of AF	12	Dronedarone significantly lengthened the time to AF recurrence [41 days vs 96 days (EURIDIS) and 59 days vs 158 days (ADONIS) for dronedarone and placebo respectively], as well as symptoms associated with atrial fibrillation, compared with placebo. Ventricular rates during AF recurrence were significantly lower with dronedarone
DIONYSOS	Persistent AF for > 3 days	504	Dronedarone (400 mg twice daily) versus amiodarone (600 mg and then 200 mg per day)	AF recurrence or drug intolerance resulting in discontinuation	7	More patients on dronedarone had AF recurrence or stopped the drug due to intolerance or lack of efficacy compared with patients receiving amiodarone (75.1% vs 58.8% for dronedarone and amiodarone respectively, HR 1.59).
ERATO	Permanent AF with ventricular rates > 80 bpm on rate-controlling agents	630	Dronedarone 400 mg twice daily versus placebo	Mean ventricular rate at 2 weeks	1	Dronedarone use was associated with decrease in ventricular rate, both at rest (12.3 bpm with dronedarone vs 0.2 bpm with placebo) and with exercise (25.6 bpm with dronedarone vs 2.2 bpm with placebo)
ATHENA	Paroxysmal or persistent AF or atrial flutter with one or more asso-ciated risk factors	4,628	Dronedarone (400 mg twice daily) versus placebo	Composite of all-cause mortality and cardiovascular hospitalization	21±5	The use of dronedarone was associated with decreased cardiovascular deaths and arrhythmic deaths compared with placebo (31.9% in dronedarone arm vs 39.8% in placebo arm, HR 0.76). There was also a decrease in hospitalizations for AF and acute coronary syndrome in patients receiving dronedarone compared with placebo
ANDROMEDA	Congestive heart failure (NYHA Class III–IV); left ventricular ejection fraction < 35%	617	Dronedarone (400 mg twice daily) versus placebo	All-cause mortality or heart failure hospitalization	2	Trial was stopped early as dronedarone was associated with a significant increase in all-cause mortality (8.1% in the dronedarone arm vs 3.8% in placebo arm, HR 2.13)

composite endpoint of death or cardiovascular hospitalizations in AF patients.[99] A total of 4,628 patients with paroxysmal or persistent AF and presence of risk factors for stroke and/or death were randomized to dronedarone or matching placebo and were followed for a median period of 21 ± 5 months. The study found that patients randomized to dronedarone had fewer cardiovascular deaths (HR = 0.71; 95% CI, 0.51–0.98; $P = 0.03$), as well as arrhythmic deaths (HR = 0.55; 95% CI, 0.34–0.88; $P = 0.01$), when compared to placebo. There were also fewer cardiovascular hospitalizations in the dronedarone arm. A post-hoc analysis of ATHENA showed that there were fewer strokes or transient ischemic attacks in the dronedarone group.[100] The ATHENA was the first trial to show mortality benefit with an AAD and was largely responsible for approval of dronedarone in the United States.

The Antiarrhythmic Trial with Dronedarone in Moderate to Severe Congestive Heart Failure Evaluating Morbidity Decrease (ANDROMEDA) compared dronedarone with placebo in patients with AF hospitalized with new or worsening heart failure and a left ventricular ejection fraction less than 35%.[93] The study had to be terminated prematurely after a median follow-up of 2 months, as mortality was significantly increased in the dronedarone arm (8.1% vs 3.8% in the placebo arm). The increased mortality was predominantly attributed to deaths from worsening heart failure and treatment with dronedarone was the most powerful predictor of death. This study resulted in a black box warning for dronedarone that warns against its use in patients with New York Heart Association (NYHA) class IV heart failure or NYHA class II and III heart failure with recent decompensation requiring hospitalization or referral to a

heart failure clinic.[94] Recent post-marketing data released by the manufacturer reports several cases of hepatocellular injury and at least two cases of acute hepatic failure requiring liver transplantation, which occurred at 4.5 months and 6 months following drug initiation. This has prompted a manufacturer recommendation to consider serial liver enzyme monitoring at least for the first 6 months while being on dronedarone.[101] PALLAS included patients at least 65 years old with at least 6-month history of permanent atrial fibrillation and risk factors for major vascular events. Patients received dronedarone or placebo. Of 3236 enrolled, the co-primary outcome of stroke, myocardial infarction, systemic embolism, or death from cardiovascular causes was higher with drenedarone (HR: 2.29; 95% confidence interval 1.34-3.94; P = 0.002). The death rate was higher with dronedarone (HR, 3.11; 95% confidence interval, 1.00-4.49; P = 0.046), including death from arrhythmia (HR, 3.26; 95% confidence interval 1.06-10.00; P = 0.03). There were more strokes (HR, 2.32; 95% confidence interval 1.11-4.88; P = 0.02) and more heart failure hospitalizations (HR, 1.81; 95% confidence interval 1.10 to 2.99; P = 0.02) with drenedarone.[101a]

Dronedarone, although not a very effective rhythm control drug by itself, remains the first AAD to show a reduction in cardiovascular mortality in AF patients with risk factors for stroke and/or death. Although mortality reduction is a significant finding, its clinical utility is unclear, as the primary goal in AF management is symptom reduction and improving quality of life. The favorable safety profile, as well as the fact that a loading dose is not needed, makes dronedarone an ideal drug to start as an outpatient. The fact that it improves mortality and reduces cardiovascular hospitalizations in patients with AF makes it attractive from a health care expenditure standpoint. On the other hand, it is our opinion that use of dronedarone should be avoided in patients with congestive heart failure and severe left ventricular dysfunction or for those patients with permanent AF. The 2011 ACCF/AHA/HRS focused update of the 2006 AF guidelines now include dronedarone.[31] It is fair to say that dronedarone has definitely expanded the horizon in terms of management options for AF.

Azimilide

Azimilide dihydrochloride is a class III AAD that blocks both the rapid (IKr) and the slow (IKs) delayed-rectifier potassium channels.[102] It is different from the other class III drugs that only block IKr. Azimilide prolongs the action potential duration and refractoriness in atrial and ventricular myocardium and has been shown to cause dose-dependent QTc prolongation.[102] Unlike other class III drugs, azimilide does not exhibit reverse use-dependence, which is thought to be secondary to IKs blockade.

The AzimiLide post-Infarct surVival Evaluation (ALIVE) trial assessed the effect of azimilide on survival in patients who were 6–21 days post-myocardial infarction and had a left ventricular ejection fraction ranging from 15% to 35%. No survival advantage was seen with azimilide but the drug caused no excessive harm.[103] Azimilide is not approved for clinical use in the United States but is available in Europe, where it has been primarily used for suppressing ventricular arrhythmias in ICD patients.

The SHock Inhibition Evaluation with azimiLiDe (SHIELD) trial was a randomized, double-blind, placebo controlled, international trial of 633 patients that evaluated the effect of azimilide, either 75 mg (n = 220) or 125 mg (n = 199) daily, versus placebo (n = 214) on all-cause shocks plus symptomatic tachycardias terminated by antitachycardia pacing and appropriate ICD therapies.[104] All patients enrolled in the trial had an ICD implanted and had either a documented episode of cardiac arrest or spontaneous sustained VT with left ventricular ejection fraction less than or equal to 0.40 during 42 days prior to the first ICD implantation or an ICD shock for spontaneous VT or ventricular fibrillation within the previous 180 days. Over a median follow-up of 367 days, there was a significant 57% reduction in all-cause shocks plus antitachycardia pacing (ATP) therapies in the azimilide 75 mg per day group compared to placebo (HR = 0.43; CI 0.26–0.69, P = 0.0006). A 47% reduction was seen in the azimilide 125 mg per day group (HR = 0.53; CI 0.34–0.83, P = 0.0053). Both doses of azimilide decreased all-cause shocks but this was not statistically significant. When compared to placebo, azimilide 75 mg and 125 mg per day reduced appropriate ICD shocks and ATP by 48% (p = 0.017) and 62% (p = 0.0004) respectively. High (35–40%) but comparable rates of drug discontinuation was seen in both azimilide and placebo groups. Four patients in the azimilide group and one in the placebo group had torsades de pointes. Thus, it appears that azimilide has beneficial effects in prevention of ventricular arrhythmias in ICD patients.

On the other hand, azimilide was disappointing as a rhythm control drug for restoration and maintenance of sinus rhythm in AF. The North American Azimilide Cardioversion Maintenance Trial (ACOMET II) study compared azimilide (125 mg daily) with sotalol (160 mg twice daily) or placebo for maintaining sinus rhythm in 658 patients with persistent AF undergoing electrical cardioversion.[105] The primary endpoint was recurrence of AF. Azimilide was found to be superior to placebo, but was significantly inferior to sotalol in maintaining sinus rhythm.

The Azimilide Supraventricular Tachyarrhythmia Reduction (A-STAR) trial evaluated the effect of azimilide in maintaining sinus rhythm in patients with structural heart disease.[106] The trial randomized 220 patients to azimilide (125 mg daily) versus matching placebo, and patients were followed for time to first symptomatic AF recurrence. There was no significant difference between the azimilide and the placebo groups with respect to the primary endpoint. In terms of adverse effects, neutropenia was seen in 1% of patients who were on azimilide. A dose-dependent increase in torsades de pointes was noted with the incidence rates ranging from 0.3% for the 75 mg dose to 1.2% for the 100 mg dose.[107] Thus, in terms of AF rhythm control, the risk-benefit ratio was definitely not in favor of azimilide, and it is doubtful that this drug will be available for use in AF.

CLASS IV ANTIARRHYTHMIC DRUGS: CALCIUM CHANNEL ANTAGONISTS

Verapamil blocks the L-type calcium channel and can be used to slow AV nodal conduction to control the ventricular response rate atrial flutter and AF, but it could also be used to prevent recurrence of AV nodal reentry and AV reentry supraventricular tachycardia. Furthermore, verapamil can prevent triggered

activity and inhibit idiopathic right ventricular outflow tract tachycardias by this mechanism. Additionally, verapamil can affect reentrant mechanisms responsible for idiopathic left VT. The dose of verapamil is 120–480 mg a day in single or divided doses. Diltiazem, another calcium channel blocker that can be used to control the ventricular response rate in AF, is available in both intravenous and oral formulations.

MISCELLANEOUS DRUGS

ADENOSINE

Adenosine is an ultrashort acting purinergic agonist; it is vagotonic. It binds to the adenosine A1 receptor. Adenosine activates the $IK_{ACH,ADO}$ channels present in the atrium, sinus node and the AV node. This results in increased outward potassium current which leads to shortening of atrial action potential and membrane hyperpolarization and transient AV nodal block and sinus node depression.[108] These IK_{ADO} channels are not present in the ventricular myocytes and, therefore adenosine has not much of an effect in the ventricular myocardium. Indirectly, adenosine has an antiadrenergic action due to a decrease in cyclic AMP. This property might be responsible for its suppressive effect on outflow tract ventricular arrhythmias as well as a subgroup of focal atrial tachycardias, which probably are delayed after depolarization-mediated triggered rhythms resulting from catecholamine-mediated calcium overload.

Adenosine has a rapid onset of action and intravenous administration of 6–12 mg adenosine results in sinus node slowing and transient AV block. This property is most often used to terminate AV node dependent paroxysmal AV nodal reentry and orthodromic AV reentry supraventricular tachycardias. Adenosine can stop idiopathic VTs, especially those that originate from the right ventricular outflow tract.[109] It can also terminate some atrial tachycardias.[110] Adenosine is commonly used during an electrophysiology study to determine the presence of a concealed accessory pathway. The vasodilatory properties of adenosine make it useful as a chemical alternative to exercise in the diagnosis of myocardial ischemia.

Adverse effects with adenosine typically include dyspnea, chest tightness, flushing and exacerbation of bronchospasm. These are typically short-lasting and resolve quickly. Adenosine should be used with caution in patients with severe reactive airway disease. Use of adenosine can result in AF in 10–15% of patients due to shortening of atrial refractory periods. Transplanted hearts are exquisitely sensitive to adenosine and significant dose reduction is required.[111] Methylxanthines, such as caffeine and theophylline, block adenosine receptors and counteract the effects of adenosine. Dipyridamole reduces the reuptake of adenosine, thereby prolonging the effect of adenosine. Due to this, those who are on oral dipyridamole undergoing a stress test should receive intravenous dipyridamole and not adenosine.

NEWER DRUGS

TEDISAMIL

Tedisamil is a class III AAD that blocks multiple potassium channels, including IKr, IKs, IKur, Ito and IKATP.[112] Tedisamil prolong atrial and ventricular action potentials, but its effects are more pronounced in the atrial tissue. It also suppresses sinus node function and has antianginal properties.[107] Tedisamil has a half-life of 8–13 hours, is not metabolized, and is renally excreted.

A randomized, placebo-controlled dose-response study (n = 175) showed that tedisamil at doses of 0.4 mg/kg and 0.6 mg/kg was superior to placebo in converting new-onset AF to sinus rhythm. Efficacy was modest with a 41% conversion rate for 0.4 mg/kg and 51% conversion rate for the 0.6 mg/kg tedisamil group. There were two cases of ventricular arrhythmias (one case of torsades de pointes and one case of monomorphic VT) in the tedisamil group.[112] Clearly, more studies are needed to evaluate the safety and efficacy of tedisamil in AF.

VERNAKALANT

Vernakalant is the first in a class of AADs that are "atrial-selective". Atrial-selective drugs are being developed to target the ion channels or currents that are present in the atria and not in the ventricles. These include the ultra rapid potassium current IKur and the acetylcholine-mediated potassium channel IK_{ACH}. The goal for developing these drugs is to restore and maintain sinus rhythm in AF while avoiding the adverse ventricular events such as QTc prolongation and torsades de pointes.[113]

Vernakalant acts selectively in the atrium, targeting the following ion channels: IKur, IK_{ACH}, Ito and late INA.[114] The efficacy and safety of intravenous vernakalant (administered as a 10-minute intravenous infusion at a dose of 3 mg/kg; if AF had not been terminated within 15 minutes, a second 10-minute infusion be followed at a dose of 2 mg/kg) for the treatment of AF was assessed in the randomized, placebo-controlled, double-blind Atrial Arrhythmia Conversion Trials (ACT) I–III.[115-117] The ACT I and ACT III trials investigated vernakalant in the treatment of patients with sustained AF (duration > 3 hours, but not more than 45 days). A total of 336 patients were enrolled in ACT I and 276 patients in ACT III. The primary endpoint was conversion to sinus rhythm for at least 1 minute within 90 minutes of drug infusion. In both these trials, vernakalant was significantly better than placebo in converting AF to sinus rhythm.

In ACT I, sinus rhythm was achieved in 62% of patients receiving vernakalant compared with 4.9% of patients receiving placebo for AF of 3–48 hour duration.[115] In ACT III, 51.2% of patients receiving vernakalant converted to sinus rhythm compared with 3.6% of patients receiving placebo for AF of 3 hours to 7 days.[117] The median time to conversion was 10 minutes from the start of infusion and sinus rhythm was maintained for more than 24 hours in 97% of patients. Data from the ACT II trial, which investigated the efficacy of intravenous vernakalant in 150 patients with sustained AF (3–72 hours duration) that occurred between 24 hours and 7 days after coronary artery bypass graft and/or valvular surgery, showed a 47% conversion rate compared to 14% for placebo.[116]

In the AVRO (A Phase III Superiority Study of Vernakalant versus Amiodarone in Subjects With Recent Onset Atrial Fibrillation) trial, 254 patients with recent-onset AF (3–48 hours duration) were randomized to receive either intravenous vernakalant or intravenous amiodarone. Treatment with vernakalant converted 51.7% of patients to sinus rhythm at

90 minutes compared with 5.2% of patients treated with amiodarone. Both drugs were well tolerated.[118]

Vernakalant does not appear to be effective in AF of longer duration (> 7 days) or in atrial flutter.[117] Preliminary studies have shown that oral vernakalant (5 mg/kg) is rapidly absorbed and well-tolerated. Studies are ongoing to determine efficacy and safety of the oral formulation. Vernakalant appears to have a good safety profile but concerns still exist. Most common side effects are nausea, dysgeusia, paresthesias and hypotension.[117] No episodes of drug-induced torsades de pointes were reported in the ACT trials.

Currently, vernakalant is approved in Europe for rapid conversion of recent-onset AF (≤ 7 days duration for non-surgery patients, and less than or equal to 3 days duration for post-cardiac surgery patients) to sinus rhythm in adults. The atrial selectivity, modest efficacy rate and excellent safety profile makes vernakalant an important addition to the armamentarium for pharmacological conversion of AF.

IVABRADINE

High resting sinus heart rates have been independently associated with mortality and adverse cardiovascular outcomes.[119,120] Ivabradine is a selective cardiac pacemaker (I_f) current blocker that slows sinus rates.[121] When compared to placebo in the BEAUTIFUL (morBidity mortality EvAlUaTion of the I_f inhibitor ivabradine in patients with coronary disease and left ventricULar dysfunction) trial, ivabradine did not improve the composite outcome of cardiovascular death, hospitalizations for heart failure and/or acute myocardial infarction in patients with coronary artery and left ventricular dysfunction.[122] However, it did reduce fatal- and non-fatal myocardial infarction and coronary revascularization[122] and so may be useful as an antianginal drug, especially in combination with a beta-blocker.[123] Recent data would suggest that slowing heart rate may, in fact, improve outcomes in select patients with congestive heart failure[124] and with inappropriate sinus tachycardia.[125] Usual dosing range is 5–7.5 mg twice daily.

RANOLAZINE

Ranolazine is an antianginal drug that also can affect the late and the peak inward sodium current, the late calcium current and the IKr and IKs currents, as well as the sodium/calcium exchanger.[126] In the Efficiency with Ranolazine for Less Ischemia in Non-ST elevation acute coronary syndromes (MERLIN)-TIMI 36 trial, ranolazine significantly lowered nonsustained VT and supraventricular tachyarrhythmias in patients with non-ST elevation myocardial infarction when compared to placebo.[127] Recent data from a canine model suggests that ranolazine, in combination with dronedarone, may be a potent combination to reduce AF.[128]

EMERGING ANTIARRHYTHMIC DRUGS

Various novel AADs are presently being tested but they are nowhere near being considered valuable and/or valid therapies for arrhythmia suppression. Research continues with nifekalant, an IKr blocker for ventricular arrhythmias, celivarone, an amiodarone analogue, several IKur (and multichannel) blockers (AVE0118, AZD7009, NIP-141/142), sodium current blockers (pilsicainide and ranolazine), other amiodarone analogues (celivarone, ATI-2042 and PM101), selective IKs blockers (HMR1556) and Kv1.5 blockers (XEN-D0101).[129] Additionally, drugs are being tested that work by novel mechanisms including those that inhibit the atrial acetylcholine regulated potassium current, IK_{ACH} (tertiapin-Q), those that target abnormal calcium handling via the ryanodine receptor RyR2 (calstabin-2), those that act as sodium/calcium exchange inhibitors (KB-R7943), those that block the stretch activated channels, those that are gap junction modifiers (rotigaptide, GAP-134), those that antagonize the serotonin 5-hydroxytryptamine receptors (RS-100-302) and those that are long-acting adenosine A1 receptors (tecadenoson and selodenoson).[129] Likely, new drugs will be developed that will focus on other approaches rather than simply blocking specific cardiac channels.

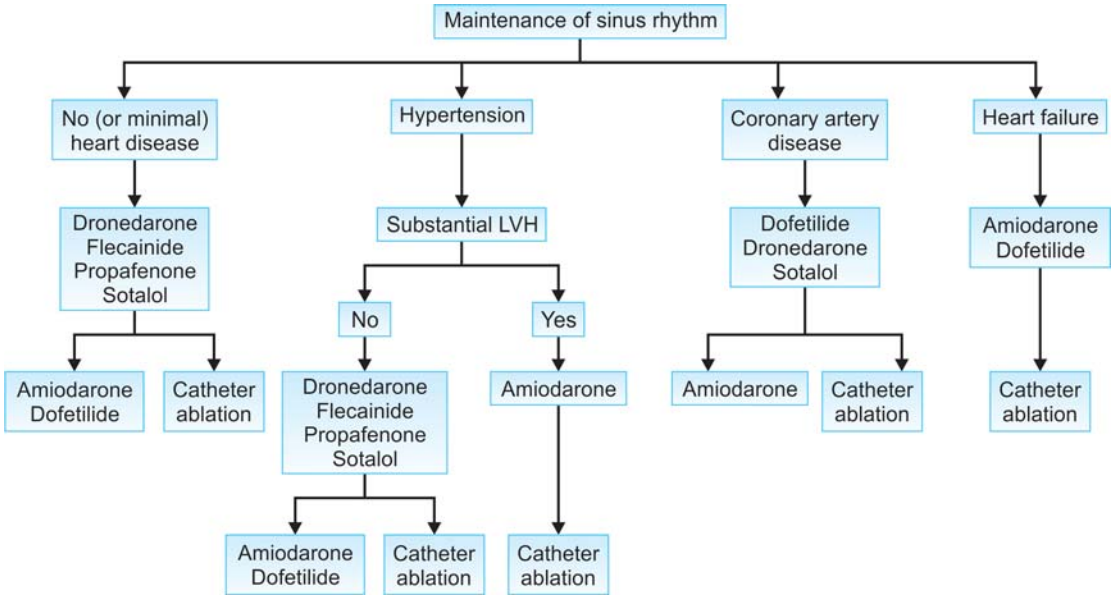
ANTIARRHYTHMIC DRUG SELECTION IN ATRIAL FIBRILLATION

The 2011 ACC/AHA/ESC Guidelines for Management of AF provides recommendations regarding AAD selection if rhythm control is planned for AF (Flow chart 1).[31] The recommendations are primarily based on AAD safety than on drug efficacy. For patients with no evidence of structural heart disease or have hypertension without substantial left ventricular hypertrophy, flecainide, propafenone, sotalol or dronedarone is first-line therapy, followed by amiodarone, dofetilide, or catheter ablation. For patients with hypertension and substantial left ventricular hypertrophy, amiodarone is the first choice drug, with catheter ablation as the second-line choice. In patients with coronary artery disease, dofetilide or sotalol is first-line, followed by amiodarone or catheter ablation. For heart failure patients, amiodarone or dofetilide is first-line therapy, followed by catheter ablation. Most recently, dronedarone has been included in the guidelines and has a role in the treatment of AF as stated in the package insert as "an AAD indicated to reduce the risk of cardiovascular hospitalization in patients with paroxysmal or persistent AF or atrial flutter, with a recent episode of AF or atrial flutter and associated cardiovascular risk factors (i.e. age > 70, hypertension, diabetes, prior cerebrovascular accident, left atrial diameter ≥ 50 mm or left ventricular ejection fraction < 40%), who are in sinus rhythm or who will be cardioverted".[94]

OUT-PATIENT VERSUS IN-HOSPITAL INITIATION FOR ANTIARRHYTHMIC DRUG THERAPY

The location of initiation of an AAD depends on the severity of the arrhythmia and the risk of starting the AAD. It is recommended that all class IA AADs be initiated in the hospital due to risk of torsades de pointes, which at times can be idiosyncratic and non-dose dependent. Class IB AADs, specifically mexiletine, can be started and titrated as an outpatient because the risk of proarrhythmia is small but, in most cases, this drug is started in the hospital due to the fact that most patients whom this drug is initiated have unstable ventricular arrhythmias. Class IC AADs can generally be started outside the hospital for AF as the early risk of proarrhythmia is low as long as the patient has no underlying structural heart disease and no evidence for cardiac ischemia. There is a small risk of rapid rates in AF with one-to-one conduction and atrial

 FLOW CHART 1: Antiarrhythmic drug selection, based on underlying structural heart disease, for maintenance of sinus rhythm in atrial fibrillation



[*Source:* Modified from Wann LS, Curtis AB, January CT, et al. 2011 ACCF/AHA/HRS focused update on the management of patients with atrial fibrillation (updating the 2006 guideline): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2011;123:104-23 (Reference 31)]

flutter but, with proper AV nodal blocking drugs, this risk can be offset. Amiodarone can be started as an outpatient for patients who have AF and atrial flutter as the proarrhythmic risk is low. On the other hand, most patients with VT are considered unstable and, therefore, the initiation of amiodarone normally begins in the hospital. A patient may not be fully loaded with amiodarone, but nevertheless the drug should be started in the hospital. Sotalol and dofetilide should be initiated in the hospital due to the risk of developing QT prolongation and torsades de pointes. Dofetilide must be started in the hospital based on strict guidelines about how the drug should be initiated and titrated. Dronedarone is generally not proarrhythmic and can be started outside the hospital.

ANTIARRHYTHMIC DRUGS IN PREGNANCY AND LACTATION

An overview of the effect of various AADs in pregnancy and lactation is presented in Table 7. Sotalol is the only pregnancy category B drug [either animal-reproduction studies have not demonstrated a fetal risk but there are no controlled studies in pregnant women, or animal-reproduction studies have shown an adverse effect (other than a decrease in fertility) that was not confirmed in controlled studies in women in the first trimester (and there is no evidence of a risk in later trimesters)], while amiodarone is classified as pregnancy category D drug [there is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g. if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective)]. Dronedarone is a pregnancy category X drug (studies in animals or human beings have demonstrated fetal abnormalities, or there is evidence of fetal risk based on human experience or both, and the risk of the use of the drug in pregnant women clearly outweighs any possible benefit. The drug is contraindicated in women who are or may become pregnant) and so is contraindicated in women who are or may become pregnant. The rest of the AADs are considered pregnancy category C drug [either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other) and there are no controlled studies in women, or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the fetus]. The use of beta-blockers during pregnancy is relatively safe. The only exception is atenolol, which is a pregnancy category D drug.

TABLE 7

Antiarrhythmic drugs in pregnancy and lactation

Drug	*Pregnancy*	*Lactation*
Quinidine	C	Excreted
Procainamide	C	Excreted
Disopyramide	C	Excreted
Mexiletine	C	Excreted
Flecainide	C	Excreted
Propafenone	C	?
Sotalol	B	Excreted
Dofetilide	C	?
Dronedarone	X	?
Amiodarone	D	Excreted

COMPARING ANTIARRHYTHMIC DRUGS TO IMPLANTABLE CARDIOVERTER DEFIBRILLATORS IN PATIENTS AT RISK OF ARRHYTHMIC DEATH

Several large, randomized, prospective, multicenter, controlled clinical trials compared ICDs versus AADs.[130,131] The Antiarrhythmics Versus Implantable Defibrillators (AVID) trial

randomized patients resuscitated from a cardiac arrest to an ICD, empiric amiodarone (mean dose of 300 mg; 90% of patients) or sotalol (mean dose 250 mg) guided by electrophysiology study or Holter monitoring. The group runnings ICDs had a significant 39% (one year), 27% (two year) and 31% (three year) mortality reduction when compared to AADs. Only those patients with left ventricular ejection fraction between 20% and 34% showed a survival benefit with ICD (83%) when compared to amiodarone (72%).[130] The multicenter, prospective Sudden Cardiac Death Heart Failure Trial (SCD-HeFT) randomly assigned 2,521 medically managed ischemic and non-ischemic cardiomyopathy patients with a left ventricular ejection fraction less than or equal to 35%, and NYHA functional class II–III heart failure to an ICD, amiodarone and placebo. Patients were followed for a median of 46 months. The primary endpoint was total mortality. The study showed that the ICD resulted in a 7.2% absolute and a 22% relative reduction in mortality, when compared to placebo and amiodarone. Amiodarone was no better than placebo in improving mortality. Patients with NYHA class III heart failure symptoms fared worse with amiodarone when compared to placebo (HR1.44, confidence interval 1.05–1.97, $P = 0.01$).[131]

In summary, ICDs are superior to AADs for both primary and secondary prevention of mortality, presumably due to sudden cardiac death. The AADs should be reserved only for patients who are not candidates for an ICD, who refuse ICD therapy, and for select patients with genetic disorders that respond well to a specific AAD.

ANTIARRHYTHMIC DRUG-DEVICE INTERACTIONS

The ICD has emerged as the primary therapeutic modality for prevention of sudden cardiac death. Concomitant AAD therapy may be required in select ICD patients to suppress recurrent atrial and ventricular arrhythmias and to reduce the incidence and frequency of both appropriate and inappropriate shocks.[40] When used in this setting, AADs can affect device functioning in several ways:

- AADs can increase defibrillation and pacing thresholds
- AADs can slow VT rate to below the programmed ICD detection rate
- AADs can cause sinus and AV node dysfunction, resulting in bradycardia and AV block
- AADs can be proarrhythmic

It is important to be aware of these potential interactions when selecting an appropriate AAD and also during device programming. Amiodarone and sotalol are the two most common AADs used in an ICD population. Table 8 lists the effect of various AADs on pacing and defibrillation thresholds. Class I AADs and amiodarone have been shown to raise the defibrillation threshold, whereas class III drugs such as sotalol and dofetilide tend to decrease the energy needed to defibrillate.[40] The results of the prospective, randomized, Optimal Pharmacologic Therapy in Cardioverter Defibrillator Patients (OPTIC) trial casts doubts regarding the clinical significance of these above-mentioned effects in the current era of high energy ICD devices. The OPTIC trial compared the effects of beta-blockers, beta-blocker plus amiodarone and sotalol on defibrillation energy requirements in 94 patients. The study showed that changes in defibrillation threshold with amiodarone and sotalol are at best modest and argues against repeat defibrillation threshold testing after initiating therapy with either drug.[132] The study also showed that amiodarone plus a beta-blocker was most effective in preventing ICD shocks at 1 year and was more effective than sotalol (10.3% vs 24.3% for sotalol; HR, 0.43; $P = 0.02$).[49]

TABLE 8

Effect of antiarrhythmic drugs on defibrillation and pacing thresholds

Drug	*Pacing threshold*	*Defibrillation threshold*
Quinidine	Increase	Increase
Procainamide	Increase	No change/increase
Lidocaine	No change	Increase
Flecainide	Increase	Increase
Beta-blockers	Increase	Decreases
Digoxin	Decrease	Decrease/no change
Ibutilide	Not known	Decrease
Sotalol	No effect	Decrease
Amiodarone	No effect	Increase
Dofetilide	No change	Decrease
Verapamil	Increase	Not known

CONCLUSION

Antiarrhythmic drug therapy continues to play a critical role in the management of atrial and ventricular arrhythmias. The role of AADs has evolved in the face of advances in curative therapy for specific arrhythmias, as well as for underlying diseases. It is fair to say that the history of AAD therapy has come full circle: from the days of the CAST and SWORD trials showing increased mortality to demonstration of mortality benefit with dronedarone in the recent ATHENA trial. Irrespective of effects on survival, AADs are an integral part of the pharmacological armamentarium to combat AF, to treat ventricular arrhythmias in the structurally normal heart and in those with channelopathies, to suppress sustained ventricular arrhythmias in patients with structural heart disease who either have an ICD or are not candidates for one. The field of AAD therapy continues to evolve as newer drugs that target novel mechanisms are being actively developed and, with currently available drugs finding new indications for their use.

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Chapter 31

Electrophysiology Studies

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Chapter Outline

- Cardiac Electrophysiology Study: Philosophy, Requirements and Basic Techniques
  - — Cardiac Access and Catheterization
  - — Signals and Filtering
- Fundamentals of the Cardiac Electrophysiology Study
  - — Conventions
  - — Normal Cardiac Electrophysiology
- Programmed Electrical Stimulation and Associated Electrophysiology
  - — Continuous Pacing
  - — Intermittent or Interrupted Pacing with Extrastimuli
  - — Significance of "Short-Long-Short" Pacing Cycles
  - — Clinical Application of "Routine" Electrophysiology Study and Anticipated Responses to Programmed Stimulation
  - — Survivors of Sudden Cardiac Arrest
- Cardiac Electrophysiology Study for Evaluation of Drug Therapy
- Electrophysiology Study to Guide Ablative Therapy
  - — Role of Three-Dimensional Mapping Systems
- Complications

INTRODUCTION

Clinical cardiac electrophysiology (EP) is a relatively new and continually evolving investigative field. Its modern underpinnings date back to the first description of the cardiac Purkinje fibers in 1839 by Czech neuroscientist Jan Evangelista Purkynê,[1] and description of the atrioventricular (AV) bundle by Wilhelm His Jr.[2] and accessory "AV bundles" by Albert Kent in 1893.[3] Such anatomic discoveries of the cardiac conduction system were the first murmurings of what would spawn an entirely independent arena of cardiac investigation that continued in this vein into the early 20th century with description of the AV node by Sunao Tawara[4] in 1906 and, finally, the sinoatrial node[5] in 1907 by Arthur Keith and his student Martin Flack. Einthoven's 1908 description of the modern electrocardiograph[6] heralded a new phase of cardiac electrophysiologic discovery, permitting arrhythmia description and electrocardiogram (ECG) correlation with clinical presentation. During his Nobel speech, Einthoven foretold that "a new chapter has been opened in the study of heart diseases ...." This was the primary mode of "electrophysiology study" during the first half of the 20th century, during which time the first case of idiopathic ventricular fibrillation (VF) was described, in 1929,[7] and the first long QT case reports were described by Jervell and Lange-Nielsen.[8]

Percutaneous and open-chest techniques for arrhythmia mapping were first described in the 1950s, but it was not until the late 1960s and 1970s that a reproducible technique for recording the His bundle potential[9] was demonstrated and utilized. Its role, as well as that of programed electrical stimulation, for identification of site of origin and arrhythmia mechanism established the invasive cardiac EP study as a mainstay in diagnostic cardiology, expanding the frontiers of cardiac EP and cardiovascular disease. This breakthrough was accompanied by an increase in open-chest surgical therapy and ablation, providing further insight into the mechanisms of arrhythmias. However, demonstration of a closed-chest catheter technique for destruction of cardiac tissue[10] truly revolutionized the field. It provided a percutaneous option for patients to undergo diagnosis and treatment in the same setting.

Since those early and formative years, the comprehensive EP study has gradually evolved from a prolonged undertaking to a streamlined diagnostic process that attempts to identify clinically relevant mechanisms of arrhythmogenesis, and correlate these with symptomatology to guide therapy. This chapter focuses on fundamental aspects of the contemporary intracardiac EP study and should serve as a foundation for all cardiovascular disease practitioners seeking further insight into the electrophysiologic mechanisms of the human heart.

CARDIAC ELECTROPHYSIOLOGY STUDY: PHILOSOPHY, REQUIREMENTS AND BASIC TECHNIQUES

The contemporary EP study has been condensed, abbreviated and streamlined to capitalize on the basic science, and clinical foundations established since the 1800s to efficiently evaluate tendency toward arrhythmia and its underlying mechanisms. The EP studies are performed to investigate clinically documented rhythm disturbances or evaluate symptoms compatible with arrhythmic etiology, such as palpitations or syncope, for risk stratification of sudden death and evaluation of pharmacologic

therapy.[11] Alternatively, not all arrhythmias and arrhythmic mechanisms may be evaluated by or necessitate study. For instance, an EP study is not generally indicated for evaluation of symptomatic bradycardia. Whether the mechanism is sinus node dysfunction or conduction disease in the AV node, His bundle or Purkinje system, permanent pacing is usually required, and demonstrating mechanism may be of more "academic" concern. In specific situations, however, demonstration of the level and mechanism of conduction block may be instrumental in guiding therapy, such as in apparent conduction block attributable to junctional extrasystoles in which beat suppression is required, whether medical or ablative, rather than pacing. Indications for EP study are shown in Tables 1 to 13.[12]

TABLE 1

Indications for electrophysiology study to evaluate sinus node function

Class I
- Symptomatic patients in whom sinus node dysfunction is suspected as the cause of symptoms, but a causal relation between an arrhythmia and the symptoms has not been established after appropriate evaluation

Class II
- Patients with documented sinus node dysfunction in whom evaluation of AV or VA conduction or susceptibility to arrhythmias may aid in selection of the most appropriate pacing modality
- Patients with electrocardiographically documented sinus bradyarrhythmias to determine if abnormalities are due to intrinsic disease, autonomic nervous system dysfunction or the effects of drugs so as to help select therapeutic options
- Symptomatic patients with known sinus bradyarrhythmias to evaluate potential for other arrhythmias as the cause of symptoms

Class III
- Symptomatic patients in whom an association between symptoms and a documented bradyarrhythmia has been established and choice of therapy would not be affected by results of an electrophysiology study
- Asymptomatic patients with sinus bradyarrhythmias or sinus pauses observed only during sleep, including sleep apnea

Abbreviations: AV: Atrioventricular; VA: Ventriculoatrial

TABLE 2

Electrophysiology study indications for acquired AV block

Class I
- Symptomatic patients in whom His-Purkinje block, suspected as a cause of symptoms, has not been established
- Patients with second-degree or third-degree AV block treated with a pacemaker who remain symptomatic and in whom another arrhythmia is suspected as a cause of symptoms

Class II
- Patients with second-degree or third-degree AV block in whom knowledge of the site of block or its mechanism or response to pharmacological or other temporary intervention may help to direct therapy or assess prognosis
- Patients with premature, concealed junctional depolarizations suspected as a cause of second-degree or third-degree AV block pattern (i.e. pseudo-AV block)

Class III
- Symptomatic patients in whom the symptoms and presence of AV block are correlated by ECG findings
- Asymptomatic patients with transient AV block associated with sinus slowing (e.g. nocturnal type I second-degree AV block)

Abbreviations: AV: Atrioventricular; ECG: Electrocardiogram

The cardiac EP study itself is a systematic evaluation of clinically relevant aspects of myocardial electrical stimulation and propagation and arrhythmic potential. It is conducted in a diagnostic cardiac EP or angiography suite, with minimum

TABLE 3

Electrophysiology study indications for chronic intraventricular conduction delay

Class I
- Symptomatic patients in whom the cause of symptoms is not known

Class II
- Asymptomatic patients with bundle branch block in whom pharmacological therapy that could increase conduction delay or produce heart block is contemplated

Class III
- Asymptomatic patients with intraventricular conduction delay
- Symptomatic patients whose symptoms can be correlated with or excluded by ECG events

Abbreviations: ECG: Electrocardiogram

TABLE 4

Electrophysiology study indications for narrow QRS complex tachycardias

Class I
- Patients with frequent or poorly tolerated episodes of tachycardia that do not adequately respond to drug therapy and for whom information about site of origin, mechanism and electrophysiological properties of the pathways of the tachycardia is essential for choosing appropriate therapy (drugs, catheter ablation, pacing or surgery)
- Patients who prefer ablative therapy to pharmacological treatment

Class II
- Patients with frequent episodes of tachycardia requiring drug treatment for whom there is concern about proarrhythmia or the effects of the antiarrhythmic drug on sinus node or AV conduction

Class III
- Patients with tachycardias easily controlled by vagal maneuvers and/or well-tolerated drug therapy who are not candidates for nonpharmacological therapy

Abbreviations: AV: Atrioventricular

TABLE 5

Electrophysiology study indications for wide QRS complex tachycardias

Class I
- Patients with wide QRS complex tachycardia in whom correct diagnosis is unclear after analysis of available ECG tracings, and for whom knowledge of the correct diagnosis is necessary for patient care

Class II
- None

Class III
- Patients with ventricular or supraventricular tachycardia with aberrant conduction or preexcitation syndromes diagnosed with certainty by ECG criteria, and for whom invasive electrophysiological data would not influence therapy. However, data obtained at baseline EP study in these patients might be appropriate as a guide for subsequent therapy

Abbreviations: ECG: Electrocardiogram; EP: Electrophysiology

TABLE 6

Electrophysiology study indications for prolonged QT intervals

Class I
- None

Class II
- Identification of a proarrhythmic effect of a drug in patients experiencing sustained ventricular tachycardia or cardiac arrest while receiving the drug
- Patients who have equivocal abnormalities of QT interval duration or TU wave configuration, with syncope or symptomatic arrhythmias, in whom catecholamine effects may unmask a distinct QT abnormality

Class III
- Patients with clinically manifest congenital QT prolongation, with or without symptomatic arrhythmias
- Patients with acquired prolonged QT syndrome with symptoms closely related to an identifiable cause or mechanism

TABLE 7

Electrophysiology study indications for Wolff-Parkinson-White syndrome

Class I
- Patients being evaluated for catheter ablation or surgical ablation of an accessory pathway
- Patients with ventricular preexcitation who have survived cardiac arrest, or who have unexplained syncope
- Symptomatic patients in whom determination of the mechanism of arrhythmia, or knowledge of the electrophysiological properties of the accessory pathway and normal conduction system would help in determining appropriate therapy

Class II
- Asymptomatic patients with a family history of sudden cardiac death or with ventricular preexcitation, but no spontaneous arrhythmia, who engage in high-risk occupations or activities, and in whom knowledge of the electrophysiological properties of the accessory pathway or inducible tachycardia may help to determine recommendations for further activities or therapy
- Patients with ventricular preexcitation who are undergoing cardiac surgery for other reasons

Class III
- Asymptomatic patients with ventricular preexcitation, except those in Class II above

TABLE 8

Electrophysiology study indications for premature ventricular complexes, couplets and nonsustained ventricular tachycardia

Class I
- None

Class II
- Patients with other risk factors for future arrhythmic events, such as a low ejection fraction, positive signal-averaged ECG, and nonsustained VT on ambulatory ECG recordings in whom electrophysiology studies will be used for further risk assessment and for guiding therapy in patients with inducible VT
- Patients with highly symptomatic, uniform morphology premature ventricular complexes, couplets and nonsustained VT, who are considered as potential candidates for catheter ablation

Class III
- Asymptomatic or mildly symptomatic patients with premature ventricular complexes, couplets and nonsustained VT without other risk factors for sustained arrhythmias

Abbreviations: ECG: Electrocardiogram; VT: Ventricular tachycardia

TABLE 9

Electrophysiology study indications for unexplained syncope

Class I
- Patients with suspected structural heart disease and syncope that remains unexplained after appropriate evaluation

Class II
- Patients with recurrent unexplained syncope without structural heart disease and a negative head-up tilt test

Class III
- Patients with a known cause of syncope for whom treatment will not be guided by electrophysiological testing

TABLE 10

Electrophysiology study indications for survivors of cardiac arrest

Class I
- Patients surviving cardiac arrest without evidence of an acute Q-wave MI
- Patients surviving cardiac arrest occurring more than 48 hours after the acute phase of MI in the absence of a recurrent ischemic event

Class II
- Patients surviving cardiac arrest caused by bradyarrhythmia
- Patients surviving cardiac arrest thought to be associated with a congenital repolarization abnormality (long-QT syndrome) in whom the results of noninvasive diagnostic testing are equivocal

Class III
- Patients surviving a cardiac arrest that occurred during the acute phase (< 48 hours) of MI
- Patients with cardiac arrest resulting from clearly definable specific causes such as reversible ischemia, severe valvular aortic stenosis or noninvasively defined congenital or acquired long-QT syndrome

Abbreviation: MI: Myocardial infarction

TABLE 11

Electrophysiology study indications for unexplained palpitations

Class I
- Patients with palpitations who have a pulse rate documented by medical personnel as inappropriately rapid and in whom ECG recordings fail to document the cause of the palpitations
- Patients with palpitations preceding a syncopal episode

Class II
- Patients with clinically significant palpitations suspected to be of cardiac origin in whom symptoms are sporadic and cannot be documented. Studies are performed to determine the mechanisms of arrhythmias, direct or provide therapy, or assess prognosis

Class III
- Patients with palpitations documented to be due to extracardiac causes (e.g. hyperthyroidism)

Abbreviation: ECG: Electrocardiogram

requirements of single-plane fluoroscopy and patient table/gantry; electrocardiac stimulator, signal filtering and recording system; and diagnostic electrode catheters through which cardiac stimulation and intracardiac signals/impulses may be sensed and delivered. Patients are generally studied in the postabsorptive state so as to minimize risk of aspiration while sedated or during arrhythmia induction that, at times, may provoke hemodynamic instability necessitating rapid arrhythmia termination including external cardioversion/defibrillation. Patients undergo sterile

TABLE 12

Electrophysiology study indications for guiding drug therapy

Class I
- Patients with sustained ventricular tachycardia or cardiac arrest, especially those with prior MI
- Patients with AVNRT, AV reentrant tachycardia using an accessory pathway, or atrial fibrillation associated with an accessory pathway, for whom chronic drug therapy is planned

Class II
- Patients with sinus node reentrant tachycardia, atrial tachycardia, atrial fibrillation or atrial flutter without ventricular preexcitation syndrome, for whom chronic drug therapy is planned
- Patients with arrhythmias not inducible during control EPS, for whom drug therapy is planned

Class III
- Patients with isolated atrial or ventricular premature complexes
- Patients with ventricular fibrillation with a clearly identified reversible cause

Abbreviations: AVNRT: Atrioventricular nodal reentrant tachycardia; EPS: Electrophysiology study; MI: Myocardial infarction

TABLE 13

Electrophysiology study indications for candidates and recipients of implantable electrical devices

Class I
- Patients with tachyarrhythmias, before and during implantation, and final (predischarge) programing of an electrical device to confirm its ability to perform as anticipated
- Patients with an implanted electrical antitachyarrhythmia device in whom changes in status or therapy may have influenced the continued safety and efficacy of the device
- Patients who have a pacemaker to treat a bradyarrhythmia and receive a cardioverter-defibrillator, to test for device interactions

Class II
- Patients with previously documented indications for pacemaker implantation to test for the most appropriate long-term pacing mode and sites to optimize symptomatic improvement and hemodynamics

Class III
- Patients who are not candidates for device therapy

skin preparation using iodine and other alcohol-based and nonalcohol-based scrubs, followed by draping to prevent cross-contamination from nonsterilized areas and to maintain patient dignity while permitting access to anticipated sites of vascular entry. Local anesthesia, as well as mild conscious sedation, is warranted to facilitate painless percutaneous vascular access, particularly in apprehensive patients. After diagnostic catheters are introduced, sedation may be lightened so as not to hinder arrhythmia induction, as some sedative drugs may alter properties of the cardiac conduction system. The awake patient should be continuously reassured to promote relaxation and to prevent sudden movements that may result in catheter dislodgement and vascular injury, not to mention intracardiac trauma. Antiarrhythmic drugs are usually withheld prior to the study, although in select cases, they may be continued if clinical events occurred on specific agents or in an effort to promote tolerability of arrhythmias that may otherwise provoke severe symptoms or hemodynamic collapse.

A complete study evaluates sinus node automaticity and impulse propagation, atrial myocardial conduction properties, anterograde and retrograde conduction patterns, ventricular myocardial conduction properties and associated arrhythmic tendency, both spontaneous and stimulated.[13] Not all assessments may be possible in every patient. Pharmacologic agents also are administered to modify intrinsic automaticity and conduction properties to expose occult arrhythmic potential.

CARDIAC ACCESS AND CATHETERIZATION

The recording of local activation signals during EP study is obtained through stationary electrode catheters (Fig. 1), usually varying in size from 4 to 8 French. Standard diagnostic multipolar electrode catheters are introduced percutaneously through peripheral veins, such as the antecubital, femoral, subclavian or internal jugular veins, and then guided fluoroscopically to their intended intracardiac position. For safety and convenience, sites accessible transvenously via right cardiac chambers are chosen, usually the high-lateral right atrium or right atrial appendage, approximating the site of sinus endocardial breakthrough; His bundle region, approximating the site of atrioventricular nodal (AVN) conduction; within the coronary sinus (CS) that is posteriorly located, approximating a septal-lateral axis of activation of both the left atrium and ventricle; and the right ventricle (RV) (Fig. 2). This "standard" catheter positioning approximates the normal conduction system axis, creating a skeleton of recording sites that define the sequence and timing of activation from all four cardiac chambers. Other recording sites, such as the right bundle-branch

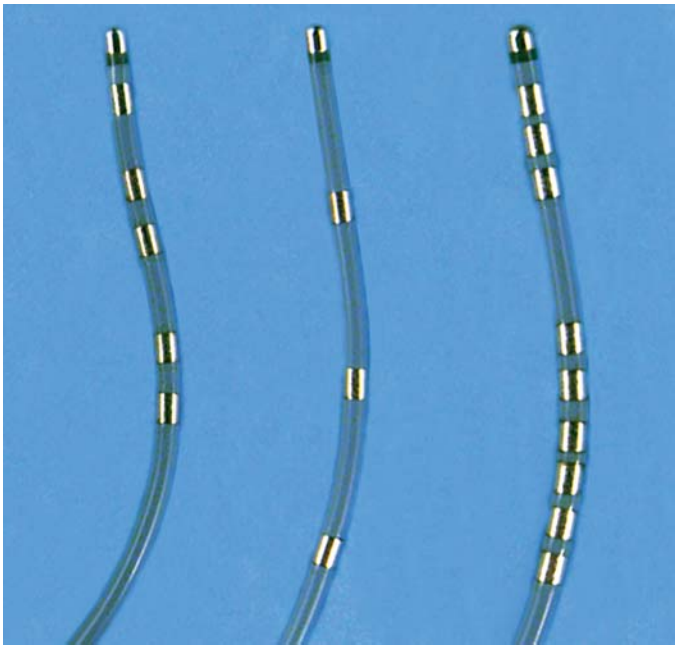


FIGURE 1: Examples of diagnostic multielectrode catheters. Three diagnostic catheters with different interelectrode spacing and electrode distribution are shown. Closer-spaced electrodes permit detection of high-frequency signals such as His or accessory pathway potentials, with high degree of localization though at the expense of signal amplitude, whereas wider-spaced electrodes yield larger-amplitude signals, at the expense of localization accuracy

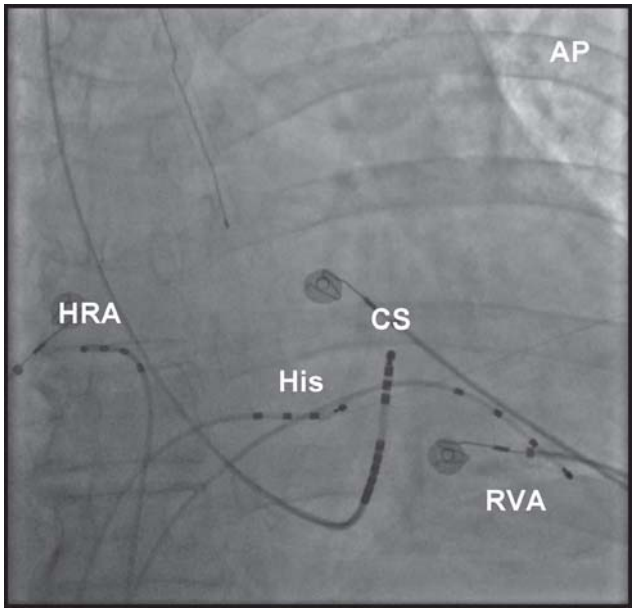


FIGURE 2: Anteroposterior (AP) fluoroscopic projection of "standard" intracardiac catheter locations. The high right atrial (HRA) catheter is positioned laterally in the right atrial appendage. The His catheter is positioned across the atrioventricular junction at the mid-to-superior septal aspect of the tricuspid valve. The right ventricular catheter is seated in the apex (RVA). The coronary sinus (CS) catheter is positioned with the proximal electrode approximately 1 cm from the CS ostium. (*Source:* Reproduced from Choudhuri et al. Principles and techniques of cardiac catheter mapping. In: Camm AJ, Saksena S (Eds). Electrophysiologic Disorders of the Heart, 2nd edition. St. Louis: Churchill-Livingstone (Elsevier) Inc; 2010. With permission from Elsevier.)

region just across the tricuspid valve and right ventricular septum or outflow tract, and even the pulmonary veins, may be sampled using traditional and specially designed catheters to further augment and enhance the diagnostic framework based on the suspected arrhythmia.

Transseptal catheterization (see below) via the right atrium to access left atrium is invaluable, particularly to approach pulmonary veins in atrial fibrillation (AF) ablation and for ventricular tachycardia (VT) ablation in patients with mechanical aortic valve in whom the left ventricle (LV) would be otherwise inaccessible through the aortic retrograde approach. Continuous heparinization is desirable for left-heart catheterization to avoid thromboembolic complications. Catheterization into the pericardial space using a subxiphoid or subcostal approach permits access for mapping and ablation of arrhythmias of epicardial origin.

SIGNALS AND FILTERING

Once intracardiac diagnostic catheters are appropriately positioned and connectivity established, the recorded signals, intracardiac electrograms (EGMs), are displayed simultaneously on a multichannel digital recording system along with several unfiltered surface ECG leads. Signal filtering between 30–40 Hz and 500 Hz is best suited for sharp intracardiac signals such as those from the His bundle and accessory pathways (Figs 3A to F). A high-pass filter setting of more than 50–100 Hz reduces undesirable low-frequency signals. In addition, 60-cycle interference and its harmonics can be eliminated with a notch filter tuned to 60 Hz,[11] although potentially at the expense of other low-amplitude physiologic signals in that frequency range.

FUNDAMENTALS OF THE CARDIAC ELECTROPHYSIOLOGY STUDY

Identifying pathology during the cardiac EP study requires a keen awareness of normal electrophysiologic characteristics, an understanding of the principles guiding intracardiac EGM interpretation and knowledge of expected responses to programed stimulation.[14] Further, these assessments must be universally understood and communicable to other practitioners at various levels of training and expertise including electrophysiologists, cardiologists, physician extenders, lab technicians, nurses and even health care providers not directly practicing in the field of cardiovascular diseases.

CONVENTIONS

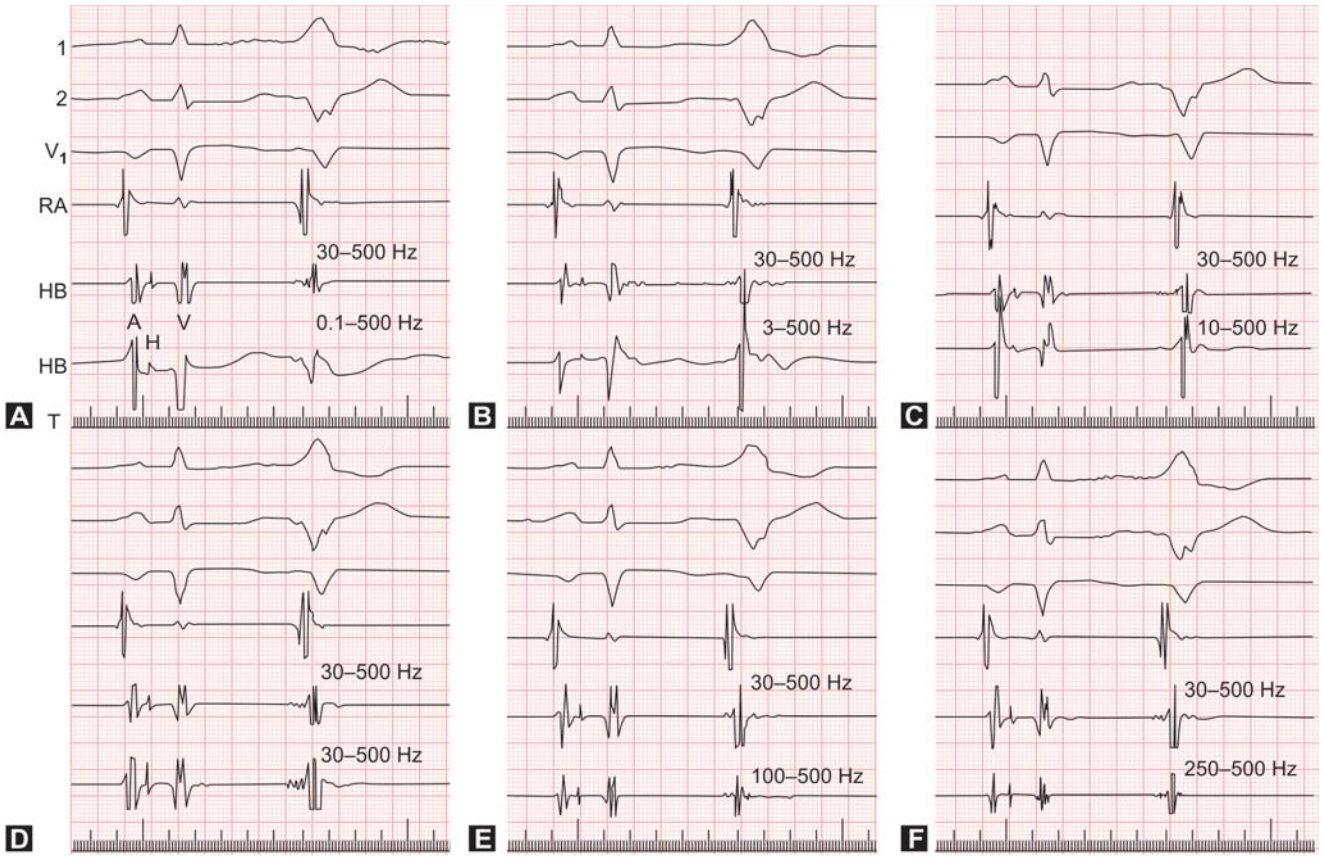
Several conventions are used to describe electrical events in a standardized manner, which are briefly described in this chapter. The most fundamental of these is that of timing and intervals. Measurements of most EP intervals are made in milliseconds, similar to usual intervals on the standard ECG. However, rates of atrial and ventricular events are determined in beats per minute and are converted to milliseconds by dividing the rate into 60,000 (the number of milliseconds per minute), yielding the rate of that particular event (e.g. heart rate) in milliseconds (per beat or occurrence). Hence sinus rhythm, usually 60–100 beats per minute, corresponds to cycle length 1,000–600 ms, respectively.

Diagnostic EP catheters have multiple electrodes, which create various recording unipoles and bipoles. By convention, the distal or tip electrode is designated electrode "1" and more proximal electrodes are numbered sequentially with increasing distance from the tip electrode. Further, whereas intracardiac EGMs are typically bipolar signals—and hence require two electrodes (usually adjacent) to generate the signal—a quadripolar catheter can generate up to three bipolar EGMs ("1–2", "2–3", "3–4"), and a decapolar catheter can display up to nine bipoles from adjacent electrodes. Other pairs can be configured as well. Often, all bipoles are not displayed; it depends on the clinical utility, particular catheter and/or its location and mapping resolution required.

NORMAL CARDIAC ELECTROPHYSIOLOGY

Normal Propagation Patterns

An awareness of two principles aids in proper interpretation of intracardiac EGMs. The first is that propagation within myocardium is generally radial, although with some directionality, due to anisotropic conduction and presence of structural barriers. This pattern of propagation during a stable rhythm results in activation at various myocardial areas simultaneously. Consider an atrial tachycardia arising from the low crista terminalis (Fig. 4A). Repetitive depolarization at this site is itself not detected, as this location is not standard for

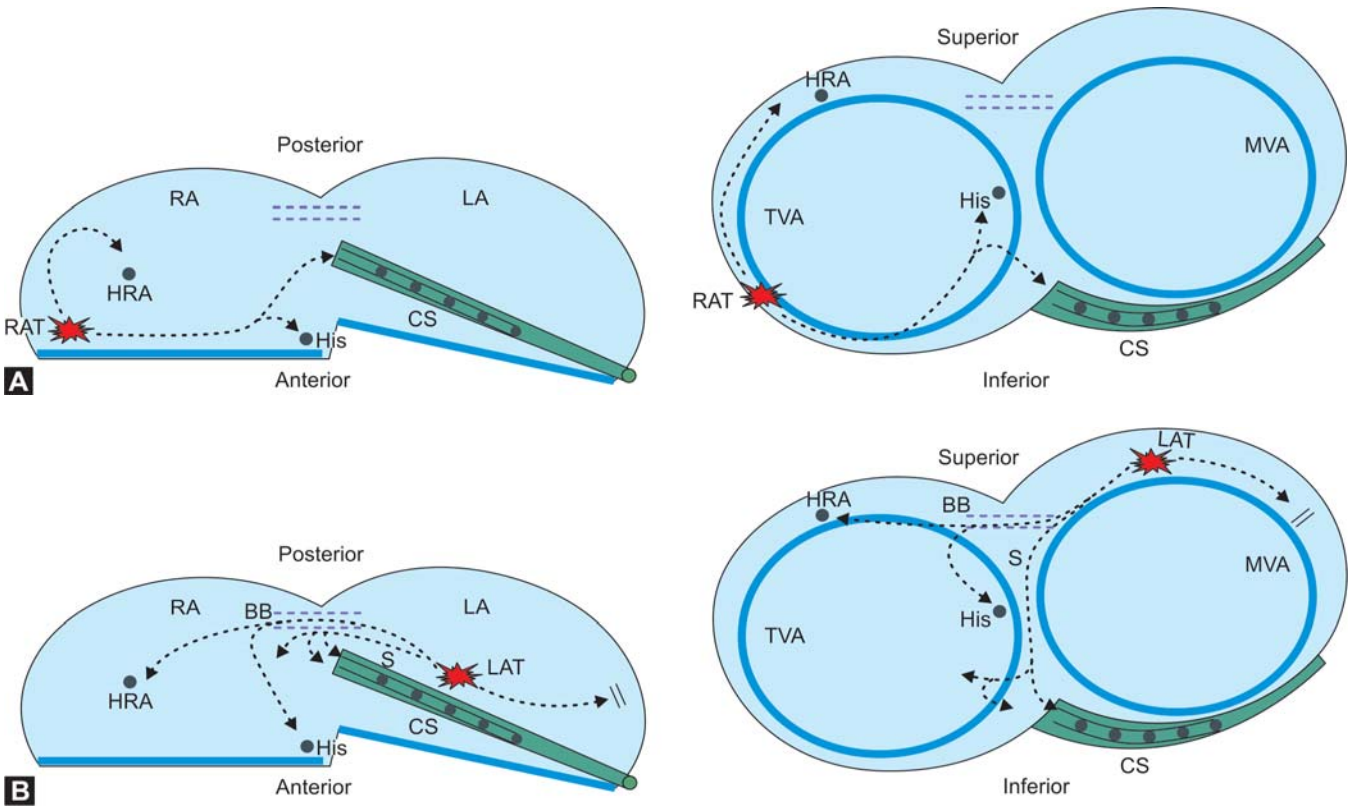


FIGURES 3A TO F: Effects of various filtering frequencies on the morphologic appearance of intracardiac electrograms. The tracings from top to bottom are electrocardiographic leads 1, 2, V1, right atrial (RA), two His bundle (HB) electrograms and timeline (T). In each Panel, the first beat is of sinus origin and is followed by a spontaneous ventricular premature beat. The top HB, RA and right ventricle are filtered at 30–500 Hz (i.e. the usual filtering frequencies). The bottom HB tracing shows the effect of various filtering frequencies on the appearance. The low-frequency signals are mostly eliminated at high-band-pass filter frequency settings above 10 Hz (Panel C). The low-band-pass filter settings above 500 Hz generally do not have a significant effect on the intracardiac electrogram appearance. It should be pointed out that the high-band-pass setting reduces the overall magnitude of the electrogram, necessitating an increase in amplification. It should also be noted that, at all frequencies depicted, the HB deflection can be clearly identified. (*Source:* Akhtar M. Invasive cardiac electrophysiologic studies: An introduction. In: Parmley WW, Chatterjee K (Eds). Cardiology: Physiology Pharmacology Diagnosis. Philadelphia: Lippincott; 1991. With permission from Lippincott Williams and Wilkins)

diagnostic catheters. Only after radial propagation through the right atrium, away from the tachycardia origin, and arrival at sites where catheters are located, e.g. the high right atrium (HRA) and His, are EGMs first recorded. In this case conduction times to these locations are fairly similar, resulting in near-simultaneous activation at both sites. The EGMs should neither be interpreted as representing a tachycardia arising simultaneously from those sites nor rapidly propagating from one site to the other so as to "appear" near-simultaneous, but rather more accurately explained by radial spread of a wave of activation arising from a location that has relatively similar conduction times to those catheter locations. This principle is inherently not specific, and other endocardial sites may also be equidistant from the HRA and His catheters (Fig. 4B). Hence, radial spread permits tachycardias arising from various intracardiac sites to produce similar EGM patterns (Fig. 4C). Definitive identification of involved sites requires more detailed cardiac mapping.

With respect to the AV conduction system, such tissues, in fact, should be considered to exhibit at least bidirectional propagation unless absence of this capability is demonstrated, even if unidirectional propagation predominates. For instance, in sinus rhythm or when pacing the atrium, it is expected that the impulse will conduct to the ventricles in an otherwise healthy heart. However, it should not be discounted that retrograde, i.e. ventriculoatrial (VA), conduction may also be responsible for cardiac rhythm events. Consider the situation of aberrant conduction induced by cycle length variation. Often one finds aberrancy, i.e. "bundle branch block," persists for several beats. This phenomenon develops due to anterograde conduction of a supraventricular impulse solely along the unblocked bundle and then spread of activation across the interventricular septum to invade and travel retrogradely along the previously blocked bundle, rendering it refractory to anterograde conduction by the next arriving supraventricular impulse and thereby maintaining aberrancy (Figs 5A to C).

In addition to these technical and physiologic aspects, it should be recognized that microscopic, molecular and cellular properties underlying myocardial membrane ion channel function, excitation-contraction, cellular automaticity, conduction velocity and tissue refractoriness to name a few, directly impact EGMs observed during EP study. These aspects are critical to a fundamental foundation on which to develop



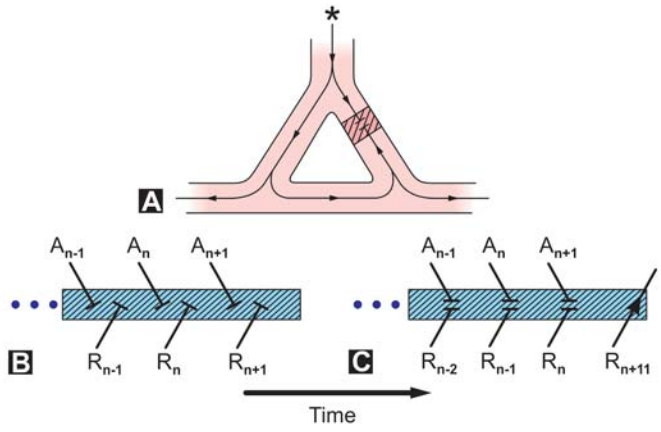


FIGURES 4A TO C: Radial propagation from two different focal tachycardia origins resulting in similar electrogram (EGM) activation sequences. (A) Cranial (upper) and left anterior oblique caudal (lower) schematic depictions of the atria with focal tachycardia site of origin in the low crista terminalis and (B) anterior left atrium (LA) above the mitral valve annulus (MVA). (A) Low crista terminalis (CT) tachycardia focus: wavefronts propagate superiorly along the CT into the right atrial (RA) appendage as well as simultaneously along the floor of the RA and then anteriorly and superiorly to arrive at the His region. Local conduction properties and similarity in distance between the tachycardia focus and the high right atrium (HRA) and His results in similar activation times to these two sites. The wavefront traveling along the RA floor also penetrates the septum posteriorly and activates the coronary sinus (CS) from proximal to distal. (B) Anterior LA tachycardia focus: wavefronts are shown to propagate along Bachmann's bundle (BB) and the interatrial septum (S). The rapidly conducted BB wavefront then propagates radially within the RA to arrive at the HRA and His electrodes with relatively similar activation times. Conduction block to the lateral LA (from scar or ablation) prevents a wavefront from activating the CS electrodes from distal to proximal. The S-wavefront travels inferiorly along the interatrial septum and then activates the CS from proximal to distal, possibly through direct penetration or after crossing the septum and entering the RA. The more rapid conduction across BB may explain earlier activation at the HRA and His as compared to the CS. (C) EGM patterns from a (left) and b (right). Surface ECG leads and intracardiac EGM channels are shown with timeline (T). In both tachycardias, activation is earliest at HRA and His, followed by proximal to distal activation in the coronary sinus. Red—arrhythmia focus; lime green—valve annuli; teal—coronary sinus; violet dashed lines—Bachmann's bundle; dotted lines with arrowhead—activation wavefronts. HRA, His and CS electrodes are shown. Gray signifies "behind" other structures. TVA: Tricuspid valve annulus

an understanding of cardiac EP in all its manifestations. As an initial consideration of the final consequence of these processes, we will introduce here normal conduction patterns, and a perspective on the most normal of electrophysiologic manifestations—sinus rhythm.

Sinus Rhythm and Normal Atrioventricular Conduction Parameters

An almost tacit assumption in the interpretation of intracardiac EGMs and, more importantly, in the understanding of cardiology



FIGURES 5A TO C: Schematic representation of a generalized linking phenomenon. (A) Depiction of a hypothetical macroreentry circuit into which successive impulses (asterisk) enter and preferentially traverse one limb as a result of persistent functional block (shaded region) in the contralateral limb. (B) and (C) Two distinct mechanisms whereby the functional block can be dynamically maintained. Each of the two Panels is a "blow-up" of the region of block as it is invaded by successive (i.e. n – 2, n – 1, n, ...) anterograde (A) and retrograde (R) impulses over time. (B) Shows impulse interference, whereas (C) depicts impulse collision. (*Source:* Lehmann MH, Denker S, Mahmud R, et al. Linking: a dynamic electrophysiologic phenomenon in macroreentry circuits. Circulation. 1985;71:254-65)

as well as EP is the recognition of sinus rhythm. It remains the most important and common cardiac rhythm, yet its study and comprehension are typically limited to the identification of regular cardiac activity with ECG demonstration of a P-wave preceding a QRS complex. Understanding sinus rhythm through intracardiac EGMs conveys a wealth of fundamental EP, and cardiovascular physiology that is critical to understanding normal phenomena and pathology. It is also important to recognize that the depiction of sinus rhythm through intracardiac EGMs, and all rhythms for that matter, is in large part dependent upon the established construct that anticipates catheters positioned in standard locations, such as HRA, CS, His bundle region and RV, as described above.

Sinus rhythm originates from the sinoatrial node, located epicardially at the junction of the right atrium with the anterolateral aspect of the superior vena cava. Its important property of automaticity generates an electrical depolarization in a regular manner that is the sinus rhythm. Depolarizations occur usually every 1,000–600 ms, termed the sinus cycle length, corresponding to a heart rate of 60–100 bpm. Once the sinus node depolarizes, resulting phenomena, including propagation to and within the atrium, atrial contraction, conduction along the normal AV pathway and activation of the ventricles, are all secondary and need not necessarily occur while in sinus rhythm. However, these secondary phenomena signify that sinus rhythm is associated with the other normal electromechanical cardiac events necessary for maintenance of circulation.

After exiting the sinoatrial node, the sinus impulse propagates both epicardially and endocardially. The endocardial breakthrough is in the posterior lateral right atrium, typically somewhat below but still in close proximity to the actual sinus node. Hence, a catheter in this region will be the first to detect an EGM during sinus rhythm. By the time endocardial breakthrough has occurred, the impulse has also stimulated enough atrial myocardium to initiate inscription of the ECG P-wave. The impulse spreads rapidly due to presence of sodium channels, with some degree of preferential conduction anteriorly toward the septum with breakthrough into the left atrium anteromedially, and inferiorly along the lateral and posterior walls and a second left atrial breakthrough in close proximity to the CS ostium.[15] In general, the resulting wavefront propagates radially away from the sinus node and toward the AV node.

The proximal electrodes of a correctly positioned His catheter lie intra-atrially, mid to anteriorly, and are the poles that typically identify the next atrial deflection of sinus rhythm as the impulse propagates toward the AV node. The time interval between the onset of the P-wave and the arrival of the atrial impulse at the His bundle catheter is a measure of intra-atrial conduction time (IACT) and typically is less than 30 ms in adults with healthy atrial myocardium (Fig. 6). The impulse also has traveled posteroseptally into and along the CS musculature that is activated, like the surrounding myocardium, through sodium channels, producing high-frequency EGMs. The septal-to-left-lateral activation along the CS results in a proximal-to-distal coronary sinus EGM activation pattern. While biatrial activation is occurring, the impulse also encounters the AVN region, where absence of sodium channels rendering conduction dependent primarily upon slow calcium channels, as well as other anatomic, histologic and electrical phenomena results in slow conduction within the AV node. The resultant low-amplitude and slowly propagating electrical wavefronts do not generate a discernable wave or deflection on surface ECG or intracardiac electrodes using standard catheters and filtering. The delay permits completion of passive ventricular filling, allowing the eventual atrial contraction to prime the ventricles, thereby augmenting stroke volume. After the impulse leaves the AV node, it encounters the His bundle where cell membranes do once again incorporate sodium channels, and rapid conduction resumes, generating a high-frequency deflection. The location of the His bundle, anatomically within several millimeters to 1 cm anterior and superior to the AV node, provides a surrogate marker to measure AVN conduction time, which is measured between the atrial EGM on the bipole identifying the largest His EGM and the first rapid deflection of the His EGM (A-H interval), and is typically less than 125 ms (Fig. 6). Propagation along the His-Purkinje system (HPS) results in myocardial breakout at various points along the LV septum and soon after at the mid-to-distal RV septum. Standard catheter positioning does not typically employ LV catheters but does incorporate an RV catheter, usually at the apex, and it is this catheter that displays the first ventricular EGM. The time for normal HPS activation to reach the ventricles, measured from the His bundle recording to the earliest ventricular activation (H-V interval), whether on surface ECG or intracardiac EGMs, is 35–55 ms (Fig. 6). The IACT, A-H and H-V intervals together comprise the ECG P-R interval.

Simultaneously or very soon after RV activation, RV septal activation is detected as ventricular EGMs on the His bundle electrodes across the tricuspid valve and along the basal ventricular septum, resulting from both transseptal impulse

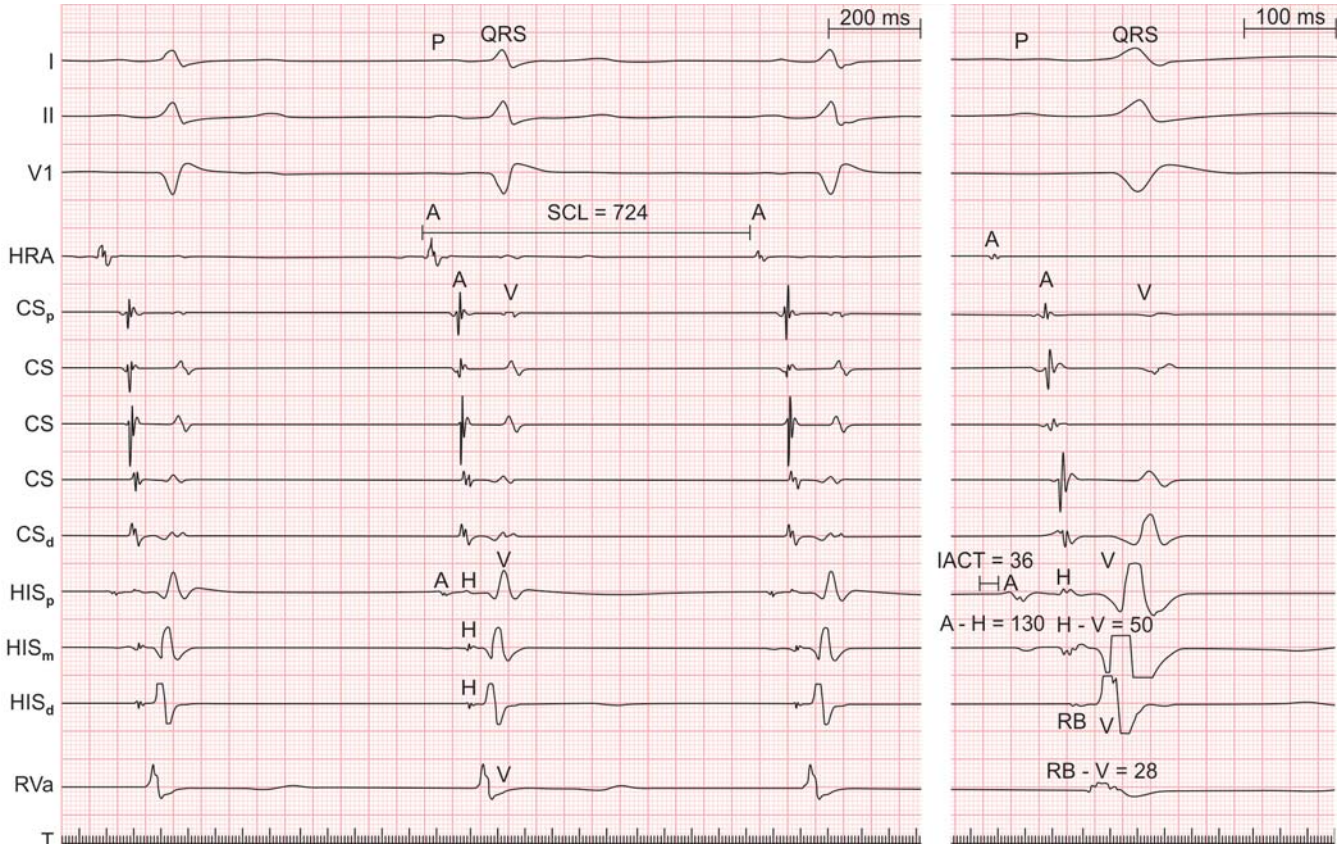


FIGURE 6: Baseline conduction parameters. Surface electrocardiographic (ECG) leads and intracardiac channels are shown during sinus rhythm at 100 mm/s (left) and 200 mm/s (right) sweep. Atrial electrograms (AEGMs) span the duration of the P-wave while ventricular electrograms (VEGMs) are aligned with and span the QRS duration. Sinus cycle length is measured from onset of AEGM on the HRA channel to the onset of the next HRA EGM (calipers, left Panel). The His bundle EGM (H) is the largest high-frequency signal between the AEGM and ventricular electrogram (VEGM) on the His recording channels. Intra-atrial conduction time (IACT) estimates the conduction time from the sinus to the atrioventricular (AV) node and is measured from onset of the P-wave to onset of the AEGM on the His catheter (calipers, right Panel). A-H interval, analogous to AV nodal conduction, is measured from onset of AEGM on His catheter to first high-frequency component of the His bundle deflection. The H-V interval assesses His-Purkinje conduction and is measured from the first high-frequency deflection of the His EGM to the onset of the ventricular depolarization whether VEGM or surface QRS. Right Panel: A low-amplitude high-frequency EGM is seen on the distal His channel just preceding the VEGM. There is no discernable AEGM on this channel, signifying the electrode is far enough distal across the tricuspid valve so as not to be able to detect atrial activity. This EGM is generated by the right bundle branch. The RB–V interval is typically less than 30 ms. (Abbreviations: CS: Coronary sinus; HRA: High right atrium; RB: Right bundle; SCL: Sinus cycle length)

spread and radial propagation of the impulse from the RV septal breakout site (Figs 6 and 7).[16] The CS catheter also detects ventricular signals; however, these are not the signals of earliest LV activation. Rather, the latest area to be activated in the LV is the base, and it is this basal posterior LV activation that is detected on the CS catheter. Unlike the ventricular EGMs seen on the RV and His catheter, the CS ventricular EGMs are of lower amplitude and lower frequency because the CS electrodes are not in contact with LV myocardium and may even reside more than 10 mm away, due to the location of the CS catheter within the coronary sinus and anatomic variations in the relationship between the coronary sinus and the mitral valve annulus.[17]

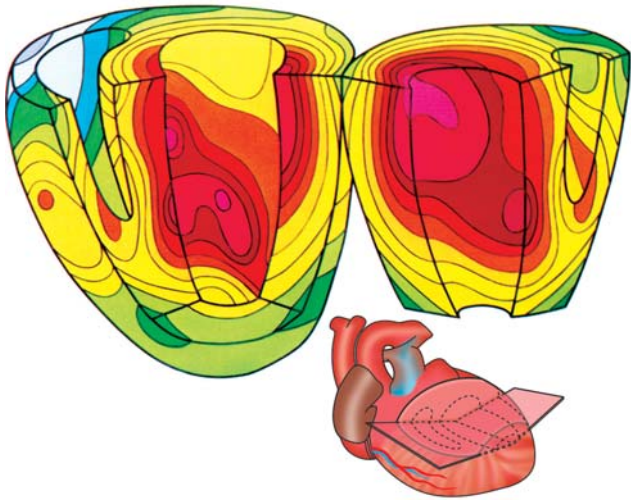


FIGURE 7: Three-dimensional isochronic representation of activation of the heart. Inset shows section levels. (*Source:* Durrer et al. Total excitation of the isolated human heart. Circulation. 1970;41: 899-912. Wolters Kluwer Health, with permission)

PROGRAMMED ELECTRICAL STIMULATION AND ASSOCIATED ELECTROPHYSIOLOGY

Two distinct patterns of pacing are applied during an EP study: (1) continuous pacing and (2) interrupted pacing. These techniques permit comprehensive assessment of all relevant

aspects of myocardial conduction and clinical arrhythmia tendency. If arrhythmia is induced, variations of these techniques may be employed during tachycardia to diagnose underlying mechanism(s).

CONTINUOUS PACING

Continuous pacing, in which each stimulus is referred to as "S1," is performed at fixed cycle lengths or with gradual decrementation in cycle length (i.e. gradual increase in heart rate). Continuous fixed-cycle-length pacing is used for study of sinus node function and integrity of subsidiary pacemakers, arrhythmia induction and overdrive pacing of a tachycardia ("entrainment," not discussed here). Continuous pacing with gradual decrementation in cycle length is performed to evaluate myocardial stimulation limits, and usually delivered until the occurrence of a desired event such as induction of tachycardia, conduction block (Fig. 8) or failure to achieve 1:1 myocardial capture. As such, this technique provides an overall measure of ability of a particular tissue, chamber or region to respond to sequential stimuli; is a measure of absolute limits of myocardial responsiveness; and may provide insight into tachycardia mechanism.

With fixed-cycle-length pacing at cycle lengths that are not excessively short, but shorter than sinus so as to avoid competition and interference, healthy atrial and ventricular tissue will respond in a 1:1 manner with minimal conduction delay (latency) between the stimulus artifact and the onset of the associated EGM and P-wave or QRS down to cycle lengths shorter than 250 ms.[14] As cycle length is decremented, a point is reached beyond which latency increases. This observation suggests the pacing cycle length is encroaching on the ability of local tissue capture and propagation to the surrounding myocardium in a 1:1 manner, and further pacing acceleration can result in failure of capture or breakup and fractionation of the propagating wavefront, provoking fibrillation, whether atrial or ventricular. The observation of increased latency should signal the operator to discontinue the pacing drive as induction of fibrillation may, at the least, prevent complete electrophysiologic evaluation in the case of AF, unless fibrillation is the desired result, and may require emergent electrical conversion if VF is induced.

INTERMITTENT OR INTERRUPTED PACING WITH EXTRASTIMULI

The second pacing format is intermittent pacing with delivery of premature (or extra) stimuli. This pacing format is advantageous for studying myocardial and conduction system refractory periods and for creation of local conduction block to facilitate induction of reentrant arrhythmias. With this approach, a series of six to ten paced beats are delivered at a constant cycle length (drive train of S1s) and are followed by at least one extrastimulus (S2) coupled to the last beat of the basic drive at a cycle length shorter than the S1 drive cycle. The S2 is initiated late during electrical diastole and the coupling interval is progressively decreased with successive drives, thereby "scanning diastole" until myocardial capture and/or conduction cannot be achieved, i.e. the effective refractory period of myocardial (Fig. 9) or AV conduction (Figs 10A to C)[11,18] or conduction delay promotes arrhythmia induction (Fig. 11). When latency or frank tissue refractoriness is encountered, the refractory period of downstream tissues may not be determinable. In such cases, the S2 coupling interval may be slightly increased so as to permit myocardial capture or avoid latency, then additional extrastimuli may be introduced (S3, S4, S5, etc.). Since antegrade AVN conduction is generally poorer than HPS conduction, evaluating the refractory period of the HPS is limited by AVN conduction and may not always be determinable. Various agents can be administered to shorten refractoriness and improve conduction, thereby permitting evaluation of HPS conduction if AVN conduction improves adequately. Refractory periods of myocardial tissue are dependent upon and vary directly with drive cycle length. Therefore multiple drive cycles are used to assess dynamicity of refractoriness. Whereas a 600 ms cycle length drive may yield a tissue-effective refractory period of 300 ms, a 400 ms cycle length drive would be expected to shorten tissue refractoriness.[19]

SIGNIFICANCE OF "SHORT-LONG-SHORT" PACING CYCLES

At times, the aforementioned pacing maneuvers are unsuccessful in inducing a suspected arrhythmia. For documented or

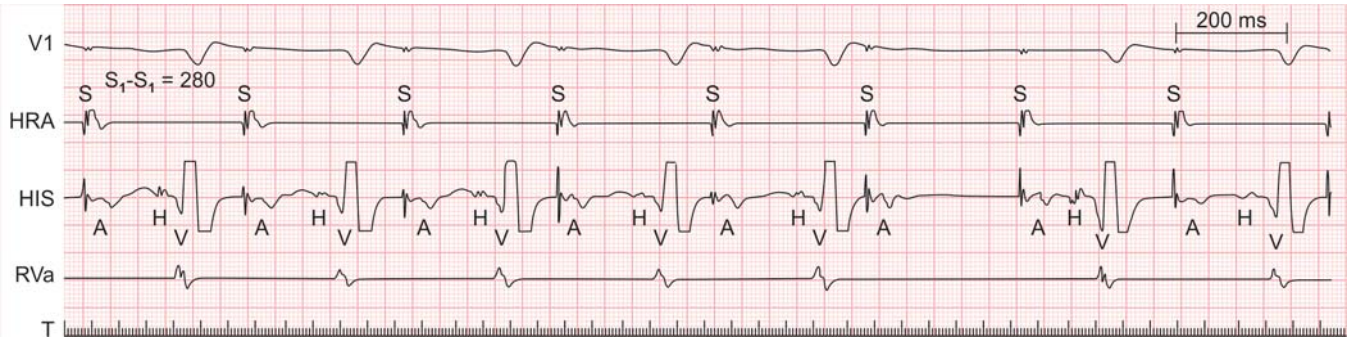


FIGURE 8: Demonstration of atrioventricular (AV) conduction block. Surface lead (V_1), intracardiac channels (HRA, His, RVa), and timeline (T) are shown. Continuous atrial pacing at 280 ms (S_1–S_1) results in conduction to the ventricle with progressive prolongation in A–H interval until conduction block. Notice that each pacing stimulus is associated with an atrial electrogram (A) and the A–H interval prolongs with each successive paced stimulus until no H is seen after the sixth paced A. Conducted beats are associated with a fixed H–V interval, confirming conduction delay above the His, i.e. in the AV node. With continued pacing, a new Wenckebach cycle ensues

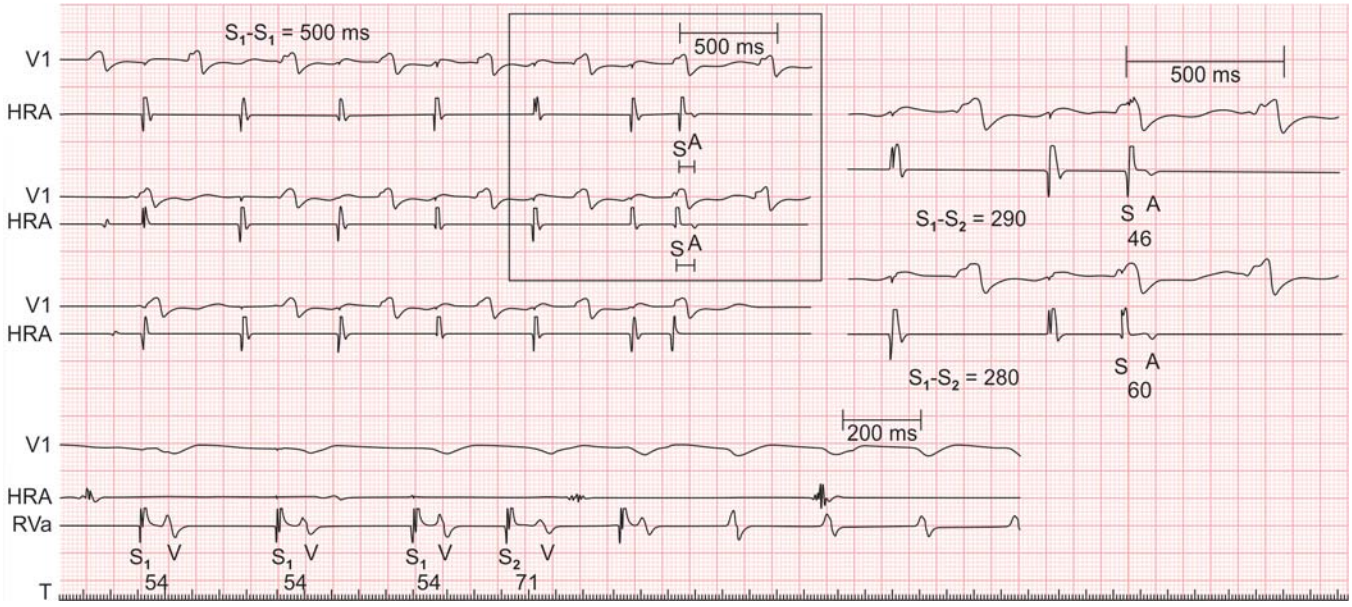


FIGURE 9: Latency and atrial effective refractory period. Surface lead (V1) and intracardiac channel (HRA) are shown with three successive atrial pacing drives at 500-ms cycle length (S_1–S_1) and progressively abbreviated extrastimuli (S_2) (upper left Panel). In the first drive, atrial extrastimulation coupled at 290 ms results in a stim-A (latency) time of 46 ms (inset; expanded view to the right). In the second drive, the extrastimulation at 280 ms is associated with increased latency (60 ms) (inset; expanded view to the right). In the third drive, further decrementation in the extrastimulus coupling interval to 270 ms results in loss of atrial capture with no atrial electrogram associated with the extrastimulus, thereby establishing the atrial effective refractory period as 600:270 ms. Surface lead (V1) and intracardiac channels (HRA, RVa) are shown (lower Panel). Ventricular pacing at 350 ms (S_1–S_1) is associated with a S_1–V time (latency) of 54 ms. The first ventricular extrastimulus is associated with increased latency, S_2–V time of 71 ms

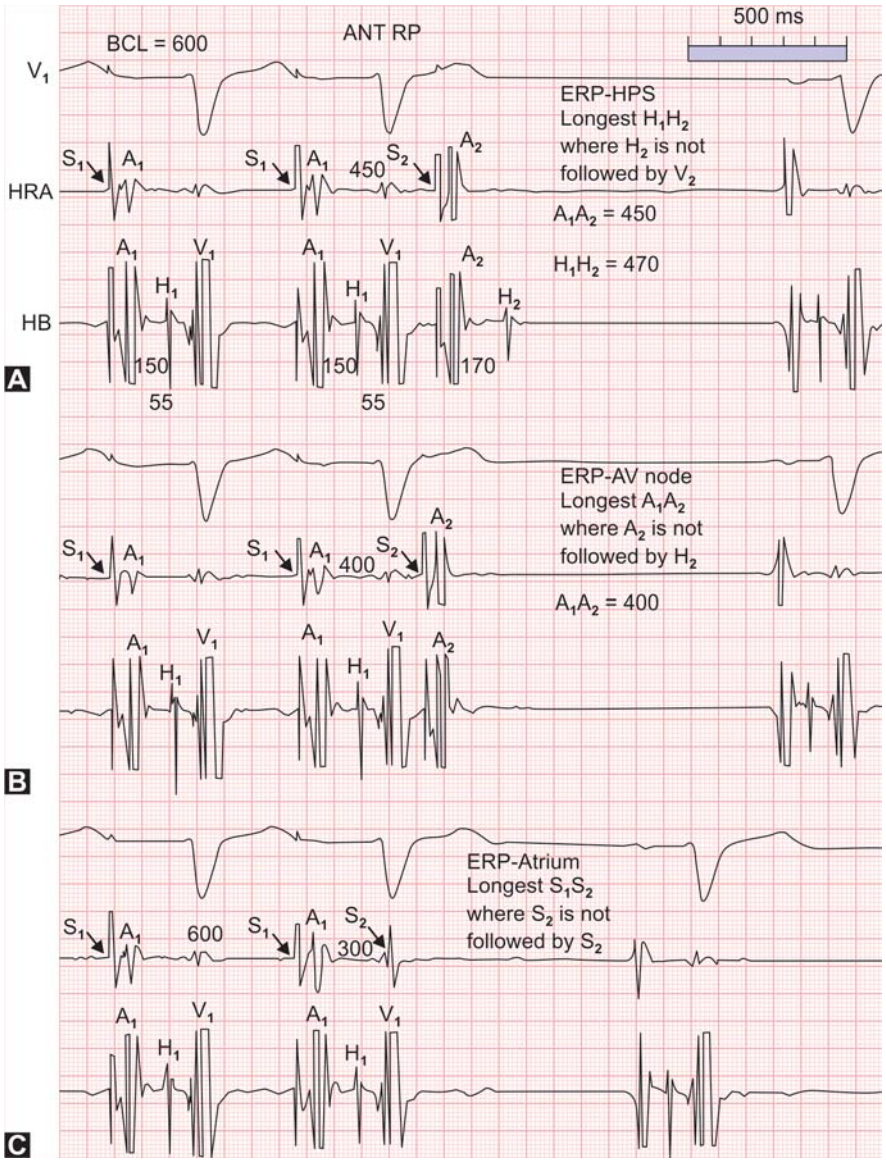
suspected arrhythmias that rely on conduction delay for arrhythmia initiation (i.e. reentrant arrhythmias), "short-long-short" pacing—a variation on the extrastimulus technique—may prove useful in promoting conduction delay that initiates tachyarrhythmias when other maneuvers do not. This is applicable to all forms of reentrant tachyarrhythmias, whether in the atrium, ventricle or involving the HPS. A drive of six to eight beats is delivered at a specific cycle length, followed by the last beat of the drive coupled at a cycle length greater than that of the preceding beats in the drive. This long-coupled beat has the effect of shortening myocardial refractoriness (Figs 12A to F).[19,20] This allows an extrastimulus to be coupled at shorter cycle lengths ("short-long-short") than with fixed-cycle-length pacing, which may then create adequate myocardial propagation slowing to support reentry. This pacing technique has a divergent effect in the HPS, that is, HPS refractoriness increases with "short-long-short" sequences, which may directly enhance conduction delay and promote reentry within the HPS (Figs 13A to F).

For induction of reentrant supraventricular tachycardias (SVTs), single, double or more extrastimuli may be delivered (Fig. 14). For induction of VT, up to three ventricular extrastimuli are typically employed. The sensitivity of pacing protocols seems to be directly related to the number of extrastimuli utilized.[16] However, this occurs at the expense of specificity as polymorphic VT/VF can be induced at very short coupling intervals by using multiple ventricular extrastimuli in patients otherwise without arrhythmic risk. Regardless of pacing protocol, induction of sustained monomorphic VT constitutes a specific response and is seldom induced in patients who are not clinically prone to such arrhythmias. In contrast, the induction of polymorphic VT/VF with three extrastimuli at short coupling intervals can be nonspecific.[11]

Relation of Pacing Technique to Anticipated Arrhythmia Mechanism and Inducibility

Reentrant arrhythmias lend themselves best to study because the reentrant nature of arrhythmias creates a reproducible and regular activation sequence that can be evaluated when the arrhythmia is sustained. Tissue refractoriness and conduction slowing are necessary factors in the initiation and maintenance of reentrant arrhythmias, which can be achieved readily through continuous pacing with progressive cycle length decrementation and premature extrastimulation, with or without pharmacologic facilitation.

Unifocal triggered rhythms also can be evaluated by EP study. However, their tendency toward arrhythmia induction can be more challenging, being somewhat more sensitive to hormonal changes and limited by sedation and attendant varying catecholamine levels. Rapid, long pacing drives, through promotion of myocyte calcium overload and associated delayed afterdepolarizations, may permit induction of arrhythmias known to occur related to this mechanism, such as focal atrial tachycardias and certain idiopathic VT. Further, catecholamine administration (e.g. isoproterenol) enhancing cAMP-mediated adrenergic stimulation and associated diastolic calcium overload may facilitate induction with or without pacing. Interestingly, often it is not a specific level of catecholamine but rather the flux in serum concentration that permits induction (e.g. wash-in or wash-out phases).



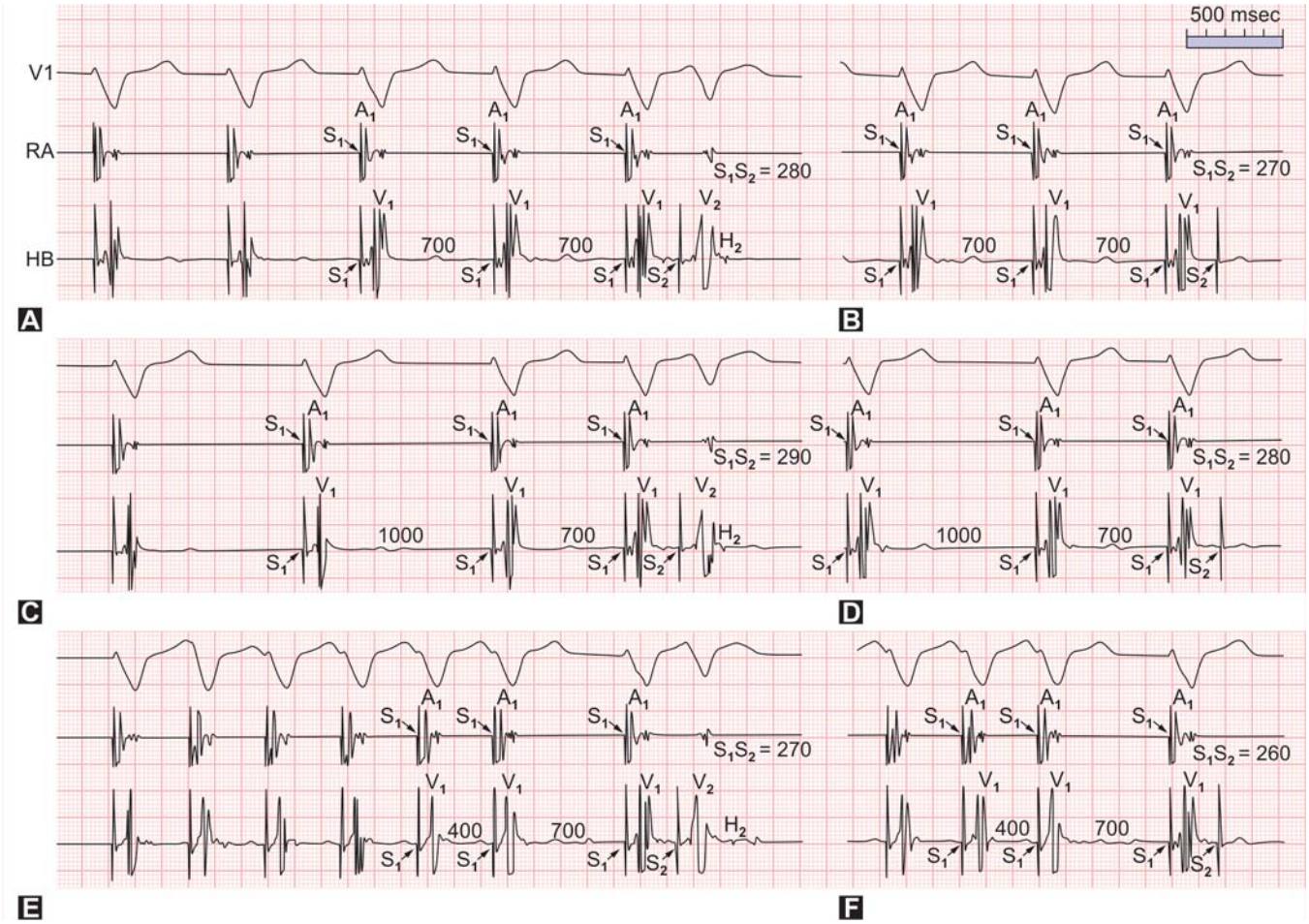
FIGURES 10A TO C: Determination of cardiac refractory periods during atrial pacing. During a basic cycle-length pacing at 600 ms (S_1S_1 or A_1A_1), atrial premature stimulation (S_2 or A_2) at progressively shorter coupling intervals (S_1S_2 or A_1A_2) is depicted. The definition of the effective refractory period (ERP) of the His-Purkinje system (HPS), atrioventricular (AV) node, and atrium are labeled. ANT RP: Antegrade refractory period. (*Source:* Reproduced from Akhtar M. Invasive cardiac electrophysiologic studies: an introduction. In: Parmley WW, Chatterjee K (Eds). Cardiology: Physiology, Pharmacology, Diagnosis. Philadelphia: Lippincott; 1991. With permission from Lippincott Williams and Wilkins)



FIGURE 11: Ventricular tachycardia (VT) induction with extrastimuli. Surface lead (V1) and intracardiac channels (HRA, RVa) are shown. A six-beat ventricular drive at 350 ms is followed by two premature extrastimuli, inducing a wide complex tachycardia (V) with left bundle branch block morphology at 230 ms and atrioventricular dissociation, i.e. VT. A, atrial electrogram

CLINICAL APPLICATION OF "ROUTINE" ELECTROPHYSIOLOGY STUDY AND ANTICIPATED RESPONSES TO PROGRAMMED STIMULATION

While few would consider the findings of even a normal comprehensive EP study "routine," it is important to utilize a systematic approach that permits complete evaluation of the myocardium and conduction system, including sinus node automaticity and impulse propagation, atrial myocardial conduction properties, anterograde and retrograde AV conduction patterns, ventricular myocardial conduction properties and associated arrhythmic tendency including



FIGURES 12A TO F: Effect of abrupt cycle length change on refractoriness of the ventricular muscle. The effective refractory period (ERP) of the ventricular muscle during constant cycle length (method I) is 270 ms (A and B). A change of $CL_p \rightarrow CL_R$ from 1,000 → 700 ms (method IIA, C and D) lengthens ERP of the ventricular muscle to 280 ms, whereas a change of $CL_P \rightarrow CL_R$ from 400 → 700 ms (method IIB, E and F) shortens the ERP of the ventricular muscle to 260 ms. Note that for the same CL_R, ERP of the ventricular muscle varies directly with CL_p. (*Source:* Modified from Denker S, Lehmann MH, Mahmud R, et al. Divergence between refractoriness of His-Purkinje system and ventricular muscle with abrupt changes in cycle length. Circulation. 1983;68;1212-21)

attempts at arrhythmia induction in the baseline state and during pharmacologic facilitation. The comprehensive EP study is performed in the following stages:

- Atrial continuous pacing with and without cycle length decrementation
- Atrial premature stimulation with extrastimuli
- Ventricular continuous pacing with and without cycle length decrementation
- Ventricular premature stimulation with extrastimuli
- Short bursts of rapid atrial or ventricular pacing[14]

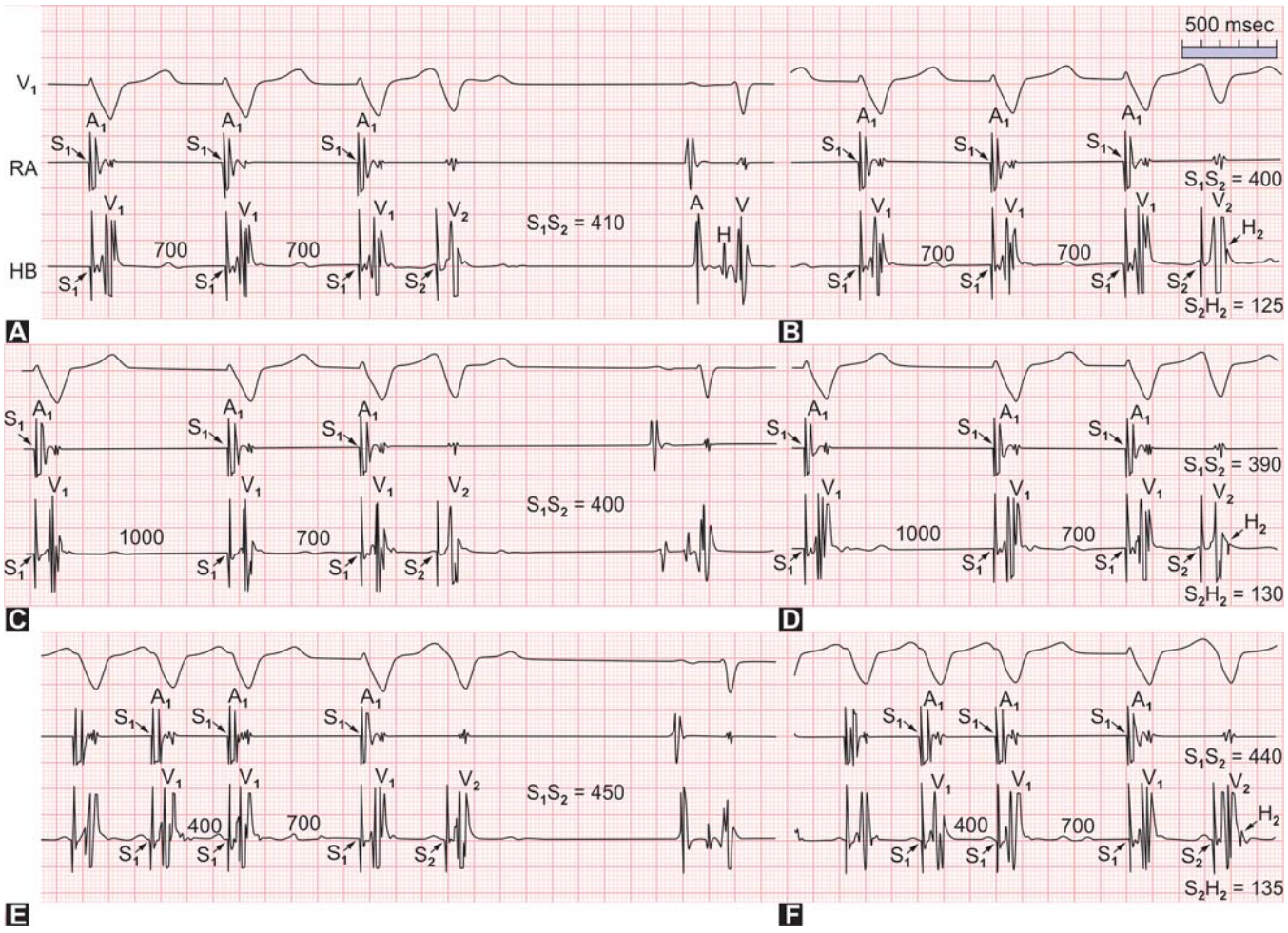
While not all aspects may be assessed in each patient and the order may vary according to patients' needs and tolerances, this framework provides a method to perform a comprehensive electrophysiologic evaluation of intrinsic conduction properties and arrhythmogenic tendency. Burst pacing is rarely employed for the study of normal cardiac EP and is generally used in arrhythmia induction or termination and will not be elaborated upon here.[14]

Baseline Observations

Irrespective of the presenting rhythm or potential rhythm of interest, the surface ECG provides valuable information against which the intracardiac patterns of activation can be compared. It is negligent to disregard the baseline surface ECG, and basic observations of P-R, R-P, QRS and QT intervals should be made at the initiation of and throughout every study. Once baseline observations have been made, including intrinsic cycle length, activation sequence and parameters of AV conduction (Fig. 6), the active study can be performed with particular attention to appropriate stimulation protocols, myocardial capture and conduction, and activation of other chambers in response to each stimulus and nonstimulated responses. The large majority of patients, undergoing diagnostic EP study, are present in sinus rhythm; hence, the study usually starts with atrial stimulation. Alternately, as induction of AF presents a barrier to study completion, it may be pragmatic to perform atrial stimulation last in patients with a history of AF or sick sinus.

Atrial Stimulation for Evaluation of Sinus Node Function; and Atrial and Atrioventricular Nodal Conduction Properties

The assessment of sinus node automaticity should be included in all comprehensive EP studies, but particularly in patients



FIGURES 13A TO F: Effect of abrupt cycle length change on refractoriness of the His-Purkinje system (HPS). The tracings show the retrograde relative refractory period (RRP) of the HPS during methods I, IIA and IIB. With method I (A and B), H_2 emergence from the local ventricular electrogram is noted at an S_1S_2, interval of 400 ms. A change of $CL_p \rightarrow CL_R$ from 1,000 → 700 ms (method IIA, C and D) shortens the RRP of the HPS to 390 ms, whereas a change of $CL_p \rightarrow CL_R$ from 400 → 700 ms (method IIB, E and F) lengthens the RRP of the HPS to 440 ms. Note that for the same CL_R, the RRP of the HPS is 50 ms longer during method IIB compared with method IIA, but remarkably CL_p is 600 ms shorter during method IIB compared with method IIA. (Abbreviations: V_1: Surface electrocardiographic lead; RA: Right atrial electrogram; HB: His bundle electrogram. All measurements are in milliseconds). (*Source:* Modified from Denker S, Lehmann MH, Mahmud R, et al. Divergence between refractoriness of His-Purkinje system and ventricular muscle with abrupt changes in cycle length. Circulation. 1983;68;1212-21)

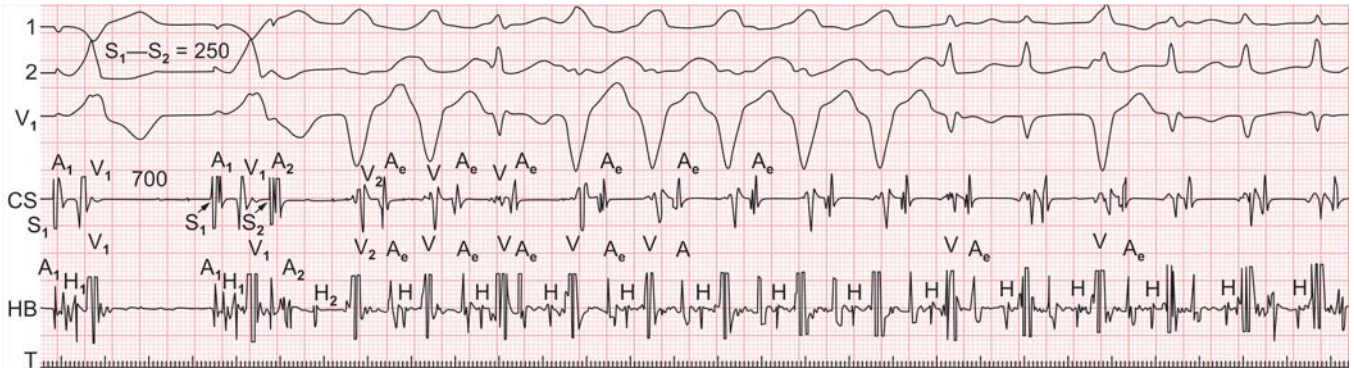


FIGURE 14: Induction of supraventricular tachycardia (SVT) in Wolff-Parkinson-White syndrome. The tracings are labeled. Atrial pacing from coronary sinus (CS) is done at a 700-ms basic cycle. During the basic drive pacing, left free-wall accessory pathway conduction to the ventricle produces ventricular preexcitation. A single premature beat (S_2) blocks in the accessory pathway and conducts over the normal pathway with a left bundle branch block morphology, and the SVT is initiated. Note the intermittent normalization of the QRS complex during this SVT. (*Source:* Modified from Jazayeri MR, Caceres J, Tchou P, et al. Electrophysiologic characteristics of sudden QRS axis deviation during orthodromic tachycardia. J Clin Invest. 1989;83:952-9. With permission from American Society for Clinical Investigation)

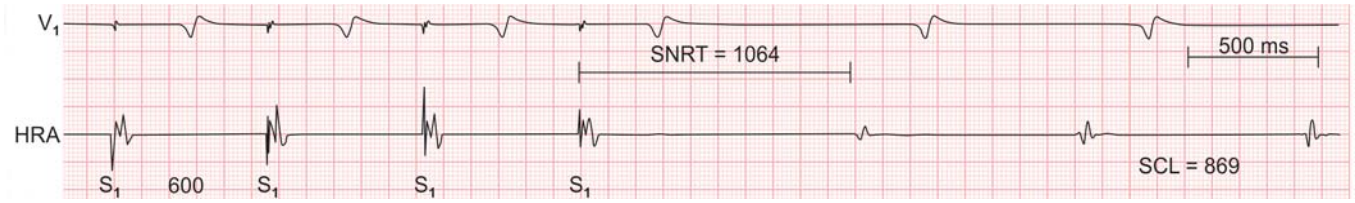


FIGURE 15: Measurement of sinus node recovery time (SNRT). A train of S_1's at 600 ms is delivered over 30 seconds to achieve sinus suppression. With discontinuation of pacing, the time for first sinus return cycle is 1,064 ms, which is within normal limits. Correcting for the predominant sinus cycle length (SCL), 869 ms, yields a corrected SNRT of 195 ms, also within normal limits

presenting with dizziness, dyspnea on exertion, presyncope, syncope or other manifestations of sinus node dysfunction in whom diagnosis cannot be made noninvasively.[14] Right atrial pacing for 30 sec to 1 min at a fixed cycle length shorter than sinus causes sinus suppression. Abrupt discontinuation of pacing permits determination of the time for the first automatic intrinsic/escape sinus beat to return, this interval is termed the sinus node recovery time (SNRT). The SNRT is evaluated at various drive cycles ranging between the sinus cycle length and usually 400 ms. Sinus node recovery times less than 1,525 ms are generally considered normal. By deducting the predominant sinus cycle length from this interval, one can obtain the so-called corrected SNRT (Fig. 15). In one series[21] the value for corrected SNRT was less than 525 ms in normal individuals but exceeded this in patients with overt sinus node dysfunction.

In the vast majority of patients with true sinus node disease, sinoatrial conduction abnormalities are the predominant reason for sinus node dysfunction. Sinoatrial conduction time (SACT) in the absence of obvious sinus node disease is less than 100 ms. The SACT is evaluated in similar fashion to the SNRT by atrial pacing, in this case, just faster than sinus, hence avoiding significant sinus node suppression. The return cycle then represents the time for the last paced beat to enter the sinus node, reset it and propagate back to the pacing catheter. Again, deducting the predominant sinus cycle from the return cycle should approximate the propagation time to and from the sinus node, and the SACT is thus one-half of this value. SACTs in excess of 125 ms[14] are felt to represent important sinoatrial conduction disease. This interval is most accurate when the HRA catheter is positioned in close proximity to the sinus node, in the posterolateral aspect of the right atrium, and not in the right atrial appendage, which may be associated with prolonged conduction intervals between it and the sinus node.

The sensitivity of SNRT for the detection of sinus node dysfunction is 54%, whereas that of SACT is 51%, with a combined sensitivity of approximately 64%. Poor sensitivity of such testing relates in part to the possibility that in previous studies, documented episodes of sinus bradycardia or sinus arrest due to neurocardiogenic mechanisms may not have been excluded.[22] The specificity of both tests combined is approximately 88%. In patients with bradycardia/tachycardia syndrome, EP testing may also be necessary for the proper diagnosis and therapy of the concomitant tachyarrhythmia or bradyarrhythmia, as AV conduction is frequently abnormal in patients with sinus node dysfunction.[14]

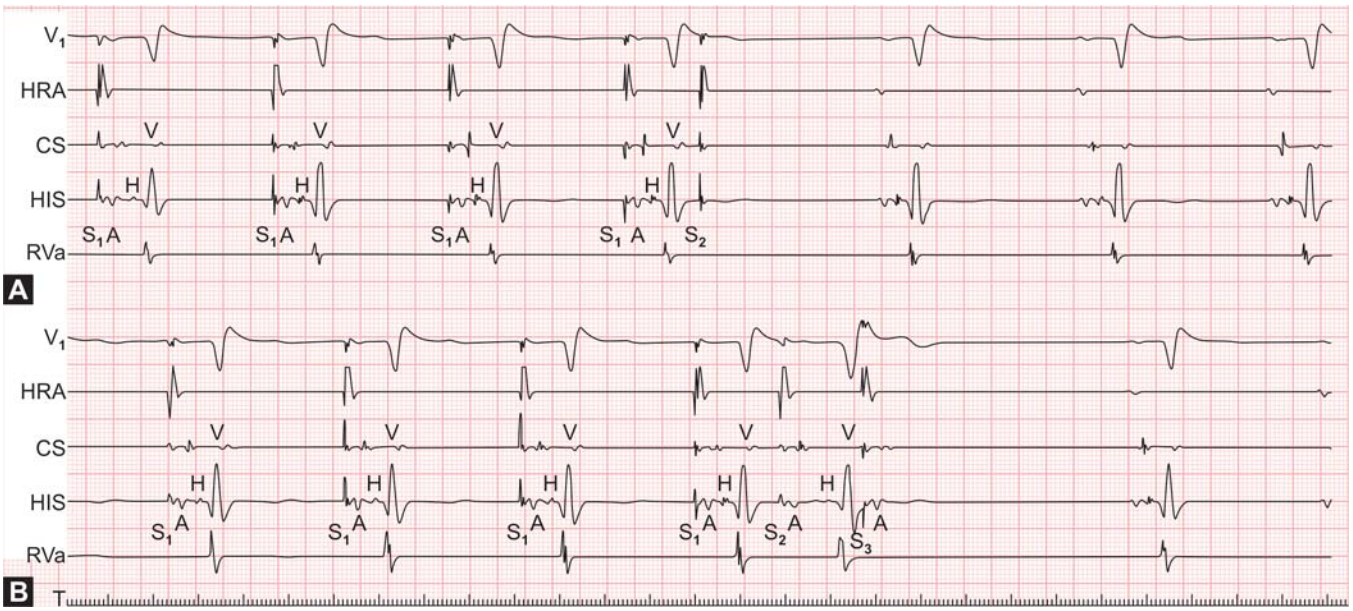
After evaluation of sinus node automaticity, AV conduction capabilities are assessed in patients presenting in sinus rhythm. With successively faster pacing or shorter cycle length, AVN conduction time as measured by the A-H interval initially accommodates to the pacing drive, then prolongs until a pacing cycle length at which the Wenckebach pattern of conduction block is observed (Fig. 8). In most, this AV block cycle length is reached between 600 ms and 300 ms, although in some patients with "enhanced AVN conduction" 1:1 conduction may be maintained at cycle lengths less than 300 ms, often with electrocardiographically abbreviated P-R intervals. The clinical significance of this is unclear but has been seen in patients with rapid ventricular response in AF and atrial flutter. At the other extreme, observing a pattern of Wenckebach at cycle lengths greater than 600 ms is unusual but may be seen in healthy young adults with elevated vagal tone and should not be considered abnormal unless it is not reversible by vagolytic or sympathomimetic agents or occurs during exercise.[14]

Next, atrial premature extrastimuli are introduced for evaluation of atrial myocardial refractoriness and effective refractory period of the AV node. As mentioned previously, a fixed drive cycle coupled with a single premature extrastimulus is repeatedly delivered to scan diastole until absence of a particular event, whether that be conduction to the ventricles, arrival at the His, or myocardial capture, thereby establishing effective refractory periods at that cycle length (Figs 10A to C). If the atrial effective refractory period is reached before demonstrating AV nodal refractoriness, then prolongation of the extrastimulus coupling interval and introduction of additional extrastimuli may permit such demonstration (Figs 16A and B).

In addition, with atrial extrastimulus testing, "dual AVN physiology" may be observed. With gradual decrementation in the extrastimulus coupling interval, there is an abrupt prolongation in the H1-H2 interval, signifying conduction block in the AVN "fast" pathway but resulting in the atrial paced impulse arriving at the AV node by an alternate pathway that is associated with longer H1-H2 intervals ("slow-pathway"). Dual AVN pathways are felt to underlie the mechanism of AVN reentry tachycardia, and both continuous atrial pacing and atrial premature extrastimuli will often induce AVN reentry (Figs 17A and B), although other SVTs may be initiated by this mechanism as well.

Evaluation of Atrioventricular Conduction Disease

In appropriate patients, EP study is warranted to evaluate the site and mechanism of AV block. A discernible His bundle



FIGURES 16A AND B: Atrial effective refractory period (AERP) and atrioventricular nodal effective refractory period (AVNERP). Surface lead (V_1) and intracardiac channels (HRA, CS, HIS, RVa) are shown. (A) Atrial pacing results in 1:1 atrial capture and conduction through AVN to the ventricle during the basic drive (S_1). The single premature atrial extrastimulus (S_2) fails to capture the atrial myocardium (AERP)—observe no atrial electrogram follows the S_2, unlike the S_1's—so no impulse propagates through the AVN to activate the ventricle. Sinus rhythm ensues in the absence of atrial pacing. (B) Having reached AERP, the S_2 coupling is increased by 30 ms to permit atrial capture and evaluation of AVN refractoriness. In this case the S_2 captures atrial myocardium as evidenced by presence of an A electrogram and conducts through the AVN to the ventricle, and an S_3 that also captures the atrium fails to conduct to the ventricles and blocks above the His bundle as no His deflection is seen, i.e. in the AVN. In this case, the AVNERP was established at 600:300:360 ms

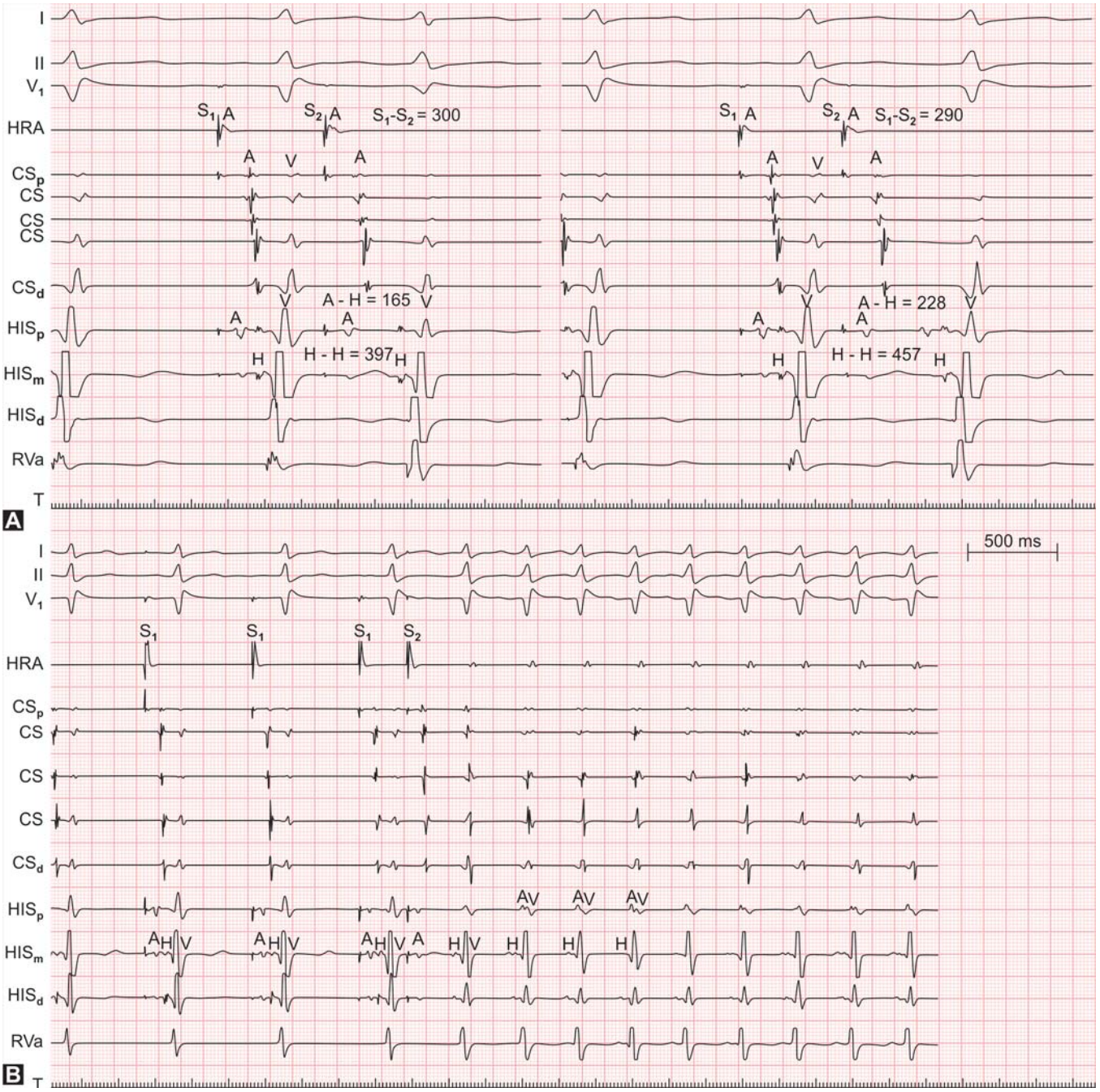
recording enables one to determine the exact site of AV conduction abnormality, i.e. proximal, within or distal to the His bundle region. This, in combination with surface ECG morphology of conducted beats, enables one to identify precisely the location of conduction abnormality. The finding of a prolonged H-V interval, greater than 60 ms, is evidence of HPS conduction disease (Figs 18A and B). If 1:1 AV conduction is present in patients suspected of intermittent AV block, atrial pacing with cycle length decrementation should be performed to evaluate reproducibility of AV block. AV block in the HPS is abnormal during continuous atrial pacing (Fig. 19) but may be a physiologic response during atrial extrastimulation or with sudden rate change related to asynchronous initiation of atrial pacing.[14]

In asymptomatic patients with first-degree AV block (prolonged P-R interval), electrophysiologic assessment is unnecessary regardless of the QRS morphology of the conducted beats, although in asymptomatic individuals with second-degree AV block electrophysiologic assessment is used to identify site of block (Figs 20A to C). Patients with intra-Hisian or infra-Hisian block tend to have a more unpredictable course, and permanent pacing is desirable.[23] Even though intranodal block usually presents as Wenckebach's phenomenon or Mobitz type I, it is not uncommon to see Wenckebach within the His or in the HPS distal to the His bundle. There is no difference in prognosis regardless of how the intra-Hisian or infra-Hisian second-degree block manifests itself, i.e. type I versus type II. In symptomatic patients with second-degree AV block, the role of EP study is limited because permanent pacing is the appropriate intervention. On the other hand, if the patient's symptoms cannot be explained on the basis of AV block and may be related to another arrhythmia such as VT, EP study should be considered. In patients with third-degree or complete AV block, EP studies are seldom required; permanent pacing is the obvious option in symptomatic patients.[11]

Ventricular Stimulation and Assessment of Ventriculoatrial Conduction, Wide QRS Tachycardia and Sudden Death Risk

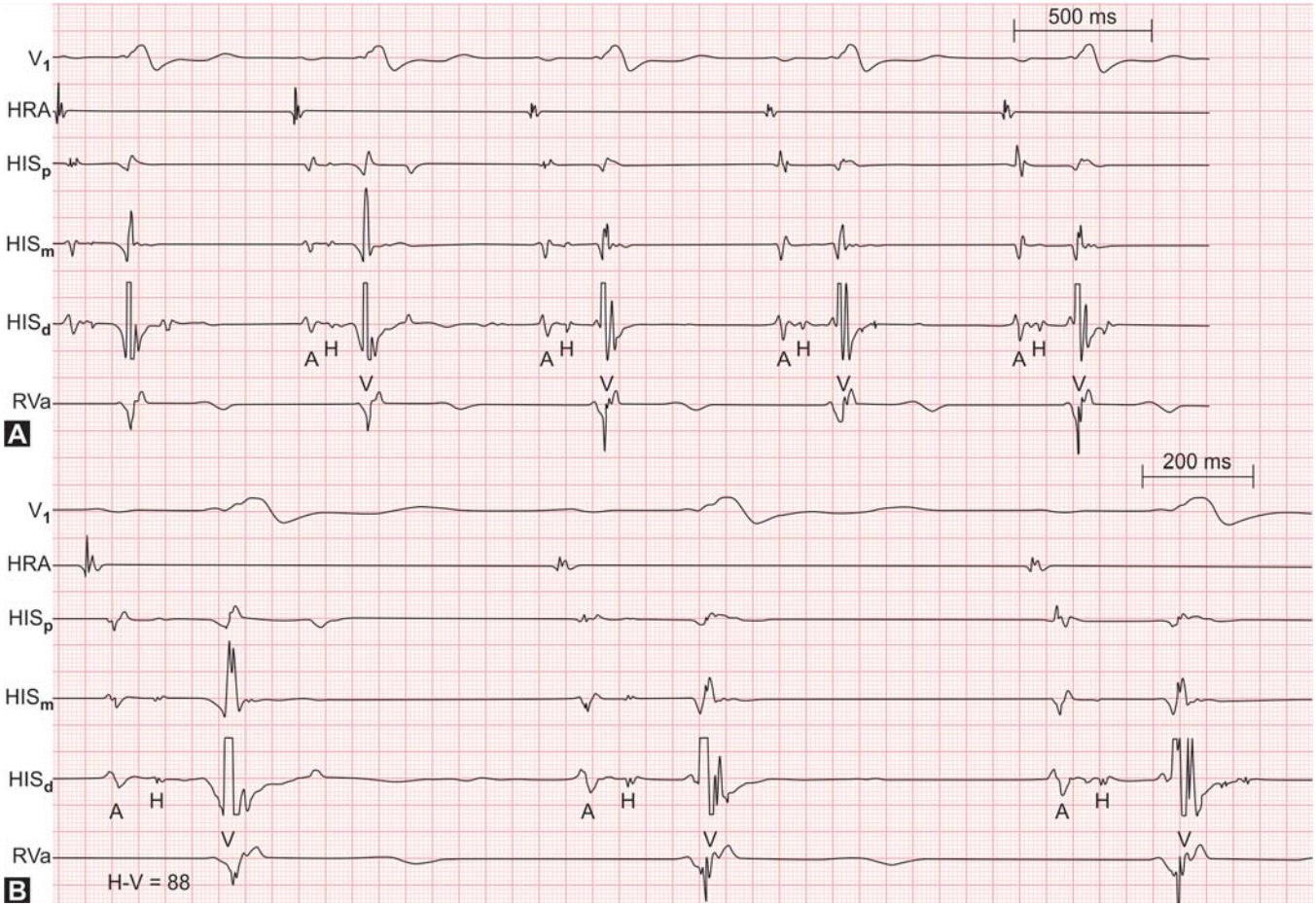
As a construct, the AV conduction system can be considered as a pair of cables, the left and right bundle branches, joined proximally at the AV junction; all capable of bidirectional conduction. Similar to anterograde conduction, retrograde AV conduction can be assessed with gradual decrementation in a continuous ventricular drive (Fig. 21). The importance of the specific cycle length at which retrograde conduction block occurs is particularly relevant in determining arrhythmia mechanisms. For example, in a patient with narrow complex tachycardia with 1:1 conduction to the ventricle of unknown mechanism at a heart rate of 190 bpm (~320 ms), identifying retrograde AV conduction block at 450 ms (~135 bpm) would suggest that the tachycardia cannot be one in which the ventricles would be required to conduct to the atrium to maintain the tachycardia. Instead, the tachycardia mechanism is more likely entirely independent of VA conduction, i.e. atrial tachycardia.

The specific pattern of VA conduction should be closely observed. Whereas retrograde conduction over the normal



FIGURES 17A AND B: Dual atrioventricular node (AVN) physiology and induction of AVNRT. (A) On left side: the last paced beat of a 600-ms basic drive (S_1) is shown, with a single atrial extrastimulus coupled at 300 ms (S_2) that conducts through the AVN to the ventricles with A-H 165 ms and H-H 397 ms. On right side: with the same basic drive, the atrial extrastimulus coupling interval is decremented by 10 ms to 290 ms, resulting in conduction through the AVN to the ventricle with marked conduction delay in excess of 50 ms (A-H 228 ms, H-H 457 ms) compared to the previous drive, compatible with "jump" to a slow AVN pathway. (B) Induction of common AVN reentry tachycardia (AVNRT). Atrial pacing at 600 ms (in a different patient) is followed by a single extrastimulus coupled at 360 ms (S_2) that is associated with A-H delay and initiation of a tachycardia with narrow QRS identical to sinus, and electrogram (EGM) pattern with nearly simultaneous atrial and ventricular activation preceded by a His deflection. A narrow QRS tachycardia preceded by His EGM must be, in general, supraventricular as each impulse activates the His before activating the ventricles and hence must be arising above the His, i.e. atrium or AVN. In AVNRT, an atrial premature complex or premature extrastimulus provokes AVN fast pathway block and results in conduction over a slow AVN pathway manifested by a prolonged P-R and A-H. After conducting over the slow AVN pathway, the wavefront reaches a lower turnaround/branch point and propagates along the AVN "fast pathway" retrogradely to the atria while continuing along the His-Purkinje system (HPS) toward the ventricles. This results in nearly simultaneous atrial and ventricular activation, and the distinctive pattern of complete alignment of all atrial and ventricular EGM and superimposed P's and QRS's

pathway would be expected to activate the atria earliest at the His catheter, which is in closest proximity to the AV node (Fig. 22A), retrograde AV conduction over other pathways would result in altered activation sequences (aside from pathways very close to the AV node such as anteroseptal accessory pathways). For instance, retrograde activation that is earliest in the proximal CS is suggestive of a posteriorly located midline pathway (Fig. 22B), such as an AVN slow pathway or a



FIGURES 18A AND B: His-Purkinje disease. Sinus rhythm is shown in a patient with recurrent syncope and right bundle branch block at 50 mm/s (A) and 100 mm/s (B) sweep. The A-H interval is 138 ms and H-V interval is 88 ms at baseline heart rate of 69 bpm

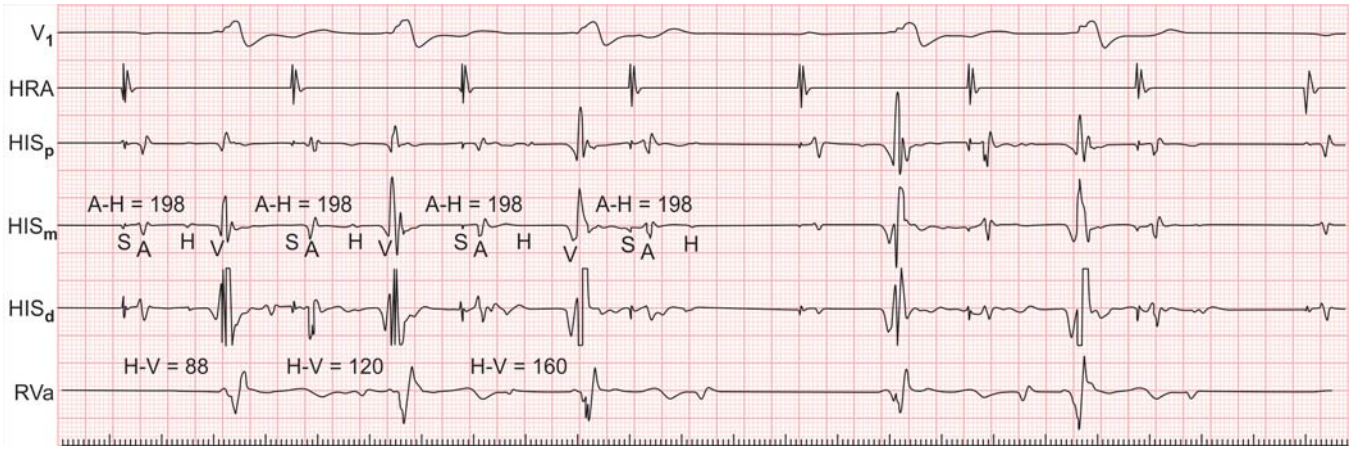
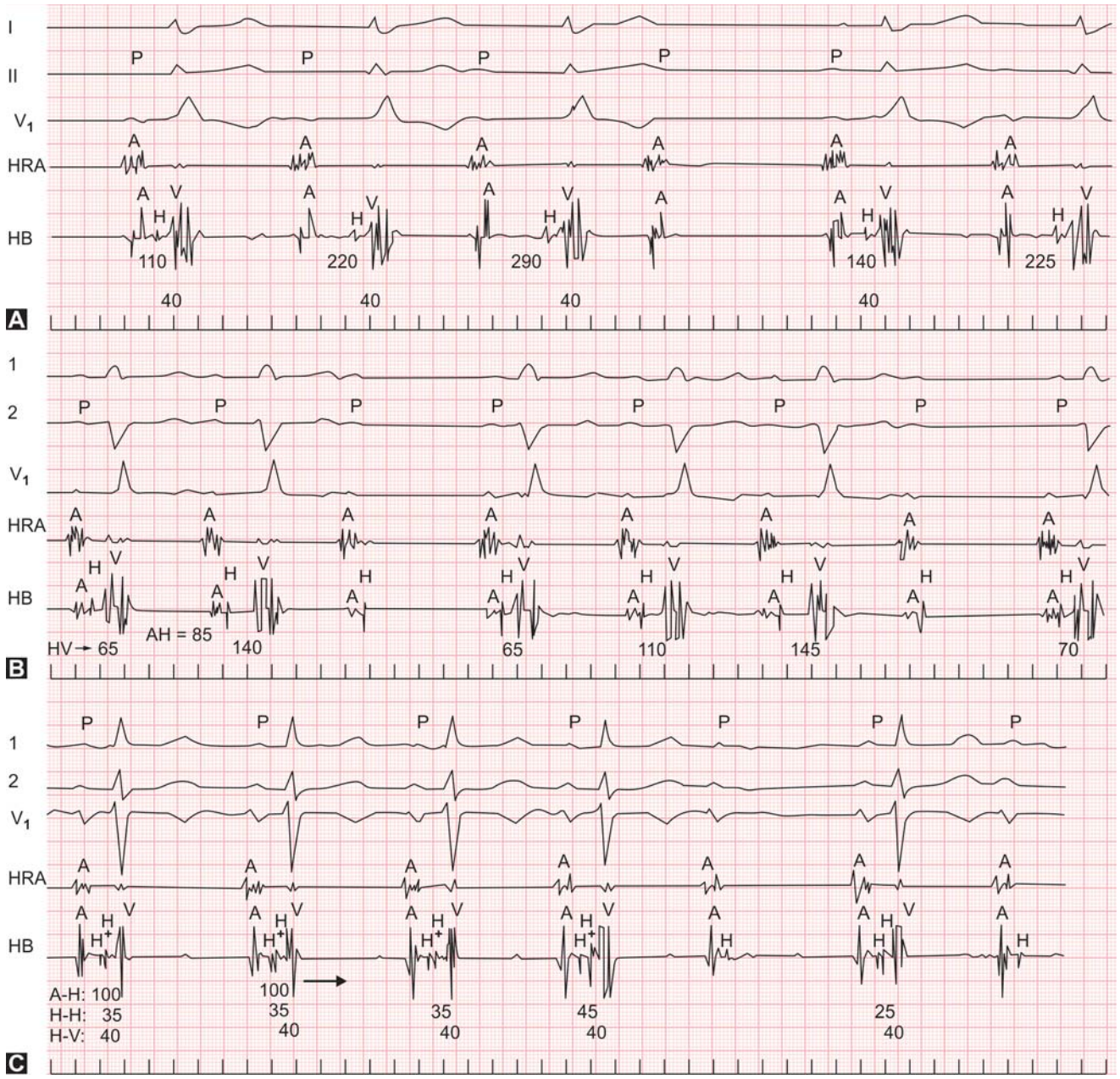


FIGURE 19: Infra-Hisian Wenckebach. With atrial pacing at cycle length 700 ms (heart rate 86 bpm), 1:1 atrial capture results in A-H stabilization at 198 ms and progressive prolongation in the H-V until the fourth paced complex fails to conduct beyond the His to reach the ventricles. The prolonged but stable A-H interval of 198 ms signifies atrioventricular conduction disease, but the Wenckebach pattern of conduction and block below the His implies significant distal conduction system disease as well

posteroseptal accessory pathway; retrograde activation earliest at the distal CS would suggest presence of a left free-wall accessory pathway or left-sided AVN;[24] and retrograde activation that is earliest at the HRA would suggest presence of a right free-wall accessory pathway.

Retrograde conduction refractory periods of HPS, AV node and accessory pathways may be determined through the use of ventricular premature extrastimuli. It is once again identified as the longest ventricular S1-S2 that fails to conduct beyond His or to the atria and is analogous to the anterograde refractory



FIGURES 20A TO C: His bundle (HB) electrograms in atrioventricular (AV) block. The tracings are from three different patients with second-degree AV block. In Figures A and B, the conducted QRS complexes are wide and associated with bundle branch block. (A) The block is within the AV node (i.e. the A-wave on the HB is not followed by an HB deflection). (B) It can be appreciated that the block is distal to the HB even though the surface electrocardiogram (ECG) demonstrates a Wenckebach phenomenon. The latter can obviously occur in the His-Purkinje system as well, as depicted in this figure. (C) The site of the block is within the HB. This is suggested by split HB potentials (labeled H and H^+), and the block is distal to the H but proximal to the H^+. Intra-His block is difficult to diagnose from the surface ECG but can be suspected when a Mobitz type II occurs in association with a normal P-R interval and a narrow QRS complex. (*Source:* Modified from Akhtar M. Invasive cardiac electrophysiologic studies: an introduction. In: Parmley WW, Chatterjee K (Eds). Cardiology: Physiology, Pharmacology, Diagnosis. Philadelphia: Lippincott; 1991. With permission from Lippincott, Williams and Wilkins)

periods. Ventricular extrastimuli are also of use in assessing ventricular refractoriness and for arrhythmia induction, whether supraventricular or ventricular. Multiple extrastimuli are important for induction protocols when assessing tendency toward arrhythmia, particularly wide QRS tachycardia, which may occur due to a variety of electrophysiologic mechanisms, both from supraventricular and ventricular origins (Figs 23A to D).[25] The underlying nature of the wide QRS tachycardia is critical for both prognosis and therapy, and EP studies have proven invaluable for distinguishing the various etiologies. With few exceptions, when the nature of the arrhythmic problem is not known and the direction of therapy is not clear, patients with wide QRS tachycardia should undergo EP study. This is particularly true in situations where nonpharmacologic therapy is the desired goal.[11]

In patients with features suggesting high risk of sudden death, such as structural heart disease and LV dysfunction as well as evidence of ventricular ectopy or arrhythmia in this

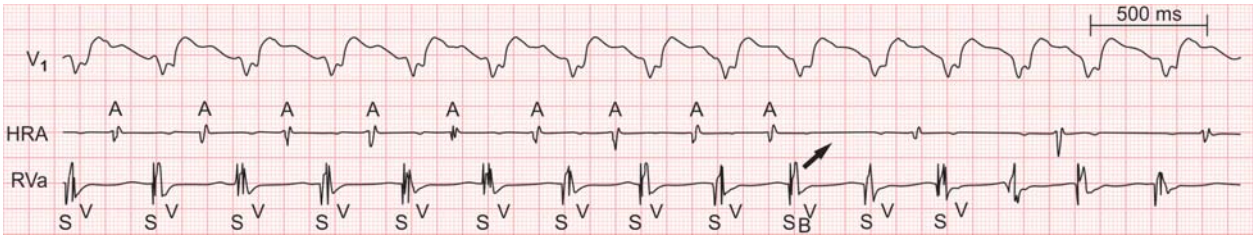
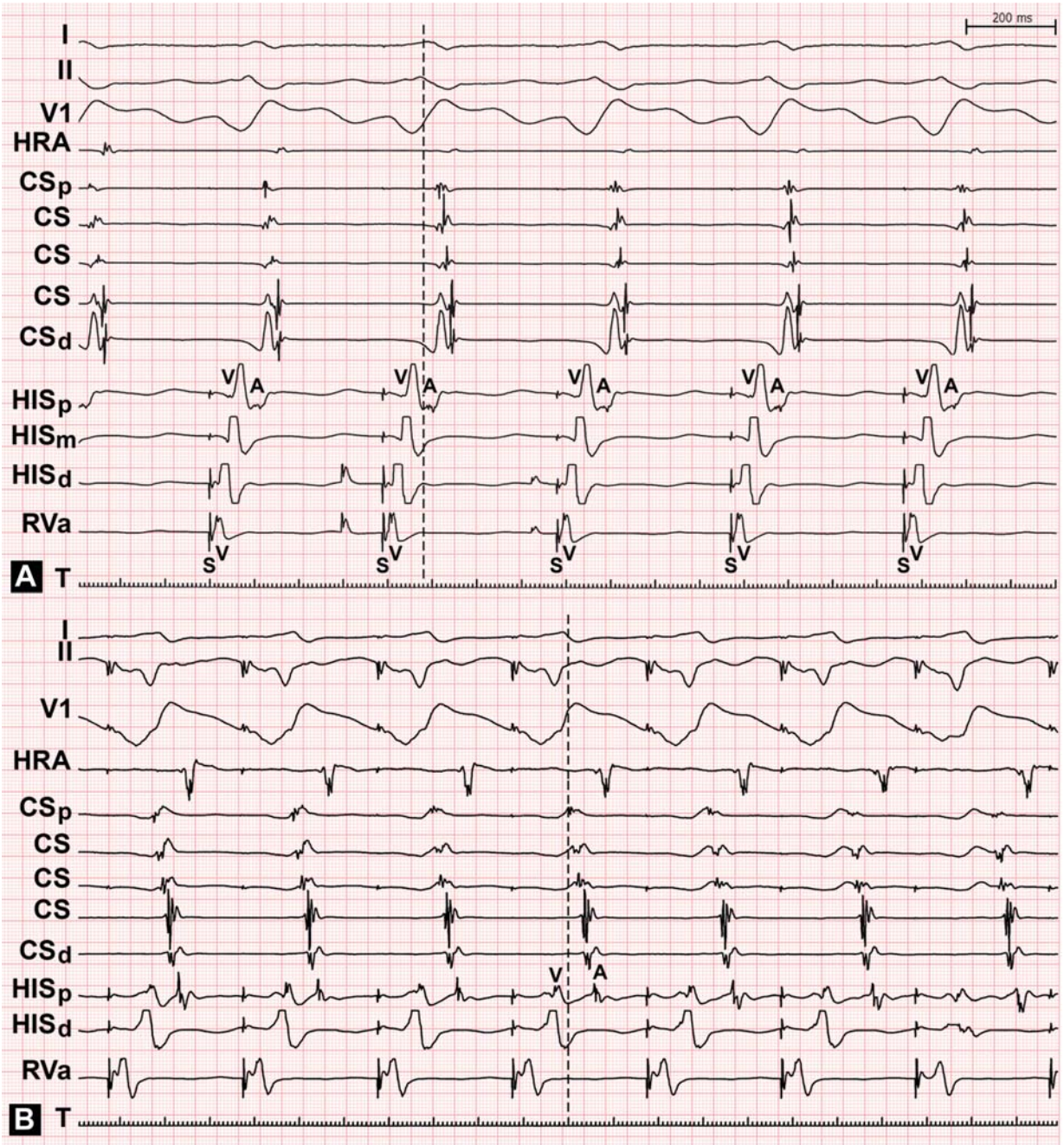
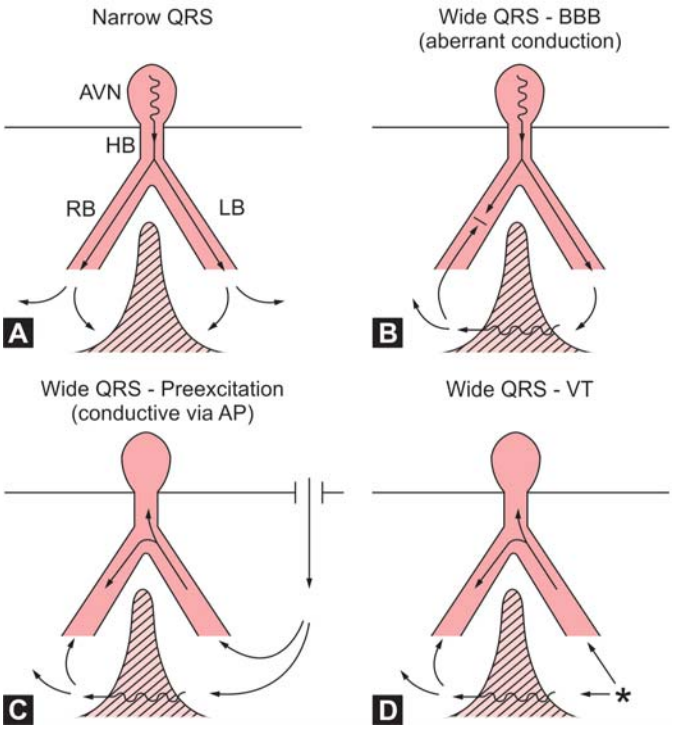


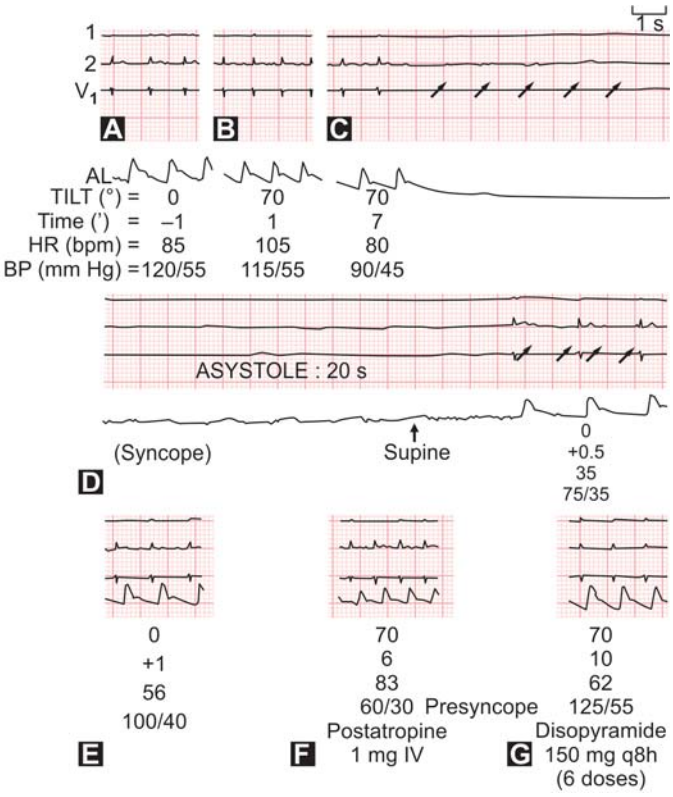
FIGURE 21: Retrograde conduction block. Continuous ventricular pacing (S) with gradual decrementation in cycle length results in 1:1 ventricular capture (V) and conduction to the atria (A) with progressive prolongation in V-A time until the 10th paced complex (S_BV) fails to conduct to the atrium and a 2:1 retrograde conduction pattern is established



FIGURES 22A AND B: Retrograde conduction patterns. Surface electrocardiogram and intracardiac channels show two examples of ventricular pacing resulting in 1:1 myocardial capture and conduction to the atria over different pathways. (A) Retrograde atrial activation is earliest at the proximal His (A) followed by coronary sinus (CS) activation from proximal to distal, suggesting retrograde conduction over an anteriorly located pathway, i.e. the atrioventricular node (AVN) fast pathway. (B) Retrograde atrial activation is earliest in the proximal CS and later in the His (A), suggesting retrograde conduction over a posteriorly located pathway, i.e. AVN slow pathway or posteroseptal accessory pathway. Dashed lines identify earliest atrial activation. (Abbreviations: V: Ventricular electrogram; S: Stimulus artifact)



FIGURES 23A TO D: Wide QRS tachycardia mechanisms. Routes of impulse propagation during a wide QRS tachycardia in various settings are depicted. It should be noted that only in A and B, His bundle activation expected to precede ventricular activation. This helps the delineation from other causes of wide QRS tachycardia, shown in C and D. (Abbreviations: AP: Accessory pathway; BBB: Bundle branch block; VT: Ventricular tachycardia). (*Source:* Modified with permission from Akhtar M. Techniques of electrophysiologic evaluation. In: Fuster V, O'Rourke RA, Walsh RA, Poole-Wilson P (Eds). Hurst's The Heart, 12th edition. New York: The McGraw-Hill Companies, Inc.; 2007. With permission from The McGraw-Hill Companies, Inc.)



FIGURES 24A TO G: Asystole in neurocardiogenic syncope. Note the normal heart rate (HR) and blood pressure (BP) in supine position. At the beginning of head-up tilt at 70 degrees (B), some degree of tachycardia is noted. Seven minutes after the onset of tilt (C), an episode of atrioventricular block occurs and is followed by sinus arrest and a total asystole of 20 seconds. Syncopal episodes follow. Presyncope is still present when asystole is prevented by atropine (F). Findings in C might tempt one to prescribe permanent pacing, an inappropriate choice of therapy. In this patient with neurocardiogenic syncope, disopyramide (G) prevented hypotension and syncope without the need for a permanent pacemaker. (*Source:* Modified from Sra JS, Jazayeri MR, Avitall B, et al. Comparison of cardiac pacing with drug therapy in the treatment of neurocardiogenic (vasovagal) syncope with bradycardia or asystole. N Engl J Med. 1993;328:1085-90. With permission from Massachusetts Medical Society)

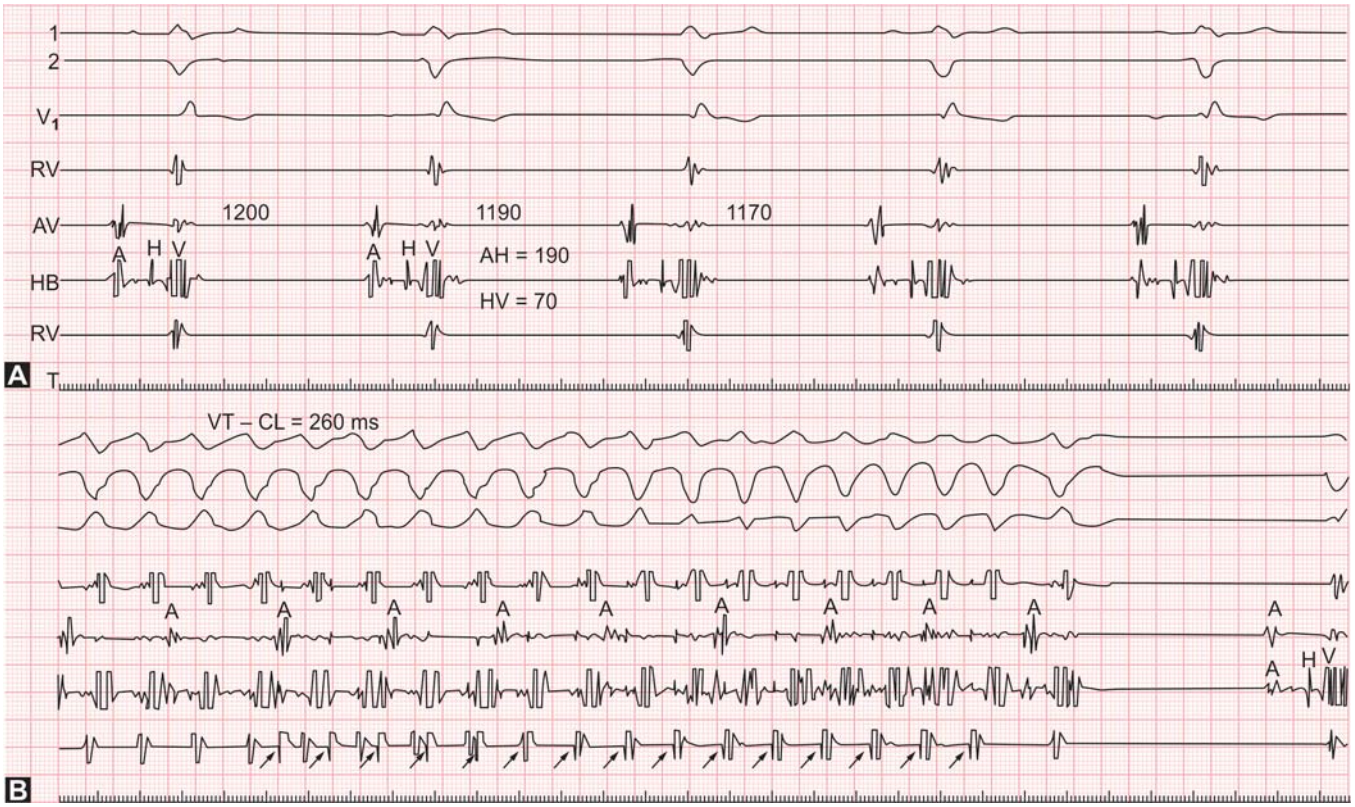
setting, utilization of multiple extrastimuli (maximum 3), including short-long-short sequences, from multiple ventricular sites in the baseline state and under pharmacologic stress or stimulation is necessary. The induction of monomorphic VT is a specific response reflecting tendency of the myocardial substrate to support this type of arrhythmia and clinically appropriate therapy should be rendered accordingly. Alternately, the induction of polymorphic VT can be a nonspecific response in patients without structural heart disease, when triple extrastimuli at short coupling intervals are utilized; hence, the delivery of additional ventricular extrastimuli should be weighed carefully against the risk of a nonspecific finding.[11]

Role of Electrophysiology Study in Evaluation of Unexplained Syncope

While neurocardiogenic mechanisms constitute the most common causes of syncope in patients with ostensibly normal hearts and should be evaluated through tilt testing (Figs 24A to G),[22,23,25,26] EP study is integral in evaluating patients with syncope that remains unexplained, particularly those with heart disease.[27] During such studies, all arrhythmic possibilities, such as sinus node dysfunction, AV conduction abnormalities, SVT and VT, should be excluded. Patients with underlying structural heart disease, such as old myocardial infarction, primary myocardial disease or poor LV function, generally have underlying VT to explain syncope (Figs 25A and B). When arrhythmias occur in patients without overt structural heart disease, sinus node dysfunction, AV block (particularly intra-Hisian block) or SVT may be more likely. Less frequently, VT can occur in the absence of an overt structural heart disease.[11]

SURVIVORS OF SUDDEN CARDIAC ARREST

In many patients with documented episodes of cardiac arrest from the onset, VF can be documented as the initial cause. Patients dying suddenly often have underlying structural heart disease (usually coronary artery disease or primary myocardial disease) and are prone to VT/VF due to electrical instability. It seems prudent to investigate both the nature and extent of organic heart disease and also to assess vulnerability to recurrent VT/VF. At present, EP study is considered a routine part of the overall patient assessment in this group of individuals.[11,28,29]



FIGURES 25A AND B: Arrhythmic causes of syncope. (A) Sinus rhythm in a patient with unexplained syncope. Sinus bradycardia, bifascicular block, and a long P-R interval from surface electrocardiogram suggest possible conduction system disease etiology. (B) In this patient, however, ventricular tachycardia was inducible with ventricular extrastimulation and was the actual cause of syncope. Control of ventricular tachycardia (VT) without a pacemaker was sufficient to prevent syncope in this patient. Termination of tachycardia and restoration of sinus rhythm are shown in Figure B. (Abbreviation: CL: Cycle length). (*Source:* Modified from Akhtar M. Techniques of electrophysiologic evaluation. In: Fuster V, O'Rourke RA, Walsh RA, Poole-Wilson P (Eds). Hurst's The Heart, 12th edition. New York: The McGraw-Hill Companies Inc.; 2007. With permission from The McGraw-Hill Companies Inc.)

In survivors of VT/VF, EP study is desirable for a variety of reasons:

- In our experience, almost 40% of patients with monomorphic VT in association with idiopathic dilated cardiomyopathy and valvular heart disease have bundle branch reentry (BBR) as the underlying mechanism (Fig. 26). We feel this arrhythmia is preferably managed with bundle branch ablation, which is curative, rather than with an implantable cardioverter-defibrillator (ICD) alone.
- Several VT morphologies or other arrhythmias may be identified in addition to the presenting/clinical VT. Lack of awareness of such arrhythmias may complicate patient management. For example, rapid SVT may require separate attention to prevent unnecessary ICD shocks, either through antiarrhythmic therapy or by ablation. The coexistence of sick sinus or conduction system disease may be aggravated by antiarrhythmic therapy and necessitate pacing. Identification preoperatively could contribute to appropriate device selection.
- Rarely, supraventricular arrhythmia may trigger VT/VF. This may happen in patients with severe coronary artery disease, congestive heart failure or Wolff-Parkinson-White syndrome to name a few scenarios. Elimination of the underlying triggers should be the primary therapeutic approach with the need for an ICD, a secondary concern.

Cardioactive Agents

The invasive EP study often incorporates a phase in which observation and programed stimulation is conducted under pharmacologic influence in an attempt to facilitate arrhythmia induction. Two agents are commonly employed, isoproterenol and procainamide.

Isoproterenol is a sympathomimetic amine with primary activity on beta-adrenergic receptors type 1 and type 2. Its overall effects are to increase inotropic and chronotropic response as well as improve conduction system and myocardial propagation. Usually a dose of 1–3 mcg/min is adequate to achieve at least a 20–25% increase in sinus rate in normal patients. Its role during EP study is primarily threefold:

1. Evaluation of chronotropic response;
2. Assessment of AV conduction; and
3. Facilitation of arrhythmia induction.

In patients being evaluated for sinus node dysfunction, in addition to SNRT and SACT evaluation, a blunted response to catecholamine stimulation correlates with impaired chronotropic response during exercise testing in patients with sinus node dysfunction. As mentioned previously, AV conduction with Wenckebach at cycle lengths greater than 600 ms should be considered unusual, but may be seen in patients with high vagal tone. However, this finding should not be considered abnormal in isolation, and only if a lack of



FIGURE 26: Induction of sustained ventricular tachycardia due to bundle branch reentry (BBR). The surface electrocardiogram and intracardiac tracings are labeled. Basic cycle length (S_1S_1) is 400 ms during ventricular pacing. Sustained BBR is induced with two extrastimuli (S_2S_3). Note that the His bundle and right bundle (RB) deflections precede the QRS, suggesting supraventricular tachycardia with aberrant conduction. However, there is 2:1 ventriculoatrial (VA) block, indicating the ventricular nature of this tachycardia. Without His bundle/right bundle (HB/RB) recordings, the diagnosis can be difficult and, consequently, the likelihood of inappropriate therapy will be high. RB-RB and V-V (ventricular) intervals are labeled. (*Source:* Modified from Caceres J, Jazayeri M, McKinnie J, et al. Sustained bundle branch reentry as a mechanism of clinical tachycardia. Circulation. 1989:79:256-70. With permission from Wolters Kluwer Health)

improvement with adrenergic stimulation is demonstrated should pathology be suspected. Isoproterenol infusion aids such evaluation in that it can improve both AVN and HPS conduction. In addition to assessment of sinus node automaticity and AV conduction, isoproterenol facilitates arrhythmia induction and sustainability both through modulation of AVN and accessory pathway conduction; and by provoking myocardial refractory period shortening that permits shorter coupling during atrial and ventricular premature extrastimulation to enhance tissue conduction delay, thereby promoting reentry. A pronounced benefit of isoproterenol is seen in patients with structurally normal hearts and idiopathic VT, in whom rapid atrial pacing and isoproterenol facilitates induction of triggered activity.[30] Finally, isoproterenol can reverse antiarrhythmic effects, primarily through its actions on ion channels. Therefore, efficacy of antiarrhythmic therapy is also an important contribution of isoproterenol to the EP study.

Procainamide is a class IA antiarrhythmic drug with primary effects in blocking sodium channels. It increases tissue refractoriness and slows conduction in the atria, HPS and ventricles, with variable effects on the AV node.[31,32] Its primary role in the clinical EP study is to assess propensity toward AV conduction block and VT induction. In patients with normal HPS conduction, procainamide may introduce mild conduction delay. However, in patients with moderate conduction disease, manifested by H-V intervals greater than 65 ms, a dose of 10 mg/kg can unmask a profound tendency toward conduction block. If the H-V prolongs beyond 100 ms, this is an indication for permanent pacing. As stated, conduction slowing is an anticipated effect of procainamide therapy and hence is the primary mechanism of its antiarrhythmic qualities in acute VT suppression. However, conduction slowing can also promote reentry, particularly in patients with structural heart disease. Hence, it is employed during EP study to evaluate VT inducibility but also explains why class I antiarrhythmics are contraindicated for long-term maintenance therapy in patients with structural heart disease.

CARDIAC ELECTROPHYSIOLOGY STUDY FOR EVALUATION OF DRUG THERAPY

In patients with relatively benign cardiac arrhythmias, EP testing to assess efficacy of pharmacologic therapy is unnecessary in most situations, and clinical course can be observed to determine whether control has been achieved. Also, in patients with ICDs, antiarrhythmic therapy can be assessed clinically as the device will record and treat events according to its specific programing. However, for patients with potentially life-threatening tachycardias like VT or with severe manifestations of cardiac arrhythmias, such as syncope or presyncope, in whom device therapy is not present, it is desirable to assess efficacy of

pharmacologic intervention. A technique of drug testing has been developed whereby the elimination of inducibility of a given tachycardia is assessed following a drug administration. If drug therapy eliminates induction, addition of isoproterenol may demonstrate reversal of therapeutic drug effect.[33] This is helpful in considering additional or alternative therapy. Failure of serial drug testing is associated with a significant recurrence rate and is a strong indication for nonpharmacologic intervention.[11]

ELECTROPHYSIOLOGY STUDY TO GUIDE ABLATIVE THERAPY

ROLE OF THREE-DIMENSIONAL MAPPING SYSTEMS

Treatment of cardiac arrhythmias is dictated by various factors impacting risk related to therapy including potential adverse effects, tolerance of the patient to specific treatment and anticipated likelihood of long-term success. One modality employed for arrhythmia diagnosis and treatment is catheter ablation, through which sites involved in arrhythmia genesis and maintenance are mapped and targeted for local tissue destruction via a percutaneous catheter-based procedure. Identification of specific location(s) that initiate or maintain arrhythmia is challenging for a variety of reasons, but particularly so due to difficulty in returning the catheter to a particular location with any measure of precision and accuracy, given the various cardiac and respiratory motions that impact how catheters and the heart interface, as well as the ambiguity of depth perception on two-dimensional (2D) fluoroscopy.

Three-dimensional (3D) electroanatomic mapping systems are an integral tool in interventional EP as they provide a manner to visualize inside of the heart and reliably guide catheters to specific locations that would otherwise prove challenging with 2D fluoroscopy alone.[34,35] These systems have two important capabilities: (1) creating and visualizing endocardial geometry as a 3D model and (2) superimposing timing and voltage information to create "maps" that visually indicate whether a particular region is activated earlier or later than others, and if a particular region is healthy or scarred according to the amplitude of the local EGM (Supplemental Video 1). These color-coded maps are displayed with a virtual rendition of the mapping catheter, so as to convey visually the relationship of the catheter to the surrounding myocardial chamber—a relationship that is often ambiguous on fluoroscopy. These systems are able to achieve a fairly high level of precision and can annotate catheter tip locations in the 3D model to provide targets for navigation and provide a "history" of previous sites mapped. However, as the true 3D anatomical position of the virtual catheter is not known to the system—only the relative position of the catheter within the mapping system's 3D coordinate space is known—accuracy is compromised. To address this, these systems can import an actual 3D anatomic volume, such as a computed tomography (CT) scan or magnetic resonance image (MRI), of a particular cardiac chamber to define the anatomic coordinate system.[36] The anatomic volume can be aligned and rotated to best approximate the orientation of 3D map, which is then superimposed (Fig. 27). This process of "registering" the volume and map permits better anatomical localization by comparing the created 3D map to the known anatomy to verify that all areas have been accounted for and to identify true location of the catheter and its relationship to sometimes highly important and sensitive structures, such as pulmonary veins for AF ablation.[37] Whether a mapping system is used with or without a 3D volume, the images are displayed on a separate view from live fluoroscopy, requiring the operator to incorporate information from both image sources and perform a mental real-time registration of these images. The latest commercial fluoroscopy systems have the capability to register a 3D volume directly with live fluoroscopy so true catheter location can be visualized within a registered anatomic model[38] (Fig. 28). The registered volumetric and fluoroscopic image can then be compared to the image of the 3D map, which may also be registered to the 3D volume. In an effort to achieve both accuracy and precision, this method still requires operator to assimilate information from multiple image sources. The systems that register various imaging modalities with live fluoroscopy must also overcome the challenges posed by cardiac and respiratory motion evident on live fluoroscopy but not accounted for by the static anatomic and virtual models. Techniques to compensate for this motion, cardiac and respiratory "gating,"[39] permit a method of continuous and real-time registration between the live fluoroscopy and the 3D model. Incorporating voltage and timing maps directly into the CT or MRI volumes that are registered to fluoroscopy would provide a means to

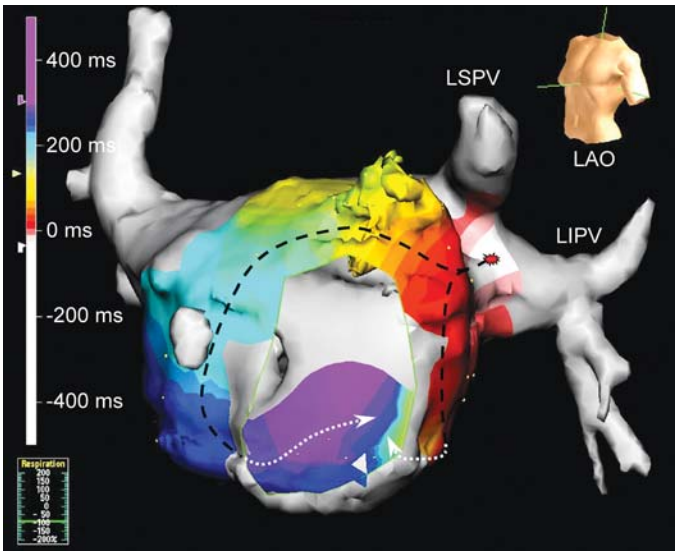


FIGURE 27: Left atrial (LA) computed tomography (CT) with 3D electroanatomic map (LAO projection). Electroanatomic mapping data is superimposed on a 3D LA geometry and then registered with a CT of the LA and pulmonary veins (PVs) to convey activation timing. Activation with respect to a timing reference is depicted according to the color scale (left). The mitral valve annulus is demarcated by a green perimeter. Earliest activation, displayed in white, is seen arising from between the left superior and inferior PVs, and then propagates (red to orange to yellow, etc. according to color scale) counterclockwise and clockwise around the mitral valve annulus (black dashed lines). The two wavefronts pass posteriorly (white dashed arrow) and meet (seen by looking through the mitral valve annulus into the LA) where crowding of isochrones suggests conduction block, in this case, between the mitral valve annulus and the inferior aspect of the inferior pulmonary vein, i.e. across the posterior mitral isthmus

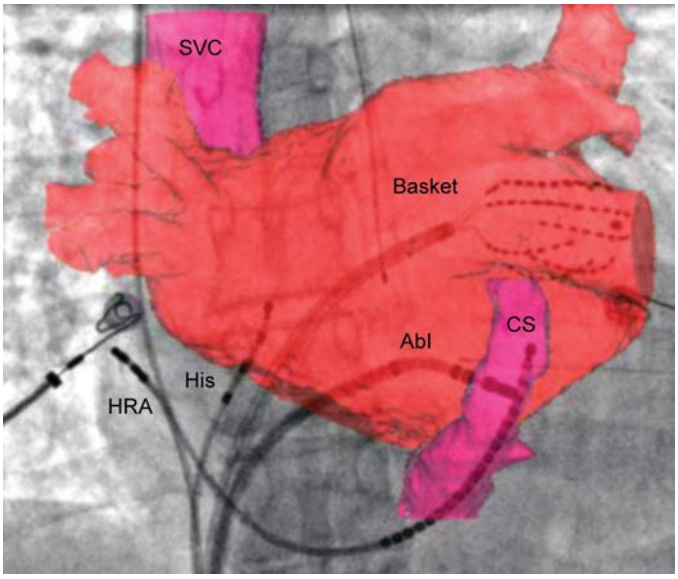


FIGURE 28: Live fluoroscopy with overlay of registered left atrial (LA) computed tomography (CT). An anteroposterior projection of live fluoroscopy shows multiple catheters including a multielectrode basket catheter and ablation catheter positioned through transseptal sheaths into the LA. The LA CT reconstruction is registered with fluoroscopy to demonstrate specific anatomy and catheter locations. The basket catheter is positioned in the left inferior pulmonary vein and the ablation catheter is positioned at the mitral valve annulus and, hence, appears in close proximity to the duodecapolar catheter within the coronary sinus (CS). The CT is depicted in posteroanterior projection in order for anatomical alignment between the two modalities. (Abbreviations: Abl: Ablation catheter; HRA: High right atrium; SVC: Superior vena cava)

unite all these imaging modalities and technologies into a single system.

COMPLICATIONS

The contemporary EP study is safe when performed in appropriate facilities by trained physicians and personnel. Although patient factors, such as age, anatomy and associated comorbidities, must be considered in individualizing procedural risk, the major complication rate is approximately 1% and for death is 1:1,000. The complications are the same as those anticipated with other forms of cardiac catheterization as well some more particular to the EP study. These include inadequate hemostasis with or without vascular injury including local bleeding from access sites with adjacent extension, hematoma, AV fistula, pseudoaneurysm and major vessel perforation; vascular and intracardiac thrombosis with or without pulmonary or systemic embolism including stroke; cardiac injury including myocardial infarction, coronary artery and CS dissection, and myocardial perforation and associated pericardial effusion with or without cardiac tamponade; tachyarrhythmias and bradyarrhythmias and injury to the conduction system rarely necessitating permanent pacing; esophageal injury and pulmonary vein stenosis in left atrial ablation; skin injuries associated with direct cardioversion and radiation/fluoroscopy exposure; phrenic nerve injury and paralysis; decompensated heart failure; infection; and allergic reactions primarily to administered agents such as iodine, anesthetics, antibiotics, blood products and protamine.

CONCLUSION

It remains a truism that the past offers insight into the present and future. The historical discoveries that have coalesced into the field of clinical cardiac EP are truly awesome and compel one to take pause and reflect on the origins of this burgeoning field. Cardiologists of the 21st century must still see in the electrocardiogram all the electrical processes and associated physical manifestations underlying cardiac EP described over the past 100 years to fully appreciate normal processes and cardiovascular pathology. These fundamental principles, outlined here, form a clinical foundation for every student of the medical arts who is interested and invested in cardiovascular diseases to begin to comprehend the most fundamental of physiologic questions, “Why does the heart beat?”

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VIDEO LEGEND

Electroanatomic mapping of VT substrate. Point-by-point mapping of the left ventricle was performed in sinus rhythm to create a “scar map.” Tissue zones are depicted through the color scheme: red—dense scar; purple—healthy myocardium; colored “infarct border zone” separates red and purple regions. The specific color scheme is determined by the voltage window shown at right. In this case dense scar is defined as tissue producing EGM amplitudes less than 0.52 mV and healthy myocardium is defined as tissue producing EGM amplitude more than 1.50 mV. EGM amplitudes between 0.52 mV and 1.50 mV then define the border zone. The left ventricle is shown in anteroposterior view with apex to the right and base to the left. The geometry is rotated to demonstrate the distribution of healthy tissue, seen involving most of the LV, and scar involving the basal septum and small portions of the lateral wall and apex. After one revolution, the LV geometry is tilted upward to show the inferior wall. The blue sphere locates the presumed VT exit site and the red spheres annotate ablation lesions that connect the exit site with the mitral valve annulus to prevent reentry. (Abbreviations: EGM: Electrogram; LV: Left ventricle; VT: Ventricular tachycardia)

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Chapter 32

Syncope

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Chapter Outline

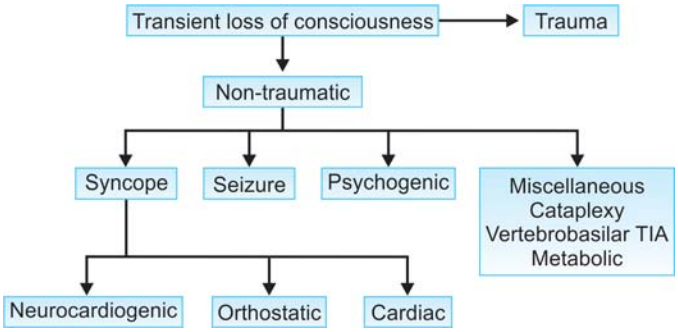
- Epidemiology
  - — Incidence and Prevalence of Syncope
  - — Economic Burden of Syncope
  - — Causes and Classification of Syncope
- Diagnostic Tests
  - — History and Physical Examination
  - — Blood Tests
  - — Electrocardiogram
  - — Echocardiography
  - — Exercise Testing
  - — Continuous ECG Monitoring
  - — Signal Averaged ECG
  - — Upright Tilt Table Testing
  - — Electrophysiology Study
  - — Cardiac Catheterization
  - — Neurologic Tests
- Approach to the Evaluation of Syncope
- Specific Patient Groups
  - — Vasovagal (Neurocardiogenic) Syncope
  - — Hypertrophic Cardiomyopathy
  - — Nonischemic Cardiomyopathy
  - — Congenital Heart Disease
  - — Elderly Patients
- Syncope and Driving
- Guidelines

INTRODUCTION

Syncope is a sudden and transient loss of consciousness associated with loss of postural tone, followed by complete and spontaneous recovery. The term "syncope" originates from the Greek word "Synkoptein" which means—cutting short (koptein-"to cut"). In the first six centuries, many Greek philosophers and physicians speculated on the causes of syncope. Claudius Galen, a famous Greek physician, suggested that syncope was a problem of both the stomach and the heart.[1] The mechanism for transient loss of consciousness associated with syncope is cerebral hypoperfusion with reduced blood flow to the reticular activating system. A common phrase used in clinical medicine is presyncope which is considered to represent a warning or prodrome for frank syncope. In the case of presyncope, symptoms, such as dizziness and graying out, are not followed by frank loss of consciousness. Many physicians evaluate and treat presyncope in a similar manner to syncope; although a reasonable approach, there is no strong clinical data to support similar etiologies and outcomes.

It is important to acknowledge that the definition of syncope (and thus etiologic classification) varies even among experts. Using a more general definition of transient loss of consciousness, some experts include neurologic (e.g. seizure and concussion), metabolic (e.g. hypoxia) and psychiatric conditions as forms of syncope, while others who emphasize cerebral hypoperfusion consider syncope as one of the several causes of transient loss of consciousness and classify some neurologic, metabolic and psychiatric mechanisms as separate entities (Flow chart 1).[2,3] Using this more restrictive definition of syncope, the three most important causes of transient loss of consciousness are: (1) syncope; (2) seizure and (3) psychogenic blackouts. Other rare causes include metabolic disorders, such as hypoglycemia or hypoxia, intoxication, and psychiatric problems such as cataplexy or pseudosyncope. Determining the correct cause of syncope is the key to approaching therapy, if the initial working clinical diagnosis is erroneous, subsequent investigations and even the final diagnosis and treatment may also be incorrect.[4] Regardless of definition, syncope may represent a harbinger for sudden death, and often the diagnostic evaluation focuses on identifying or ruling out potential life-threatening causes of syncope such as ventricular arrhythmias or aortic stenosis. For this reason, the diagnostic workup for the patient with syncope revolves around two different but related issues: (1) identification of the specific mechanism for syncope and (2) risk stratification to estimate short-term and long-term risk of adverse outcomes. It is important for the clinician to remember that the diagnostic workup of syncope requires a patient-specific approach and diagnostic tests must carefully be chosen. Several medical societies including the European Society of Cardiology (ESC) and the American Heart Association/American College of Cardiology Foundation (AHA/ACCF) have provided comprehensive guidelines or scientific statements for the diagnosis and management of syncope, although some aspects are not without controversy.[2-5]

FLOW CHART 1: Classification of mechanistic causes for transient loss of consciousness and syncope



EPIDEMIOLOGY

INCIDENCE AND PREVALENCE OF SYNCOPE

Several studies have attempted to evaluate the incidence and prevalence of syncope. Obtaining accurate figures is difficult, since it has been estimated that only 25–50% of syncopal episodes are reported to medical professionals and only 2–5% of episodes are evaluated in emergency department settings.[2] In the most recent report from the Framingham study, the incidence of a first report of syncope was 6.2/1000 person-years follow-up and a ten-year cumulative incidence of 6%.[6] In addition, a sharp increase in the incidence of syncope after age 70 years, particularly in the presence of cardiovascular disease, was reported. Several studies suggest that syncope is quite common in younger populations.[7–9] For example, in a cohort of 62 medical students, 32% reported a prior episode of syncope, with a higher rate in women than in men (42% and 31% respectively).[9] Collectively, the data suggest a bimodal distribution of a first episode of syncope, with a first peak between the first and the second decade (with a female predominance) and another peak that begins after the age of 60 years and is gender-independent.[2] To summarize, up to approximately 30–40% of people will have an episode of syncope during their lifetime, and of these 30–40% will have a recurrent episode within three years.[1–9]

Although syncope may be the first symptom for a patient at high risk for sudden death and adverse clinical outcomes, examination of cohort studies suggests that the mortality rate ranges from 1–2% at 30 days to 7–8% at one year.[6,10] Examination of large hospital databases suggests that in-hospital mortality for syncope is also low (0.28%) with almost all deaths occurring in patients over 60 years of age.[8] However, in the Framingham report, patients who were thought to have a cardiac cause of syncope had a six month mortality rate of 10%.[6] The additional risk conferred simply by the presence of syncope is controversial and has varied from no additional risk to a 30% increase in risk in cohort studies using matched controls.[6,11] For example, Kapoor and his colleagues found that mortality was the same in patients with or without syncope and was instead dependent on the presence and type of underlying cardiac disease and other comorbidities.[11] In contrast, in a population based study from the Framingham data, syncope was associated with a 30% increase in mortality compared to patients without syncope (Fig. 1).[6]

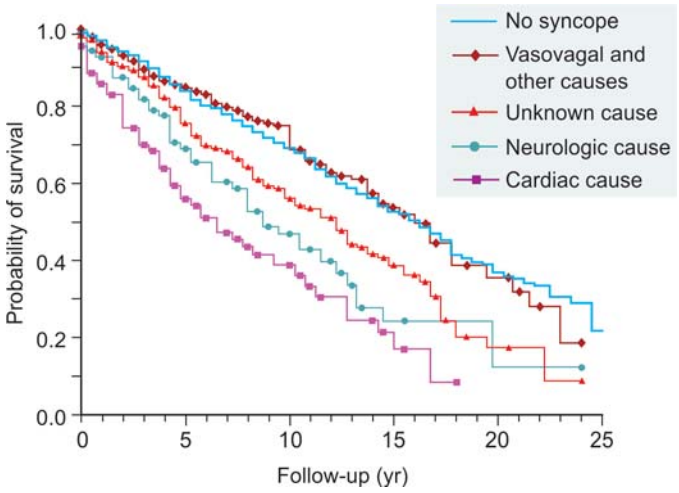


FIGURE 1: Survival curves from Framingham data for patients with different types of syncope. (*Source:* Soteriades ES, Evans JC, Larson MG, et al. Incidence and prognosis of syncope. N Engl J Med. 2002;347: 878-85)

ECONOMIC BURDEN OF SYNCOPE

It has been estimated that syncope accounts for 1–3% of emergency department evaluations and 1–6% of hospital admissions.[12,13] Several studies have estimated that the annual cost of management and treatment of patients with syncope ranges 1.7–2.4 billion dollars in the United States.[8,14] The cost for the management of patients with syncope varies widely, dependent on the diagnostic tests ordered and whether or not an implantable cardiac rhythm device (pacemaker or ICD) is used.[8] In addition to the cost of diagnostic evaluation and specific therapies, syncope can be associated with injuries and significant psychological disability that can increase cost and have a significant impact on quality-of-life.[15–17] Major injuries, such as fractures and motor vehicle accidents were reported in about 6% of patients.[15] Minor injuries including bruises and lacerations were reported in 27–29% of patients with syncope.[15] Elderly patients have a higher incidence of injuries when compared to younger patients, with a dramatic increase after age of 70 years, the incidence almost doubles between the sixth and the seventh decades of life.[15–17] Syncope is associated with a significant reduction in quality-of-life indices, particularly in the presence of recurrent episodes, associated comorbidities and in women.[15–17]

CAUSES AND CLASSIFICATION OF SYNCOPE

As discussed earlier, syncope is but one cause of transient loss of consciousness. Syncope can further be classified into three general causes: (1) reflex or neurally mediated syncope; (2) syncope due to orthostatic hypotension and (3) cardiac syncope (Flow chart 1).

Reflex or neurally mediated syncope is the most common cause of syncope. One form, often called vasovagal syncope or the "common faint", is the single most common cause of syncope. The pathophysiological basis for vasovagal syncope was described by Sir Thomas Lewis in the early 1900s and importantly noted that although the bradycardia component

could be reversed by atropine, hypotension and altered state of consciousness persisted. Although vasovagal syncope is the most common cause of syncope in younger patients, accounting for up to 50% of cases, it is important to recognize that even in patients more than 65 years old vasovagal syncope accounts for approximately 30% of cases. In all forms of reflex syncope, triggering of the afferent limb of a reflex arc leads to hypotension due to vasodilation (vasodepressor effect) and decreased heart rate (vagal effect). In vasovagal syncope the afferent limb can be triggered by a variety of conditions such as heat, hypovolemia, pain, or fear and anxiety while in conditions often called—situational syncope, triggering occurs from specific actions such as micturition, cough or swallow. Finally, particularly in older patients, the afferent limb can be triggered by carotid sinus stimulation.

A second cause of syncope is orthostatic hypotension. Normally with standing, accumulation of fluid in the legs results in the initiation of a complex neurologic reflex response that maintains systemic blood pressure. In orthostatic hypotension this response is insufficient, leading to a decrease in systemic blood pressure. An abnormal response is usually defined as a 20–30 mm Hg drop in systolic blood pressure on standing. Reduction in blood pressure and the increase in heart rate (which may be attenuated in older patients and in those with diabetes) are usually observed immediately after standing but can be delayed for a short period of time and thus blood pressure measurements should continue for several minutes after standing. Orthostatic hypotension can be due to a primary abnormality of the autonomic nervous system (either isolated or affecting multiple systems) or secondary (e.g. diabetes, Parkinson's disease and uremia). Diabetes is the most common cause of autonomic neuropathy in the United States and can be associated with relatively high mortality rates (25–50% mortality at 5–8 years).[18] Another form of autonomic dysfunction that can be associated with syncope is the postural orthostatic tachycardia syndrome (POTS); up to 20–30% of patients with POTS will report a prior history of syncope or presyncope.[19] Investigators believe that in POTS, hypotension on standing does not occur but maintenance of upright blood pressure requires an abnormal increase in heart rate, leading to sustained sinus tachycardia (usually > 110 bpm). Although patients with POTS and orthostatic hypotension can present with symptoms of syncope they more commonly complain of symptoms such as fatigue, palpitations, rapid and pounding heart rates, and dizziness.

The third cause of syncope is a cardiac abnormality. Etiologies of cardiac syncope can broadly be divided into abnormal heart rhythms and obstruction to flow. Both rapid heart rates and slow heart rates can cause cerebral hypoperfusion and syncope. Obstruction to blood flow can be due aortic stenosis, pulmonary valve stenosis or dynamic left ventricular outflow tract obstruction in some patients with hypertrophic cardiomyopathy (HCM). Patients with anomalous coronary arteries can sometimes present with exertional syncope, particularly in those whose right coronary artery originates from the left system with the right coronary artery passing between the aorta and pulmonary artery.[20] Large population studies have shown that of the multiple causes of syncope, a cardiac etiology carries the worst prognosis (Fig. 1).[6]

DIAGNOSTIC TESTS

The evaluation of syncope is often challenging and in up to 40% of cases no specific cause can be identified; this is specially true in older patients.[2,3,6] The history and physical examination play an essential role in evaluating patients with syncope. Several studies have attempted to evaluate the diagnostic yield of different tests in clinical practice.[2,3,21] It is important to acknowledge that the highest diagnostic yield of any test in unselected populations of patients with syncope is at best probably 25–30% with no test providing a "gold standard", underscoring the importance of careful initial evaluation by the history and the physical examination and choosing subsequent tests based on this initial assessment.[2–4]

HISTORY AND PHYSICAL EXAMINATION

The history and physical examination play an important role in establishing cause of transient loss of consciousness and, in particular, for differentiating between syncope and seizure as this distinction can be difficult (Flow chart 1). For example, up to 40% of patients with syncope will have generalized seizure-like activity and myoclonic jerking due to cerebral hypoperfusion.[22] Symptoms, such as prolonged confusion after the episode (postictal state) and tongue biting, are suggestive of seizure.[23,24] An altered sense of smell, taste or an aura such as a sense of déjà vu prior to the event are suggestive of a temporal lobe seizure.[24] Focal neurologic signs and symptoms during or after the event (Todd's palsy), also make seizure more likely than syncope. Urinary incontinence, although more commonly observed with seizures, does not completely rule out syncope. In syncopal patients, recovery is complete and often, but not always, rapid, as contrasted with seizures in which recovery is slow due to the postictal state and associated confusion. Petit mal or absence seizures are occasionally misdiagnosed as syncope. A key feature that favors the diagnosis of absence seizures is preserved postural tone despite unresponsiveness. Temporal lobe seizures can have a long duration with varied levels of consciousness. Several investigators have evaluated specific characteristics of the history for differentiating among the various causes of syncope and between syncope and seizure.[24,25] In a cohort of 539 patients a simple point score system correctly differentiated seizure from syncope in 94% of patients with a sensitivity of 94% and a specificity of 94%.[24] Tongue biting, postictal confusion, head turning to one side and prodromal déjà vu or jamais vu were more suggestive of seizures while presyncope, diaphoresis prior to the episode, or loss of consciousness associated with standing made seizure less likely.

Once the clinician has decided that an episode of transient loss of consciousness is most likely due to syncope, the history and physical examination can provide further clues as to its specific cause.[26,27] Pertinent questions should include a history prior of cardiac disease and diagnosis, if known; family history of arrhythmias, syncope and sudden death; knowledge of an abnormal electrocardiogram; medications; positional changes that occurred prior to the syncopal spell (including head-turning); prodromal symptoms; and history of prior syncopal events. Features of the clinical history that are more commonly associated with significant arrhythmias such as ventricular tachycardia or bradycardia due to advanced or complete heart

block include male sex, age older than 50 years, fewer than three episodes of syncope and duration of warning prior to syncope of less than 6 seconds.[26–28] Conversely, symptoms, such as blurred vision, nausea, vomiting, warmth, diaphoresis and prolonged fatigue after syncope, have been associated with neurally mediated syncope rather than ventricular tachycardia or complete heart block. In a cohort of 341 patients, the presence of suspected cardiac disease was the strongest predictor of cardiac cause of syncope and absence of cardiac disease had a negative predictive value for a cardiac cause of 97%.[26] However, a more recent study found that the value of clinical history for distinguishing between cardiac and neurally mediated syncope was significantly reduced in older patients.[21] Finally, syncope associated with exertion has traditionally been identified as "high-risk" due to its association with valvular aortic stenosis, HCM, congenital coronary anomalies and channelopathies such as Long QT syndrome, but no large studies have been performed in these groups.[29] Using a similar approach for distinguishing between syncope and seizure, Sheldon and his coworkers identified several historical features that can help to differentiate between vasovagal syncope and cardiac causes of syncope (Fig. 2).[30,31] Symptoms such as lightheadedness associated with pain or medical settings or with prolonged sitting or standing, and a sensation of warmth or sweatiness prior to the episode made vasovagal syncope more likely. Conversely, a history of diabetes, prior arrhythmia, no recollection of the episode and palpitations preceding syncope more likely made a cardiac cause. Similarly a first event over 35 years of age or bystanders describing the patient "turning blue" were also associated with a cardiac cause of syncope.

The physical examination has a central role in evaluation of syncope. A complete cardiac examination should be performed to assess the presence of structural cardiac disease. Orthostatic vital signs are an essential part of the physical examination in a patient. A drop of systolic blood pressure exceeding 20 mm Hg or a decrease in diastolic blood pressure of more than 10 mm Hg is considered to be diagnostic for orthostatic hypotension. The POTS is defined as an increase in heart rate more than 25–30 beats per minute within 5 minutes of standing with symptoms. Cardiac auscultatory findings, such as murmurs or gallops, are important for identifying the presence and severity of structural cardiac disease such as aortic stenosis and HCM. On palpation, findings, such as a left ventricular heave or a sustained left ventricular impulse, can alert the clinician to the presence of structural heart disease, such as left ventricular hypertrophy or ventricular dilation, due to cardiomyopathy or past myocardial infarction that will make more likely a cardiac cause of syncope.

Finally, performing carotid sinus massage (CSM) is important in patients with syncope over 40 years of age.[2] Neurologic complications during CSM occur rarely (0.17–0.45% of patients) and it is important to confirm the absence of carotid bruits or neurologic symptoms suggestive of a stroke or transient ischemic attack and before performing the maneuver.[2] Continuous electrocardiographic monitoring is essential and continuous blood pressure monitoring is highly desirable. To perform CSM, firm continuous pressure for 5–10 seconds should be applied to the right carotid artery at the level of the cricoid cartilage and after several minutes the same maneuver should be repeated on the left side. Ideally, CSM should be performed in both the supine and upright positions since an abnormal vasodepressor response may be detected only when the patient is upright. An abnormal response (carotid sinus hypersensitivity) is usually defined as ventricular asystole more than 3 seconds (due either to sinus pause or AV block) or a fall in systemic blood pressure more than 50 mm Hg (Fig. 2). Formal CSM is often included as a part of the tilt table test in some institutions. It is important to remember that the history and physical examination play a critical role for risk stratification of the patient with syncope.[2,3] As outlined previously, patients with a cardiac cause of syncope have a far worse short-term and long-term prognosis compared to syncope due to other causes. For this reason, the history and physical examination help the clinician decide whether structural cardiac disease is present and provide an initial estimate for the likelihood of a cardiac cause for syncope.

BLOOD TESTS

Routine blood tests including electrolytes, tests for anemia (hematocrit or hemoglobin) and glucose, although commonly performed, generally have a low diagnostic yield in evaluation of syncope.[2,3] The exception may be the presence of anemia; anemia has been incorporated into several prognostic algorithms used for risk stratification of patients with syncope.[32,33] Frequently, patients with syncope are evaluated for myocardial infarction, even in the absence of an infarction pattern on the electrocardiogram. Despite this approach, the yield of diagnostic evaluation for myocardial infarction for patients with syncope is less than 1%.[34] In a small study investigators found that higher brain natriuretic peptide (BNP) levels could be used to identify patients with syncope due to cardiac causes or worse outcomes, and a recently published risk stratification schema for patients with syncope used a BNP more than 300 pg/ml as one criteria for identifying high-risk patients.[33,35] It is important to note that the most recent guidelines do not specifically recommend any blood tests for the evaluation of syncope.[2,3]



FIGURE 2: Simultaneously recorded leads aVR and aVF rhythm strips obtained during carotid sinus massage (CSM). Initially sinus slowing is observed and ultimately a 3.5 second sinus pause is noted. A pause with ventricular asystole more than 3 seconds, due either to sinus pause/arrest or AV block, defines carotid sinus hypersensitivity

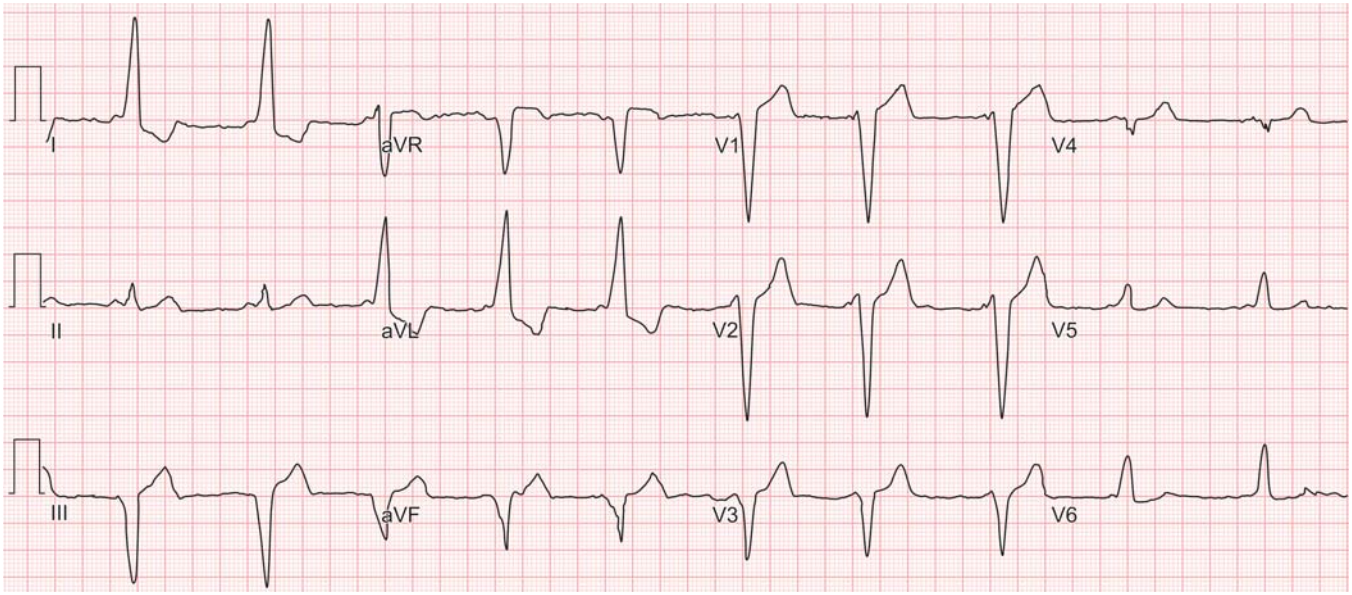


FIGURE 3: ECG from a patient with Wolff Parkinson White syndrome due to the presence of a right freewall accessory pathway. Pre-excitation of the right ventricle leads to a short PR interval and a QRS complex with a left bundle branch block morphology and a negative delta wave in aVR [*Source:* Kusumoto FM. ECG Interpretation. Pathophysiology to Clinical Application. New York: Blackwell-Springer; 2009 (with permission)]

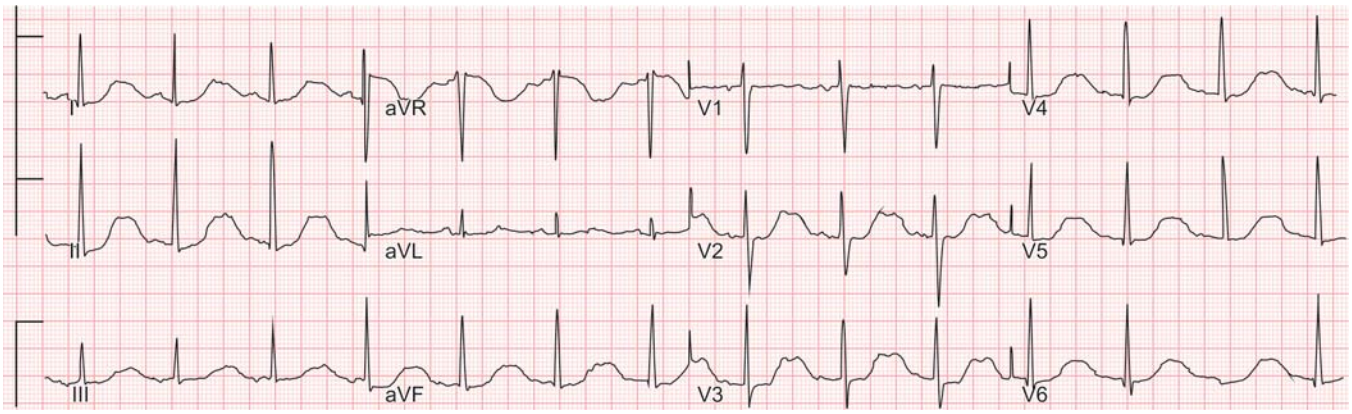


FIGURE 4: ECG from a patient with syncope and long QT syndrome (*Source:* Kusumoto FM. ECG Interpretation. Pathophysiology to Clinical Application. New York: Blackwell-Springer; 2009)

ELECTROCARDIOGRAM

A 12 lead ECG is a basic part of the workup in all patients with syncope.[2,3] Although the diagnostic yield of a baseline ECG is low (5–10%), it is an inexpensive and widely available test that can be used to quickly risk stratify patients, particularly if it is abnormal.[2,3,29] Baseline sinus bradycardia, atrioventricular block and intraventricular conduction block (left or right bundle branch block) suggest the possibility of bradycardia as a cause for syncope. Presence of Q waves that suggest the possibility of a prior myocardial infarction or other findings such as left ventricular hypertrophy make structural heart disease, and thus a cardiac cause of syncope, more likely. The presence of premature ventricular depolarizations may have some prognostic information in patients with syncope. In an older study of 235 patients with syncope, the presence of frequent or paired premature ventricular contractions was associated with higher mortality and risk of sudden death.[36]

Finally, there are some ECG patterns that can be used to identify potential causes for syncope: Wolff Parkinson White Syndrome, Long QT Syndrome, Brugada syndrome, arrhythmogenic right ventricular cardiomyopathy and HCM (Figs 3 to 7A and B).

ECHOCARDIOGRAPHY

Both the AHA/ACCF and ESC guidelines state that the echocardiogram plays a central role in syncopal patients with suspected cardiac disease.[2,3] In a review of over 2,000 elderly patients admitted for syncope at a single center, echocardiograms were obtained in 40% of patients and abnormalities were identified in almost 70%.[21] However, results from the echocardiogram affected management in less than 5% of the cases.[21] Echocardiography has a low diagnostic yield in patients with a normal physical examination and normal ECG and need not necessarily be obtained in all patients with syncope. A structural abnormality noted during echocardiography does not per se establish a diagnostic cause for syncope. However, the presence of severe aortic stenosis or rarer conditions, such as atrial myxoma, is usually diagnostic of etiology (Figs 8A and B).

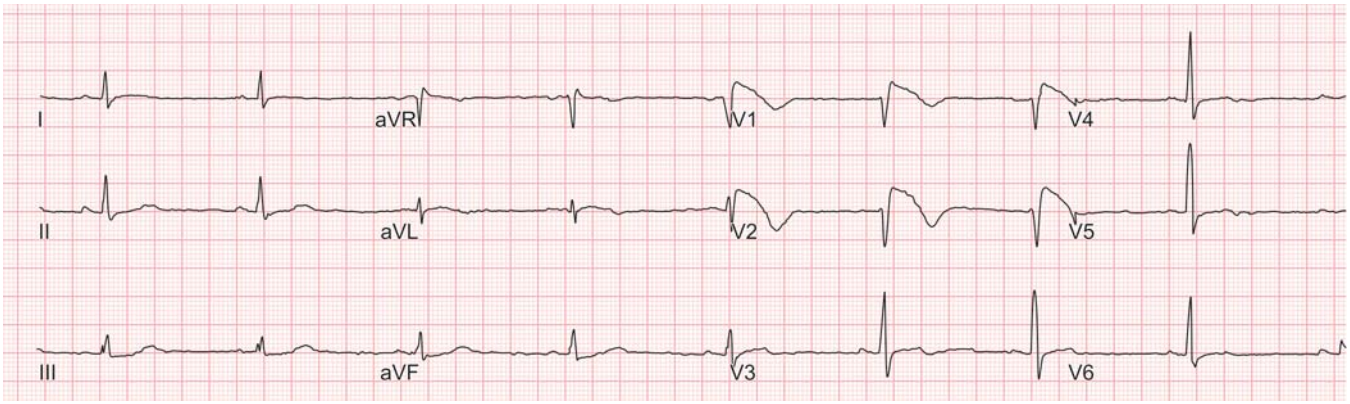


FIGURE 5: ECG from a patient with Brugada syndrome showing the characteristic Type I right bundle branch block pattern and downsloping ST segment elevation in V_1 and V_2. Type I Brugada syndrome is more specific than the "saddle back" ST segment contour in the Type II pattern. ECG patterns in Brugada syndrome can be quite variable, even over short periods of time; questionable diagnoses can be clarified during the intravenous infusion of a sodium-channel blocking drug (*Source:* Kusumoto FM. ECG Interpretation. Pathophysiology to Clinical Application. New York: Blackwell-Springer; 2009)

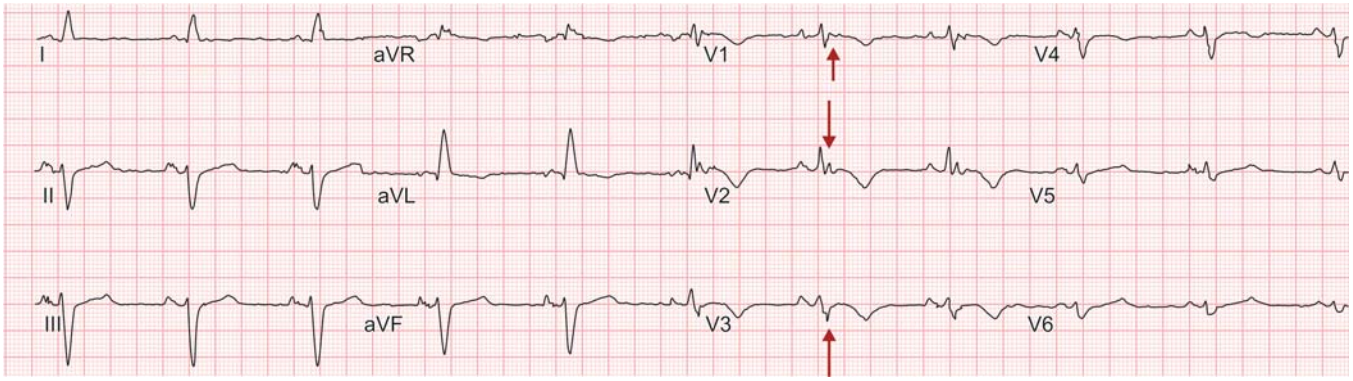


FIGURE 6: ECG from a patient with arrhythmogenic right ventricular cardiomyopathy. There are prominent anterior forces and precordial T wave inversion is present in addition to the highly specific epsilon waves (arrows) that represent delayed conduction in the right ventricle. (*Source:* Kusumoto FM. ECG Interpretation. Pathophysiology to Clinical Application. New York: Blackwell-Springer; 2009)

EXERCISE TESTING

Exercise testing has a low diagnostic yield in the evaluation of syncope (< 5%).[29] However, it may particularly be useful in those patients with exertional syncope. Published guidelines are not uniform in their recommendations; however, the AHA/ACCF scientific statement (but not the ESC guidelines) suggest that exercise testing should be more widely applied to any patient with unexplained syncope, particularly those with coronary artery disease or those at risk for coronary artery disease.

Perhaps even more useful than the identification of ischemia in the patient with syncope is the evaluation of hemodynamic and heart rhythm responses to exercise testing. Development of atrioventricular block with exercise is always abnormal and suggests bradycardia as the mechanism for symptoms. An abnormal decrease in blood pressure during or after exercise may be an important clue for the mechanism of exertional syncope in a patient with HCM.

CONTINUOUS ECG MONITORING

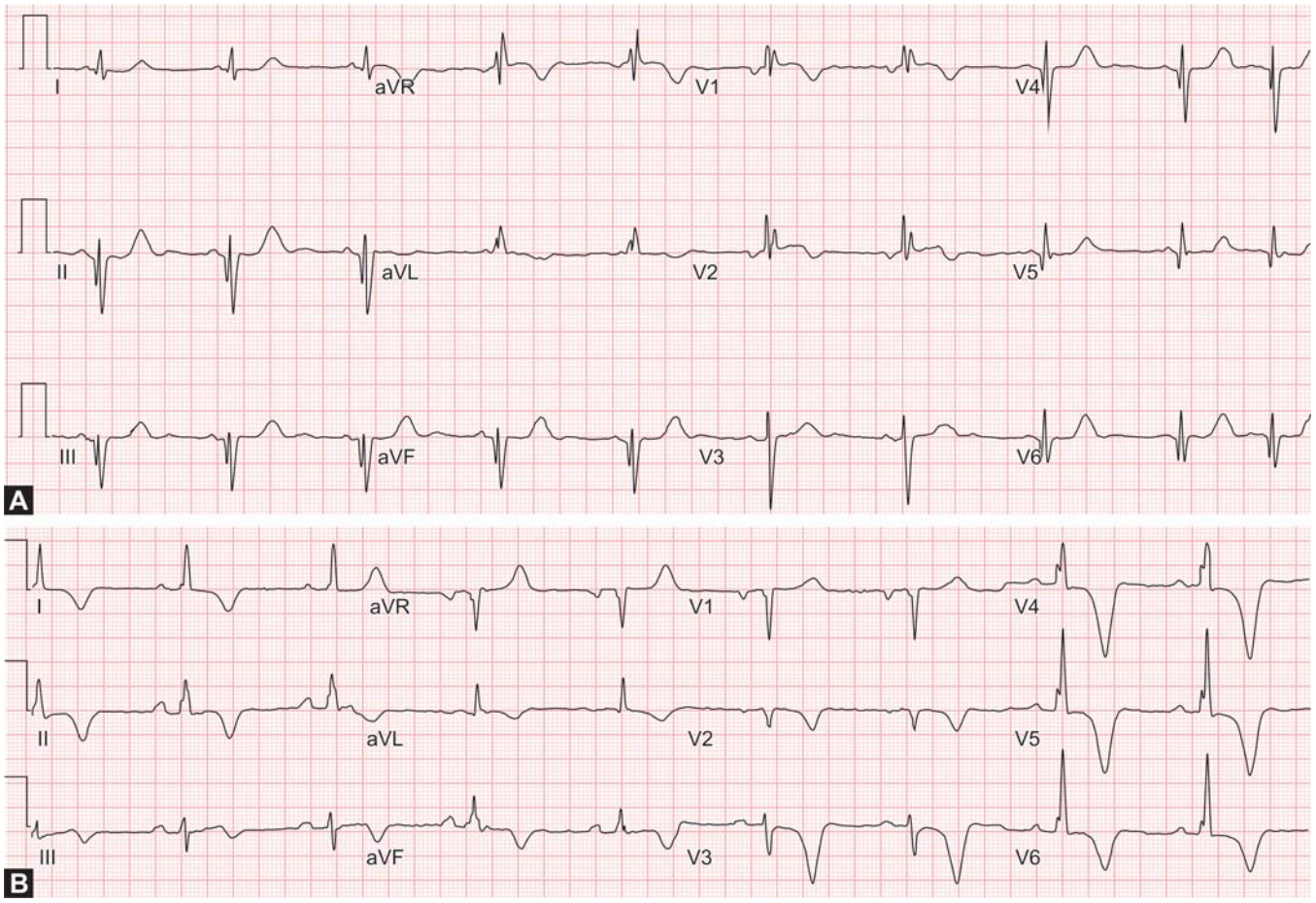
External Devices (24 Hours Ambulatory ECG Recorders, Event Recorders)

Since intermittent bradycardia or tachycardia are the most common cardiac etiologies for syncope, an ECG obtained when the patient is having symptoms is critical for determining whether an arrhythmia is the cause of symptoms. Although asymptomatic arrhythmias can be helpful in suggesting a possible mechanism in some settings, the diagnostic yield of short periods of rhythm monitoring, whether telemetry monitoring during a hospital admission or traditional 24–48 hours ambulatory ECG (Holter) monitoring, is very low.[29] Since most episodes of syncope are usually separated by long periods of time the yield of monitoring less than 48 hours is at best 1–2%.[29]

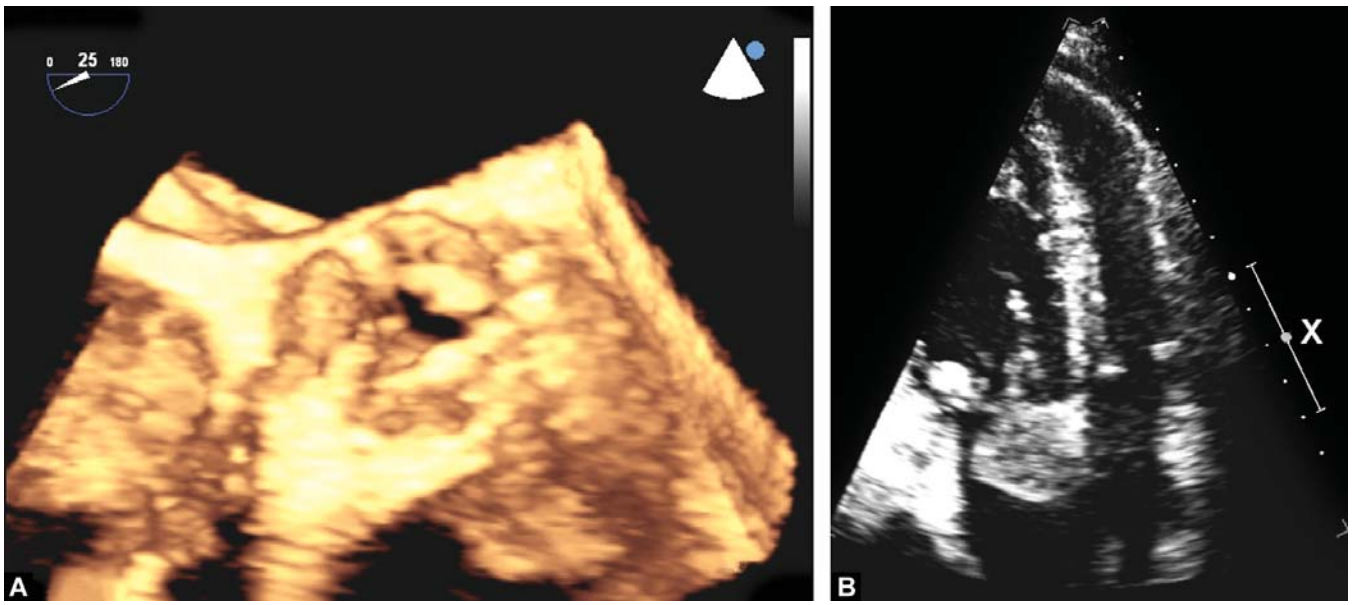
External recorders that have a loop memory that continuously acquires and deletes ECG information can provide longer periods of rhythm monitoring but studies have provided conflicting reports on the utility of these devices due to the sporadic nature of syncope events. An external event recorder is an attractive diagnostic test for patients with near syncope that occurs frequently (e.g. weekly) (Fig. 9). Event monitors that do not provide continuous ECG monitoring and instead are applied by the patient to the chest when symptoms occur may be useful in the patient with palpitations or dizziness, but are of little use in the diagnostic evaluation of syncope due to patient incapacitation during the episodes.

Implantable Loop Recorders

More recently implantable loop recorders (ILRs) that are placed subcutaneously in the left upper chest and that have larger



FIGURES 7A AND B: (A) ECGs from two patients with hypertrophic cardiomyopathy. Hypertrophy predominantly affecting the septum, leading to a larger than expected R wave in V1 and "pseudo Q waves in the inferolateral leads. (B) Hypertrophy affecting the cardiac apex, leading to deep lateral T wave inversions (*Source:* Kusumoto FM. ECG Interpretation. Pathophysiology to Clinical Application. New york: Blackwell-Springer; 2009)



FIGURES 8A AND B: (A) Diagnostic echocardiographic images in patients that presented with syncope. Three-dimensional transesophageal echocardiographic image of a patient with severe aortic stenosis. (B) Four chamber transthoracic echocardiographic image of a sessile left atrial myxoma attached to the interatrial septum (*Source:* Emery Kapples, Jeannine Hiers and Carolyn Landolfo)



FIGURE 9: Simultaneously recorded rhythm strips from an external ECG event monitor with looping memory documenting intermittent high grade AV block associated with symptoms. The patient had a prior positive tilt table test for a diagnosis of vasovagal syncope, but due to continued symptoms despite medical treatment underwent further diagnostic testing for arrhythmias. A permanent pacemaker was placed with resolution of symptoms

memories and the ability to continuously monitor the ECG for more than 1 year have been developed by several manufacturers. These small devices have a battery life that lasts for 18–24 months. Some clinicians use a program system analyzer to optimize placement of the device to obtain good cardiac signals. The two electrodes used for recording cardiac electrical activity are usually placed on either end of a rectangular shaped device.

Once implanted the ILR will record tachycardia or bradycardia using rate parameters defined and programmed by the clinician. The ILR can also be manually activated with a hand-held activator by a bystander or by the patient after the episode. The ILR is usually programmed to save data for a prespecifed time (e.g. 5 minutes) prior to manual activation. Several studies have documented the usefulness of the ILR for evaluating patients with syncope.[2,37–39] In the largest study to date, of 392 patients with syncope who underwent placement of an ILR, 103 (26%) had recurrent syncope and of these, 53 received specific therapy based on the findings recorded on the ILR (usually bradycardia requiring implantation of a permanent pacemaker).[39] Patients that received specific therapy based on the ILR results had a significant reduction in the incidence of recurrent syncope (10% vs 41%).[39] Importantly, approximately 30–40% of patients will have a recurrent episode of syncope not associated with an arrhythmia, and while this finding does not allow definitive therapy it does essentially rule out arrhythmia as a cause for the patient's symptoms and can be reassuring to the patient.[40]

Current guidelines recommend an ILR for patients with recurrent but infrequent episodes of syncope in whom there is a high index of suspicion for an arrhythmogenic cause after a negative initial workup.[2,3] The ILR has gradually supplanted invasive electrophysiology studies and tilt table testing as the diagnostic test of choice for patients with syncope. The ILR is ideal for obtaining a heart rhythm correlation for a patient with intermittent symptoms. As discussed above, the most common abnormal finding recorded by the ILR is transient bradycardia, although supraventricular and ventricular tachycardias (Fig. 10) can sometimes be observed. In addition, identifying normal heart rates during an episode of syncope is extremely useful as this finding essentially rules out a primary arrhythmia mechanism for syncope.

SIGNAL AVERAGED ECG

In some patients with structural heart disease (cardiomyopathy or prior myocardial infarction), low amplitude signals in the terminal portion of the QRS complexes can sometimes be observed using special recording techniques that obtain a number of QRS complexes (allowing random noise to cancel out) and use special filtering algorithms. Late potentials are thought to arise from delayed depolarization of the abnormal myocardium and thus reflect nonhomogeneous depolarization. The signal averaged ECG (SAECG) may be useful in rare circumstances, for example in some cases the SAECG can help to identify patients with arrhythmogenic right ventricular cardiomyopathy.[41] In these patients, fatty infiltration of the right ventricle leads to an abnormal SAECG recording that appears to correlate with myocardial fibrosis obtained by biopsy. Other preliminary data suggest that the SAECG may also be useful in identifying patients with Brugada syndrome who are at higher risk for ventricular arrhythmias.[42] In general, however, the SAECG provides little additional diagnostic information and is not routinely used.

UPRIGHT TILT TABLE TESTING

Upright tilt table testing is commonly obtained in the diagnostic workup of syncope.[2,43] The physiology of standing is complex, but when the patient is moved from the supine to the upright position, approximately 300–600 ml of blood pools in the lower extremities and lower portion of the abdomen, which in turn

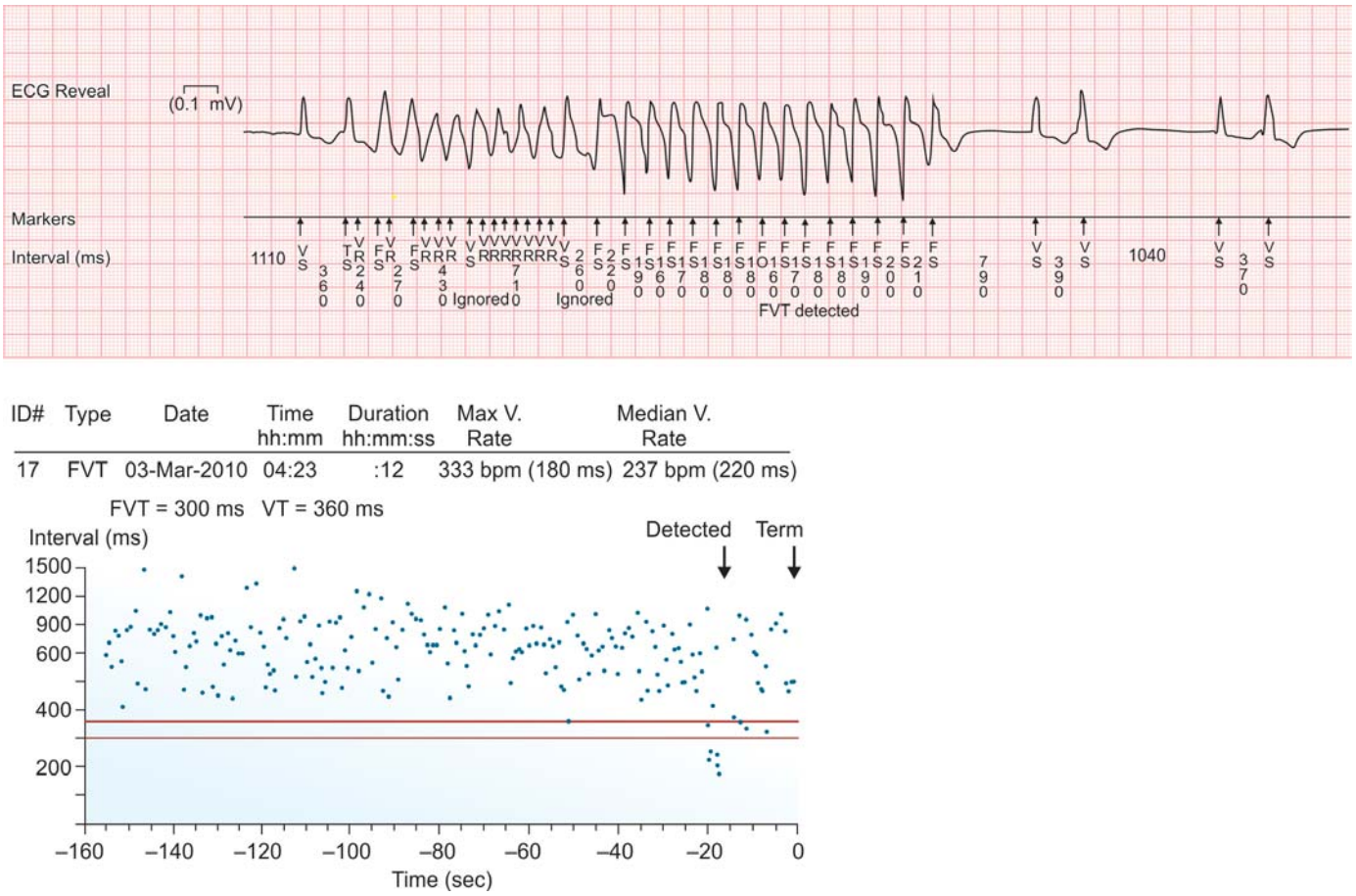


FIGURE 10: Tracings from an ILR showing nonsustained polymorphic ventricular tachycardia that was recorded during sleep (04:23). The device was set to automatically capture rapid heart rates (FVT: Fast ventricular tachycardia, in this case defined as a rhythm with a cycle length < 300 ms). Actual electrograms (Top) and histograms (Bottom) from the event can be obtained. The histogram shows sudden onset of rapid ventricular activity (FS: fibrillation sense) separated by short cycle lengths. The rhythm spontaneously terminates with normal ventricular signal and bigeminy (VS: ventricular sense). Although this abnormal rhythm was not recorded during symptoms results from the ILR suggest ventricular arrhythmias as the cause for the patient's symptoms

leads to a 25–50% decrease in intravascular volume.[43] In response to the decrease in stroke volume a complex interplay of various cardioregulatory systems normally results in maintenance of blood pressure despite the redistribution of blood.

Upright tilt table testing was first applied in clinical medicine 25 years ago as a method for evaluating a patient's hemodynamic response to orthostatic stress and identifying patients likely to develop vasovagal syncope.[44] Several protocols have been developed and there is no uniformity of approach, but generally the patient is positioned on a table at an angle of 60–70 degrees for 30–45 minutes, with only foot support. Some protocols use isoproterenol infusion or nitroglycerin to increase the likelihood of eliciting a vasovagal response. The tilt table test is used to quantify orthostatic hypotension and to attempt to induce a vasovagal response. In those patients who have a vasovagal response, hemodynamic monitoring during the test can quantify the relative and absolute changes in blood pressure and heart rate. Several different hemodynamic responses to tilt table testing can be observed in (Fig. 11):

1. The *normal response* consists of an increase in heart rate of approximately 10–15 beats per minute, an elevation of diastolic blood pressure of about 10 mm Hg and little change in systolic blood pressure.
2. *Orthostatic/POTS response*: Orthostatic hypotension is defined as a reduction in systolic blood pressure of at least 20 mm Hg or a reduction in diastolic blood pressure of at least 10 mm Hg. The POTS pattern consists of a sustained increase in heart rate of at least 30 beats/min or a sustained pulse rate of 120 beats per minute with no profound hypotension. Both of these responses are usually observed within the first 5–15 minutes of tilting; however, in older patients the orthostatic response may be delayed.[45]
3. *Neurocardiogenic response*: Initially, blood pressure and heart rate remain stable. However, after 10–20 minutes a sudden decrease in blood pressure and heart rate will be observed. Some investigators further divide this response into primary vagal, primary vasodepressor or a mixed response, depending on the relative magnitude of blood pressure and heart rate changes.
4. Some investigators also classify as a response of *psychogenic reaction* in which patients develop symptoms with no changes in heart rate or blood pressure.

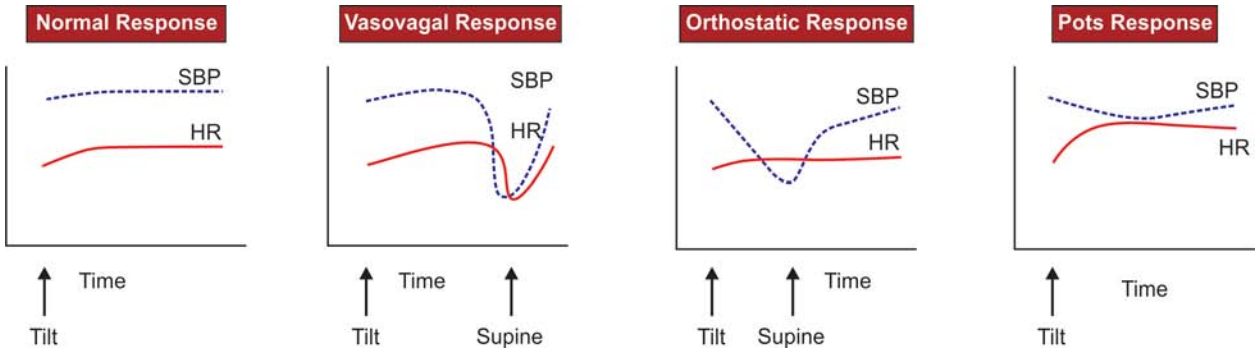


FIGURE 11: Tilt table hemodynamic responses in different conditions. Normally in tilt table testing, with the upright position normal baroceptor function maintains a relatively constant heart rate (HR) and systolic blood pressure (SBP). In the vasovagal response after a relatively long period of time a drop in SBP rapidly followed by a drop in HR is observed. In the orthostatic response, with standing an almost immediate but gradual drop in SBP is observed and HR remains unchanged. In the postural orthostatic tachycardia syndrome (POTS) response SBP is maintained by a significant increase in HR

In patients referred for evaluation for syncope, the most commonly observed abnormal finding during tilt table testing is a mixed form of the neurocardiogenic response (35–45%) in all age groups. The second most common response is age dependent: a bradycardia response observed in patients less than 35 years of age and a pure vasodepressor response in older patients.[46]

Although tilt table testing has been useful as an experimental test for providing physiologic data in patients with vasovagal syncope and orthostatic hypotension and is widely performed, its clinical application has not been well defined. First, it is important to note that the tilt table test has poor reproducibility. When patients with a positive tilt table test are subsequently reevaluated, approximately 50% will have a negative test regardless of whether they were treated or not.[47,48] Second, several studies have found that the likelihood of recurrent episodes of syncope was similar in patients with a positive response and a negative response. Third, abnormalities identified by tilt table testing do not predict the likelihood of bradycardia events that are documented by stored ILR data.[49] Despite these shortcomings tilt table testing may be useful for evaluating some patients with syncope, particularly those with orthostatic hypotension. The ESC has developed detailed guidelines for the methodology, indications and diagnostic criteria for tilt table testing.[2] In general, tilt table testing is recommended when it is important to identify whether the patient is susceptible to vasovagal syncope (e.g. a patient with a structurally normal heart that has a single episode of syncope associated with significant injury) or to help differentiate between reflex syncope from orthostatic hypotension. The tilt table test has been shown to have little use for guiding therapy or as a follow-up tool.[50]

ELECTROPHYSIOLOGY STUDY

The electrophysiology study (EPS) is an invasive test that may be useful for workup of syncope in selected patients.[29] In EPS, using specialized electrode catheters placed in the heart, the clinician can define cardiac electrophysiologic properties, such as sinus node and AV node function, and evaluate the mechanism for any inducible ventricular tachycardia or supraventricular tachycardia under controlled conditions.

Bradycardia can be due to siunus node dysfunction and/or atrioventricular conduction abnormalities. There are several parameters used in EPS for evaluation of the sinus node. The most commonly used parameter is the sinus node recovery time (SNRT). To measure the SNRT, atrial pacing is performed for 30 seconds and the sinus node response on cessation of pacing is evaluated. An abnormal SNRT is shown in Figure 12. In this case, sinus node activation is observed 2.2 seconds after cessation of pacing. Unfortunately, parameters for sinus node dysfunction have highly variable sensitivity (25–70%) and specificity (45–100%) for the clinical diagnosis. The EPS is more useful for evaluation of atrioventricular function and can be used to determine the site of AV conduction block (Fig. 13). Atrioventricular block that develops at or below the level of the His bundle (infra-Hisian block) portends a poor prognosis since intrinsic pacemaker activity of ventricular tissue is not only slow and unresponsive to autonomic influences, but is also notoriously unreliable, even in the short term. A baseline His-to-ventricular (HV) interval more than 100 ms or prolongation of the HV interval to more than 100 ms with procainamide stress has also been shown to be useful for identifying patients at high risk for the development of syncope due to bradycardia. It is important to acknowledge that EPS is useful for defining the site of block in the presence of fixed block but is not useful for evaluating the patient that develops intermittent atrioventricular block at the level of the AV node.

Tachycardia accounts for approximately 15–25% of patients with syncope.[51,52] The EPS may be useful for identifying supraventricular tachycardia but usually this diagnosis is made with continuous ECG monitoring since any arrhythmia induced at EPS may not represent a clinically relevant arrhythmia or the mechanism for syncope. Traditionally, the utility of EPS in the patient with syncope has focused on induction of ventricular tachycardia. In patients with myocardial scars (due to past myocardial infarction or any process that produces myocardial fibrosis) and ventricular tachycardia due to reentry utilizing slowly conducting channels within the scar, programmed stimulation of the ventricle during EPS can be used to assess risk for future ventricular arrhythmias. Although protocols vary among institutions, generally pacing is performed from two sites in the right ventricle delivering one, two or three extrastimuli

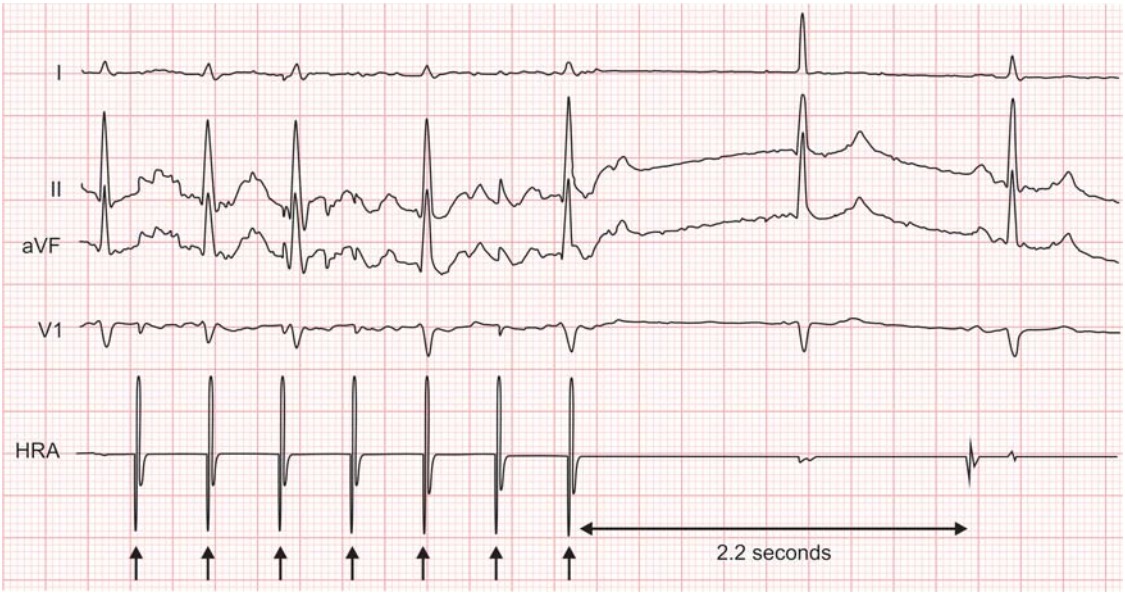


FIGURE 12: Abnormal sinus node recovery time (SNRT). The atria are paced (arrows) at 150 bpm for 30 seconds. Notice the patient has AV block during atrial pacing (this would be expected due to normal decremental conduction properties of the AV node). With cessation of pacing a junctional beat occurs but it takes 2.2 seconds for sinus node activity to return. (*Source:* Kusumoto FM, Goldschlager N. Cardiac Pacing for the Clinician, 2nd edition. New York: Springer; 2008. pp. 647-94)

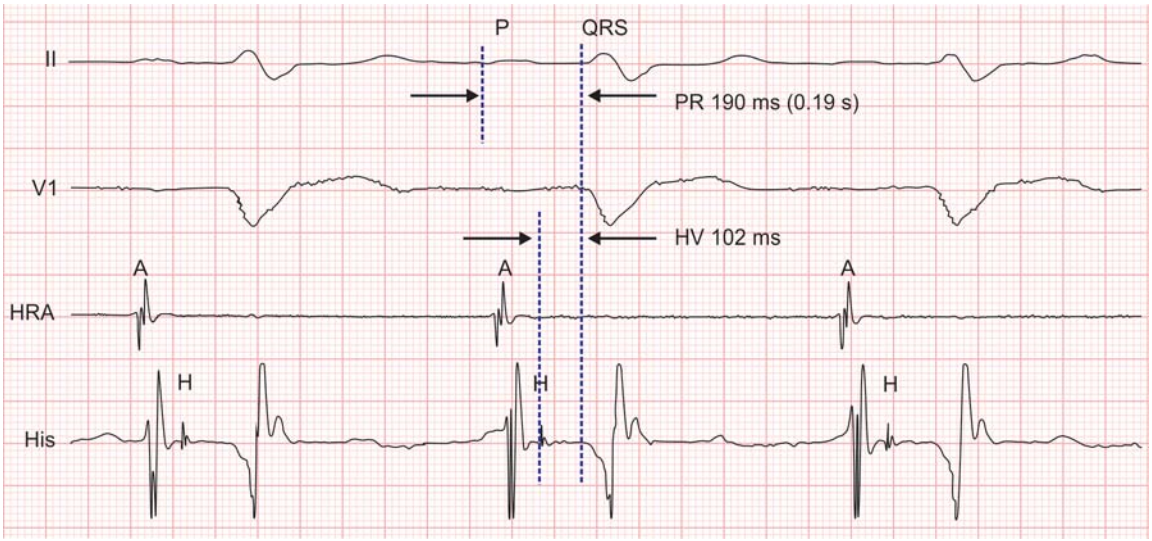


FIGURE 13: Electrograms demonstrating significant prolongation of the HV interval (102 ms) in the setting of a PR interval at the upper limit of normal (190 ms) that suggests infra-Hisian disease. (Abbreviations: H: His bundle electrogram; A: Atrial electrogram). (*Source:* Kusumoto FM. Understanding Intracardiac EGMs and ECGs, 1st edition. Hoboken New Jerse: Wiley-Blackwell; 2010)

after a basic pacing train of eight beats that ensures uniform capture of ventricular tissue. Data from older studies suggest that EPS can be useful for evaluating risk of sudden death in patients with syncope and a prior myocardial infarction.[53,54]

A decade ago, EPS and ventricular stimulation protocols for induction of ventricular tachycardia played a central role in the diagnostic evaluation of syncope in patients with structural heart disease. Since then several important trends have relegated EPS to only occasional use in certain patient groups with syncope. First, several landmark studies have shown that many patients with structural heart disease will receive a mortality benefit from an empiric implantable cardiac defibrillator (ICD) irrespective of the presence or absence of syncope. For example, many patients with an ejection fraction less than 30% due to prior myocardial infarction or an ejection fraction less than 35% in the presence of heart failure symptoms are candidates for ICD placement whether or not they have syncope.[55,56] Second, the ILR appears to be an excellent option for many patients with structural heart disease and syncope who are not candidates for empiric ICD implantation based on ejection fraction and heart failure symptoms alone.[51,52,57] Currently, EPS is reasonable for evaluating patients with syncope and coronary artery disease with prior myocardial infarction that do not meet criteria for an ICD implant or those patients that meet criteria for ICD implant,

but where further risk stratification information might change a clinical decision (usually whether or not to implant an ICD). The EPS is also reasonable for the patient with syncope and evidence for abnormal atrioventricular conduction where defining the site of block will impact clinical decision-making. For example, if infra-Hisian block was found at EPS a permanent pacemaker would be implanted.

CARDIAC CATHETERIZATION

Cardiac catheterization is generally not indicated for the workup of syncope unless accompanied by symptoms suggestive of significant coronary artery disease.

NEUROLOGIC TESTS

Computed tomography (CT) scans, electroencephalography (EEG) and carotid duplex scans are often obtained for the evaluation of patients with transient loss of consciousness. Multiple studies have shown that the diagnostic yield of these tests is extremely low (1–3%) in unselected patient populations.[2,3,29] It is recommended that these tests should be ordered only if indicated by clinical findings that specifically suggest a neurologic process.

APPROACH TO THE EVALUATION OF SYNCOPE

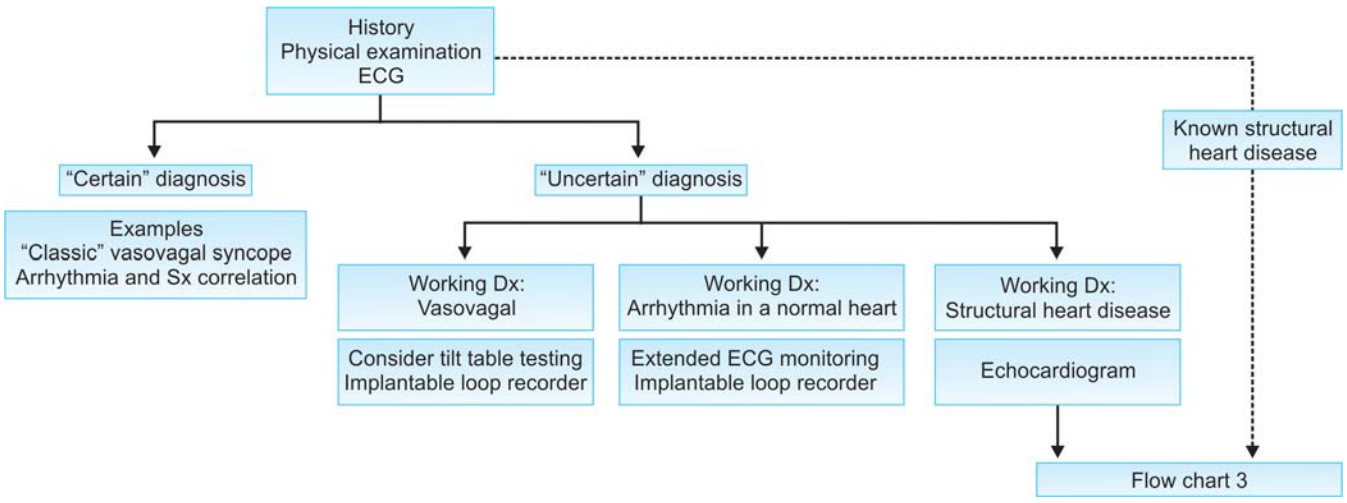
As outlined in the preceding sections, there are many tests available for the assessment of syncope and indiscriminate use of diagnostic tests can lead to an expensive evaluation that provides little insight into the management of the patient. Although it is difficult to provide a "one size fits all" algorithm for managing patients with syncope some general guidelines are useful. Recently published guidelines emphasize the importance of the history and a comprehensive physical examination in the initial evaluation of syncope and also recommend a baseline ECG. Since future risk is largely dependent on whether the patient has a cardiac cause of syncope and whether the patient has structural heart disease most diagnostic and risk-stratification algorithms use this issue as the first decision point (Flow chart 2).

Patients with no history, physical examination or ECG findings suggestive of cardiac disease have a fairly low likelihood of a significant cardiac cause for syncope. If the history is suggestive of vasovagal syncope no further evaluation will be required in many patients. Similarly if the patient presents to the emergency department with symptoms that correlate with an arrhythmia then specific treatment can be initiated. However, even after a comprehensive initial evaluation, the clinician may be unsure of the mechanism of syncope. If the clinician is confident that the patient has no cardiac disease, but is uncertain of whether an arrhythmia is present extended ECG monitoring will be useful. Particularly, in patients with syncope associated with injury, an external event recorder or an ILR may be appropriate depending on the frequency of symptoms. If the patient does not have structural heart disease and the clinician is unsure of the patient's hemodynamic response to orthostatic stress, tilt table testing may be a reasonable next test. Tilt table testing may be helpful particularly for identifying patients with orthostatic hypotension or POTS.

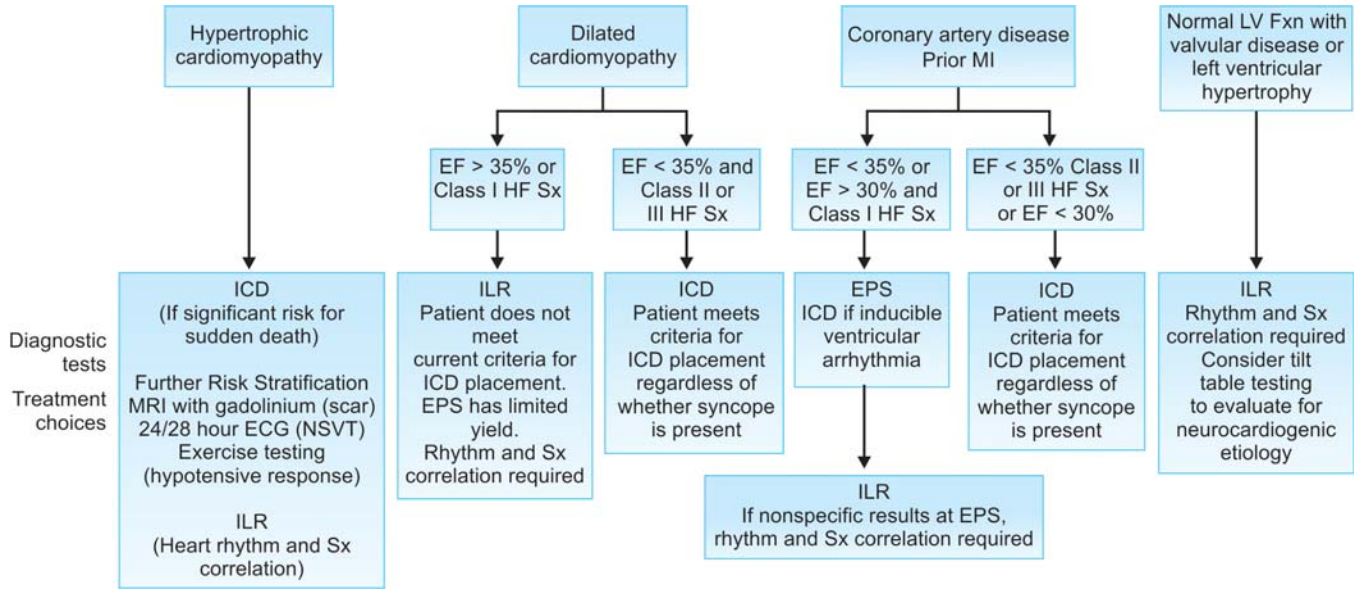
When the clinician is uncertain as to whether structural heart disease is present an echocardiogram can be extremely useful for obtaining information on cardiac anatomy and function. An exercise test may be useful in selected patients with exertional syncope. Cardiac tests, such as 24-hour ambulatory ECG monitoring (duration of evaluation is too short), cardiac enzymes, electrophysiologic tests and cardiac catheterization, and neurologic tests, such as carotid ultrasound, CT scan and EEG, have very little utility.

In the patient with structural heart disease identified by history, physical examination and ECG the appropriate workup will depend on the type of disease present (Flow chart 3). Issues with specific cardiac conditions are described in the following section, but several general comments can be made. Patients with structural heart disease can often have vasovagal syncope but the physician should have a low threshold for further cardiac evaluation. Patients at high risk for ventricular arrhythmias (prior myocardial infarction and EF < 30%, EF < 30–35% with Class II or III heart failure symptoms) can be referred directly for an ICD. For patients with syncope who have coronary artery disease and prior myocardial infarction associated with wall

FLOW CHART 2: Diagnostic evaluation of a patient with syncope



FLOW CHART 3: Diagnostic and therapeutic considerations in a patient with syncope and structural heart disease



(Abbreviations: ICD: Implantable cardiac defibrillator; ILR: Implantable loop recorder; EF: Ejection fraction)

motion abnormalities, EPS may be useful for determining whether ventricular arrhythmias can be induced with premature ventricular stimulation. The EPS may also be useful for patients with atrioventricular conduction disease identified on ECG to assess the site of block and therefore prognosis and management strategies. Often, an ILR to evaluate the cardiac rhythm during a subsequent episode of syncope will be the most useful diagnostic test for determining the cause of syncope.

SPECIFIC PATIENT GROUPS

VASOVAGAL (NEUROCARDIOGENIC) SYNCOPE

In vasovagal syncope there are widely spaced episodes of a temporary loss of consciousness associated with a fall in arterial blood pressure followed by an almost instantaneous profound slowing of the heart rate. Neurocardiogenic fainting usually occurs in a standing position and is triggered by stressful conditions or pain. The onset may be abrupt or associated with warning symptoms such as fatigue, weakness, nausea, sweating, pallor, visual disturbances, abdominal discomfort, headache, pins-and-needles sensations and feelings of depersonalization, lightheadedness or vertigo. Vasovagal syncope is the most common etiology of syncope regardless of the population studied. The diagnosis of vasovagal syncope is generally made by the history and physical examination although tilt table testing may be necessary in some cases to provide confirmatory evidence in some patients; this may especially be the case in patients who are amnesic for the syncopal spell and who cannot therefore provide a sufficiently detailed history.

Treatment of vasovagal syncope, particularly in patients with frequent symptoms, can be challenging due to the sporadic nature of symptoms and the absence of therapeutic options that have been validated by large clinical trials. As emphasized by the 2009 European Society Guidelines, explanation of the diagnosis and counseling and reassurance of the patient remain the cornerstone of treatment for patients with neurally mediated syncope.[2] About one-third of patients will have recurrent symptoms but many patients will have only a single event. Recurrent episodes of vasovagal syncope are more likely in women and in patients with more than 3 prior episodes.[58]

Physical counter pressure maneuvers have emerged as a first line therapy in management of neurally mediated syncope.[2,59] These maneuvers include leg crossing, hand gripping and arm or buttock muscle tensing in an effort to raise the blood pressure during the impending phase. A recent multicenter trial found that training in counter pressure maneuvers was associated with a 40% decrease in the likelihood of recurrent syncope. Similarly, "tilt training" or "standing training" is a management option in a patient who is educated and highly motivated.[60] Patients are asked to stand approximately 10–15 cm from a wall (to reduce the likelihood of significant injury in case of a fall) for gradually longer periods, usually 3–5 minutes twice daily initially, increasing to 30 minutes twice daily over time. This form of training improves tolerance to standing although long-term compliance with the training regimen can sometimes be a limiting factor in successful treatment.

Many drugs including beta blockers, selective serotonin receptor inhibitors (SSRI), disopyramide, theophylline, scopolamine, ephedrine, midodrine, clonidine and other medications have been tried in treatment of this condition.[47,61–64] Although small studies and trials have been published that suggest benefit from therapy, the intermittent and inconsistent occurrence of symptoms make evaluation of treatment extremely difficult. In addition, the pathophysiology-triggers, relative degrees/importance of bradycardia and hypotension are probably extremely heterogeneous and thus it is not surprising that individual responses vary markedly. Beta blockade, although traditionally popular, has recently been shown in a randomized multicenter trial to have no clinical benefit.[61] In the prevention of syncope trial (POST), 208 patients with vasovagal syncope were randomized to metoprolol or placebo, and after one year

follow-up there were no differences in symptoms or quality-of-life detected between the two groups.[61] At least in part due to these results, beta blockade is no longer considered a front-line therapy for neurocardiogenic syncope. Vasoconstrictors, such as the alpha-agonist midodrine, have been used for treatment of neurocardiogenic syncope in an effort to treat the hypotension associated with the episodes. In one placebo controlled study, 80% of patients randomized to midodrine did not have recurrent symptoms at one year follow-up compared to 13% in the placebo group.[62] In general, midodrine was well tolerated although it should be noted that older patients who may develop hypertension while taking midodrine were not evaluated. Since patients may identify periods when they are more likely to develop symptoms, midodrine has also been administered as a "pill in pocket" strategy in certain patients who are educated and motivated. Not all studies using vasoconstriction for treating vasovagal syncope have been successful. In the vasovagal syncope international study (VASIS), etilefrine, another alpha agonist, was studied in patients with vasovagal syncope.[47] One hundred twenty six patients were randomized to oral etilefrine or placebo and after one year follow-up syncope occurred in 22–24% of patients, without a difference between the two treatment arms and no change in the time to first occurrence of syncope.

Almost two decades ago, permanent cardiac pacing was proposed as a potential treatment option for patients with neurally mediated syncope associated with significant bradycardia.[65,66] Initial nonrandomized trials suggested an important effect of pacing for reducing episodes of syncope.[65,66] Subsequent placebo controlled studies, however, suggested that there was a significant placebo effect associated with pacing therapy and that therefore pacing therapy per se could not be shown to have a beneficial effect.[67,68] The most recent study, the International Study of Syncope of Uncertain Etiology (ISSUE)-2 evaluated whether significant bradycardia identified by ILRs could be used to better identify patients that could benefit from pacing therapy.[69] Interestingly, 53 patients that received pacemakers due to bradycardia identified by ILR reported a statistically significant 41% decrease in recurrent syncope compared to those patients that did not receive an ILR (and consequently did not receive a permanent pacemaker). A large randomized trial (ISSUE-3) has been initiated to validate this diagnostic and therapeutic strategy. At this time, pacing therapy plays a small role in management and only in selected patients with neurocardiogenic syncope who have frequent recurrent symptoms primarily associated with bradycardia or asystolic pauses in rhythm.

HYPERTROPHIC CARDIOMYOPATHY

Hypertrophic cardiomyopathy (HCM) is a diverse genetic disorder that often affects proteins in the sarcomere and that is associated with left ventricular hypertrophy. In a small percentage of patients the interventricular septum is preferentially affected and during systole a dynamic gradient in the left ventricular outflow tract can be observed (hypertrophic obstructive cardiomyopathy or HOCM). Several cohort studies have found that the occurrence of syncope is a major risk factor for sudden death with a 1.7–5-fold increase in risk.[70–72] Although ventricular arrhythmias are the most concerning possibility for the cause of syncope in these patients, they can have syncope from many other mechanisms, including supraventricular arrhythmias (particularly atrial fibrillation with loss of atrial contraction and rapid ventricular rates), bradycardia, left ventricular outflow tract obstruction and abnormal reflex peripheral blood pressure responses (hypotension) due to stimulation of pressure receptors in the body of the left ventricle. In the largest study to date, in 1,511 patients with HCM followed for more than 5 years, syncope occurred in 205 (14%), of these, 52 had symptoms suggestive of a neurally mediated episode (episode associated with a trigger such as coughing, micturition or change in position) and 153 patients had "unexplained" syncope.[73] Risk of sudden death was 5-fold higher in patients with syncope within 6 months of their evaluation; conversely, older patients (> 40 years old) and an episode of syncope more than 5 years before the initial evaluation were not found to be at increased risk of sudden cardiac death.

Collectively, the data from published studies suggest that while syncope is an important symptom that may herald an increased risk of sudden death, it requires thoughtful clinical evaluation of the patient. Family history of sudden cardiac death (first degree relative with sudden death before age 50), documented nonsustained ventricular tachycardia and degree of left ventricular hypertrophy (> 3 cm) have been identified as risk factors for sudden death. Emerging risk factors include a hypotensive response after exercise and late gadolinium enhancement on magnetic resonance imaging. Although some have advocated ICD placement in HCM patients with multiple risk factors, one cohort study found similar rates of appropriate ICD therapy in patients with 1, 2 or 3 risk factors.[72] For patients who do not receive an ICD, an ILR may be a reasonable diagnostic option.[53,71,74]

NONISCHEMIC CARDIOMYOPATHY

For many years the presence of syncope in a patient with nonischemic cardiomyopathy has been considered an ominous sign, associated with increased risk of sudden cardiac death due to ventricular arrhythmias.[75,76] In the largest cohort to date, 26% of 108 patients with nonischemic cardiomyopathy and syncope had significant ventricular arrhythmias during follow-up, a rate that was not statistically different from a comparison group of patients that presented with sustained ventricular arrhythmias.[76] Post-hoc analysis from two of the large ICD trials suggests that syncope in patients with nonischemic cardiomyopathy can have multiple mechanisms other than ventricular arrhythmias. In the defibrillators in non-ischemic cardiomyopathy treatment evaluation (DEFINITE) Trial, 458 patients with nonischemic cardiomyopathy were randomized to receive standard medical therapy or standard medical therapy and an ICD.[77] After randomization, there was no significant difference for the development of syncope between the two groups (standard therapy: 34% vs standard therapy + ICD: 39%). Of the patients in the ICD arm that had syncope, two-thirds were not associated with delivery of ICD therapy, suggesting a mechanism other than ventricular arrhythmias for the symptoms. The sudden

cardiac death heart failure trial (SCD-HeFT) randomized patients with heart failure symptoms and reduced ejection fraction less than 35% (approximately 50% were nonischemic) to placebo, ICD or amiodarone.[78] Regardless of the treatment arm, syncope occurred in approximately 14% of patients after randomization. Although syncope was associated with appropriate ICD therapy in patients randomized to the ICD arm, total mortality was increased by 40% equally in all three arms. Ventricular arrhythmias were thought to be the presumptive cause of syncope in less than 15% of cases. Syncope may be an important symptom for increased risk of sudden death in patients with nonischemic cardiomyopathy but may be due to mechanisms other than ventricular arrhythmias and may identify a group of patients at higher risk for total mortality.

CONGENITAL HEART DISEASE

Approximately one million adults in the United States have congenital heart disease. Depending on the abnormality, patients with congenital heart disease are at higher risk for different arrhythmias. For example, significant arrhythmias will develop in approximately 80% of patients with D-transposition of the great arteries (dTGA) who have undergone an atrial switch repair (Mustard or Senning) (Fig. 14).[79–85] Sinus node dysfunction (20–40%) that often requires permanent pacing is very common as are development of atrial tachycardias (4–20%).[79–81] Atrioventricular block and ventricular tachycardia (due to right ventricular dysfunction and fibrosis that develop due to long-term contraction against systemic pressures) have all been described as causes of syncope. In one long-term follow-up study, syncope developed in 6% of patients. In addition, sudden death occurred in approximately 7% of patients between 6–19 years after repair.[82] In a recently published multicenter study of a 149 patient cohort, sudden death and sustained ventricular arrhythmias occurred in approximately 9% of patients.[83] A QRS duration more than 140 ms was associated with a 14-fold increase in risk of ventricular arrhythmias. Atrial tachycardias were present in 44% of patients but was not a significant predictor for risk of ventricular arrhythmias or sudden death. Finally, in a cohort study of 37 patients with d-TGA who received ICDs, the annual rate of appropriate shocks was 0.5% for primary prevention and 6.0% for secondary prevention.[84] Taken together the data illustrate the complexity of managing adults with repaired congenital heart disease who present with syncope.

ELDERLY PATIENTS

Syncope in the elderly patients can particularly be difficult from both a diagnostic and therapeutic viewpoint. First, there is significant overlap between syncope and "unexplained falls" and many older patients have limited recall of events surrounding the symptoms.[84] In studies that have specifically evaluated syncope in the elderly patients, in approximately 50% the mechanism cannot be determined, although neurally mediated syncope was, somewhat surprisingly, found to be the most common cause (22%).[19,21,45,46] The natural history of vasovagal syncope may be different in the elderly patients with some reports suggesting an association with malignancy and other terminal conditions.[86] Elderly patients often do not have the typical prodrome of vasovagal syncope that is commonly noted in younger patients.[19,21,46] In addition, there is more overlap between vasovagal symptoms and orthostatic hypotension and carotid hypersensitivity, both are more common in the elderly patients, with the former often iatrogenic in origin. Although a vasovagal etiology is most commonly found in the elderly patients with syncope, orthostatic hypotension (13%) and arrhythmia (12%) are also more commonly observed in the elderly patients than in younger patients.[19]

Treatment of syncope in the elderly patients can be more challenging due to the multifactorial etiology and difficulty in determining a precise cause despite multiple diagnostic tests. In particular, neurologic tests, such as CT scans and EEGs, have very low diagnostic yield (< 5%), as is true for younger patients.[19] Some treatment strategies are limited in the elderly patients, as, for example, the older patient with vasovagal syncope, in whom medications, such as midodrine and fludrocortisone, are not tolerated due to accompanying hypertension.



FIGURE 14: Three lead ECG rhythm strip from a syncopal patient with d-transposition of the great arteries who had undergone a Mustard procedure. Severe sinus node dysfunction is present with a slow sinus rate. In addition a prominent R wave diagnostic for right ventricular hypertrophy is observed in lead V_1. Cardiac rhythm causes for syncope in this patient include bradycardia due to sinus node dysfunction, ventricular tachycardia due to right ventricular dilation and, less likely, atrial flutter

The clinician is often faced with questions about the safety of driving in patients with syncope. In the largest study to date, 3,877 consecutive patients with syncope were identified from a large database.[87] Within this group, 381 patients (9.8%) had an episode of syncope while driving (driving group). When compared to the non-driving group, the syncope while driving group was younger, more likely to be male, and more likely to have cardiovascular disease. Syncope during driving was most commonly due to neurocardiogenic causes (37%) with no cause determined in 23% and arrhythmia in 12%. Patients in the driving group had a slightly higher prevalence of accompanying injury (driving: 29% vs non-driving: 24%) but no difference in hospitalization rates (driving: 17% vs non-driving: 15%). Recurrent syncope in the driving group occurred in 72 patients, out of which 35 of whom had recurrent syncope more than 6 months after the initial evaluation.

Driving has become almost an essential component for functioning in today's society for many people. Driver incapacitation for medical reasons (e.g. seizure or syncope) has important public safety ramifications.[88–90] Laws for mandatory physician reporting of medical conditions that can impact driving exist in some states (e.g. New Jersey, Pennsylvania), but not in other states (e.g. Florida, New Mexico). What constitutes an important reportable medical condition varies significantly, particularly in the case of syncope where etiology and prognosis vary widely. In the United Kingdom, for a noncommercial license, a simple faint with definite provocative factors does not lead to any driving restrictions, while unexplained syncope with a high risk of recurrence leads to a mandatory 6 month period during which driving is not permitted. The overall impact of mandatory physician reporting of patients with cardiac conditions probably has a negligible impact on motor vehicle accident-related mortality and morbidity in a larger population. As emphasized in a recent editorial, the risk of driving accidents related to recurrent syncope is significantly lower than the risk of severe accidents from high risk groups such as young drivers, the elderly patients, or distracted drivers.[88] The most recent published guidelines recommend a minimum of 6 months of abstinence from driving after a syncopal event, with resumption of driving permitted if no further episodes have occurred.[90]

GUIDELINES FOR EMERGENCY DEPARTMENT EVALUATION

One of the most significant sources for high cost in patients with syncope is hospital admission that ranges 26–60%.[2,3,37,91] For this reason a number of investigators have evaluated the utility of algorithms for identifying patients at higher risk for significant events and have developed syncope management units (similar to the concept of chest pain units) that allow expedited and more efficient management of patients with syncope. The components of the risk stratification rules vary and some have debated whether the rules are effective for reducing cost (Table 1).

The Osservatorio Epidemiologico sulla Sincope nel Lazio (OESIL) risk score was derived from a patient cohort of 270 patients that presented with syncope in 6 community hospitals in the Lazio region of Italy.[91,92] Multivariate analysis identified four independent predictors that predicted risk: History of cardiovascular disease, age more than 65 years, syncope without a prodrome and an abnormal ECG. The 12 month mortality increased linearly from 0% (no risk factors present) to 57% (all four risk factors present). Several subsequent studies have validated the OESIL risk score for predicting one year risk in other patient cohorts.[91–93]

The San Francisco Syncope Rule was developed to predict short-term outcomes (7 days after the index event).[32] The investigators evaluated multiple variables but simplified their rule to include five elements: (1) abnormal ECG; (2) shortness of breath; (3) hematocrit less than 30%; (4) systolic blood pressure less than 90 mm Hg and (5) a history heart failure. Often the mnemonic chess is used to more easily remember the components: C: Congestive heart failure; H: Hematocrit; E: ECG; S: Systolic blood pressure; S—shortness of breath. Similar to the OESIL risk score subsequent studies have generally validated the utility of the San Francisco Syncope Rule.[93]

In the short term prognosis of syncope (STePS) study 676 patients with syncope were evaluated at both 10 days and 1 year.[94] Severe outcomes (death, major therapeutic procedures, readmission to the hospital within 10 days) were observed in 6.1% of patients (mainly rehospitalization) at 10 day follow-up. Severe outcomes were observed mainly in patients who were admitted (14.7%) compared to those who were discharged from the emergency department (2.0%). The main mechanistic cause for severe outcomes was arrhythmia-related (25/41 patients, most often due to implantation of a permanent pacemaker), although five patients died had a variety of causes, none specifically arrhythmia related (disseminated intravascular coagulation, pulmonary edema, aortic dissection, pulmonary embolism and stroke). Predictors of short-term risk included an abnormal ECG, concomitant trauma and absence of preceding symptoms. Interestingly, factors associated with long-term adverse outcomes were different from the short-term risk predictors and included age more than 65 years and history of neoplasm, cerebrovascular disease and heart disease (structural heart disease or ventricular arrhythmias).

In the risk stratification of syncope in the emergency department (ROSE) study a cohort of 550 patients with syncope was evaluated.[33] One-month serious outcome (acute myocardial infarction, life-threatening arrhythmia, requirement for ICD or permanent pacemaker implant, hemorrhage requiring transfusion, pulmonary embolus or significant neurologic event) or all-cause death occurred in 40 (7.3%) patients in the derivation cohort. Independent predictors were B-type BNP concentration $\geq$ 300 pg/ml [odds ratio (OR): 7.3], positive fecal occult blood (OR: 13.2), hemoglobin $\leq$ 9.0 g/dL (OR: 6.7), oxygen saturation $\leq$ 94% (OR: 3.0) and Q-wave on the presenting ECG (OR: 2.8). One-month serious outcome or all-cause death occurred in 39 (7.1%) patients in the validation cohort. The ROSE rule (the presence of any of the independent predictors) had a sensitivity

TABLE 1

Comparison of the components and primary outcomes for four different risk stratification schemes

Algorithm	*Age*	*Sx and Hx*	*PE*	*Components: ECG*	*Anemia*	*O_2*	*BNP*	*Endpoint*
OESIL	≥ 65 y	Sudden onset CVD		Q waves, ST Δ's, LVH, BBB, Arrhythmia				1 year Mortality
SFSR*		SOB, HF Hx	SBP < 90 mm Hg	Δ's, from a prior ECG, Arrhythmia	Hct ≤ 30%			7 day Mortality and serious outcomes
STePS†	> 65 y	Trauma, Sudden onset Hx CVA or CVD, Male		Q waves LVH, LBBB, Arrhythmia				10 day and 1 year Mortality and serious outcomes
ROSE**		Chest pain		Q waves, LBBB, HR ≤ 50 bpm	Hb ≤ 9 g/dL; fecal blood	≤ 94%	> 300 pg/ml	30 day serious outcomes

(Abbreviations: OESIL: Osservatorio Epidemiologico sulla Sincope nel Lazio; SFSR: *San Francisco Syncope Rule. Serious Outcomes: Myocardial infarction, arrhythmia, pulmonary embolism, stroke, subarachnoid hemorrhage, significant hemorrhage or any condition causing or likely to cause a return ED visit and hospitalization for a related event; †STePS: Short Term Prognosis of Syncope. Serious Outcomes: Need for major therapeutic procedures and early (within 10 days) readmission to hospital; **ROSE: Risk stratification of Syncope in the Emergency Department. Serious Outcomes: Acute myocardial infarction, serious arrhythmia, hemorrhage, pulmonary embolus; Hx: History; PE: Physical examination; O_2: Oxygen saturation; BNP: Brain natriuretic peptide; Time frame: Time of endpoint evaluation; HR: Heart rate; PVC: Premature ventricular contractions; SOB: Shortness of breath; CVD: Cardiovascular disease; CVA: Cerebrovascular accident; LVH: Left ventricular hypertrophy; LBBB: Left bundle branch block)

and specificity of 87.2% and 65.5% respectively, and a negative predictive value of 98.5% for a serious outcome or death at one month. An elevated BNP concentration alone was a major predictor of serious cardiovascular outcomes (8 of 22 events, 36%) and all-cause deaths (8 of 9 deaths, 89%).

Another strategy for reducing the cost of syncope is streamlining the process of evaluation using syncope or transient loss of consciousness units. In the Syncope Evaluation in the Emergency Department Study (SEEDS), 103 patients were randomized to standard care or a specialized syncope unit that provided early evaluation and focused diagnostic testing.[95] Patients randomized to the syncope unit were less likely to require hospital admission (syncope unit: 43% vs standard care: 98%) and more likely to have a presumptive diagnosis (syncope unit: 67% vs standard care: 10%) on discharge from the emergency department or from the syncope unit.

Several groups have argued the obvious importance of developing a consistent method for risk stratification of patients with syncope.[2,3,37] Although the currently published rules vary some basic points can be made. First it is important to decide whether or not to assign a working diagnosis of a cardiac cause of syncope. All of the risk stratification schemes use two or more criteria for identifying a group of patients with a higher likelihood for cardiac syncope. An abnormal ECG (Q waves, bundle branch block or atrioventricular block) is a component in all of the risk stratification schemes. Criteria, such as age more than 65 (OESIL),[90] history of cardiovascular disease (OESIL)[91] or presence of congestive heart failure (San Francisco Syncope Rule)[32] and elevated BNP (ROSE)[33] are all parameters that increase the likelihood of identifying a patient with a cardiac cause for syncope. Second, criteria that evaluate for noncardiac causes of syncope focus on conditions associated with higher short-term risk such as pulmonary embolus (O_2 saturation < 90% in the San Francisco Syncope Rule or < 94% in ROSE),[32,33] significant anemia (hematocrit < 30% in the San Francisco Syncope Rule and hemoglobin < 9.0 g/dL in ROSE),[32,33] or shock from any cause (SBP < 90 mm Hg in the San Francisco Syncope Rule)[32] or gastrointestinal bleeding (fecal occult blood in ROSE).[33]

GUIDELINES/OFFICIAL RECOMMENDATIONS

There have been formal statements on syncope from two cardiology groups. The AHA/ACCF in collaboration with the Heart Rhythm Society published a scientific statement on the evaluation of syncope in 2006.[3] The writing group recommends a history, physical examination and ECG in all patients with syncope. If the cause of syncope remains unexplained (not neurally mediated or orthostatic) they recommend an echocardiogram, an exercise test and ischemia evaluation. If these tests are normal, no additional testing is required for an isolated benign event. However, if recurrent episodes of syncope or if the episode is associated with significant injury, the clinician should use tests that evaluate the cardiac rhythm during symptoms. The choice among 24–48 hour ambulatory ECG monitoring, external event recorder or an ILR will depend on the frequency of the episodes and the severity of symptoms (syncope vs presyncope). The scientific statement provides a concise practical framework on the evaluation of syncope but does not address emergency room evaluation or subsequent treatment.

More recently, the ESC has published a comprehensive guidelines document that discusses both diagnosis and management of syncope.[2] Similar to the scientific statement from the cardiology societies based in the United States, they recommend an initial evaluation that includes history, physical examination (with orthostatic blood pressure measurements) and an ECG. They emphasize that the clinician should attempt to answer three specific questions:

1. Is it a syncopal episode or not?
2. Has an etiologic diagnosis been determined?
3. Is there evidence for a high risk of a cardiovascular event or death?

If these questions cannot be answered with the initial evaluation, additional tests, such as an echocardiography and other types of cardiac imaging, exercise testing, tilt table testing, cardiac rhythm monitoring and other tests, can be chosen depending on the clinical situation. The European Guidelines do not provide a simple algorithmic approach but rather emphasize that the clinician must carefully choose tests in individual patients to risk stratify the patient and identify a specific etiology of syncope so that a diagnosis for specific treatment plan can be developed.

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Chapter 33

Atrial Fibrillation

Vasanth Vedantham, Jeffrey E Olgin

Chapter Outline

- Definition and Classification
- Epidemiology
  - Incidence and Prevalence
  - Natural History
- Etiology and Pathogenesis
  - Structural Heart Disease
  - Electrophysiological Abnormalities
  - Non-Cardiac Causes
  - Lone Atrial Fibrillation
- Diagnosis
  - Presentation
  - Physical Examination
  - Electrocardiogram
  - Diagnostic Testing
- Management
  - New-Onset Atrial Fibrillation
  - Rate Control versus Rhythm Control in Recurrent AF
  - Restoration of Sinus Rhythm
  - Maintenance of Sinus Rhythm—Pharmacological Approaches
  - Maintenance of Sinus Rhythm—Invasive Approaches
  - Strategies for Rate Control
  - Prevention of Thromboembolism
- Guidelines

INTRODUCTION

Atrial fibrillation (AF) is the most common sustained arrhythmia in adults and is associated with substantial morbidity, mortality and cost. AF is characterized by disorganized atrial electrical activity and irregular ventricular rates. AF can result in heart failure, thromboembolism, impaired quality of life and may increase mortality. While AF is frequently associated with structural heart disease, it can occur in isolation (lone AF) or in association with non-cardiac diseases. In the coming years it is projected that AF will be seen with increasing frequency both by cardiologists and by non-specialists. The purpose of this chapter is to provide a broad overview of our current understanding of this complex arrhythmia, and to provide a framework for clinical decision making in patients with AF.

DEFINITION AND CLASSIFICATION

Atrial fibrillation (AF) is easily recognized on the surface of ECG as an irregular supraventricular rhythm (irregular QRS complexes), with a loss of clear P-waves and/or the presence of fibrillatory waves (Fig. 1). AF in response to a reversible cause (e.g. hyperthyroidism, pericarditis, hypoxia, pneumonia, surgery, pulmonary embolism) is called "secondary AF". AF can also occur in association with valve disease (typically mitral stenosis or regurgitation), in association with other structural heart disease (congestive heart failure, right ventricular dysfunction) or other known risks (e.g. hypertension, pulmonary disease, sleep apnea). AF that occurs without any overt heart disease, pulmonary disease or hypertension (HTN) is called "lone AF".

While several classification schemes have been proposed for AF, the most widely used is based on the duration of AF episodes and whether intervention is required to terminate AF.[1] AF is called "paroxysmal" when episodes terminate spontaneously in less than seven days from onset. When two or more such episodes occur, paroxysmal AF is called "recurrent". When AF lasts longer than seven days or requires pharmacological or electrical conversion, it is called "persistent". AF that is resistant to drugs or cardioversion is called "permanent". It should be noted that these definitions are not necessarily always clean; for example, some patients with persistent AF may have periods where their AF is paroxysmal. Moreover, while there is evidence that there is a progression of AF from paroxysmal to persistent to permanent, this does not occur in every patient.

EPIDEMIOLOGY

INCIDENCE AND PREVALENCE

Atrial fibrillation is the most common clinical arrhythmia, both in the population at large and in hospitalized patients. According to a large population-based study (ATRIA), the prevalence of AF in the general population is roughly 1%, translating to about 3 million patients in the United States.[2] The prevalence of AF in ATRIA also rose steeply with age, with a prevalence of 0.1% in patients less than 50 years old and 9% in patients over 80 years old. Data from ATRIA also show higher incidence of AF

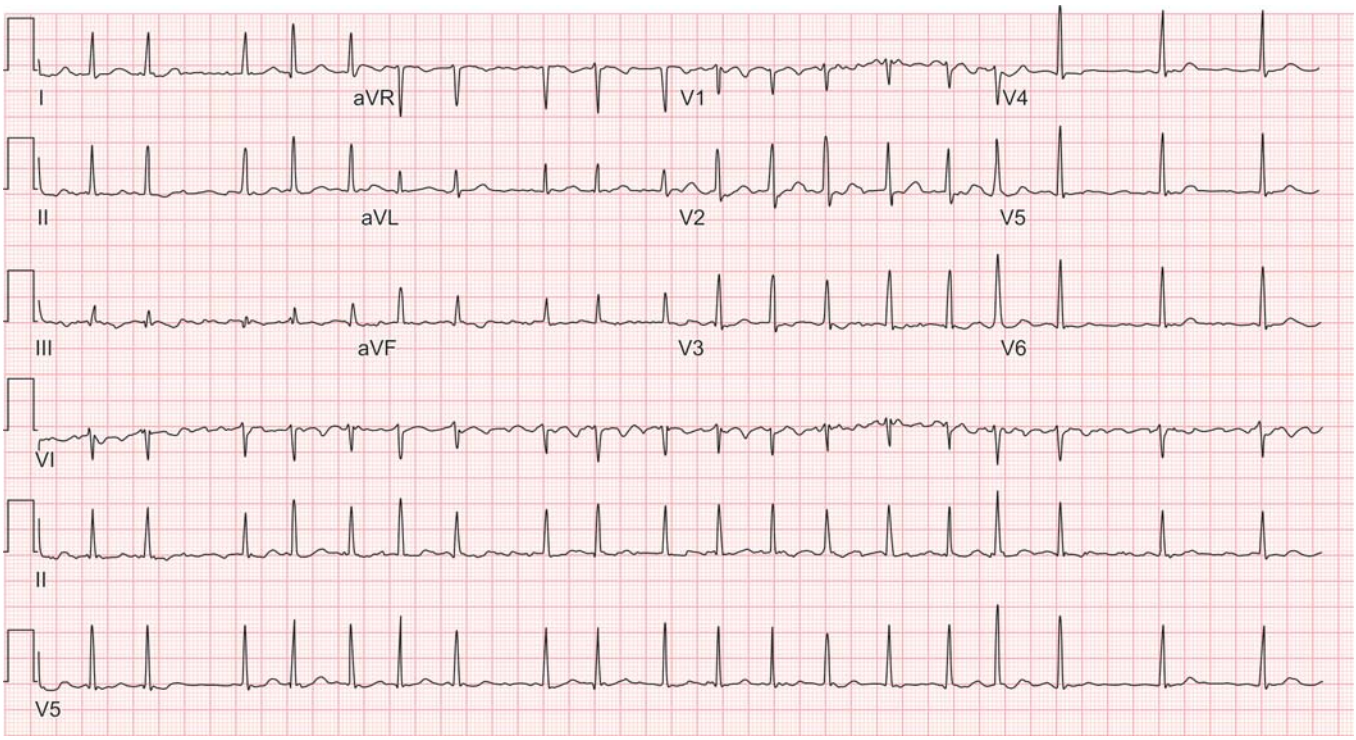
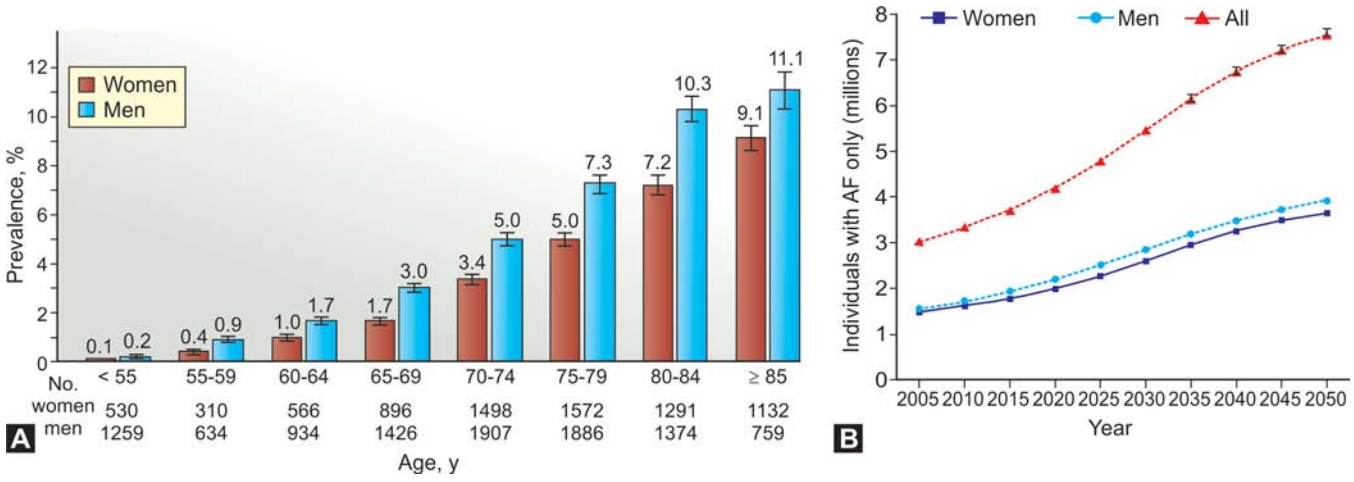


FIGURE 1: Typical ECG of atrial fibrillation showing an absence of P waves, the presence of fibrillatory waves (visible in lead V1), and a rapid, irregular ventricular response

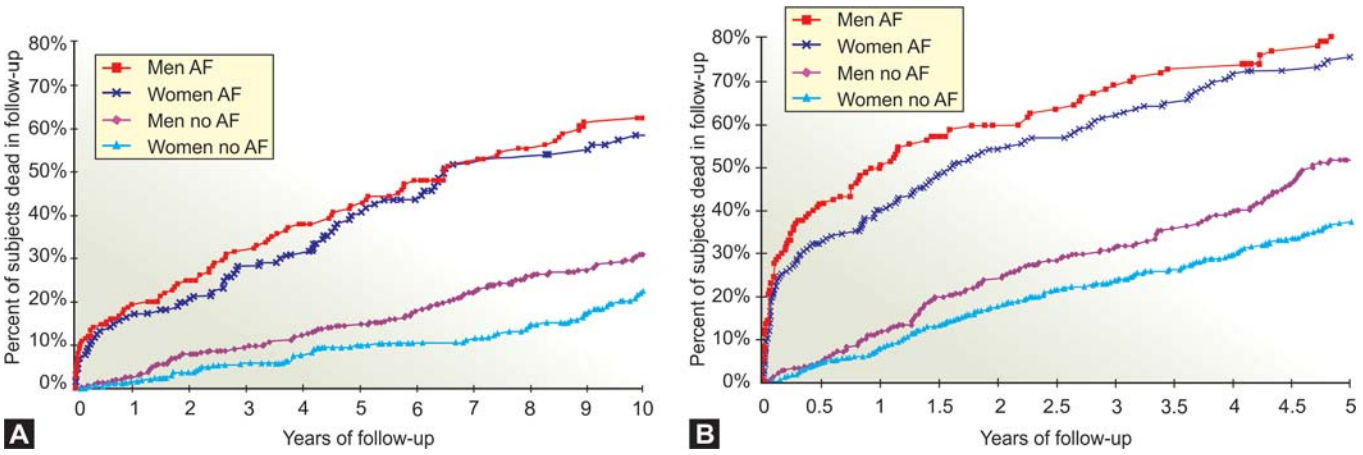


FIGURES 2A AND B: (A) Increasing prevalence of AF as a function of age in men and women in a large cross-sectional study. (B) Projected increase in the prevalence of AF to 2050. (*Source:* Reproduced with permission from reference 2 (A) and reference 5 (B)

among men than women (1.1% vs 0.9%), and among whites than blacks (2.2% vs 1.5% among patients older than 50 years). Other prospective longitudinal population-based studies[3,4] have explored the incidence of AF, and have shown a marked increase with age, from about 0.1% per year in patients between 55–60 years old to as high as 5% per year in patients older than 80 years, consistent with the studies of AF prevalence (Fig. 2A). Since the age distribution of the population in the developed world is shifting toward older ages, the overall incidence of AF is rising. Available projections based on these longitudinal studies forecast about 5 million patients in the United States with AF by 2025 (Fig. 2B).[5] In addition, since many episodes of paroxysmal AF are either asymptomatic, self-limited or occur in unmonitored patients, the true prevalence of AF is likely to be significantly higher than that of diagnosed AF.

NATURAL HISTORY

Left untreated, the rapid ventricular rates associated with AF and the loss of atrial mechanical activity can lead to cardiomyopathy and heart failure, conditions which themselves can perpetuate AF through their effects on cardiac hemodynamics. While AF is often thought of as a progressive disease, with paroxysmal AF eventually progressing to persistent and permanent AF, they are patients in whom it does not progress. Although long-term data from large studies are not available, smaller studies have shown that about 25% of patients with paroxysmal AF will progress to permanent AF within 5 years.[6]



FIGURES 3A AND B: Kaplan-Meier curves for patients with AF and matched controls from the Framingham Study cohort. (A) Data for patients aged 55–74 (B) Data from patients aged 75–94. (*Source:* Modified from reference 9)

Not surprisingly, given its association with cardiovascular and systemic disease, the diagnosis of AF is associated with adverse long-term and short-term clinical outcomes. Although longitudinal studies in patients with lone AF have not revealed an adverse prognosis,[7] patients with AF in the context of cardiovascular disease had an approximate doubling of all-cause mortality in two large population-based studies, even after adjustment for the contributions of age, sex and comorbid conditions (Figs 3A and B).[8,9]

The most common serious complication of AF is thromboembolic stroke. Compared to the general population, the relative risk of stroke in patients with AF is 2.4 for women and 3.0 for men.[10] Additional factors, such as congestive heart failure, diabetes, HTN, prior stroke and age, increase the risk of stroke. The CHADS2 score is a useful risk assessment tool to calculate risk of stroke in patients with AF.[11] Compared to patients with carotid artery disease, strokes associated with AF are on average more severe (larger territory) and transient ischemic attacks are longer lasting, presumably because embolic particles are larger in AF patients.[12] As a result, long-term outcomes, both in terms of morbidity and mortality, are worse for patients who suffer strokes due to AF than for those whose strokes are due to carotid disease.[13–15] Recent epidemiological studies have also shown an increased risk of Alzheimer's disease and other forms of dementia in patients with AF, even in the absence of stroke.[16,17] This association appears to be independent of common risk factors for both conditions and confers increased mortality in the subset of AF patients who experience cognitive decline.[18] Conflicting data exists on the effect of AF on heart failure progression and mortality in heart failure patients. In the studies of left ventricular dysfunction (SOLVD) and Candesartan in heart failure—assessment of reduction in mortality (CHARM) trials, development of AF was associated with significantly worse outcomes than patients without AF.[19,20] However, no significant outcomes differences attributable to AF were observed in the vasodilator heart failure trial (V-HeFT) studies.[21]

ETIOLOGY AND PATHOGENESIS

While short episodes of AF lasting a few seconds can be induced in normal atria, longer episodes require a vulnerable atrial substrate. This vulnerable substrate can be due to atrial enlargement, atrial fibrosis or other electrophysiological abnormalities of the atrial myocardium (Table 1). For spontaneous

TABLE 1

Factors predisposing to atrial fibrillation

Electrophysiological abnormalities
- Enhanced automaticity (focal AF)
- Conduction abnormality (reentry)

Atrial pressure elevation
- Mitral or tricuspid valve disease
- Myocardial disease (primary or secondary, leading to systolic or diastolic dysfunction)
- Semilunar valve abnormalities (causing ventricular hypertrophy)
- Systemic or pulmonary hypertension
- Intracardiac tumors or thrombi

Atrial ischemia
- Coronary artery disease

Inflammatory or infiltrative atrial disease
- Pericarditis
- Amyloidosis
- Myocarditis
- Age-induced atrial fibrotic change

Drugs
- Alcohol
- Caffeine

Endocrine disorders
- Hyperthyroidism
- Pheochromocytoma

Changes in autonomic tone
- Increased parasympathetic activity
- Increased sympathetic activity

Primary or metastatic disease in or adjacent to the atrial wall

Postoperative
- Cardiac, pulmonary or esophageal surgery

Congenital heart disease

Neurogenic
- Subarachnoid hemorrhage
- Nonhemorrhagic, major stroke

Idiopathic (lone AF)

Familial AF

(*Source:* Reference 1)

AF to occur, there also needs to be a trigger. This is typically premature atrial depolarizations or short bursts of atrial tachycardia that interact with a vulnerable substrate to spontaneously induce AF. While the triggering activity may arise from anywhere in the atria, evidence to date suggests that majority arise from the pulmonary veins.

STRUCTURAL HEART DISEASE

AF is most frequently associated with underlying structural heart disease. In the Framingham Study cohort, the major echocardiographic predictors of the development of AF, apart from valvular disease, were LV systolic dysfunction, LV hypertrophy and atrial enlargement.[22] In addition, a variety of non-cardiac conditions can result in AF, and AF can occur in the absence of any other discernable cardiac or non-cardiac disease.

Valvular Heart Disease

Diseases of the mitral and tricuspid valves result in pressure and/or volume overload of the atria, causing marked dilation and adverse atrial remodeling, predisposing to AF. Depending on the number of valves involved and the severity of the lesions, the prevalence of AF in patients with rheumatic heart disease ranges from 16% for isolated mitral regurgitation to as high as 70% for patients with a combination of mitral stenosis, mitral regurgitation and tricuspid regurgitation.[23]

Heart Failure

Heart failure is a major cause of AF, due to the effects of chronically elevated left-sided pressures on left atrial structure and function, and the activation of neurohormonal cascades that lead to atrial remodeling. Between 10 and 50% of patients with LV dysfunction have also AF, depending on the severity of LV dysfunction and NYHA functional class.[24] Rapid rates associated with AF can also cause heart failure. In such cases, treatment of AF or rate control can result in significant improvement in heart failure symptoms and ejection fraction.[25,26]

Ischemic Heart Disease

Cardiac ischemia is a common cause of AF, likely due to a combination of elevated filling pressures in the left atrium, metabolic stress and inflammation. Approximately 5–10% of patients experiencing an acute MI will present in AF and this subset has a worse prognosis.[27,28]

Hypertrophic Cardiomyopathy

The estimated incidence of AF among patients with hypertrophic cardiomyopathy varies from around 10% to 30%.[29] Because of poor LV compliance, these patients often depend on the atrial contribution to cardiac output and require relatively longer times for ventricular filling. As a result, they tolerate AF poorly, and can exhibit marked hemodynamic deterioration and severe symptoms associated with rapid AF.

In addition to the above-mentioned lesions, adult survivors of congenital heart disease often develop AF, either alone or in combination with other atrial tachyarrhythmias. Pericardial disease can also cause AF, both due to the effects of inflammation and hemodynamic sequelae of compromised ventricular filling. Related to this, patients undergoing cardiac surgery have an incidence of mostly self-limited postoperative AF as high as 30–40%.[30,31]

ELECTROPHYSIOLOGICAL ABNORMALITIES

AF is associated with several other electrophysiological disorders of the heart, which in some cases may trigger episodes of AF directly and in other cases may be indicators of a diseased atrial substrate that is prone to developing AF.

Atrial Tachycardia and Pulmonary Venous Activity

The pulmonary venous myocardium has been identified as a major source of AF triggers, through a combination of abnormal automaticity, triggered activity and the proximity of autonomic ganglia.[32,33] Other thoracic venous structures (superior vena cava and coronary sinus) and embryological venous remnants (vein and ligament of Marshall) may also trigger AF.[34] The precise mechanisms that regulate electrical activity of the pulmonary venous myocardium are unknown. Intensive research is ongoing into the anatomy, embryology and electrophysiological properties of the myocardial cells within the pulmonary veins.[35]

Supraventricular Tachycardia

AV node reentry tachycardia and AV reentry tachycardia utilizing an accessory pathway can trigger AF. In such cases, elimination of the SVT with catheter ablation or treatment with medications may eliminate the trigger for AF.[36,37] Other reentrant arrhythmias, such as atrial flutter, can similarly degenerate into AF, and catheter ablation of the predisposing arrhythmia may reduce AF frequency. An increased incidence of AF has been documented in patients with ventricular preexcitation due to an accessory pathway, even in the absence of spontaneous or inducible tachycardia.[38,39]

Conduction System Disease

Sinus node dysfunction and prolongation of the PR interval are both associated with AF, presumably due to common underlying atrial pathophysiology.[40,41] Some evidence supports the idea that bradycardia in patients with sinus node dysfunction may itself predispose to AF episodes, and that atrial pacing may reduce AF burden in such patients.

Cardiac Nervous System Dysfunction

Imbalance between the sympathetic and parasympathetic arms of the cardiac autonomic nervous, in either direction, can lead to AF. Sympathetic activation can lead to enhanced activity of ectopic foci, which can trigger AF.[42] Prolonged sympathetic activation, as occurs in heart failure, can also lead to adverse structural remodeling of atrial tissue. On the other hand, enhanced vagal tone shortens the refractory period of atrial tissue, facilitating atrial reentry. The latter mechanism may account for a subset of patients with lone AF, such as highly trained athletes with high vagal tone, and those whose episodes of AF occur predominantly in sleep.[43]

NON-CARDIAC CAUSES

Hypertension is the most common non-cardiac cause of AF, with a prevalence of 70% among AF patients enrolled in the atrial fibrillation follow-up investigation of rhythm management (AFFIRM) trial.[44] In population-based series, hypertension confers an adjusted relative risk of 1.5 for the development of AF.[45] While hypertension undoubtedly can lead to AF via an increased LV stiffness and left-sided filling pressures, the increased activation of the renin-angiotensin-aldosterone system (RAAS) may directly cause adverse electrical remodeling within the atria. Hyperthyroidism is common cause of AF. One percent of patients with new-onset AF have overt hyperthyroidism, while an additional 5–6% have subclinical hyperthyroidism.[46] In other studies, subclinical hyperthyroidism confers a relative risk of 3–5% for the development of AF.[47,48] Conversely, about 5–15% of patients with hyperthyroidism develop AF.[49] Conditions associated with systemic inflammation, metabolic stress or atrial enlargement, such as diabetes,[45] obesity,[50] postsurgical state[51] and sepsis[52] are all associated with the development of AF.

Chronic obstructive pulmonary disease (COPD) is associated with a relative risk of 1.3–1.8 for the development of AF, depending on the severity of lung disease.[53] The pathogenesis of AF in the setting of lung disease is likely to be a combination of direct effects of inflammation on the atria, metabolic stress of hypoxia and hemodynamic effects of chronically elevated right-sided pressures. Obstructive sleep apnea (OSA) is also associated with AF, and may be an under-recognized cause of the arrhythmia. The relative risk of AF in patients with OSA is as high as 2.8.[54] Treatment of OSA with continuous positive airway pressure can reduce the frequency of episodes of AF. With the increasing incidence of obesity, AF related to OSA is likely to occur with increasing frequency.

A number of substances are known causes of AF. While moderate alcohol consumption does not significantly increase the risk of AF, heavy alcohol use is strongly associated with AF.[55–57] In addition, a variety of medications can precipitate episodes of AF, including modulators nervous system function, diuretics and cardiac inotropic agents.[58] Although anecdotal evidence exists in support of caffeine as a precipitant of AF, an association between AF and caffeine consumption has not been proven in larger studies.[59]

LONE ATRIAL FIBRILLATION

About 20–30% of patients with AF have no discernable cardiac or non-cardiac cause.[60,61] Studies of tissue in patients with lone AF have identified numerous abnormalities including subclinical cardiomyopathy as well as atrial fibrosis, but it is not clear whether these are a cause or a consequence of the arrhythmia.[62] Propensity to develop AF is highly heritable, even after adjustment for other risk factors.[63,64] Genetic mapping studies in patients with familial AF have identified rare monogenic causes for AF, including mutations in cardiac ion channels and accessory proteins, gap junctions, and other genes relevant to atrial biology (Table 2).[65] However, the vast majority of lone AF appears to be non-Mendelian, implying polygenic or epigenetic etiology. Candidate gene association studies in AF have identified several alleles that confer increased risk of AF,

TABLE 2

Genetic causes of atrial fibrillation

Mendelian AF, Candidate gene resequencing, and rare variants	
Gene symbol/ Locus	*Gene name*
GJA5	Connexin 40
KCNQ1	Potassium voltage-gated channel, KQT-like subfamily, member 1
NPPA	Natriuretic peptide precursor A
LMNA	Lamin A/C
KCNA5	Potassium voltage-gated channel, shaker-related subfamily, member 5
KCNE2	Potassium voltage-gated channel, Isk-related family, member 2
KCNH2	Potassium voltage-gated channel, subfamily H, member 2
KCNJ2	Potassium inwardly rectifying channel, subfamily J, member 2
SCN5A	Sodium channel, voltage-gated, type V, alpha-subunit
Chr 5p13	Unknown
Chr 6q14-q16	Unknown
Chr 10q22-q24	Unknown
Chr 10p11-q21	Unknown
Candidate gene association studies	*Gene name*
ACE	Angiotensin-converting enzyme
AGT	Angiotensinogen
GJA5	Connexin 40
KCNE1	Potassium voltage-gated channel, Isk-related family, member 1
KCNH2	Potassium voltage-gated channel, subfamily H, member 2
Genome-Wide association studies	*Candidate gene symbol and name*
Chr 4q25	PITX2 Paired-like homeodomain 2
Chr 16q22	ZFHX3 Zinc finger homeodomain
Chr 1p21	KCNN3 Calcium-activated potassium channel
(Source: Reference 65)	

including variants in ion channels and associated proteins as well as regulators of the RAAS system (Table 2). More recent candidate gene data have uncovered genetic mosaicism in AF patients, in which atrial cardiomyocytes, but not peripheral blood lymphocytes, harbor disease-causing gap junction mutations.[66,67] Unbiased genome-wide association studies have also identified risk-conferring polymorphisms, including one at a non-coding locus on Chr 4q25, which confers a roughly fourfold lifetime relative risk for AF in carriers.[68] The polymorphism is in a non-transcribed area of the genome where it likely confers a regulatory function on nearby genes. PITX2c is located downstream of this polymorphism, and is important for establishing the identity of the pulmonary venous myocardium and in suppressing automaticity in left-sided remnants of embryonic cardiac pacemaking tissue.[69] Intensive research is ongoing to determine precisely how this allele might contribute to AF pathogenesis via an effect on PITX2C. Clinical

implications of this research might include identifying novel drug targets, but such advances will require considerable progress in our understanding of the regulatory networks controlling atrial structure and function.

DIAGNOSIS

PRESENTATION

As assessed by remote monitoring, most individual episodes of AF are asymptomatic and many patients are unaware of their arrhythmia.[70] Those who are symptomatic exhibit a broad spectrum of complaints, most commonly palpitations, dyspnea and symptoms of congestive heart failure.[71] The hemodynamic consequences and symptoms associated with AF are usually related to the ventricular rate and the presence or absence of underlying heart disease such as valvular disease, LV dysfunction or active coronary disease. Patients in any of the latter categories may tolerate AF poorly. Rarely, when a rapidly conducting accessory pathway is present (WPW syndrome), AF can lead to ventricular fibrillation and sudden cardiac death.[72] In otherwise healthy patients without accessory pathways, syncope is an unusual presentation for AF. Non-cardiac symptoms associated with AF include polyuria (related to ANF release by distended atria) and thromboembolic events, most commonly acute embolic stroke.

PHYSICAL EXAMINATION

The physical examination of patients with AF is also highly variable. Patients in AF can have heart rates ranging from bradycardia to extreme tachycardia depending on the integrity of AV nodal conduction, medications, autonomic tone and the presence of accessory pathways. Due to loss of atrial mechanical function, A-waves are absent from the jugular venous pulsation and a fourth heart sound is not audible in AF. Owing to the variable ventricular filling time in AF, the intensity of heart sounds can change beat to beat. It should also be recognized that commonly used diagnostic maneuvers used to evaluate heart murmurs, such as Valsalva, handgrip and respiratory variation, are of limited utility in the patient with AF because the variable filling time will cause variation in murmur intensity independent of the effects of preload and afterload. Signs of poor perfusion or congestive heart failure can be seen when AF occurs in the setting of valvular disease, LV systolic or diastolic dysfunction, acute myocardial infarction, or when long-standing tachycardia leads to cardiomyopathy.

ELECTROCARDIOGRAM

Although the hallmarks of AF on the surface ECG are loss of P-waves and an irregular ventricular response, AF must still be distinguished from other supraventricular tachycardias associated with an irregular ventricular response, including atrial flutter with variable block and multifocal atrial tachycardia (Fig. 4). The latter is typically associated with lung disease, and is characterized by at least three distinct P-wave morphologies on the surface ECG, whereas the fibrillatory waves in AF are more rapid and variable in morphology. In certain patients, however, fibrillatory waves can be "coarse" and at first glance may be difficult to distinguish from flutter waves. Careful examination of the surface ECG in such patients usually

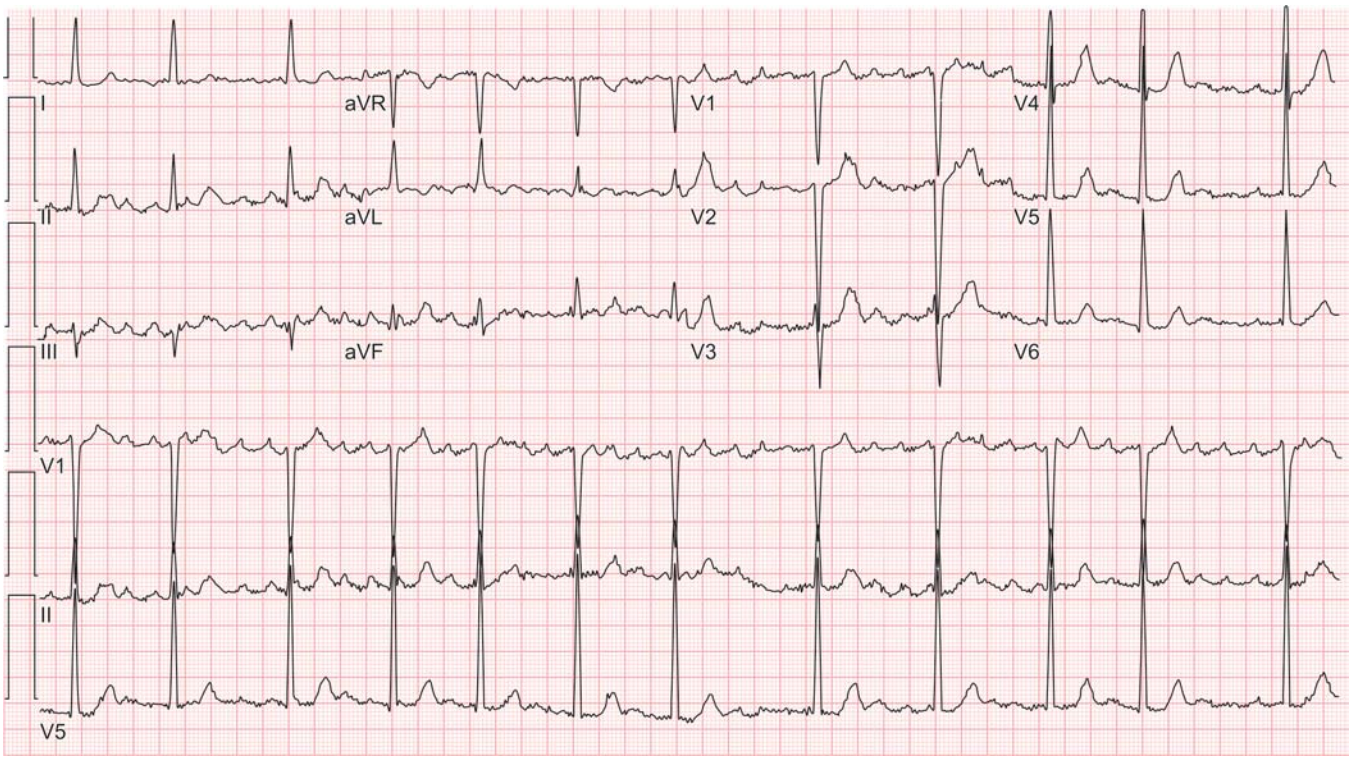


FIGURE 4: ECG shows coarse atrial fibrillation, sometimes mistaken for atrial flutter or erroneously called "fib-flutter" due to the apparent flutter waves in lead V1. However, the variable atrial cycle length and changing morphology of atrial depolarizations makes this ECG diagnostic of atrial fibrillation

unmasks subtle variation in the amplitudes and frequency of apparent flutter waves that reveal the true rhythm to be AF. In the setting of complete AV block with a junctional escape, accelerated junctional rhythms, ventricular tachycardia or ventricular pacing, the ventricular rate in AF can be regular. In such cases, it is important to focus on the nature of the atrial activity to make the diagnosis of AF. Sometimes, temporary inhibition of pacing function may be necessary to unmask AF. When QRS morphology is highly variable in AF and ventricular rate exceeds 200 beats per minute, ventricular pre-excitation or ventricular tachycardia should be suspected.

DIAGNOSTIC TESTING

All patients presenting with new-onset AF should undergo appropriate testing for a reversible cause.[1] A careful history of medication use and substance use, particularly alcohol, should be obtained. AF can often be the only presenting sign of hyperthyroidism, so all patients with new-onset AF should receive an assessment of thyroid function. Additional laboratory testing should be guided by the history and physical examination. Although AF frequently accompanies acute coronary syndromes and stable coronary artery disease, it is rarely the only sign of active ischemia. Thus, in the absence of other symptoms suggestive of active ischemic heart disease, it is not necessary for patients with AF to undergo stress testing or coronary angiography. All patients with AF should receive an echocardiogram, since the most common cause of AF is structural heart disease.

Because episodes of AF can be brief, can occur in sleep and can be asymptomatic, the clinical history is often not reflective of a patient's overall burden of AF (the fraction of time the patient is in AF).[70,73] In patients with symptoms compatible with AF, but no clear evidence at presentation, cardiac monitoring for extended periods can be helpful. Unless episodes are very frequent, Holter monitoring is often of insufficient duration to capture the episodes. Event monitors with telephonic transmission and automatic triggering algorithms for detecting and recording AF can be very useful to confirm a diagnosis, determine whether symptoms are due to AF, determine the burden of AF and determine whether symptoms are due to poorly controlled ventricular rates.[74]

MANAGEMENT

NEW-ONSET ATRIAL FIBRILLATION

Newly diagnosed AF should prompt a diagnostic work up as outlined above for a reversible cause. In general, when a reversible cause is identified, initial treatment should be directed at the underlying precipitating factor rather than the AF. Patients with new-onset AF presenting to the emergency room can in most cases be managed safely without hospital admission.[75] Hospital admission may be warranted for patients with concurrent medical conditions requiring inpatient treatment, for the elderly, and for patients with significant structural heart disease, ischemia, hemodynamic instability or preexcited AF.

Immediate reversion to sinus rhythm is warranted in patients with hemodynamic instability, active ischemia, severe heart failure symptoms, or AF with ventricular preexcitation.[1] In such cases, while it is ideal to confirm absence of an intracardiac thrombus using a transesophageal echocardiogram, this may not be possible due to the urgency of the situation. At a minimum, systemic anticoagulation should be administered prior to cardioversion unless strongly contraindicated.

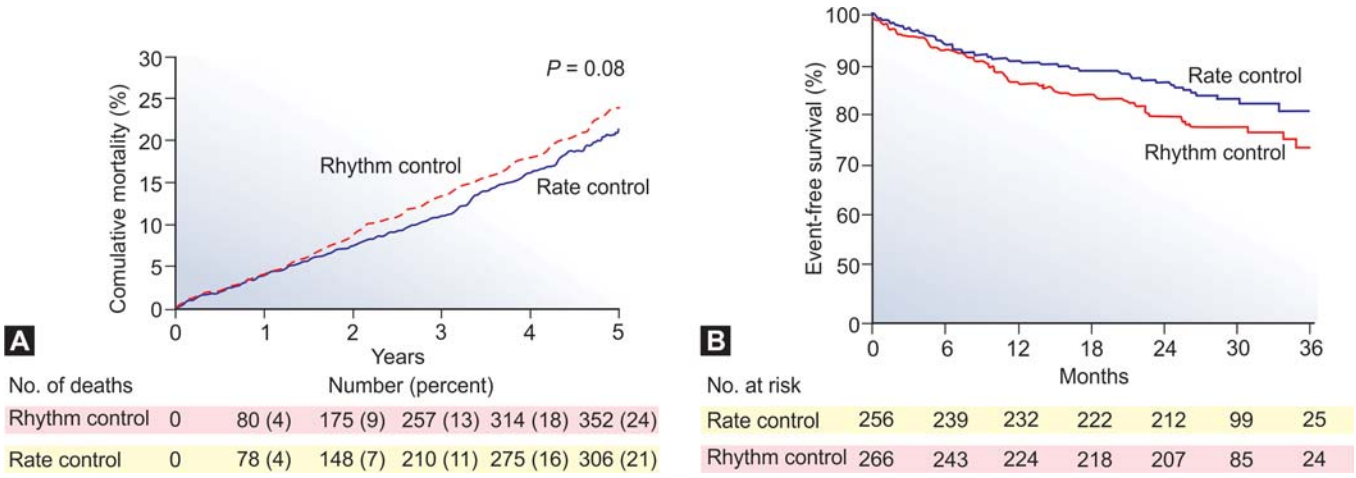
When urgent cardioversion is not indicated, it is acceptable to pursue an initial rate control strategy for patients who are mildly or moderately symptomatic. This approach allows time for a diagnostic workup, treatment of a potentially reversible cause of AF, and for an assessment of thromboembolic risk. About 70% of patients with new-onset AF of less than 72 hours duration will spontaneously convert to sinus rhythm without intervention.[76] For the remainder, reversion to sinus rhythm with cardioversion, either electrical or chemical, may be reasonable if the risk of short-term AF recurrence is relatively low or unknown. This is the case in younger patients (< 65) with structurally normal hearts and in patients with reversible causes for AF once the underlying cause is addressed. Antiarrhythmic drug therapy is generally reserved for patients with recurrent AF and is not routinely administered to patients after cardioversion for new-onset AF. Appropriate thromboembolic prophylaxis is essential before and after cardioversion (discussed under heading "Prevention of Thromboembolism").

RATE CONTROL VERSUS RHYTHM CONTROL IN RECURRENT AF

In approaching the patient with recurrent paroxysmal or persistent AF, the clinician must decide whether to attempt to maintain sinus rhythm. Theoretically, maintaining sinus rhythm would prevent symptoms associated with AF, normalize heart rate, maintain AV synchrony and the atrial contribution to cardiac output, and prevent deleterious atrial remodeling. Moreover, the epidemiological data on outcomes in AF raise hope that patients in whom sinus rhythm can be maintained might have improved quality of life and reduced mortality. On the other hand, the pharmacological tools available to maintain sinus rhythm are limited, and the attempt to maintain AF may be associated with side effects of these medications.

Two large clinical trials, AFFIRM and rate control versus electrical cardioversion (RACE), along with several smaller trials, have tested prospectively whether attempting to maintain sinus rhythm using antiarrhythmic drugs in patients with AF results is better clinical outcomes than simply controlling the ventricular rate in AF.[77,78] Two critical findings emerged from these studies: first, that there was no clear mortality benefit, cardiovascular benefit or clinically significant functional improvement associated with pursuing a rhythm control strategy in the patients enrolled in these studies; and second, that the incidence of thromboembolic events was similar regardless of the strategy chosen (Figs 5A and B). The latter finding likely reflected the relatively poor efficacy of rhythm control in these patients: although 63% remained free of symptomatic AF in AFFIRM at 5 years after randomization, many of these patients had subclinical episodes of AF that contribute to thrombo-embolic risk.

It is important to recognize that the failure to demonstrate benefit to rhythm control is not due to a clinical equivalence



FIGURES 5A AND B: Comparison of outcomes in patients with AF pursuing a rhythm control and rate control strategy in two large clinical trials: (A) Data from AFFIRM shows no statistically significant difference in overall mortality, although there is a trend toward increased mortality with rhythm control. (*Source:* Wyse DG, Waldo AL, DiMarco JP, et al. A comparison of rate control and rhythm control in patients with atrial fibrillation. N Engl J Med. 2002;347:1825-33, with permission). (B) Similar findings were seen in the RACE trial for a composite endpoint including mortality and other adverse events. (*Source:* Van Gelder IC, Hagens VE, Bosker HA, et al. A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation. N Engl J Med. 2002;347:1834-40, with permission)

between sinus rhythm and rate-controlled AF. Rather, patients in the rhythm control arms of these trials had antiarrhythmic drug-related side effects and an overall increase in non-cardiovascular death,[79] along with frequent recurrences of AF despite the attempt at rhythm control. Indeed, analysis of mortality data from AFFIRM and RACE has shown that patients who were in sinus rhythm throughout the study, regardless of treatment arm chosen, had a hazard ratio for mortality of 0.53 compared to those in AF.[79,80] However, it is unclear whether the improved mortality was due to the fact that they were in sinus rhythm or whether those patients in whom sinus rhythm could be maintained with available therapy had fewer co-morbidities or other factors that was associated with lower mortality risks regardless of what rhythm they were in. In these studies, any benefit was likely counterbalanced by drug toxicity and limited efficacy in the other patients, yielding a net equivalence of the two approaches. Thus, while maintaining sinus rhythm is in general a desirable outcome, the pharmacological tools employed in these studies lacked the safety and efficacy to do so in a way that provided net benefit in an unselected patient population. It should be noted that these studies were undertaken prior to the wide availability of catheter ablation for AF, which might significantly change the efficacy of sinus rhythm maintenance and the frequency of adverse events associated with rhythm control.

At a minimum, these studies legitimized rate control as a reasonable treatment option in asymptomatic patients. Currently, there is no algorithmic or guideline-driven approach that determines in whom rhythm control should be attempted. Relevant considerations are age, comorbidities, patient preference, risk of antiarrhythmic drugs, the likelihood of maintaining sinus rhythm, and whether the patient has symptoms due to AF even with adequate rate control. Thus, in older patients with structural heart disease and/or hypertension and no symptoms, rate control may be a reasonable first strategy; while in younger patients or in patients with lone AF with symptoms, rhythm control may be a reasonable initial choice.

RESTORATION OF SINUS RHYTHM

Once a rhythm control strategy is selected, the initial step is to restore sinus rhythm. Reversion to sinus rhythm without early recurrence of AF is more likely when the duration of AF is less than one year, the left atrium is not markedly enlarged, and structural heart disease is minimal.[81] In unselected patients with AF, electrical cardioversion is associated with a 1–2% short-term risk of clinical thromboembolism in the absence of anticoagulation.[82] This risk can be reduced to an acceptable level if patients are therapeutic on warfarin for 1 month prior to the procedure, or if a transesophageal echo performed immediately prior to cardioversion reveals no intracardiac thrombus and intravenous heparin is administered prior to cardioversion.[83] It is also safe to cardiovert low-risk patients without a history of rheumatic heart disease or prior thromboembolism when the duration of the AF episode is less than 48 hours without a TEE. In these cases, intravenous heparin or equivalent should be administered before cardioversion.[84] After cardioversion, either electrical or chemical, a period of atrial stunning ensues, in which atrial function is reduced and the potential for thrombus formation remains high.[85] For that reason, patients should be therapeutically anticoagulated from the time of cardioversion for at least 1 month. After that, thromboembolic risk should be reassessed and addressed as indicated.

Electrical cardioversion is highly effective for restoration of sinus rhythm in patients with paroxysmal AF. Seventy to ninety percent of patients can be converted to SR using biphasic shocks.[86] Chemical cardioversion is also effective for reversion to sinus rhythm, but in general it is not as effective as electrical cardioversion. Class III agents, such as amiodarone, ibutilide and dofetilide, are the most effective drugs for cardioversion of long-standing AF, while class 1C agents flecainide and propafenone are also effective when the duration of AF is less than 7 days.[1] When using ibutilide or dofetilide, special attention should be paid to electrolytes and QT interval, as these medications confer a significant short-term risk of torsades-de-

pointes. Facilitated electrical cardioversion, in which patients are loaded on an antiarrhythmic drug prior to cardioversion, can improve the success rate for patients who fail conventional electrical cardioversion.[87]

MAINTENANCE OF SINUS RHYTHM—PHARMACOLOGICAL APPROACHES

In general, once a decision to attempt rhythm control has been made, the choice of anti-arrhythmic drugs is primarily dictated by risks and side-effect potential, which are largely determined by the presence or absence of structural heart disease. Flow chart 1 shows a scheme recommended in the 2006 ACC/AHA/ESC Guidelines for management of AF. This section presents an overview of the Class 1 and Class 3 medications used to maintain sinus rhythm and the evidence supporting their use in specific populations.

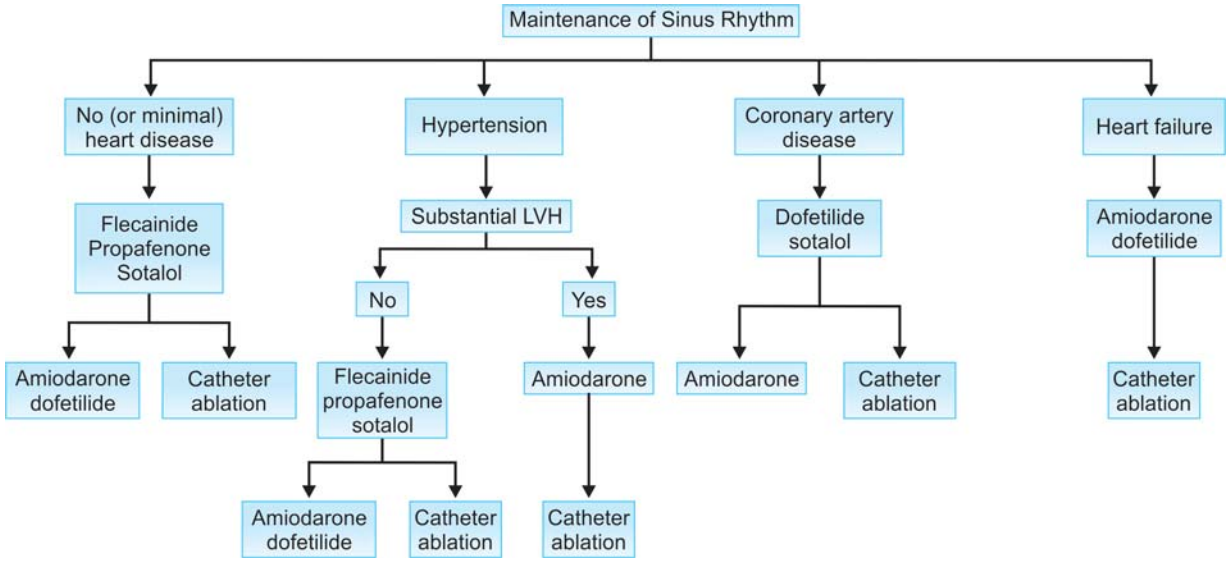
Class 1: Antiarrhythmic Drugs

The class 1C medications flecainide and propafenone are effective for maintaining sinus rhythm in patients with paroxysmal AF and are widely used as first-line therapy in selected patients.[88–90] While these medications can be taken on a standing basis for rhythm maintenance, they can also be used on an as-needed basis ("pill-in-the-pocket" approach) for patients with symptomatic paroxysmal AF.[91] The main cardiac side effects of these agents are pro-arrhythmia and increased mortality in patients with ischemic or structural heart disease,[92] brady-arrhythmias in patients with infranodal conduction system disease, and worsening heart failure in patients with LV dysfunction. 1C agents are therefore not recommended for use in patients with any structural heart lesions. Since the ventricular pro-arrhythmia is thought to occur during ischemia, even asymptomatic patients on 1C agents should be screened for ischemic heart disease while receiving drug therapy. In addition, class 1C medications can convert AF to atrial flutter that can be conducted 1:1 by the AV node, resulting in extremely rapid ventricular response.[93] Patients on 1C medications should therefore also take an AV nodal blocking agent unless AV conduction is not present or is significantly impaired. In the past, the Class 1A antiarrhythmic drugs, such as quinidine or procainamide, have been used for sinus rhythm maintenance in patients with AF. These agents are no longer widely used for treatment of AF because they are often poorly tolerated.[94]

Class 3: Antiarrhythmic Drugs

Although amiodarone is not FDA approved for the treatment of AF, it is widely used for this indication and is the most effective antiarrhythmic agent for sinus rhythm maintenance.[95] Although it has minimal proarrhythmic effects, its extra-cardiac side effect profile is significant, particularly at higher doses and with prolonged treatment.[96] In clinical trials, amiodarone was discontinued due to side effects more often than sotalol or propafenone. Nevertheless, amiodarone had significantly greater efficacy than the other drugs.[97] Despite its side effects, it is also safe to use in patients with heart failure and in patients with CAD.[98,99] For these reasons (efficacy and safety), amiodarone is frequently the drug of choice for short-term use and for patients with significant comorbidities. Nevertheless, because of extra-cardiac side effects, the 2006 ACC/AHA/ESC guidelines recommend that amiodarone be used as a second-line therapy except for patients with heart failure, moderate-to-severe systolic dysfunction, or hypertension and significant left ventricular hypertrophy. Amiodarone has an additional use in the prevention of postoperative AF after cardiac surgery, where a short perioperative course cuts the incidence of AF by about 50%.[100]

FLOW CHART 1: 2006 American College of Cardiology (ACC)/American Heart Association (AHA)/European Society of Cardiology (ESC) algorithm for antiarrhythmic drug therapy to maintain sinus rhythm in patients with recurrent paroxysmal or persistent AF. Patients should first be categorized by severity of heart disease (left to right) and treatment selection should proceed from top to bottom. Within boxes, drugs are listed alphabetically and not by order of preference



(*Source:* Reference 1)

Sotalol is roughly equal in efficacy to propafenone in randomized trials and significantly less effective that amiodarone in maintaining sinus rhythm.[97] Its effects are highly dose-dependent, with greater rhythm maintenance effects at higher doses and predominantly beta-blocking effects at lower doses.[101] The presence of beta-blocking effects can be helpful in slowing ventricular rate during recurrences of AF.[102] Side effects can include bradycardia and QT interval prolongation. For that reason, it is essential to monitor the QT interval in patients taking sotalol and to avoid use of the drug in patients at risk for QT interval prolongation or with significant impairment in drug clearance due to kidney disease. In most cases, inpatient monitoring is required for initiation of sotalol due to the risk of torsades de pointes and bradyarrhythmias.

Dofetilide is at least as effective as sotalol in maintaining sinus rhythm in patients with recurrent AF.[103] Although dofetilide prolongs the QT interval in a dose-dependent fashion and can cause torsades de pointes, an increase in mortality has not been observed in clinical trials of dofetilide use for AF.[104] This is likely because dofetilide is administered during inpatient monitoring with careful assessment of QT interval and dose adjustment or discontinuation as needed. Dofetilide is also safe and effective in patients with severe heart failure, in whom it reduces AF recurrences and heart failure hospitalizations without affecting mortality.[105] However, because of the potential for proarrhythmia with this medication, dofetilide is as considered a second-line medication except for patients with heart failure or coronary artery disease.

Dronedarone is a non-iodinated chemical derivative of amiodarone that lacks extracardiac side effects such as pulmonary, thyroid and ocular toxicity. Several large clinical trials have found that it can be effective in maintaining sinus rhythm, although less than amiodarone. However, unlike amiodarone, dronedarone appears to cause increased mortality in patients with severe heart failure.[106] In patients with normal cardiac function or mild-to-moderate heart failure, a large prospective randomized trial found a significant reduction in a composite primary outcome of hospitalization for cardiovascular causes and cardiovascular death, without a significant effect on overall mortality.[107]

Modulators of the RAAS System

Due to the role of the RAAS system in the pathogenesis of AF, the use of angiotensin receptor blockers (ARB) and angiotensin converting enzyme inhibitors has been explored in AF. A recent meta-analysis of 23 randomized trials showed a roughly 33% reduction in AF episodes associated with RAAS inhibition.[108] Particularly for patients with hypertension, left ventricular dysfunction or diabetes, but possibly even for patients without many comorbidities, RAAS inhibition can be an important adjunctive therapy for AF.

MAINTENANCE OF SINUS RHYTHM—INVASIVE APPROACHES

Nonpharmacological approaches to maintenance of sinus rhythm include catheter ablation, surgical ablation, pacing, and atrial defibrillation. The finding that physiological pacing modes in bradycardic patients with AF can prevent recurrences has led to a variety of pacing strategies to maintain sinus rhythm, including multisite pacing, alternative site pacing, and overdrive suppression of AF. With the exception of small subpopulations these strategies have not been shown to be effective.[109] Patients with AF should therefore not receive permanent pacemakers for the purpose of AF suppression, although selection of physiological pacing modes and minimization of ventricular pacing can prevent AF episodes in patients receiving pacemakers for other reasons. Thus far, the safety, efficacy and tolerability of implantable atrial defibrillators have not been demonstrated in large trials, and therefore these devices remain largely investigational.

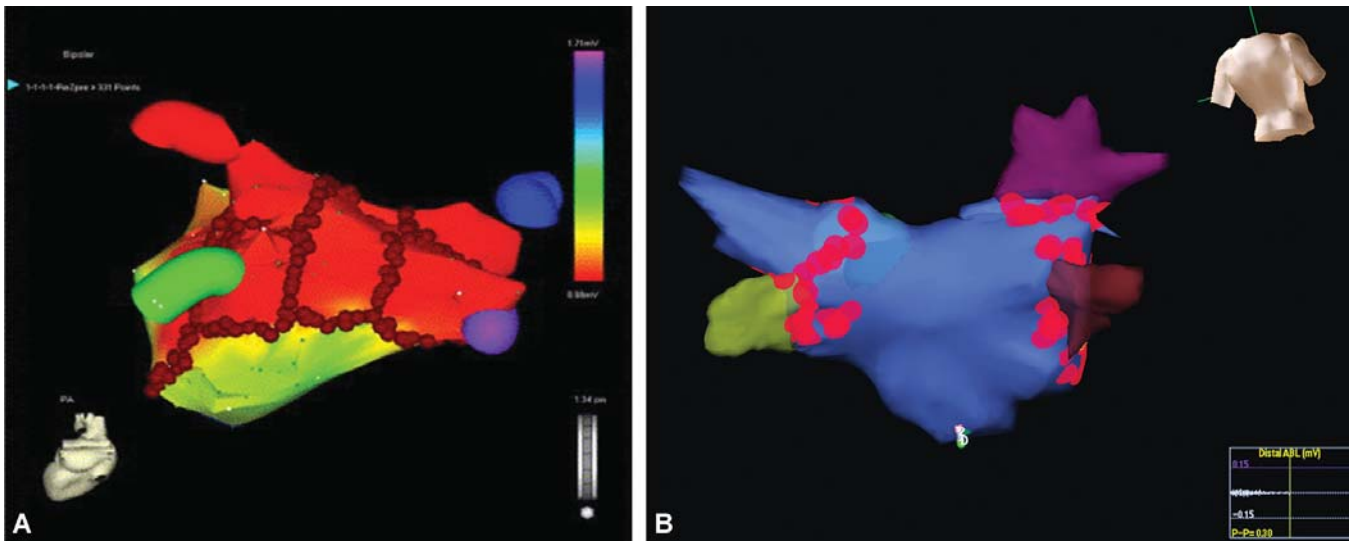
Catheter Ablation

The development of catheter ablation for AF began with the observation that rapid firing originating in the pulmonary veins frequently triggered AF.[32] This finding led to the idea of electrically isolating the pulmonary venous myocardium from the left atrium using radiofrequency ablation.[110–112] Since the original description of this approach, intensive development and testing of different approaches and techniques has taken place (Figs 6A and B).

At present, ablation techniques for AF vary widely among practitioners and the optimal approach has yet to be defined.[113] Most commonly, contiguous or nearly contiguous lesions are created around each of the four pulmonary veins, and electrical isolation is confirmed with a combination of recording and pacing within the pulmonary veins. Many ablationists also target non-pulmonary vein AF triggers such as autonomic ganglia, the ligament and vein of Marshall, the superior vena cava,[114] the posterior left atrial wall and the left atrial appendage.[115] There has also been interest in modifying the atrial substrate using catheter ablation, particularly for patients with permanent AF. Additional ablations are sometimes performed in areas displaying complex, fractionated electrograms that may play a role in AF maintenance,[116] although the added benefit of such an approach has yet to be established in large clinical trials.[117]

Because ablation causes atrial inflammation in the short run, early recurrence of AF is common after ablation and does not necessarily indicate long-term procedural non-success.[118] For this reason, success is usually defined as symptomatic improvement with no evidence of AF after a post-procedure blanking period. When AF recurs after the blanking period, the most common reason is reconnection of pulmonary venous myocardium to the atria, which may necessitate additional ablation procedures.[119] Catheter ablation is most effective in patients with paroxysmal AF, normal atrial size and minimal structural heart disease.[120] Success rates of 70–90% at 1 year have been reported for such patients.[113] When patients with structural heart disease, heart failure and increased atrial size are included in such studies, success rate declines. Success can be achieved in some patients by adding an antiarrhythmic medication after ablation, even when the medication was not effective prior to ablation.

Although AF ablation has become safer as techniques have improved, there is potential for serious complications. In addition to the usual risks associated with invasive cardiac procedures, such as thromboembolism, cardiac perforation, and vascular complications, AF ablation also carries the risks of



FIGURES 6A AND B: Two approaches to atrial fibrillation ablation: (A) Linear left atrial ablation. Linear lesions (red balls) are shown superimposed on a posterior-anterior view of the left atrium generated with the CARTO electroanatomical mapping system (Biosense). The following lines are represented: A wide area circumferential ablation around the left and right pulmonary veins, a line from the left inferior pulmonary vein to the mitral annulus, lines between the upper and the lower pulmonary veins, and two lines along the posterior left atrium connecting the circumferential ablations. Reproduced with permission from: Pappone C and Santinelli V. Heart Rhythm. 2006;3:1105-9. (B) Segmental pulmonary vein isolation. In this approach, lesions (red balls) are created surrounding the ostia of the four pulmonary veins in ordert to achieve electrical isolation. A PA view is shown, with lesions superimposed on a CT registered electroanatomic map created with the NavX system (St. Jude Medical). (*Source.* Dr Nitish Badhwar)

iatrogenic left atrial flutter,[121] pulmonary vein stenosis,[122] extracardiac nerve injury[113] and atrial-esophageal fistula.[123] Although these complications are uncommon, they can be devastating when they occur. These concerns, along with limited data on long-term efficacy, are reflected in the 2006 ACC/AHA/ESC guidelines, in which ablation is second-line therapy for AF. While the results of initial trials of ablation versus antiarrhythmic drug therapy for paroxysmal AF have generally favored the invasive approach,[124–126] this comparison has not yet been made in large multicenter trials, nor has the question of whether anticoagulation can be discontinued after successful AF ablation. Trials currently underway will hopefully shed additional light on these issues and help to clarify the proper place of catheter ablation in a rhythm maintenance strategy.

Surgical Procedures for AF Maintenance

Surgical procedures to maintain sinus rhythm in patients with AF predate the era of catheter ablation.[127] The Cox MAZE procedure, which may include a "cut and sew" approach or an ablation approach, involves making a patchwork of lesions in the atrium to create lines of scar. The lines of scar presumably prevent reentry circuits from sustaining and are believed to prevent vulnerable atrial substrate from maintaining AF. As with catheter ablation, many different lesion sets, ablative methods and strategies have been employed for surgical AF ablation.[128–130] Observational studies suggest that these techniques are highly effective; however, large randomized trials have not been carried out and surgical technique is highly variable, so overall efficacy of surgical management of AF is not known.[131,132] In addition, sinus node injury or exit block requiring permanent pacing can complicate the procedures, and atrial function may be permanently impaired.[133,134] Finally, as with catheter ablation, lesion sets can be proarrhythmic by creating conduction barriers and slowing conduction velocity, thereby facilitating macro-reentrant circuits.[135] Because these procedures require open cardiac surgery with cardioplegia and cross-clamping of the aorta, they are usually performed on patients who require cardiac surgery for a structural lesion associated with AF such as mitral valve disease.

STRATEGIES FOR RATE CONTROL

The recommended target for rate control in AF is 80 bpm at rest and less than 120 bpm with moderate activity, although these numbers are not based on prospective trials.[1] Recent prospective data, in which patients randomized to a permissive rate control arm had no worse outcomes than patients in whom strict rate control was achieved have called these numbers into question.[136] Further research will be necessary to determine the optimal targets for rate control.

The mainstays for rate control in AF are beta-adrenergic blockers and the non-dihydropyridine calcium channel blockers diltiazem and verapamil. These medications slow AV nodal conduction and prolong AV nodal refractoriness, thereby reducing the frequency of fibrillatory waves that can be conducted to the ventricles. In retrospective studies of AFFIRM patients, beta-blockers alone or combined with digoxin were most effective for rate control.[137] In patients with reduced EF and symptoms of heart failure in AF, intravenous calcium channel blockers should be avoided due to the potential for causing symptomatic hypotension and in severe cases precipitating cardiogenic shock. In such patients, beta-blockers, amiodarone or digoxin are preferred. As oral therapy for ambulatory AF patients, digoxin can be a useful adjunctive agent for rate control, but is less effective as monotherapy for rate control in AF and should not be used in this way.[137] Dronederone is also an effective rate control agent and can be used for this purpose even if not effective at maintaining sinus rhythm. The

side-effect profile and pharmacokinetics may make this more attractive than amiodarone for this purpose.

Not infrequently, patients with paroxysmal AF and rapid ventricular response requiring rate control medications will experience sinus pauses or symptomatic bradycardia when AF converts spontaneously to sinus rhythm. Since rate control medications are essential in these patients, permanent pacemaker implantation may become necessary to permit higher doses of nodal agents. Conversely, in patients in whom attempts at rate control have failed or are not tolerated and are not candidates for rhythm control, catheter ablation of the AV junction with pacemaker implantation is highly effective for rate control.[138,139] For patients whose symptoms are primarily due to elevated heart rates, this is a very effective therapy for symptomatic AF.

PREVENTION OF THROMBOEMBOLISM

It is imperative that all patients with AF undergo risk stratification for thromboembolic events, regardless of AF type and regardless of treatment strategy (rhythm control vs rate control).[1] Anticoagulation with warfarin lowers the risk of stroke for nearly all patients with AF;[140] however, in the lowest risk patients, the risk of major bleeding due to warfarin therapy exceeds the value of this marginal risk reduction.[141] For such patients, aspirin can be an acceptable alternative. To facilitate the categorization of AF patients by stroke risk, prediction tools have been developed based on pooled data from several large stroke prevention trials and other smaller studies.

Patients with AF due to rheumatic heart disease represent the highest risk group because of the marked atrial enlargement and consequent stasis that typically accompanies mitral stenosis. These patients should be anticoagulated with warfarin unless a strong contraindication is present. For patients with non-valvular AF, several studies have evaluated the clinical predictors for stroke. The Atrial Fibrillation Investigators (AFI), using pooled data from several trials, and the Stroke Prevention and Atrial Fibrillation (SPAF) investigators each used data from the non-treatment arms of primary prevention trials of stroke in AF patients.[142,143] Clinical factors that predicted risk of stroke were then integrated to form the CHADS2 score, and this tool was validated using results from the National Registry of Atrial Fibrillation.[11] The CHADS2 score assigns 1 point each for a history of congestive heart failure, hypertension, age greater than 74, diabetes mellitus and two points for a prior history of systemic embolic event. An overall risk score of 0 suggests low risk, 1 or 2 suggests intermediate risk and greater than 2 is considered high risk (Table 3). Based on these data, current guidelines recommend aspirin for patients with a CHADS2 score of 0 and warfarin in patients with a CHADS2 score of 2 or greater. Patients with a CHADS2 score of 1 may use aspirin or warfarin depending on comorbidities and patient preference. Currently there are no other approved pharmacological treatments to prevent strokes; however, there are several direct thrombin inhibitors and factor Xa inhibitors under various phases of study.[144] Nonpharmacological treatments to prevent strokes in AF have targeted the left atrial appendage, either by occlusion or removal. While this has traditionally been accomplished by surgery,[145] there are several transvenous devices under investigation that occlude or ligate the left atrial appendage.[146] These approaches may be useful in patients at high risk for stroke, but who are not capable of taking Coumadin or in patients who have had a stroke from AF on therapeutic doses of Coumadin. While small clinical trials have demonstrated the feasibility of percutaneous approaches,[147,148] large randomized clinical trials to test rigorously for reduction in stroke have not been carried out.

CONCLUSION

Although major advances in the understanding and treatment of AF have occurred recently—such as the understanding of the role of the pulmonary veins in AF and the development of catheter ablation for AF—we still do not have an understanding of the etiology of the underlying substrate of AF and thus no targeted treatments to prevent or reverse AF exist. Current treatment strategies are aimed at preventing stroke, and either rate control or rhythm control to prevent rapid ventricular rates and symptoms. If the latter approach is chosen, the choice of rhythm control drugs is dictated by side-effect profile and risk, rather than efficacy, since efficacies are similar for long term. Until rigorous multi-center randomized trials have been completed, ablation is reserved for symptomatic patients with paroxysmal AF who are intolerant or resistant to pharmacological rhythm control. Success rate for ablation of persistent and permanent AF is significantly lower than that for paroxysmal AF. In general, treatment options for persistent and permanent AF are limited to stroke prevention and rate control. Future research will hopefully define the substrate(s) that predispose to AF and thereby allow directed therapy to prevent or reverse AF.

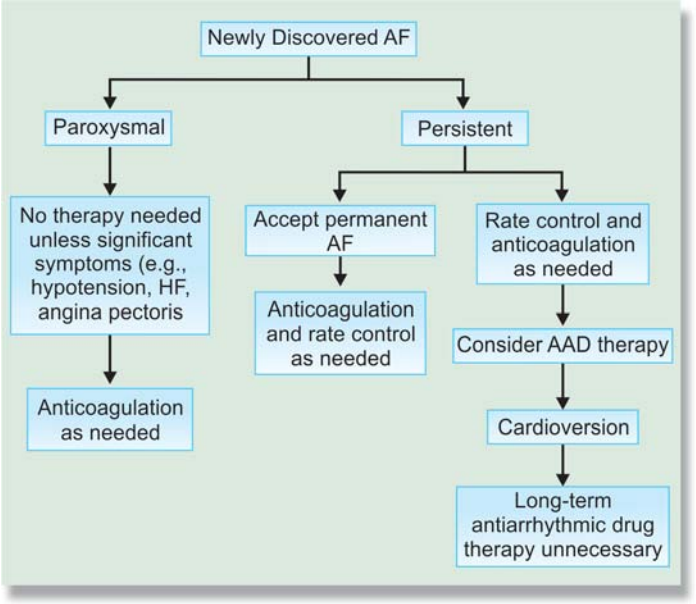
TABLE 3

Event rates by stroke risk factor, baseline CHADS2 score, and anticoagulation status in 11,526 adults with atrial fibrillation and no conraindications to warfarin therapy at baseline

	Event rate (per 100 person-years) (95% confidence interval)		
CHADS2 score (no. of patients)	*Taking warfarin*	*Not taking warfarin*	*Crude rate ratio (95% confidence interval)*
0 (2557)	0.25 (0.11–0.55)	0.49 (0.30–0.78)	0.50 (0.2–1.28)
1 (3662)	0.72 (0.50–1.03)	1.52 (1.19–1.94)	0.47 (0.30–0.73)
2 (2955)	1.27 (0.94–1.72)	2.50 (1.98–3.15)	0.51 (0.35–0.75)
3 (1555)	2.20 (1.61–3.01)	5.27 (4.15–6.70)	0.42 (0.28–0.62)
4 (556)	2.35 (1.44–3.83)	6.02 (3.90–9.29)	0.39 (0.20–0.75)
5 or 6 (241)	4.60 (2.72–7.76)	6.88 (3.42–13.84)	0.67 (0.28–1.60)

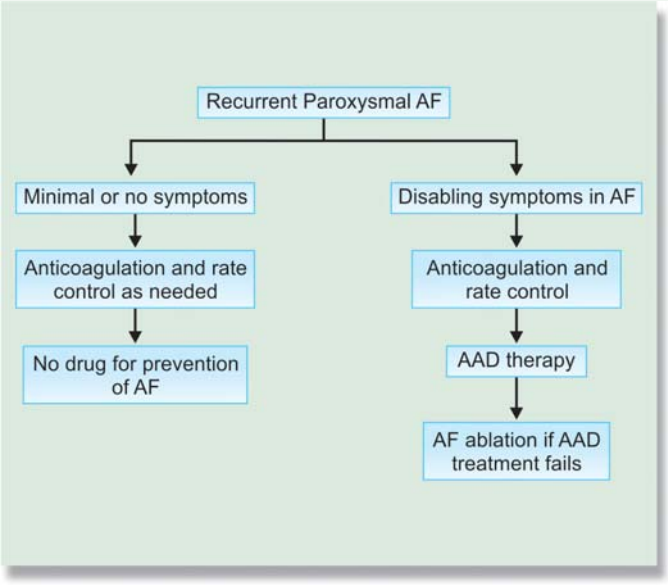
(*Source:* Reference 148)

2006 ACC/AHA ESC guidelines: Pharmacological management of newly discovered AF



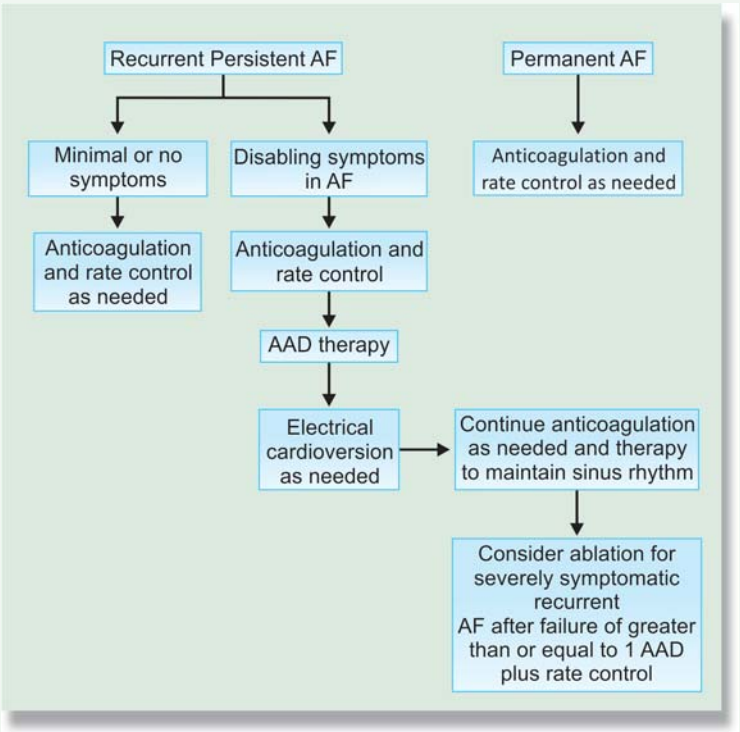
(Abbreviation: AAD: Antiarrhythmic drugs). (*Source:* Fuster V, et al. J Am Coll Cardiol. 2006;48(4):e149-e246)

2006 ACC/AHA/ESC guidelines: Pharmacological management of recurrent paroxysmal AF



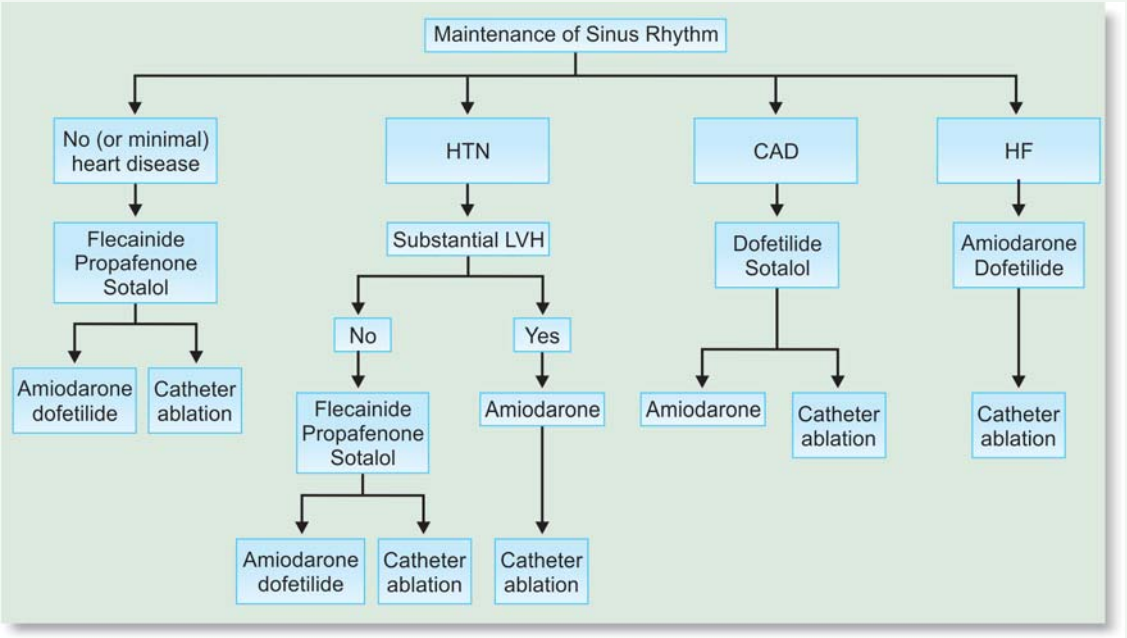
(*Source:* Fuster V, et al. J Am Coll Cardiol. 2006;48(4):e149-e246)

2006 ACC/AHA ESC guidelines: Pharmacological management of recurrent persistent or permanent AF



(*Source:* Fuster V, et al. J Am Coll Cardiol. 2006;48(4):e149-e246)

2006 ACC/AHA/ESC guidelines: Antiarrhythmic approaches to maintain sinus rhythm in patients with recurrent paroxysmal or persistent AF who require sinus rhythm*



*Within each box, drugs are listed alphabetically and not in order of suggested use. The vertical flow indicates order of preference under each condition. The seriousness of heart disease proceeds from left to right, and selection of therapy in patientw with multiple conditions depends on the most serious condition present. (Abbreviation: LVH: Left ventricular hypertrophy). (*Source:* Fuster V, et al. J Am Coll Cardiol. 2006;48(4):e149-e246).

2007 HRS/EHRA/ECAS EXPERT CONSENSUS STATEMENT

INDICATIONS FOR CATHETER AF ABLATION

- Symptomatic AF refractory or intolerant to at least one Class 1 or 3 antiarrhythmic medication
- In rare clinical situations, it may be appropriate to perform AF ablation as first-line therapy
- Selected symptomatic patients with HF and/or reduced ejection fraction
- Potential rare, life-threatening complications include atrio-esophageal fistula and pulmonary vein stenosis

[Presence of a LA thrombus is a contraindication to catheter ablation of AF]

(*Source:* Calkins H, et al. *Heart Rhythm*. 2007;4(6):816-861)

2007 HRS/EHRA/ECAS EXPERT CONSENSUS STATEMENT

INDICATIONS FOR SURGICAL ABLATION

- Symptomatic AF patients undergoing other cardiac surgery
- Selected asymptomatic AF patients undergoing cardiac surgery in whom the ablation can be performed with minimal risk
- Stand-alone AF surgery should be considered for symptomatic AF patients who prefer a surgical approach, have failed one or more attempts at catheter ablation, or are not candidates for catheter ablation

(*Source:* Calkins H, et al. *Heart Rhythm*. 2007;4(6):816-861)

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Chapter 34

Supraventricular Tachycardia

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Chapter Outline

- Classification
  - Atrial-based AV Nodal Independent SVT
  - AV Nodal Dependent SVT
- Diagnosis
  - Electrocardiographic Recordings
  - Electrophysiology Studies
- Treatments
  - Acute Care
  - Long-term Management

INTRODUCTION

Supraventricular tachycardia (SVT) is a heart rhythm disturbance, initiated in the atria or ventricles, with atrial rates exceeding 100 beats per minute (bpm), that requires tissue above the His bundle in order to be perpetuated (Fig. 1). SVTs can be symptomatic or asymptomatic, slow or fast, regular or irregular, sustained or nonsustained, paroxysmal, persistent or permanent, and may be due to various mechanisms involving tissue in the atria, AV node, His Purkinje system and/or the ventricles. SVT is generally not life threatening. Occasionally, SVT impairs hemodynamics, provokes hypotension, precipitates heart failure (either acutely or as a result of long-standing tachycardia), or leads to syncope or causes debilitating symptoms including palpitations, lightheadedness, dizziness, chest discomfort, dyspnea or weakness. The treatment depends upon each patient's specific symptom complex, the hemodynamic response to the tachycardia, the relationship of the tachycardia to other comorbidities and the concerns of each patient.

Tremendous advances have occurred in the management of SVT over the past 60 years. No longer do we use deslanoside, lantanoside, atabrine, quinidine, pressors, cholinergics or a host of other therapies[1-9] to attempt to convert episodes of SVT; we have much better therapies. No longer do we have to worry about side effects and long-term treatment of highly symptomatic episodes of SVT as we now have ablation to cure many forms of SVT. While advances continue in the field, most of the attention on the management of SVT has shifted to atrial fibrillation (AFib), leaving few new therapies or modalities to evaluate or manage SVT in the past decade.

This chapter will address a modern approach to the overall evaluation and the management of those patients who have SVT.

CLASSIFICATION

Supraventricular tachycardias are either AV nodal dependent or AV nodal independent (Table 1). AV nodal dependent SVTs require AV nodal conduction in order to perpetuate. These SVTs generally have a regular ventricular rate. The two common forms of SVT are atrioventricular nodal reentry tachycardia (AVNRT) and atrioventricular reciprocating tachycardia

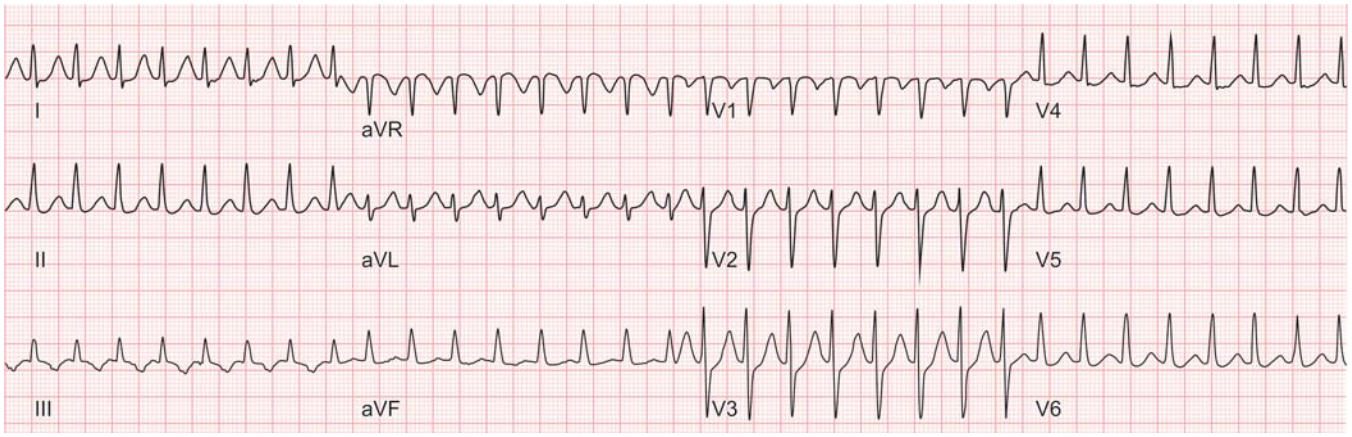


FIGURE 1: Typical regular supraventricular tachycardia. No P wave is visible. The most likely diagnosis of this particular supraventricular tachycardia is AV nodal reentry supraventricular tachycardia

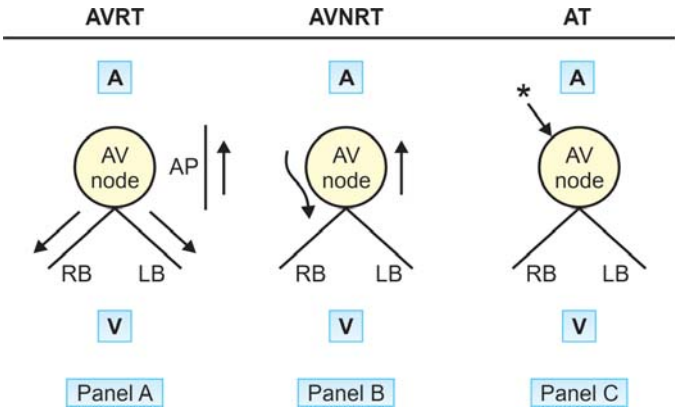
TABLE 1

Classification of supraventricular tachycardias

- AV nodal dependent
  - AV nodal reentry
  - AV reentry
    - Orthodromic AV reciprocating tachycardia
    - Antidromic AV reciprocating tachycardia
- AV nodal independent
  - Atrial tachycardias
    - Sinoatrial reentry
    - Focal (triggered, automatic, microreentry)
    - Macroreentry (scar mediated, congential heart disease)
  - Junctional ectopic tachycardia
  - Atria flutter
    - Right atrial flutter
      - Clockwise
      - Counterclockwise
    - Left atrial flutter
      - Mitral reentry
      - Scar mediated
      - Pulmonary vein
  - Atrial fibrillation

(AVRT). AV nodal independent SVTs require only atrial tissue and do not require AV nodal activation for the tachycardia to occur. They can have a regular ventricular response, as seen in sinoatrial reentry, nonparoxysmal junctional ectopic tachycardia (JET), monomorphic atrial tachycardia (AT), and atrial flutter (AFL) with a fixed or variable AV conduction ratio or an irregular ventricular response as seen with AFib (discussed in detail in another chapter), AFL with variable AV conduction and multifocal atrial tachycardia (MAT). Almost all irregular SVTs are AV nodal independent. AV nodal dependent SVTs can occasionally be irregular, especially at the initiation and termination of the tachycardia. AV nodal independent SVTs can be associated with complete AV block such that the ventricular rhythm is a junctional or ventricular escape (Flow chart 1).

FLOW CHART 1: Supraventricular tachycardia—AVRT (Panel A), AVNRT (Panel B) and AT (Panel C)



ATRIAL-BASED AV NODAL INDEPENDENT SVT

Sinus Tachycardia

Sinus tachycardia is ubiquitous, occurs with sympathetic activation and may be due to specific triggers such as infection, heart failure, pulmonary embolus or hyperthyroidism,[10] to name a few. It is not generally considered to be SVT. Sinus tachycardia tends to start with gradual acceleration and usually stops with an even more gradual deceleration. In some instances, it can be difficult to distinguish sinus tachycardia from SVT. The P wave morphology in sinus tachycardia is similar to that in sinus rhythm (Fig. 2), although due to sympathetic stimulation of the sinus node, exit from the sinus node may be more superior and thus the P wave may shift slightly in sinus tachycardia. Rates rarely exceed 200 bpm, except in children or during extreme physical activity. The P wave normally precedes the QRS complex but this depends on AV nodal conduction. Adenosine may appear to stop the tachycardia, but after slowing, the rate will increase gradually, indicative of sinus tachycardia rather than SVT.

Sinus tachycardia, considered abnormal for the physiological condition, is termed "inappropriate". If extreme sinus tachycardia is dependent upon an upright posture, and unrelated to fluid depletion or other explainable cause, it is termed Postural Orthostatic Tachycardia Syndrome (POTS).[11]

In some instances, it can be difficult to distinguish POTS from inappropriate sinus tachycardia or an AT.[12] When SVT persists without change during day or night and is independent of activity, fever or another explainable cause, it is more likely

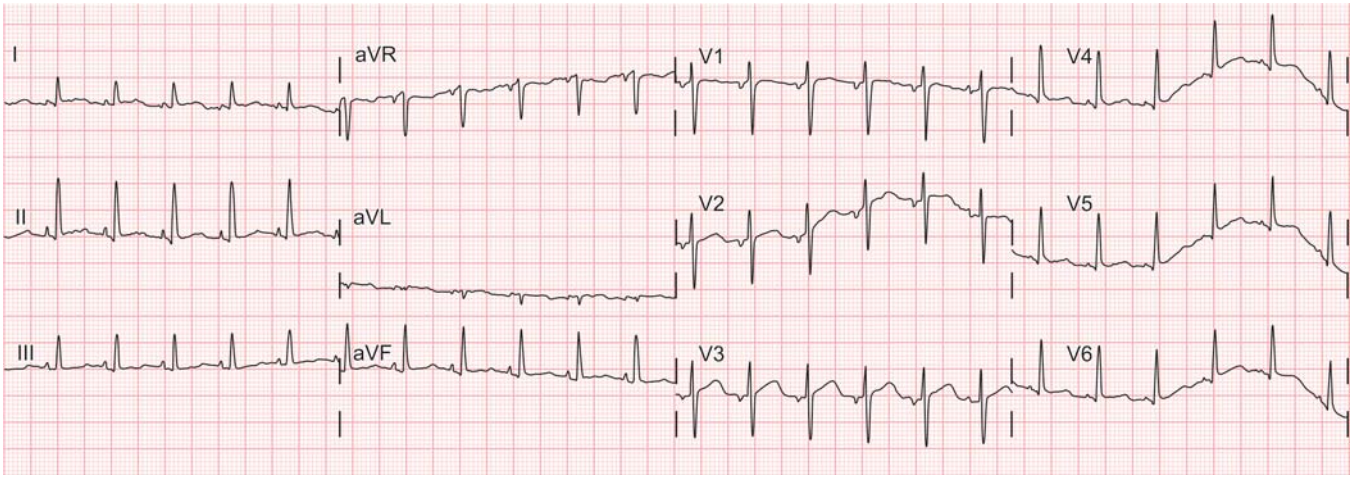
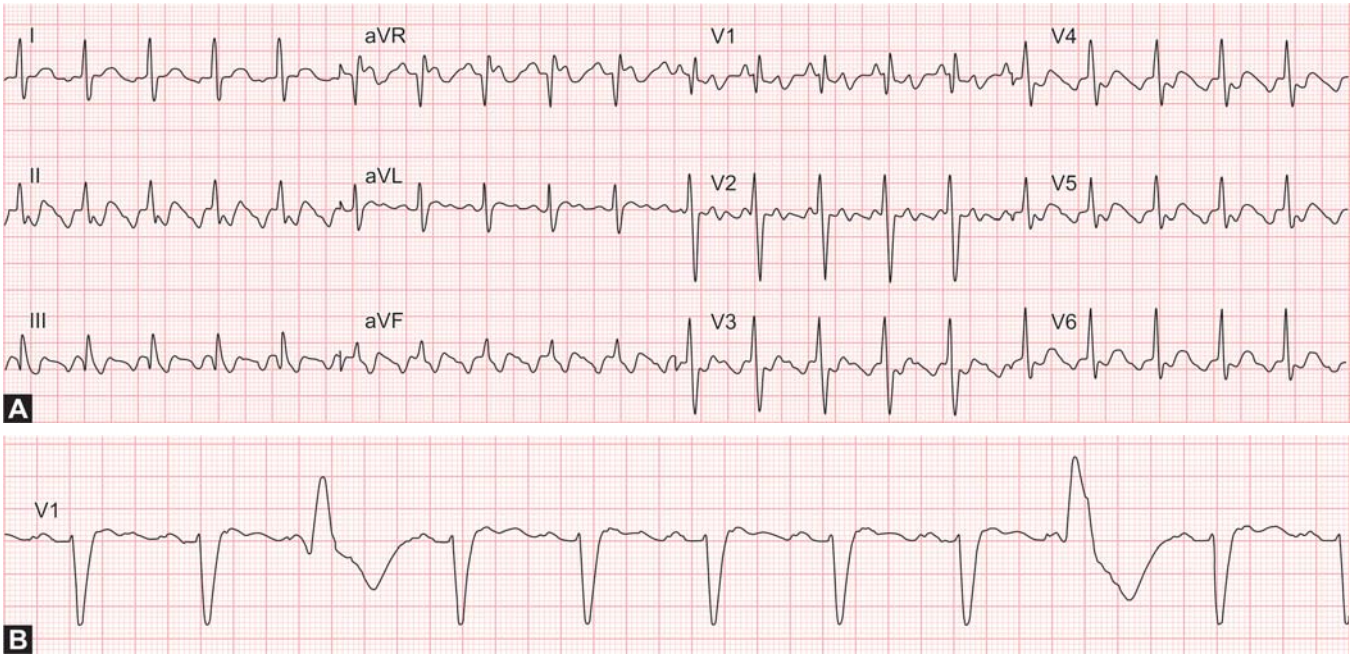


FIGURE 2: In sinus tachycardia, the P wave is similar to that seen during sinus rhythm and the PR interval is normal. In some instances, it can be difficult to distinguish sinus tachycardia from an atrial tachycardia but there is generally more variability in the rate in patients with persistent narrow QRS tachycardia due to sinus tachycardia



FIGURES 3A AND B: (A) In atrial flutter with a 2 to 1 conduction ratio, the ventricular rate is constant at rest and with activity. There appears to be an upright P wave in V_1 that may be suspicious for sinus tachycardia but it is clear looking at the inferior leads that this is atrial flutter with 2:1 AV conduction with a flutter wave buried in the ST segment. The fact that the rate does not change is a tipoff that this is not sinus tachycardia as well. (B) This is a constant atrial tachycardia with 2 to 1 conduction and PVCs. The fact that the rate does not change again is an indication that this is not sinus tachycardia

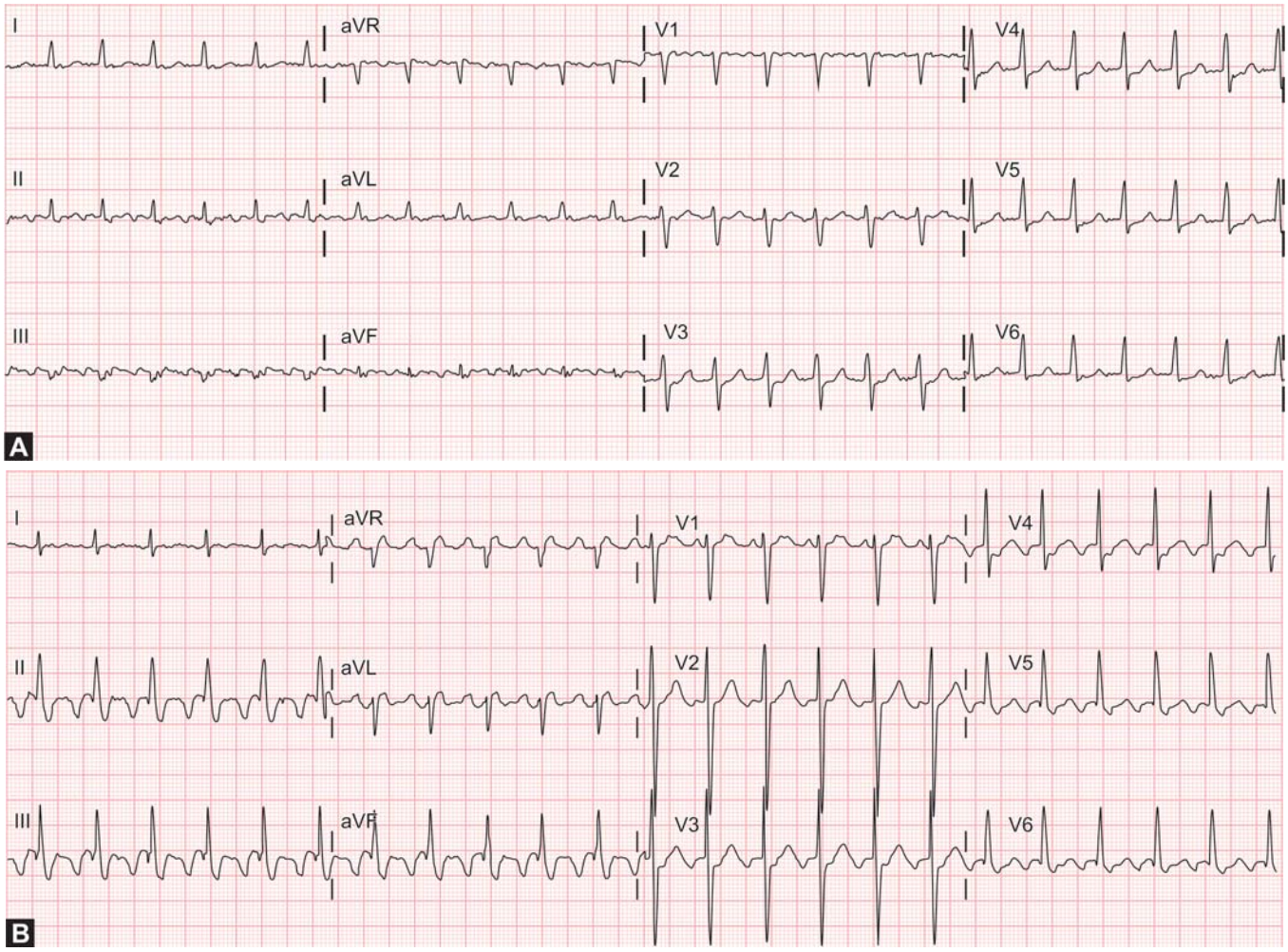
to be AT or AFL with a fixed AV conduction ratio (Figs 3A and B). Vagal maneuvers or adenosine may be required to secure the diagnosis.

Atrial Flutter

Atrial flutter is a macroreentrant rapid AT typically involving the right atrium.[13] It tends to coexist with AFib (although most AFib originates from the left atrium) and tends to occur in patients with structural heart disease. The atrial rate, without drug therapy, exceeds 200 bpm but can be as high as 350 bpm. In patients treated with antiarrhythmic drugs, such as amiodarone, flecainide or propafenone, and in patients with large atria, the rates of AFL can be slower than 200 bpm. The most common form of AFL, due to counterclockwise electrical activation in the right atrium around the tricuspid ring utilizing an isthmus of tissue, the cavotricuspid isthmus, has a "saw tooth" appearance in the inferior leads with no isoelectric segment between beats (Fig. 4). Approximately 10% of typical AFL is perpetuated by clockwise activation around the tricuspid ring. Atypical forms of right AFL involve upper loop or lower loop reentry mechanisms[14,15] (Figs 5A and B). These flutters do not show the "typical" electrocardiographic appearance or rate and may require an alternative approach during ablation procedures. Left AFL not only often involves a reentry circuit around the mitral annulus but also can be due to reentry around or in



FIGURE 4: "Saw tooth" flutter waves are seen in the inferior leads in "typical" counterclockwise, isthmus dependent atrial flutter. Usually, this form of atrial flutter demonstrates upright P waves in lead V1. Here, there is variable AV conduction



FIGURES 5A AND B: Unusual flutter waves in the inferior leads. These flutters may not be isthmus dependent. It can be difficult to distinguish from left atrial flutters and unusual right atrial reentry circuits in some instances

pulmonary veins and/or scar (Fig. 6).[16] Left AFL is often associated with, and may be present after attempts to ablate AFib,[17] requiring further ablation procedures.[18] Some AFL due to scar can be associated with congenital heart disease; these often have very unusual reentrant pathways. The distinction between AFL and AT in complex congenital heart disease (or its repair) is more dependent on the rate than the mechanism or the appearance on the surface electrocardiogram (ECG).

Atrial Tachycardia

Atrial tachycardia can originate from the left atrium, right atrium, vena cavae or pulmonary veins [Flow chart 1 (panel C)]. The tachycardia can be focal or macroreentrant involving large areas of the atria. Focal forms can be microreentrant or due to an automatic or triggered mechanism.

Monomorphic AT represents about 5–10% of all regular SVTs. The P wave precedes the QRS complex but generally has a morphology distinct from the sinus P wave. The PR interval may vary. The atrial rates are generally 120–200 bpm. The conduction can be 1:1 but AV block can be present. An "A-A-V" pattern can be seen during AT.[19] Adenosine may occasionally stop the tachycardia;[20] more commonly, only AV block occurs. Digoxin toxicity may precipitate AT with AV block.

Focal Atrial Tachycardia

Automatic AT represents less than 2–5% of SVTs. It may have a gradual onset and offset, sometimes similar to sinus tachycardia, in contrast to atrial reentrant tachycardias that start with a premature beat and have a sudden offset. As such, focal ATs may be difficult to distinguish from sinus tachycardia but tend to be faster and occur at rates inappropriate for physiological needs. Furthermore, the P wave morphology is usually distinctly different from that seen in sinus tachycardia.

Triggered ATs have a sudden onset and offset. Some ATs are catecholamine-dependent and begin with exercise. ATs can be associated with acute myocardial infarction (AMI), alcohol intoxication, exacerbation of chronic obstructive lung disease, electrolyte abnormalities, and digoxin use. Chronic, persistent, automatic AT, like other forms of persistent SVTs, can cause tachycardia-induced cardiomyopathy.

Intra-atrial Reentrant Tachycardia

Macroreentry or microreentry AT often utilizes areas of scar at incisions from prior cardiac surgery or corrected congenital heart disease (such as a Fontan procedure) and represents 5–10% of SVTs.[21-24] This type of tachycardia is distinguishable from AFL as there are discrete P waves separated by an

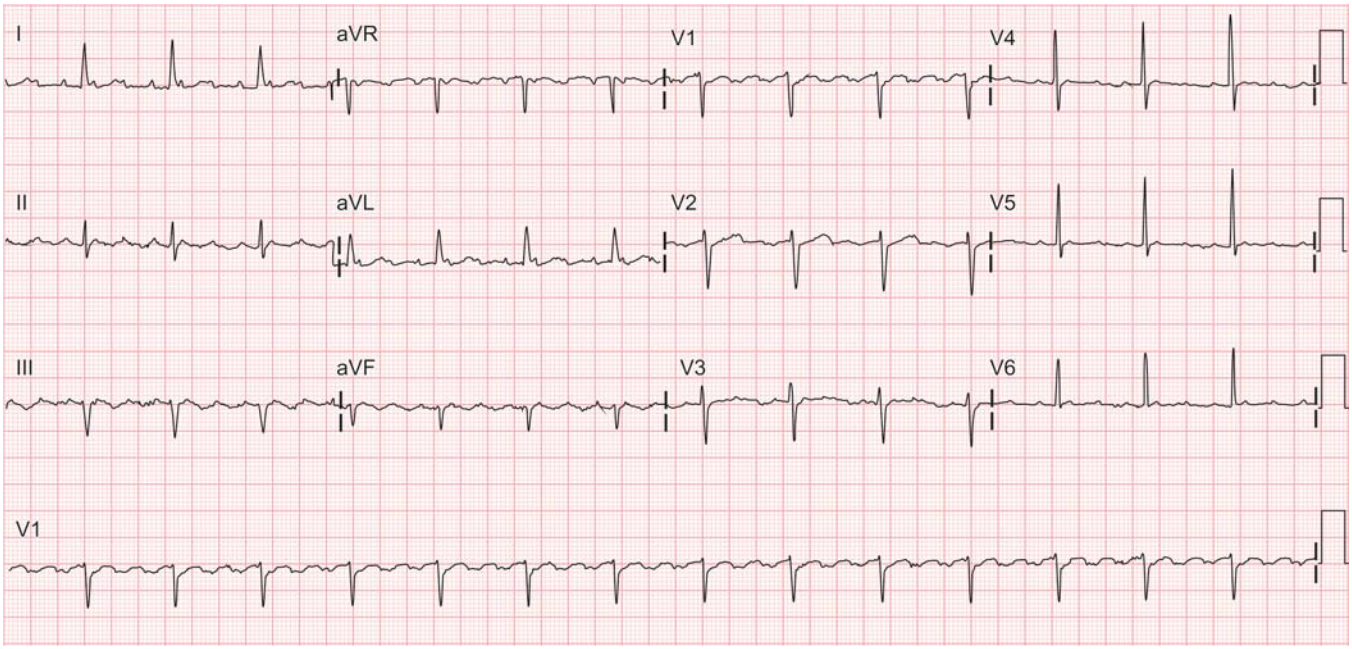


FIGURE 6: The left atrial flutter shown here has negative flutter waves in V1 and upright flutter waves in the inferior leads

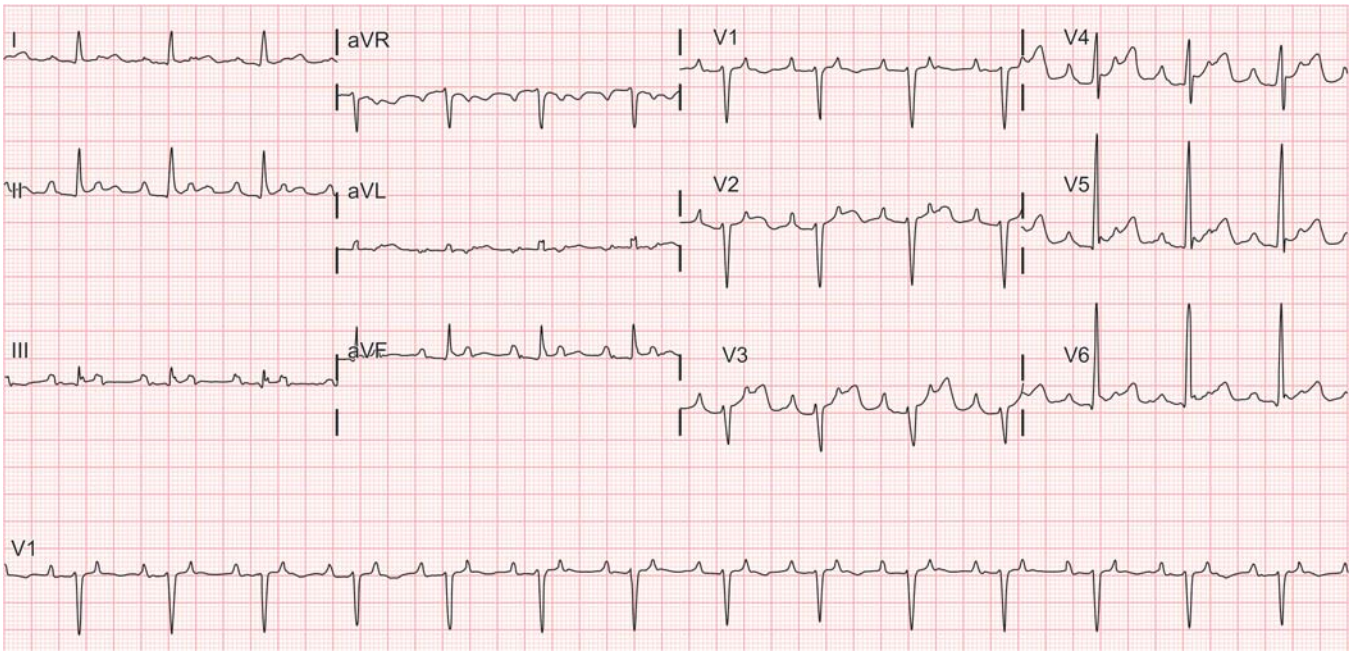


FIGURE 7: Atrial tachycardia with 2:1 AV conduction. Discrete P waves are separated by an isoelectric interval, in sharp contrast to atrial flutter in which an isoelectric interval is usual, not present. Occasionally, an atrial flutter is slow, especially if an antiarrhythmic drug is given, but generally, the rate is faster than 250 bpm. This atrial tachycardia is due to attempted ablation of atrial fibrillation in the left atrium and this is a left atrial tachycardia. The P wave morphology can help distinguish the location of atrial tachycardia origination

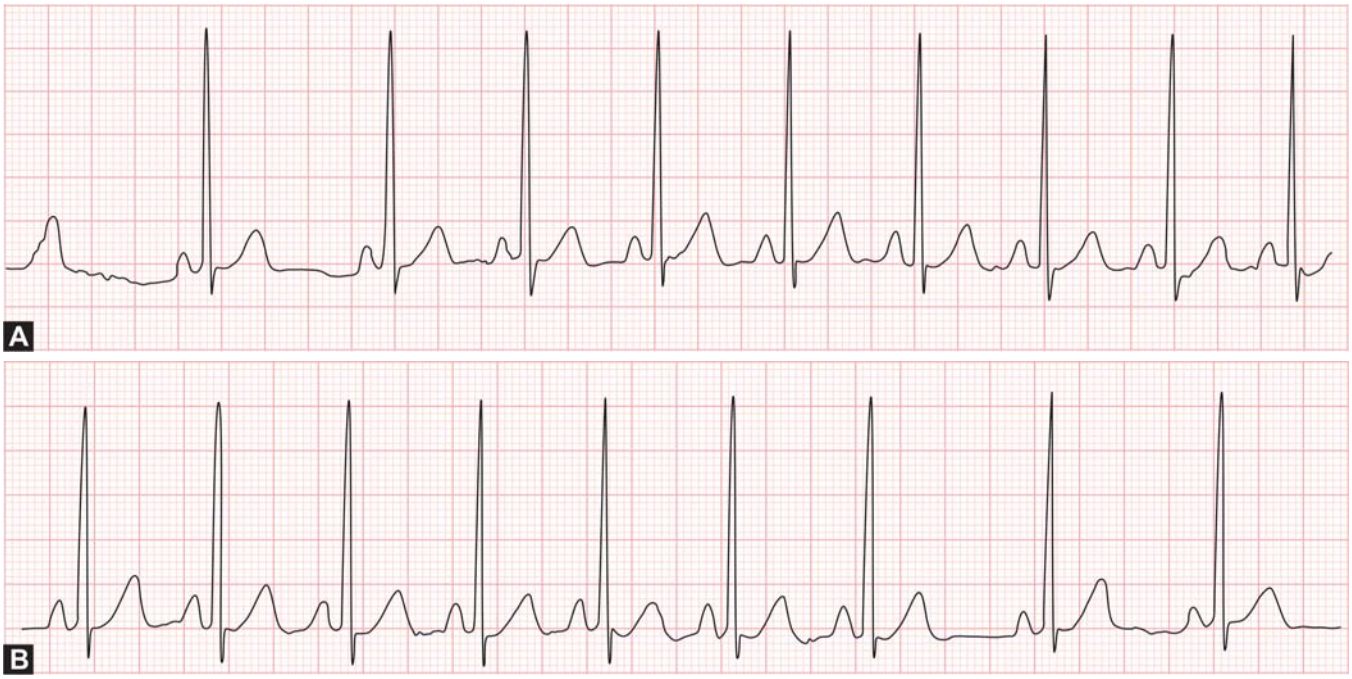
isoelectric baseline. Adenosine may terminate atrial reentrant SVTs in 15% of cases.

Sinoatrial Re-entry Tachycardia

Sinoatrial re-entry tachycardia (SART) is a unique, uncommon form of regular AT due to a re-entrant mechanism involving the sinoatrial node.[25] The P wave morphology is often similar to that in sinus rhythm with the exit point in the right atrium slightly below the sinus node (Figs 8A and B) but it can masquerade as other forms of SVT.[26] This tachycardia starts and stops abruptly and tends to be slower and more irregular than other types of SVT. Patients with AVNRT may also have associated SVTs such as sinoatrial reentry.[27]

Multifocal Atrial Tachycardia

In MAT, atrial activation occurs from multiple locations leading to at least three different morphologies of P waves (Fig. 9). The atrial rate is between 110 bpm and 170 bpm. In some cases, it



FIGURES 8A AND B: This rhythm strip demonstrates an abrupt change (speeding and slowing) in heart rate with an upright P wave in the inferior leads. The P wave morphology does not change and is similar to that in sinus rhythm. This is expected in typical sinoatrial reentrant supraventricular tachycardia



FIGURE 9: This rhythm strip shows multifocal atrial tachycardia, with at least three distinct P wave morphologies present. This type of tachycardia is often related to severe pulmonary disease and treatment of the underlying disease is the best way to eliminate the tachycardia. The prognosis is generally poor but not directly related to the atrial tachycardia itself. While there is no specific antiarrhythmic treatment for this tachycardia, amiodarone or verapamil may be effective



FIGURE 10: Coarse atrial fibrillation with atrial activation that continuously changes. This is not flutter or atrial tachycardia

can be difficult to distinguish from "coarse" AFib (Fig. 10). The vast majority (60–85%) of cases occurs in acutely ill, older individuals and those with severe chronic obstructive lung disease but also can occur in patients with cor pulmonale, pneumonia, sepsis, hypertensive heart disease, and systolic heart failure. Approximately up to 0.40% of hospitalized patients have this arrhythmia.[28] Exacerbating factors include theophylline toxicity, hypokalemia, hypoxia, acidosis and catecholamine infusion. The acute mortality associated with, but not directly due to, MAT is 30–60% but this reflects the underlying disease and not necessarily the arrhythmia itself. Treatment is aimed at the underlying disease and while verapamil has been advocated, it is not particularly effective in all patients.[29]

AV NODAL DEPENDENT SVT

Atrioventricular Nodal Reentrant Tachycardia

Atrioventricular nodal reentrant tachycardia is due to the presence of two physiological and anatomical ("slow" and "fast") AV nodal pathways.[30] About 65% of all regular SVTs are due to AVNRT. Typically, activation proceeds down the "slow" perinodal pathway and returns via the retrograde "fast"



FIGURE 11: Atrioventricular nodal reentrant supraventricular tachycardia AVNRT is a narrow QRS complex tachycardia with no obvious P waves present. A pseudo R' can be observed in lead V1 as depicted here. The initiation is with a long PR interval suggesting conduction down a slow AV nodal pathway. This tachycardia can generally be terminated by carotid sinus massage, vagal maneuvers or adenosine



FIGURES 12A AND B: Comparing baseline sinus rhythm tracing to that during tachycardia shows a retrograde P wave buried at the end of the QRS complex. In this particular instance, it occurs in lead AVF rather than in V1

perinodal pathway [Flow chart 1 (Panel B)]. The rates of AVNRT are usually between 150 bpm and 200 bpm but it can be as fast as 250 bpm. Slow or fast AVNRT usually begins with a premature atrial depolarization followed by a long PR interval. There can be a pseudo R' in lead V1 (Fig. 11) and a pseudo S wave in the inferior leads, a retrograde P wave seen in other leads (Figs 12A and B) or not (Fig. 13). AVNRT can be present with a bundle branch block (Fig. 14) and this can be tachycardia dependent. The atypical form of AVNRT involves a short PR (long RP) interval with antegrade conduction down a fast pathway and retrograde conduction via the slow pathway. A rare form of AVNRT involves slow antegrade activation and slow retrograde activation ("slow-slow" AVNRT).[31]

Atrioventricular nodal reentry tachycardia (AVNRT) can begin at any age and occurs more commonly in women than men. It is more likely to occur in the adult population even

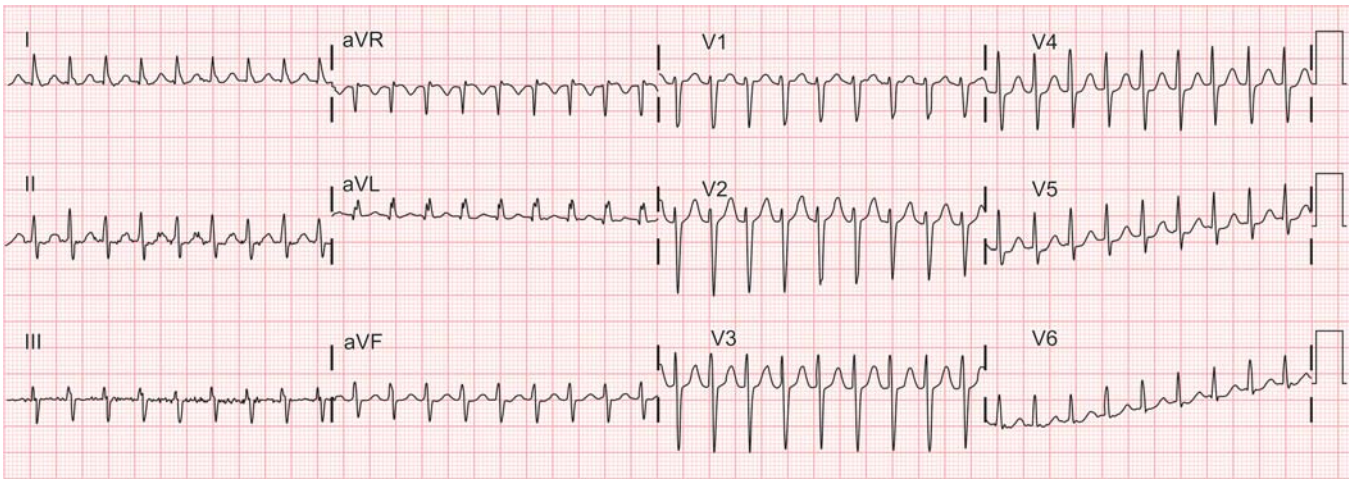


FIGURE 13: Typical AVNRT with a faster rate and no obvious P waves associated with the QRS complexes. A regular narrow QRS complex supraventricular tachycardia in which P waves are absent is most likely to be AVNRT

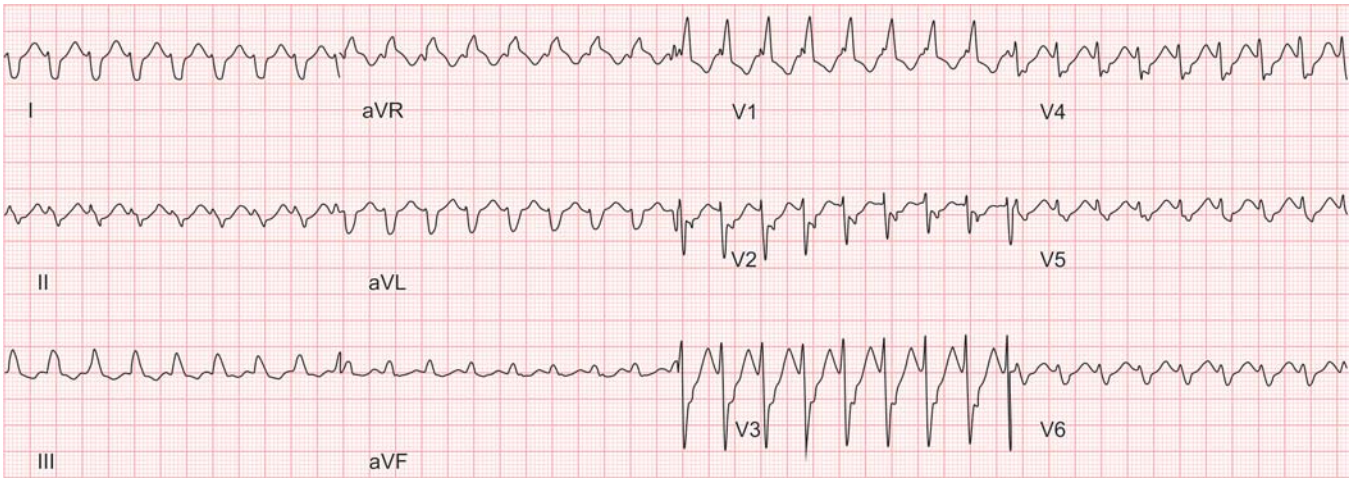
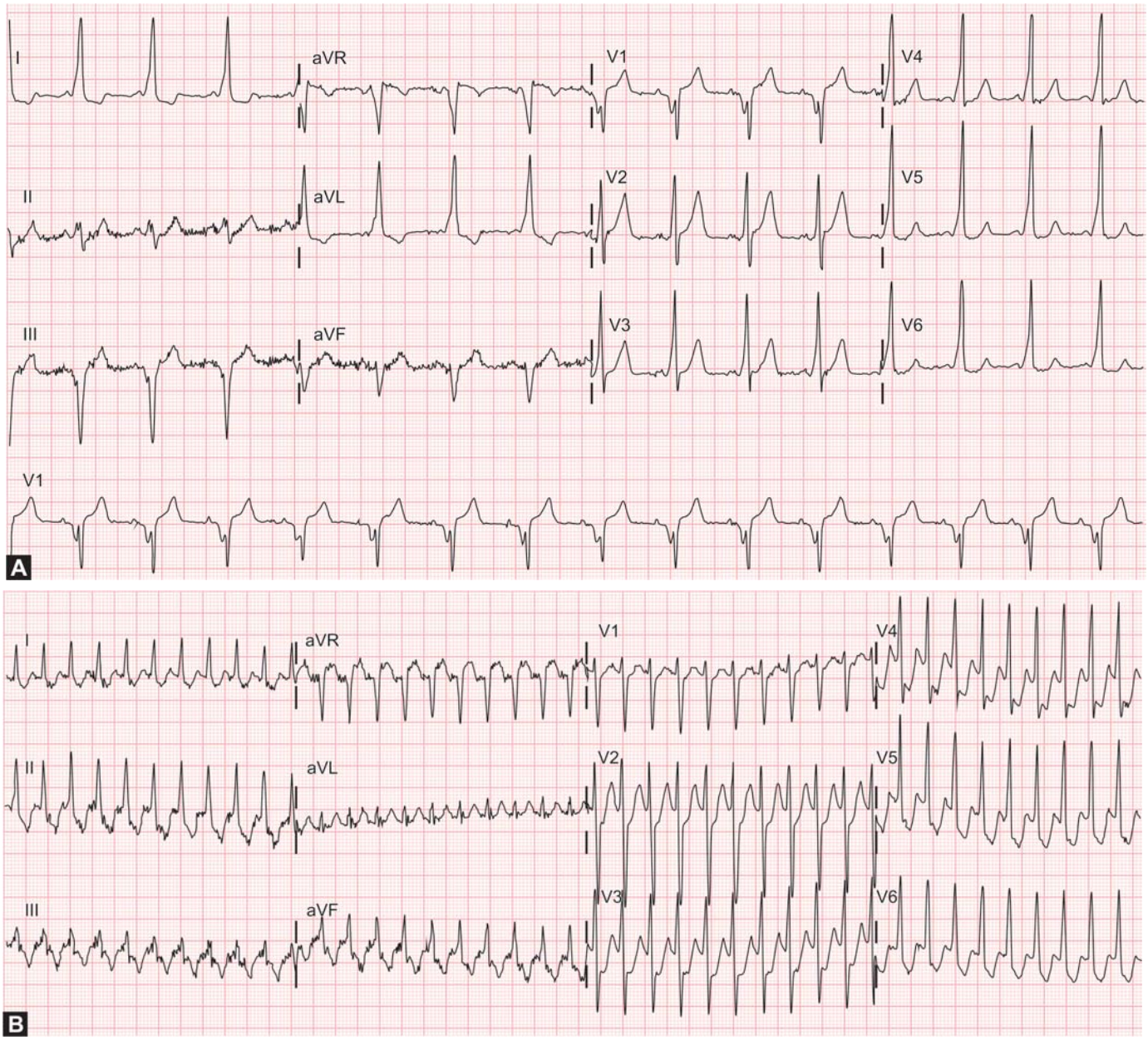


FIGURE 14: Example of AVNRT associated with a right bundle branch block. Supraventricular tachycardia can be associated with a wide or narrow QRS complex. In some cases a wide QRS complex supraventricular tachycardia is due to an underlying bundle branch block. Alternatively, there can be tachycardia dependent right bundle branch block aberration. In this case, it is possible to see a retrograde P wave in leads V2–V5



FIGURES 15A AND B: (A) This tracing shows evidence for a posteroseptal accessory pathway in sinus rhythm. There is evidence that this is Wolff-Parkinson-White syndrome with a negative delta wave in V1 and a positive delta wave in V2. The delta wave in the inferior leads, i.e. III and AVF, are negative. This delta wave vector is consistent with a posteroseptal accessory pathway (B) This tracing, seen in the same patient who had an EKG in sinus rhythm shown in 15A, shows a rapid narrow QRS complex supraventricular tachycardia with a retrograde inverted P wave present in the ST segment. The P wave is best seen in leads II, III and AVF. This is orthodromic AV reciprocating tachycardia. The supraventricular tachycardia does not demonstrate conduction down the accessory pathway. Since conduction is going down the AV node and up the accessory pathway, there is no evidence for a delta wave during tachycardia. This is typical orthodromic AV reciprocating tachycardia

though dual AV nodal pathways are common in children.[32] Likely, AV nodal pathways change over time. Although dual AV nodal pathways are common, only a small percentage of individuals with dual pathways have AVNRT as specific characteristics are required for the tachycardia to occur: the slow pathway must have a longer refractory period than the fast pathway[33] and there may be specifics about AV nodal pathway conduction and connectedness that play a role.[34,35] High catecholamine states can exacerbate AVNRT. Symptoms, such as palpitations, neck pounding, lightheadedness, weakness, anxiety, shortness of breath, chest discomfort, pulmonary congestion and syncope due to simultaneous atrial and ventricular contraction, may occur during typical forms of AVNRT.[36,37] Although conceivable but rare, AVNRT may occur with conduction block at the lower portion of the AV node or below, demonstrating 1:1 conduction but no evidence for conduction block between the atria and the ventricles. These forms of AVNRT stop abruptly with adenosine, vagal maneuvers, and verapamil.

Atrioventricular Re-entry Tachycardia

Atrioventricular reciprocating tachycardia is a macroreentrant tachycardia involving activation of the atria and ventricles through anterograde and retrograde conducting AV pathways [the AV node and an accessory pathway[38] (Figs 15A and B)]. Typically, the antegrade conduction during AVRT is via the

AV node with retrograde conduction via an independent accessory pathway. When this occurs, it is known as "orthodromic AV reciprocating tachycardia" [Flow chart 1 (Panel A)], representing approximately 30% of all regular SVTs. It is more common in young males and tends to be faster than AVNRT. During this tachycardia, the P wave is distinctly after the QRS complex and this tachycardia is often termed "long RP tachycardia". The symptoms of neck pounding experienced by the patients with AVNRT tend not to be present for those with AVRT as atrial and ventricular activation is not simultaneous. Cannon A waves do not tend to occur in AVRT.

As AVRT can be faster than AVNRT, it is more often associated with QRS alternans[39] (Fig. 16). The accessory pathway responsible for AVRT can be "concealed", that is, not present as a "delta wave" on the ECG recording. Like AVNRT, this tachycardia stops abruptly with vagal maneuvers or adenosine due to blockage in the AV node.

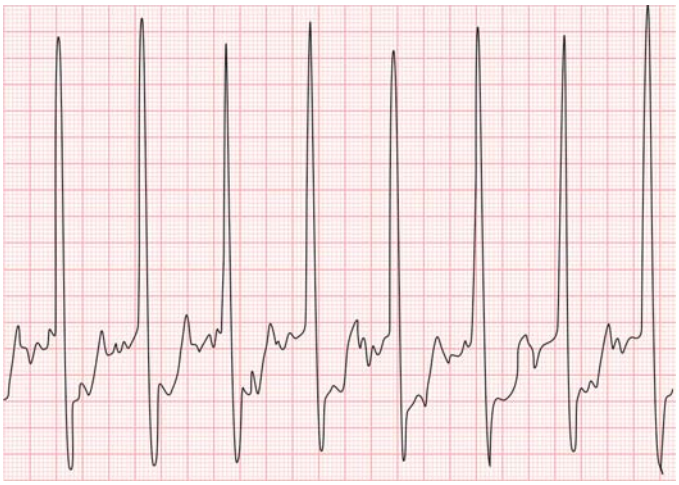


FIGURE 16: Example of a recording orthodromic AV reciprocating tachycardia in which there is a retrograde P wave and evidence for QRS alternans

Pre-excitation Syndromes

Manifest antegrade conduction through an accessory pathway can "pre-excite" the ventricles and cause a fusion complex or complete conduction via the antegrade accessory pathway. The AV connection can occur by way of the left ventricle, the right ventricle, or the septum at virtually any location between the atria and the ventricles. When this is present in sinus rhythm, the pattern on the ECG is known as the "Wolff-Parkinson-White" (WPW) pattern.[40] When this pattern is associated with palpitations, this is known as WPW syndrome.

Orthodromic atrioventricular re-entry tachycardia (AVRT) is the most common SVT that occurs with the WPW syndrome and other preexcitation syndromes. In less than 10% of cases of WPW syndrome, antegrade conduction is via an accessory pathway and retrograde conduction is via the AV node ("antidromic tachycardia") (Fig. 17). In rare instances, antegrade conduction proceeds down an accessory pathway and comes up another accessory pathway (Fig. 18). In the case of AVRT, in which conduction proceeds antegrade via an accessory pathway, the QRS complex is bizarre and wide. Irregular and rapid conduction via an accessory pathway during AFib can be potentially life-threatening and is dependent upon conduction via the AV node and/or the accessory pathway (Fig. 19).



FIGURE 17: 12 lead ECG demonstrates antidromic AV reciprocating tachycardia. It is a rare form of supraventricular tachycardia present in patients with preexcitation syndromes. This wide QRS complex tachycardia can be difficult to distinguish from ventricular tachycardia. Preexcitation is likely to be seen in sinus rhythm with a similar QRS complex morphology. An electrophysiology study might be necessary to confirm that this is in fact antidromic tachycardia rather than ventricular tachycardia. During an electrophysiology study, an atrial premature can preexcite the ventricle with a similar QRS morphology when retrograde His bundle activation is refractory during antidromic AVRT. Antegrade conduction proceeds via the accessory pathway rapidly, with a short PR interval (best seen here in lead aVL). There is retrograde conduction via the AV node. This pathway is right-sided based on the QRS morphology (a negative QRS in lead V1). It was located close to the His bundle/AV node region

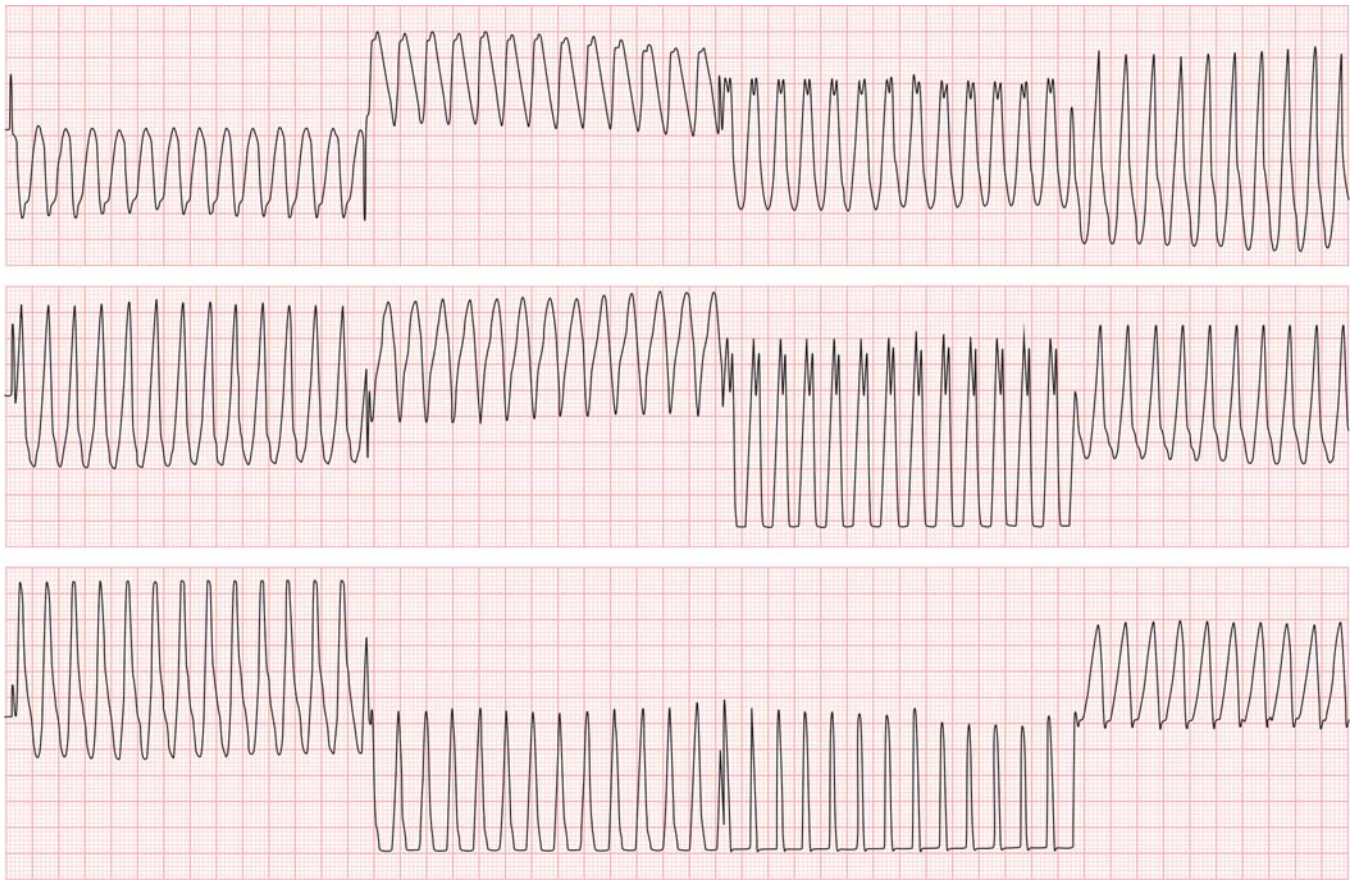


FIGURE 18: Very rapid wide QRS complex tachycardia is difficult to distinguish from ventricular tachycardia but is a form of antidromic AV reciprocating tachycardia in which antegrade conduction proceeds down an accessory pathway and goes up another accessory pathway. In this particular case, adenosine changed a slower form of antidromic tachycardia to a faster form after blocking the AV node. In this particular patient, the retrograde accessory pathway was a septal pathway and the antegrade pathway was a left-sided pathway that was anterior. The location of the antegrade conducting accessory pathway is the reason for the morphology of the QRS complex

Other "preexcitation syndromes" can be due to His-Purkinje system preexcitation, particularly of the right bundle. An atriofascicular pathway can occur that bypasses the AV node and inserts into or next to the right bundle known as a "Mahaim fiber". Such a pathway tends to have "decremental" properties in which premature beats can be associated with progressively slower conduction through the pathway.[41] These are antegrade only conducting "atriofascicular" pathways (Fig. 20). Mahaim fibers can be "innocent bystanders" whereby AVNRT proceeds down the Mahaim fiber to the ventricles or they can be the antegrade limb of a macroreentrant SVT in which the retrograde limb involves the AV node.[42]

Permanent Junctional Reciprocating Tachycardia

Permanent junctional reciprocating tachycardia (PJRT) is a persistent form of AVRT in which conduction proceeds down the AV node and up a posteroseptal, slowly conducting accessory pathway (Fig. 21). As this tachycardia is persistent and often rather slow, it may go undetected for years and lead to tachycardia-induced cardiomyopathy.[43,44] In some instances, a macroreentrant SVT involving the AV node is dependent upon slow conducting accessory tissue that is independent of the AV node and often (but not always) in a portion of the posterior right atrium.[45]

Junctional Ectopic Tachycardia

Junctional ectopic tachycardia is an automatic or triggered tachycardia that originates from tissue surrounding the AV node (Fig. 22). The rhythm tends to be persistent and nonparoxysmal and may slow but does not generally terminate with adenosine. This rhythm is more common in children but also tends to occur after cardiac surgery, during AMI, after cardioversion of AFib, with myocarditis, during exercise, and in healthy individuals and those with sinus node dysfunction. This tachycardia may also occur under situations of catecholamine excess or in digoxin toxicity. SVT with AV dissociation is most likely JET. The JET can be associated with a poor prognosis but a recent multicenter report suggests that treatment with antiarrhythmic drugs (particularly amiodarone) or ablation can be associated with good outcomes.[46] Rarely, rapid forms of JET can be seen in specific situations, such as the postoperative period, in which catecholamine stimulation is high (Fig. 23).

DIAGNOSIS

The clinical presentation can be diagnostic of SVT and it may be possible to proceed with further evaluation and therapy on this basis alone. Classic symptoms include the abrupt onset of rapid palpitations with associated dyspnea, chest discomfort,

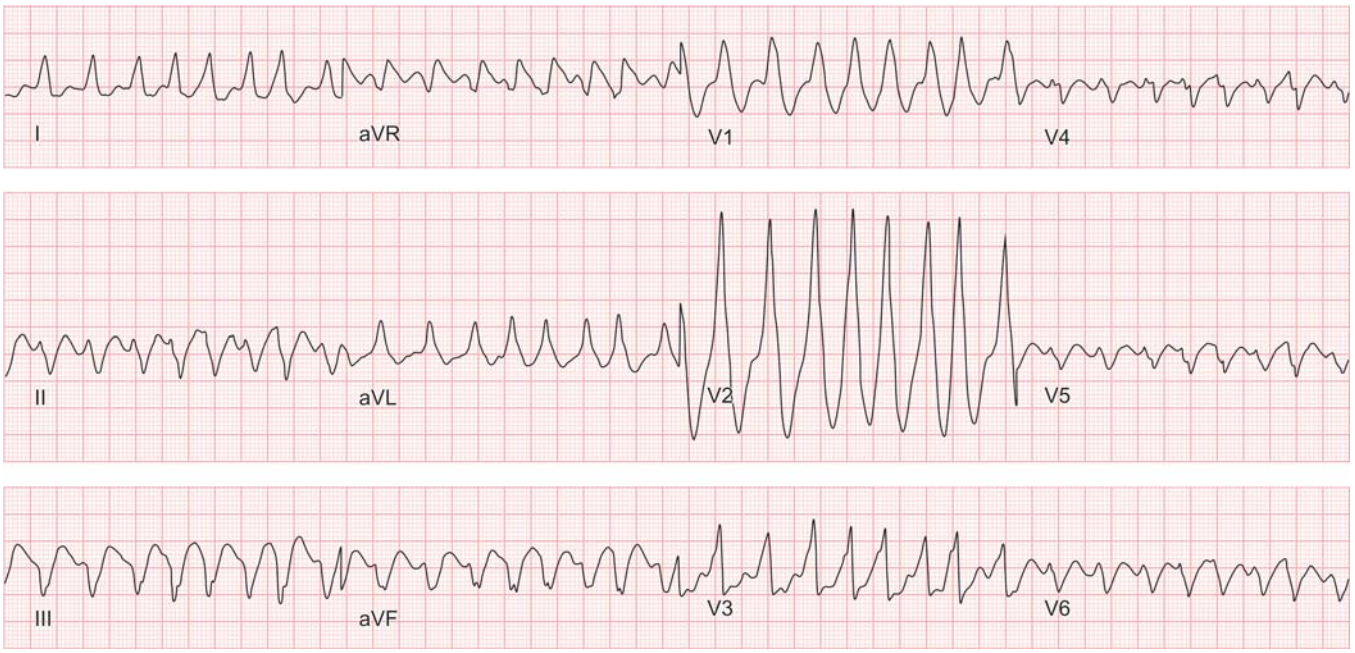


FIGURE 19: Atrial fibrillation in a patient with the Wolff-Parkinson-White. This is an irregularly irregular wide QRS complex tachycardia with occasional conducted beats via the AV node. The QRS complexes are due to ventricular activation by way of the left-sided posterior accessory pathway (as determined by the QRS morphology with a positive delta wave in V1). The best long-term treatment is ablation of the accessory pathway. Acutely, cardioversion or drug therapy (procainamide or amiodarone) are the treatments of choice. If the patient is not tolerating this tachycardia hemodynamically, it is important to proceed rapidly to electrical cardioversion. It is important to avoid digoxin, calcium channel blockers and even beta blockers acutely in patients who present with this tachycardia

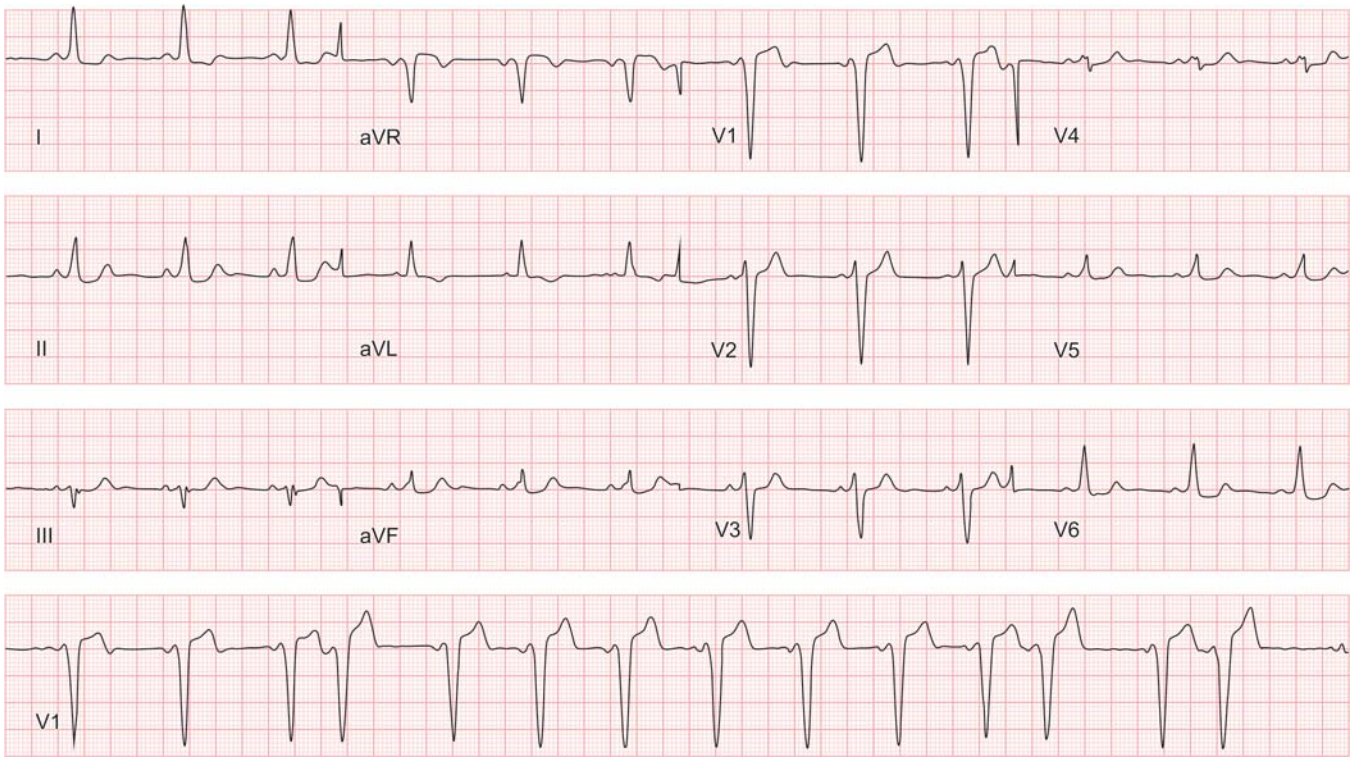


FIGURE 20: A Mahaim fiber is noted in sinus rhythm in this tracing from a 19-year-old female who has supraventricular tachycardia. There is evidence for a left bundle branch block without manifest preexcitation but with a short PR interval. There is no obvious delta wave but the QRS morphology becomes slightly wider. There may be slight accentuation of the QRS width with the premature atrial contraction as it may be fused conduction between the atriofascicular ("Mahaim") fiber, connecting the right atrium to the right bundle and normal antegrade AV nodal conduction. A Mahaim fiber may be suspected based on the clinical presentation. It is unlikely for a 19-year-old to have a left bundle branch block with a short PR interval. Patients with this abnormality can have a macroreentrant supraventricular tachycardia involving antegrade conduction down the Mahaim fiber and retrograde conduction up the AV node or they may have AV nodal reentry with "innocent bystander" Mahaim conduction. Mahaim fibers tend to conduct only in the antegrade direction. These are right-sided pathways that insert into the right bundle

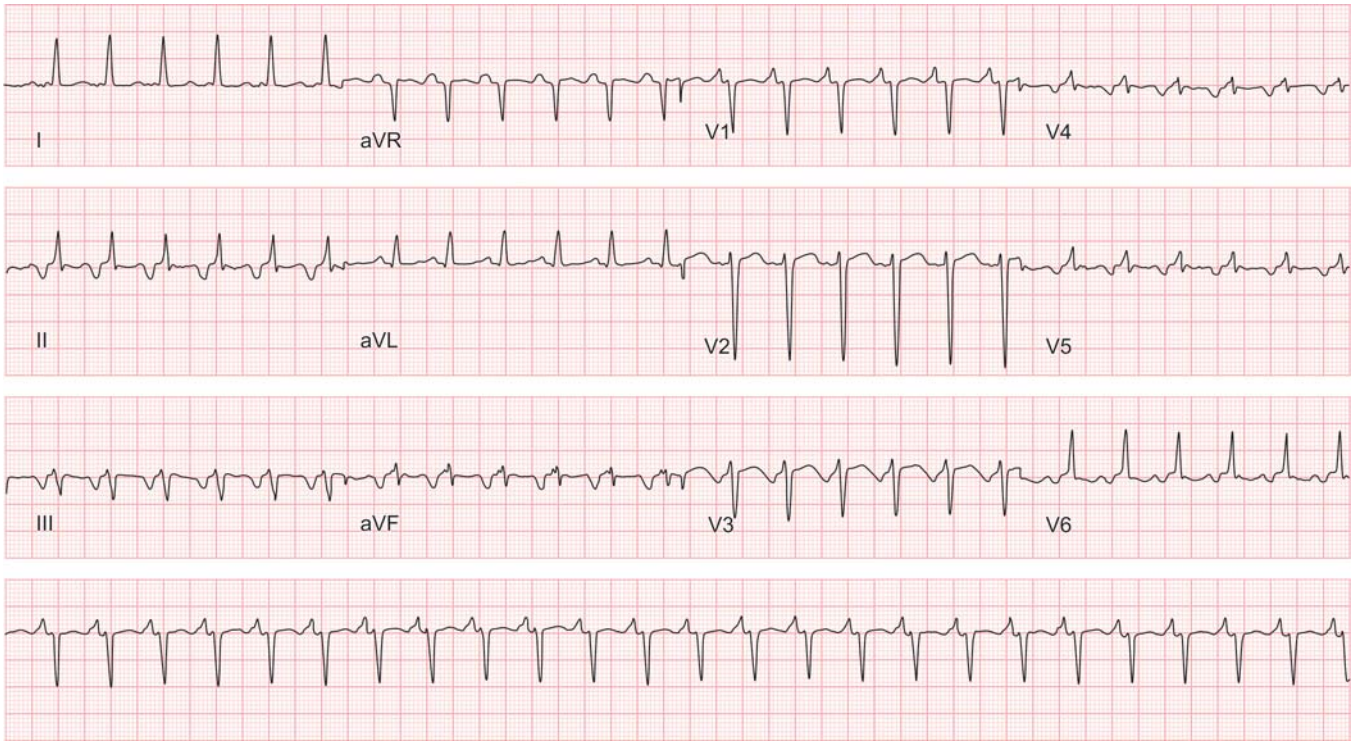


FIGURE 21: Supraventricular tachycardia is permanent junctional reciprocating tachycardia (PJRT). The P wave precedes the QRS complex and is inverted in leads II, III and AVF and upright in V1. The differential diagnosis for this tachycardia is atypical AV nodal reentry (antegrade fast pathway and retrograde slow pathway), atrial tachycardia and permanent junctional reciprocating tachycardia. This patient had permanent junctional reciprocating tachycardia with retrograde conduction by way of an accessory pathway that was conducting slowly as determined by electrophysiology testing. This patient developed heart failure and a cardiomyopathy due to persistent tachycardia. With ablation of the slow retrograde accessory pathway, the tachycardia was eliminated, thereby returning the ejection fraction to normal and resolving the heart failure

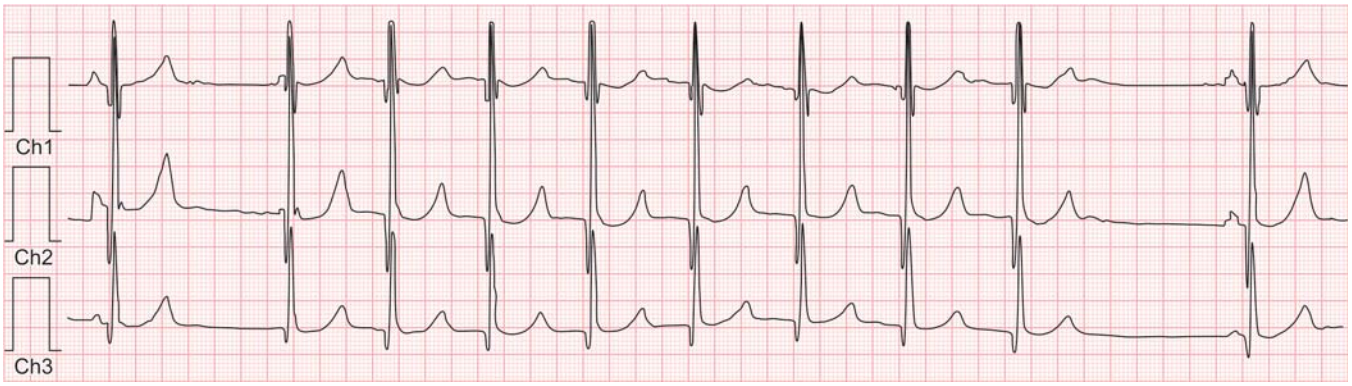


FIGURE 22: Tracing shows evidence for a junctional ectopic tachycardia. These tachycardias are most commonly present in younger patients and they originate from tissue surrounding the AV node. This tachycardia can be associated with AV dissociation. The first beat of this tachycardia occurs at the same time as a P wave demonstrating the dissociation of the A and the V during the tachycardia



FIGURE 23: Rarely, an accelerated junctional tachycardia, faster than junctional ectopic tachycardia, can occur in older people who have high catecholamine states. In this particular case, the patient was postoperative after cardiac surgery. There is a narrow complex tachycardia with retrograde atrial activation but not in a one-to-one fashion. There is retrograde a conduction block

dizziness, and lightheadedness. These symptoms often abruptly terminate when the patient utilizes vagal maneuvers that are learned over time in an attempt to abate the symptoms.

The physical examination can aid in determining the specific type of SVT. The neck veins may show prominent pulsations with each beat, consistent with cannon A waves, common in typical AVNRT. Alternatively, patients with AFL may have flutter waves seen as pulsations in the neck at a rate faster than the pulse itself. An irregularly irregular pulse or a pulse deficit would be consistent with AFib. Additionally, important information from the physical examination includes blood pressure recordings as well as evidence for hemodynamic compromise or the presence of congestive heart failure. These findings are indicators that a more aggressive approach is necessary to control the rate and the rhythm.

Bedside maneuvers, such as carotid sinus massage or Valsalva, can terminate tachycardia abruptly. They can also uncover the presence of an AV nodal independent tachycardia such as AFL (Fig. 24). These maneuvers can also slow down the sinus rate and stop sinoatrial reentry as well. Adenosine can stop some ATs.

ELECTROCARDIOGRAPHIC RECORDINGS

Supraventricular tachycardia may be diagnosed by a single ECG lead but a multiple lead ECG recording is generally more useful to help distinguish one form of SVT from another. A 12-lead ECG during sinus rhythm can help to determine if there is preexcitation or a bundle branch block. Ambulatory event recorders, including Holter monitors or even an implantable loop recorder, may be necessary to detect intermittent episodes of SVT.

During recorded episodes, clues to the diagnosis of the presence and type of SVT can be discerned from the initiation and termination of the tachycardia (Fig. 11), the relationship between the P waves and the QRS complexes (Fig. 7), the P wave and QRS morphologies, as well as the presence of AV block and the tachycardia regularity and rate. In some cases, the type of SVT may not be clear based on available recordings even with bedside interventions (vagal maneuvers or intravenous adenosine) (Fig. 24). An invasive electrophysiology test may be needed to ascertain the SVT type and mechanism.



FIGURE 24: In this particular tracing, a patient who had atrial flutter was given adenosine to secure the diagnosis. There was transient AV block with a long pause and the presence of flutter waves becoming evident. Prior to the adenosine, there was 2 to 1 conduction during atrial flutter and it was difficult to make the diagnosis for certain. This tracing shows the effect of adenosine uncovering the mechanism of this particular tachycardia, typical atrial flutter. Adenosine will not stop atrial flutter but will stop AV nodal dependent supraventricular tachycardias such as AVNRT and AVRT. It can also stop sinoatrial reentry and some atrial tachycardias. Adenosine can be useful to help distinguish atrial versus AV nodal dependent supraventricular tachycardias

P Wave Characteristics

In typical (slow antegrade, fast retrograde) AVNRT, the P wave is nearly simultaneous with the QRS complex. Characteristically there is a small upright P wave in lead V1 just at the end of the QRS complex known as a pseudo R' (Fig. 11). At tachycardia initiation, a long PR interval may be seen indicating antegrade conduction via a slow conducting AV nodal pathway. In atypical (fast antegrade, slow retrograde) AVNRT, there is an inverted P wave in the inferior leads often just before the next QRS complex. AVNRT of this type or AVRT should be suspected if inverted P waves are present in leads II, III and aVF.

In monomorphic AT, the P wave is inconsistent with sinus tachycardia. AV block may be present but conduction tends to be at a fixed ratio (Fig. 7). Similarly, for AFL, variable conduction or 2:1 conduction may occur and one of the P waves could be buried in the ST segment (Fig. 3A). In sinus tachycardia, the P wave is before the QRS complex and is upright in the inferior leads (Fig. 2). It may be difficult to distinguish from SART as the P wave morphology can be virtually identical (Figs 8A and B). In JETs, AV dissociation may be present as the tachycardia can be independent of atrial activation. In MAT, at least three morphologies of P waves are present (Fig. 9).

Wide QRS Tachycardia—Is It SVT?

Wide QRS complex tachycardia (QRS width $\geq$ 120) is generally ventricular tachycardia but approximately 10% of wide QRS tachycardias are SVT (Table 2). A wide QRS complex during SVT can be due to a bundle branch block that may be present in sinus rhythm. The baseline ECG can, therefore, be of some help in diagnosing the mechanism as the morphology may be the same as in sinus rhythm but the QRS can change during SVT when there is an underlying bundle branch block[47] and the QRS morphology during ventricular tachycardia can mimic the morphology in sinus rhythm.[48]

There can be rate-dependent ("phase 3") aberration (QRS widening with a bundle branch block pattern) that is due to rate dependent block in one of the bundles due to rate related refractoriness. When this occurs, it is often present when there is an acceleration of the tachycardia or if there is irregular AV conduction such that there is long-short conduction. This is known as "Ashman's phenomenon" which tends to occur during AFib. Tachycardia-dependent aberration can be continuous or intermittent and related to refractoriness in the right or left bundle branch. A phenomenon of "concealed perpetuated aberration" is also possible in which persistent bundle branch

TABLE 2

Differential diagnosis of wide QRS tachycardia

- SVT with fixed bundle branch block
- SVT with intermittent aberration including concealed perpetuated aberration
- SVT with persistent rate dependant aberration
- SVT with passive conduction down a bypass tract
- SVT due to antidromic AV reciprocating tachycardia
- Ventricular tachycardia

block aberration can occur even though there is fluctuation in rate.

In some patients, both wide and narrow QRS SVT coexist. If the rates of the wide and narrow QRS SVT are similar, or if the rate during the wide QRS tachycardia is faster, the cause of the tachycardia remains uncertain. If the wide QRS SVT is due to bundle branch block aberration and it is slower than the narrow QRS SVT, this likely indicates the presence of AVRT with retrograde conduction via the accessory pathway on the same side as the bundle branch block. The slower rate during the wide QRS complex tachycardia is because the bundle branch block causes the contralateral ventricle to activate first and there is conduction delay through the ventricular myocardium before conduction can proceed up the retrograde pathway. A bundle branch block located on the side ipsilateral to the accessory pathway will lengthen the reentry circuit pathway (e.g. a left bundle branch block tachycardia with a left sided retrograde accessory pathway is likely to be slower than SVT with a narrow QRS complex in the same patient) and the VA interval can lengthen with the bundle branch block aberration. Occasionally, tachycardia can begin in a fascicle with a relatively narrow, yet wide, QRS complex, and with AV dissociation. This tachycardia can be confused with SVT.

In rare instances, antegrade conduction via an accessory pathway during tachycardia can present as a wide QRS complex SVT. Antidromic AVRT (conduction down an accessory pathway and up the AV node or another accessory pathway) occurs rarely. Preexcited AFib with intermittent AV conduction down an accessory pathway is also possible.

Adenosine is potentially diagnostic and can be given in a patient with a wide QRS complex tachycardia that is well tolerated.[49] If adenosine or a vagal maneuver stops a wide QRS tachycardia, it is likely SVT even though some idiopathic ventricular tachycardias may stop with adenosine or even a vagal maneuver. Despite careful analysis, and even bedside maneuvers, the diagnosis of the type of SVT may be incorrect in as many as 20% of recorded episodes.

ELECTROPHYSIOLOGY STUDIES

Invasive electrophysiology studies are used either for diagnosis of SVT in patients with classic symptoms or for determination of the mechanism of SVT for those who have recorded episodes or have a wide QRS tachycardia that may be SVT or VT. During the electrophysiology study, 2–5 intravenous catheter sheaths are placed and recording and stimulating catheter electrodes are placed in specific sites of the heart to record electrical activation and to stimulate the heart to initiate tachycardia and understand its mechanism. Catheters can also be used to locate specific tissues that are responsible for the tachycardia. SVTs with regular rate (AVNRT and AVRT), if present, are often readily inducible with delivery of premature atrial or ventricular extrastimuli. In some cases, AT and rare cases of AVNRT or AVRT, the SVTs are not inducible. Increasing the aggressiveness of the atrial and ventricular extrastimuli by pacing at faster rates and adding more extra stimuli may be useful. Sometimes, catecholamine stimulation with isoproterenol, and/or atropine may be necessary to initiate the tachyarrhythmia during extrastimulus testing. In rare instances, a beta-blocker is required to initiate SVT.

After SVT is initiated in the electrophysiology laboratory, the relationships of the atria, ventricles and His bundle during extrastimulus testing and during tachycardia can help to determine the tachycardia mechanism. Transient entrainment may help to understand the location and mechanism of the SVT.[50]

During SVT, if specifically timed ventricular extrastimuli activate the atria when the His bundle is refractory, the presence of an accessory pathway is diagnosed and the tachycardia is likely orthodromic AVRT. Similarly, if during SVT specifically timed atrial extrastimuli activate the ventricles when the His bundle is refractory, the tachycardia is like antidromic AVRT. AV relationships can also help to determine if there is an accessory pathway.

In some instances, detailed electroanatomical mapping is necessary to understand the tachycardia mechanism or the origin of the tachycardia (such as focal or reentrant AT). Similarly, simultaneous atrial record map may be helpful to understand the mechanism of the tachycardia. In some instances, it is a transseptal catheterization or even an arterial approach in needed to reach the tissue responsible for tachycardia.

TREATMENTS

The goal of treatment is to terminate tachycardia acutely, maintain normal sinus rhythm, control ventricular response rate, eliminate symptoms, normalize hemodynamics, and prevent worsening of any underlying cardiovascular conditions due to SVT.

ACUTE CARE

Acute management depends on the type and severity of symptoms related to the SVT and the type of SVT (Table 3). Acute interventions are designed to slow the ventricular rate (for AV nodal independent SVTs) and/or terminate the tachycardia. Therapies include drugs to cardiovert and prevent recurrence, drugs used to slow the AV conduction and the ventricular rate, and direct current cardioversion. Acute management requires careful electrocardiographic and hemodynamic monitoring. Patients remaining in SVT and having ventricular rates that cannot be controlled require hospital admission. Other indications for admission include frequent recurrences, resistance to initial drug therapy, initiation of new antiarrhythmic drugs, radiofrequency (RF) catheter ablation (elective or urgent) or adverse consequences from SVT (heart failure exacerbation, hypotension, myocardial ischemia) (Flow chart 2).

AV Nodal Dependent SVT or Regular SVT

AV Nodal dependent SVT or regular SVT for which mechanism is unknown. The first line treatment for an AV nodal dependent tachycardia is a vagal maneuver, such as carotid sinus massage, to create transient AV block and terminate the tachycardia. Patients can learn to perform vagal maneuvers and stop tachycardia on their own without the need for medical intervention.

TABLE 3

Pharmacologic management for supraventricular tachycardia

Drugs	*Mechanisms*	*Dosage*	*Side effects*	*Contraindications*
Adenosine	Purinergic agonist Inhibition sinus node and AV node	6 mg by rapid IV. If ineffective,12 mg and 18 mg	Nausea, light-headedness, headache, flushing, chest pain, bradycardia, brief asystole	Persantine Cardiac transplant Bronchospasm
Verapamil	Slow or block AV nodal conduction and slow sinus rate	2.5–5 mg over 1–2 min	Negative inotropic effect, hypotension, cardiogenic shock, marked bradycardia	Hypotension Systolic dysfunction Atrial fibrillation with preexcitation
Diltiazem	Slow or block AV nodal conduction and slow sinus rate	0.25 mg/kg IV bolus then 5–15 mg/hour gtt	Negative inotropic effect, hypotension, bradycardia	Hypotension Systolic dysfunction Atrial fibrillation with preexcitation
Metoprolol	Block β-sympathetic nervous system at the receptor level Inhibitory effects on sinus node, AV node and myocardial contraction	2.5–5 mg 3x at 2-min interval	Negative inotropic effect, hypotension	Hypotension Cardiogenic shock Bradycardia Decompensated heart failure Bronchospasm
Esmolol	Inhibitory effects on sinus node, AV node and myocardial contraction	IV 500 mcg/min loading dose over 1 min before each titration	Negative inotropic effect, hypotension, peripheral ischemia, confusion, bradycardia, bronchospasm	Hypotension Cardiogenic shock Bradycardia Decompensated heart failure Bronchospasm
Digoxin	Na^{+}/K^{+} ATPase inhibition Parasympathetic activation leading to sinus lowing and AV nodal inhibition	0.75–1.5 mg in divided doses over 12–24 hours	Nausea, vomiting, diarrhea, fatigue, confusion, colored vision, palpitation, arrhythmia, syncope	WPW syndrome Atrial fibrillation with preexcitation
Amiodarone	Class III AAD but with classes I, II and IV activity, block sodium, calcium and potassium channels	Oral: loading 1200–1600 mg daily, maintenance 200–400 mg daily IV: 150 mg over 10 min, then 360 mg over 6 hours, 540 mg over remaining 24 hours, then 0.5 mg/min	Thyroid abnormalities, pulmonary fibrosis, QT prolongation, liver function abnormalities	Severe sinus node dysfunction Hepatic dysfunction Pregnancy

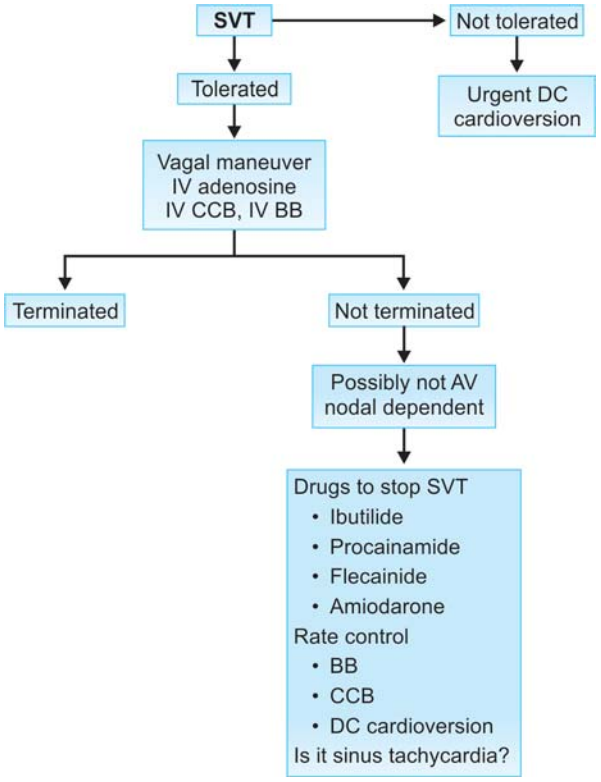
Carotid sinus massage is an easy and effective methodology to stop AV nodal dependent SVT but should only be used in the absence of a carotid bruit and/or absence of significant carotid disease.[51] In this procedure, the head should be turned away from the side being compressed (usually the right side) and a firm compression with 2–3 fingers is applied over the bulb of the carotid. A strong arterial impulse must be felt with firm pressure and rubbing. Sometimes, carotid massage can be combined with a Valsalva maneuver and even the Trendelenburg position to facilitate conversion. The success of the carotid sinus massage depends, in part, on the technique. A Valsalva maneuver can similarly increase parasympathetic tone and therefore slow down the conduction in the antegrade slow pathway. Another vagal reflex, the "diving reflex" in which the face is placed in cold water, may be effective.[52] These maneuvers are unlikely to be effective if hypotension is present.

Adenosine (Flow chart 3) can differentiate AV nodal independent versus AV nodal dependent SVT and can be used to help to make a diagnosis (Fig. 24) but, like AVNRT, SART can respond to autonomic maneuvers and adenosine. Adenosine effectively and rapidly terminates AV nodal dependent SVTs.[53] It is generally effective even if borderline hypotension is present. The advantage of adenosine is its rapid onset and short half-life. Adenosine must be given as a rapid intravenous bolus followed by a rapid saline infusion and should be given via a reliable, large bore IV access. The doses are between 6 mg and 12 mg, and occasionally up to 18 mg for highly resistant patients.

Adenosine must be used with caution in patients who are already taking persantine and also in patients who have cardiac transplant because asystole may occur. Furthermore, adenosine can cause long-lasting bronchoconstriction in patients with chronic obstructive lung disease or uncontrolled asthma. Caffeine and phosphodiesterase inhibitors will inhibit the effects of adenosine.[54] Some patients are reticent to have adenosine due to its short but potentially noxious side effects. Nevertheless, it is the preferred intervention to stop AVNRT and AVRT and it is effective in over 95% of individuals.[55,56]

Intravenous calcium channel antagonists, verapamil and diltiazem, can also terminate SVT.[57-59] Intravenous verapamil at doses of 5 mg, 10 mg and 15 mg can be effective; the duration of action is 5–45 minutes. Intravenous diltiazem can be used in doses of 0.15 mg/kg, 0.25 mg/kg and 0.45 mg/kg. Calcium channel blockers have negative inotropic effects and therefore can cause hypotension; use is not recommended when the patient

FLOW CHART 2: Management of regular SVT in an acute setting



is hypotensive or has ventricular dysfunction. It should be avoided in patients with preexcited AFib (i.e. antegrade activation via an accessory pathway). It should never be used when there is an undiagnosed wide QRS complex tachycardia as the results could be disastrous. Verapamil (and, less commonly, diltiazem) can be used when SVT is terminated with adenosine but recurs or in patients who ingest large amounts of caffeine.

Intravenous beta-adrenergic blockade (metoprolol or esmolol) may be effective in terminating SVT as well.[59] Esmolol has a short half-life of less than 10 minutes. Metoprolol has a longer half-life but is less expensive. Both of these drugs have a negative inotropic effect and may cause hypotension. Beta blockade and intravenous digoxin are third line drugs for termination of AV nodal dependent SVT.

The use of digoxin for the acute management of SVT is now rare. Digoxin requires a loading dose and takes prolonged time to effect. It is less efficacious than other drugs and contraindicated in the WPW syndrome. It may be used in combination with beta-adrenergic blockers or calcium channel blockers to control recurrent episodes of SVT.

AV Nodal Independent SVT

Intravenous beta-blockers, digoxin and/or calcium channel blockers can control the ventricular rate in patients who have atrial-based, AV nodal independent SVT (AT, AFL and AFib). The one exception is SART that responds reliably to adenosine.

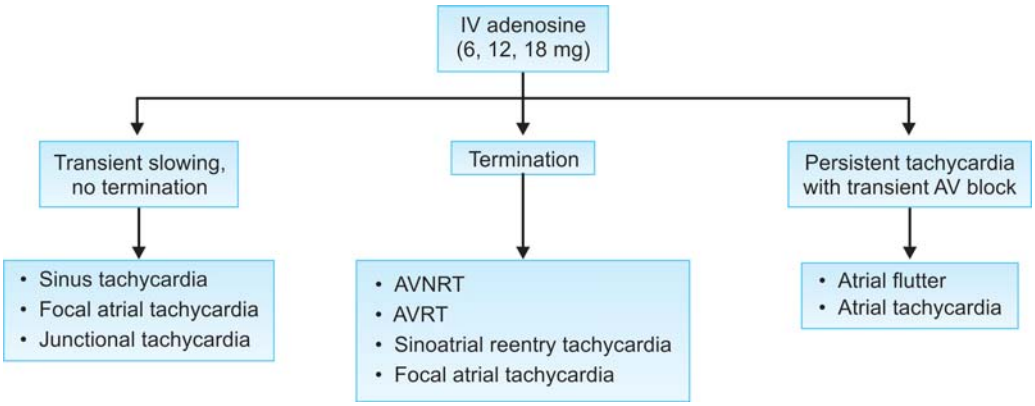
The preference of the drug class is related to the underlying conditions, blood pressure and ventricular function. Beta-blockers (in combination with digoxin), for example, are useful in controlling the ventricular response rate in AFL and AFib, especially in the postoperative period. Intravenous diltiazem has less negative inotropic effect than verapamil and can be used to control the ventricular rate when there is borderline low blood pressure. Diltiazem also may be useful when there is concern about bronchospasm. Digoxin may require a large loading dose and a protracted period but is more useful for patients with ventricular dysfunction or hypotension.

For patients with poorly tolerated AV nodal independent SVTs (AFL, AT and AFib), IV amiodarone is used to control the ventricular response rate.[60,61] Amiodarone has little role in the management of SVT otherwise.[62] For children, procainamide appears more effective than amiodarone for SVT.[63] Several drugs can stop AFL and AFib including intravenous procainamide and ibutilide. Acute treatments for AFL and AFib have been discussed in this chapter.

The WPW syndrome, when it is manifest as rapid AFib, should be treated with a drug that blocks the accessory pathway: either procainamide or amiodarone.[64,65] Digoxin, calcium channel blockers and beta-adrenergic blockers are strictly prohibited in these patients during acute management.[65]

Sinus tachycardia and MAT are likely due to underlying conditions. There is no specific treatment for the tachyarrhythmia and the goal is to treat the underlying conditions that are responsible for these problems.[66] When it is uncertain if a wide QRS complex tachycardia is SVT, drugs that block the AV node are not recommended.

FLOW CHART 3: Response of SVT to IV adenosine



When to Use DC Cardioversion

Cardioversion is the best option for patients with an undiagnosed wide QRS complex tachycardia not tolerated hemodynamically and for any poorly tolerated (hemodynamic instability or evidence of heart failure or myocardial ischemia) SVT in which the rate cannot be controlled and the rhythm cannot be restored to sinus.

In patients who have hemodynamic collapse due to any type of SVT other than sinus tachycardia, synchronized DC cardioversion is recommended. However, it is important to ascertain that the SVT is not sinus tachycardia, as it will not respond to cardioversion.

LONG-TERM MANAGEMENT

Several issues must be considered before the long-term treatment is contemplated:

- Is it required?
- What are the implications of no treatment?
- How old is the patient? Are there comorbidities?
- Is the rhythm triggered by any acute nonarrhythmic condition such as pneumonia or pulmonary embolus?
- Is there any evidence of worsening congestive heart failure?
- How chronic is the rhythm and what is the rate of the tachycardia?
- Is there hemodynamic compromise?
- How symptomatic is the patient?
- How often does tachycardia occur?
- What are the patient's wishes regarding treatment?

The long-term management of SVT depends on multiple factors, including the symptoms related to SVT, the recurrence rates, the underlying clinical conditions and the presence of structural heart disease. For example, the treatment of a patient who has one episode of a mildly symptomatic SVT terminated by vagal maneuvers or adenosine, treatment will be different from a person with frequent recurrence. Other ensuing factors must be considered such as the necessity for medication to prevent SVT during pregnancy. In this case, more definitive treatment by an ablation would likely be the primary choice.

The choice of drug for long-term management of SVT depends on the mechanism of the SVT and the goal of treatment. For ATs, AFL and AFib a simple strategy is to control the ventricular rate instead of maintaining sinus rhythm (Fig. 25). Beta-adrenergic blockers, calcium channel blockers and digoxin, in combination, can be effective.[66,67] This approach alone may not make sense as symptoms continue. Furthermore, it can be very difficult to control the ventricular response rate for some SVTs, such as in AT and AFL. Therefore, it may be necessary to cardiovert the patient, use an antiarrhythmic drug or even ablate the tachycardia. Antiarrhythmic drugs are often not effective for AFL and ablation may be necessary.[68,69] Occasionally, the ventricular rate cannot be controlled and maintenance of sinus rhythm is not an option; in this case, AV nodal ablation with permanent pacemaker may be required (Fig. 26).



FIGURE 25: Atrial fibrillation with a controlled ventricular response rate. Normally, the ventricular response rate to atrial fibrillation is fast as long as there is an intact AV node and the patient is not taking medical therapy to slow or block conduction in the AV node

For monomorphic AT, antiarrhythmic drugs can be given to help to maintain the sinus rhythm. The choice of antiarrhythmic drugs is similar to a methodology used for AFib, mainly based on the underlying structural heart disease. For patients without underlying structural heart disease, sotalol, propafenone and flecainide are possibilities. For patients with underlying structural heart disease, sotalol and amiodarone could be used to maintain sinus rhythm without a proarrhythmic effect.[70]

Like AFib and AFL, ATs can increase the risk of thromboembolic events.[71] Consideration must be given to the use of routine long-term anticoagulation for SVTs at risk for stroke. While guidelines address this issue for patients with AFib, they do not for ATs as data are scarce in this regard. Various antiarrhythmic drugs may suppress AFL. However, the safety and efficacy of antiarrhythmic drugs for AFL have not been well tested in the long term.[71] Furthermore, recent data suggest that ablation techniques especially for isthmus-dependent right AFL are more effective and cost-effective than drug therapy. Similarly, there are no specific guidelines with respect to anticoagulation for AFL. Recent data indicate that AFL has a similar or slightly lower risk of thromboembolic risk when compared with AFib. Therefore, AFL should be considered very much like AFib when contemplating the use of anticoagulation.

Catheter Ablation

Catheter ablation has emerged as a curative approach for the patients who have SVT.[72-75] The mechanism by which catheter ablation may work is dependent upon the type of tachycardia. Catheter ablation involves the purposeful destruction or isolation of selective tissue responsible for the tachycardia. Even extensive ablation rarely has a significant effect on cardiac function and may only require lesions that are rather small. Delivery of heat to the tissue via RF energy remains the standard approach in the ablation of most arrhythmias. Cryoablation has



FIGURE 26: Irregularly irregular narrow QRS complex tachycardia is atrial fibrillation with a rapid ventricular response rate

been used with some success in selected patients who have arrhythmias.[76]

RF ablation can successfully cure AVNRT,[77] AVRT,[74] sinoatrial reentry,[78] WPW,[79] Mahaim tachycardias,[80] focal AT,[81,82] AFL,[83,84] and even AFib.[85] Additionally, ablation may be useful for JETs and occasionally for inappropriate sinus tachycardia.[11,86] Ablation can substantially improve the quality of life in patients with SVT.[87] Candidates for ablation include those patients who want their SVT eliminated and for whom the benefits outweigh the risks. The success rates for RF ablation vary by the rhythm disturbance and its location. RF ablation is strongly considered for those patients who have frequent, recurrent and symptomatic episodes that are either fast and/or refractory to the drugs.[88] The age distribution of RF ablation is a bell shaped curve with the average being 27 ± 17 years for accessory pathways and 44 ± 18 years for AVNRT.[75] Data suggests that there is a substantial decrease in frequency and severity of arrhythmias and decrease in self-imposed restrictions.[87] Cost-effectiveness data, based on older studies, indicates that the cost per quality adjusted life-year gained is $6,600 to $19,000.[89-91]

Generally, an electrophysiology study is performed as a diagnostic procedure with an ablation.[92] The procedure includes arrhythmia induction, mapping of the pathways or location, ablation and post-ablation attempts at arrhythmia induction. Conscious sedation is used and 3–5 transvenous catheters are placed. A transseptal approach may be needed to ablate a left-sided accessory pathway or for a left AT or AFL. In some instances, retrograde ablation approaches are performed from the aortic route.

Catheter ablation with a 4 mm tip catheter can eliminate the slow pathway in AVNRT, the accessory pathway in AVRT, and select focal ATs safely and effectively. In most cases, the lesions are focal but for AFL and specific ATs associated with complex macroreentry circuits (including patients with congenital heart disease)[93] linear lesions must be delivered to achieve the success. In rare instances, irrigated tipped catheters or an 8 mm tipped catheter is required to deliver extensive or deep lesions.[94] For younger patients and for specific tachycardias that originate from areas directly adjacent to the AV node, such as JET or in some cases, AVNRT, cryoablation may be safer and yet potentially effective.[95] However, RF generally remains the standard for ablation for most SVTs.

The success rate for ablation of AVNRT and many accessory pathway related SVTs exceeds 95%.[96] For typical AVNRT, the success rate is approximately 98% in experienced laboratories. The success rates for accessory pathway ablation may vary depending upon the location and are between 85% and 99% even for PJRT[45] and Mahaim tachycardias.[97] The recurrence rates after ablation, especially for accessory pathways, can be between 3% and 9%. The success rate for typical AFL is greater than 90% and recurrence rates are less than 10%[83,96] but AFib can follow.[98] The success rates for more unusual or AFib ablation-created AFL is less.[99] Ablation of AT has an approximately 70–90% success rate depending on the location and mechanism of the tachycardia.[100] In some instances, the tachycardias are close to the normal conduction system or in unusual locations.[101-105] The efficacy of ablation for ATs is from 80% to 98% with recurrences between 5% and 20% and complications of 1.6% in one series.[106] AFib ablation is not as successful as ablation of AVNRT or AVRT and complication rates are higher.

TABLE 4

Complications of catheter ablation for SVT (depends on SVT type)

Complications	*Prevalence*
AV block	0.67–1%
Cardiac tamponade	0.22–1.1%
Pericarditis	0.31%
Pneumothorax	0.15–0.22%
Tricuspid regurgitation	0.22%
Acute myocardial infarction	0.15%
Femoral artery pseudoaneurysm	0.15%
Death	0.1%

Complications in ablation include death (0.1%)[107,108] (Table 4). There is approximately 0.4% risk of AV nodal block requiring a pacemaker with AVNRT "slow pathway" ablation. There are also risks of cardiac tamponade, pericarditis, hematoma and deep venous thrombosis. In general, the risks of the procedure are relatively low and all risks are less than 1%. Thus, ablation should be performed in patients who are highly symptomatic and with frequent recurrences, for those who have a high-risk profession, and for those with hemodynamic impairment or cardiomyopathy due to the persistent tachycardia.[92]

CONCLUSION

Supraventricular tachycardia remains a common and often symptomatic problem for many patients. A wide variety of types and clinical presentations of SVT exist. The diagnosis requires careful observation and interpretation of electrocardiographic recordings. Evaluation involves thoughtful assessment of the relationship between the tachycardia, hemodynamics and symptoms. While rarely life-threatening, treatment is often required. Remarkable advances have been made in the treatment of most forms of SVT.

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Chapter 35

Clinical Spectrum of Ventricular Tachycardia

Masood Akhtar

Chapter Outline

- Monomorphic Ventricular Tachycardia
  - — Myocardial VT in Association with Structural Heart Disease
  - — Monomorphic VT in Association with Structurally Normal Heart
- Polymorphic Ventricular Tachycardia
  - — PVT in Association with Long QT Interval
  - — PVT with Normal QT Prolongation
  - — PVT in Association with Short QT Syndrome

INTRODUCTION

In this communication, it is assumed that the clinician has already made the distinction between the various causes of wide QRS tachycardias, of which ventricular tachycardia (VT) is only one, albeit the most common one.[1-4]

As the field of invasive interventional electrophysiology has grown, interest in finding the cellular/molecular basis for arrhythmias has escalated. At this time, however, we clinically deal with myriad complex VTs, often with incomplete understanding and the desire to simplify information for clinical purposes.[5-10] While ultimately VT-VF (ventricular fibrillation) may find a better classification based solely on genetic and cellular knowledge, their definition within the parameters of the current science is still evolving and mostly based on clinical presentation. For all practical purposes, generally only the clinical classifications are used to manage patients. When the word VT is mentioned, a number of natural questions cross one's mind. Is the episode brief or sustained? What are the patient's symptoms? Is there underlying heart disease? In this chapter, we have taken a clinician's approach as practiced today. It is, however, important to realize that, increasingly, new entities are being introduced that may or may not fit into a given classification, and words, like miscellaneous, idiopathic and other descriptive terms, will continue to be used.

Table 1 is an attempt to present a simple and clinically relevant classification. The usual first encounter for an arrhythmologist to a patient with documented VT is a rhythm strip from telemetry, monitor, ambulatory recorder, during device interrogation or, occasionally, a 12-lead ECG (Fig. 1) showing a monomorphic (Panel A) or polymorphic (Panel B) VT. This is a striking feature of VT and is seldom missed by a clinician, unless, in a given lead, the polymorphic nature of the VT is not appreciable. There can be serious consequences for not knowing polymorphic versus monomorphic VT (MMVT). For example, administering an additional dose of an antiarrhythmic drug in the presence of a polymorphic variant of VT may aggravate the situation. Hence, it is prudent to emphasize at the outset that the distinction between the monomorphic and the polymorphic nature of the VT is important and can be deciphered by recording two leads perpendicular to each other.



FIGURE 1: Rhythm strip (V1) shown. Note the monomorphic appearance of the VT in the top panel. P-wave is not clearly visible but its presence is suggested in some ST-T signals. The bottom tracing shows a prolongation of the QT interval, an episode of torsades de pointes, with rapid polymorphic VT of a constantly changing morphology that appears to be twisting around a central axis, which is the literal meaning of torsades de pointes (twisting of the points)

TABLE 1

Clinical spectrum of ventricular tachycardia

Monomorphic VT			*Polymorphic VT*	
SHD Myocardial Fibrosis	No SHD RV outflow	Long QT Congenital (QT-1 to QT-12)	Normal QT Brugada* (Type 1-3)	Short QT Short QT (1-5)
BBR (HPS Disease)	Idiopathic LV-VT	Acquired: Drugs, electrolyte (Table 2)	Active ischemia	
ARVD (RV fatty infiltration) regional and familial forms of ARVD Naxos, Venetian	From Sinus Valsalva, Mitral, Pulmonic Cusp		Myocardial hypertrophy	
VT Post Surgical Scar	Bidirectional		LV Noncompaction	
	Iatrogenic device leads		Catecholaminergic PVT J-wave syndromes early repolarization syndrome hypothermia Idiopathic VF	

(Abbreviations: SHD: Structural heart disease; BBR: Bundle branch reentry; ARVD: Arrhythmic RV dysplasia; RV: Right ventricular; LV: Left ventricular; PVT: Polymorphic ventricular tachycardia; VF: Ventricular fibrillation.
• Regional expressions for Brugada-like syndromes:
— Thailand – Tai Lai (death during sleep)
— Phillipines – Bangungut (scream followed by sudden death-at night)
— Japan – Pokkuri – (unexpected sudden death at night)

Once that distinction is settled, the usual next line of questioning regards the underlying pathology or structural heart disease (SHD) such as ischemia, myopathy, etc. When there is no SHD detected, attention is then directed to various VT syndromes. These somewhat newer entities are currently hard to classify. In the future, expressions, like channelopathies, repolarization syndromes, J-wave abnormalities or other such terminology, will be used routinely, and it seems this trend has already begun.[11,12]

MONOMORPHIC VENTRICULAR TACHYCARDIA

MYOCARDIAL VT IN ASSOCIATION WITH STRUCTURAL HEART DISEASE

Myocardial VT in Association with Fibrosis/Scar[8-10,13-15] (Table 1)

Coronary artery disease (CAD) remains the most common form of VT. Both monomorphic and polymorphic forms exist. However, the monomorphic forms [Fig. 1 (top panel)] are better understood and the underlying mechanism is easier to comprehend. Its distinction from other forms of wide QRS tachycardias has been extensively published.[1-4] The classic model used to visualize this circuit of reentry is depicted in Figure 2.[9] The fibrotic scar zone, shown as islands, the paths of impulse propagation in various directions, is indicated by arrows. On the surface ECG, QRS starts when the impulse exits from within the circuit. If one was to electrically stimulate this exit site, the surface ECG QRS would look identical to the spontaneous VT with a short stimulus artifact to QRS interval (Fig. 3). Depending upon the geometry of the scar, the impulse could go in several directions, dictated by the shape of the scar and the state of the myocardium. As an example shown in Figure 2, the impulse travels in all the directions in a three-dimensional tissue. During activation of a normal myocardium

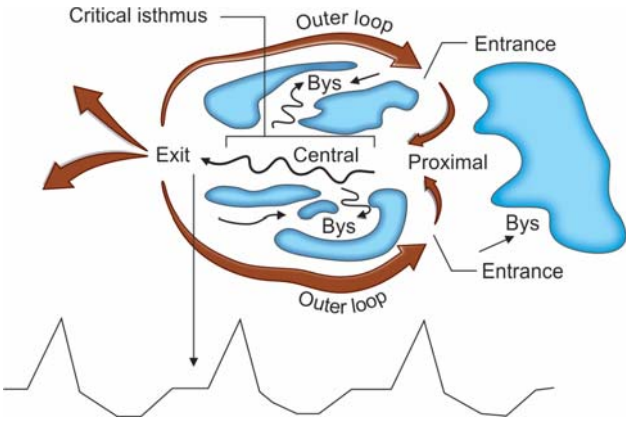


FIGURE 2: Classical model used to demonstrate reentry through the surviving muscle bands among the myocardial scar (shown as five islands). The QRS on the surface ECG starts where the impulse exits from the critical isthmus and turns around in a figure-of-eight fashion to reenter from the proximal end. Ablation at sites other than beside the central blue line is unlikely to be successful. This is why it is termed a critical area of slow conduction or as critical isthmus. (*Source:* Modified from Stevenson W, Soejima K. Catheter ablation of ventricular tachycardia. In: Zipes DP, Jalife J (Eds). Cardiac Electrophysiology: From Cell to Bedside, 4th edition. Philadelphia: WB Saunders; 2004. pp. 1087-96)

the impulse will reenter the circuit at the proximal end or some other points. Depending on its length, the location of surviving myocardial cells within the scar and the speed of conduction, the local electrical signal produced may bear a variable relation with the surface QRS. For example, the interval recorded between the electrogram and pacing artifact from the same catheter site in the critical isthmus to the next QRS will measure the same.[9] However, from the adjacent bystander, the interval from the local electrogram to next QRS will be considerably shorter compared to the pacing to the next artifact QRS interval from the same site. These maneuvers are very helpful in finding the right location for catheter ablation.

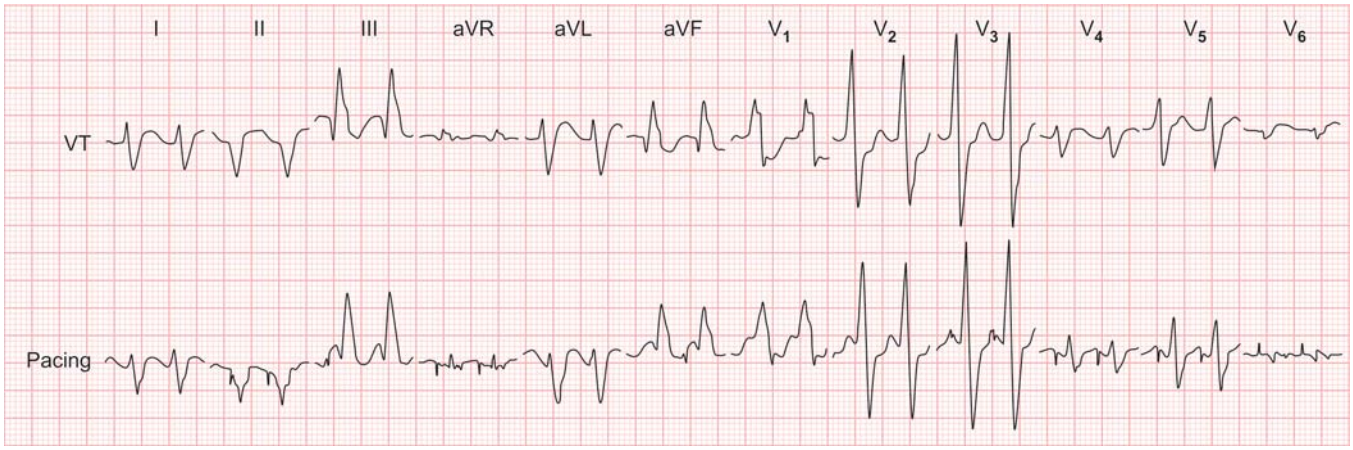


FIGURE 3: Example of spontaneous ventricular tachycardia (VT) recorded on a 12-lead ECG. The bottom shows 12-lead pace map. Note that the QRS is identical to spontaneous VT and the stimulus artifact to QRS is relatively short—best appreciated in leads II, $V_{4–6}$

It should be pointed out that the diastolic interval between the QRS complexes is increased when the reentrant impulse is travelling through the isthmus (surviving muscle band, area of slow conduction), which is critical for the VT to continue. While this electrical activity is not visible on the surface ECG, it can be recorded by placing electrode catheters along the pathway. Penetration of this pathway occurs during sinus rhythm as well, and it can be recorded both by intracardiac recording techniques as well as from the surface by proper magnification and filters (the so-called signal-averaged ECG).[16]

While the actual reentrant circuits may be more complex, the schema shown in Figure 2 gives one broad concept of how a VT can be mapped. When appropriate location of slow conduction is isolated, it leads to a successful ablation using radiofrequency or another form of energy. The baseline ECG is seldom normal in these patients, and likely to be suggestive of some cardiac pathology.

Therapy for a scar-related VT can be manifold:[17,18]

- In patients with an ejection fraction of less than 35%, implantable cardioverter defibrillator (ICD) is advised. The main reason is the prevention of sudden VT-related death from an existing or new arrhythmia (Fig. 4).[19] In many cases, particularly with slow VT ($\geq$ 280 ms), antitachycardia pacing will also terminate an organized MMVT, which is more comfortable for the patient
- With better left ventricular ejection fractions (LVEF), antiarrhythmic agents, particularly Class III drugs, such as sotalol, amiodarone and dronedarone, may be sufficient. In patients with CAD and VT, the addition of beta-blockers is beneficial because the role of ischemia in the initiation and maintenance of VT cannot be excluded with certainty at a given time. In high-risk patients post-myocardial infarction or cardiac surgery, an external defibrillator in the form of a life vest can be recommended

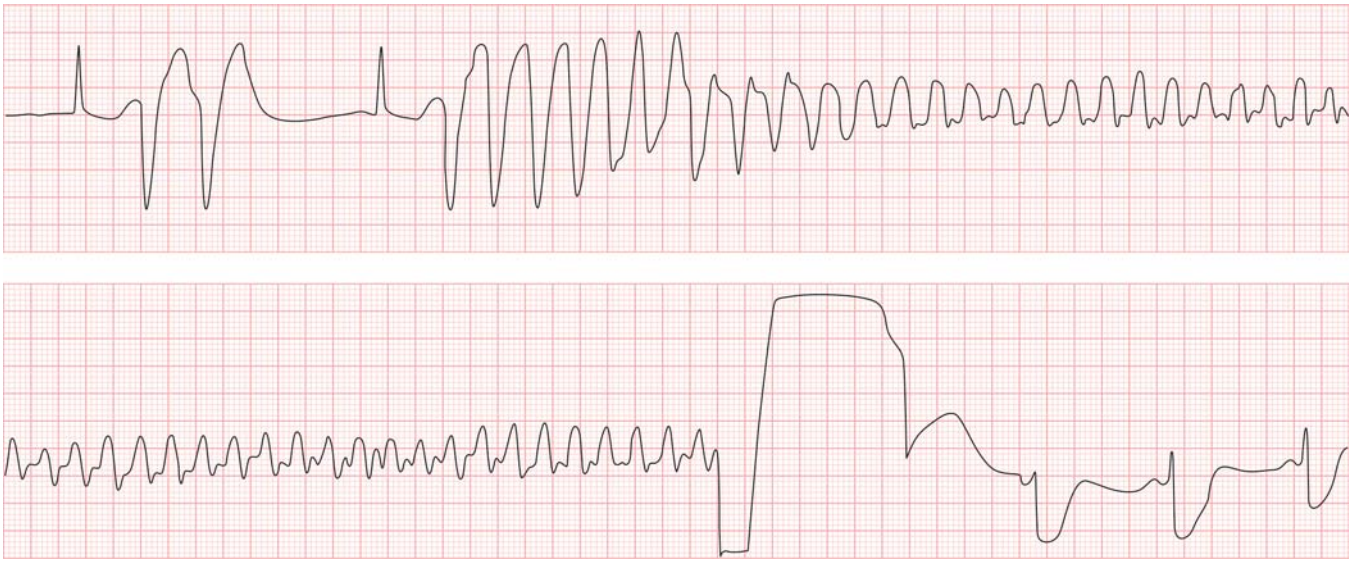


FIGURE 4: The ICD shock and defibrillation. The figure displays the onset of a rapid VT and a period of sensing and defibrillation shock with an ICD and restoration of sinus rhythm. The effect of acute injury from ICD can be appreciated in subsequent sinus complexes. This tachycardia was different than previously documented (*Source:* Tchou PJ, Kadri N, Anderson J, et al. Automatic implantable cardioverter defibrillators and survival of patients with left ventricular dysfunction and malignant ventricular arrhythmias. Ann Intern Med. 1988;109:529-34, with permission)

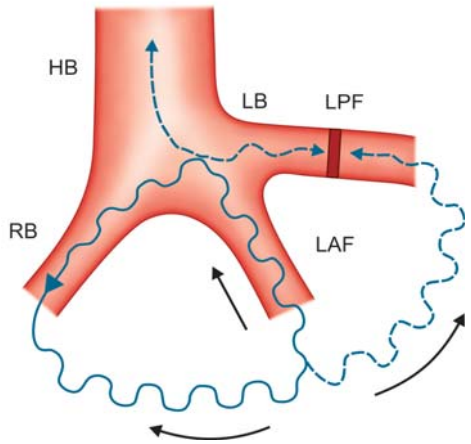
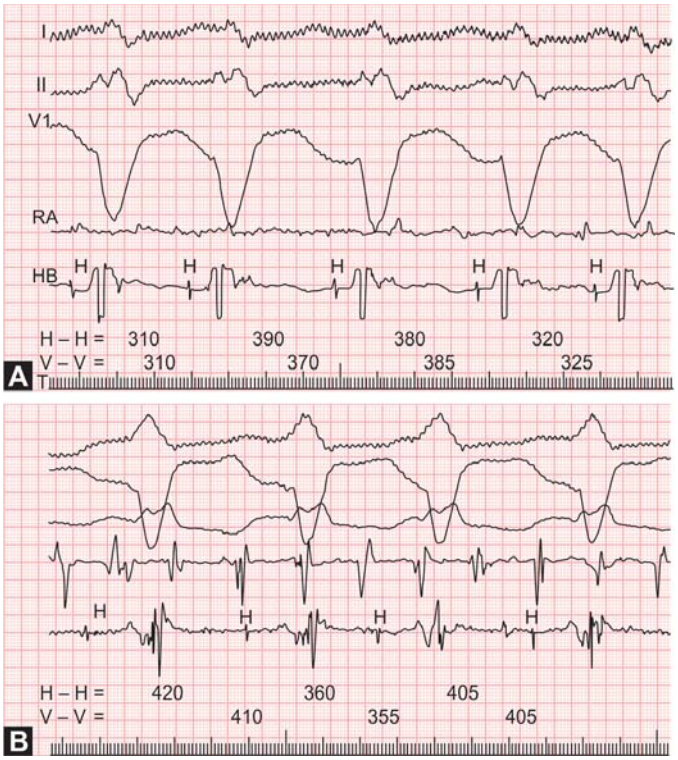


FIGURE 5: Schema demonstrates the circuit of bundle branch reentry VT. In this example, the impulse reaches the right ventricle via the right bundle (RB) and returns to the His bundle through the inferior fascicle of the left bundle (LB). While the same impulse approaches the His bundle via the superior fascicle, the two impulses will collide somewhere in that region. Activation of the His bundle will occur as a necessity since the left and right bundle are connected via the His bundle. The arrows depict the direction of impulse propagation. Tracings from top to bottom in each panel are surface ECG leads I, II and V_1. The intracardiac tracings are HRA (high right atrial electrogram) and HB (His bundle electrogram). Time lines at the bottom are consecutive (Abbreviations: LAF: Left anterior fascicle; LPF: Left posterior fascicle)



FIGURES 6A AND B: Bundle branch reentry with a left bundle branch block pattern (A) and right bundle branch block pattern (B) are shown. The axis is normal in A and leftward in B. The atrial rhythm is atrial fibrillation. Note that His deflection precedes the QRS and the change in the cycle length of H-H (labeled) precedes that of V-V (also labeled). In other words, the His bundle activation drives the ventricle, which is the opposite of what happens in myocardial VT, where the His bundle deflection follows the local V electrogram or is obscured by it. Nonetheless, the V-V cycle drives the H-H cycle in myocardial VT. (*Source:* Blanck Z, Jazayeri M, Akhtar M. Facilitation of sustained bundle branch reentry by atrial fibrillation. J Cardiovasc Electrophysiol. 1996;7:348-52, with permission)

- When VT is incessant, endocardial and/or epicardial mapping and catheter ablation may be necessary
- Although surgical ablation is seldom necessary, it remains an option
- In rare situations, cardiac transplantation with or without ventricular assist devices may be the only option when there are no contraindications

Monomorphic VT due to Bundle Branch Reentry[20-25]

In this form of monomorphic VT, the underlying pathological substrate is the His-Purkinje system, which has markedly prolonged conduction time. More specifically, the right and left bundle branches are used for propagation to the ventricle via one bundle, returning to the His bundle through the contralateral bundle branch. Sometimes the electrical circuit is localized to the two fascicles of the left bundle; in that case it is termed interfascicular reentry. The schema in Figure 5 depicts the reentry circuits and Figures 6A and B shows bundle branch reentry (BBR)-VT, both a left bundle branch block (LBBB) pattern (A) and a right bundle branch block (RBBB) pattern (B). While the general incidence of BBR as the mechanism of MMVT is 6%, it is much higher in patients with idiopathic dilated cardiomyopathy and aortic valve disease.[24-26] In patients with aortic valve disease, this is particularly common in the early post-surgical period.[24] This form of VT is apparently a common finding in patients with myotonic dystrophy, when VT is observed in that population.[25] The common theme among all of the above scenarios is the presence of His-Purkinje pathology manifested by nonspecific intraventricular conduction defect (IVCD), incomplete-to-complete bundle branch block on surface ECG with prolonged H-V interval on the His bundle electrogram recording.[20] Unlike patients with myocardial disease, where the His bundle potential follows QRS, in BBR it always precedes QRS with equal to or longer H-V than sinus, and H-H cycle length changes precede V-V cycle length changes (Fig. 6).

While typically these individuals have low LVEF, BBR can recur in patients without SHD and normal LVEF[27] and in some patients with valvular disease, myocardial dystrophy and preserved left ventricular (LV) function.[24,25] Common to all of the above is the IVCD, and prolonged H-V interval and myocardial damage is not a prerequisite.

The tachycardia morphology is either an LBBB or, less frequently, an RBBB pattern (Figs 6 and 7). Since the reentrant impulse depolarizes the ventricle via the bundle branch, the surface ECG appearance of the QRS has some features common to QRS complex due to aberrant conduction, such as rapid initial inscription of the QRS, unlike the slurred beginning of QRS seen in myocardial VT or pre-excited QRS. These tachycardias are often rapid and poorly tolerated by patients with poor LV function, frequently lead to syncope and may degenerate into VF.

Bundle branch ablation is the preferred therapy in patients with good LV function (Fig. 7), while an ICD should be

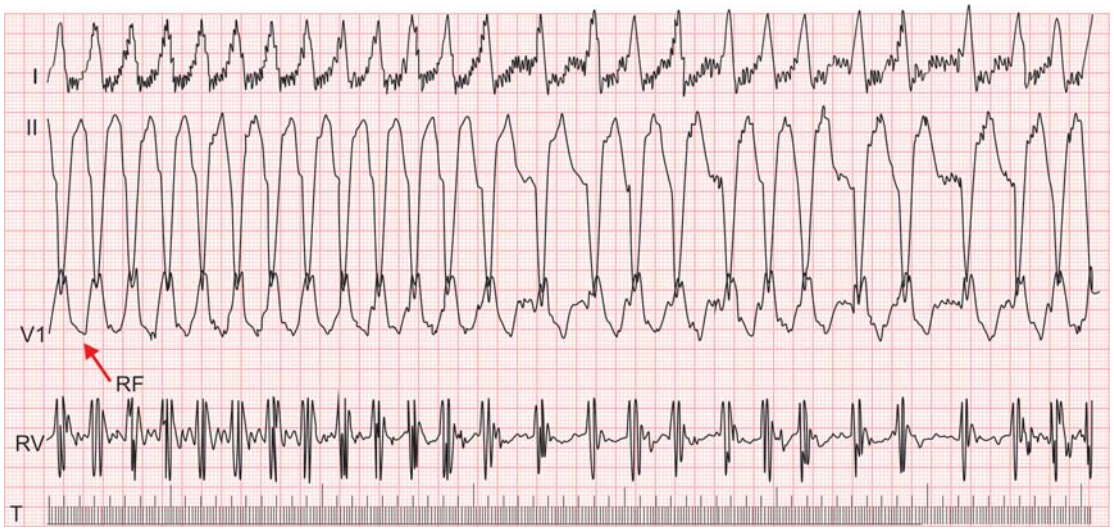


FIGURE 7: Ablation of bundle branch reentry (BBR). The first 13 complexes are due to BBR-VT. The underlying atrial rhythm is atrial fibrillation, which becomes obvious when the VT stops due to right bundle ablation. Note, there is no change in QRS configuration but now the ventricular rate is irregular due to AF

implanted in cases where the LVEF is less than 35%. Although BBR is easily pace-terminable, RBBB ablation may still be necessary in some cases to prevent frequent recurrences.

Monomorphic VT in Association with Arrhythmogenic Right Ventricular Dysplasia[28,29]

In arrhythmogenic right ventricular dysplasia (ARVD), the right ventricular (RV) muscle is replaced by fatty tissue, which in effect creates a model very similar to that shown in Figure 2. The disease may be patchy; affecting only RV apex, outflow or other parts, but may be quite extensive, replacing most RV myocardium with fatty infiltrates. At times the LV may also be affected.

For the most part, the main clinical problem these patients have is with nonsustained or sustained VT with a left bundle branch configuration with variable axis. While any axis may be noted, left bundle and left atrial (LA) morphology is very suggestive of ARVD; surface ECG also characteristically shows T-wave inversion in V_1–V_3 (Fig. 8) and may extend to V_4 or V_5. A late small deflection may be seen at the end of the QRS (epsilon wave) (Fig. 8 inset). Signal-averaged ECG is often positive. Diagnostic work should include magnetic resonance imaging (MRI), which is more sensitive than ultrasound, particularly in the early stages when the dysplasia is patchy.

Several genetic abnormalities are associated with this syndrome. In several areas of the world, such as Naxos (Greece) and the Venetian region (Italy), a large prevalence of these VTs is noted among some families.[30] The VTs generally have a monomorphic configuration, but sudden cardiac death (SCD) may occur. Sotalol and amiodarone have been used to control VT. Catheter ablation is not encouraged due to the risk of perforation. The ICD therapy is recommended for the prevention of SCD. This topic is more extensively covered elsewhere in this book.

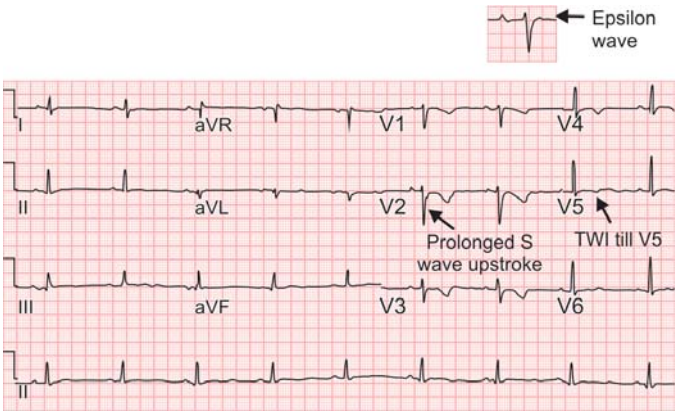


FIGURE 8: Twelve-lead ECG in arrhythmic right ventricular dysplasia (ARVD), the T-wave inversion $V_{1–5}$ (usually up to V_3) and late wave (epsilon wave in the insert) are characteristic findings in the baseline ECG of these patients (*Source:* Nasir K, Bomma C, Tandri H, et al. Electrocardiographic features of arrythmogenic right ventricular dysplasia/cardiomyopathy according to disease severity: a need to broaden diagnostic criteria. Circulation. 2004;110:1527-34, with permission)

Monomorphic VT Post Surgery for Congenital Heart Disease[31,32]

This type of tachycardia is mechanistically akin to a scar-related reentry. Since most of these incisional scars are in the right ventricle, the morphology is likely to be an LBBB configuration and a variable axis, usually right. Associated congenital heart disease (CHD), adhesions post surgery and other factors, such as development of thorax, etc., may create a somewhat atypical QRS configuration, but endocardial mapping will localize the VT in the neighborhood of the scar. Antiarrhythmic drugs and catheter ablation (while they may be sufficient to control the VT), concomitant pulmonary hypertension or pulmonic valve regurgitation would increase the risk for SCD. This scenario may require serious consideration for ICD implant; not an easy decision in this young population.

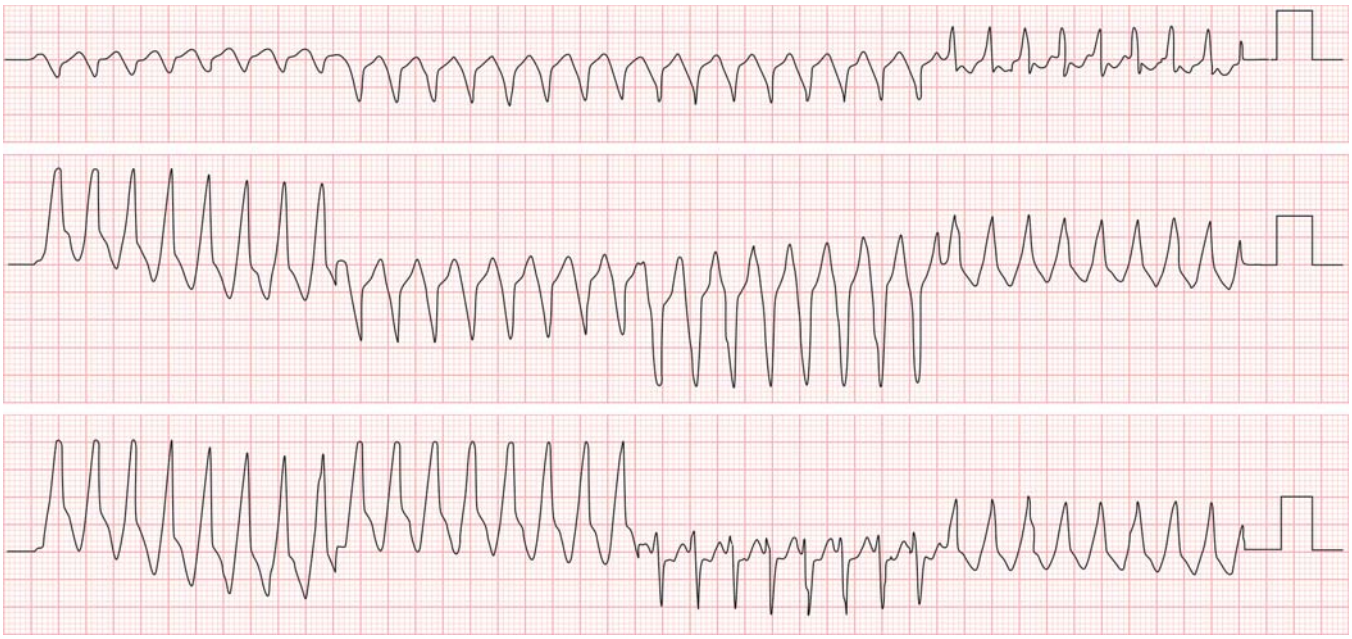


FIGURE 9: Right ventricular outflow tract (RVOT) VT. Typically, VT arises in RVOT. The orientation of the 12-lead ECG is leads I, II and III are on the left from top to bottom. The AVR, AVL, AVF are the next three leads, $V_{1–3}$ and $V_{4–6}$ are next. The same designation is used with all of the 12-lead ECGs unless labeled otherwise. Note left bundle branch block pattern and right axis typical of this type of VT

MONOMORPHIC VT IN ASSOCIATION WITH STRUCTURALLY NORMAL HEART

VT from Right Ventricular Outflow Tract

As the name suggests, the most common location of this VT is outflow which produces a characteristic LBBB and right atrial morphology (Fig. 9).[33,34] If the breakthrough occurs on the left side, an RBBB morphology may be seen. The baseline ECG is usually normal. The process could present in the form of isolated premature ventricular complexes, repetitive MMVT, nonsustained or sustained VT. When RV outflow VT is symptomatic, palpitation, lightheadedness and presyncope are common. Syncope may occur, but SCD is rare in these patients. The mechanism is not completely clear, but the tachycardia often is initiated by isoproterenol. Triggered delayed afterdepolarization driven by catecholamines is the prevailing view regarding the arrhythmogenic mechanism. Clinically increased sympathetic drive, such as physical exercise, often triggers the episode and, not infrequently, beta-blockers may be effective in controlling the VT. Thus, antiarrhythmic drugs, such as sotalol and amiodarone, may also be effective. Considering a good long-term outcome, catheter ablation is increasingly used as a preferred form of therapy. Even though the diagnosis is often clear from clinical data, ARVD should be excluded with MRI prior to catheter ablation.

Idiopathic Left Ventricle VT[35,36]

The electrophysiologic basis of this VT is reentry within the peripheral Purkinje system. The QRS morphology is that of right bundle and LA (Fig. 10), but other ranges of axis are occasionally observed. The baseline ECG and LVEF as a rule are normal. Intravenous verapamil will often terminate the VT but is less effective orally. Class III antiarrhythmic agents, such as amiodarone, are effective, but, at this time, catheter ablation is the first-line treatment considering this VT is easily inducible in the laboratory.

As with RV outflow VT, the ventricle is usually normal. Sudden death is rare but the usual symptoms of arrhythmias, such as palpitations, dizziness and occasional presyncope and syncope, are noted.

Aortic Sinus of Valsalva, Pulmonic, Mitral Cusp VT

Monomorphic VT with right axis occasionally arises from structures outside the traditional ventricular myocardium.[37,38] While they mimic the outflow VT, awareness of these loci helps to improve mapping. Catheter ablation is the usual treatment. Although experience with these types of VT is limited, it is likely that the traditional antiarrhythmic drugs may be successful.

Bidirectional Tachycardia

Bidirectional tachycardia seen with digitalis toxicity is rare, but is seen in the early stages of the exercisein patients with catecholaminergic VT (discussed later). Its classic picture is that of two sets of monomorphic QRS complexes alternating in QRS morphologies. In a sense, bidirectional tachycardia has not a true polymorphic but rather a pleomorphic appearance.

Iatrogenic VT

Whenever a lead is placed in the ventricle, it is not surprising that a monomorphic VT from mechanical movement may be created that can be mistaken for a spontaneous VT, particularly with ICD leads since these patients also have clinical VT. Whenever a resistant VT is found with morphology that could be generated from the location of the catheter, nothing but catheter withdrawal and repositioning will fix this type of VT,

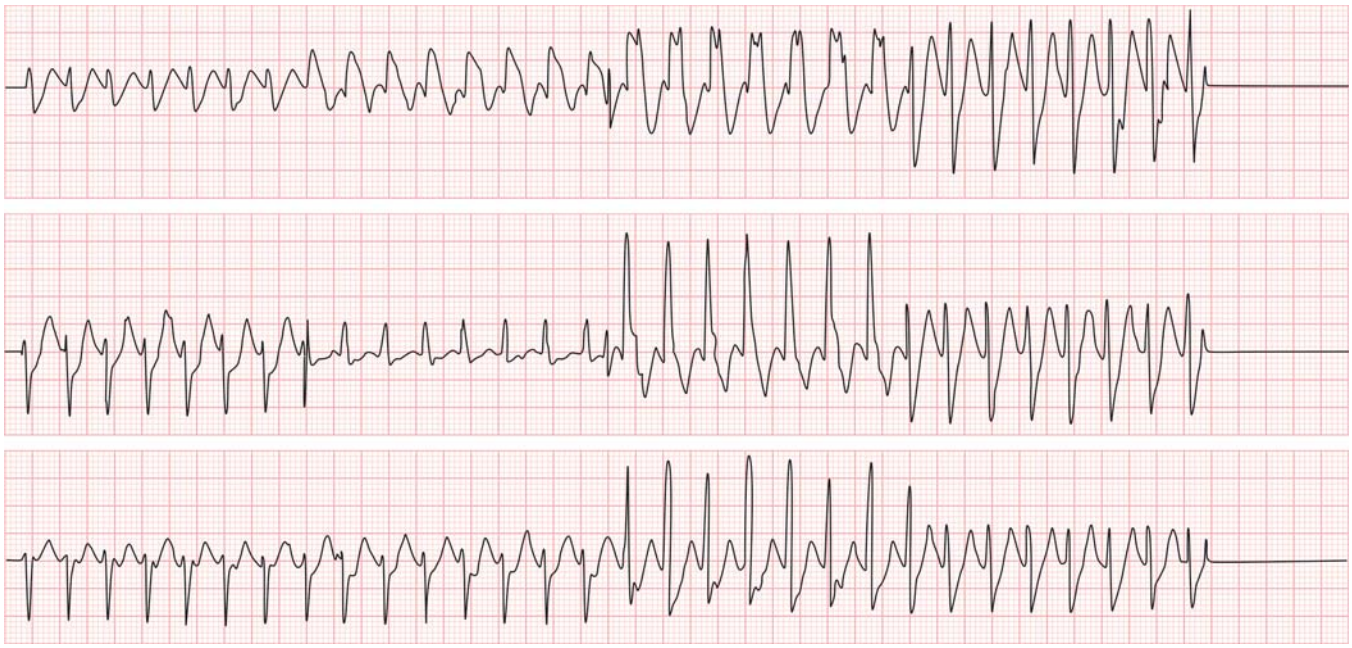


FIGURE 10: Idiopathic left ventricular VT. The typical QRS morphology is that of right bundle branch block and left-axis pattern. Note the initial part of the QRS has rapid inscription due to the fascicular origin of this VT. Contrast this with Figure 9 where the initial part of the QRS has a slow inscription

so keeping this in mind is important as part of the differential diagnosis in patients with device implant.

POLYMORPHIC VENTRICULAR TACHYCARDIA

Polymorphic ventricular tachycardia can be broadly separated into three categories: (1) PVT in association with long QT interval; (2) PVT in association with normal QT and (3) VT in association with short QT interval. Long QT itself has been traditionally divided into congenital and acquired forms.

PVT IN ASSOCIATION WITH LONG QT INTERVAL (TABLE 1)

Congenital Long QT Interval Syndrome[39-42]

At this writing, at least 12 entities (QT-1–12) have been described here briefly, as long QT syndrome is covered elsewhere in the book. Other less-understood entities will not be discussed here.

QT-1: QT-1 is the most common form [Fig. 11 (left panel)]. The recessive variety may be associated with deafness. The PVT is typically triggered with physical activity, emotional stress, diving and swimming. Syncope, presyncope and SCD are the most serious clinical manifestations. The surface ECG shows a broad, prolonged T-wave and a long QT interval (Fig. 11). Early onset of symptoms, syncope, excessive QT prolongation is more than or equal to 550 msec in QT-1 and QT-2, and males with QT-3 are associated with a high risk of SCD (Fig. 11). Nonselective beta-blockers, such as propranolol and nadolol, are preferred, but others have been used. A dose of propranolol (5 mg/kg is usual) and avoidance of triggering events, such as adrenergic stress or diving, is highly recommended. Drugs that prolong QT (Table 2) and electrolyte imbalance, such as hypokalemia, can be lethal in this population with prolonged QT syndrome.

The gene involved in QT-1 is $KCNQ^1$ and affects K^+ current (delayed rectifier current 1Ks), which is reduced, causing the lengthening of QT [Fig. 11 (left panel)]. If a proband is found, it is likely that a high percentage of blood relatives may carry the abnormal gene. Genetic screening should be recommended. Beta-blockers are effective in controlling the symptoms. Left stellate ganglionectomy has been successful in controlling symptoms. In patients with malignant manifestation, i.e. SCD or PVT-related syncope, ICD should be seriously considered.



FIGURE 11: Congenital long QT (LQT). The three most common genetic varieties are shown. The corresponding chromosomes are labeled. See text for other details. (*Source:* Moss AJ, Zareba W, Benhorin J, et al. ECG T-wave patterns in genetically distinct forms of the hereditary long QT syndrome. Circulation. 1995;92:2929-34, with permission)

QT-2: QT-2 [Fig. 11 (middle panel)] is the second most common, and carried by 1Kr (delayed rectifiers), which encodes the gene KCNH2. The QT is prolonged as expected, but the T-wave is somewhat flat and less pronounced than QT-1. While adrenergic stress remains important, auditory stimuli in particular may trigger malignant arrhythmia.

QT-3: Compared to QT-1 and QT-2, QT-3 is less common but has a worse outcome. The QT-3 is prolonged [Fig. 11 (right panel)] due to increased inward Na^+ current. The Na^+ channel is encoded by the gene SCN5A and, consequently, the ECG shows a prolonged ST segment, short T-wave and a long QT

TABLE 2

Abbreviated list of drugs reported to cause prolongation of the QT interval or torsades de pointes

Antiarrhythmic:	
Class 1A	Disopyramide, procainamide, quinidine
Class III	Amiodarone, bretylium, sotalol, dofetilide, ibutilide
Antimicrobial	Erythromycin, trimethoprim-sulfamethoxazole, clarithromycin
Antifungal	Fluconazole, ketoconazole, itraconazole
Antimalarial or antiprotozoal	Chloroquine, halofantrine, mefloquine, pentamidine, quinine
Antihistamine	Astemizole, terfenadine, diphenhydramine
Gastrointestinal prokinetic	Cisapride
Psychoactive	Chloral hydrate, haloperidol, lithium, phenothiazines, pimozide, tricyclic antidepressants
Anti-human immunodeficiency virus	Efavirenz
Miscellaneous	Amantadine, indapamide, probucol, tacrolimus, vasopressin

Source: Modified from El-Sherif N, Turitto G. Torsades de pointes. In: Zipes DP, Jalife J (Eds). Cardiac Electrophysiology: From Cell to Bedside, 4th edition. Philadelphia: WB Saunders; 2004. pp. 687-98

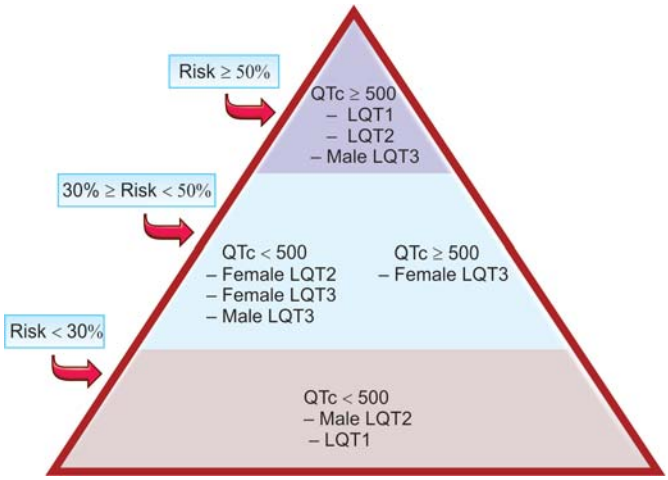


FIGURE 12: A pyramid showing risk stratification in congenital long QT (LQT) syndrome. (*Source:* Modified from Schwartz PJ, Priori SG. Long QT syndrome: genotype-phenotype correlations. In: Zipes DP, Jalife J (Eds). Cardiac Electrophysiology: From Cell to Bedside, 4th edition. Philadelphia: WB Saunders; 2004. pp. 651-9

interval. Prognosis without therapy is poor, particularly in young males (Fig. 12). Bradycardia is one of the main triggers, such that the most fatal events occur at night or during sleep. The role of beta-blockers is still controversial and, without bradycardia support (i.e. pacemaker), somewhat risky. Patients who have exhibited symptoms due to PVT, such as syncope or cardiac arrest, should have ICD implantation. The role of gene-specific drugs and other agents that shorten the QT interval, such as mexiletine, has not been systematically studied sufficiently to be utilized as the sole therapy for prevention of SCD. Risk stratification among patients with congenital long QT is shown in Figure 12.

Acquired Long QT Syndrome

Although the exact underlying etiology of acquired long QT is not understood, it is widely believed and sometimes reported that a genetic basis with low penetrance may account for some of these cases.[43,44] An external trigger, such as an antiarrhythmic drug, electrolyte imbalance, etc., is required for the clinical manifestations of this form, i.e. prolongation of QT and torsades de pointes.

There are an increasing number of pharmaceutical agents that have been documented to be the culprit (Table 2). In addition to the Class I or Class III antiarrhythmic drugs [Fig. 1 (top panel)], many other agents and situations have produced similar adverse affects. Low Mg^{++}, Ca^{++} and K^{+} may trigger torsades de pointes in vulnerable populations. Some drugs, by blocking or binding with certain liver enzymes, may lower metabolism, raising the blood level of the parent compound that in turn may produce prolonged QT and torsades de pointes.

Acute treatment is usually the administration of IV Mg^{++}, which often effectively halts torsades, but recognizing and discontinuing the offending agent is usually sufficient. Isoproterenol infusion and overdrive pacing are also used to stop the torsades de pointes. Patients are advised to avoid similar agents and situations, such as over-the-counter medication, where the contents are not clearly labeled. This aspect of long QT is important to realize because the blood relatives of a person with congenital long QT may be prone to the same hazards and a caution regarding this possibility may be wise.

PVT WITH NORMAL QT PROLONGATION

Brugada Syndrome

Brugada syndrome was initially described by the Brugada brothers as the presence of an injury pattern in leads V_1 and V_2 with ST elevation followed by T-wave inversion (Fig. 13) and a history of syncope and SCD.[45-48] Since then, more has been learned regarding the role of ionic currents, the underlying mechanism and the worldwide prevalence of this potentially malignant syndrome.

The exact preponderance is unknown, but Pokkuri in Japan, Bangungut in the Philippines and Tai Lai in Thailand seem to be the same affliction (Table 1). Mostly seen in young males, death from PVT-VF occurs at night. The ECG abnormalities (Fig. 13) may not always be present. However, Class I agents, such as ajmaline and procainamide, can unmask the abnormality. In many cases, the genes that encode SCN5A can be detected. Quinidine has been identified as a potentially effective agent to prevent SCD in this population. However, ICD remains the most reliable therapy to prevent PVT-VT related deaths in patients with Brugada syndrome.

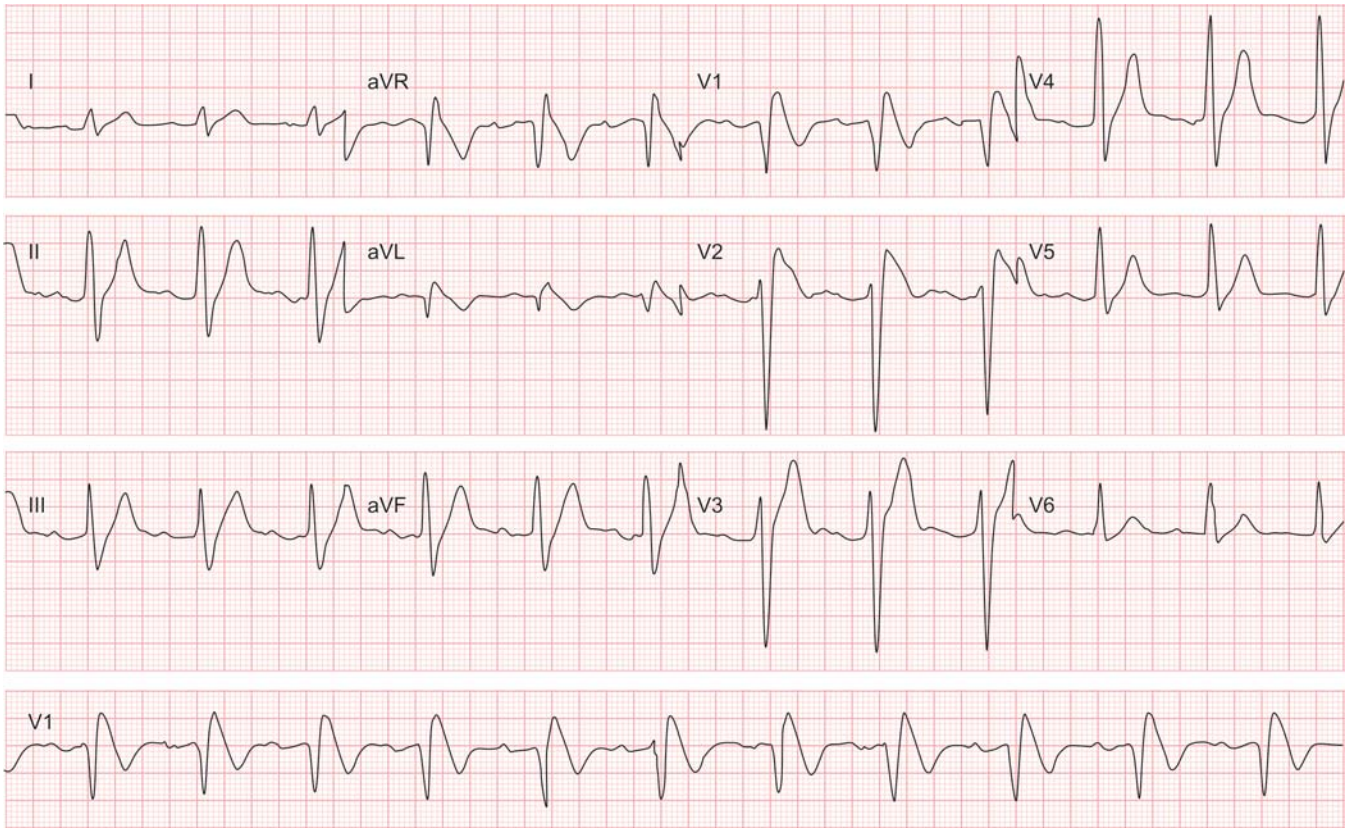


FIGURE 13: Typical 12-lead ECG of Brugada syndrome. The most characteristic features are seen in leads V_1 and V_2. ST elevation and T-wave inversion gives the impression of a right bundle branch block pattern (*Source:* Modified from Dorian P, Bharati S, Myerburg RJ, et al. Ventricular fibrillation. In: Saksena S, Camm AJ (Eds). Electrophysiological Disorders of the Heart. New York: Churchill-Livingston; 2005. pp. 419-53

Active Ischemia

In patients with clinically significant CAD, some degree of ischemia may exist at all times, but a critical degree of ischemia with exercise, spontaneously or with spasm, can induce a PVT-VF. This is a highly malignant arrhythmia and usually fatal unless it stops spontaneously or is terminated. Anti-ischemic therapy and revascularization are the preferred treatment modalities. The tracing in Figure 14 is from a 60-year-old male who underwent coronary artery bypass grafting, was continued on beta-blockers and still had 3–4 episodes of VT per year.[5] He received an ICD, which intervened several times over the years. This occurred primarily due to incomplete revascularization—partly due to some areas of inoperable disease, not an infrequent clinical scenario.



FIGURE 14: Polymorphic ventricular tachycardia (top panel) and onset of VF (bottom panel) in a patient with CAD post-coronary artery bypass surgery. Incomplete revascularization may lead to this and, in patients present with VF, ICD may still be necessary. (*Source:* bottom panel Akhtar M. Clinical spectrum of ventricular tachycardia. Circulation. 1990;82:1561-73, with permission)

Acute ischemic-related PVT-VF should be addressed promptly since patients have died while waiting for revascularization. Three decades ago, large infarcts resulting in aneurysms were associated with monomorphic VT. With early intervention and the use of several effective anti-ischemic agents, large infarcts and ventricular aneurysms are less frequently encountered. The PVT seems to be more common. Since it degenerates into VF quickly, the true incidence of PVT is difficult to estimate, but it certainly constitutes a significant cause of the SCD from CAD.

Myocardial Hypertrophy

The VF and consequent SCD remain one of the main causes of cardiovascular death in patients with hypertrophic cardiomyopathy.[49] Apical hypertrophy has a particularly malignant outcome. Syncope, near-syncope and nonsustained VT define a particularly high-risk population. The SCD is seen in both obstructive and nonobstructive forms. High-risk patients should be considered for ICD therapy, both for primary and for secondary prevention of SCD.

LV Noncompaction[50]

Isolated LV noncompaction (LVNC) is a rare myopathy, primarily of autosomal inheritance. The main structural abnormality is intrauterine failure of LV muscle compaction.



FIGURE 15: Progressive increase in ventricular ectopy as the exercises load increases. The 4th panel shows bidirectional tachycardia, and the last two panels show further polymorphism during recovery phase of exercise (*Source:* Modified from Napolitano C, Priori SG. Catecholaminergic polymorphic ventricular tachycardia and short-coupled Torsades de Pointes. In: Zipes DP, Jalife J (Eds). Cardiac Electrophysiology: From Cell to Bedside, 4th edition. Philadelphia: WB Saunders; 2004. pp. 633-9)

The main clinical manifestations are congestive heart failure and ventricular arrhythmias with around 20% incidence of SCD.

Catecholaminergic PVT[51,52]

Catecholaminergic PVT (CPVT) can be a dominant or recessive inheritance, mostly manifested in childhood or young adults. The heart is structurally normal as is the baseline ECG. Adrenergic drive brings out characteristic bidirectional [Fig. 15 (4th panel from top)] or PVT. There is a high incidence of SCD (> 30% mortality by age 30). The basis is mutation in the genes, encoding ryanodine receptor 2 (RyR2) or calsequestrin 2 (CASQ2) triggering activity from delayed afterdepolarization due to abnormalities of Ca^{++} handling, which is responsible for arrhythmogenesis. The conversion to PVT is most likely related to transmural dispersion of repolarization between the various myocardial layers. Degeneration to VF is the most likely cause of SCD.

J-Wave Syndromes[12,53,54]

This category includes several entities, where the individuals are prone to arrhythmic death. The primary defect seems to be imbalance of current during Phase 1 of the action potential producing Phase 2 reentry leading to VF. Some examples include Brugada syndrome, early repolarization, short QT syndrome and perhaps many cases of so-called idiopathic VF. Rapid outward current plays a significant role and may be the reason that quinidine, which blocks K^+ current, is effective in preventing recurrence. This subject is covered in greater detail elsewhere in this book.

Idiopathic VF

This fascinating entity is described in greater detail by Belhassan and Viskin, and is associated with identifiable SHD.[55] It is characterized by the occurrence of spontaneous VT with inducible PVT and VF, which respond to oral guideline both in the electrophysiology laboratory (i.e. not inducible after drug) and in the excellent clinical response seen over many years. Nonetheless, as Brugada syndrome and the various J-wave syndrome have been described, it is not clear how many of these cases will continue to be called idiopathic.

PVT IN ASSOCIATION WITH SHORT QT SYNDROME[56,57]

This topic is somewhat new and with very limited experience and follow-up. Figure 16 shows an example of short QT, usually

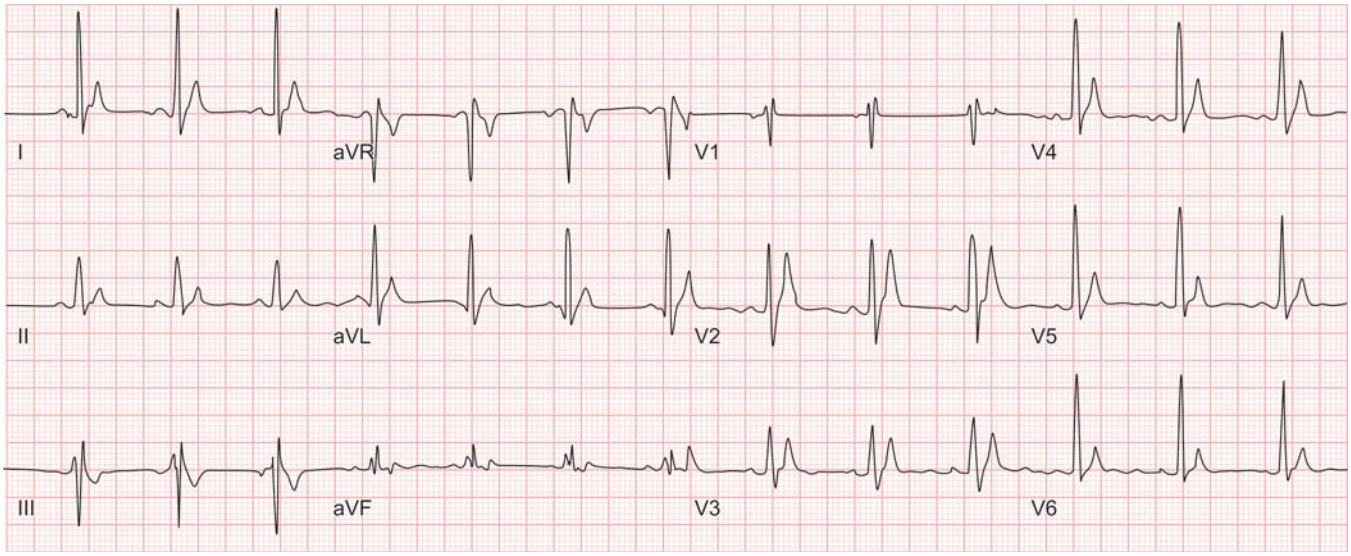


FIGURE 16: Example of a short QT, which can lead to fatal arrhythmia. The coexistence of short QT and Brugada has also been described (*Source:* Bjerregaard P, Gussak I. Short QT syndrome: mechanisms, diagnosis and treatment. Nat Clin Pract Cardiovasc Dis. 2005;2:84-7, with permission)

described as QT less than 300 msec, but some cases with similar genetic mutation had QT of 320 msec. At least five mutations have been described.

The foregoing outline is a summary of VT as the subject is clinically viewed. For a comprehensive review and ACC/AHA/ESC guidelines on work-up and management of VT, the reader is referred to the most recent literature.[17,18]

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Chapter 36

Bradycardia and Heart Block

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Chapter Outline

- Conduction System Anatomy and Development
- Bradycardia Syndromes/Diseases
  - Iatrogenic and Noncardiac Causes
  - Familial
  - Vagal Tone
  - Cardiac Transplantation
- Clinical Presentation
- Measurement/Diagnosis
- Sinus Node Disease
  - Sick Sinus Syndrome
- AV Node Disease
  - Pathology
  - First-Degree AV Block
  - Second-Degree AV Block
  - Third-Degree AV Block
  - Paroxysmal AV Block
- Hemiblock
- Bundle Branch Block
  - LBB Block
  - RBB Block
- Treatment

INTRODUCTION

Bradycardia is generally defined as a heart rate less than 50 beats per minute. However, this simple definition is a gross oversimplification of what is a multifaceted and multifactorial issue. Bradycardia is a dichotomy of sorts, in some cases being a marker of excellent cardiovascular fitness, or conversely, a sign of cardiovascular disease, especially when it is symptomatic.

CONDUCTION SYSTEM ANATOMY AND DEVELOPMENT

On the most basic level, the normal specialized electrical tissue is comprised of the sinoatrial (SA) node (dominant pacemaker), atrioventricular (AV) node and His-Purkinje system. Embryologically, the conduction system of the human heart begins very early in development, with an ECG recording at 4–6 weeks gestation being similar to what is seen in an adult.

The SA node, first described by Keith and Flack in 1907, is located in the lateral right atrium in the sulcus terminalis. It is first noted at around 20 days into embryonic development, when a primitive SA node is formed in the slow-conducting inflow region of the heart. The inflow region is initially bilateral, with the developing heart's pacemaker on the left side. By 35 weeks, the SA node becomes a more distinct entity in the posterolateral region of the early four-chambered heart's right atrium, with impulses directed with a posterior to anterior vector, toward the AV node. Even after completion of its development, and into adulthood, the SA node is a heterogeneous structure, and essentially a loose collection of cells. Only a portion of these cells act as initiating pacemakers; the rest conduct the signals sent to them. There is also a hierarchy of pacemakers, with overdrive suppression by those with faster rates, of those with lower rates (the AVN and His-Purkinje).

The AV node itself located along the interatrial septum in the Triangle of Koch—which is composed posteriorly of the tendon of Todaro, and anteriorly by the septal leaflet of the tricuspid valve and inferiorly by the coronary sinus os—is also formed around 5 weeks into embryonic development. Like the SA node, it exhibits its conduction properties in its adult role prior to being noted as a distinct identifiable entity.

The His bundle is located anteriorly to the compact AV node along the interatrial septum and near the AV groove. The Purkinje fibers continue from the His into the ventricles and divide into the right, left anterior and left posterior fascicles. Embryologically, the cells making up the His-Purkinje system are derived from already present cardiac myocytes, differentiating into conduction system cells after exposure to endothelin. Interestingly, in animal models, the conduction system is present and functioning prior to coronary vessel formation.[1–5]

BRADYCARDIA SYNDROMES/DISEASES

IATROGENIC AND NONCARDIAC CAUSES

Before considering intrinsic conduction disease, in light of many patients living with multiple medical comorbidities as well as complex medical regimens being commonplace, it is of utmost importance to consider iatrogenic and noncardiac causes of bradycardia and heart block.

TABLE 1

Common noncardiac and iatrogenic causes of bradycardia and heart block

Cardiac medications	*Noncardiac medications*	*Medical disease*
BARBs (including eye drops)	SSRIs	Lyme disease
Calcium channel blockers	Opiates	Renal/Hepatic disease
Digoxin	Succinylcholine Lithium	Hypothyroidism Carotid hypersensitivity
Amiodarone	Cholinesterase inhibitors (e.g. donepezil for Alzheimer's)	Renal/Hepatic disease
Sotalol	Propofol	Endovascular cooling after cardiac arrest
Sodium channel blockers		
Clonidine		

First, in terms of medications, the most common agents related to this issue are those already diagnosed for cardiovascular disease including tachycardias. Examples include beta-adrenergic receptor blockers (BARBs, both ophthalmologic and oral),[6] calcium channel blockers, digoxin[7] and clonidine[8,9] (Table 1).

Noncardiac medications as culprits include lidocaine spray or topical such as is used for endoscopic procedures,[10] selective serotonin reuptake inhibitors (SSRIs) such as escitalopram,[11] cholinesterase inhibitors (via enhancement of vagal tone) commonly used for treatment of Alzheimer's disease[12] and succinylcholine.[13]

Propofol is a commonly used sedation agent which, in rare cases, may lead to the development of propofol infusion syndrome. This includes a sudden-onset of bradycardia and possibly asystole, with other effects such as fatty liver, metabolic acidosis or rhabdomyolysis. Risk factors include prolonged (> 48 hours) use at high doses, patient age less than 19 years and low carbohydrate reserves.[14]

In terms of medical syndromes, potential causes include: hypothyroidism; Lyme disease;[15] endovascular cooling after cardiac arrest;[16] and renal or hepatic disease. The latter two are more related to decreasing medication clearance and metabolism, thus increasing serum drug levels and potentiating a drug's effect. This is especially salient with digoxin and renally cleared BARBs such as atenolol. Again, it is important to note that medication and medical disease-related bradycardia and heart block are potentially reversible, that is why these need to be considered early in the differential diagnosis.

FAMILIAL

Development of the cardiac conduction system does not always occur in a normal fashion. When mutations occur, different syndromes may develop. One example of this (specifically related to sinus bradycardia) is familial sinus bradycardia. In a recent paper, the HCN4 channel (located near the cAMP-binding site) was identified as the mutation causing this syndrome, which acts much like a vagally mediated bradycardia.[17]

VAGAL TONE

Although the cardiac conduction system is primarily derived from myocardial cells and not neural crest cells (which differentiate into neural tissue), there is still a rich two-way interaction with the nervous system communication. In 1867, von Bezold first described cardioinhibitory reflexes initiating from the heart itself. It was found that receptors located primarily in the posterior left ventricle, sensitive to mechanical stretch or certain chemicals, when stimulated, increase parasympathetic and decrease sympathetic tone via the vagus nerve, resulting in—among other reactions—sinus bradycardia.[18]

This mechanism may cause bradycardia commonly in diverse situations, all of which could be called vaso-vagal reactions since they may be triggered by psychiatric stressors like fear or sight of blood as well as volume depletion from many etiologies. The fact that animal models show similar responses with, for example, hemorrhage suggests that this mechanism may be in most or all humans as well. Therefore most physicians will see bradycardia due to this mechanism which is best prevented and treated by increasing vascular volume.

Interestingly, trained athletes, especially elite ones, frequently have asymptomatic bradycardia.[19] Commonly elite athletes may also have orthostatic hypotension. Rarely, vagally mediated bradycardia severe enough to cause presyncope or syncope may also (somewhat paradoxically) be seen in trained athletes, where high vagal tone assists in rapid post-exercise heart rate recovery, but in some cases may go too far in lowering heart rate, causing symptoms.[19] The sinus node as well as the subsidiary pacemakers may be influenced by this vagal tone, at times leading to asystole. Nevertheless, the vagal influence never permanently stops the heart; it only delays its next beat for a matter of seconds. Meantime, in this brief period of time, syncope may occur because of loss of cardiac output as well as peripheral resistance.

CARDIAC TRANSPLANTATION

In post-cardiac transplant patients, bradycardia—specifically sinus bradycardia—occurs in approximately 18% of patients, and ultimately 4–7% require a permanent pacemaker (usually atrial pacing only). One of the primary risk factors for development of sinus bradycardia is ischemic time.[20] Another related risk factor is surgical technique, with biatrial anastomosis (Shumway-Lower) resulting in less ischemic time, but increased risk of physical damage to the SA node, while the bicaval (Wythenshawe) approach keeps the atria intact, but increases ischemic time.[21–24] Other risk factors for post-transplant bradycardia include SA nodal artery lesions and transplant vasculopathy.[25,26]

Due to vagal and sympathetic denervation resulting from the surgical procedure, these patients have relative bradycardia and some degree of chronotropic incompetence, but are somewhat shielded from bradycardia by the standard definition due to high intrinsic heart rate. The transplanted ventricle increases stroke volume to compensate for the lack of sympathetically increased heart rate with exercise; even though cardiac output may be normal at rest the transplant cannot increase HR enough to make up for the lesser heart rate with

exercise. Reinnervation can occur, but the extent to which it happens varies from patient to patient.

CLINICAL PRESENTATION

Depending on the patient's heart rate and robustness of so-called "back-up" pacemakers, patients may entirely be asymptomatic, symptomatic with exertion only or at rest. Common symptoms include lightheadedness, dizziness, syncope, palpitations, shortness of breath at rest, dyspnea on exertion, angina, and progressive lower extremity edema.

MEASUREMENT/DIAGNOSIS

The diagnosis of bradycardia, regardless of the mechanism, is primarily made by obtaining an ECG or rhythm strip from surface leads at the time of symptoms. Other times, bradycardia may be found serendipitously by an ECG or telemetry strip performed for other reasons. When a patient's symptoms suggest an arrhythmia of a low rate, occur paroxysmally, and the patient has a normal ECG or rhythm strip at presentation while asymptomatic, monitoring via a Holter (24 or 48 hour) if symptoms occur daily, a 21+ day event recorder if occurring monthly, or if rarely occurring but with significant symptoms at the time of the event, an implantable loop recorder may be appropriate. These methods of measurement are discussed in this textbook in more detail.

Another issue in diagnosing bradycardia is relative bradycardia, also known as chronotropic incompetence. This describes a scenario where at rest, the patient does not demonstrate significant symptoms, but with exertion, is unable to mount an appropriate heart rate to increase cardiac output appropriate for increased needs of exercise. A common definition of this is failure to obtain greater than 85% of age-predicted maximum heart rate with exercise testing. A postulate for an etiology is decreased responsiveness of the heart to increased sympathetic input. Evaluation is primarily via exercise testing. In some cases, direct measurement of cardiac output is performed via right heart catheterization before, during and after temporary pacing at higher rates than baseline; if cardiac output significantly improves with a modest increase in heart rate, then chronotropic incompetence may be assumed.[27]

SINUS NODE DISEASE

SICK SINUS SYNDROME

Sick sinus syndrome (SSS), in its most rudimentary sense, is defined as sinus node dysfunction which results in an inadequate heart rate physiologically, and may include sinus bradycardia, sinus arrest, or sinus node exit block, and may lead to takeover of cardiac pacemaking and atrial contraction by subsidiary intrinsic cardiac pacemaker sites. The mere present of SSS without symptoms is not an indication for any therapy, but cautious use of agents listed in the Table 1.

In a clinicopathological study of six cases of SSS in patients ranging 69–91 years of age, Sugiura et al. found that in patients with SA block and bradycardia-tachycardia syndrome, the SA node and AV node regions showed 70–80% decrease in nodal cells, infiltration of the SA node by connective tissue and left bundle branch (LBB) fibrosis.[28] SSS has also been reported to be caused by cardiac lipomatosis.[29]

During ageing, the sinus node itself changes. A rat model comparing what was equivalent to a young adult and 69 year old showed that in older animals, the heart rate is lower, the pacemaker action potentials were slower, more widely distributed (enlargement of the SA node), and located more toward the inferior vena cava in the RA. Moreover, histologically, the SA nodal cells demonstrated hypertrophy and extracellular matrix remodeling.[30]

The I(f) "funny" current, although first discovered more than 30 years ago, has recently been found, albeit controversially, to have a significant role in spontaneous cardiac pacemaker activity. Basically, these channels determine the slope of phase 4 (depolarization), thereby playing a role in the frequency of cardiac pacing. A mutation in the HCN4 gene, which encodes this channel, demonstrates sinus bradycardia. Thus an abnormality in this channel may be at least partially at fault for some sinus bradycardias.[31]

Recently, genetic factors related to this disease have been elucidated, specifically SCN5A mutation related functional loss of the sodium channel.[32]

In terms of association with other conduction diseases, a recent retrospective study suggests Brugada-type ECG and Brugada syndrome are associated with SSS; 2.87% had Brugada-type ECGs (0.82% with Type I, and 2.05% with Type II). Generally, in the population at large, in recent studies, the prevalence has ranged from 0.07% (7/10,000) in a Danish population[33] and 0.012% (120/10,000)[34] to 0.14%.[35] Moreover, in the above noted study, during a 7-year follow-up period, 50% of those with Type I and none of those with Type II ECGs experienced VF events. Thus, SSS is associated with an increased prevalence of Brugada-type ECG and Brugada syndrome compared to the general population. This may be associated with the aforementioned SCN5A mutations.

Wu et al. performed EP studies in 38 patients with SSS. The mean sinus pause was 5.6 +/- 2.8 sec. Three predominate groups were discovered. Nine patients had SA block, with sinus node function intrinsically noted during pauses. Seven had unidirectional exit block, and two others bidirectional, all of which had evidence of an atrial impulse to conduct into the SA node and inhibit SA node firing. A second group of 22 patients showed slow 1:1 conduction, second degree SA node exit block, with 17/22 patients showing abnormal sinus node recovery times. A third group had no sinus node electrograms measurable.[36]

Frequently patients will have symptoms shown to be due to sinus bradycardia, but careful clinical evaluation will reveal that symptoms began upon institution of BARBs or other drugs listed in the Table 1. Usually the symptoms will resolve if the offending drug can be discontinued or replaced by one which does not aggravate SSS.

AV NODE DISEASE

PATHOLOGY

The most common cause of permanent AV block is idiopathic bundle branch fibrosis. This may include the main AV bundle

and LBB, as a result of aging fibrosis of the cardiac skeleton, referred to as Lev's disease, or in fibrosis of the left and right bundles themselves, referred to as Lenègre's disease, occurring in younger people in certain families. Other etiologies include interruption of the AV node related to aortic or mitral valve calcification, myocardial infarction leading to ischemic damage to the AV node, or cardiomyopathy. Other causes, although rare, include: congenital AV block; infiltration by tumor and surgical or other trauma.[37]

FIRST-DEGREE AV BLOCK

Although a relatively common and seemingly benign finding of a prolonged PR interval (> 200 msec) on ECG, it has recently been postulated that this may precede more advanced AV block, and even itself serve as a marker of increased risk of other arrhythmic and mortality concerns. Cheng described long-term outcomes of patients with first-degree AV block.[38] Within the Framingham Heart Study cohort, and found that when compared to control patients with a prolonged PR interval at baseline had twice the risk of developing atrial fibrillation, three times the risk of requiring a pacemaker and almost one-and-a-half times the risk of all-cause mortality. At this point however, despite these findings, management of these patients with only a prolonged PR interval is unclear.

SECOND-DEGREE AV BLOCK

Second-degree AV block is commonly divided into two varieties, and was first classified in this manner by Woldemar Mobitz in the early 1920s.[39] Type I (Mobitz I, also "Wenckebach" named for Karel Wenckebach who discovered "Wenckebach periodicity" in 1906) second-degree AV block presents as a normal or near-normal PR interval (120–200 msec) which gradually prolongs with successive beats, until only a P wave is seen, and a "dropped" QRS occurs, which is the absence of AV conduction. After a brief reset, the next cycle begins, again with a normal PR interval, progressively lengthening again until a drop occurs. There may be the same number of beats prior to that which is dropped, or at times, variable numbers. Type I basically demonstrates AV nodal decremental conduction.

Type II (Mobitz II) second-degree AV block, similar to Type I, has dropped ventricular beats due to AV block. However, in this scenario, there is no PR lengthening, only dropped beats, which may occur after one, two or any number of normally conducted beats, and may or may not be a consistent number. An easy way to diagnose this mechanism is to evaluate the PR before and after the regular blocked P wave; if the PR after the block is not shorter by more than 20 msec then Type II block must be considered. False Type II may be diagnosed if irregular P-P intervals, owing to sinus arrhythmia or atrial prematures, or frequent junctional prematures (suggesting concealed His extrasystoles) produce block.[40] Patients with Type II block also tend to have concomitant QRS prolongation.

2:1 AV block, due to 2:1 conduction, may be Type I or II, but which one is not able to be ascertained because there is no PR lengthening—or lack thereof—to be seen because block occurs after only one beat. It may be a progression from either. Anatomically, 80% of the time, 2:1 AV block occurs in the His-Purkinje system, and 20% in the AV node itself. Careful examination of the ECG for more typical 3:2 Type I block will suggest the right mechanism. Interestingly, atropine may increase the degree of AV block.[40–42] The importance of differentiating Type I versus Type II AV block is that even if asymptomatic, the latter requires a permanent pacer, but in the former a permanent pacemaker is not needed unless symptoms are present.

THIRD-DEGREE AV BLOCK

Third-degree AV block is defined as a complete electrical dissociation of the atria and ventricles. The ventricular rhythm in this case, referred to as an escape rhythm, may either be a junctional, which is a normal, narrow-complex rhythm emanating more proximally to the AV node and generally faster (40–60 bpm), or ventricular where the rhythm is abnormal, wide complex and slower (< 30 bpm). Rarely no escape rhythm is present whatsoever.

Treatment entails eliminating or neutralizing reversible causes, such as AV nodal blockers (e.g. BARBs). If a patient has complete heart block and is unstable with symptoms, such as chest pain, shortness of breath, lightheadedness and/or hypotension, then atropine should be given, especially if a junctional escape is present. If not effective, temporary pacing (first transcutaneous, then transvenous) is recommended. If the patient has what appears to be a permanent complete heart block, then permanent pacing is recommended. Of note, some sources state that an escape rhythm of greater than 40 beats per minute is adequate, and is not an indication for permanent pacing. However, as noted in the recent ACC/AHA device therapy guidelines, this arbitrary number is not based on strong data.[43]

PAROXYSMAL AV BLOCK

Paroxysmal AV block has been defined by Lee et al. as "a sudden," "paroxysmal pause-dependent phase 4 AV block occurring in diseased conduction system". It is essentially the change from 1:1 AV conduction, suddenly to complete heart block. There is no official definition for this type of AV block and the prevalence may be underestimated because of this and difficulty in recording this arrhythmia. The most common risk factor is apparently right bundle branch (RBB) block. Since paroxysmal AV block originates in the distal portion of the AV node, it most often is seen in older patients, with the commonest presentation being syncope. As noted above, the mechanism has been postulated to be block due to phase 4 depolarization of the distal AV node, more specifically in the His-Purkinje system itself. Factors differentiating this from vagally mediated complete heart block include rapid or sudden onset, no change in P-R interval, and infranodal versus nodal level of block. Treatment includes pacemaker implantation and removal of culprit AV nodal blocking agents if present.[44]

HEMIBLOCK

Although not necessarily a bradycardia *per se*, or AV block, such as those described above, the hemiblocks (first described by Rosenbaum, et al. in 1968 are nevertheless important findings which may be intricately related to AV block.[45]

First of all, building on the concept of the right and left bundles in the His-Purkinje system, the LBB is generally found

to divide into two discrete—yet somewhat interconnected—branches, the anterior and the posterior fascicles. Thus, the ventricular system, including the right bundle, is essentially trifasicular.

The left anterior fascicle, being anteriorly located as the name implies, is the more vulnerable of the two LBBs. For one, there is only a single coronary artery distribution (anterior descending) for blood supply. In addition, this fascicle is smaller and thinner than its posterior counterpart. A left anterior hemiblock (LAH) (also known as a fascicular block) is defined as a leftward axis of less than –45 degrees, an "rS" pattern in II, III, aVF and with a narrow QRS complex. The most common causes include hypertension, cardiomyopathy, VSD closure (spontaneous or iatrogenic), and Lev and Lenegre disease. In the case of the latter two causes, the RBB is commonly affected concurrently, and by the nature of these progressive diseases, patients often eventually develop complete heart block. Generally, without significant coronary artery disease or infarction, the finding of isolated LAH does not appear to portend an increased risk of morbidity or mortality, although LAH is associated with risk of disease in the Framingham study.

The left posterior fascicle is supplied by both the anterior and the posterior descending coronary arteries. This dual blood supply source is beneficial especially in the setting of myocardial infarction, where if one of the supplying coronary arteries is the site of occlusion or stenosis, the fascicle is unlikely to sustain significant ischemic damage, and thus is less prone to infarction and hemiblock. Left posterior hemiblock is defined as a rightward axis of greater than +100 degrees, narrow QRS and an rS in I and aVL. A pure left posterior fascicular block is rare, but tends to be found coexisting with a RBB block. This combination, if occurring in the setting of a myocardial infarction, significantly increases mortality to over 80% within a few weeks after infarction. The risk of progression to complete heart block with this bifascicular block is 42%. Because of the dual-coronary artery supply, however, the cause of the block is more likely due to Lenegre disease, or even Chagas disease in endemic regions.[46]

That said, the concept of trifasicular block is uncommon as opposed to bifasicular block (LAH and RBB block) and concomitant first degree AVB which is usually in the AVN.[40] Patients with LAH and RBB block frequently have no symptoms or VT inducible.[47] Differentiation from trifasicular block is usually easy (lack of symptoms) but exercise testing or EPS may be necessary if a certain diagnosis is necessary.

BUNDLE BRANCH BLOCK

The concept of the existence of the LBB and RBB coming off of the His was first published by Eppinger and Rothberger in 1909.[48]

LEFT BUNDLE BRANCH BLOCK

Left bundle branch (LBB) block is defined grossly as a QRS duration greater than or equal to 120 msec with left axis deviation. As early as 1940, Rasmussen and Moe determined via clinical, ECG, radiography, and necropsy in 100 patients with LBB block, that the most common cause, comprising approximately 72% of cases was left ventricular hypertrophy and/or enlargement (with associated increased weight of the heart), primarily due to hypertension or aortic valve disease.[49] Early data from the Framingham Study had similar findings, including hypertension, "cardiac enlargement" and/or coronary artery disease. It was further noted that the mean age of onset of new LBB block was 62 years of age. The 10-year prognosis was poor, with one-half of these patients expiring due to cardiovascular disease.[50] Other etiologies for LBB block include myocardial infarction, electrolyte abnormalities, and fibrosis (Lev's and Lenegre's disease).[51]

A salient issue with LBB block is in myocardial infarction. It may be the presenting ECG finding for MI. If an old finding, it may hinder interpretation of the ECG in the setting of suspected acute coronary syndrome. The specific method of diagnosing an MI in this setting is discussed in this book.[52]

Moreover, and discussed earlier, LBB block is important in selecting patients with interventricular dyssynchrony who would be candidates for cardiac resynchronization therapy, in that most studies suggest that interventricular dyssynchrony due to LBB block responds better to CRT than those with RBB block.[53,54]

RIGHT BUNDLE BRANCH BLOCK

Right bundle branch (RBB) block is grossly defined as a QRS duration greater than or equal to 120 msec with right axis deviation, and commonly an RSR pattern in lead V_1.

From the same follow-up data from the Framingham Study noted above, patients with new onset RBB block over an 18-year-follow-up period were identified. These patients were more likely to have hypertension prior to the development of RBB block; these patients were 2.5–4 times more likely to have coronary artery disease or congestive heart failure than their age-matched controls. A QRS of greater than or equal to 130 ms with an axis –45° to –90° was associated with increased risk of cardiovascular issues. Common causes of or association with RBB block include pulmonary embolism (acute or chronic), pulmonary hypertension, left sided heart failure causing RV volume or pressure overload, severe MR, pulmonic valve stenosis.

In patients with a new RBB or LBB block associated with high grade AV block during an acute myocardial infarction, permanent pacing is indicated as is infarction with bilateral BB block.

TREATMENT

Treatment of bradycardia and heart block is primarily initiated if there are symptoms such as syncope, lightheadedness, chest pain, shortness of breath and/or evidence of hemodynamic compromise or low cardiac output. Obviously, if offending agents—be it cardiac drugs such as AV nodal blocking agents, digoxin or noncardiac such as opiates—are in use and thought to be the perpetrators, these should be discontinued, if possible. However, if cessation of drug therapy for a reasonable duration of time does not result in improvement, or drug therapy is needed for an indication such as a tachyarrhythmia, then permanent pacing should be considered.

If cessation of an agent does not result in improvement, and a more rapid means of treating bradycardia is needed, the next step would be pharmacologic therapy such as atropine. There

are special circumstances, such as BARB toxicity or digoxin toxicity where an antidote of sorts is available, such as glucagon or Digibind, respectively. For more acutely decompensated patients, beta-agonsists, such as isoproterenol, may be required until pacing may be initiated.

Beyond pharmacologic measures are the electromechanical therapies. External pacing is considered, but is only of benefit in a very short period of time, due to the unpredictable transcutaneous capture and is poorly tolerated by the patient unless sedated, which itself may perpetuate bradycardia. Temporary pacing is indicated if the above noted therapies are unhelpful and the patient requires more time for conservative measures (holding medications, pharmacologic therapy) to work, or as a bridge to permanent pacing which is commonly not as rapidly available. Permanent pacing is discussed in this book in detail.[43]

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Chapter 37

Arrhythmogenic Right Ventricular Dysplasia/ Cardiomyopathy

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Chapter Outline

- Molecular and Genetic Background
  - Desmosome Structure and Function
  - Desmosomal Dysfunction and ARVD/C Pathophysiology
  - Autosomal Recessive Disease
  - Autosomal Dominant Disease
  - Other Non-desmosomal Genes
- Epidemiology
- Clinical Presentation
- Clinical Diagnosis
  - Global and/or Regional Dysfunction and Structural Alterations
  - Endomyocardial Biopsy
  - ECG Criteria
  - Depolarization Abnormalities
  - Repolarization Abnormalities
  - Arrhythmias
  - Family History
- Non-classical ARVD/C Subtypes
  - Naxos Disease
  - Carvajal Syndrome
  - Left Dominant ARVD/C (LDAC)
- Differential Diagnosis
- Molecular Genetic Analysis
- Prognosis and Therapy

INTRODUCTION

Arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C) is a disease characterized histopathologically by progressive fibrofatty replacement of the myocardium, primarily of the right ventricle (RV).[1-3] Affected individuals typically present between the second and the fourth decade of life with monomorphic ventricular tachycardia (VT) originating from the RV. ARVD/C can be the cause of sudden death in all stages of the disease, but particularly in adolescence.[4] From autopsy studies, it is known that fibrofatty tissue can replace major parts of normal myocardium in teenagers (Fig. 1). Sudden death may occur in the early concealed phase of the disease.

The first series of ARVD/C patients was published in 1982. It was described as a disease in which "the right ventricular musculature is partially or totally absent and is replaced by fatty and fibrous tissue".[1] This disease was initially thought to be a defect in RV development, which is why it was first called "dysplasia". In the past 25 years, increased insight in the development of the disease as well as the discovery of pathogenic mutations involved led to our current understanding that ARVD/C is a genetically determined "cardiomyopathy".[3,5] However, since non-familial sporadic cases occur even after extensive family screening, non-genetic causes cannot be excluded. It is now clear that ARVD/C is a desmosomal disease resulting from defective cell adhesion proteins. Desmosomes maintain mechanical coupling of cardiomyocytes. The first disease-causing gene, encoding the desmosomal protein

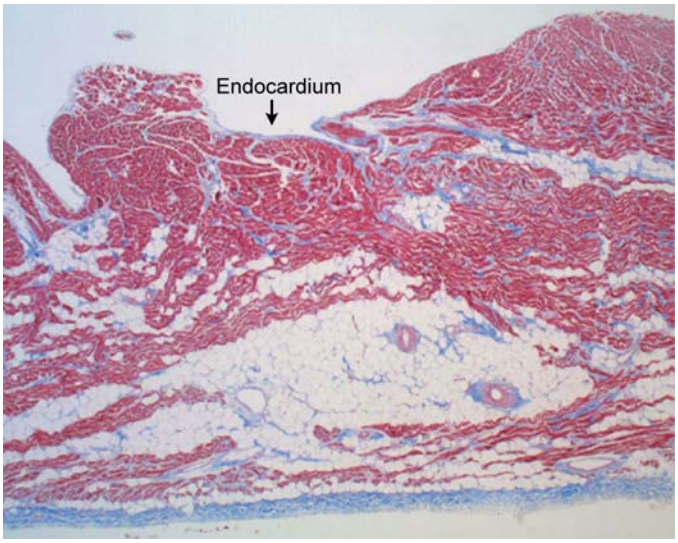


FIGURE 1: Histology of right ventricular wall (x400) of a 13-year-old girl who died suddenly during exercise. AZAN stain with cardiac myocytes (red), collagen (blue) and adipocytes (white). Shown is the typical pattern of ARVD/C with strands of fibrosis reaching all the way to the endocardium (particularly just to the right of the arrow). Bundles of cardiac myocytes are embedded in between the fibrotic strands, particularly in the subendocardial layers. These interconnecting bundles of myocytes give rise to activation delay and re-entrant circuits, the typical electrophysiologic substrate for ventricular arrhythmias in ARVD/C. The large homogeneous subepicardial area of adipose tissue is not arrhythmogenic, although it may be observed in ARVD/C. However, it is a typical feature of the cor adiposum, a non-arrhythmogenic condition

plakoglobin (JUP), was identified in patients with Naxos disease, an autosomal recessive variant of ARVD/C, reported from the Greek island of Naxos.[6] This discovery stimulated research in the direction of other desmosomal genes. Until 2004, only three genes were identified as responsible for the autosomal dominantly inherited ARVD/C.[7-15] Since *RyR2* mutations are typically associated with catecholaminergic polymorphic VT, it is less certain that these *RyR2* mutations are a cause of ARVD/C. The desmoplakin gene (*DSP*) was the first desmosomal protein gene associated with the autosomal dominant form of ARVD/C.[15] It was followed by discovery of mutations in plakophilin-2 (*PKP2*), desmoglein-2 (*DSG2*) and desmocollin-2(*DSC2*), all components of the cardiac desmosome.[16-18] Impaired desmosomal function results in myocardial cell-to-cell uncoupling, followed by cell death and fibrofatty replacement, and thus disruption of the myocardial architecture leading to activation delay and arrhythmias. In a few rare cases, autosomal dominant ARVD/C has been linked to other genes unrelated to the cell adhesion complex, i.e. the genes encoding the cardiac ryanodine receptor (RyR2), the transforming growth factor-β3 gene (*TGFβ3*), and transmembrane protein 43 (*TMEM43*).[13,14,19] Since *RyR2* mutations are typically associated with catecholaminergic polymorphic VT it is less certain that these *RyR2* mutations are a cause of ARVD/C.

With mutations found in about half of the patients, mainly in desmosomal genes and *PKP2* in particular, ARVD/C is currently considered a genetically determined desmosomal disease.

This chapter provides an overview of ARVD/C, starting from the genetic defects that are responsible for the pathophysiologic mechanisms to clinical diagnosis, treatment and prognosis.

MOLECULAR AND GENETIC BACKGROUND

DESMOSOME STRUCTURE AND FUNCTION

The cellular adhesion junctions in the intercalated disk are vital for the structural and functional integrity of cardiac myocytes. Intercalated disks are located between cardiomyocytes at their longitudinal ends and contain three different kinds of intercellular connections: (1) Desmosomes; (2) Adherens junctions and (3) Gap junctions.

Desmosomes are important for cell-to-cell adhesion and are predominantly found in tissues that experience mechanical stress—the heart and the epidermis. They couple cytoskeletal elements to the plasma membrane. Desmosomes also protect the other components of the intercalated disk from mechanical stress and are involved in structural organization of the intercalated disk. Desmosomes consist of multiple proteins which belong to the following three different families:

1. Transmembranous cadherins (desmogleins and desmocollins)
2. Linker armadillo repeat proteins (plakoglobin and plakophilin)
3. Plakins (desmoplakin and plectin).

Figure 2 schematically represents the organization of the various proteins in the cardiac desmosome.

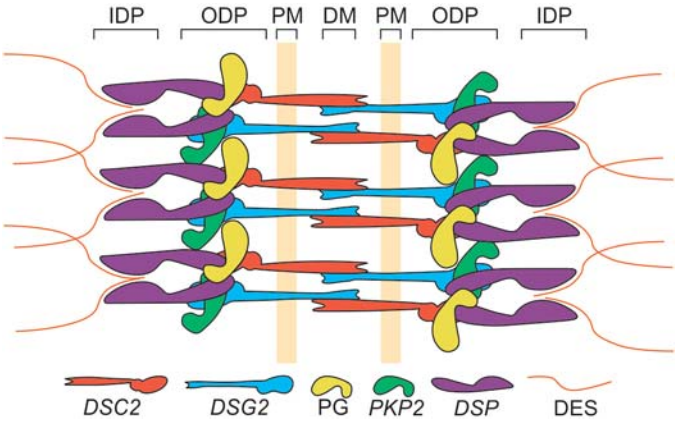


FIGURE 2: Schematic representation of the molecular organization of cardiac desmosomes. The plasma membrane (PM) spanning proteins desmocollin-2 (DSC2) and desmoglein-2 (DSG2) interact in the extracellular space at the dense midline (DM). At the cytoplasmic side, they interact with plakoglobin (PG) and plakophilin-2 (PKP2) at the outer dense plaque (ODP). The PKP2 and PG also interact with desmoplakin (DSP). At the inner dense plaque (IDP), the C-terminus of DSP anchors the intermediate filament desmin (DES) (*Source:* Modified from: Van Tintelen et al. Curr Opin Cardiol. 2007;22:185-92)

Within desmosomes, cadherins are connected to armadillo proteins which interact with plakins. The plakins anchor the desmosomes to intermediate filaments, mainly desmin. They form a three-dimensional scaffold providing mechanical support.

Adherens junctions act as bridges that link the actin filaments within sarcomeres of neighboring cells. These junctions are involved in force transmission and, together with desmosomes, these mechanical junctions act as "spot welds" to create membrane domains that are protected from shear stress caused by contraction of the neighboring cells. Furthermore, they facilitate assembly and maintenance of gap junctions, securing intercellular electrical coupling.

Cardiomyocytes are individually bordered by a lipid bilayer which gives a high degree of electrical insulation. The electrical current that forms the impulse for mechanic contraction travels from one cell to the other via gap junctions. Gap junctions provide electrical coupling by enabling ion transfer between cells. The number, size and distribution of gap junctions all influence impulse propagation in cardiac muscle. Consequently, alterations in function of gap junctions can lead to intercellular propagation disturbances and arrhythmogenesis.[20]

The intercalated disk is an intercellular structure, where desmosomes and adherens junctions not only provide mechanical strength but also protect the interspersed gap junctions, enabling electrical coupling between cells.

DESMOSOMAL DYSFUNCTION AND ARVD/C PATHOPHYSIOLOGY

It is not well known how mutations of desmosomal protein genes are related to the ARVD/C phenotype. Several mechanisms have been proposed.

First, alterations in desmosomal proteins are thought to lead to mechanical uncoupling of myocytes at the intercalated disks, particularly under mechanical stress (e.g. exercise, sports activities, etc.). Mechanical uncoupling will be followed by: (1) Electrical uncoupling due to dysfunction of gap junctions

and (2) Cell death with fibrofatty replacement. Both electrical uncoupling and interconnecting bundles of surviving myocardium embedded in the fibrofatty tissue lead to lengthening of conduction pathways and load mismatch. This results in marked activation delay and conduction block, which are pivotal mechanisms for re-entry and thereby VT. Invasive electrophysiologic studies have confirmed that VT in patients with ARVD/C is due to re-entrant circuits in areas of abnormal myocardium.[21] In addition, environmental factors, such as exercise or inflammation from viral infection, could aggravate impaired adhesion and accelerate disease progression. The RV may be more vulnerable to histopathologic alteration than the left ventricle (LV) due to its thinner walls and its normal dilatory response to exercise.

Secondly, recent studies have shown that impairment of cell-to-cell adhesion due to changes in desmosomal components may affect the amount and distribution of other intercalated disk proteins, including connexin 43, the major protein forming gap junctions in the ventricular myocardium.[22-24] This was shown for *DSP* and *JUP* by Western blotting and confocal immunofluorescence techniques, but alterations in other desmosomal components, such as *PKP2*, *DSG2* and *DSC2*, are thought to have similar effects. Changes in number and function of gap junctions will diminish intercellular electrical coupling contributing to intraventricular activation delay.

The third hypothesis involves the canonical Wnt/β-catenin signaling pathway. Plakoglobin can localize both to the plasma membrane and the nucleus. It was demonstrated that disruption of desmoplakin frees plakoglobin from the plasma membrane allowing it to translocate to the nucleus and suppress canonical Wnt/β-catenin signaling. Wnt signaling can inhibit adipogenesis by preventing mesodermal precursors from differentiating into adipocytes.[25] Suppression of Wnt signaling by plakoglobin nuclear localization could, therefore, promote the differentiation to adipose tissue in the cardiac myocardium in patients with ARVD/C.[26]

Finally, since ion channels, like the Na^+ channel, are also located in the intercalated disk, they might be disrupted and contribute to arrhythmogenicity.

The pathophysiological mechanisms proposed above are not mutually exclusive and could occur simultaneously.

Two patterns of inheritance have been described in ARVD/C. The most common or classical form of ARVD/C is inherited as an autosomal dominant trait. Naxos disease and Carvajal syndrome are rare, inherited as autosomal recessive. Table 1 summarizes the different genes involved in ARVD/C with the corresponding phenotypes.

TABLE 1

Mutated genes and concurrent types of autosomal dominant ARVD/C

	Gene	*Type of disease*
Desmosomal	*PKP2*	ARVD/C
	DSG2	ARVD/C
	DSC2	ARVD/C
	JUP	Naxos disease*
	DSP	Carvajal syndrome*
		ARVD/C
		LDAC
Non-desmosomal	*RyR2*	CPVT ARVD/C
	TGF-β	ARVD/C
	TMEM43	ARVD/C

*Autosomal recessive inheritance;
(Abbreviations: CPVT: Catecholaminergic polymorphic VT; LDAC: Left dominant arrhythmogenic cardiomyopathy. See text for other abbreviations. (*Source:* Modified from: Van Tintelen et al. Curr Opin Cardiol. 2007;22:185-92)

AUTOSOMAL RECESSIVE DISEASE

In Naxos disease, affected individuals were found to be homozygous for a 2-base pair deletion in the *JUP* gene.[6] All patients who are homozygous for this mutation have diffuse palmoplantar keratosis and woolly hair in infancy. Children usually have no cardiac symptoms, but may have electrocardiographic abnormalities and nonsustained ventricular arrhythmias.[27] In one report, an Arab family was found to have an autosomal recessive mutation in the desmoplakin gene that caused ARVD/C with a classical ARVD/C cardiac phenotype, that was also associated with woolly hair, and a pemphigus-like skin disorder.[28] A different autosomal recessive disease, Carvajal syndrome, is associated with a desmoplakin gene mutation. It manifests by woolly hair, epidermolytic palmoplantar keratoderma and cardiomyopathy.[29] The cardiomyopathy of Carvajal syndrome was thought to have a predilection for the LV, but subsequent evaluation of a deceased child revealed typical ARVD/C changes in both ventricles.[24]

AUTOSOMAL DOMINANT DISEASE

Mutations in the gene encoding the intracellular desmosomal component desmoplakin can cause "classic ARVD/C" with a clinical presentation of VT, sudden death as well as LV involvement as the disease progresses.[15,30,31] Desmoplakin gene mutations have also been associated with predominantly left-sided ARVD/C and, as noted above, with autosomal recessive disease.

Various authors identified mutations in the *PKP2* gene as the most frequently observed genetic abnormality. Figure 3 shows the pedigree of a family with a *PKP2* mutation. Incomplete penetrance and clinical variability are well documented. In four studies from different countries, analyzing 56–100 ARVD/C patients each, the following observations were made.[16,32-34] *PKP2* mutations were found in 11–43% of unrelated index patients who fulfilled diagnostic task force criteria for ARVD/C. In a Dutch ARVD/C cohort, 78 of 149 (52%) probands had a pathogenic *PKP2* mutation. This high yield of *PKP2* mutations is partly due to occurrence of founder mutations in the Netherlands. Haplotype analysis previously performed suggested founder mutations were responsible for 4 of the 14 different mutations identified.[34] Among index patients with a positive family history of ARVD/C, 70% had a *PKP2* mutation.[34]

Pilichou et al. screened patients with ARVD/C for mutations in the transmembranous desmosomal component *DSG2*.[17] Among 80 unrelated probands, 26 were found to have *DSP* or *PKP2* mutations. Direct sequencing of *DSG2* in the other 54 patients revealed nine distinct mutations in eight individuals. These individuals demonstrated typical clinical characteristics of ARVD/C. An analogous study of 86 ARVD/C probands

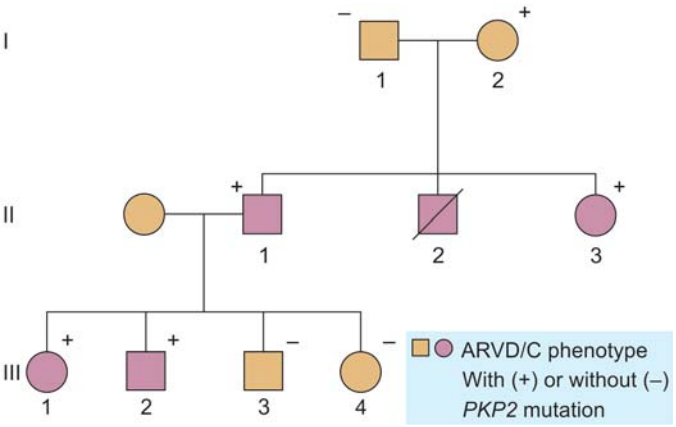


FIGURE 3: Pedigree of family with ARVD/C and *PKP2* mutation. This figure shows incomplete penetrance and variability of clinical expression. Both the 72-year-old grandmother (I:2) and 20-year-old grandson (III:2) are free of any signs of disease, despite carrying the mutation. The proband (II:1) was resuscitated at age 35, his brother (II:2) died suddenly at age 18. Both the proband's sister (II:3) and daughter (III:1) were diagnosed with the disease due to a positive family history, arrhythmias and RV structural abnormalities. The sister (II:3) of the proband has structural and ECG abnormalities, but no symptomatic arrhythmias

identified eight novel *DSG2* mutations in nine probands. Clinical evaluation of family members with *DSG2* mutations revealed a penetrance of 58% using task force criteria from 1994 and 75% using proposed modified criteria.[35] Morphological abnormalities of the RV were present in 66% of gene carriers, LV involvement in 25% and classical right precordial T-wave inversion in only 26%. The authors noted that disease expression of *DSG2* mutations was of variable severity, but that overall penetrance was high and LV involvement prominent.[36]

In *DSC2*, another important transmembranous desmosomal cadherin, two heterozygous mutations (a deletion and an insertion) were identified in 4 of 77 probands with ARVD/C.[18] Finally, a dominant mutation in the plakoglobin (*JUP*) gene has been identified.[37] The identification of so many desmosomal cell adhesion gene abnormalities supports the hypothesis that ARVD/C is predominantly a disease of cell-to-cell coupling.

OTHER NON-DESMOSOMAL GENES

Mutations in the cardiac ryanodine receptor *RyR2*, which is responsible for calcium release from the sarcoplasmic reticulum, have been described in only one Italian ARVD/C family.[13] Affected patients have exercise-induced polymorphic VT.[38] Mutations in *RyR2* have primarily been associated with familial catecholaminergic polymorphic VT without ARVD/C.[19,39] Although the general opinion is that *RyR2* mutations lead to catecholaminergic polymorphic VT without structural abnormalities, the mutations in ARVD/C have been advocated to act differently from those in familial polymorphic VT without ARVD/C.[40-42]

The *TGFβ3* regulates the production of extracellular matrix components and modulates expression of genes encoding desmosomal proteins. The gene has been mapped to chromosome 14. Sequencing studies failed to identify any disease-causing mutations in the exonic regions of *TGFβ3*. This led to screening of the promoter and untranslated regions, where a mutation of the *TGFβ3* gene was found in all clinically affected members of a large family with ARVD/C.[14] The mutation is predicted to produce an amino acid substitution in a short peptide with an inhibitory role in *TGFβ3* regulation. The implication of these observations is that regulatory mutations resulting in overexpression of *TGFβ3* may contribute to the development of ARVD/C in these families. The *TGFβ* family of cytokines stimulates production of components of the extracellular matrix. It is therefore possible that enhanced *TGFβ* activity can lead to myocardial fibrosis. However, genetic analysis of two other families with ARVD/C failed to identify mutations in any of the regions of the *TGFβ3* gene.

A missense mutation in the *TMEM43* gene was found in 15 unrelated ARVD/C families from a genetically isolated population in New Foundland and caused a fully penetrant, sex-influenced, high risk form of ARVD/C.[19] The *TMEM43* gene contains the response element for PPAR gamma, an adipogenic transcription factor. The *TMEM43* gene mutation is thought to cause dysregulation of an adipogenic pathway regulated by PPAR gamma, which may explain the fibrofatty replacement of myocardium in ARVD/C patients.

EPIDEMIOLOGY

Estimations of the prevalence of ARVD/C in the general population vary from 1:2000 to 1:5000.[43] The real prevalence of ARVD/C, however, is unknown and is presumably higher due to many non-diagnosed and misdiagnosed cases.

The disease appears to be especially common in adolescents and young adults in northern Italy, accounting for approximately 11% of cases of sudden cardiac death overall and 22% in athletes.[44,45] In as many as 20% of sudden deaths occurring in people under 35 years of age, features of ARVD/C were detected at post mortem evaluation.[45] In nearly half of them, no prior symptoms had been reported.

ARVD/C has incomplete penetrance and extremely variable clinical expression. For instance, family screening has identified pathogenic mutation carriers, who had remained free of any sign of disease up to or over 70 years of age (Fig. 3).

From the genetic aspect, both men and women should be equally affected. However, men are more frequently diagnosed with ARVD/C than women. In a recent large multicenter study, 57% of affected individuals were male.[46] As many women as men show at least some signs of disease, but women more often do not fulfill criteria to meet the diagnosis. Factors explaining this difference in severity of disease expression have not yet been elucidated. It is speculated that (sports) activity or hormonal factors may play a role. Familial disease has been demonstrated in greater than 50% of ARVD/C cases.

CLINICAL PRESENTATION

ARVD/C patients typically present between the second and the fourth decade of life with monomorphic VT originating from RV. However, in a minority of patients, sudden death, frequently at a young age, or RV failure are the first signs. Based on clinicopathologic and patient follow-up studies, four different disease phases have been described for the classical form of ARVD/C, i.e. primarily affecting the RV (Table 2):

1. Early ARVD/C is often described as "concealed" owing to the frequent absence of clinical findings, although minor

TABLE 2

Different phases of disease severity

Phase	*Characteristics*
1. Concealed	Asymptomatic patients with possibly only minor ventricular arrhythmia and subtle structural changes
2. Overt	Symptoms due to LBBB VT or multiple premature complexes, with more obvious structural RV abnormalities
3. RV failure	With relatively preserved LV function
4. Biventricular	Significant overt LV involvement

ventricular arrhythmias and subtle structural changes may be found. Although patients tend to be asymptomatic, they may nonetheless be at risk of sudden death, mainly during vigourous exercise.

2. The overt phase follows, in which patients suffer from palpitations, syncope and ventricular arrhythmias of left bundle branch block (LBBB) morphology, ranging from isolated ventricular premature complexes to sustained VT and ventricular fibrillation (VF).
3. The third phase is characterized by RV failure due to progressive loss of myocardium with severe dilatation and systolic dysfunction, in the presence of preserved LV function.
4. Biventricular failure occurs due to LV involvement at a later stage. This phase may mimic dilated cardiomyopathy (DCM) and may require cardiac transplantation.

In the initially described classical form of ARVD/C, the RV is primarily affected with possibly (in a later stage) some LV involvement. Two additional patterns of disease have been identified by clinicogenetic characterization of families. These are the left dominant phenotype, with early and predominant LV manifestations, and the biventricular phenotype with equal involvement of both ventricles.

Recent immunohistochemical analysis of human myocardial samples demonstrated that both ventricles are affected by the disease.[47] A marked reduction in immunoreactive signal levels for plakoglobin was observed both in RV and LV, independent of genotype. Thus at a molecular level ARVD/C is a global biventricular disease. However, histologically and functionally overt manifestations of the disease usually start in the RV. The reason for this is still unclear. The most commonly advocated hypothesis is that the thin walled RV is less able to withstand pressure (over)load in the presence of impaired function of mechanical junctions.

CLINICAL DIAGNOSIS

Diagnosis of ARVD/C can be very challenging. Although VF and sudden death may be the first manifestations of ARVD/C, symptomatic patients typically present with sustained VT with LBBB morphology, thus originating from the RV. The occurrence of VT episodes is usually induced by adrenergic stimuli mainly during exercise, especially competitive sports. The ARVD/C is a disease that shows progression over time.

In ARVD/C demonstration of transmural fibrofatty replacement primarily of right ventricular myocardium can be determined at surgery or autopsy (Fig. 1). Predilection sites for these structural abnormalities are the so-called triangle of dysplasia formed by the RV outflow tract, the apex and the subtricuspid region.[1] In clinical practice, diagnosis based on cardiac pathology is not practical. Endomyocardial biopsies have major limitations. Tissue sampling from the affected often thin RV free wall, directed by imaging techniques or voltage mapping, is associated with a slight risk of perforation. Sampling from the interventricular septum is relatively safe. However, the septum is histopathogically rarely affected in ARVD/C. In addition, histology may be classified as normal due to the focal nature of the lesions. Finally, since subendocardial layers are usually not affected in an early stage of the disease, histological diagnosis may be hampered by the non-transmural nature of endomyocardial biopsies.[48]

Clinical diagnosis has been facilitated by a set of clinically applicable criteria for ARVD/C diagnosis defined by a Task Force based on consensus in 1994, and modified in 2010.[49,50] The current Task Force criteria are the essential standard for classification of individuals suspected of ARVD/C. In addition, its universal acceptance contributes importantly to unambiguous interpretation of clinical studies and facilitates comparison of results. The Task Force criteria included six different categories. They are derived into: (1) Global and regional dysfunction and structural alterations; (2) Tissue characterization; (3) Depolarization abnormalities; (4) Repolarization abnormalities; (5) Arrhythmias and (6) Family history, including pathogenic mutations. Within these groups, diagnostic criteria are categorized as major or minor according to their specificity for the disease. In order to fulfill ARVD/C diagnosis it is required to have either two major or one major plus two minor or four minor criteria. From each different group, only one criterion can be counted for diagnosis, even when multiple criteria in one group are present. Table 3 gives an overview of the Task Force criteria which is defined in 2010.

Specific evaluations are recommended in all patients suspected of ARVD/C. Detailed history and family history, physical examination, 12-lead ECG, signal averaged ECG (SAECG), 24-hours Holter monitoring, exercise testing and 2D echocardiography with quantitative wall motion analysis. When appropriate, more detailed analysis of the RV can be done by cardiac magnetic resonance imaging (MRI). Invasive tests are also useful for diagnostic purposes: RV and LV cineangiography, electrophysiological testing, and endomyocardial biopsies.

GLOBAL AND/OR REGIONAL DYSFUNCTION AND STRUCTURAL ALTERATIONS

Evaluation of RV size and function can be done by various imaging modalities, including echocardiography, cardiac MRI, computed tomography and/or cineangiography. According to the Task Force criteria, major criteria are defined as presence of an akinetic or dyskinetic areas in the RV (Fig. 4) combined with severe dilatation of the RV or RV ejection fraction 40% or lower.[50] With RV cineangiography the finding of only regional akinesia, dyskinesia or aneurysm is considered sufficient for qualification as a major criterion. RV cineangiography has historically been considered the most sensitive method to visualize RV structural abnormalities, with a high specificity of 90%.[51] Compared to cineangiography, the non-invasive

TABLE 3

New task force criteria

I. Global and/or regional dysfunction and structural alterations

Major (2D echo)

Regional RV akinesia, dyskinesia or aneurysm
and one of:

- Parasternal long axis view
  RVOT (PLAX) ≥ 32 mm
  Corrected for body size (PLAX/BSA) ≥ 19 mm/m^2
- Parasternal short axis view
  RVOT (PSAX) ≥ 36 mm
  Corrected for body size (PSAX/BSA) ≥ 21 mm/m^2
- Fractional area change (FAC) ≤ 33%

Major (MRI)

Regional RV akinesia or dyskinesia or dyssynchronous RV contraction
And one of:

- RV end diastolic volume (RVEDV/BSA) ≥ 110 ml/m^2 male ≥ 100 ml/m^2 female
- RV ejection fraction (RVEF) ≤ 40%

Major (RV cineangiography)

Regional RV akinesia, dyskinesia or aneurysm

Minor (2D echo)

Regional RV akinesia or dyskinesia
And one of:

- Parasternal long axis view
  RVOT (PLAX) ≥ 29–≤ 31 mm
  Corrected for body size (PLAX/BSA) ≥ 16–≤ 18 mm/m^{2i}
- Parasternal short axis view
  RVOT (PSAX) ≥ 32–≤ 35 mm

Corrected for body size (PSAX/BSA) ≥ 18–≤ 20 mm/m^2

- Fractional area change (FAC) ≤ 40%

Minor (MRI)

Regional RV akinesia or dyskinesia or dyssynchronous RV contraction
And one of:

- RV end diastolic volume/BSA ≥ 100 ml/m^2 male ≥ 90 ml/m^2 female
- RV ejection fraction (RVEF) ≤ 45%

II. Tissue characterization of wall

Major

Residual myocytes < 60% by morphometric analysis, (or < 50% if estimated), with fibrous replacement of the RV free wall myocardium in at least 1 sample, with or without fatty tissue replacement

Minor

Residual myocytes 60–75% by morphometric analysis, (or 50–65% if estimated), with fibrous replacement of the RV free wall myocardium in at least 1 sample, with or without fatty tissue replacement

III. Repolarization abnormalities

Major

Negative T waves in at least leads V1-3

Minor

Negative T waves only in leads V1 and V2 or in V4-6
In case of complete right bundle branch block: negative T waves in leads V1-4

IV. Depolarization/Conduction abnormalities

Major

Epsilon wave in one of leads V1-3

Minor

Late potentials by signal averaged ECG in at least one of three parameters in the absence of a QRS duration of ≥ 110 msec on the standard ECG

- Filtered QRS duration (fQRS) ≥ 114 msec
- Duration of terminal QRS < 40 μV (LAS) ≥ 38 msecs
- RMS voltage of terminal 40 msecs ≤ 20 μV
- Terminal activation duration ≥ 55 ms

V. Arrhythmias

Major

- (Non-)sustained VT of left bundle branch block morphology with superior axis

Minor

- (Non-)sustained VT of left bundle branch block morphology with inferior axis or unknown axis
- > 500 ventricular extrasystoles/24 hours by Holter

VI. Family history

Major

- ARVD/C confirmed in a first-degree relative who meets current task force criteria
- ARVD/C confirmed pathologically at autopsy or surgery in a first-degree relative
- Identification of a pathogenic mutation associated with ARVD/C

Minor

- History of ARVC/D in a first-degree relative in whom it is not possible or practical to determine if the family member meets current task force criteria
- Premature sudden death (< 35 years) due to suspected ARVD/C in a first-degree relative

(*Source:* Modified from: Marcus FI et al. Circulation. 2010;121:1533-41)·



FIGURE 4: An MRI image of ARVD/C patient at end of systole. Dyskinetic areas are visible in the RV free wall (arrow)

technique of echocardiography is widely used and serves as the first-line imaging technique in evaluating patients suspected of ARVD/C and in family screening. Especially with improvement of echocardiographic modalities, such as 3-dimensional echocardiography, strain and tissue Doppler, the sensitivity and specificity of echocardiography have improved in recent years. Cardiac MRI has the unique ability to characterize tissue composition, by differentiating fat from fibrous tissue by using delayed enhancement. However, this technique is expensive, not widely available and requires great expertise to prevent misdiagnosis of ARVD/C.[52] Also; this technique cannot be applied in patients with an implantable cardioverter-defibrillator (ICD). Incorrect interpretation of cardiac MRI is the most common cause of overdiagnosis and physicians should be reluctant to diagnose ARVD/C when structural abnormalities are present only on MRI.[53] Furthermore, it is important to note that the presence of fat in the epimyocardial and midmyocardial layers (without fibrosis) can be a normal finding and should not be considered diagnostic of ARVD/C (Fig. 1).

ENDOMYOCARDIAL BIOPSY

For reasons previously noted, undirected endomyocardial biopsies are infrequently diagnostic. However, it had been included as a major criterion by the Task Force, since the finding of fibrofatty replacement was considered to strongly support any findings derived from other clinical investigations. The rather vague terminology of any "fibrofatty replacement of myocardium" has been quantified. Diagnostic values according to the new Task Force criteria are considered major if histomorphometric analysis of endomyocardial biopsies shows that the number of residual myocytes is below 60% or below 50% by estimation, with fibrous replacement of the RV free wall in at least one sample, with or without fatty tissue replacement.[54] If the number of residual myocytes is higher but still below 75% (morphometric) or below 65% (estimated), only a minor criterion is fulfilled.

ECG CRITERIA

The 12-lead ECG is most important for diagnosis of ARVD/C. Consistent with early electrical uncoupling, ECG changes and arrhythmias may develop before histologic evidence of myocyte loss or clinical evidence of ARVD/C. ECG criteria on depolarization and repolarization have to be obtained during sinus rhythm and while off antiarrhythmic drugs. These drugs may cause misinterpretation of ECG criteria due to their contribution on activation delay and repolarization abnormalities.

DEPOLARIZATION ABNORMALITIES

The RV activation delay is a hallmark of ARVD/C. This delay is reflected by the presence of an epsilon wave, prolonged terminal activation duration (TAD) in the terminal part and after the QRS complex, and also by recording of late potentials on SAECG.

Epsilon waves are defined as low amplitude potentials after and clearly separated from the QRS complex, in at least one of precordial leads, V1-V3 (Fig. 5).[55] This highly specific major criterion is observed in only a small minority of patients.[56,57]

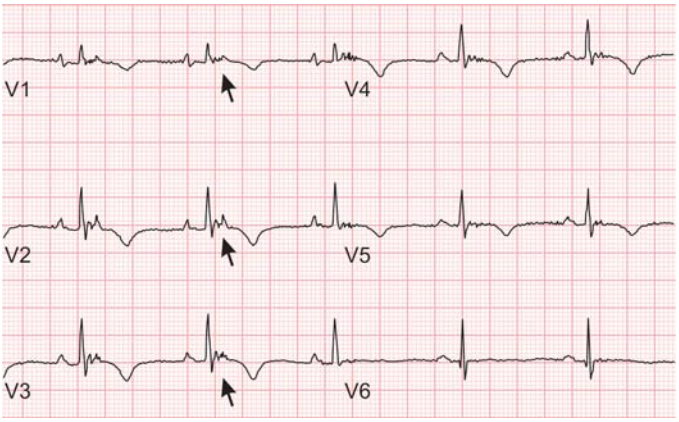


FIGURE 5: Epsilon waves indicated by arrows (also prolonged terminal activation duration; 120 ms) and negative T waves in V1-5

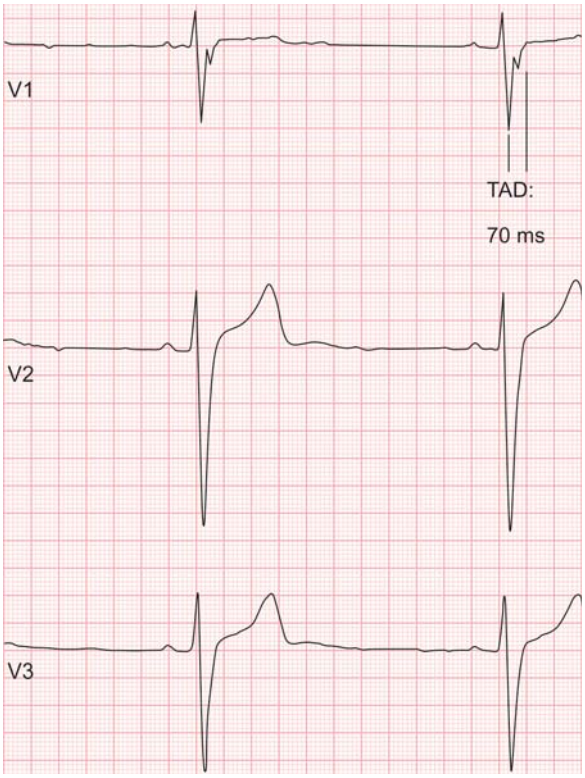


FIGURE 6: Prolonged terminal activation duration (70 ms from nadir of S wave to end of depolarization). Paper speed 25 mm/s

TAD has been defined as the longest value measured from the nadir of the S wave to the end of all depolarization deflections in V1-V3, thereby including not only the S wave upstroke but also both late and fractionated signals and epsilon waves (Figs 5 and 6).[58] Thus, total activation delay presumably from the RV is conveyed by this new parameter. The TAD is considered prolonged if greater than or equal to 55 ms, and only applicable in the absence of complete right bundle branch block (RBBB). Prolonged TAD, introduced as minor criterion, appears to be equally sensitive as the presence of late potentials and much more sensitive than epsilon waves. Prolonged TAD was recorded in 30 of 42 ARVD/C patients and in only 1 of 27 patients with idiopathic VT.[58] Both epsilon waves and prolonged TAD are measured only in V1-V3, which face the RV outflow

tract. Activation delay in other areas of RV is not reflected by these criteria.

The detection of late potentials on SAECG is the surface counterpart of delayed activation or late potentials detected during endocardial mapping in electrophysiologic studies. They are frequently found in patients with documented VT. However, these late potentials can also be observed after myocardial infarction and with other structural heart diseases. Due to this lack of specificity, SAECG abnormalities were considered a minor criterion. For all the depolarization criteria, it is apparent that they will correlate with disease severity. For instance, a positive correlation has been found between late potentials and the extent of RV fibrosis, reduced RV systolic function and significant morphological abnormalities on imaging.[59-61]

REPOLARIZATION ABNORMALITIES

In the new Task Force criteria negative T waves in leads V1, V2 and V3 form a major ECG criterion in the absence of complete RBBB, and only if the patient is older than 14 years of age (Fig. 5). Studies have reported variable prevalences of right precordial T wave inversion, ranging from 19% to 94%.[49,55-57,62] The lower rates are often due to evaluation of family members, while higher rates are seen in series consisting of unrelated index patients. In the recent study by Cox et al. this criterion was identified in 67% of exclusively ARVD/C index patients and in none of the patients with idiopathic VT.[58] T wave inversion can be a normal feature of the ECG in children and in early adolescence. Therefore, this finding is not considered abnormal in persons at the age of 14 years and younger.

In the new Task Force criteria, two minor repolarization criteria were included:

1. Inverted T waves only in leads V1-V2 or in V4-V6 in individuals older than 14 years of age and in the absence of complete RBBB.
2. Inverted T waves in leads V1-V4 in individuals older than 14 years of age in the presence of RBBB. This was included since T wave inversion in RBBB seldom extends to V4 in otherwise healthy individuals.

ARRHYTHMIAS

In ARVD/C, ventricular arrhythmias range from premature ventricular complexes to sustained VT and VF, leading to cardiac arrest.[58,63] Due to their typical origin in the RV, QRS complexes of ventricular arrhythmias show a LBBB morphology. Moreover, the QRS axis indicates the VT origin, i.e. superior axis from the RV inferior wall or apex (major criterion) and inferior axis (minor criterion) from the RV outflow tract (RVOT) (Figs 7 and 8). The VT of LBBB configuration with an unknown axis counts as minor criterion. Patients with extensively affected RV often show multiple VT morphologies.[58,64]

VF is the mechanism of instantaneous sudden death especially occurring in young people and athletes with ARVD/C, who were often previously asymptomatic. In this subset of patients, VF may occur from deterioration of monomorphic VT, or in a phase of acute disease progression, due to myocyte death and reactive inflammation.[3]

Finally, in the new Task Force criteria the number of premature ventricular complexes on 24-hours Holter recordings is reduced to 500 or more for a minor criterion.

FAMILY HISTORY

Before the discovery of pathogenic mutations underlying the disease, it was recognized that ARVD/C often occurs in family members.[1] Having a family member with proven ARVD/C is considered an increased risk for other family members to be affected. Therefore, having a first-degree relative who meets the current Task Force criteria, or having ARVD/C confirmed pathologically at autopsy or during surgery, or identification of a pathogenic mutation in the family, is included as major

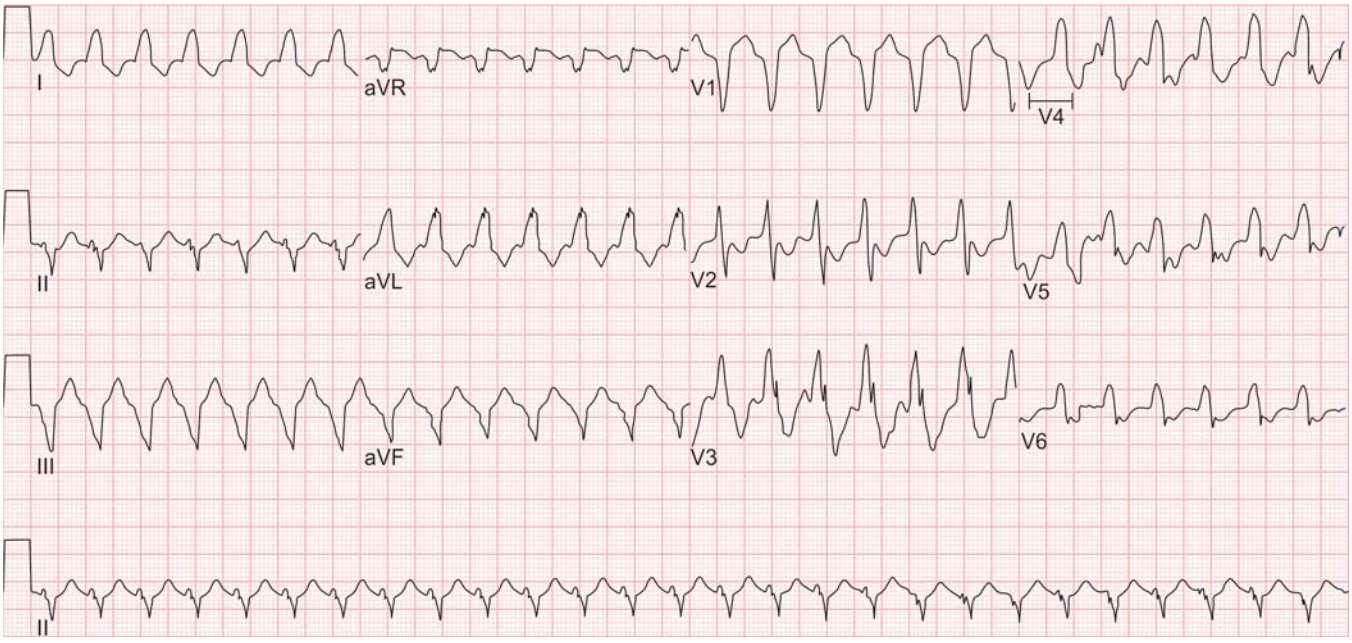


FIGURE 7: An ECG (25 mm/s) from ARVD/C patient with *PKP2* mutation. This VT has an LBBB morphology and superior axis (with positive QRS complex in aVL), thus originating inferiorly from the RV

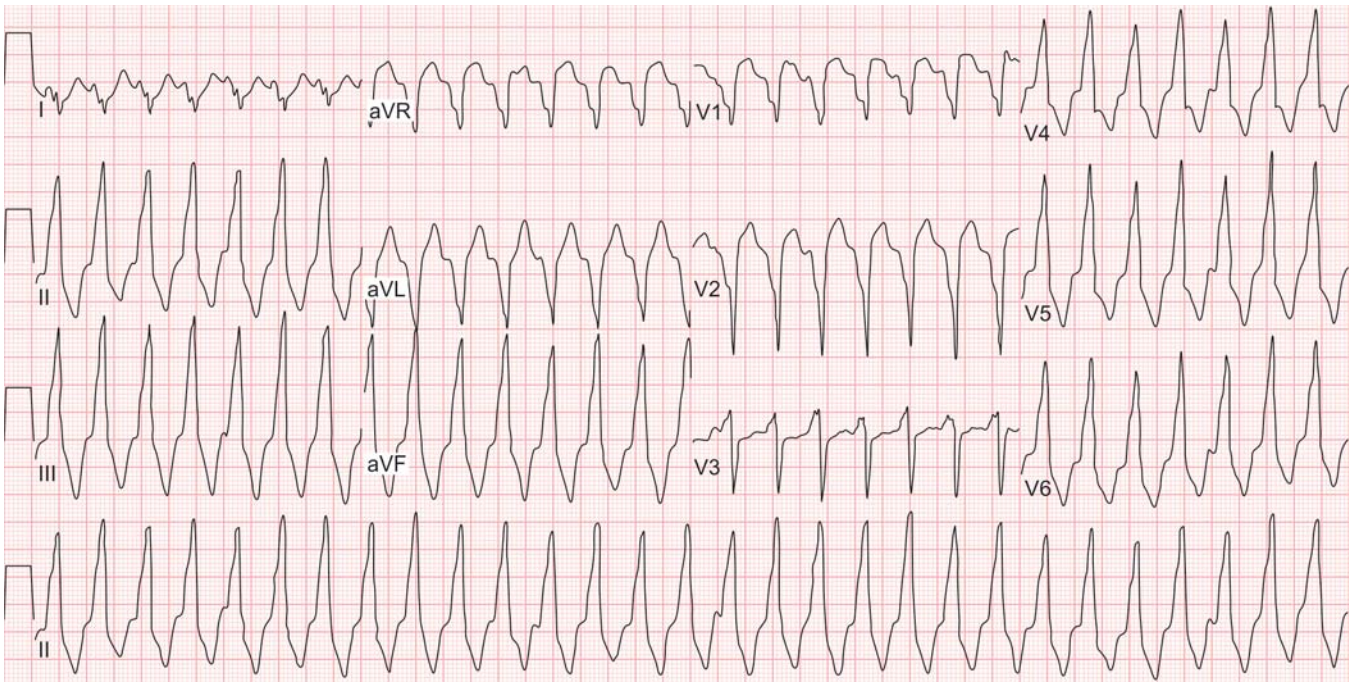


FIGURE 8: An ECG (25 mm/s) from ARVD/C patient without identified mutation. This VT has also LBBB morphology, but with inferior axis, originating from RV outflow tract. Note the typical negative QRS complex in aVL

diagnostic criteria. If a first-degree relative is diagnosed with ARVD/C but does not fulfill the diagnostic criteria, only a minor criterion is counted. Sudden death of a family member under the age of 35 years, presumably but not proven to be due to ARVD/C related arrhythmias, is a minor criterion. Pathologic confirmation of transmural fibrofatty replacement of the RV at autopsy or after surgical resection is considered a major criterion for the diagnosis.[50]

NON-CLASSICAL ARVD/C SUBTYPES

NAXOS DISEASE

All patients who homozygously carry the recessive *JUP* mutation for Naxos disease have diffuse palmoplantar keratosis and woolly hair in infancy. Children usually have no cardiac symptoms, but may have ECG abnormalities and nonsustained ventricular arrhythmias.[6,27] The cardiac disease is 100% penetrant by adolescence, being manifested by symptomatic arrhythmias, ECG abnormalities, right ventricular structural alterations and LV involvement. In one series of 26 patients followed for 10 years, 62% had structural progression of right ventricular abnormalities and 27% developed heart failure due to LV involvement.[27] Almost half of the patients developed symptomatic arrhythmias and the annual cardiac and SCD mortality were 3% and 2.3% respectively, which are slightly higher than seen in autosomal dominant forms of ARVD/C. A minority of heterozygotes has minor ECG and ECG changes, but clinically significant disease is not present.

CARVAJAL SYNDROME

Carvajal syndrome is associated with a *DSP* gene mutation, and is also a recessive disease manifested by woolly hair, epidermolytic palmoplantar keratoderma and cardiomyopathy.[29] All diagnosed patients have been from Ecuador. The cardiomyopathy of Carvajal syndrome was first thought to be mainly left ventricular, with dilated left ventricular cardiomyopathy. A number of the patients with Carvajal syndrome had heart failure in their teenage years, resulting in early morbidity. Further research revealed that the disease is characterized mainly by ventricular hypertrophy, ventricular dilatation and discrete focal ventricular aneurysms. In the RV, focal wall thinning and aneurysmal dilatation were identified in the triangle of dysplasia.

LEFT DOMINANT ARVD/C (LDAC)

As previously mentioned, in classic ARVD/C the histologic process predominantly involves the RV and extends to the LV in more advanced stages.[52,62,65-67] In contrast, patients with left-dominant arrhythmogenic cardiomyopathy (LDAC, also known as left-sided ARVD/C or arrhythmogenic left ventricular cardiomyopathy) have fibrofatty changes that predominantly involve the LV.[68] Clinically, this disease entity is characterized by (infero)lateral T-wave inversion, arrhythmias of LV origin and/or proven LDAC.

Patients may present with arrhythmias or chest pain at ages ranging from adolescence to over 80 years. By cardiac MRI about one-third of patients show a LV ejection fraction less than 50%. Furthermore, MRI with late gadolinium enhancement (LGE) of the LV demonstrated late enhancement in a subepicardial/midwall distribution. Similar to ARVD/C, some patients with LDAC have desmosomal gene mutations (see below).

DIFFERENTIAL DIAGNOSIS

Although the diagnosis in an overt case of ARVD/C is not difficult, early and occasionally late stages of the disease may

show similarities with a few other diseases. In particular, differentiation from idiopathic VT originating from the RVOT can be challenging. However, idiopathic RVOT VT is a benign non-familial condition, in which the ECG shows no depolarization or repolarization abnormalities and no RV structural changes can be detected. Furthermore, VT episodes have a single morphology (LBBB morphology with inferior axis) and are usually not reproducibly inducible by premature extrastimuli at programmed stimulation during electrophysiologic studies.[69,70] Idiopathic RVOT VT may be inducible by regular burst pacing and isoproterenol infusion. It is important to differentiate idiopathic RVOT VT from ARVD/C for several reasons. The first is the known genetic etiology in ARVD/C. A genetic abnormality is not present in patients with idiopathic VT originating from the RVOT. Therefore, it has implications with regards to screening of family members. The prognosis of RVOT tachycardia is uniformly excellent with sudden death occurring rarely. Finally, in contrast to ARVD/C, catheter ablation is usually curative in idiopathic RVOT tachycardia.

Another disease mimicking ARVD/C is cardiac sarcoidosis. Sarcoidosis is a disease of unknown etiology, characterized by the presence of noncaseating granulomas in affected tissues, mainly lungs, but heart, skin, eyes, reticuloendothelial system, kidneys and central nervous system can also be affected. The prevalence of this condition varies in different geographical regions, and the disease may also be familial and occurs in specific racial subgroups.[71] Clinical symptoms of cardiac involvement are present in about 5% of all patients with sarcoidosis. The clinical manifestations of cardiac sarcoidosis depend upon the location and extent of granulomatous inflammation and include conduction abnormalities, ventricular arrhythmias, valvular dysfunction and congestive heart failure. Myocardial sarcoid granulomas or areas of myocardial scarring are typically present in the LV and septum of patients with this condition, and the RV can be predominantly affected. The VT associated with right ventricular abnormalities can, therefore, result in diagnostic confusion, especially if there is no systemic evidence of sarcoidosis. Patients can present with clinical features similar to those of ARVD/C including arrhythmias and sudden cardiac death.[72] Cardiac sarcoidosis can be diagnosed definitively by endomyocardial biopsy if granulomas are visualized.[73] To strengthen differentiation from ARVD/C, gadolinium-enhanced MRI may be beneficial by detecting located abnormalities in the septum, which is typical for sarcoidosis but seldom seen in ARVD/C. Active foci of sarcoidosis can be visualized by positron emission tomography (PET) scan. Therapy with corticosteroids is recommended for patients diagnosed with cardiac sarcoidosis. Treatment aims to control inflammation and fibrosis in order to maintain cardiac structure and function.

Myocarditis has to be excluded in patients suspected of ARVD/C. Myocarditis may arise from viral or other pathogens as well as toxic or immunologic insult. In general, endomyocardial biopsy is required to distinguish ARVD/C from myocarditis.

ARVD/C may mimic DCM, especially in the more advanced stages of disease. Patients with DCM usually present with heart failure or thromboembolic disease, including stroke. Since it is uncommon to have sustained VT or sudden death as the initial presenting symptom of DCM, patients with these symptoms should be first suspected of having ARVD/C.

MOLECULAR GENETIC ANALYSIS

It is important to realize that the clinical diagnosis of ARVD/C is based exclusively on fulfillment of the diagnostic Task Force criteria. Mutations underlying the disease show incomplete penetrance and variable clinical expression. Some genetically affected patients may have no signs or symptoms whatsoever, whereas no mutations can be identified in a large minority of clinically diagnosed patients. Therefore, genetic analysis may not be of any critical diagnostic value for the index patient who meets Task Force criteria, but can be used to identify if family members are predisposed to disease development.

The strategy for genetic testing in ARVD/C is as follows:

Individuals with clinical diagnosis of ARVD/C are the first to be tested. The detection of a pathogenic mutation does not make a clinical diagnosis of ARVD/C. In contrast, if no mutation can be identified in a patient diagnosed with ARVD/C, the clinical diagnosis of ARVD/C is still applicable. If a pathogenic mutation is identified in the proband, parents, siblings and children of this patient can be tested for the mutation via the cascade method. When an (asymptomatic) relative is found to carry a pathogenic mutation, periodic cardiologic screening is required.

Table 1 shows the different genes related to ARVD/C. Currently, DNA analysis for *PKP2*, *DSG2*, *DSC2*, *DSP* and *JUP* is recommended in ARVD/C patients with an appropriate indication for this analysis.

PROGNOSIS AND THERAPY

The prognosis of classical ARVD/C is considerably better than that of patients with sustained VT from left ventricular structural heart disease. However, ARVD/C is a progressive disease and may lead to RV and also LV failure or sudden cardiac death. The death rate for patients with ARVD/C has been estimated at 2.5% per year.[74] Retrospective analysis of clinical and pathologic studies identified several risk factors for sudden death, such as previously aborted sudden death, syncope, young age, malignant family history, severe RV dysfunction and LV involvement.[75,76]

Electrophysiologic induction of VT with LBBB morphology and superior axis is a major diagnostic criterion.[58,64] However, electrophysiologic studies have not proven to be useful in risk stratifying patients with ARVD/C. This was illustrated in a multicenter study of 132 patients with ARVD/C in whom electrophysiologic study was performed prior to ICD implantation.[77] The positive and negative predictive values of VT inducibility for subsequent appropriate device therapy were 49% and 54% respectively.

In addition to symptomatic treatment, prevention of sudden death is the most important therapeutic goal in ARVD/C. Most data on effective treatment strategies refer to retrospective analyzes in single centers with only limited numbers of patients, and results are difficult to compare due to different patient selection and treatment strategies. There is limited data on long-term outcomes and no controlled randomized trials have been performed. International registries have been established, but have not yet reported results on treatment.

Evidence suggests that asymptomatic patients and healthy mutation carriers do not require prophylactic treatment. They should undergo regular cardiac evaluations including 12-lead ECG, 24-hours Holter monitoring, echocardiography and exercise testing for early identification of unfavorable signs. In patients diagnosed with or have signs or symptoms of ARVD/C as well as mutation carriers, specific life style advice is advisable. Sports participation has been shown to increase the risk of sudden death fivefold in ARVD/C patients.[78] Furthermore, excessive mechanical stress, such as during competitive sports activity and training, may aggravate the underlying myocardial abnormalities and accelerate disease progression. Therefore, patients with ARVD/C should be advised against practicing competitive and endurance sports, such as running marathons.

Therapeutic options in patients with ARVD/C include antiarrhythmic drugs, catheter ablation and ICD.

Patients with VT have a favorable outcome when they are treated medically and therefore pharmacologic treatment is the first choice. This concerns not only patients who have presented with sustained VT but also patients and family members with nonsustained VT or greater than 500 ventricular extrasystoles on 24-hours Holter monitoring. Since ventricular arrhythmias and cardiac arrest occur frequently during or after physical exercise or may be triggered by catecholamines, antiadrenergic β-blockers are recommended. Sotalol is the drug of first choice. Alternatively, other β-receptor blocking agents, amiodarone and flecainide have all been reported as useful.[79] Efficacy of drug treatment has to be evaluated by serial Holter monitoring and/or exercise testing. This strategy has proven to have better long-term outcome when compared to standard empirical treatment.[79]

Catheter ablation is an alternative in patients who are refractory to drug treatment and have frequent VT episodes with a predominantly single morphology. Marchlinski et al. performed VT ablation in 19 ARVD/C patients by the use of focal and/or linear lesions; in 17 no VT recurred during the subsequent 7±22 months.[80] In a series of 50 consecutive patients studied during 16 years, Fontaine et al. reported a 40% success rate by radiofrequency ablation after multiple ablation sessions, that increased to 81% when fulguration was used additionally.[81] However, these reports are from single centers with highly experienced electrophysiologists, and may not be reproducible in general practice. Catheter ablation is generally considered to be palliative and not curative. Long-term success rates are poor. Due to disease progression, new VTs with different morphologies will usually occur.[82]

Although antiarrhythmic drugs and catheter ablation may reduce VT burden, there is no proof from prospective trials that these therapies will also prevent sudden death. The ICD implantation is indicated in patients who are intolerant of antiarrhythmic drug therapy and who are at serious risk for sudden death. Implantation of an ICD has to be considered in ARVD/C patients with aborted cardiac arrest, intolerable fast VT and those with risk factors as mentioned above.

SUMMARY

Arrhythmogenic right ventricular dysplasia cardiomyopathy is most often a genetically determined disease characterized by fibrofatty replacement of myocardial tissue. Primarily affecting the RV, but extension to the LV occurs, especially in more advanced stages of the disease. At the molecular level, both ventricles are affected, presumably in all stages of the disease. Its prevalence has been estimated to vary from 1:2000 to 1:5000. Patients typically present between the second and the fourth decade of life with exercise induced tachycardia episodes originating from the RV. It is also a major cause of sudden death in the young and athletes.

The causative genes encode proteins of mechanical cell junctions (e.g. plakoglobin, plakophilin-2, desmoglein-2, desmocollin-2, desmoplakin) and account for intercalated disk remodeling. The classical form of ARVD/C is inherited in an autosomal dominant trait, but has variable expression. The rare recessively inherited variants are often associated with palmoplantar keratoderma and woolly hair. The diagnosis is made according to a set of Task Force criteria, based on family history, depolarization and repolarization abnormalities, ventricular arrhythmias with an LBBB morphology, functional and structural alterations of the RV, and fibrofatty replacement in endomyocardial biopsy. Two dimensional echocardiography, cineangiography and magnetic resonance are the imaging tools to visualize structural-functional abnormalities. The main differential diagnoses are idiopathic right ventricular outflow tract tachycardia, myocarditis and sarcoidosis. Palliative therapy consists of antiarrhythmic drugs, catheter ablation and implantable cardioverter defibrillator. Young age, family history of juvenile sudden death, overt left ventricular involvement, VT, syncope and previous cardiac arrest are the major risk factors for adverse prognosis.

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Chapter 38

Long QT, Short QT and Brugada Syndromes

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Chapter Outline

- LQT Syndrome
  - Clinical Manifestations
  - Pathogenesis
  - Molecular Genetics
  - Genotype-Phenotype Correlation Studies and Risk Stratification Strategies
  - Diagnosis
  - Genetic Testing
  - Therapy
  - ICD Therapy
  - Left Cardiac Sympathetic Denervation
  - Genotype-Specific Therapy
- SQT Syndrome
  - Clinical Manifestations
  - Molecular Genetics
  - Pathogenesis
  - Diagnosis
  - Therapy
- Brugada Syndrome
  - Clinical Manifestations
  - Genetics
  - Pathogenesis
  - Diagnosis
  - Prognosis, Risk Stratification and Therapy

INTRODUCTION

Over the past two decades, ample information has been accumulated on cellular mechanisms and genetics of arrhythmias in structurally normal heart. The basic pathogenic mechanism for these arrhythmias may involve hereditary disturbances in ionic currents at the cellular level while the heart remains grossly normal. The high rate of sudden death (especially in the young) due to congenital arrhythmias, coupled with the potential availability of preventive measures, mandate the need for higher awareness of the medical community of these potentially lethal arrhythmia syndromes. In this chapter, we will review the current state of understanding of inherited arrhythmias including long QT (LQT) syndrome, short QT (SQT) syndrome and Brugada syndrome. This review focuses on inherited arrhythmias and will not cover acquired LQT syndrome.

LQT SYNDROME

Jervell and Lange-Nielsen, in 1957, firstly described the congenital LQT syndrome in a Norwegian family with four members suffering from prolonged QT, syncope and congenital deafness.[1] Three of the four affected patients died suddenly at the age of 4, 5 and 9 years.[1] Jervell and Lange-Nielsen syndrome, is inherited in an autosomal recessive pattern. Several years later, Romano et al. and Ward et al. independently described a similar syndrome but without deafness and with an autosomal dominant pattern of inheritance.[2,3] The underlying genes for LQT syndrome, however, were not discovered until more recently; in 1995 and 1996, the first three genes associated with the most common forms of the LQT syndromes (types 1, 2 and 3) were identified.[4–6] Since then, the scientific and medical community has witnessed discovery of hundreds of variants in nearly a dozen genes associated with a wide variety of LQT or related arrhythmia syndromes.

CLINICAL MANIFESTATIONS

The congenital LQT syndrome is a common identifiable cause of sudden death in the presence of structurally normal heart.[7] The natural history of LQT syndrome is highly variable.[8–12] The majority of patients may be entirely asymptomatic with the only abnormality being QT prolongation in the ECG.[8–12] Some gene variant carriers of LQT syndromes may not even display the prolonged QT interval (silent carriers).[13,14] Symptomatic patients typically, present in the first two decades of life including the neonatal period, with recurrent attacks of syncope precipitated by *torsade de pointes* type of ventricular arrhythmias.[8,11] This form of tachycardia is characterized by cyclical changes in the amplitude and, polarity of QRS complexes such that their peak appears to be twisting around an imaginary isoelectric baseline. *Torsade de pointes* may resolve spontaneously, however, it has a great potential to degenerate into ventricular fibrillation and is an important cause of sudden death.[9]

PATHOGENESIS

As the QT interval represents a combination of action potential (AP) depolarization and repolarization, variations in QT

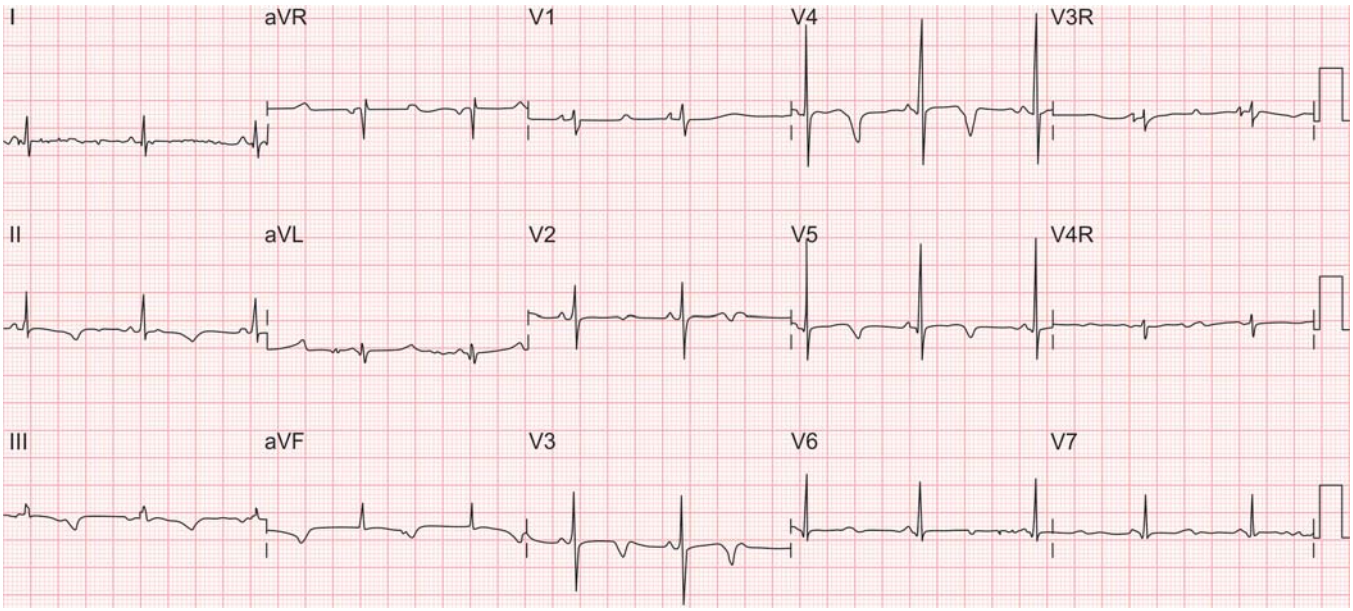


FIGURE 1: LQT1 ECG belongs to a 7-year-old boy with history of cardiac arrest during swimming. Note the prolonged QT with inverted, broad-based and T-wave pattern

interval may arise from the dysfunction of ion channel, responsible for the timely execution of the cardiac AP. A decrease in the outward repolarizing currents (mainly potassium currents) or an increase in the inward depolarizing currents (mainly sodium and calcium) may increase action potential duration (APD) and QT prolongation. The increases in APD result in lengthening of effective refractory period (ERP) that in turn predisposes to the occurrence of early after depolarizations (EADs), due to enhancement of the sodium-calcium exchanger (NCX) current and reactivation of the L-type calcium channels.[15–18] These EADs are known to support ventricular arrhythmias.[16–18]

MOLECULAR GENETICS

Over the last fifteen years, gain- or loss-of-function variants in nearly a dozen genes have been associated with development of LQTS. LQT1 is the most common form of the LQT syndrome and results from loss-of-function variants in *KCNQ1*, which encodes the alpha subunit of I_{Ks}, the cardiac slowly activating delayed-rectifier potassium channel current.[6] The mechanism(s) by which, each variant causes decreased I_{Ks} current varies among the gene variant carriers. Variant sub-units may co-assemble with the wild-type protein and render them defective causing more than 50% loss-of-function (i.e. dominant-negative effect).[19] Alternatively, the variants may result in haploinsufficiency with ~ 50% reduction in protein expression and the resultant current.[19] In addition to the biophysical function (dominant-negative vs haploinsufficiency), the location of variants appears to significantly influence the severity of phenotype. For example, Moss et al. demonstrated significantly higher cardiac event rates in patients with transmembrane variants in *KCNQ1* gene[19] (Fig. 1).

LQT2 results from loss-of-function variants in *KCNH2* (also known as *HERG*), which encodes the alpha-subunit of I_{Kr}, the rapidly activating delayed-rectifier potassium current in the heart.[5] The loss-of-function in the genes responsible for I_{Ks} and IKr reduces the outward potassium current and prolongs APD, leading to QT prolongation in LQT1 and LQT2, respectively[5,6] (Fig. 2)

LQT3 arises from variants in *SCN5A* that encodes the alpha-subunit of $Na_V1.5$, the primary cardiac voltage-gated sodium-channel.[4] These variants disrupt fast inactivation of $Na_V1.5$ leading to excess late inward sodium current that in turn results in prolonged repolarization and APD.[4] The three most common LQTS, i.e. LQT 1-3, vary significantly in their natural history and clinical presentation, which will be discussed later in this chapter.

Unlike LQT1-3, LQT4 is not caused by an ion channel gene variant. LQT4 arises from variants in *ANK2*, which encodes ankyrin-B in cardiomyocytes.[20] The human *ANK2* gene was the first LQT syndrome gene that was discovered to encode a membrane associated protein (ankyrin-B) rather than an ion channel or channel subunit.[20] Ankyrin-B is an adaptor protein that interacts with several membrane-associated ion channels and transporters in ventricular myocytes including Na^+/K^+ ATPase, Na^+/Ca^{2+} exchanger-1 (NCX1) and IP3 receptors.[20] Dysfunction of Na/K ATPase and NCX1 are associated with a significant increase in $[Ca^{2+}]_i$ transient amplitude, SR calcium load and catecholamine-induced after depolarizations.[20] Abnormal intracellular calcium homeostasis is thought to be the central mechanisms underlying ventricular arrhythmias.[20] Symptomatic patients with specific *ANK2* variants may display significant QT prolongation (mean QTc: 490 ± 30 ms), ventricular tachycardia, syncope and sudden death.[21] However, many variant carriers do not display prolonged QTc, but display other ventricular phenotypes with risk of syncope and death. Additionally, *ANK2* variant carriers may manifest with sinus node dysfunction and/or atrial fibrillation in addition to ventricular arrhythmias and sudden death, hence, the name ankyrin-B syndrome.[20,21] Notably, ventricular phenotypes are often triggered by catecholamines, and thus, ankyrin-B syndrome may ultimately be more appropriately described as a

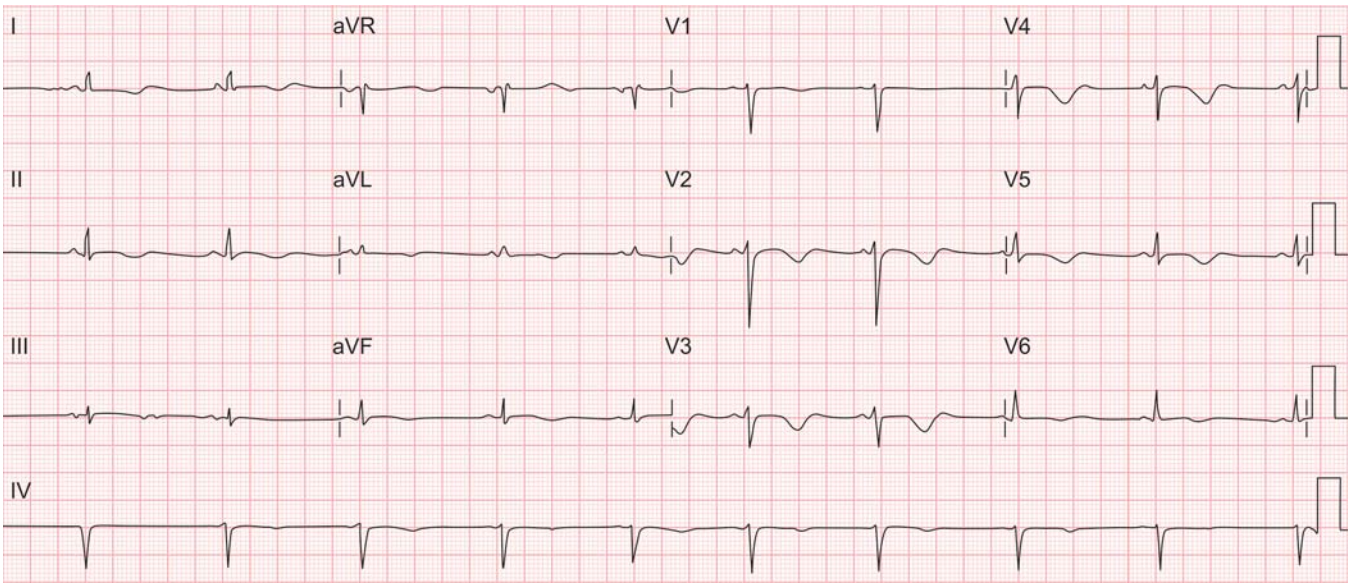


FIGURE 2: LQT2 ECG belongs to a 19-year-old female with history syncope and polymorphic ventricular tachycardia. ECG shows QT prolongation with low-amplitude inverted T-waves

class of catecholaminergic polymorphic ventricular tachycardia (CPVT).

LQT5 and LQT6 arise from loss-of-function variants in *KCNE1* and *KCNE2*, that encode the beta subunit of I_{Ks} and I_{Kr}, respectively (same currents in which the alpha subunit variants cause LQT1 and LQT2).[22–24] Akin to LQT1 and LQT2, these variants reduce outward potassium current leading to subsequent QT prolongation.[22–24]

LQT7 arises from loss-of-function variants in *KCNJ2* that encodes inward rectifying potassium channels (Kir2.1), responsible for I_{K1}.[25] I_{K1} represents the major ion conductance in the later stages of repolarization and during diastole, and reduced I_{K1} is associated with QT prolongation. Linkage studies on patients with LQT7 variants demonstrate a wide range of extra-cardiac findings associated with this form of LQTS.[25,26] These patients suffer from an autosomal dominant multisystem disease, also known as Andersen-Tawil syndrome, characterized by a combination of potassium-sensitive periodic paralysis, cardiac arrhythmia and distinctive facial or skeletal dysmorphic features such as low set ears and micrognathia.[25,26]

LQT8 is related to variants in *CACNA1c* that encodes the alpha-1C subunit of the voltage-gated calcium channel (CaV1.2) responsible for L-type calcium current ($I_{Ca,L}$) in myocytes.[27] These variants are associated with loss of voltage-dependent CaV1.2 inactivation, leading to Ca^{2+} overload and delayed repolarization due to prolonged inward, Ca^{2+} current during the plateau phase of the AP.[27] Similar to LQT7 syndrome, patients with LQT8 variants display a variety of extra-cardiac signs and symptoms (also termed Timothy syndrome) including syndactyly, abnormal teeth, immune deficiency, intermittent hypoglycemia, cognitive abnormalities, autism and baldness at birth[27] consistent with the critical role of $I_{Ca,L}$ in other tissues. Cardiac manifestations include patent foramen ovale (PFO) and septal defects, in addition to ventricular arrhythmias.[28] The condition is severe, with most affected patients dying in early childhood.[27,28]

LQT9 is associated with variants in *CaV3*, that encodes caveolin-3.[29] Caveolins are the principal proteins required for the assembly of caveolae, 50–100 nm membrane invaginations involved in the localization of membrane proteins including $Na_v1.5$ (LQT3 associated channel).[29,30] These variants interfere with the regulatory pathways between caveolin-3 and $Na_v1.5$, disrupting inactivation of $Na_v1.5$, resulting in a gain-of-function effect on late I_{Na}; the same pathological mechanism that underlies LQT3.[29]

LQT10 is linked to variants in *SCN4B*, which encodes $Na_v1.5$ one of four auxiliary subunits of $Na_v1.5$.[31] $Na_v\beta$ dysfunction is associated with a significant increase in late sodium current that affects the terminal repolarization phase of the AP, and prolongs the QT interval by a similar mechanism as LQT3-associated variants in the alpha subunit of $Na_v1.5$.[31]

LQT11 is associated with variants in *AKAP9.* that encodes A-kinase anchoring protein (AKAP), also known as yotiao, involved in the subcellular targeting of protein kinase A (PKA).[32] Yotiao is a PKA targeting protein for multiple cardiac ion channel complexes including the ryanodine receptor, the L-type calcium channel, and the slowly activating delayed rectifier I_{Ks} potassium channel (*KCNQ1*).[32,33] Variants in the *AKAP9* are associated with disruption of the interaction between *KCNQ1* and yotiao, reducing the cAMP-induced phosphorylation of the channel, that in turn eliminates the functional response of the I_{Ks} channel to cAMP, prolongs the APD and QT interval.[32,33] LQT12 is associated with variants in *SNTA1*, which encodes for ?-1syntrophin, a scaffolding protein with multiple molecular interactions including $Na_v1.5$, plasma membrane Ca^{2+}-ATPase (PMCA4b) and neuronal nitric oxide synthase (nNOS).[34] The variants in *SNTA1* are associated with increased direct nitrosylation of $Na_v1.5$ and increased late I_{Na}.[34] Akin to the mechanism in LQT3 syndrome, the increase in late sodium current causes prolonged QT interval.

GENOTYPE-PHENOTYPE CORRELATION STUDIES AND RISK STRATIFICATION STRATEGIES

The pattern of inheritance of LQTS varies depending on the type of the syndrome. Most LQTS are inherited as autosomal

dominant Romano-Ward syndrome. LQT syndrome types 1 and 5 (representing variants in alpha and beta subunit of I_{Ks}) are inherited as either autosomal recessive Jervell and Lange-Nielsen or autosomal dominant Romano-Ward syndrome.[35] Additionally, a host of factors may influence disease severity. Recently, the genotype-phenotype correlation studies on the most common forms of LQTS (type 1-3) have allowed for more in-depth understanding of natural history of each variant. For example, Priori et al. prospectively studied a large data base of unselected, consecutively, genotyped patients with LQTS (n = 647) and developed a risk stratification scheme based on gender, genotype and QTc interval after a mean observation period of 28 years.[13] The authors showed that different genotypes may manifest differently in males versus females. For example, the incidence of a first cardiac arrest or sudden death was greater among LQT2 females than LQT2 males and LQT3 males than LQT3 females.[13]

The duration of QT interval may be influenced by the genetic locus, and may also predict the likelihood of future cardiac events (defined as syncope, cardiac arrest or sudden death). In the Priori study, mean QTc was 466 ± 44 msec in LQT1, 490 ± 49 msec in LQT2 and 496 ± 49 msec in LQT3.[13] Event free survival was higher in LQT1 than LQT2 and LQT3.[13] Within each LQTS category, QTc of patients with cardiac events was significantly, longer than asymptomatic patients.[13] Amongst LQT1 patients, mean QTc was 488 ± 47 msec in those with cardiac events versus 459 ± 40 msec in asymptomatic subjects.[13] These data suggest that LQTS may have a normal or near normal QTc and sustain a cardiac event (albeit at a very low rate) and vice versa. However, irrespective of the genotype, the risk of becoming symptomatic was associated with QTc duration; a QTc of 500 msec or more was the most significant predictor of potential cardiac events.[13]

Notably, the percentage of silent variant carriers (those with gene variants but normal QT interval) was higher in the LQT1 (36%) than LQT2 (19%) or LQT3 (10%).[13] Higher percentage of silent carriers in LQT1 may at least partly explain the lower rate of cardiac events in patients with LQT1 compared to LQT2 and LQT3.[14,36–38] The fact that silent variant carriers may have normal QT interval, yet to be at increased risk of cardiac events indicates that LQTS cannot be excluded solely based on ECG findings. Furthermore, the silent carrier state may confer susceptibility of drug-induced QT prolongation and Torsade de pointes arrhythmias.[36,38,39]

Triggers of cardiac events in LQT syndrome have been shown to be largely gene specific. Schwartz et al. studied specific triggers of cardiac events in 670 LQTS patients (types 1, 2 and 3) with known genotype.[40] In LQT1, nearly 80% of cardiac events occurred during physical or emotional stress, whereas LQT3 patients experience 40% of their events at rest or during sleep and only 13% during exercise.[40] In LQT2 patients, the events occurred during emotional stress in 43% of patients. For lethal cardiac events (cardiac arrest and sudden death), the difference among the groups were more dramatic. In LQT1, 68% of lethal events occurred during exercise, whereas this rarely occurred for LQT2 and occurred in only 4% of cases for LQT3 patients.[40] In contrast, 49% and 64% of lethal events occurred during rest/sleep without arousal for LQT2 and LQT3 patients, respectively, whereas this occurred in only 9% of cases for LQT1 patients.[40] Auditory stimuli particularly clustered among LQT2 patients, whereas swimming as a trigger was more frequent in LQT1 patients.[40] A stunning percentage of patients who experienced their cardiac events during swimming were LQT1.[40]

Criteria	*Point*
ECG criteria	
QTc	
> 480	3
460–479	2
450–459	1
Torsade de pointes	2
T-wave alternans	1
Notched T-wave in 3 leads	1
Low heart rate for age	0.5
Clinical history	
Syncope with stress	2
Syncope without stress	1
Congenital deafness	1
Family history	
Definite LQT syndrome in family	1
Unexplained SCD < 30 y/o in immediate family	0.5
Scoring	
≤ 1 point = low probability for LQTS	
2–3 points = intermediate probability for LQTS	
≥ 3.5 points = high probability for LQTS	

The T-wave repolarization pattern varies according to genotype. Patients with LQT1 variant positive genotype display a distinct, inverted, broad-based, prolonged T-wave pattern that is different from the low-amplitude and sometimes, notched T-wave observed in LQT2 patients.[41] Both of these repolarization patterns are different from late-appearing T-wave seen in LQT3 patients.[41] Patients with LQT4 genotype display a characteristic notched, biphasic T-wave morphology in ECG.[21]

DIAGNOSIS

The typical case of LQTS, characterized by syncope or cardiac arrest associated with QT prolongation on ECG is fairly straightforward to diagnose. However, borderline cases may be more complex and pose a diagnostic challenge to the practicing clinician. Schwartz and his colleagues devised a diagnostic criteria based on a scoring system first in 1985 and then, updated in 1993.[37,42] Based on this scoring system, a score of one or less indicates low probability for LQTS; 2-3 denotes intermediate probability and higher than 3.5 indicates high probability for LQTS. If a patient receives a score of 2-3, serial ECG and 24-h Holter monitoring may be obtained as the QT interval may vary from time to time.[38] Short-term variability of QT interval has recently been demonstrated to correlate with high risk LQT syndrome.[43]

GENETIC TESTING

The diagnostic criteria based on ECG and clinical history were primarily devised before the human genome project era and therefore, may not always account for many new advances in molecular genetics. As mentioned earlier, individuals may harbor disease-associated variants and yet have normal ECG parameters

and QT interval (silent carriers). In select cases, genetic testing and molecular diagnostic methods may complement the ECG and clinical criteria; allowing for screening of proband family members to detect silent variant carriers that may predispose individuals to potential events.[36,39,44,45] For example, HERG inhibition is commonly the mechanism associated with drug-induced QT prolongation, and variants in other ion channel/ion channel modulator genes may also predispose individuals to QT prolongation and ventricular arrhythmias.[36,45,46] Therefore, identifying gene variants that promote arrhythmia susceptibility (either congenital or acquired) may provide important information to a physician in their clinical practice (i.e. avoiding QT prolonging drugs in patients harboring specific channel variants). It is important to note that current genetic testing for arrhythmias may harbor its own drawbacks. For example, false negative results may occur when the patient has a variant in a gene not covered in the testing panel (the relevant gene or gene variant may not have even been discovered!). Moreover, the significance of a positive test result may often be difficult to ascertain. As reviewed by others, it will be critical to continue to define genotype-phenotype relationships to provide additional new data that can be carefully considered when utilizing patient genotype to predict and/or manage clinical phenotypes.

THERAPY

As the risk of cardiac events in LQTS is genotype, age and gender dependent, therapy should be carefully tailored to the individual patients according to their risk factors. According to a recently published study from the International LQTS Registry, beta blocker therapy, significantly, reduces the risk of cardiac events in LQT1 and LQT2 patients.[47] This is not surprising as the most common triggers of cardiac events in LQT1 and LQT2 patients are exercise and emotional stress, respectively.[40] Furthermore, LQT1 patients harbor I_{Ks} dysfunction, which has been shown to activate in higher heart rates and is necessary for QT interval shortening with tachycardia.[6] In contrast, beta blockers may offer limited efficacy among LQT3 patients; as they display further QT prolongation at slower heart rates.[48] Moreover, according to the International LQT Registry data, beta blocker therapy reduces the risk to similar extent in LQT1 and LQT2 patients (67% and 71% risk reduction, respectively).[47] Different beta blockers displayed differential effects in each category of LQTS. Atenolol, but not nadolol, reduced the risk significantly in LQT1 patients, whereas nadolol, but not atenolol was associated with a significant risk reduction in LQT2 patients.[47] Higher risk patients, such as LQT1 males and LQT2 females gained more benefit from beta blocker therapy compared to lower risk subsets. Despite the significant risk reduction with beta blocker therapy, high risk patients experienced considerable residual event rates during beta blocker therapy.[47] History of syncope during beta blocker therapy was associated with higher event rates.[47] LQT2 genotype was associated with significantly higher residual event rates while taking beta blockers compared to LQT1.[47,49]

ICD THERAPY

Insofar, as high risk patients with LQT syndrome continue to have a residual event rate while receiving beta blocker therapy, there may be a need for additional protection against potentially fatal arrhythmias. Current guidelines recommend ICD therapy as a class IIa indication for primary prevention of cardiac events in LQTS patients who experience syncope or ventricular tachycardias during beta blocker therapy.[50] These guidelines provide a class IIb recommendation for ICD therapy in patients with risk factors for SCD, irrespective of medical therapy.[50]

LEFT CARDIAC SYMPATHETIC DENERVATION

Left cardiac sympathetic denervation (LCSD) was introduced in 1971 as the first therapy for LQT syndrome.[51] The contemporary LCSD techniques use extrapleural approach and obviate the need for thoracotomy.[52] A recent study of 147 very high-risk LQTS patients, who underwent LCSD over a span of 35 years (average follow-up period of 8 years) demonstrated that LCSD reduced the number of cardiac events by 91% per patient per year.[52] According to the result from this study, LCSD may be considered in patients with recurrent syncope despite beta-blockade, and in patients, who experience arrhythmia storms with ICD therapy.[52]

GENOTYPE-SPECIFIC THERAPY

As cardiac events may be clustered around exercise or emotional stress in LQT1 patients, these individuals may be advised to avoid competitive sports and/or stressful situations. For example, swimming has previously been particularly discouraged in LQT1 patients. Beta blockers remain the mainstay of therapy in LQT1 syndrome.

In patients with LQT2, maintaining adequate serum potassium level is essential, as I_{Kr} activity may vary with serum potassium levels.[53] Therefore, use of potassium supplements in combination with potassium sparing diuretics may be recommended in LQT2 patients.[53] Since arousal from sleep, especially with a sudden noise may be a triggering a risk factor in LQT2 patients, the use of alarm clock or telephone in the patient's bedroom should also be carefully considered.[40]

Sodium channel blockers have been proposed for gene-specific treatments in LQT3, which is associated with variants in the sodium channel gene (*SCN5A*).[48] Early clinical studies demonstrated efficacy of mexiletine or flecainide in shortening of repolarization period and QT interval.[48] Indeed, ACC/AHA 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death recommended sodium channel blockers for treatment of LQT3 patients as a class IIb indication.[54] However, more recently, Ruan et al. in an elegant study, provided *in vitro* cellular evidence that different *SCN5A* variants may display heterogeneous biophysical properties; and the use of sodium channel blockers may be deleterious in selected group of LQT3 patients.[55] The study was prompted by the death of a young child affected by an *SCN5A* variant whose QT interval not only shorten, but also prolonged in response to mexiletine treatment.

SQT SYNDROME

SQT syndrome is a rare channelopathy associated with increased risk of atrial and ventricular arrhythmias. The association of SQT interval with sudden cardiac death was first described near

two decades ago by Algra and his colleagues.[56] They reported a two-fold risk of sudden death in patients with a QTc less than 400 milliseconds, as compared with patients with a QTc between 400 and 440 milliseconds.[56] In the year 2000, Gussak et al. reported the first familial cases of idiopathic SQT syndrome associated with paroxysmal atrial fibrillation. A few years later, Gaita et al. described additional cases of SQT syndrome associated with sudden cardiac death.[57] To date, the number of identified patients with SQT syndrome is low.[58,59] However, with increasing awareness of medical community of the relationship of SQT with AF and sudden cardiac death, the prevalence is expected to rise.

CLINICAL MANIFESTATIONS

The clinical manifestations of SQT syndrome include propensity to AF, syncope and sudden death.[57,60,61] In most reported cases, the QTc was less than 320 ms and often less than 340 ms.[62,63] Therefore, it is prudent to suspect SQT syndrome in patients with a QT interval of less than 340 ms and personal and/or family history of lone AF, ventricular fibrillation, syncope or sudden cardiac death. To date, there is no gender predilection for SQT syndrome.[63] Age at onset of symptoms vary widely with reported cases from one year old (sudden infant death syndrome) to age 80 year old.[63] One study reported the mean age at diagnosis of 30 years.[63] Cardiac arrest has been reported to occur both at rest and under stress.[63,64]

MOLECULAR GENETICS

To date, three genes with an association with SQT syndrome have been identified. All three genes encode potassium channel proteins. SQT1 is associated with variants in *KCNH2* (also LQT2 gene), that result in increases in I_{Kr}.[60] SQT2 is associated with variants in *KCNQ1* (also LQT1 gene) that result in increased I_{Ks}.[65] SQT3 is associated with variants in *KCNJ2* (also LQT7 gene) that encodes the inwardly rectifying potassium channel protein, Kir2.1.[66] Gain-of-function variants in *KCNJ2* may result in increased outward I_{K1} current and SQT syndrome type 3.[66]

PATHOGENESIS

Gain-of-function variants in specific cardiac potassium channels may cause acceleration of repolarization and abbreviation of APD leading to shortening of ERP.[60,61,65,66] Shortened refractory period is a well established substrate for re-entrant tachycardias; hence, predisposition to atrial fibrillation and ventricular tachycardias in patients with SQT syndrome.[67] A second proposed mechanism for predisposition to re-entrant arrhythmias in SQT syndrome is the increases in transmural dispersion of repolarization. The ECG of affected individuals has distinctive features including tall, peaked, symmetrical T-waves with prolonged T_{peak}-T_{end}.[68] Prolonged T_{peak}-T_{end} has been proposed to be indicative of augmented transmural dispersion of repolarization.[68] Exaggerated transmural heterogeneity during repolarization forms the substrate for the development of re-entrant arrhythmias.[68] Extramiana and colleagues demonstrated that QT-interval abbreviation in the absence of transmural dispersion of repolarization was not sufficient to induce ventricular arrhythmias.[68] Therefore, the combination of short refractory periods and increased dispersion of refractoriness may result in patients with SQT syndrome vulnerable to arrhythmias.

DIAGNOSIS

The precise cut-off point for QT interval in SQT syndrome is still somewhat debated. Currently, based on several reports, the upper limit of QT interval suggestive of SQT syndrome is considered 320–340 ms.[62,63] However, the mere presence of SQT interval does not necessarily appear to be sufficient to make the diagnosis. Anttonen et al. screened a population of over 1000 healthy volunteers for SQT interval and followed them up for a mean of 29 years.[69] The prevalence of QTc interval less than 320 ms (very short) and less than 340 ms (short) was 0.10% and 0.4%, respectively.[69] All cause or cardiovascular mortality did not differ between subjects with a very short or SQT interval and those with normal QT intervals (360–450 ms).[69] There were no sudden cardiac deaths, aborted sudden cardiac deaths, or documented ventricular tachyarrhythmias among subjects with SQT interval.[69]

In addition to shortened QT interval, patients with SQT syndrome may display a peculiar ECG morphology.[62,70,71] Affected patients often demonstrate absent ST segment with the T-wave attached to the S-wave.[71,72] A second finding, that is seen in at least about half of the patients, is a tall, peaked, narrow-based T-waves in the right precordial leads.[69,70,72] Another distinctive ECG feature of patients with SQT syndrome is the relatively prolonged T_{peak}-T_{end} interval which may indicate enhanced transmural dispersion of repolarization.[68] Electrophysiological studies have been reported in a limited number of patients with SQT syndrome. Both atrial and ventricular ERP were reported to be shortened.[61,63,73] Furthermore, ventricular tachycardias were inducible in nearly all patients.[61,63,73]

As part of the diagnostic evaluation of SQT syndrome, acquired causes of QT interval shortening are often excluded. Electrolyte/acid-base abnormalities, such as hyperkalemia, hypercalcemia and acidosis, are well known to shorten QT interval. Other causes include hyperthermia and QT shortening medications such as digoxin and mexiletine. Finally, QT measurements are commonly made at heart rates less than 80 beat/min, as the QT interval in SQT syndrome patients may fail to adapt to increase heart rates.

THERAPY

The paucity of SQT syndrome cases may limit the opportunity to systematically study treatment of this recently recognized arrhythmia syndrome. Nonetheless, drugs that block outward potassium current and prolong repolarization seem attractive and have been tested in a limited number of cases. The class Ia anti-arrhythmic agents, quinidine and disopyramide have been demonstrated to prolong QT interval and ventricular ERP and reduce inducibility of ventricular arrhythmias.[63,74–76]

The high incidence of fatal cardiac events associated with SQT suggests the use of ICD therapy, early on, in the management of the symptomatic patients.[62] In asymptomatic patients, however, the indications for ICD may be less clear. Patients with SQT interval and implanted ICD may be at

increased risk for inappropriate therapy due to oversensing as a result of the detection of short-coupled and prominent T-waves.[77] Reprogramming of the ICD with adaptation of sensing levels and decay delays without sacrificing correct arrhythmia detection may be helpful in these patients.[77]

BRUGADA SYNDROME

In 1992, Brugada and Brugada described a hereditary arrhythmia syndrome characterized by ST segment elevation in the right precordial leads, right bundle branch block and increased vulnerability to ventricular tachycardias and sudden death in the absence of any structural heart disease.[78] Although the Brugada brothers are the first to formally describe and characterize the syndrome, the history of the syndrome dates back to several decades prior. A similar syndrome manifested as sudden death during sleep frequently after a heavy meal, most often affecting young men, has long been noted in the south Asian culture. The terms sudden unexplained nocturnal deaths (SUND) or sudden unexplained death in sleep (SUDS) are used to explain this folk illness with various local names including *Bangungot* (in Philippines), *Pokkuri* (in Japan) or *Lai Tai* (in Thailand). Although Brugada syndrome seems to be endemic in south-east Asian countries, cohorts of the syndrome have been reported across the world.[79] Currently, Brugada syndrome is considered as a major cause of sudden cardiac death in the young. Timely identification of symptomatic Brugada syndrome patients is important, as implantable cardioverter defibrillators (ICD) may be life-saving in these individuals.

CLINICAL MANIFESTATIONS

Brugada syndrome is characterized by the occurrence of polymorphic ventricular tachycardias in patients with the ECG patterns of a peculiar ST-segment elevation in right precordial leads and **right bundle branch block** (RBBB).[78] An increased propensity to atrial fibrillation and supraventricular arrhythmias has also been reported.[80] Patients with Brugada syndrome have structurally normal hearts; and are typically, otherwise healthy and active.[80] Notwithstanding, recent research suggests that with the use of high resolution magnetic resonance imaging, subclinical structural abnormalities in right ventricle may be identified.[81] Many patients with the syndrome may have the characteristic ECG findings; however, remain asymptomatic until the first arrhythmic episode that may lead to syncope or sudden death. On the other hand, the symptomatic patients with positive ECG findings may transiently display normal ECG which makes the diagnosis more challenging.

GENETICS

Brugada syndrome is a familial arrhythmia syndrome with autosomal dominant pattern of inheritance, incomplete and gender-dependent penetrance. The mean age of clinical manifestations is 40 years with a wide range from infancy to the eighth decade of life.[82,83] Men are affected much more commonly than women with a male to female ratio of 3/1.[82,83] The true prevalence of the disease is unknown. A great deal of work has been published during the last two decades, since the Brugada brothers' authored the initial report.

In 1998, Chen et al. identified the first loss-of-function gene variant related to the Brugada syndrome on *SCN5A*, that encodes cardiac voltage gated sodium channels.[84] Since then, over 100 associated variants have been reported in the literature with 15–30% of them located on *SCN5A* gene.[85,86] Another 11–12% have been attributed to *CACNA1C* and *CACNB2*.[85] Variants in other genes (*GPD1L, SCN1B, KCNE3* and *SCN3B*) likely contribute to the Brugada phenotype, although to a lesser extent.[85] Notably, all the genes discovered to date explain only one-third of Brugada syndrome cases, indicating that there is, still an important amount of work to be done to unravel the genetic basis of this lethal disease.

PATHOGENESIS

In 2001, Antzelevitch et al. proposed the dispersion of repolarization model, which hypothesizes a pathophysiological mechanism of re-entrant arrhythmias in Brugada syndrome.[87] This model is based on the demonstration that the density and kinetics of currents underlying phase-1 of AP (Ito), exhibit transmural dispersal.[88] The Ito current density is more profound in epicardium compared to endocardium.[88] In Brugada syndrome, the impaired sodium influx in epicardial cells is subject to exaggerated Ito defect leading to accentuated AP morphology variability between epicardial cells and endocardial cells. The arrhythmic substrate is, therefore, the result of increased transmural heterogeneity of the currents involved in the phase-I depolarization of the ventricle, enabling local re-excitation via re-entry.[87,89]

DIAGNOSIS

Electrocardiographic signs of Brugada syndrome are classified into three types as follows:[80]

- Type I: Coved ST-segment elevation greater than 2 mm followed by negative T-wave in greater than 1 mm right precordial lead (V1–V3)
- Type 2: Saddleback ST-segment elevation with a high takeoff ST-segment elevation of greater than 2 mm, a trough displaying greater than 1 mm ST-elevation followed by a positive or biphasic T-wave
- Type 3: Saddleback or coved appearance of ST-elevation less than 1 mm, present in greater than 1 mm right precordial lead (V1–V3)

Type 2 ST-segment elevation is less specific and more common in general healthy population.[80] Type 1 (coved type) ST-segment elevation is more specific and more predictive of future arrhythmic events, and is considered the diagnostic ECG abnormality for Brugada syndrome.[80] The coved type ST-elevation is less sensitive owing to its dynamic nature. In up to 50% of patients with coved ST-segment elevation, the ECG may normalize or the ST-segment elevation may convert from the coved type to the saddle type periodically.[80] However, the coved-type ECG pattern, can be unmasked by administration of sodium channel blockers, ajmaline, flecainide or procainamide in the electrophysiology laboratory.[90] Additionally, vagotonic agents and fever are known to bring about the ECG signs when concealed.[91,92]

Brugada syndrome is diagnosed on the basis of a spontaneous or drug-induced type 1 (coved-type), ST-segment

elevation in the right precordial leads plus one of the following conditions:[80]

- Documented VF or polymorphic VT
- Unexplained syncope
- Nocturnal agonal respiration
- Inducibility of VT/VF with programmed electrical stimulation
- A family history of SCD at a young age (< 45 years) or a coved-type ECG pattern.

The differential diagnosis of syncope and the ECG abnormalities is broad and the following conditions may be considered and ruled out: atypical right bundle branch block, left ventricular hypertrophy, early repolarization, acute pericarditis, acute myocardial ischemia or infarction, pulmonary embolism, Printzmetal angina, dissecting aortic aneurysm, central or peripheral nervous system abnormalities, Duchenne muscular dystrophy, thiamine deficiency, hyperkalemia, hypercalcemia, arrhythmogenic right ventricular cardiomyopathy, pectus excavatum, hypothermia, or mechanical compression of the right outflow tract (RVOT) as seen with mediastinal tumors or hemopericardium.[80]

PROGNOSIS, RISK STRATIFICATION AND THERAPY

Patients displaying the Brugada syndrome, ECG pattern were initially thought to carry a high risk of cardiac events. The second consensus conference report on Brugada syndrome recommended electrophysiology studies (EPS) as a valuable tool in risk stratifying asymptomatic patients with spontaneous type 1 ECG pattern or with drug induced type 1 ECG pattern plus positive family history of SCD.[80] Subsequent studies, however, have questioned the role of EPS in risk stratification of asymptomatic patients.[93] The role inducibility of ventricular arrhythmias by EPS remains debatable. Recently, the investigators of the FINGER Brugada syndrome registry addressed the long-term prognosis of Brugada syndrome and the role of EPS in risk stratifying asymptomatic patients.[93] In the largest cohort of symptomatic and asymptomatic patients with Brugada syndrome to date, following a 32-month follow-up period of the cohort, they demonstrated the following results:[93]

- The risk of arrhythmic events is low in asymptomatic patients (0.5% event rate per year)
- The presence of symptoms and a spontaneous type 1 ECG are the only independent predictors of arrhythmic events
- Genders, family history of SCD, inducibility of ventricular tachyarrhythmias during EPS and presence of a variant in the *SCN5A* gene, have no predictive value.

In view of these results, the risk stratification strategy proposed in the second consensus report may be revised to reflect the decreased value of EPS as a predictor of future cardiac events. Recommendations to implant ICD at the present time may be limited to symptomatic patients with type 1 ECG pattern. To date, no pharmacologic intervention has been approved for the treatment of Brugada syndrome. However, active research is underway to define potential pharmacologic options to treat this potentially lethal arrhythmia syndrome.[94–96]

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Chapter 39

Surgical and Catheter Ablation of Cardiac Arrhythmias

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Chapter Outline

- Supraventricular Tachycardia
  - — Introduction
  - — History of Clinical Electrophysiologic Studies
  - — Cardiac-Surgical Ablation
  - — Catheter Ablation
- Atrioventricular Nodal Re-entrant Tachycardia
  - — Electrophysiology of AVNRT
  - — Surgical Ablation of AVNRT
  - — Catheter Ablation of AVNRT
- Wolff-Parkinson-White Syndrome and Atrioventricular Re-entrant Tachycardia
  - — Historical Evolution of Ventricular Pre-excitation and AVNRT
  - — Cardiac-Surgical Contribution
  - — Development of Catheter Ablation
  - — Clinical Implications of WPW Syndrome and AVRT
  - — Classification and Localization of Accessory Pathways
  - — Efficacy and Challenges of Catheter Ablation for Accessory Pathways
  - — Complications of Catheter Ablation
- Focal Atrial Tachycardia
  - — Mechanisms and Classification of AT
  - — Differentiation of the Mechanisms of AT
  - — Indications of Catheter Ablation for Focal AT
  - — Techniques of Catheter Ablation for Focal AT
  - — Efficacy of Catheter Ablation of AT
- Atrial Flutter
  - — Clinical Implications of AFL and Indication for Catheter Ablation
  - — History of Nonpharmacologic Treatment in Patients with AFL
  - — Ablation of CTI Dependent AFLs
  - — End-point of CTI Ablation
  - — Ablation of Non-CTI Dependent AFLs
  - — Right Atrial Flutter Circuits
  - — Left Atrial Flutter Circuits
- Ablation of Ventricular Tachycardia in Patients with Structural Cardiac Disease
  - — Anatomic Substrate
  - — Patient Selection
  - — Prior to Ablation
  - — 12-Lead Localization
  - — Approach to Ablation
  - — Activation Mapping (Focal Tachycardias)
  - — Re-entrant Tachycardia
  - — Entrainment Mapping
  - — Electroanatomic Three-dimensional Mapping
  - — Voltage Mapping
  - — Pace Mapping
  - — Substrate-based Ablation
  - — Safety
  - — Epicardial VT
- Idiopathic Ventricular Tachycardia
  - — Outflow Tract-Ventricular Tachycardia
  - — RVOT VT
  - — VT Arising from the Pulmonary Artery
  - — LVOT VT
  - — Cusp VT
  - — Epicardial VT
  - — Management
  - — Catheter Ablation
  - — Idiopathic Left Ventricular Tachycardia (ILVT) or Fascicular VT
  - — ECG Recognition
  - — Management
  - — Catheter Ablation
  - — Mitral Annular VT
  - — ECG Recognition
  - — Catheter Ablation
  - — Tricuspid Annular VT

SUPRAVENTRICULAR TACHYCARDIA

INTRODUCTION

Supraventricular tachycardias (SVTs) arise from the atrium or atrioventricular (AV) junction and include atrial tachycardia (AT), AV nodal re-entrant tachycardia (AVNRT), AV re-entrant tachycardia (AVRT), atrial flutter (AFL) and atrial fibrillation (AF). Re-entry is the mechanism for the majority of SVTs, while triggered activity and abnormal automaticity are the mechanisms for the others.[1] Paroxysmal SVT (PSVT) denotes a clinical

syndrome characterized by SVT associated with sudden onset and termination. The most common causes of PSVT are AVNRT (56%), AVRT (27%) and AT (17%).[2]

Pharmacological management of SVT was used as a first-line approach in the past. However, as knowledge of tachycardia mechanisms and technology advanced, nonpharmacological therapy allows for safe and curative treatment. Current guidelines consider ablation as first-line therapy for most forms of SVT.[3]

HISTORY OF CLINICAL ELECTROPHYSIOLOGIC STUDIES

The modern era of invasive electrophysiologic studies begin with the work of Drs Durrer and Wellens[4,5] who were the first to use programmed electrical stimulation in the heart to define the mechanism(s) of arrhythmias and Dr Scherlag and his colleagues[6] were the first to systematically record the His bundle activity in humans. Drs Durrer and Wellens showed that reciprocating tachycardia could be induced by premature atrial or ventricular stimulation and could be either orthodromic or antidromic; they also defined the relationship of the accessory pathway refractory period to the ventricular response during AF. These workers provided the framework for the use of intracardiac electrophysiological studies to define re-entrant circuit in patients with SVT.[7,8]

CARDIAC-SURGICAL ABLATION

Prior to the era of catheter ablation, patients with SVT that were refractory to medical therapy underwent direct surgical ablation of the AV junction.[9,10] This approach, however, is not appropriate for the management of the patient with AF with rapid conduction over a bypass tract. In 1960s, Durrer and Roos[11] were the first to perform intraoperative mapping and cooling to locate an accessory pathway. Later, using intraoperative mapping, Burchell et al.[12] showed that the accessory pathway conduction could be abolished by injection of procainamide (1967). Sealy and the Duke team were the first to successfully ablate a right free-wall pathway (1968).[13] Dr Iwa of Japan also concurrently demonstrated the effectiveness of cardiac electrosurgery for these patients.[14]

CATHETER ABLATION

The technique of catheter ablation of the AV junction was introduced by Scheinman et al. in 1981.[15] The initial attempts used high energy DC countershocks to destroy cardiac tissue, but expansion of its use to other arrhythmias was limited due to risk of causing diffuse damage from barotrauma. In 1984, Morady and Scheinman introduced a catheter technique for disruption of posteroseptal accessory pathways.[16] This technique was associated with 65% efficacy.[17] Later, successful ablation of nonseptal pathways was reported by Warin et al.[18] The introduction of radiofrequency (RF) energy in the late 1980s[19,20] completely altered catheter ablation procedures. The salient advances in addition to RF energy included much better catheter design, together with better understanding in the mechanism of SVTs.[20-22] A variety of both registry and prospective studies have documented the safety and efficacy of ablative procedures for these patients.[23,24]

ATRIOVENTRICULAR NODAL RE-ENTRANT TACHYCARDIA

Atrioventricular nodal re-entrant tachycardia (AVNRT) is the most common regular, narrow-complex tachycardia. In order to better diagnose this tachycardia and guide the ablation procedure, it is important to understand the anatomy of AVN and the pathophysiology of AVNRT.

ELECTROPHYSIOLOGY OF AVNRT

The seminal findings by Moe and Mendez[25,26] of reciprocal beats in animal models were rapidly applied to humans and introduced just as the field of clinical invasive electrophysiology began to emerge. Early invasive electrophysiologic studies[27,28] attributed AV nodal re-entry as cause of paroxysmal SVT. The work of Dr Ken Rosen and his colleagues[28] demonstrated evidence for dual AV nodal physiology manifest by an abrupt increase in AV nodal conduction time in response to critically timed atrial premature depolarizations. These data served as an excellent supportive compliment to the original observations of Moe and Mendez.[25,26] By the end of the 1970s, the concept of dual AV nodal conduction in humans had been well established.

The working model used to explain the electrophysiological behavior of the AVNRT circuit involves two pathways: one is the so-called "fast pathway" which conducts more rapidly and has a relatively longer refractory period; while the other is the "slow pathway" which conducts slower than the fast pathway but has a relatively shorter refractory period (Fig. 1). The fast pathway constitutes the normal, physiological AV conduction axis.

Traditionally AVNRT has been categorized into typical and atypical forms. Such categorization is based on the retrograde limb of the re-entrant circuit (Fig. 1). Typical AVNRT has antegrade conduction through slow pathway and the retrograde limb is the fast pathway (so-called "slow-fast"); whereas atypical AVNRT shows retrograde conduction via slow pathway, which is less common and includes "fast-slow" and "slow-slow" variants.

In addition, there are several case reports that documented the need to ablate AVNRT from the left annulus or left posteroseptal area.[29,30] One source of LA input is via the left-sided posterior nodal extension.

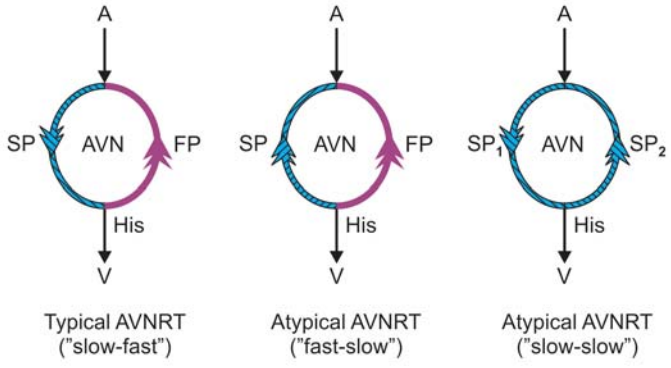


FIGURE 1: A schema of different AVNRT circuits. The broken line indicates the slow pathway (SP) and the solid line represent the fast pathway (FP). (Abbreviations: A: Atrium; V: Ventricle; AVN: Atrioventricular node; His: His bundle)

Ross et al.[31] first introduced nonpharmacologic therapy of AVNRT that involved surgical dissection in Koch's triangle, and their results were confirmed by a number of surgical groups.[32-34] In most patients the retrograde fast pathway (either during tachycardia or ventricular pacing) showed earliest atrial activation over the apex of Koch's triangle while in the minority earliest atrial activation occurred near the CS. This observation nicely compliment the current designation of AVNRT subforms.[35]

CATHETER ABLATION OF AVNRT

In 1989, two groups[36,37] almost simultaneously reported success using high energy discharge in the region of slow pathway. The subsequent use of RF energy completely revolutionized catheter cure of AVNRT. The initial attempts targeted the fast pathway by applying RF energy superior and posterior to the His bundle region (so-called anterior approach) until the prolongation of AV nodal conduction occurred. Initial studies[36-38] showed a success rate of 80–90%, but the risk of AV block was up to 21%. Due to the high-risk of developing AV block, fast pathway ablation is no longer used as the primary approach. Jackman et al.[39] first introduced the technique of ablation of the slow pathway for AVNRT. Ablation of the slow pathway is achieved by applying RF energy at the posterior-inferior septum in the region of the CS_{OS}. This technique can be guided by either discrete potentials[39,40] or via an anatomic approach,[41] both have equal success rate. The safest and most effective approach is to combine anatomic and eletrogram approaches together, in which RF lesions are applied at the posteroseptal sites with slow pathway potentials (Fig. 2). The RF energy is usually applied until junctional ectopics appear and diminish, but at times successful slow pathway ablation may result without eliciting the junctional ectopic complexes. The end point for slow pathway ablation involves the proof either that the slow pathway has been eliminated of which there is no more evidence of dual AV nodal physiology (i.e. no AH "jump" with atrial programmed stimulus) or that no more than one AV nodal echo is present.[39]

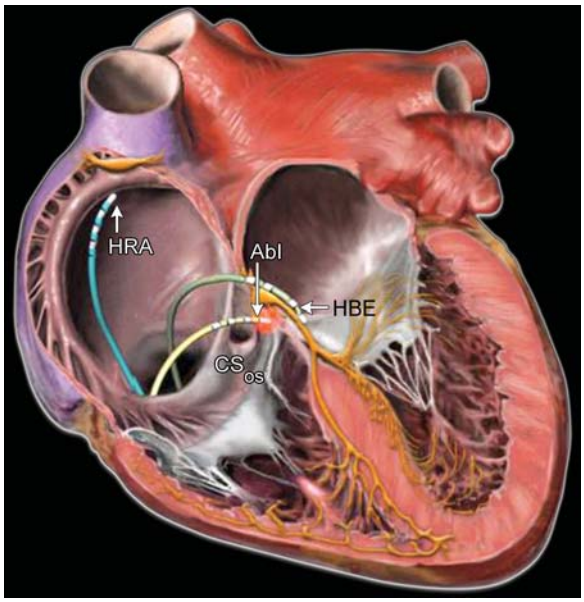


FIGURE 2: Typical slow pathway ablation site. This diagram shows catheter positions for slow pathway ablation in patients with typical AVNRT. The ablation catheter is positioned at the posterior septum just above the CS_{OS}. (Abbreviations: HRA: High right atrium; HBE: His bundle electrogram; Abl: Ablation catheter; CS_{OS}: The ostium of coronary sinus)

Among experienced centers the current acute success rate for this procedure is 99% with a recurrence rate of 1.3%, and a 0.4% incidence of AV block requiring a pacemaker.[42] Although the risk of AV block from selective slow pathway ablation in patients with normal baseline PR interval is very low, some reports have suggested that the risk may be higher in patients with pre-existing PR prolongation and/or older age (> 70 years old).[43] In those patients at higher risk, delayed onset of symptomatic AV block can develop and vigilant follow-up may be needed.[43,44] An approach of retrograde fast pathway ablation has been used in patients with baseline PR prolongation and is associated with no delayed development of AV block.[45]

Technologic advances continue to improve the safety of ablation procedures. Besides significantly reducing radiation time to both patient and operator, the development of sophisticated, real-time, 3D mapping systems has allowed for precise localization of the His bundle, reducing the risk of AV block. In addition, cryoablation may be used for slow pathway ablation.[46] The advantage of this technology includes catheter sticking to adjacent endocardium during application of energy, avoiding inadvertent catheter displacement and damage to the node or His bundle. In addition, any AV conduction delay during test ablation is reversible.

WOLFF-PARKINSON-WHITE SYNDROME AND ATRIOVENTRICULAR RE-ENTRANT TACHYCARDIA

HISTORICAL EVOLUTION OF VENTRICULAR PRE-EXCITATION AND AVNRT

The first complete description of WPW syndrome was by Drs Wolff, Parkinson and White in 1930s.[47] They reported 11 patients without structural heart disease who had a short P-R interval, "bundle branch block (BBB)" ECG pattern and episodes of PSVT. At the time, the wide QRS patterns seen in ventricular pre-excitation were thought to be related to a short P-R interval and BBB. Discrete extranodal AV connections accounting for ventricular pre-excitation were initially proposed by Kent[48] and later confirmed by Wood,[49] Öhnell[50] and others.

CARDIAC-SURGICAL CONTRIBUTION

Sealy et al.[13] were the first to successfully ablate a right free-wall pathway. Their subsequent results conclusively showed that a vast majority of patients with the WPW syndrome could be cured by either direct surgical or cryoablation of these accessory pathways. Simultaneously, Iwa et al. also demonstrated the efficacy of cardiac electrosurgery in these patients.[14] He should be credited for being among the first to use an endocardial approach for accessory pathway ablation. The endocardial approach was independently used by the Duke team of Sealy and Cox. Only later was the "closed" epicardial approach reintroduced by Guiraudon.

DEVELOPMENT OF CATHETER ABLATION

The technique of catheter ablation was first introduced by Scheinman and his colleagues in the early 1980s,[15-17] but ablation using DC shocks was limited due to its high-risk of causing diffuse damage from barotrauma. The introduction of RF energy in the late 1980s[19,20] along with better catheter design and the demonstration of accessory pathway (AP) potential for facilitating localization of AP have dramatically improved the safety and efficacy of catheter ablation. The remarkable work of Jackman,[20] Kuck[21] and Calkins[22] ushered in the modern era of ablative therapy for patients with accessory pathways in all locations. A variety of both registry and prospective studies have documented the safety and efficacy of ablative procedures for these patients.[23,24] Nowadays, catheter ablation is the procedure of choice for patients with symptomatic WPW syndrome. In most experienced centers, the success rate is 95–97% with a recurrence rate of approximately 6%.

CLINICAL IMPLICATIONS OF WPW SYNDROME AND AVRT

Patients with WPW syndrome may experience very rapid conduction over the AP during AF. In some patients, ventricular fibrillation (VF) may be the first manifestation of this syndrome.[51] In a symptomatic patient with WPW syndrome, the lifetime incidence of sudden cardiac death (SCD) has been estimated to be approximately 3–4%.[52]

CLASSIFICATION AND LOCALIZATION OF ACCESSORY PATHWAYS

The accessory pathways (APs) are classified into three different types: (1) manifest APs which show a typical WPW pattern on surface ECG; (2) concealed APs are those that lack antegrade conduction but only show retrograde conduction over the APs and (3) a third group known as latent WPW syndrome shows pre-excitation when pacing close to the atrial insertion of the AP.

Precise mapping of APs is critical to the success of ablation procedure. The delta waves and QRS morphologies of the 12-lead ECG in patients with WPW syndrome can help predict the AP location and guide ablation. A successful ablation site can be identified an AP potential (Fig. 3), early onset of local ventricular activation compared to the onset of delta waves on surface ECG during antegrade pre-excitation and fused local atrial and ventricular electrogram.



FIGURE 3: Electrogram in sinus rhythm during application of radiofrequency energy. Kent potential (AP potential) on ablation catheter (Abl) disappears (*) and there is abrupt local A-V interval prolongation and a subtle change in the surface QRS, indicating loss of pre-excitation. (Abbreviations: Abl: Ablation catheter; KP: Kent potential)

EFFICACY AND CHALLENGES OF CATHETER ABLATION FOR ACCESSORY PATHWAYS

The majority of the APs are located at the left free wall, 20–30% are located in the posteroseptum, 10–20% along the right free wall and 5–10% at the anteroseptum. The left free-wall APs can be mapped and ablated along the mitral annulus (MA) via either a transseptal or a retrograde transaortic approach. Overall, catheter ablation of left free-wall APs are associated with a high success rate (95%); while ablation of the right free-wall APs is associated with a lower success rate (90%) and a recurrence rate of 14%.[53] The relatively low success rate of right-sided AP ablation is due to the more poorly formed tricuspid annulus (TA) resulting in problems with catheter stability and lack of an accessible right-sided CS-like structure that parallels the TA to facilitate AP localization. Ablation of right-sided APs may be improved by using long deflectable sheaths and a small multipolar mapping catheter placed in the right coronary artery to assist AP mapping.

Ablation of septal APs can be challenging due to the anatomic relationship to the normal conduction system. Therefore, catheter ablation in these areas has the potential risk of producing AV block. The electrogram recorded from the ablation catheter should be carefully assessed and monitored before and during RF delivery. Using 3D electroanatomic mapping (EAM) system to localize the His bundle and track the ablation catheter may prevent or reduce the risk of AV block. Lately cryomapping and cryoablation have improved the safety in difficult cases.[54] Most posteroseptal APs can be ablated from the right side, although up to 20% of the cases require a left-side approach.[55] About 5–17% of the posteroseptal and left posterior APs are located epicardially and require ablation within the CS or middle cardiac vein.[56] Coronary sinus diverticulum may harbor the posteroseptal APs, and CS angiography can confirm such an anomaly. In some patients RF ablation at the neck of the diverticulum may be required to eliminate the APs.[57,58] Applying RF ablation within the CS should be initiated with low energy in order to prevent the risk of perforation and tamponade.

A small percentage of APs are epicardial, suggested by the finding of small or no AP potential during endocardial mapping but with a large AP potential recorded within the CS.[59] Left-side epicardial AP can be successfully ablated within the CS. However, ablation of some epicardial APs may require a percutaneous epicardial approach.[60]

COMPLICATIONS OF CATHETER ABLATION

Overall, catheter ablation of APs is associated with a complication rate of 1–4%, including life-threatening complications (such as perforation, tamponade and embolism) (0.6–0.7%), and procedure-related death (approximately 0.2%).[22,56,61] Complete AV block occurs in about 1% of the patients and is mostly associated with the ablation procedures for septal APs.

FOCAL ATRIAL TACHYCARDIA

Atrial tachycardia (AT) is a group of SVT that is confined to the atrium without involvement of AV node. It is a relatively uncommon arrhythmia, comprising less than 10% of

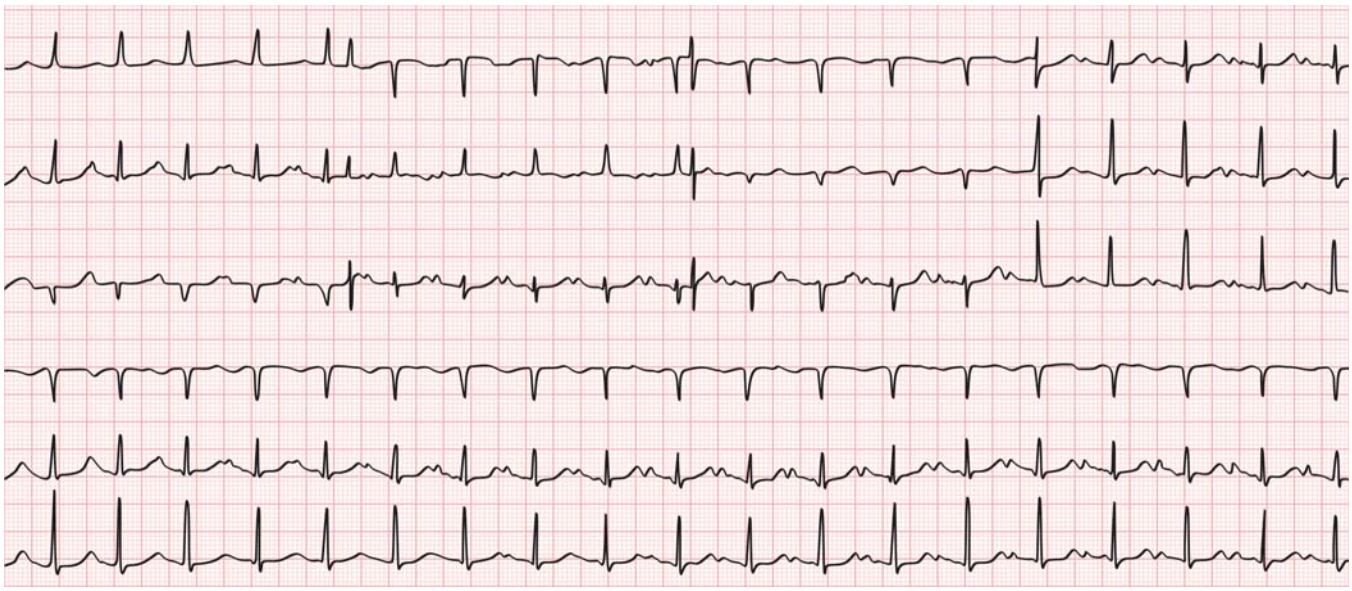


FIGURE 4: Surface ECG in a patient with focal AT arising from the high crista terminalis. Note the P waves in the inferior leads (II, III and aVF) are positive, and negative in V1

symptomatic SVTs encountered in the adult electrophysiological laboratory.[62] However, AT is more common in children (up to 14–23%).[63]

MECHANISMS AND CLASSIFICATIONS OF AT

The AT can be classified into two types: (1) focal AT and (2) macro-re-entry. The mechanism of focal AT can be due to abnormal automaticity or triggered activity. In adults, macro-re-entry is the most common mechanism for AT,[62] while automatic or triggered mechanisms are more common in children.[63]

DIFFERENTIATION OF THE MECHANISMS OF AT

Distinguishing the mechanisms of focal AT may be difficult. In general, a focal AT due to abnormal automaticity tends to have spontaneous initiations or initiation with isoproterenol. It can be suppressed but not terminated by atrial overdrive pacing, and lacks response to adenosine, verapamil or vagal maneuvers.[64,65] The AT with triggered activity can be initiated or terminated by rapid atrial overdrive pacing, and it is sensitive to large-dose of adenosine or vagal maneuvers.[65]

Differentiating focal from macro-re-entrant AT is important to the ablation procedure. Ablation of focal AT is accomplished by targeting the discharging focus (usually it is a single source, except for multifocal AT); whereas ablation of macro-re-entrant AT requires delineation of a critical isthmus that allows for tachycardia perpetuation. Detailed atrial activation mapping, including electrogram and EAM mapping, can distinguish focal from macro-re-entrant AT.

INDICATIONS OF CATHETER ABLATION FOR FOCAL AT

Pharmacologic therapy in patients with focal AT is often ineffective. The proarrhythmia effects of these drugs also limit the long-term efficacy of pharmacologic therapy. Therefore, catheter ablation of focal AT may be considered as a first-line option, especially in those patients who have incessant tachycardia or baseline ventricular dysfunction.[3]

TECHNIQUES OF CATHETER ABLATION FOR FOCAL AT

Most focal ATs arise from the right atrium (67%), especially from the crista terminalis and TA.[66] Left atrial focal ATs mostly involve the pulmonary veins (PVs) and MA, and less often from the CS, atrial appendages and atrial septum. The surface P wave morphology facilitates the mapping and ablation of AT (Fig. 4). Left-sided ATs require a transseptal approach.

Successful ablation of AT relies on detailed atrial activation mapping during the tachycardia, and use of multipolar catheters and/or 3D EAM systems (Fig. 5).[67,68] A successful ablation site

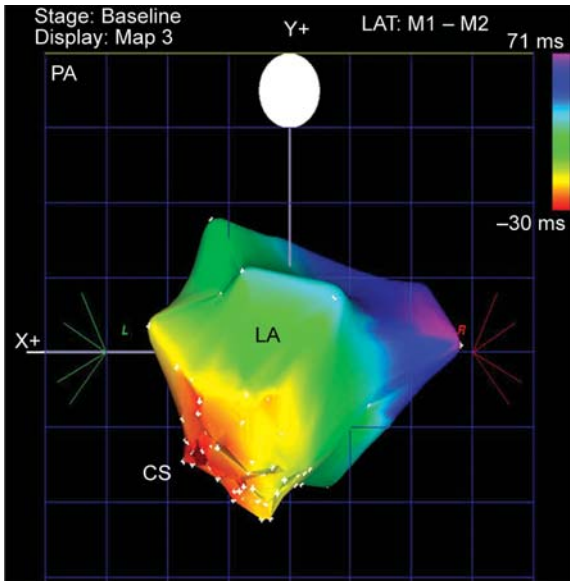


FIGURE 5: A 3D activation map (by CARTO system) of the left atrium (LA) during tachycardia in a patient with a focal AT originating from the CS musculature. The posteroanterior projection (PA) view showed the earliest activation (red area) at the posterior lateral wall

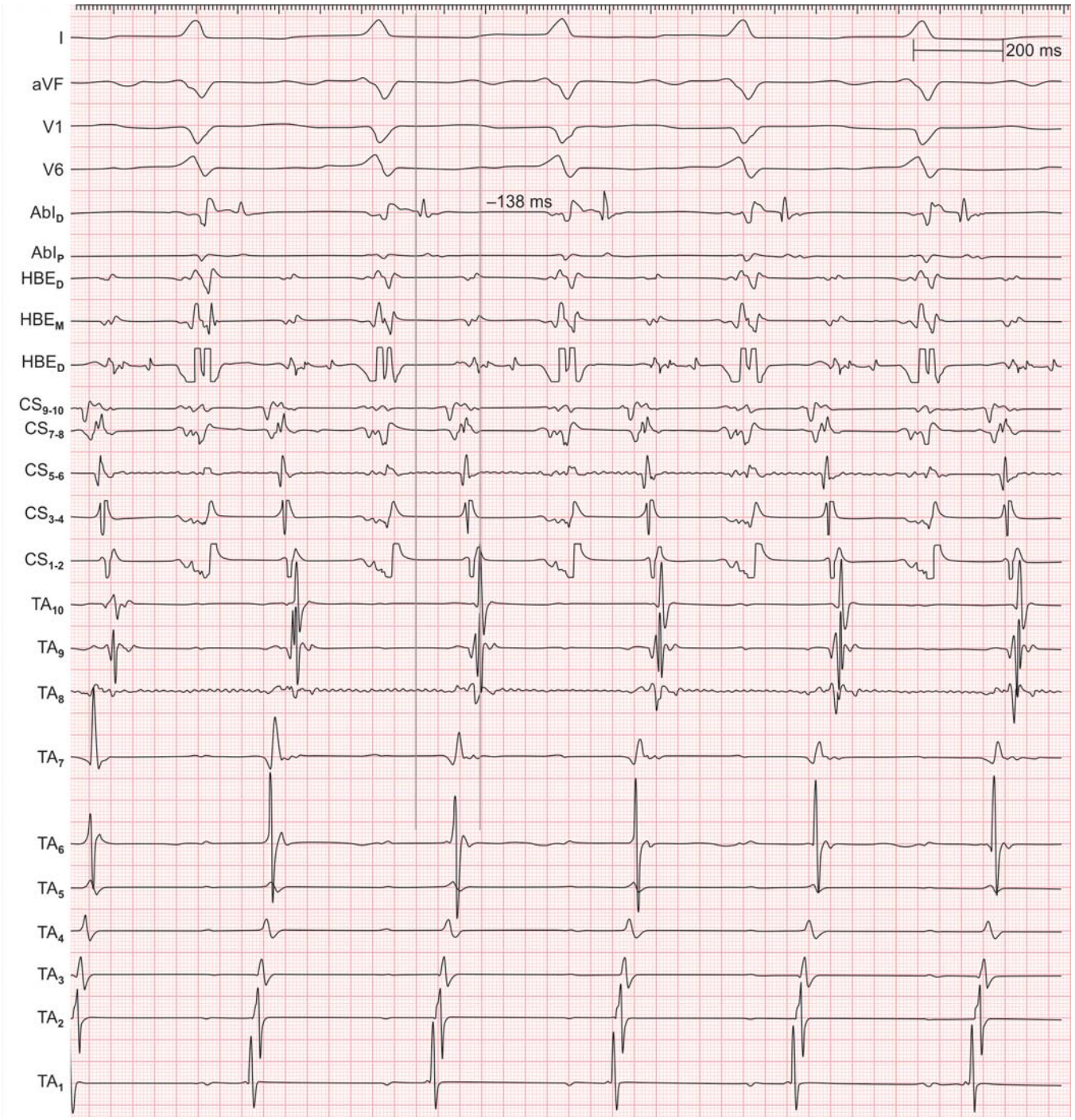


FIGURE 6: Simultaneous recordings from surface leads and catheters placed at ablation site (Abl), His bundle region (HBE), the CS and a 20-pole catheter around the TA with its distal pair of electrodes (TA1) at low lateral TA and proximal at the high septum during tachycardia in a patient with a focal AT originating from inferior TA. Note the earliest atrial activation, which was recorded by the distal ablation catheter, was 138 ms earlier than the onset of surface P waves. The RF delivered at this site abolished the tachycardia without inducibility

can be identified by early local endocardial activation (usually preceding the surface P wave by ≥ 30 ms) and/or low-amplitude, fractionated electrograms (Fig. 6). The RF energy is typically delivered during tachycardia. Acceleration of the tachycardia during ablation is usually a reliable predictor for successful ablation of automatic AT,[69] and noninducibility is the end-point of ablation procedure for focal AT.

Caution should be taken during ablation of focal ATs originating from the areas where important anatomic structures situated such as sinus node and AV node. Lately, cryoablation has been used for ATs originating from the region of His bundle to reduce the potential risks of AV block.[70]

EFFICACY OF CATHETER ABLATION OF AT

The success rate of ablation for focal AT is about 93% with a recurrence rate of 7%.[71] Left-sided ATs have a lower success rate than the right-sided ATs. Patients with multifocal AT have a higher recurrence rate than those with single tachycardia foci. Also, elder patients and patients with structural heart disease

tend to have a higher recurrence rate after initial "successful" ablation.

ATRIAL FLUTTER

CLINICAL IMPLICATIONS OF AFL AND INDICATION FOR CATHETER ABLATION

Atrial flutter is a rapid macro-re-entrant circuit that is confined to either atrium, and bounded by either functional or anatomic barriers. Due to its rapid and regular atrial rate, AFL often produces more rapid ventricular responses. Hence, chronic AFL can result in tachycardia-mediated cardiomyopathy and heart failure. It also predisposes to intracardiac thrombus formation and the risk for stroke. Although antiarrhythmic agents can suppress paroxysmal AFL, the long-term efficacy is poor.[72] Therefore, with technological advances in catheter ablation and better understanding of locating re-entrant circuits, catheter ablation should be considered as first-line treatment for AFL.

HISTORY OF NONPHARMACOLOGIC TREATMENT IN PATIENTS WITH AFL

In the late 1970s, the seminal observations by Waldo and his colleagues, who studied patients with postoperative flutter by means of fixed atrial electrodes, confirmed re-entry as the mechanism of AFL in humans and demonstrated the importance of using entrainment for detection of re-entrant circuits.[73] Klein and Guiraudon mapped two patients with AFL in the operating room found evidence of a large RA re-entrant circuit and the narrowest part of the circuit lay between the TA and the IVC.[74] They successfully treated the flutter by using cryoablation around the CS and surrounding atrium.

Following the report of Klein et al., there appeared several studies using high-energy shocks in an attempt to cure AFL (Saoudi,[75] Chauvin and Brechenmacher[76]). Subsequently both Drs Feld and Cosio almost simultaneously described using RF energy to disrupt cavotricuspid isthmus (CTI) conduction in order to cure patients with AFL. Feld et al. contributed an elegant study using endocardial mapping techniques and entrainment pacing to prove that the area posterior or inferior to the CS was a critical part of the flutter circuit and application of RF energy to this site terminated AFL.[77] Cosio et al. used similar techniques but placed the ablative lesion at the area between the TA and IVC.[78] The latter technique forms the basis for current ablation of CTI dependent flutter.

ABLATION OF CTI DEPENDENT AFLs

In the majority of patients with RA flutter, the CTI is a critical part of the re-entrant circuit. The CTI dependent AFL circuits include those with counterclockwise (CCW) and clockwise (CW) re-entrant circuits around the TA;[79] double-wave re-entry (DWR) which has two wavefronts traveling around the TA simultaneously;[80] lower-loop re-entry (LLR) around the inferior vena cava (IVC)[81–83] and intraisthmus re-entry (IIR).[84,85]

Detailed electrogram mappings as well as entrainment techniques are required to diagnose the flutter circuits. Electrograms recorded from the multielectrode catheter placed around the TA demonstrate the RA activation sequence such as CCW or CW pattern (Fig. 7A). Entrainment pacing at different atrial sites can help identify the re-entrant circuit and its critical isthmus (Fig. 7B). In addition, using 3D EAM mapping systems can facilitate illustrating the re-entrant circuit and guide catheter ablation over the CTI. A complete linear lesion from TA to IVC

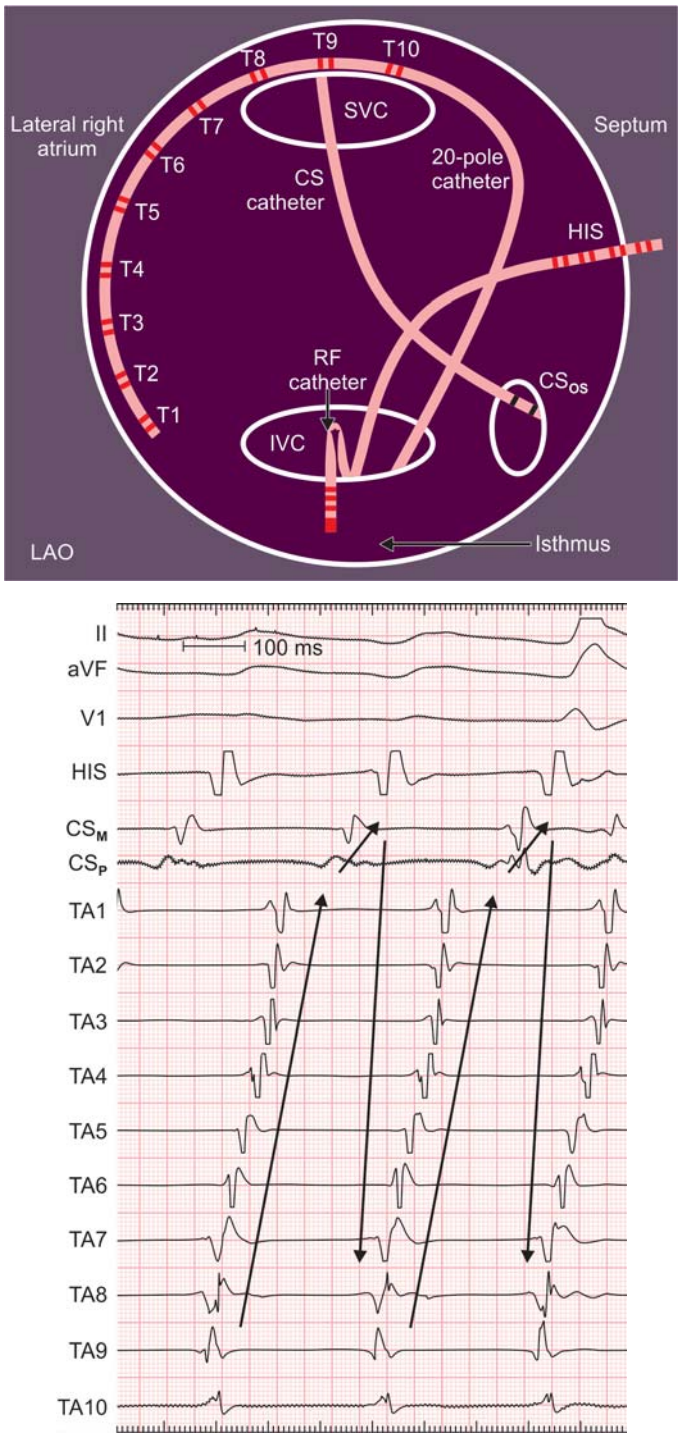


FIGURE 7A: Left panel shows the schema of catheter positions in the left anterior oblique projection (LAO) view during ablation for CTI dependent AFL. A duo-decapolar catheter is positioned along the TA, as well as a quadrupolar catheter at His bundle region and a decapolar catheter inside of the CS. Right panel shows the simultaneous recordings from surface ECG and these catheters. The intracardiac electrogram demonstrates a counterclockwise activation sequence (as shown by the arrows) around the TA

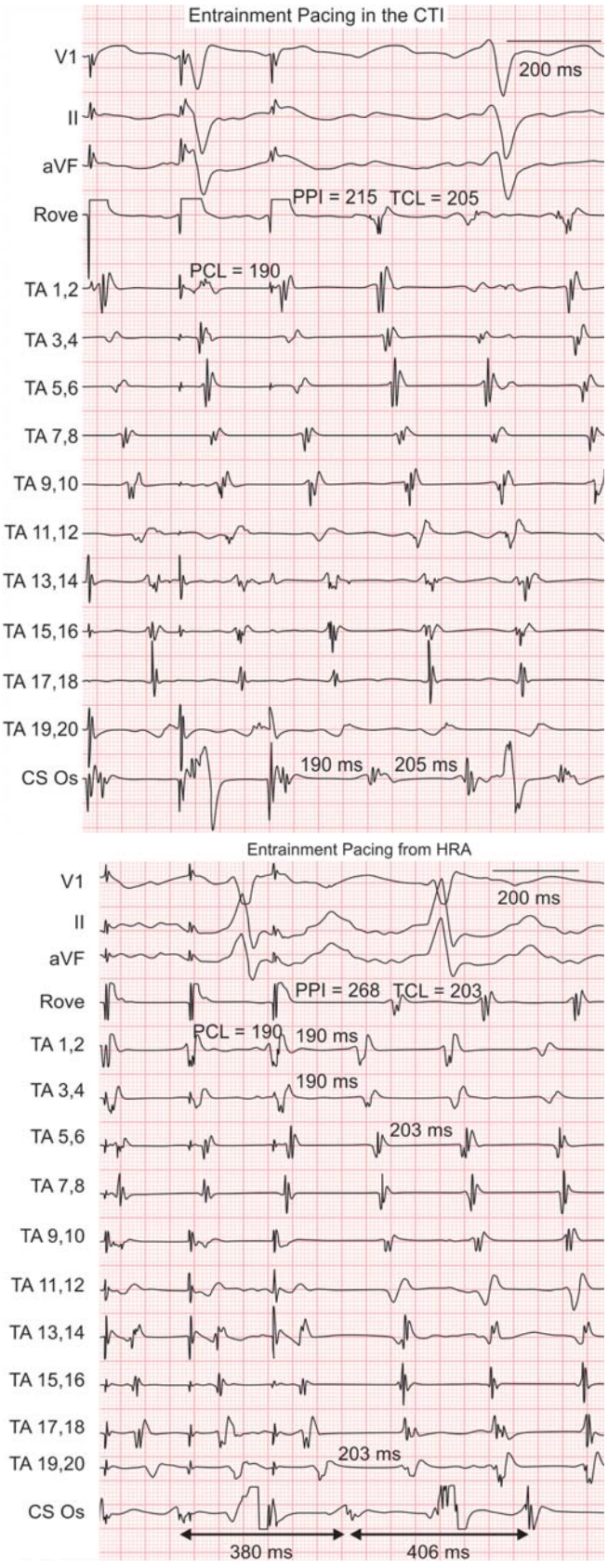


FIGURE 7B: Entrainment pacing from the mapping catheter (Rove) during tachycardia in a patient with clockwise CTI dependent AFL. The left panel shows the difference between PPI and TCL (< 30 ms) when pacing within the CTI, and the atrial activation sequence was same compared to that of the tachycardia, which indicated that the CTI is the critical part of the flutter circuit. The right panel showed the "PPI-TCL" was greater than 30 ms when pacing from the high right atrium (HRA), which suggested that this area is out of the circuit

during AFL results in interrupting the CTI-dependent flutter circuit and terminating the tachycardia.

END-POINT OF CTI ABLATION

Initially it was felt that a good end point for successful CTI ablation was tachycardia termination during RF application. However, many patients suffered recurrences, and eventually it was recognized that it was important to achieve true bidirectional block in the isthmus. Many studies have shown that recurrence rates of AFL are much improved when bidirectional block is achieved.[86] Currently there are many techniques for assessing bidirectional isthmus block.[87-89]

ABLATION OF NON-CTI DEPENDENT AFLs

As shown in Flow chart 1, non-CTI dependent AFL circuit can be classified into two categories: (1) RA and (2) LA flutter circuits. Ablation of non-CTI dependent AFLs can sometimes be challenging, but using 3D EAM system can facilitate the procedure.

RIGHT ATRIAL FLUTTER CIRCUITS

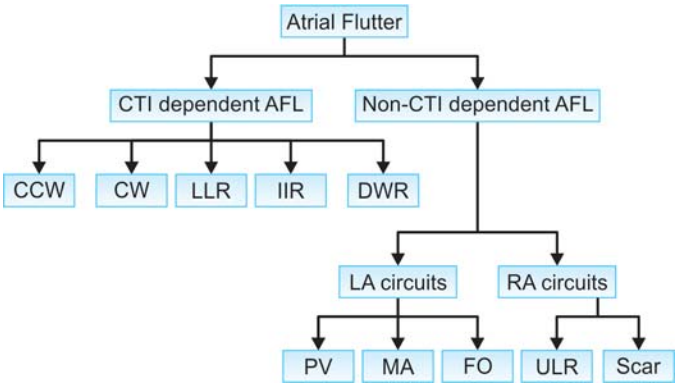
In the RA, non-CTI dependent AFL includes scar-related macro-re-entrant tachycardia and upper loop re-entry (ULR). It has been shown that macro-re-entrant AT can occur in patients with or without atriotomy or congenital heart disease.[82,90,91] In these patients, the 3D electroanatomic voltage maps from the RA often show "scar(s)" or low-voltage area(s) (< 0.2 mV) which act(s) as the central obstacle or channels for the re-entrant circuit. The morphology of surface ECG varies depending on where the scar(s) and low-voltage area(s) are and how the wavefronts exit the circuits. The critical isthmus of the re-entrant circuit can be identified by entrainment pacing, and the electrogram recorded at such a site often shows low-amplitude, fractionated, long duration mid-diastolic potentials. Catheter ablation of scar-related macro-re-entrant tachycardia involves deliver RF energy within the critical channel/isthmus or linear lesion connecting from the scar to an anatomic barrier, such as IVC or super vena cava (SVC).

The ULR is a form of AFL only involving the upper portion of RA with transverse conduction over the CT and wavefront collision occurring at the lower part of RA or within the CTI.[82,92] It was initially felt to involve a re-entrant circuit using the channel between the superior vena cava (SVC), fossa ovalis (FO) and CT.[82] A study by Tai et al. using noncontact mapping technique showed that this form of AFL was a macro-re-entrant tachycardia in the RA free wall with the CT as its functional obstacle.[92] They successfully abolished ULR by linear ablation of the gap in the CT.

LEFT ATRIAL FLUTTER CIRCUITS

Left AFL circuits are often seen in patients post-AF ablation. In recent years, these circuits have been better defined by the use of electroanatomic or noncontact mapping techniques.[93] Cardiac surgery involving the LA or atrial septum can produce various left flutter circuits. But, left AFL circuits also can be found in patients without a history of atriotomy. Electroanatomic maps in these patients often show low voltage or scar areas in

FLOW CHART 1: Nomenclature of atrial flutter (AFL)



(Abbreviations: CTI: Cavotricuspid Isthmus; CCW: Counterclockwise AFL around the tricuspid annulus (TA); CW: Clockwise AFL around the TA; LLR: Lower Loop Re-entry around inferior vena cava; IIR: Intraisthmus Re-entry; DWR: Double-wave Re-entry around the TA; LA: Left Atrium; RA: Right Atrium; PV: Re-entrant circuit around the Pulmonary Vein (s) with or without scar(s) in the LA; MA: re-entrant circuit around mitral annulus; FO: re-entrant circuit around the fossa ovalis; ULR: Upper Loop Re-entry in the RA)

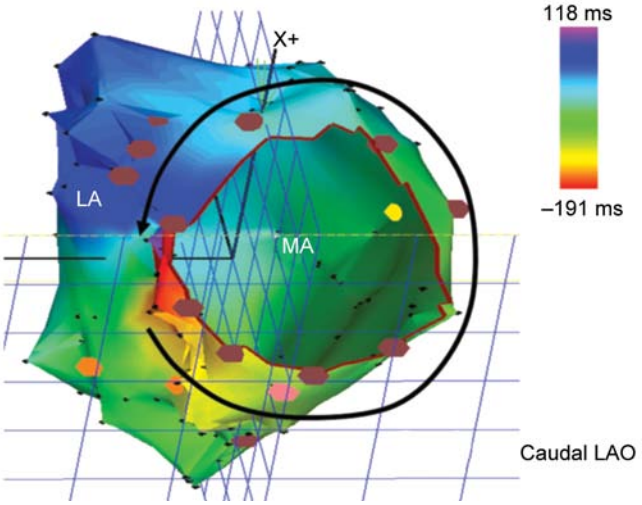


FIGURE 8: A CARTO activation map of the left atrium in a caudal LAO view in a patient with CCW AFL around the mitral annulus (MA). The map shows "early meets late activation" at the spetal MA and the mapped cycle length spanned the TCL. Ablation was completed with a line from the left inferior pulmonary vein (PV) to the MA

the LA, which act as a central obstacle in the circuit. There are several subgroups of left AFLs (Flow chart 1).

Mitral annular AFL involves re-entry around the MA either in a CCW or CW direction (Fig. 8). The surface ECG of MA flutter can mimic CTI-dependent CCW or CW flutter, but with low-amplitude flutter waves in most of the 12 leads.[94] This arrhythmia is more common in patients with structural heart disease. However, it has been described in patients without obvious structural heart disease.[93,94] Electroanatomic voltage map from the LA often shows scar(s) or low-voltage area(s) at the posterior wall as a posterior boundary of this circuit. A linear RF lesion is usually applied at the mitral isthmus, i.e. from the ostium of left lower PV to the lateral MA.[94] Bidirectional mitral isthmus block should be assessed after completing the ablation line.

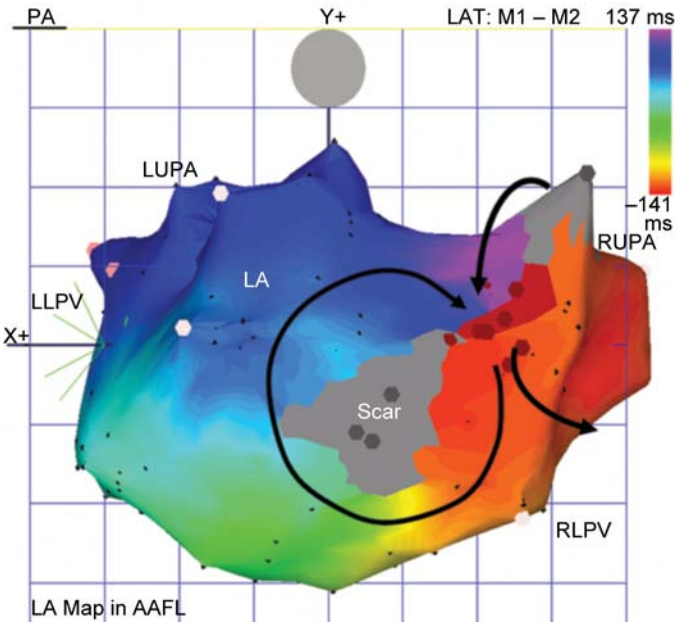


FIGURE 9: A CARTO activation map of the LA in a patient with LA AFL. The map shows a scar over the posterior LA wall. The tachycardia wave front traveled in a "Figure-of-8" pattern around the scar and the right upper pulmonary vein (RUPV) respectively and through the common channel between the scar and the right upper pulmonary vein (RUPV). Successful ablation was achieved with an RF line from the RUPV to the scar. (Abbreviations: LUPV: Left upper pulmonary vein; LLPV: Left lower pulmonary vein; RLPV: Right lower pulmonary vein)

Various left AFL circuits involve the PVs, especially in those patients who underwent AF ablation or those with mitral valve disease. Re-entry can circle around one or more PVs and/or posterior scar or low-voltage area(s).[93,94] In order to cure these complex circuits, 3D EAM is required to reveal the circuit and guide ablation (Fig. 9). Since these circuits are related to low voltage or scar area(s), the surface ECG usually shows low amplitude or flat flutter waves.

In summary, modern mapping techniques allow for identification and successful ablation of complex AFL circuits.

ABLATION OF VENTRICULAR TACHYCARDIA IN PATIENTS WITH STRUCTURAL CARDIAC DISEASE

Ventricular tachycardia (VT) is an important source of morbidity and mortality among patients with ischemic heart disease. Patients with VT and a history of myocardial infarction are at high-risk of recurrent VT, VF and SCD. Internal cardiac defibrillators (ICDs) have become the mainstay of therapy in this patient population and are effective at terminating episodes of VT and VF. Among patients at high-risk for VT and SCD, ICD therapy has been shown to reduce SCD and all-cause mortality.[95-98] Although ICDs are highly effective, they do not prevent VT or VF, and ICD shocks have been associated with decreased quality of life, increased anxiety and depression and increased mortality.[99-105] While antiarrhythmic therapy is frequently used to prevent ICD shocks, its efficacy is limited and frequently associated with untoward side effects.[106,107]

Catheter ablation for scar-based VT has emerged as an important treatment option, particularly among individuals who

have received recurrent ICD shocks. Several studies have demonstrated that this approach can reduce the incidence of ICD shocks and/or VT burden.[108-110] In the case of incessant VT or VT storm (three or more episodes within a 24 hour period), catheter ablation can be a lifesaving measure. However, catheter ablation in patients with ischemic heart disease can be technically challenging. Patients with ischemic heart disease and VT are by definition, a vulnerable population, and are often unable to tolerate long procedure-times and VT rates frequently induced during ablation. This section will provide an overview of catheter ablation for patients with scar-related VT. It will review the mechanisms of scar-related VT, indications for ablation and describe the various mapping and ablation techniques commonly employed.

ANATOMIC SUBSTRATE

The vast majority of VT in patients with ischemic heart disease is due to re-entry involving a healed scar. Unidirectional block is a necessary condition for re-entry. Areas of conduction block can be anatomically fixed (present during tachycardia and sinus rhythm) or can be functional (present only during tachycardia).[111] The sites of VT origin are frequently located adjacent to and within scar locations where surviving bundles of muscle fiber can be found. These muscle bundles are isolated from neighboring bundles by strands of fibrous tissue. Endocardial recordings form these sites demonstrate fractionated (low-amplitude and disorganized) potentials which serve as regions of slow conduction and provide the substrate for re-entrant VT (Fig. 10).[112] Although scar based re-entry is the most common arrhythmia associated with ischemic heart disease, other clinical VTs, such as focal tachycardia, bundle branch re-entry and fascicular re-entry, are also observed on occasion.

PATIENT SELECTION

In general, ablation for scar-related VT is reserved for patients with recurrent monomorphic VT and/or frequent ICD shocks.

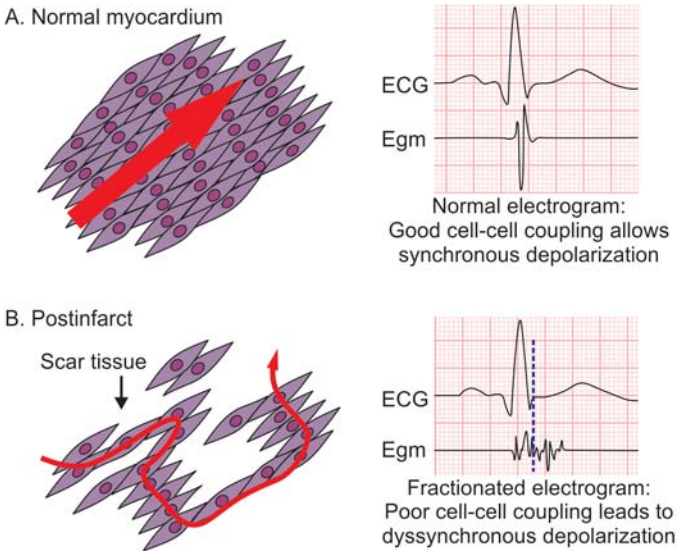


FIGURE 10: Slow conduction through scarred myocardium provides the substrate for re-entry. This is often accompanied by the presence of fractionated electrograms as seen on the right (*Source:* John Miller)

There is, however, a growing interest in performing early or even prophylactic ablation to prevent VT episodes and ICD discharges.[109,110] In general, ablation is not considered for patients with recurrent polymorphic VT. However, it is important to recognize the occasional patient with idiopathic polymorphous VT or VF due to short coupled premature ventricular complexes (PVCs). If the triggering PVC can be identified and ablated in these patients, it may result in cure or significant attenuation of the VT/VF burden.[113]

The most recent American College of Cardiology/American Heart Association Task Force/European Society of Cardiology guidelines for management of patients with ventricular arrhythmias and the prevention of sudden death recommends catheter ablation for VT as adjunctive therapy for patients with an ICD who have had multiple shocks due to sustained VT, not amenable to ICD reprogramming or drug therapy (Class I, level of evidence C).[114] In addition, ablation may be considered as an alternative to long-term drug therapy. A more recent consensus document expands on these guidelines and recommends catheter ablation for patients with structural heart disease in each of the following conditions:

- Symptomatic sustained monomorphic VT (SMVT), including VT terminated by an ICD, that recurs despite antiarrhythmic drug therapy or when antiarrhythmic drugs are not tolerated or not desired.
- Incessant SMVT or VT storm that is not due to a transient reversible cause.
- Patients with frequent PVCs, nonsustained VT (NSVT) or VT that is presumed to cause ventricular dysfunction.
- Bundle branch re-entrant or interfascicular VTs.
- Recurrent sustained polymorphic VT and VF that is refractory to antiarrhythmic therapy when there is a suspected trigger that can be targeted for ablation.[115]

It is generally agreed that the role of catheter ablation for scar-related VT is to reduce a patient's arrhythmic burden. As such, even successful ablations do not obviate the need for an ICD. There have been several studies that have prospectively evaluated the role of catheter ablation for VT.

The multicenter thermocool ventricular tachycardia ablation trial examined the role of catheter ablation for VT in patients with reduced ejection fraction (EF) and recurrent monomorphic VT.[108] Around 231 patients were enrolled and underwent ablation. The median number of VT morphologies per patient was three. All inducible VTs with rates near to or less than the clinical VT were targeted. Ablation abolished all inducible VTs in 49% of patients. At six months, 53% of patients achieved the primary endpoint of freedom from recurrent incessant or sustained VT. In 142 patients with ICDs VT episodes were reduced from a median of 11.5 to 0 ($p < 0.0011$). The 1-year mortality rate was 18%, with 72.5% of deaths attributed to ventricular arrhythmias or heart failure. The procedure mortality rate was 3%, with no strokes. Although this was a nonrandomized trial, it demonstrated moderate success for VT ablation in carefully selected patients.

Two prospective trials have evaluated the role of VT ablation for the prevention of SMVT. The SMASH-VT trial enrolled 128 subjects with an ICD placed either for secondary prevention (for VF or hemodynamically unstable VT or syncope with inducible VT) or for primary prevention with subsequent

delivery of an appropriate ICD therapy.[110] Patients were randomly assigned to defibrillator implantation alone or defibrillator implantation with adjunctive catheter ablation (64 patients in each group). Ablation was performed using a substrate-based approach (see below). The primary end point was survival free from any appropriate ICD therapy. During the mean 23 month follow-up period, appropriate ICD therapy occurred more frequently in the ICD alone group and than in the ablation group (33 vs 12%, P = 0.007). There was a trend toward decreased mortality in the ablation group (9 vs 17%, P = 0.29). Ablation-related complications occurred in three patients (pericardial tamponade, HF requiring prolonged hospitalization and deep venous thrombosis) and there were no procedural deaths.

The VTACH trial, enrolled 110 subjects with stable VT, prior MI and LVEF less than or equal to 50% who were randomly assigned to either catheter ablation plus an ICD or ICD alone.[109] The primary endpoint was the time to first recurrence of VT or VF. After a mean follow-up duration of 22.5 months, time to VF or recurrent VT was longer in the ablation group than in the control group (median 18.6 vs 5.9 months p = 0·045). According to the Kaplan-Meier analysis, 59% of patients in the ablation group and 40% of patients in the control group were free from any VT or VF episode after 12 months. No significant difference in quality of life was found. Ablation-related complications occurred in two patients (transient ST-segment elevation in one patient and a transient cerebral ischemic event in the other) and there were no procedural deaths.

PRIOR TO ABLATION

Since patients with scar-based VT frequently have coronary artery disease (CAD), it is important to understand a patient's coronary anatomy and ischemic burden prior to ablation. Patients with unrevascularized CAD are unlikely to tolerate prolonged periods of VT. It is therefore prudent to obtain a noninvasive or invasive assessment of a patient's coronary anatomy prior to the procedure. Ideally, a patient should be revascularized before catheter ablation. In some instances, revascularization itself may reduce a patient's arrhythmic burden. For some patients, inotropic support, balloon pump or other forms of hemodynamic support (e.g. left ventricular assist-device or extracorporeal membrane oxygenation) may be required to perform the case.[116-118]

Prior to ablation, all patients should undergo a transthoracic echocardiogram to assess for left ventricular thrombus. The presence of thrombus is a contraindication to endocardial VT ablation due to the risk of thrombus dislodgement. In patients without ICDs, preprocedural magnetic resonance imaging (MRI) can be used to guide ablation by identifying areas of scar. Finally patients should be assessed for peripheral arterial disease (PAD) prior to ablation. Frequently, access to the LV is achieved retrogradely across the aortic valve. For patients with extensive PAD a transseptal approach may be more desirable.

12-LEAD LOCALIZATION

Planning for scar-based monomorphic VT ablation first requires analysis of the 12-lead ECG during tachycardia (providing it is available). For re-entrant VT, the QRS morphology represents the exit point of the circuit. In general, VTs arising in the septum (or fascicular system) are more narrow than VTs originating on the free wall. Positive concordance (dominant R wave in all precordial leads) is associated with VTs that exit from the posterior base of the heart. Negative concordance (QS in all precordial leads) is associated with VTs that exit from the anterior left ventricular apex.[119] A left bundle branch block (LBBB) pattern (R < S in lead V1) is observed with VTs from the right ventricle or ventricular septum. Right bundle branch block (RBBB) morphologies (R > S in lead V1) are almost invariably associated with VTs that arise in the left ventricle. In patients with prior infarction, the frontal axis of the VT is also influenced by the location of the VT exit site. The VTs that exit on the inferior wall produce a superiorly directed axis. An inferiorly directed axis usually reflects a VT from the anterior wall. A negative deflection in lead I and AVL indicates a lateral exit.[111] The VTs of epicardial origin typically have a longer QRS duration and slurred QRS upstrokes in the precordial leads.[120]

APPROACH TO ABLATION

The term "mapping" is a broad term that refers to number of electrophysiological techniques that are used to gain insight about the nature and location of an arrhythmia. There are a variety of mapping techniques that are used in scar-based VT ablations. Many of these techniques require the presence of sustained VT. In many instances patients are unable to tolerate sustained VT, and alternative approaches must be taken (see substrate-based ablation below). In order to induce VT, an operator usually performs a pacing stimulation protocol from the right ventricular apex or right ventricular outflow tract (RVOT). Frequently, the resulting VT is not the patient's "clinical VT" (e.g. it may have a different cycle length or morphology). Moreover, many patients will have multiple inducible VTs. Ideally all VTs that are reproducibly inducible and hemodynamically tolerated should be mapped and ablated.

ACTIVATION MAPPING (FOCAL TACHYCARDIAS)

One common form of mapping used in the electrophysiology lab is "activation mapping". This form of mapping is performed while a patient is in VT. To accomplish this, a mapping catheter is maneuvered to different sites in the chamber of interest, focusing on areas suggested by the 12-lead ECG or over scars detected by Echo or MRI. The recording electrode at the catheter tip reflects local myocardial activation. By comparing the timing of the local electrogram to a standard reference (typically the onset of the QRS for VT), a great deal can be learned about the arrhythmia. Activation mapping is of particular use in focal tachycardias where the local electrogram (EGM) typically precedes the onset of the QRS by 20–30 ms at site of the focus. By locating areas with very early EGM-QRS timings the arrhythmia focus can be localized and ablated.

RE-ENTRANT TACHYCARDIA

In contrast to focal VTs, re-entrant VTs demonstrate continuous electrical activity as the wavefront propagates around a circuit. Strictly speaking, there is no "earliest" point in the circuit.[121] Operators frequently use this form of mapping to identify a

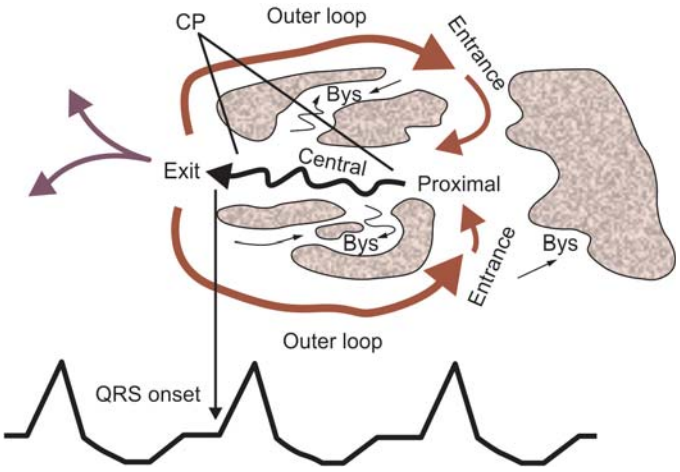


FIGURE 11: Hypothetical VT circuit consisting of a central isthmus with entrance and exit zones. The outer loops course around the scarred areas (border zones) and bystander loops (Bys) are found within the scar. (*Source:* Modified from reference 123)

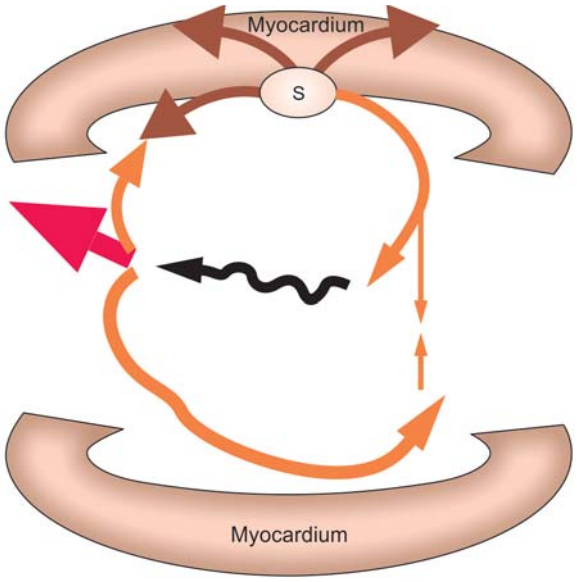


FIGURE 12: Stimulation is performed at an outer loop site (S) in the re-entry circuit that shown in Figure 12. The stimulated orthodromic wavefront propagates through the circuit, resetting the re-entry circuit. After the last stimulus, the pacing site is next depolarized by the orthodromic wavefront that has made one revolution through the circuit. The PPI therefore approximates the TCL. Pacing at this site also directly stimulates surround myocardial tissue. The QRS morphology therefore differs from that of the VT. (*Source:* Modified from reference 123)

critical isthmus (or zone of slow conduction) where the VT is likely to be terminated (Fig. 11). Typically, these sites are characterized by a diastolic electrogram that is low amplitude and fractionated. However, the specificity of isolated diastolic potentials is limited as they can be observed in regions other than a critical isthmus.[122]

ENTRAINMENT MAPPING

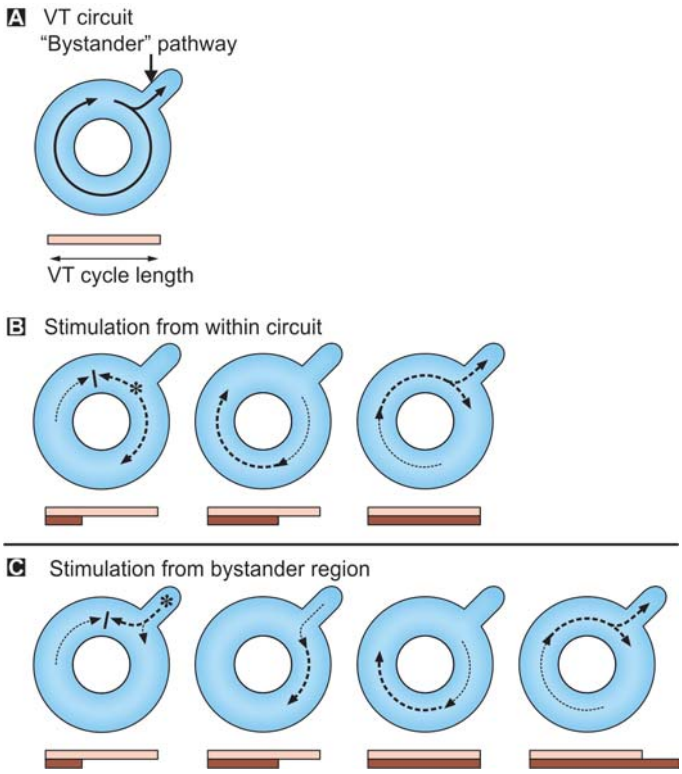
During activation mapping it is not uncommon to encounter areas with fractionated diastolic potentials that may or may not be participating in the VT circuit. In order to determine whether such a site is participating in the VT circuit, a technique known as entrainment mapping can be used. Entrainment refers to the continuous resetting of a tachycardia circuit by pacing at a cycle length slightly faster than the tachycardia cycle length (TCL). To demonstrate entrainment, the tachycardia must be accelerated to the pacing cycle length and tachycardia resumption upon cessation of pacing. When pacing from a site remote from the circuit, the pacing impulse travels toward the circuit and penetrates it in two directions. In the antidromic direction, the impulse collides with the previous circulating orthodromic wavefront. In the orthodromic direction, the impulse travels around circuit, resetting the tachycardia. The result of entrainment from a site remote to the VT circuit is QRS fusion where the resulting QRS morphology represents a fusion between the tachycardia circuit and a purely paced beat.

If entrainment is performed from a site within the circuit, the resulting QRS morphology should replicate the VT morphology exactly. This is known as concealed entrainment. If concealed entrainment is observed, several other features can be examined to confirm that the pacing catheter is located within the tachycardia circuit. The stimulus-QRS interval can be compared to the electrogram-QRS interval during VT. These intervals should be similar if pacing is taking place along the circuit (generally within 10 ms).

The post-pacing interval (PPI) refers to the duration between the last pacing stimulus artifact and the return of next local EGM at that pacing site. This represents the time that it takes for the last orthodromically stimulated wavefront to revolve around the circuit. If pacing is performed from a site within the circuit, the PPI should equal the TCL. A PPI-TCL less than or equal to 30 ms suggests that pacing site is within the VT circuit. Pacing at a site remote from the re-entry circuit can also entrain tachycardia, but in this instance the PPI is equal to the conduction time from the pacing site to the circuit through the circuit and back to the pacing site and therefore exceeds the TCL.[123]

The VT model proposed by Stevenson and others have greatly enhanced out understanding about the entrainment of these circuits.[124] The hypothetical VT shown in Figures 11 and 12 depicts a "figure of eight" circuit with a common central isthmus.[123] The common isthmus has an entrance and exit as well as central regions. The QRS complex is inscribed after the wavefront leaves the exit site and begins propagating around the border of the scar around two outer loops. The wavefronts then enter the infarct region through entrances to reach the entrance of the isthmus. Regions that are within scar do not participate in the circuit are labeled as bystanders.

Analysis of the PPI can reveal a great deal about the location of the pacing catheter with respect to this hypothetical circuit. As above, when pacing from within the VT circuit (i.e. from the exit, or critical isthmus) the QRS morphology will be identical to the VT and the PPI-TCL should be less than or equal to 30 ms (Figs 13A to C). Pacing from a bystander site will, however, produce a PPI-TCL that is greater than or equal to 30 ms as it reflects the time for the stimulus to leave the bystander region, propagate around the circuit and return to the site of pacing. In this instance the QRS morphology will resemble the VT so long as the bystander is insulated by scar from surrounding myocardium. Entrainment from the true isthmus



FIGURES 13A TO C: Stimulation during VT is shown: (A) A VT circuit is depicted with an arrow showing the direction of impulse propagation. The impulse also enters a bystander or dead-end pathway to the side. The length of one complete VT cycle is shown as a white bar below; (B) A stimulus (*) is delivered from within the circuit; propagation occurs in the same direction around the circuit path as during VT as well as in the opposite direction, where it collides with the advancing "head" of the prior VT beat (dimmed arrow). A black bar beneath tracks the progress of the stimulated wave front during the figure. At right, the wave front has continued propagating around the circuit until it reaches the site of stimulation. The time required to return to the site of stimulation (the postpacing interval) just equals the VT cycle length (black bar = white bar); (C) A stimulus is given from a bystander pathway. The impulse must travel a short distance to arrive at the circuit, after which it propagates as in (B). However, the PPI (black bar) exceeds the VT cycle length by the time required to exit from and return to the point of stimulation. (*Source:* Modified from reference 138)

will result in stimulus to QRS = mid-diastolic EGM to QRS. Pacing from the innerloop bystander shows that the stimulus to QRS will be greater than EGM to QRS onset. Entrainment from an outerloop site will generally produce a PPI-TCL less than or equal to 30 ms (as it is within the circuit), however, the resulting QRS morphology will represent fusion between the circuit's propagating wavefront and direct depolarization of surrounding myocardium (Figs 13A to C).

Entrainment can also be used to differentiate a diastolic potential that reflects activation of the VT circuit and a "far field potential" which is due to depolarization of tissue remote from the circuit. During entrainment, a potential that is participating the VT circuit will be captured by the entrainment maneuver and will be obscured by the pacing artifact. In contrast, the inability to "entrain" the potential whereby it appears dissociated from the pacing suggests that the potential is a far field electrogram and not part of the VT circuit.

It can be challenging to localize an ideal target for ablation even under the best of circumstances. The size and location of an isthmus can vary widely depending on a patient's substrate. On most occasions, ablation of a critical portion of a VT circuit requires multiple lesions depending on the volume of the isthmus. While any one of the above mentioned findings (i.e. mid-diastolic potential, concealed entrainment, Stim-QRS ~ EGM-QRS, PPI-TCL < 30 ms) does not itself predict an ideal site for ablation, the presence of multiple findings is likely to increase the rate of success.[125]

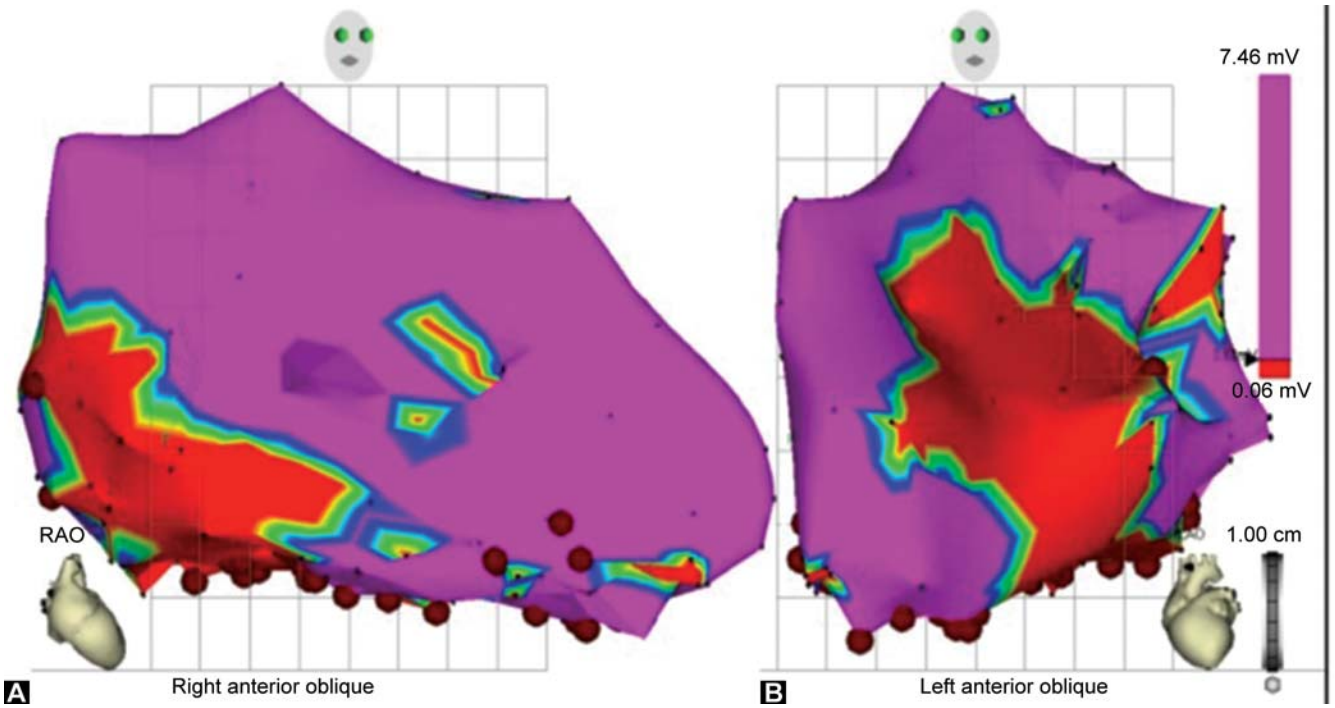
ELECTROANATOMIC THREE-DIMENSIONAL MAPPING

The advent of three-dimensional EAM systems, such as CARTO (Biosense Webster, Baldwin Park, CA) or EnSite/NavX (St. Jude Medical, St. Paul, MN), has greatly enhanced the ability to perform complex ablations. Whereas conventional mapping relies on interpretation of intracardiac electrograms and two-dimensional fluoroscopic imaging, EAM provides additional real-time three-dimensional data about a patient's arrhythmogenic substrate. Although there are differences in their underlying technologies, in general, these systems allow operators to determine the spatial orientation of catheters in three-dimensions, delineate anatomic areas of interest, define cardiac chamber geometry and locate areas of scar. In addition, they can be used to create detailed activation maps that help to accurately locate the region and nature of the arrhythmia (e.g. focal versus macro-re-entrant). Given the complexity of the procedure, EAM systems are particularly useful for ablation in patients with scar-based VT.

Both CARTO and EnSite can be used to perform activation mapping during VT. To perform this, a designated catheter is moved to various locations in the chamber of interest. At each point, the mapping software is able to integrate the position of the catheter and the timing of the local electrogram with respect to an arbitrarily designated reference (or fiducial) point. The temporal relationship of the local activation to the reference point is color coded with red generally representing early activation sites, purple representing late activation sites and other colors, such as yellow, green and blue, representing intermediate activation times. This isochronal map is displayed in real-time on a review screen and can be used to distinguish focal from re-entrant arrhythmias. In addition to this, it localizes the source or circuit in the cardiac chamber. Focal arrhythmias generally have a small site of early activation with centrifugal spread away from the source. In contrast, macro-re-entrant rhythms display transitions from early (red) to intermediate (yellow-green-blue) to late (purple) as the wavefront propagates around the circuit with characteristic early-meets-late patterns. By tracing this propagation map around the chamber, the location of the circuit can be visualized.

VOLTAGE MAPPING

Another powerful application of EAM is its ability to delineate areas of scar. Areas of scar typically exhibit low voltage electrograms. A cardiac chamber can be readily mapped by placing a catheter at various locations and recording the signal amplitude. As with endocardial activation, a color-coded voltage scale can be used to display areas of low voltage amplitude, to distinguish between areas of scar, dense scar and relatively



FIGURES 14A AND B: Voltage map of the left ventricle (LV), RAO and LAO view, in an individual with large, healed inferolateral myocardial infarction. Local bipolar electrogram voltage of less than or equal to 0.5 mV has been arbitrarily selected as the threshold for delineating low electrogram amplitude, as seen on the voltage scale on the right. Areas of red coloration represent sites with the lowest electrogram amplitude, with the area of next lowest voltage demarcated by yellow, followed by green, etc. The area colored in magenta indicates normal electrogram voltage. (*Source:* Modified from reference 139)

normal tissue (Figs 14A and B). Voltage mapping is critical for re-entrant VT as the majority of these circuits are intimately related to scar border zones and other anatomic obstacles. Understanding the location and density of scar can be used to perform VT ablations in patients during sinus rhythm (see substrate-based ablation below).

PACE MAPPING

Pace mapping is a useful technique for individuals with hemodynamically unstable VT in whom entrainment or activation mapping is not possible. The 12-lead ECG of the paced site is compared to the 12 lead of the VT. When the paced and comparison QRS morphologies are identical, this is referred to as a 12/12 match. When performing pace mapping, it is essential to confirm that the lead placement for the pace map is identical to the 12 lead used for comparison. Often times, the precordial leads are placed in modified locations during EP studies. If the comparison ECG has been performed outside of the EP lab, alternate lead placement may render an inaccurate pace map.

Pace mapping can be useful for focal VTs where a 12/12 match is presumed to represent the site of origin.[126] However, its utility is somewhat limited in patients with macro-re-entrant VT. In patients with scar-related VT, a perfect or near perfect pace map usually indicates that the catheter is located near the VT exit site. However, ablation at a VT exit site may merely result in shifting the exit to a new location and fail to eliminate the circuit. Ablation at isthmus sites are more likely to be successful, however this can be difficult to perform with pace mapping alone. Regions of functional block that may define activation pathways during VT may not be present while pacing during sinus rhythm. When pace mapping in a defined isthmus, the stimulated wavefront can propagate in both antidromic and orthodromic directions.[127] The resulting QRS may be a fusion between these two wavefronts and differ from the morphology of the VT circuit under investigation.

Pace mapping can be used to identify areas of slow conduction which are typically found within infarct zones, and may represent positioning in a critical isthmus. When pacing normal myocardium, there is typically little or no delay between the pacing stimulus and the surface ECG complex (S-QRS). Since the isthmus of VT circuit usually represents a zone of slow conduction, pacing from this region can sometimes result in S-QRS delay. Brunckhorst and his colleagues performed pace mapping at 890 sits in 12 patients with postmyocardial infarction VT. Their data demonstrated that areas with S-QRS delay were always localized to an infarct region (as identified by electrogram voltage) and 13 of 14 areas of conduction delay were associated with the isthmus of a re-entrant circuit.[128] In a similar study, this group combined pace mapping data with S-QRS data to localize successful sites of ablation in patients with scar-related VT.[127]

Pace mapping within scar at sites with an isolated diastolic potential during sinus rhythm has also been shown to be an indicator of a critical isthmus (Fig. 15). In one study, application of this strategy resulted in freedom from recurrent VT in 16 of 19 patients (84%) during a mean follow-up period of 10 months.[129] Finally, pace mapping can be useful to define regions within scar that are electrically unexcitable. Soejima and his colleagues demonstrated that in some patients, re-entry circuit isthmuses can be identified by delineation of electrically

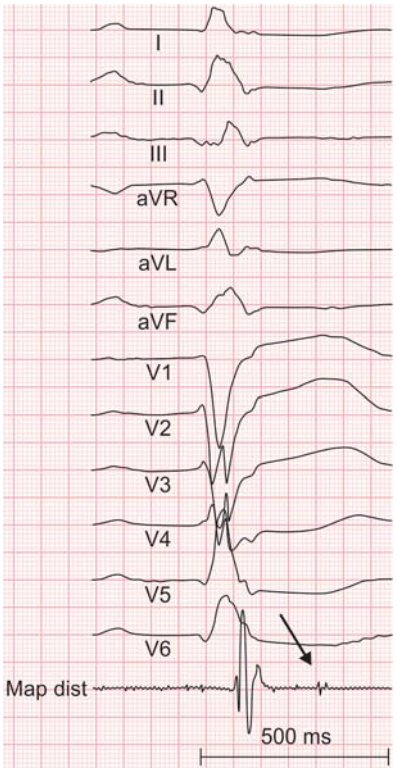


FIGURE 15: Example of an isolated diastolic potential recorded during sinus rhythm within left ventricular scar. (*Source:* Modified from reference 129)

unexcitable scar that defines their borders.[130] The RF ablation in these regions abolished inducible VT in 10 of 14 patients and abolished or markedly reduced spontaneous VT during follow-up.

SUBSTRATE-BASED ABLATION

The term "substrate based ablation" has been used to describe the combination of techniques used to perform VT ablations in patients with hemodynamically unstable VT who cannot tolerate entrainment or activation mapping. The specific protocols for substrate ablation vary from center to center. However, in general, the following steps are taken (Flow chart 2 and Fig. 16):

- A voltage map of the chamber of interest is created such that areas of scar can be defined.
- Areas with diastolic potentials and fractionated electrograms are tagged and noted on the electroanatomic map.
- Pace mapping is performed in multiple areas with particular attention to QRS morphology and S-QRS duration and electrically unexcitable scar.
- Probable VT exit sites as well as isthmuses are identified based on the above information.
- Ablations in regions of potential isthmus sites are undertaken.

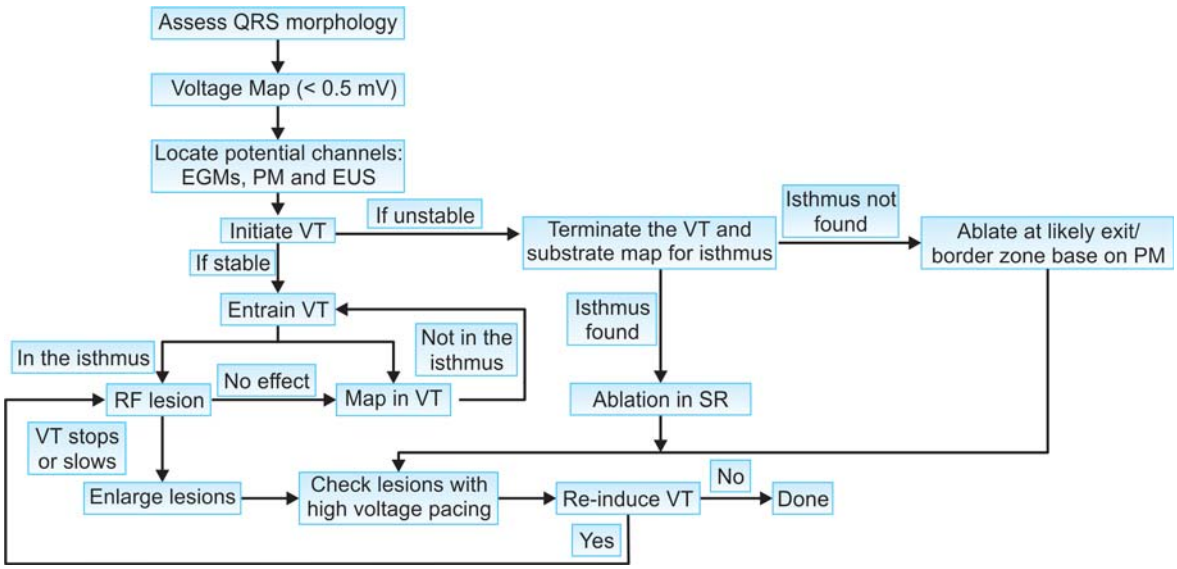
Although substrate-based ablation is often performed in patients with poorly tolerated VT, it can also be used in conjunction with other mapping techniques such as entrainment mapping. Substrate mapping may help to operators to identify areas likely to be of particular interest for re-entrant circuits. Following this an operator may induce VT for short periods of time and further localize potential ablation sites.

SAFETY

The VT ablation is complex procedure performed in patients who frequently have advanced illness. These features coupled with long procedure times and extensive ablation in the left-sided circulation creates risk for a myriad of serious complications, including stroke, valvular injury, major bleeding, tamponade, hemodynamic collapse and death. In two prospective trials in which VT ablation was performed for recurrent VT the periprocedural mortality was 2.7–3%.[108,131] The risk of a major complication, such as the ones mentioned above, was 8–10%. The risk of minor complications was 6–7.3%.

The 1998 North American Society of Pacing and Electrophysiology (NASPE) Prospective Catheter Ablation Registry, significant procedural complications were observed in 3.8% of

FLOW CHART 2: Steps of VT ablation



(Abbreviations: EGM: Electrogram; EUS: Electrically unexcitable Scar; PM: Pace-map). (*Source:* Modified from reference 111)

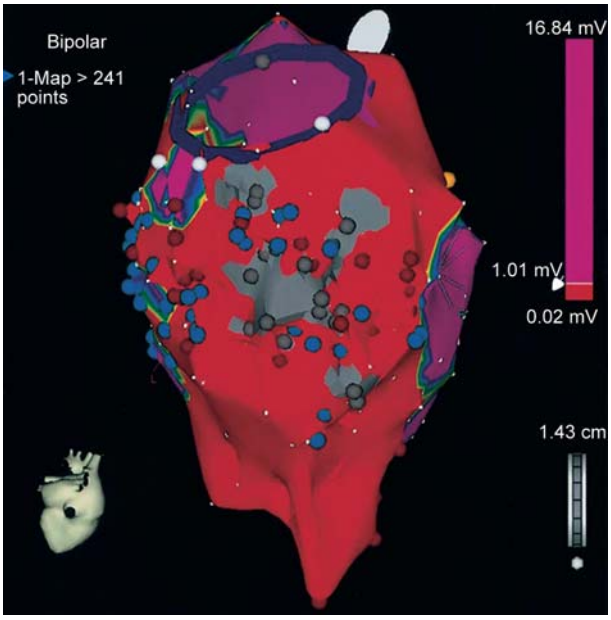


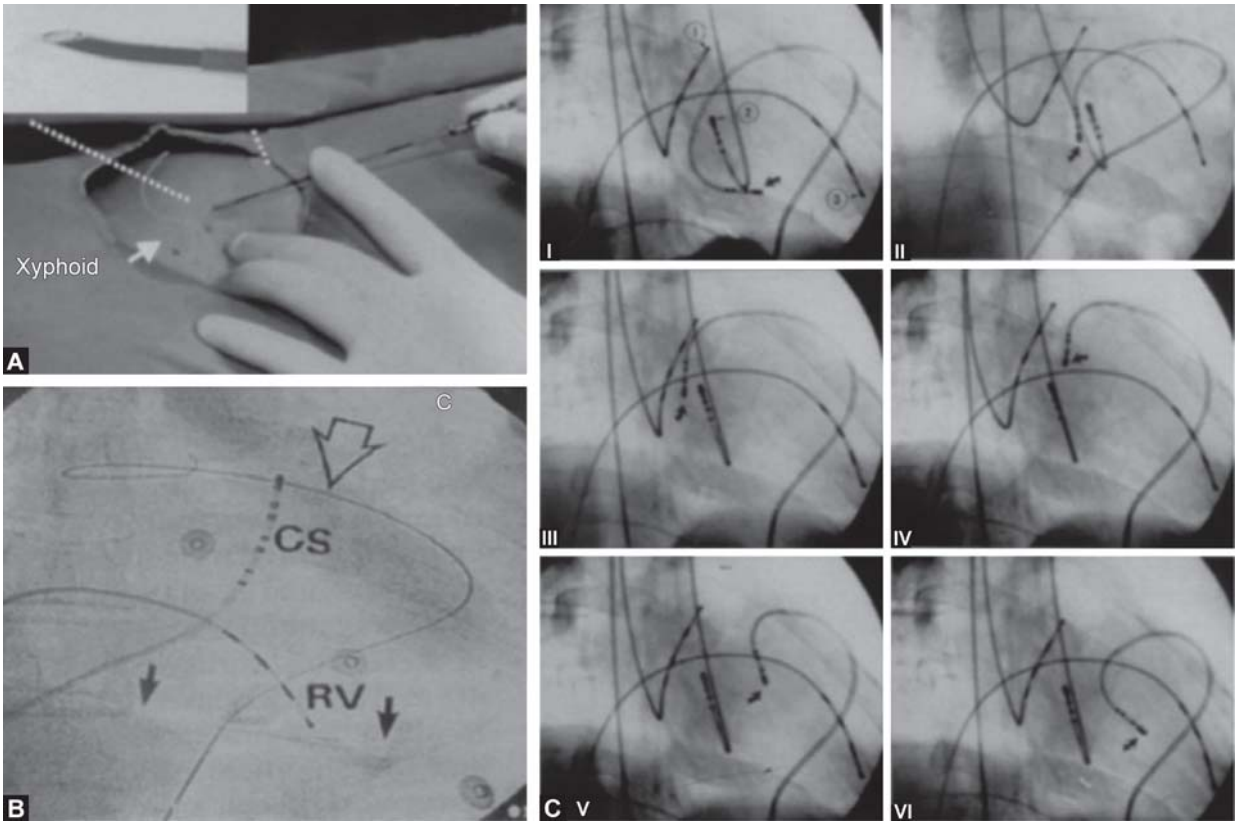
FIGURE 16: Voltage map of the posterior aspect of the left ventricle. Radiofrequency energy was delivered at points marked in red. Sites with an isolated potential during sinus rhythm are marked in blue and sites where there was noncapture are marked in grey[129]

patients undergoing a VT ablation.[132] However, this registry included idiopathic VT patients and the higher complication rates should be expected in sicker patient populations. As with most complex procedures, complication rates may vary significantly depending on the patient population and operator experience.

EPICARDIAL VT

It is increasingly recognized that VT may arise from the epicardial surface of the heart. Re-entrant epicardial circuits are particularly common among patients with nonischemic cardiomyopathies as well as arrhythmogenic right ventricular dysplasia (ARVD).[133] However, epicardial re-entry has also been documented in 15–23% of patients with postmyocardial infarction VT.[133,134] The presence of an epicardial circuit may be the cause of failure for many endocardially based VT ablations. Various ECG criteria have been proposed to recognize the presence of an epicardial VT circuit.[120,135,136] In general, epicardial circuits manifest a QRS onset that is often slurred, with pseudodelta wave appearance. A pseudodelta wave of more than 34 ms is quite specific for epicardial VT (95%), but less sensitive than an intrinsicoid deflection time of more than 85 ms (defined as the interval measured from the earliest ventricular activation to the peak of the R wave in V2).[120]

Access to the epicardial space can be accomplished by the approach described by Sosa and his colleagues.[134] Using a needle originally designed to enter to epidural space, fluoroscopy is used to approach the epicardium. Contrast injection confirms proper placement of the needle and an introducer sheath is subsequently advanced over a guidewire into the



FIGURES 17A TO C: Technique used to insert the mapping and ablation catheter in the pericardial space. (A) A touchy needle is advanced into the pericardial space with the aid of fluoroscopy and contrast injection; (B) A soft guidewire is introduced into the pericardial space (large arrow), where contrast is also present (panel 2). An introducer is then advanced, the guidewire is removed and an ablation catheter is introduced into the pericardial sac to perform epicardial mapping and/or ablation; (C) Demonstrates a right anterior oblique view at 60° obtained by fluoroscopy during epicardial mapping procedure. The epicardial catheter (arrow) is manipulated and placed in different locations of the epicardial space (I to VI), where epicardial electrograms are obtained. (*Source:* Modified from reference 132)

pericardial space (Figs 17A to C). Once access to the pericardial space is achieved, mapping of VT can be performed using methods similar to endocardial ablation. Access to the pericardial space can be challenging in patients with prior cardiac surgery or pericarditis due to the presence of dense adhesions. In these instances, hybrid surgical approaches, such as the use of a subxiphoid window or limited anterior thoracotomy, can be employed to access the epicardium.[137]

The risk of injury to the coronary arteries is a significant concern with epicardial VT ablation and coronary angiography is usually performed to ensure that an ablation site is safe. In addition, the left phrenic nerve courses along the lateral aspect of the left ventricle and pacing should be performed at all ablation sites to confirm the absence of phrenic nerve capture. Sacher and his colleagues recently evaluated the safety of epicardial ablation through retrospective analysis of 156 epicardial VT procedures at three tertiary care centers.[133] Major periprocedural complications occurred in 9% of patients approximately half of which were due to epicardial bleeding. One patient developed asymptomatic right coronary artery stenosis due to cryoablation. There were no periprocedural deaths. It is important to note that these procedures were performed at experienced centers in carefully selected patients. The safety and efficacy of this procedure will likely continue to evolve over the next several years.

IDIOPATHIC VENTRICULAR TACHYCARDIA

Most causes of VT are due to underlying structural heart disease (mainly ischemia or cardiomyopathy). Idiopathic VT (VT in patients without structural heart disease) accounts for 10–20% of VT cases evaluated by electrophysiology centers.[140,141] It is important to recognize these patients as they frequently respond to nonpharmacologic ablative techniques. Idiopathic VT can be broadly classified as polymorphic VT and monomorphic VT (Table 1). In this chapter we will describe the clinical, electrocardiographic (ECG) and electrophysiologic findings for patients with monomorphic idiopathic VT.

OUTFLOW TRACT-VENTRICULAR TACHYCARDIA (OT-VT)

This form of idiopathic VT arises from the outflow tract of the right or the left ventricle. Based on its origin it can be classified as VT that arises from the right ventricular outflow tract (RVOT VT), the left ventricular outflow tract (LVOT VT) and the aortic cusps (Cusp VT) (Table 2).

TABLE 1

Idiopathic ventricular tachycardia

Monomorphic ventricular tachycardia	*Polymorphic ventricular tachycardia*
• Outflow tract VT-RVOT-VT, LVOT-VT, aortic cusp VT, Epicardial VT • Fascicular VT-LAF-VT, LPF-VT, Septal VT • Adrenergic monomorphic VT • Annular VT-mitral annular, tricuspid annular	• Long QT syndrome • Brugada syndrome • Short coupled torsades • Short QT syndrome • Catecholaminergic polymorphic VT • Idiopathic VF

(Abbreviations: LAF: Left anterior fascicular; LPF: Left posterior fascicular; LVOT: Left ventricular outflow Tract; RVOT: Right ventricular outflow tract; VF: Ventricular fibrillation; VT: Ventricular tachycardia)

The RVOT VT is more common in females and is usually seen in third to fifth decade of life while LVOT VT is equally distributed between males and females.[142] Symptoms include palpitations, dizziness, atypical chest pain and syncope. There are three predominant clinical forms of this syndrome: (i) non-sustained repetitive monomorphic VT alternating with periods of sinus rhythm; (ii) paroxysmal exercise-induced sustained VT[143] and (iii) frequent premature ventricular contractions (PVCs) often in a bigeminal fashion. There are also reports of tachycardia-induced cardiomyopathy in patients with a high PVC burden.[144]

RVOT VT

This form of VT is associated with a characteristic ECG morphology of LBBB with inferior axis suggesting origin from the right ventricle outflow tract (Fig. 18). Jadonath et al.[145] evaluated the utility of 12-lead ECG in localizing the site of origin of RVOT VT. A QS pattern in lead avR and monophasic R waves in leads II, III, avF and V6 were noted in each patient at all pacing sites. The anterior sites showed a dominant Q wave or a qR complex in lead I and QS complex in avL. Pacing at

TABLE 2

Electrocardiographic findings in outflow tract VT

RVOT VT	*LVOT/aortic cusp VT*
• QS in avR • Monophasic R wave in II, III, avF, V_6 • Septal sites have negative qrs in avL • Free-wall sites have wider notched qrs in inferior leads and later precordial transition (V_4) • Lead I shows Q wave in anterior sites and dominant R wave in posterior sites • Phase analysis as measured from the earliest QRS onset to: a. Earliest QRS onset is V_2 b. Initial peak/nadir in III ≥ 120 ms c. Initial peak/nadir in V_2 ≥ 78 ms	• Early precordial transition (V_2 V_3) • Taller and broader R wave or RBBB in V_1 V_2 • Septal LVOT has dominant Q in V_1, qrs II/qrs III > 1 • Aortomitral LVOT has qR in V_1, qrs II/qrs III < 1 • Cusp VT – notch in V_5, lack of S in V_5-V_6, taller R in inferior leads • Lead I – rS in left cusp VT, notched R in noncoronary cusp VT • Phase analysis (Cusp VT) as measured from the earliest QRS onset to: d. Earliest QRS onset not in V_2 e. Initial peak / nadir in III ≤ 120 ms f. Initial peak/nadir in V_2 ≤ 78 ms

(Abbreviations: LVOT: Left ventricular outflow tract; RVOT: Right ventricular outflow tract)

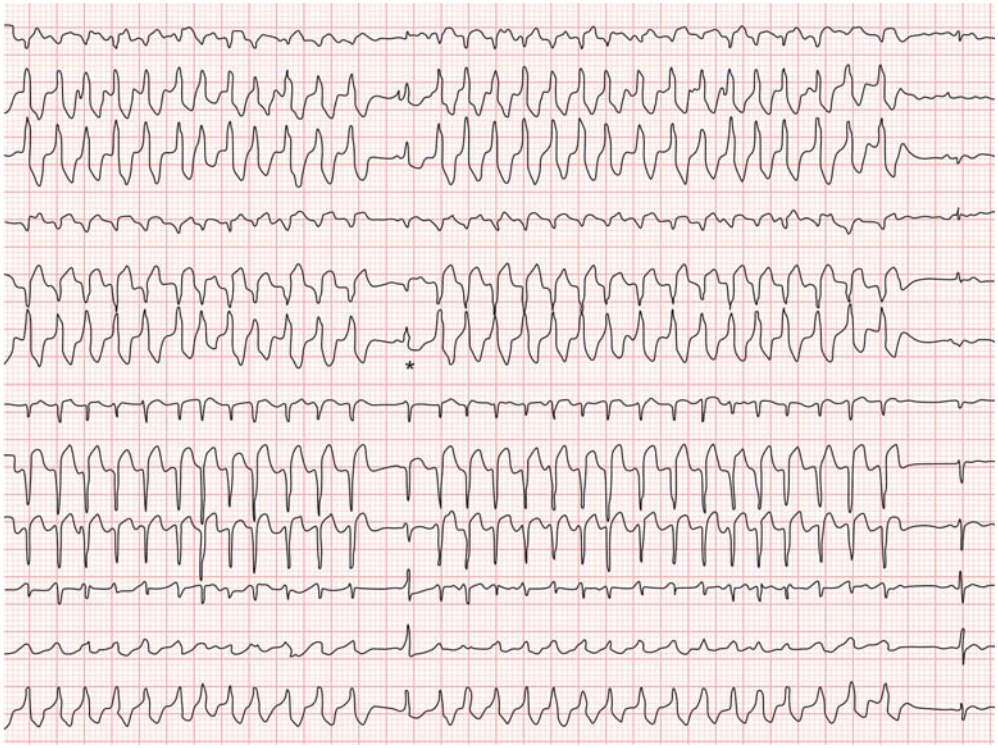


FIGURE 18: Twelve-lead ECG of ventricular tachycardia arising from the right ventricular outflow tract. There is left bundle branch block morphology with late transition (V4) in the precordial leads and an inferior axis in the limb leads. Negative QRS complex in lead avL suggests a septal origin while a q wave in lead I points to anterior focus. Fusion beat is noted in the middle of the tracing (*)

the posterior sites produced a dominant R wave in lead I, QS or R wave in avL and an early precordial transition (R/S ≥ 1 by V3). Coggins et al. showed that septal RVOT VT was associated with negative QRS complex in avL while RVOT VT arising from the lateral wall produced a positive QRS complex in avL.[146] Dixit et al.[147] used pace-mapping techniques to differentiate between RVOT VT arising from the free wall versus the septal wall. They showed that free-wall RVOT VT was associated with wider and notched QRS complexes in the inferior leads and the precordial R wave transition was late (R/S ≥ 1 by V4). Recently OT-VTs arising from near the His-bundle region have been described.[148,149] The characteristic ECG abnormalities for VT arising from this site include a R/RSR' pattern in avL, taller R wave in I, small R waves in inferior leads, taller R waves in V5, V6 and QS pattern in V1 (Fig. 19). Representative example of RVOT VT is shown in Figure 18.

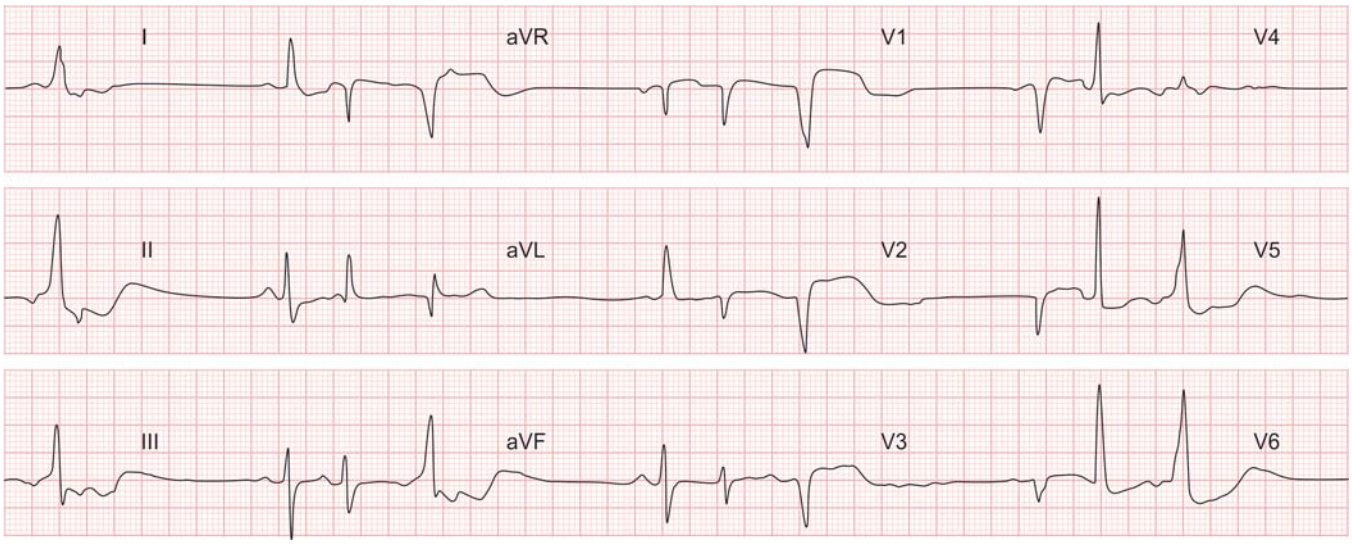


FIGURE 19: Twelve-lead ECG during sinus rhythm showing PVC arising from the para-Hisian region. There is tall R wave in lead I, QS in V1, R in lead II > R in lead III, taller R waves in V5 and V6 and a characteristic rSR in lead avL. Local intracardiac signal at this site preceded the QRS onset by 25 ms

Idiopathic VT may arise just proximal to the outflow tract in the para-Hisian region. This ECG will mimic that of RVOT except for the characteristic rSr1 in avL (Fig. 19).

Idiopathic VT arising from the pulmonary artery (PA) has also been described.[150,151] The origin of VT from the PA is thought to be from remnants of embryonic muscle sleeves that have been noted in amphibian and mammalian outflow tract.[152] This is supported by the presence of a sharp potential at these sites that preceded the onset of ventricular activation during VT.[150] Sekiguchi et al.[151] noted the following ECG characteristics during VT that favor PA VT as compared to RVOT VT: (i) Larger R-wave amplitude in inferior leads; (ii) The ratio of the Q-wave amplitude in avL/avR was larger in the PA group; (iii) Significantly larger R/S amplitude in lead V2 in patients with PA VT than in those with RVOT VT.

LVOT VT

The VT arising from the LVOT shares similar characteristics to the RVOT VT due to a common embryonic origin. This form of VT can be differentiated from the RVOT VT by differences in QRS morphology (Fig. 20). The LVOT VT is suggested by LBBB morphology with inferior axis with small R waves in V1 and early precordial transition (R/S $\geq$ 1 by V2 or V3) or RBBB morphology with inferior axis[153-156] and presence of S wave in V6.[157,158] The LVOT VT arising from the septal para-Hisian region has an ECG pattern of QS or Qr in V1 with early precordial transition and ratio of QRS in leads II/III greater than 1 while LVOT VT arising from the aortomitral continuity has a characteristic qR pattern in V1 with a ratio of QRS in leads II/III less than or equal to 1.[159]

CUSP VT

Case reports of idiopathic VT with LBBB morphology and inferior axis that failed ablation in the RVOT but were successfully ablated in the left coronary cusp[160,161] were described in 1999. Kanagaratnam et al.[162] reported the ECG characteristics of 12 patients with outflow tract VT that required ablation in the aortic sinus of Valsalva. All patients had LBBB inferior axis morphology with taller monophasic R waves in inferior leads and an early precordial R wave transition by V2 or V3. The VT arising from the left cusp had an rS pattern in lead I, and VT arising from the noncoronary cusp had a notched R wave in lead I. Ouyang et al.[163] evaluated the ECG differences between 8 patients with RVOT VT and 7 patients with VT arising from the aortic sinus cusp (5 from left sinus and 2 from right sinus). They found that a broader R wave duration and a taller R/S wave amplitude in V1 and V2 favored VT arising from the aortic cusp. Yang[164] used phase differences in the 12-lead ECG to differentiate between RVOT VT (32 patients) and aortic cusp VT (15 patients). They showed that RVOT VT was associated with earliest ventricular activation in V2 and a shorter time from onset of ECG to peak/nadir in lead III and V2.

EPICARDIAL VT

Outflow tract VT occasionally arises from the epicardial surface of the heart that requires ablation in the great cardiac vein or via pericardial approach.[148,165-167] Ito et al.[148] showed that the Q wave ratio of avL to avR greater than 1.4 or an S wave amplitude in V1 greater than 1.2 mV was useful in differentiating between epicardial VT from aortic cusp VT. Daniels et al.[167] showed that 9% of the patients with idiopathic VT referred to their institution had an epicardial focus. They found that a

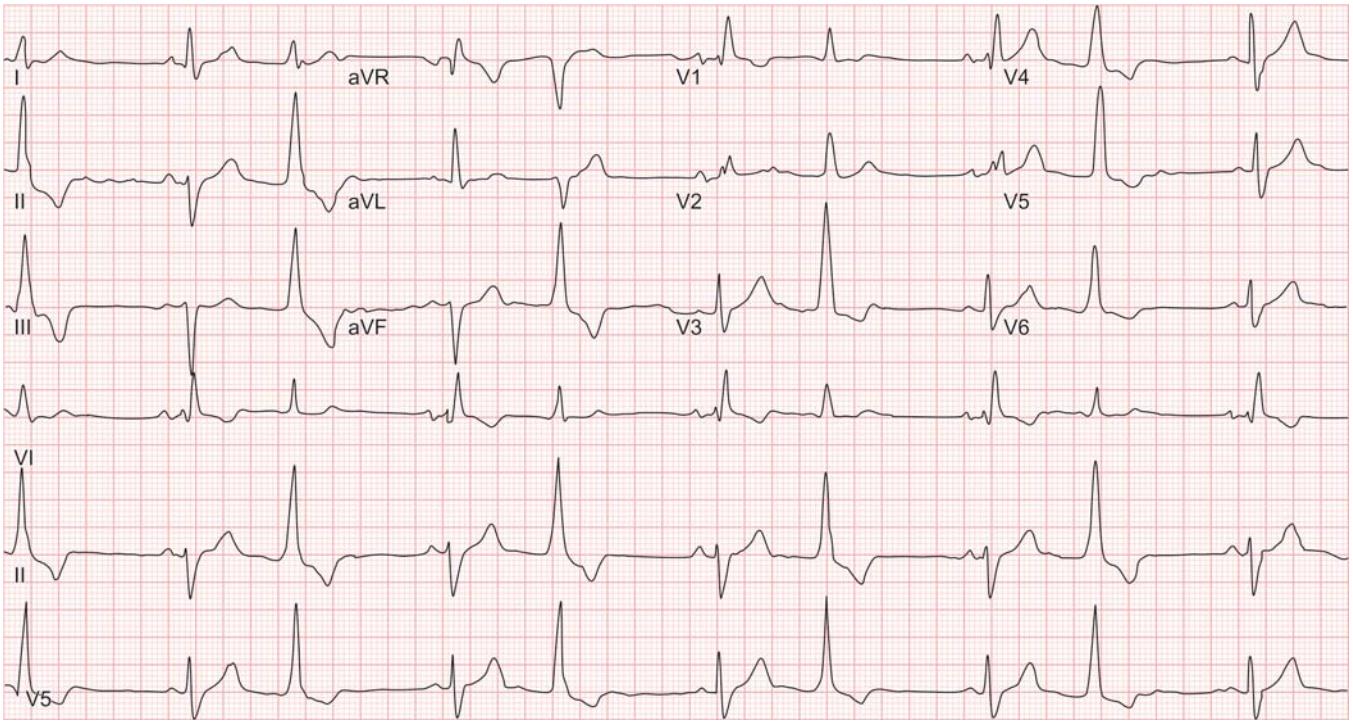
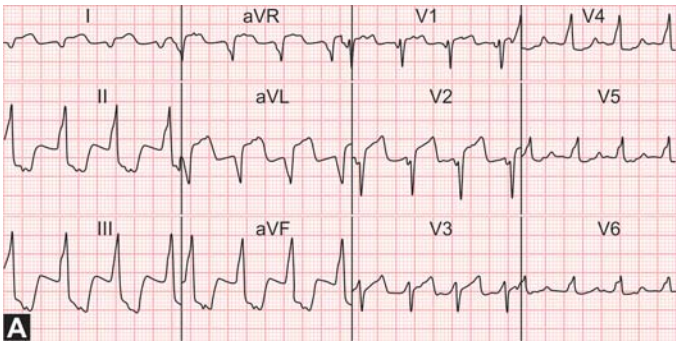
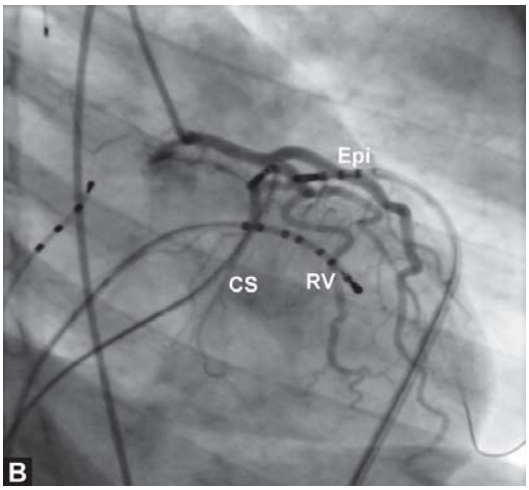


FIGURE 20: Twelve-lead ECG during sinus rhythm showing PVC arising from the left ventricular outflow tract that was successfully ablated in the aortomitral continuity region. There is qR wave in lead V1 that differentiates this from a septal LVOT focus that has a QS or Qr pattern in lead V1





FIGURES 21A AND B: (A) Twelve-lead ECG of VT that was successfully ablated on the epicardial surface of the heart. The precordial maximum deflection index is greater than 55 (calculated by measuring the time from the QRS onset to the earliest maximum deflection (nadir or peak) in precordial leads and dividing it by the total QRS duration). (B) Fluoroscopic view of the catheter position with ablation catheter (Epi) on the epicardial surface of the heart, right ventricular (RV) catheter and coronary sinus catheter (CS). The site of origin of the VT is very close to the left anterior descending (LAD) coronary artery

delayed precordial maximum deflection index greater than or equal to 55 (calculated by measuring the time from the QRS onset to the earliest maximum deflection (nadir or peak) in precordial leads and dividing it by the total QRS duration) differentiates this form of idiopathic epicardial VT from other forms of outflow tract VT (Figs 21A and B). Recently idiopathic VT arising from the crux of the heart has been described that presents as rapid VT usually triggered by exercise and can lead to hemodynamic compromise.[168]

The 12-lead ECG morphology of this VT is similar to that of maximally pre-excited posteroseptal accessory pathways with QRS transition from V1 to V2 and QS complexes in inferior leads (Fig. 22). This can be successfully ablated in the middle cardiac vein or via an epicardial approach.

MANAGEMENT

The majority of the patients with outflow tract VT have a benign course with a very low-risk of sudden death.[169-171] It can be associated with tachycardia-induced cardiomyopathy that improves after successful treatment.[144,172] It is important to differentiate this form of VT from VT associated with arrhythmogenic right ventricular cardiomyopathy (ARVC) that is also associated with LBBB morphology. The ARVC is associated with a worse prognosis and is responsible for sudden death especially in young adults less than 35 years old.[173,174]

Acute termination of RVOT VT can be achieved with adenosine, carotid sinus massage, verapamil and lidocaine. Beta-blockers are especially effective for those with exercise-induced outflow tract VT and a synergistic action is noted with calcium channel blockers. Antiarrhythmic agents like procainamide, flecainide, amiodarone and sotalol are also effective in these patients. There was a trend toward greater efficacy with sotalol in a study of 23 patients with RVOT VT.[175] Nicorandil, a

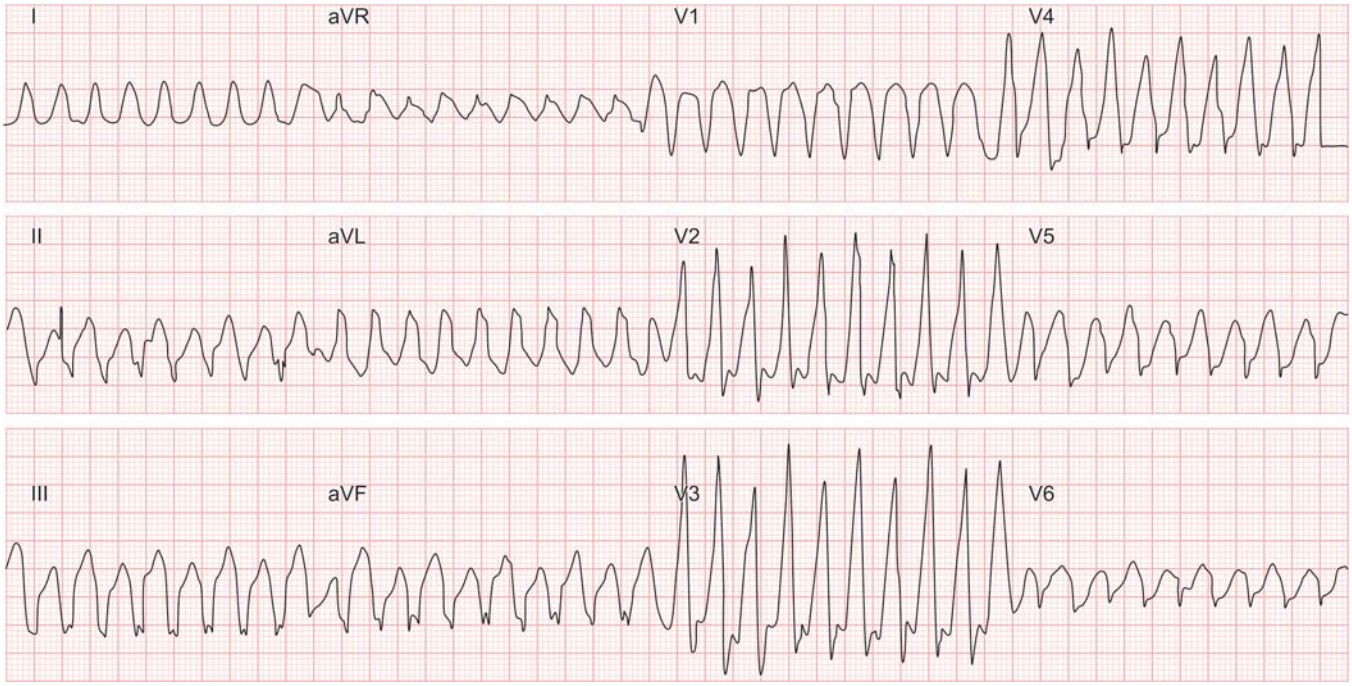


FIGURE 22: Twelve-lead ECG of ventricular tachycardia arising from the crux of the heart. There is left bundle branch block morphology with early transition (V2) in the precordial leads and qs complex in the inferior leads. This matches the 12-lead ECG morphology of maximally pre-excited posteroseptal accessory pathway. This VT was successfully ablated via an epicardial approach

potassium channel opener, has been reported to terminate and suppress adenosine-sensitive VT.[176]

CATHETER ABLATION

Catheter ablation using RF energy to cure patients with outflow tract VT is associated with a high success rate due to the focal origin of this form of VT. The 12-lead ECG is a useful initial guide to localize the site of origin of the tachycardia. Intracardiac mapping to select the optimal site for ablation include activation mapping (earliest local intracardiac electrogram that precedes the onset of surface QRS during VT) and pace mapping (pacing the ventricle from a selected site in sinus rhythm to match the 12-lead morphology of the spontaneous or induced VT). The use of three dimensional (3D) electroanatomical mapping systems reduces fluoroscopic exposure and improves the efficacy of catheter ablation.[177,178] The success rate of catheter ablation for outflow tract VT reported from various series is greater than 90%[132,179] with a recurrence rate of 5% (mainly in the first year). Serious complications include induction of RBBB (2%), cardiac perforation and tamponade (1%); there has been one death reported secondary to complications from RVOT perforation.[146] Ablation for LVOT VT has been associated with occlusion of a coronary artery.[180] Failure of endocardial RF ablation can be due to epicardial location of the VT focus (Fig. 21). Epicardial ablation can be achieved by a subxiphoid technique of pericardial puncture as described by Sosa[181] or by ablating within the great cardiac vein. Coronary angiograms are performed prior to epicardial ablation and ablation in the aortic sinus to avoid ablation close to the coronary arteries that can lead to arterial damage and thrombus formation. Intracardiac echocardiography has also been used to provide real time visualization of the relationship between the ablation site and the coronary arteries during ablation in the aortic sinus.[182]

IDIOPATHIC LEFT VENTRICULAR TACHYCARDIA (ILVT) OR FASCICULAR VT

This form of VT arises from the fascicles in the left ventricle. Based on the QRS morphology and the site of origin it can be classified as left posterior fascicular VT (LPF VT), left anterior fascicular VT (LAF VT) and left upper septal VT (Septal VT).[183]

This form of idiopathic VT was first described by Zipes et al.[184] in 1979 with the following characteristic triad: (i) induction with atrial pacing; (ii) the RBBB morphology with left axis deviation and (iii) occurrence in patients without structural heart disease. In 1981, Belhassen et al.[185] showed that this form of VT could be terminated by verapamil, the fourth identifying feature. In 1988, Ohe et al.[186] described another form of this VT with RBBB and right axis deviation that required ablation in the region of the left anterior fascicle. Shimoike[187] and Nogami[183] described a form of idiopathic VT with narrow QRS that required ablation in the upper LV septum.

The ILVT is typically seen in patients between the ages of 15–40 years with an earlier presentation in females.[142,188-193] Most of the affected patients are males (60–70%). The symptoms include palpitations, fatigue, dyspnea, dizziness and presyncope. Syncope and sudden death are very rare.[188] Most of the episodes occur at rest; however, this form of VT can be triggered by exercise and emotional stress.[193,194] Incessant tachycardia leading to tachycardia-induced cardiomyopathy has also been described.[191]

ECG RECOGNITION

The baseline 12-lead ECG is normal in most patients or it may show transient T wave inversions related to T wave memory shortly after a tachycardia episode terminates. The 12-lead ECG of left posterior fascicular VT (LPF VT) shows RBBB with left axis deviation suggesting an exit site from the inferoposterior ventricular septum (Fig. 23). Nogami et al.[195] reported 6 patients with left anterior fascicular VT (LAF VT) that showed a RBBB with right axis deviation with the earliest ventricular activation in the anterolateral wall of the LV in all patients. Three patients had a distal type of LAF VT with QS or rS morphology in leads I, V5 and V6 and the other 3 had proximal type of LAF VT with RS or Rs morphology in the same leads. Figure 24 shows PVCs that were successfully ablated at the distal LAF. The QRS duration in fascicular VT varies 140–150 msec and the duration from the beginning of the QRS onset to the nadir of the S-wave (RS interval) in the precordial leads is 60–80 msec unlike VT associated with structural heart disease that is usually associated with longer duration of QRS and RS intervals. This makes it difficult to differentiate fascicular VT from SVT with aberrancy using the criteria based on QRS morphology and RS interval.[196-198]

MANAGEMENT

The long-term prognosis of patients with fascicular VT without structural heart disease is very good. Patients with mild symptoms without medical therapy did not show progression of their arrhythmias in a study of 37 patients with verapamil sensitive VT during an average follow-up of 5.8 years,[190] however those with incessant tachycardia can develop a cardiomyopathy.[191] Acute termination of VT can be achieved with intravenous verapamil (adenosine and Valsalva maneuvers are ineffective). Patients with moderate symptoms can be treated with oral verapamil (120–480 mg/day).

CATHETER ABLATION

The RF catheter ablation is an appropriate management strategy for patients with severe symptoms or those intolerant or resistant to antiarrhythmic therapy. Nakagawa[194] and Wen[199] showed that successful ablation could be performed by targeting the earliest high-frequency Purkinje potential (and not the earliest ventricular activation) during VT and this could be recorded far from the exit site that shows the perfect pace map. Tsuchiya et al.[200] targeted a site recording both a late diastolic potential and a presystolic potential and showed tachycardia termination with catheter pressure at these sites. Nogami et al.[201] used an octapolar catheter to record double potentials during VT from the mid-septal LV and successfully terminated VT during catheter ablation at these sites. Ouyang et al.[202] used a 3D electroanatomical mapping system to record sites with retrograde Purkinje (retro PP) potential during sinus rhythm (sharp low amplitude potentials that followed a Purkinje potential and local ventricular electrogram) in patients with ILVT. They showed that the site recording the earliest retro PP during sinus rhythm correlated with early diastolic potential during VT. They suggest

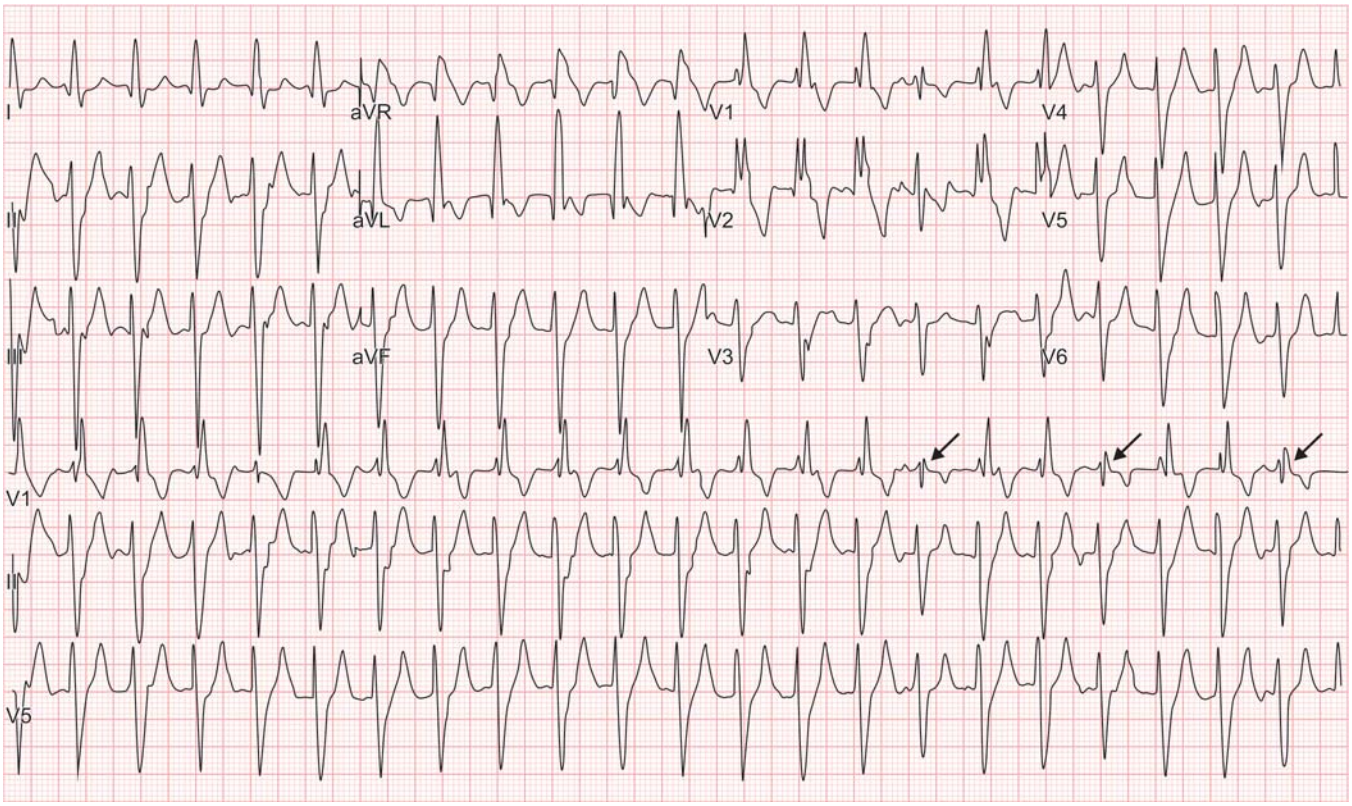


FIGURE 23: Twelve-lead ECG of VT arising from the left posterior fascicle (ILVT) with an RBBB superior axis morphology. The duration of the QRS complex and the RS interval are narrower than that of noted in VT associated with structural heart disease. However, the presence of AV dissociation and fusion beats (arrows) is diagnostic of VT. (*Source:* Modified from Badhwar et al. Idiopathic ventricular tachycardia: diagnosis and management. Curr Probl Cardiol. 2007;32:7-43)

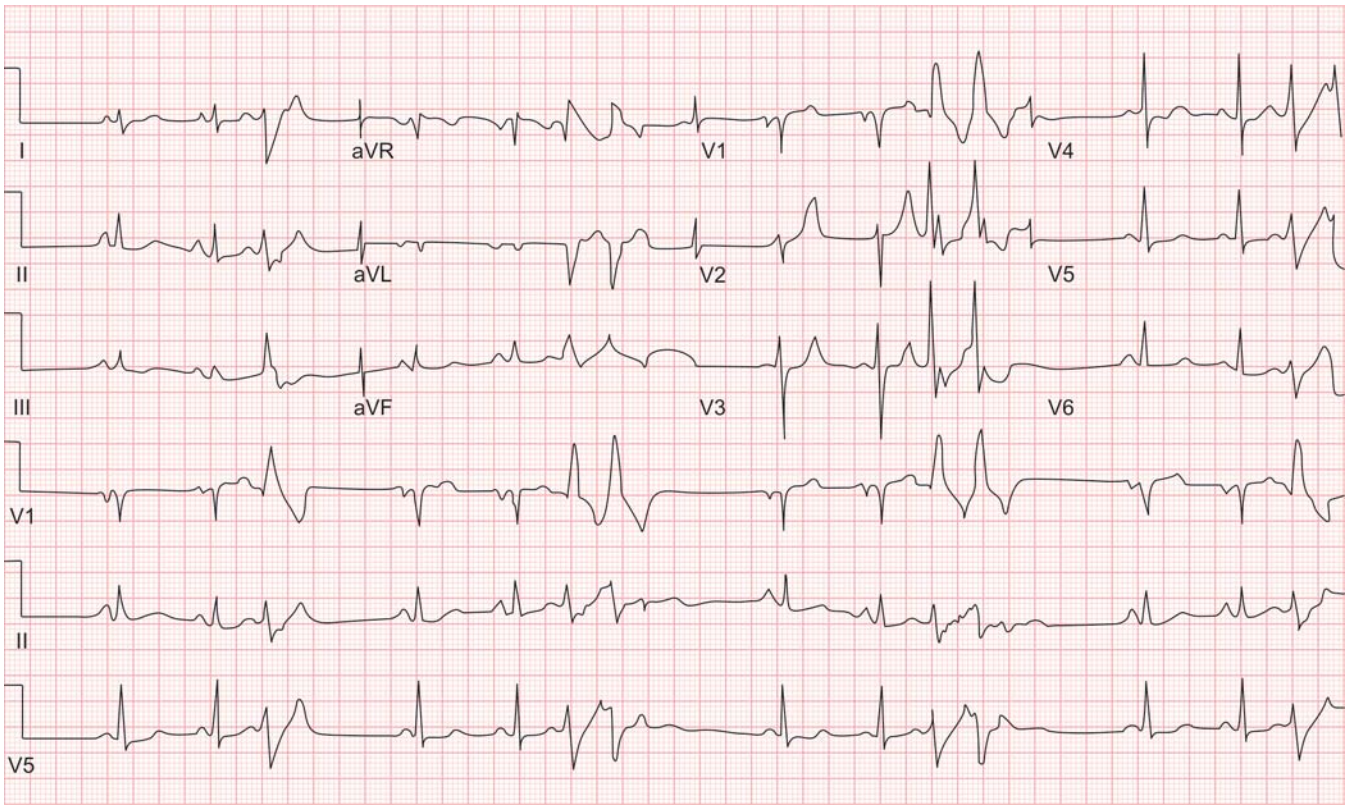


FIGURE 24: Twelve-lead ECG showing PVCs and couplets with RBBB inferior axis morphology suggestive of origin from the left anterior fascicle. The QRS complex in leads I, V5 and V6 show an rS morphology that is consistent with an exit site in the distal part of the left anterior fascicle where this VT was successfully ablated (*Source:* Modified from Badhwar et al. Idiopathic ventricular tachycardia: diagnosis and management. Curr Probl Cardiol. 2007;32:7-43)

that use of the earliest retro PP as a target for ablation when VT cannot be induced in the electrophysiology lab. Chen et al.[203] used a noncontact mapping system to create a successful linear ablation line perpendicular to the wavefront propagation direction of the left posterior fascicle in sinus rhythm in patients with nonsustained or noninducible VT. Ma et al.[204] have used development of a left posterior fascicular block (LPFB) pattern on the surface ECG as an end point for successful ablation in patients with noninducible ILVT. However, most authors have found that successful ablation occurs in majority of the patients without the need for LPFB pattern on the ECG. Long-term success after catheter ablation is more than 92% with rare complications that include mitral regurgitation due to catheter entrapment in the chordae of the mitral valve leaflet and aortic regurgitation due to damage to the aortic valve using a retrograde aortic approach.[146,193,194,199, 205-207]

MITRAL ANNULAR VT

There have been case reports of adenosine sensitive monomorphic VT that was successfully ablated at the anterobasal LV.[208-210] Tada et al.[211] were the first group to describe the prevalence and ECG characteristics of mitral annular VT (MAVT). Their definition was based on the ratio of atrial to ventricular electrograms less than 1 and the amplitude of the atrial and ventricular electrograms greater than 0.08 and 0.5 mV respectively at the successful ablation site.

Tada et al. reported that MAVT was noted in 5% of all the cases of idiopathic VT while Kumagai et al. showed that MAVT accounts for 49% of idiopathic repetitive monomorphic VT arising from the left ventricle (other sites included coronary cusps and inferoseptal region). Patients presented with palpitations and were noted to have repetitive monomorphic VT or frequent monomorphic PVCs. Tachycardia was noted spontaneously or initiated with isoproterenol. Termination was noted with adenosine (10–40 mg) and intravenous verapamil in some patients. The VT entrainment was not observed in any of the sustained episodes.

ECG RECOGNITION

Tada et al.[211] showed that the surface ECG in all patients with MAVT had an RBBB pattern (transition in V1 or V2); S-wave in V6 and monophasic R or Rs in leads V2–V6. They further classified MAVT into three categories depending on the site of origin as being anterolateral (AL) MAVT (58%), posterior (Pos) MAVT (11%) and posteroseptal (PS) MAVT (31%). In AL-MAVT, the polarity of the QRS complex in leads I and avL was negative and positive in the inferior leads; Pos-MAVT and PS-MAVT showed a negative polarity in the inferior leads and positive in leads I and avL. The AL-MAVT and Pos-MAVT showed a longer QRS duration and "notching" in the late phase of the R wave/Q wave in the inferior leads suggesting an origin from the free wall. This feature was not observed in PS-MAVT. Pos-MAVT showed a dominant R in V1 while PS-MAVT had a negative QRS component in V1 (qR, qr, rs, rS or QS). The Q-wave amplitude ratio of lead III to lead II was greater in PS-MAVT than in Pos-MAVT. Figure 25 shows the representative ECG from PVCs arising from the lateral MA. Kumagai et al.[212] illustrated the delta-wave like beginning on the QRS complex during VT and showed a similarity between the MAVT and the maximally pre-excited left-sided accessory pathways in terms of QRS morphology.

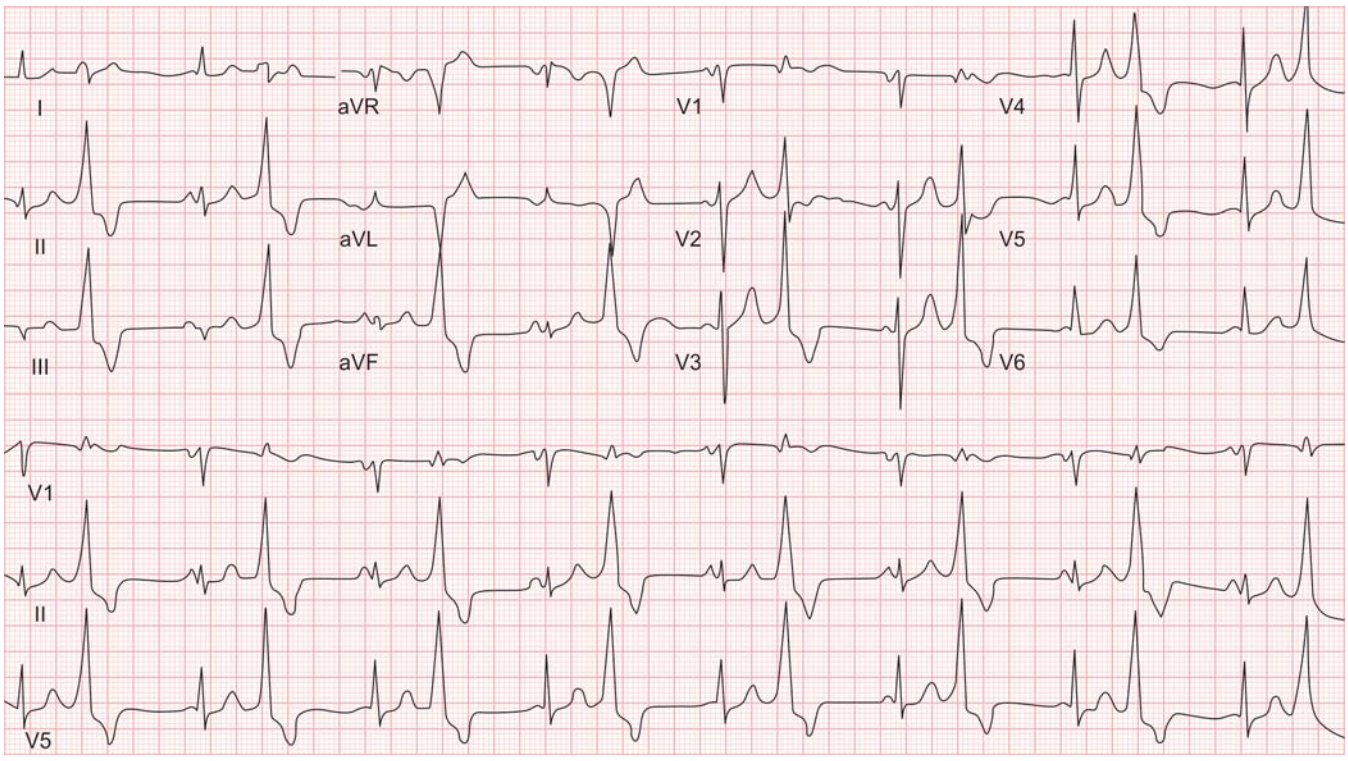


FIGURE 25: Twelve-lead ECG during sinus rhythm showing PVCs arising from the lateral mitral annulus. There is precordial concordance with negative QRS complexes in leads I, avL and inferior axis which is similar to the ECG morphology of a maximally pre-excited accessory pathway located on the lateral mitral annulus

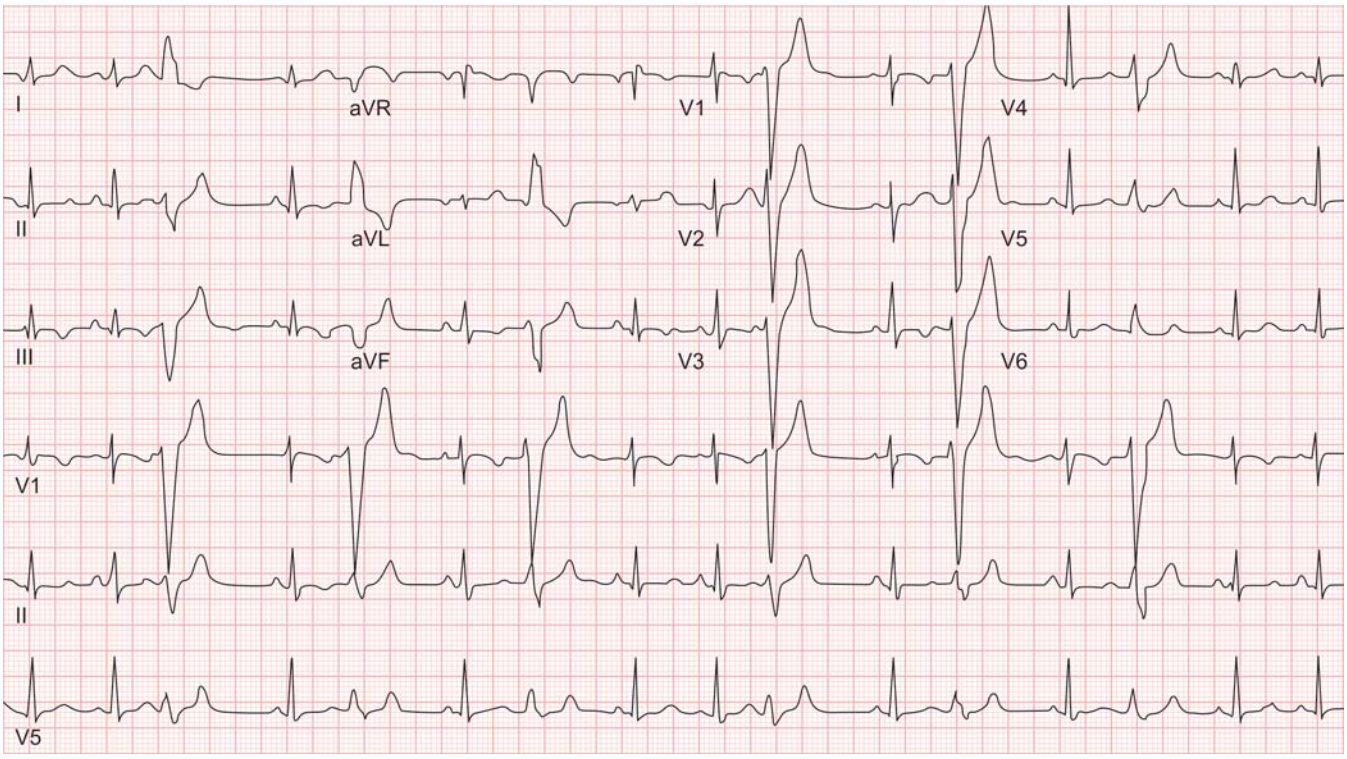


FIGURE 26: Twelve-lead ECG during sinus rhythm showing PVCs arising from the posterolateral tricuspid annulus. There is LBBB in V1 with late transition, left axis and notching in the inferior leads

CATHETER ABLATION

Electrophysiology mapping was performed using activation mapping and pace mapping to localize the site of origin of the VT. All successful sites had an adequate atrial and ventricular electrogram satisfying the criteria for mitral annular origin and a potential was noted before the local ventricular electrogram in most of the patients. Pace mapping was useful in patients with nonsustained tachycardia. Acute success was obtained in all the patients in both the series; however, there was a recurrence rate of 8% in one series.[212]

TRICUSPID ANNULAR VT

Recently VT arising from the TA has been described. This form of VT was noted in 8% of the patients presenting with idiopathic VT.[213] This was preferentially seen to originate from the septal region (74%) than the free wall (26%). Most of the septal VT was seen to arise from the anteroseptal region (72%). The septal VT had an early transition in precordial leads (V3), narrower QRS complexes, Qs in lead V1 with absence of "notching" in the inferior leads while the free-wall VT was associated with late precordial transition (> V3), wider QRS complexes, absence of Q wave in lead V1 and "notching" in the inferior leads (the timing of the second peak of the "notched" QRS complex in the inferior leads corresponded precisely with the left ventricular free-wall activation). Figure 26 shows ECG characteristics of PVCs originating from posterolateral TA. The success rate for catheter ablation of the free-wall VT was 90% as compared to 57% in the septal group due to the presence of junctional rhythm and the likelihood of impairing AV nodal conduction with catheter ablation.

SUMMARY

In summary, VT occurring in patients without structural heart disease accounts for approximately 10–20% of VTs evaluated at large referral centers. It is often difficult to differentiate this form of VT from SVT with aberration based on morphology alone. Depending on tachycardia mechanism the arrhythmia may respond to beta-blockers, Ca^{++} channel blockers or to vagal maneuvers. In addition, these arrhythmias are susceptible to cure by catheter ablation.

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Chapter 40

Cardiac Resynchronization Therapy

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Chapter Outline

- CRT: Rational for Use
- CRT in Practice
  - Miracle Study
  - Companion Study
  - Care-HF
- Summary of CRT Benefit
- Prediction of Response to CRT Therapy
  - Is there Adequate BIV Capture?
  - Optimization of CRT Device
- Role of Dyssynchrony Imaging
  - Septal to Posterior Wall Motion Delay
  - Tissue Doppler Imaging
  - Tissue Synchronization Imaging
  - Strain Rate Imaging
  - Speckled Tracking
  - The Prospect Trial
  - Other Dyssynchrony Imaging Techniques
  - Magnetic Resonance Imaging
  - Nuclear Imaging
  - Real-time Three-dimensional Echocardiography
  - Multidetector Computed Tomography
- Dyssynchrony Summary
- LV Lead Placement
- CRT Complications
  - Phrenic Nerve Simulation
  - Loss of CRT
  - CRT and Ventricular Arrhythmias
- Emerging CRT Indications
  - Narrow QRS
  - Atrial Fibrillation
  - Pacemaker Dependant Patients
  - Minimally Symptomatic Heart Failure
  - CRT for Acute Decompensated Heart Failure
- Guidelines

INTRODUCTION

Despite major advances in the treatment of systolic heart failure (HF), it continues to enact a large burden on healthcare systems around the world. The estimated direct and indirect cost of HF in the United States alone for 2010 was $39.2 billion. In the United States, 1 out of 5 individuals in the age group of 40 years and above will develop a clinical HF syndrome.[1] Advances in pharmacological therapy, most notably the use of beta-blockers, ace inhibitors, angiotensin receptor blockers and aldosterone antagonists have reduced mortality in this population.[2-7] Despite this, HF patients have a poor prognosis with a 20% annual and nearly 50% five-year mortality rate.[1]

The introduction of device-based therapies including internal cardiac defibrillators (ICD) and cardiac resynchronization therapy (CRT) also known as biventricular (BIV) pacing have transformed the landscape of HF management. Both of these modalities have been independently shown to improve survival among patients with systolic HF.[8-10] Based on estimates between 2001 and 2005, as many as 500,00 CRT devices have been implanted in the United States.[11]

Despite these advances, the prevalence of HF remains high and is estimated to affect 5.8 million individuals in the United States.[12] Paralleling, this has been a rise in HF related hospitalizations.[12] The complexity of acute HF management has increased considerably over the past decades. In addition to an ever-expanding armamentarium of HF medications, device-based therapies have become more sophisticated with each generation. Thus the need for clinicians who are well versed in all the aspects of HF management has never been greater. Proper management of these patients requires an interdisciplinary approach, including intensivists, cardiologists, HF specialists, nurses and electrophysiologists.

CRT: RATIONAL FOR USE

The contractile apparatus of the human heart is influenced by a myriad of factors including the highly coordinated electrical activation of the atria and ventricles. Disruption to this activation pattern [for example, in the case of left bundle branch block (LBBB)] can impede ventricular performance. In advanced HF, it is common to see abnormal electrical conduction which promotes asynchronous activation of the ventricles, reduced cardiac output and, in the long-term, adverse ventricular remodeling.[13] The term mechanical dyssynchrony has been used to describe the loss of synchronized contraction both between and within the right and left ventricles. This phenomenon is usually, but not always the result of disorganized electrical activation.

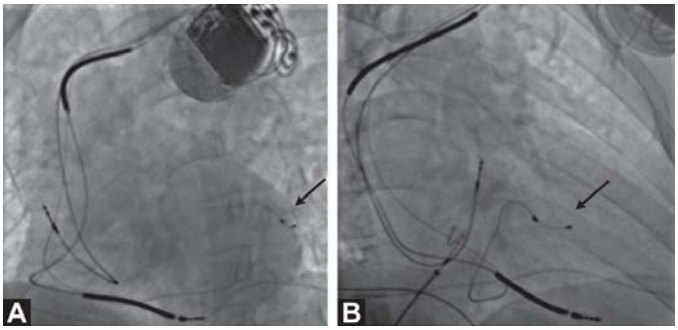
Patients with depressed systolic function are more susceptible to the adverse effects of conduction disturbances and mechanical dyssynchrony. Patients with first-degree heart block have suboptimal contribution of atrial systole, less filling time for the LV, and can have diastolic mitral regurgitation (MR)[14,15] Among HF patients, the most common conduction abnormality is LBBB. In LBBB, the electrical activation of the ventricles occurs first through the right bundle to the RV followed by trans-septal conduction that eventually results in activation of the lateral LV myocardium. The delayed contraction of the LV lateral wall occurs during the period of septal relaxation. This results in inefficient LV contraction since the septum and lateral walls fail to move in unison to eject blood. While this may be one of the most common forms of mechanical dyssynchrony, any variation in the timing of regional contraction can impede ventricular performance.

CRT IN PRACTICE

The CRT typically involves placing pacing leads in the right atrium, right ventricle and a branch of the coronary sinus (CS) (Figs 1 and 2). The CRT implantation is performed using a transvenous approach whereby the CS is cannulated and a pacing lead is advanced into a lateral CS branch. The CS lead is also known as the LV lead as it activates LV myocardium. Optimal lead placement is the subject of ongoing research and is dependant on many factors including scar location and the regional mechanics of an individual's ventricle. However, it is generally accepted that optimal placement involves maximal separation of the RV and LV leads ideally in a posterolateral branch of the CS.[16]

The CRT can be utilized to influence several key elements of ventricular performance. The AV interval can be adjusted to optimize ventricular preload. The timing of RV and LV pacing can be adjusted to improve interventricular (VV) dyssynchrony. Intraventricular dyssynchrony (LV) can be improved by coordinating the contraction between the LV septum and the lateral wall. Finally, earlier activation of the lateral wall can help to reduce MR, which is likely related to the improved timing of papillary muscle contraction and augmented dP/dt (Figs 3A and B).[17,18] All of these mechanisms contribute to the improvements in myocardial function associated with CRT.

To date, CRT has demonstrated a number of beneficial effects in patients with advanced systolic HF. Several studies have demonstrated its impact on physiologic endpoints such as improved hemodynamics, reduction in MR, increased ejection fraction, increased blood pressure and reverse remodeling.[10,17-23] In addition, randomized and observational studies have shown that CRT favorably impacts clinical endpoints including, exercise capacity, New York Heart Association (NYHA) functional class, hospitalization rate and quality of life (QOL).[18,21,24-26] More recently, at least one randomized controlled trial (RCT) and a meta-analysis of 14 RCTs have shown that CRT reduces mortality among patients with wide QRS and NYHA class III or IV HF.[26,27] Table 1 illustrates the results of randomized clinical trials of CRT in patients with advanced HF. The following section will detail the results of three landmark trials involving CRT.



FIGURES 1A AND B: (A) Left anterior oblique; (B) Right anterior oblique fluoroscopic views of a biventricular pacemaker-defibrillator with left ventricular lead positioned in a lateral branch of the coronary sinus (arrows)

MIRACLE STUDY

The multicenter insync randomized clinical evaluation (MIRACLE) trial was the first large scale, prospective, randomized, double-blind trial of CRT.[28] A total of 453 patients with NYHA class III or IV HF, EF less than or equal to 35%, and QRS duration greater than or equal to 130 millisecond were enrolled. Patients were randomized to have the CRT feature turned on or off. At 6 months, patients randomized to CRT on had significant improvement in QOL, 6-minute walking distance (39 meters vs 10 meters, $p = 0.005$), NYHA functional class ($p < 0.001$) and exercise treadmill time, EF (+ 4.6 vs – 0.2%, $p < 0.001$). Furthermore, patients in the CRT on group had significantly fewer hospitalizations (15 vs 7%, $p = 0.02$) and improved peak oxygen consumption (+ 0.2 vs + 1.1, $p = 0009$).

COMPANION STUDY

The comparison of medical therapy, pacing and defibrillation in heart failure (COMPANION) study was the first large scale, randomized CRT trial to suggest that in addition to symptomatic improvement, CRT may confer mortality benefit.[25] A total of 1,520 patients with NYHA class III and IV HF due to ischemic or nonischemic causes, and QRS duration greater than or equal to 120 milliseconds were randomized to optimal medical therapy, implantation of CRT device or implantation of a CRT device with defibrillator. The mean follow period was 12 months. As with the MIRACLE trial, COMPANION showed that CRT improved HF symptoms based on exercise tolerance testing and QOL surveys. In addition, there was a significant 20% reduction in the primary composite endpoint of all-cause mortality of hospitalization for any cause among those randomized to the CRT arm as compared to medical therapy. Although patients in the CRT-ICD arm experienced a significant reduction in all-cause mortality (HR 0.64, $p = 0.003$), the implantation of CRT device alone was associated with a marginally nonsignificant reduction with respect to this endpoint (HR 0.76, $p = 0.06$).

CARE-HF

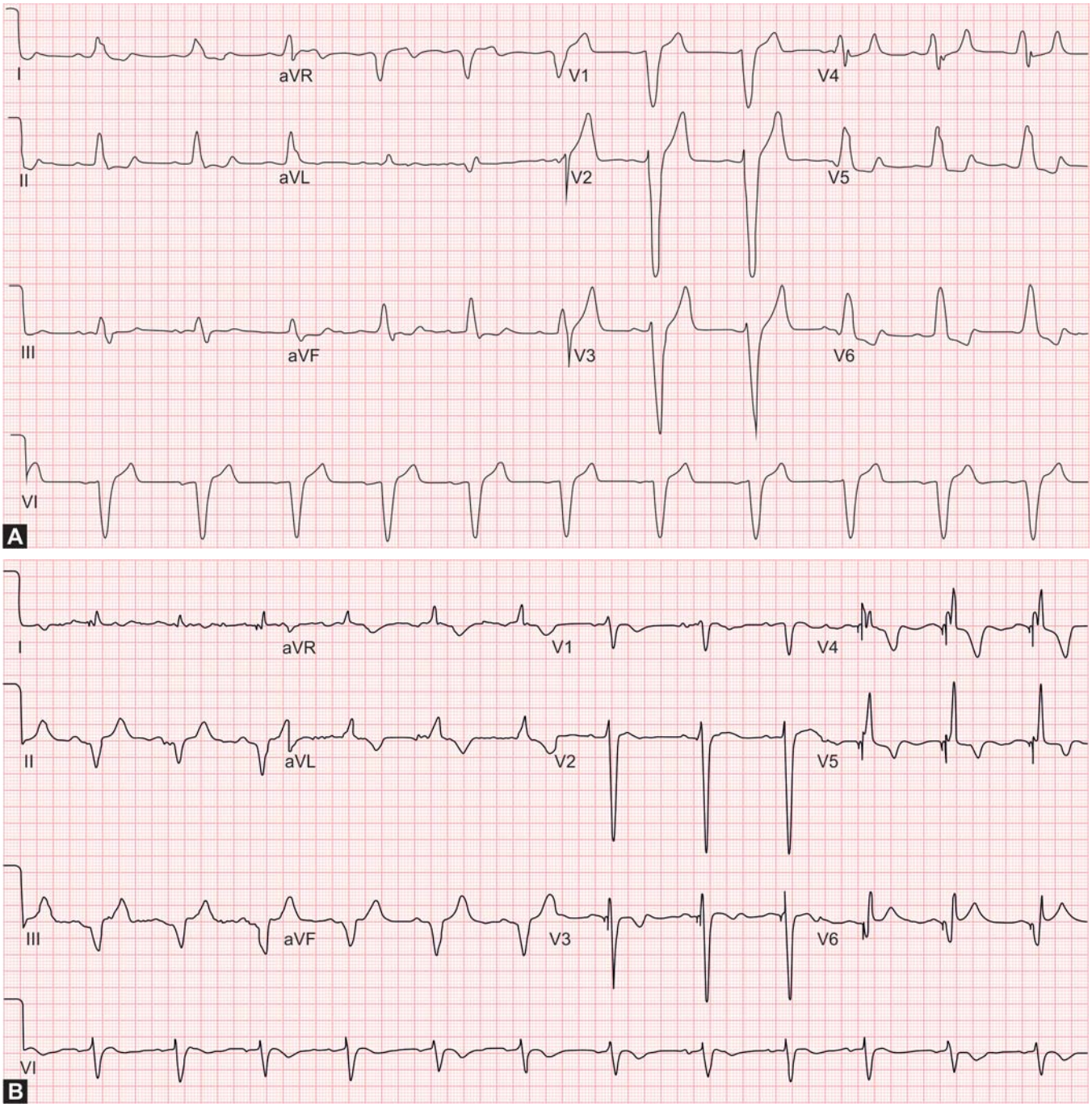
The cardiac resynchronization-heart failure (CARE-HF) trial randomly assigned 813 patients with NYHA class III or IV HF (ischemic and nonischemic) with EF less than 35% and QRS prolongation to optimal medical therapy or CRT.[26] Patients with

TABLE 1

Randomized clinical trials of cardiac resynchronization therapy

Study	*Design*	*No. of patients*	*Mean follow-up (months)*	*Results*	*P value*
MUSTIC (NEJM 2001)	Crossover CRT vs no CRT in patients with CHF NYHA III, EF < 35%, QRS > 150 ms, LVEDD > 60 mm, NSR	58	6	Improved 6 MWT QOLHospitalization Peak V_{O2}	< 0.001 < 0.001 < 0.05 < 0.03
MIRACLE (NEJM 2002)	Parallel arms CRT vs no CRT in patients with CHF NYHA III, EF < 35%, QRS > 130 ms, LVEDD > 55 mm, 6 MWT < 450 m, NSR	453	6	Improved 6 MWT NYHA class QOL LVEF Peak V_{O2}	= 0.005< 0.001 = 0.001< 0.001 = 0.009
PATH-CHF (JACC 2002)	Crossover CRT (LV or BiV) vs no CRT in patients with CHF NYHA III-IV, EF < 35%, QRS > 120 ms, PR > 150 ms, NSR	41	12	Improved 6 MWT Peak V_{O2} QOL NYHA class LV and BiV had similar improvement	= 0.03 = 0.002 = 0.062 < 0.001
MIRACLE ICD (JAMA 2003)	Parallel arms CRT + ICD vs CRT in patients with CHF NYHA III, EF < 35%, QRS > 130 ms, LVEDD > 55 mm, cardiac arrest due to VT/VF, spontaneous VT or inducible VT/VF, NSR	369	6	Improved NYHA class QOL No change 6 MWT	= 0.007 = 0.02 = 0.36
CONTAK CD (JACC 2003)	Crossover, parallel controlled CRT vs no CRT in patients undergoing ICD implantation with CHF NYHA II-IV, EF < 35%, QRS > 120 ms, NSR, indications for ICD implantation	490	6	Improved 6 MWT Peak V_{O2} LVEF LV volumes No significant change NYHA class QOL HF progression	= 0.043 = 0.030 < 0.001 = 0.02 = 0.10 = 0.40 = 0.35
PATH-CHF II (JACC 2003)	Crossover CRT (LV only) vs no CRT in patients with CHF NYHA II-IV, EF < 30%, QRS > 120 ms, NSR, Peak V_{O2} < 18 ml/min/kg	86	6	Improved 6 MWT QOL Peak V_{O2} No benefit in QRS 120–150 ms	= 0.021 = 0.015 < 0.001
COMPANION (NEJM 2004)	Parallel arms Optimal pharmacological therapy (OPT) vs CRT vs CRT + ICD (CRT-D) in patients with CHF NYHA III-IV, EF ≤ 35%, QRS > 120 ms	1520	16 Stopped early by DSMB	Death or hospitalization for CHF reduced by 34% in CRT, 40% in CRT-D As compared to OPT All cause mortality reduced by 36% in CRT-D 24% in CRT	< 0.002 < 0.001 = 0.003 = 0.05
CARE-HF (NEJM 2005)	Open label, randomized Medical therapy vs Medical therapy + CRT in patients with CHF NYHA III-IV, EF ≤ 35%, QRS > 120 ms with dyssynchrony (aortic pre-ejection > 140 ms, interventricular mechanical delay > 40 ms, delayed activation of postlateral LV) QRS > 150 ms (no dyssynchrony evidence needed)	814	29.4	All cause mortality/ hospitalization reduction by 37% in CRT All cause mortality reduced by 36% in CRT Improvement in QOL LVEF LVESV NYHA class	< 0.001 < 0.002 < 0.01

(Abbreviations: 6 MWT: 6-Minute walking test; AF: Atrial fibrillation; CARE-HF: Cardiac resynchronization-heart failure study group; CHF: Congestive heart failure; CONTAK-CD: CONTAK-Cardiac defibrillator; COMPANION: Comparison of medical therapy, resynchronization, and defibrillation therapies in heart failure study group; CRT: Cardiac resynchronization therapy; DSMB: Data safety monitoring board; EF: Ejection fraction; ICD: Implantable cardioverter-defibrillator; JACC: Journal of American College of Cardiology; JAMA: Journal of American Medical Association; LVEDD: LV end diastolic diameter; LVESV: LV end systolic volume; MIRACLE: Multicenter insync randomized clinical evaluation trial; MUSTIC: Multisite stimulation in cardiomyopathies study group; NEJM: New England Journal of Medicine; NSR: Normal sinus rhythm; NYHA: New York Heart Association; QOL: Quality of life; PACE: Pacing and clinical electrophysiology; PATH-CHF: Pacing therapies in heart failure study group; VT: Ventricular tachycardia; VF: Ventricular fibrillation)

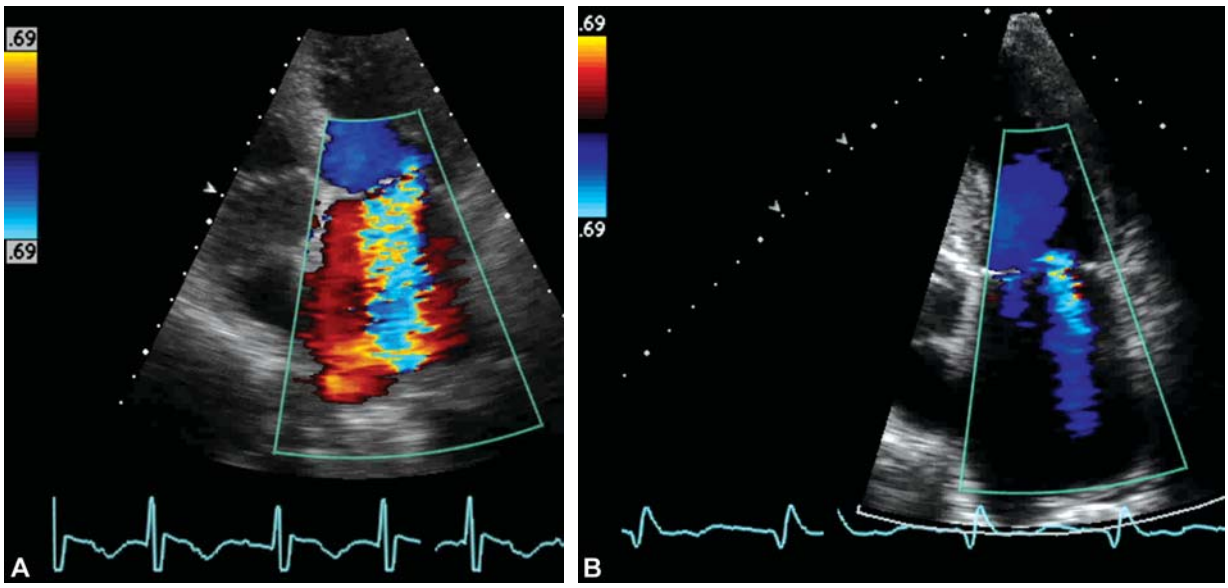


FIGURES 2A AND B: (A) ECG before; (B) ECG after implantation of cardiac resynchronization therapy (CRT) device. Note the considerable QRS narrowing and change in QRS morphology with small Q wave in lead I, positive QRS in aVR that is consistent with biventricular pacing

QRS duration of 120–149 milliseconds were required to have echocardiographic evidence of dyssynchrony for enrollment. There was a 37% reduction in the primary endpoint of death from any cause or unplanned hospitalization for a major cardiac event ($p < 0.001$). The major secondary endpoint in CARE-HF was all-cause mortality. The CRT was associated with a 36% reduction in this endpoint as compared to medical therapy alone ($p < 0.002$). As per previous studies, CRT was associated with improvements in a number of parameters including ejection fraction, reverse remodeling, systolic blood pressure, MR and QOL.

SUMMARY OF CRT BENEFIT

These and other trials have provided robust evidence that CRT has a favorable impact on many important physiologic and non-physiologic endpoints in HF. In addition, there is evidence that CRT alone (without back-up defibrillator) reduces mortality. There is some uncertainty about whether CRT coupled to ICD therapy confers additional mortality benefit (in COMPANION, the risk reductions associated with CRT and CRT + ICD were similar). However, due to the wide range of benefits associated with CRT, it is reasonable to combine CRT and ICD therapy in



FIGURES 3A AND B: Echocardiographic images (A) and (B) showing significant improvement in mitral regurgitation after cardiac resynchronization therapy (CRT)

patients who meet criteria for both. In accordance with this, the most recent ACC/AHA/HRS guidelines recommend CRT (with or without ICD) in patients who have left ventricular ejection fraction (LVEF) less than 35%, QRS duration more than 120 millisecond, and NHYA III or IV on optimal medical therapy.[29]

PREDICTION OF RESPONSE TO CRT THERAPY

One of the great challenges associated with CRT is how to determine which patients are likely to derive the most benefit. Response to CRT is dependant on the endpoint evaluated. When a clinical endpoint, such as NHYA classification, is used to determine response to CRT, there appears to be a consistent 20–30% nonresponder rate. However, when more objective measures, such as echocardiographic parameters, are employed, nonresponder rates may be closer to 40%.[30-32] It remains unknown whether this discrepancy is related to the placebo effect from device implantation or for some other reason.

The reasons for lack of response include suboptimal HF drug therapy, end stage HF, significant MR and other comorbidities such as obesity. Device-related reasons include ineffective biventricular pacing (BiV), suboptimal atrioventricular (AV) and VV timing, suboptimal LV lead position and absence of mechanical dyssynchrony in selected patients. An illustration of a step-by-step approach to CRT nonresponders is given in Flow chart 1.

IS THERE ADEQUATE BIV CAPTURE?

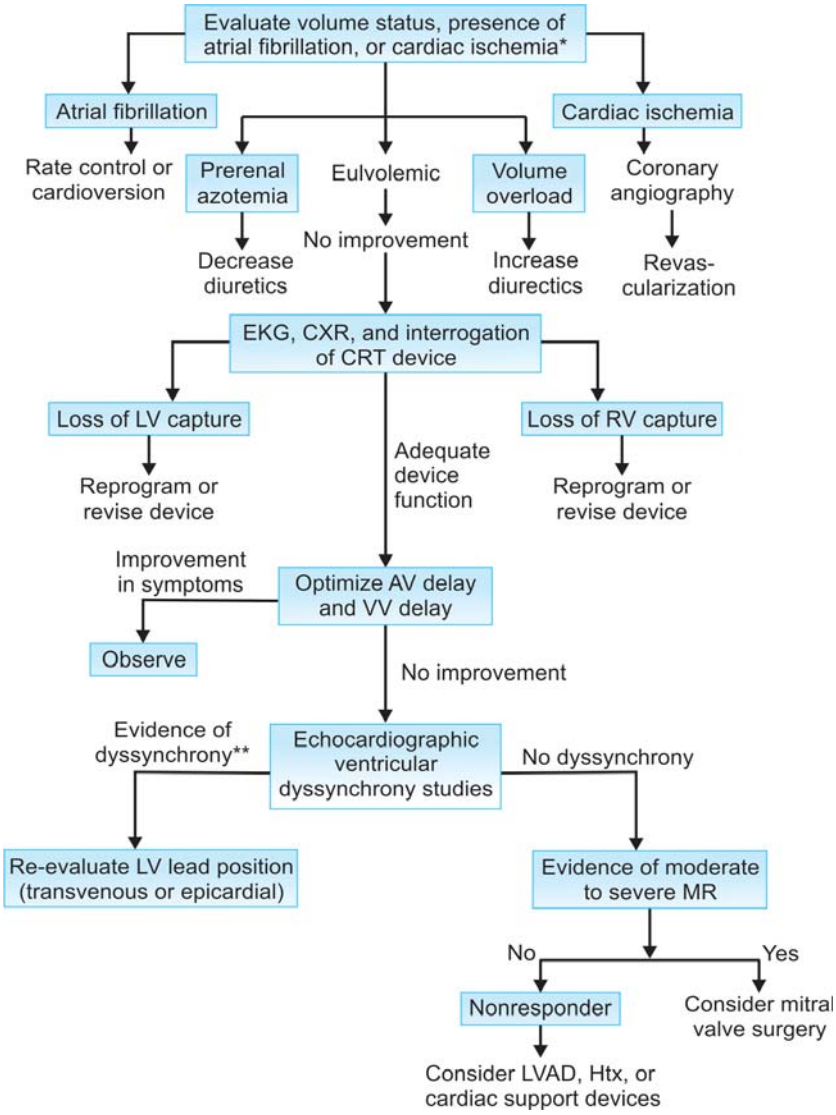
Optimal delivery of CRT requires continuous ventricular pacing. Although a formal device interrogation may be necessary to assess effective BIV pacing, a great deal can be learned from the surface 12-lead electrocardiogram (ECG). Prior to inspection of the ECG, it is helpful to examine a patient's chest radiograph to determine the position of the RV and LV leads. Several pacing patterns can be observed with: (1) BIV pacing; (2) Complete BIV capture; (3) Isolated RV capture; (4) Isolated LV capture; (5) Absence of BIV capture (native QRS) and (6) BIV capture with fusion.[33]

Traditional RV pacing (with the RV lead in an apical position) activates the myocardium in an inferior-superior and right-left fashion. The surface ECG therefore usually demonstrates a "superior axis" (negative in the inferior leads) and LBBB. Isolated LV pacing can produce a variety of patterns depending on the location of the LV lead. In general, the activation of the ventricle proceeds from left to right producing a "rightward axis" (negative or initial negative QRS complex in leads I and AVL) and a right bundle branch pattern (RBBB).

The pattern of BIV pacing represents the summed vector of RV and LV lead activation. The ECG pattern of BIV capture can vary widely depending on device programming and the placement of the RV and LV leads. In general BIV capture produces a rightward axis (negative or initial negative in leads I, AVL and positive in aVR) and R greater than S in lead V_1 (Figs 3A and B). The inferior leads (II, III and aVF) can be positive or negative depending on the location of the LV lead. The absence of this pattern should not however be interpreted to mean the loss of BIV capture. Often there is narrowing of the intrinsic QRS complex with BIV pacing. This has been shown to correlate with clinical benefit.[34,35] However, it has also been shown that wide QRS with BIV pacing also correlates with clinical benefit.[36] Hence, the duration of the BIV paced QRS complex cannot be used to assess presence or absence of BIV pacing although a narrower BIV paced QRS (when compared to intrinsic QRS) suggests a good prognosis.

Georger and his colleagues analyzed ECG patterns of patients with CRT and observed a Q wave in lead I in 17 out of 18 patients during BIV pacing.[37] A Q wave in lead I with RV pacing alone was found to extremely uncommon. In this series, the absence of a Q wave in lead I was 100% predictive of loss of LV capture. Although this was a small study, the assessment of lead I may be a simple way to assess the presence of LV capture during BIV pacing.

FLOW CHART 1: Stepwise algorithm for management of heart failure patients who are nonresponders to CRT



(Abbreviations: AV: Atrioventricular; CXR: Chest X-ray; EKG: Electrocardiogram; Htx: Heart transplant; LV: Left ventricular; LVAD: Left ventricular assist device; MR: Mitral regurgitation; RV: Right ventricular; VV: Interventricular).
*Cardiac ischemia is evaluated in patients with ischemic cardiomyopathy. **Evidence of dyssynchrony includes septal to posterior wall motion delay ≥ 130 ms, intraventricular mechanical delay ≥ 40 ms and tissue Doppler imaging ≥ 65 ms. (*Source:* Modified from Aranda, et al, Management of heart failure after cardiac resynchronization therapy: integrating advanced heart failure treatment with optimal device function. J Am Coll Cardiol. 2005;46:2193-8)

A simple algorithm to assess LV capture among patients with baseline LBBB and RV apical leads was developed by Ammann and his colleagues using leads V_1 and I.[38] An R-S ratio greater than or equal to 1 in lead V_1 reliably detected left ventricular capture. In the absence of this finding, lead I was analyzed. An R-S ratio of less than or equal to 1 suggested the presence of LV capture. The sensitivity of the algorithm to correctly identify loss of left ventricular capture was 94% (95% CI, 88.2–97.7%), and the specificity was 93% (CI, 86.3–95.8%).

Adequate BIV pacing can only occur if the programmed AV delay is shorter than a patient's native PR interval. When BIV output competes with native AV nodal conduction the result is called fusion. In such cases, both the BIV device and native conduction contribute to the ventricular depolarization. Pseudofusion refers to the phenomena of a pacemaker stimulus that appears to precede ventricular depolarization, but does not contribute to ventricular depolarization. In this case, the QRS complex should be identical to a nonpaced beat. To determine this, it is necessary to compare the ECG in question with a prior ECG that is known to represent nonpaced intrinsic conduction. We recommend performing 12-lead ECG on patients with CRT during their device visit and compare it to previous BIV paced ECG and intrinsic ECG to ensure effective delivery of BIV pacing (Figs 3A and B).

OPTIMIZATION OF CRT DEVICE

Manipulation of AV and VV delays to achieve an optimal hemodynamic response in patients with CRT devices is known as

"optimization". Commonly, noninvasive optimization protocols utilize echocardiography to achieve the desired hemodynamic changes. A number of optimization methods have been developed to establish the optimal AV and VV delays using a variety of different echo parameters. Although alterations in AV delay are more established with respect to their hemodynamic benefits, changes in VV delays are more contentious. At least two randomized trials have failed to show benefit associated with optimization of VV delays.[39,40]

Although echo optimization protocols vary widely, they are usually performed by systematically altering the AV and VV delays to achieve a desired hemodynamic response. The AV and VV delay with the best hemodynamic profile is considered to be "optimal". Some of the hemodynamic parameters used for echo optimization include, mitral inflow doppler patterns, time velocity integral of the left ventricular outflow tract (which is proportional to stroke volume), and dP/dt (which can be assessed noninvasively through analysis of continuous wave doppler of an MR jet).[41-43] In addition to echo-guided optimization, a number of other noninvasive optimization techniques have been reported including impedance cardiography, finger plethysmography and radionuclide ventriculography.[44-46] In addition, some CRT devices possess intracardiac electrogram-based (IEGM) algorithms that can determine optimal AV and VV delays.[47]

Although optimization studies have demonstrated improved ejection fraction, NYHA class, QOL, 6-minute walking distance and cardiac hemodynamics, in general, these studies have been small, nonrandomized and frequently lack control groups.[43,48-50] There is therefore no consensus regarding the optimal optimization method or universally accepted protocol for patients with CRT devices. Although some practitioners utilize optimization more frequently, in most institutions, only patients who gain suboptimal benefit from CRT undergo optimization as it can be costly, time-consuming and requires specialized skill and expertise.

ROLE OF DYSSYNCHRONY IMAGING

Cardiac dyssynchrony can occur with respect to atrio-ventricular (A-V) VV delay (RV-LV) or LV. In general, patients with LV dyssynchrony are more likely to response to CRT.[51,52] While QRS duration is a reasonable marker of VV (RV-LV) dyssynchrony; it does not predict LV dyssynchrony (as assessed by echocardiogram) with great accuracy.[53,54]

There have been a number of dyssynchrony criteria that have been shown to predict response to CRT. In general, these trials have been conducted at single centers, with relatively small numbers of patients using a variety of echocardiographic techniques. While a complete review of dyssynchrony parameters is beyond the scope of this paper, a brief review of some of these techniques is provided below.

SEPTAL TO POSTERIOR WALL MOTION DELAY

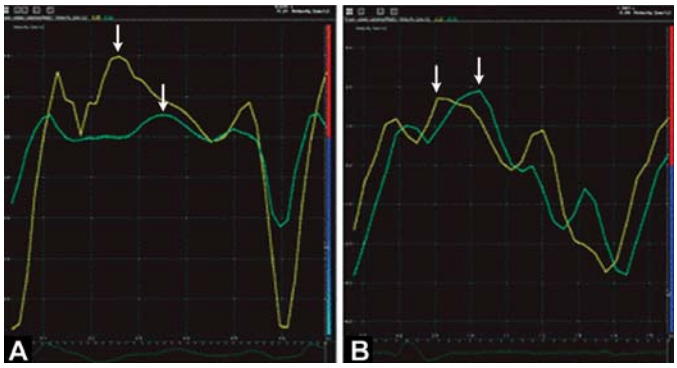
The LV dyssynchrony was initially assessed with conventional M-Mode echocardiography that measured the delay in contraction between the septum and the posterior wall. This measure is obtained by taking the shortest interval between the maximal posterior displacement of the septum and the maximal displacement of the left posterior wall using an M-Mode short-axis view of the left ventricle at the level of the papillary muscle. Several observational studies demonstrated that a SPWMD greater than 130 millisecond predicted a favorable response to CRT.[55-57] However, a recent study showed that this technique was not predictive of response to CRT in a larger study cohort.[58]

TISSUE DOPPLER IMAGING

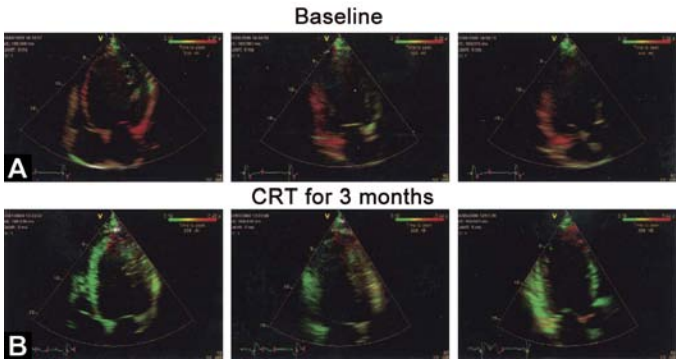
The tissue doppler imaging (TDI) is an echocardiographic technique that uses ultrasound to image the velocity of cardiac tissue. The TDI is used to assess LV dyssynchrony by comparing the time to peak velocity of various myocardial segments. Measurements are obtained for the time to peak systolic velocity (from the onset of QRS complex) in different segments of the LV and the delay between them is used as a marker of LV dyssynchrony (Figs 4A and B). There have been a number of dyssynchrony indices that have been derived using this technique. Initial studies used a four-segment model (septal, lateral, inferior and anterior) and showed that a delay greater than 65 millisecond predicted response to CRT.[59] Yu et al. used a 12-segment model (6 basal and 6 mid segment) and derived an LV dyssynchrony index from the standard deviation of all 12 intervals.[60,61] An LV dyssynchrony index greater than 31 millisecond yielded a sensitivity and specificity of 96 and 78% to predict LV reverse remodeling.[62]

TISSUE SYNCHRONIZATION IMAGING

The tissue synchronization imaging (TSI) builds upon the technique of TDI by transforming the timing of regional peak velocities into color codes (Figs 5A and B). This allows visual identification of regional delay in systole by comparing the color-coding of opposing walls, thus providing rapid identification of dyssynchrony by simple visual evaluation. As with TDI, quantitative assessment of regional delay is possible, and



FIGURES 4A AND B: Regional myocardial velocity curves obtained by tissue Doppler imaging (TDI) at the basal septal (yellow) and basal lateral (green) segments. (A) In a patient with left bundle branch block with QRS duration of 180 ms, there was delay in peak systolic contraction (arrows) of 95 ms in the lateral wall compared to the septal wall; (B) After biventricular pacing, there was improvement in synchronicity as reflected by the near overlapping of myocardial velocity curves with a difference of only 20 ms. (*Source:* Modified from Yu et al. Comparison of efficacy of reverse remodeling and clinical improvement for relatively narrow and wide QRS complexes after cardiac resynchronization therapy for heart failure. J Cardiovasc Electrophysiol. 2004;15:1058-65)



FIGURES 5A AND B: Tissue synchronization imaging (TSI) on three apical views showing the presence of extensive regional wall delay in a heart failure patient with prolonged QRS duration. The TSI method was set up to measure the time to peak myocardial systolic velocity (Ts) at ejection phase. The Ts values were then transformed into various color coding depending on the severity of delay, in the sequence of *green, yellow, orange and red*. (A) Before cardiac resynchronization therapy (CRT), this patient had severe delay over the basal to mid-lateral wall and the whole septal wall (*red* color in four-chamber view), severe delay over the whole inferior wall (*red* color in two-chamber view) and moderate to severe delay over the whole posterior wall (*orange* to *red* color in long-axis view); (B) Three months after CRT, corresponding views showed dramatic improvement of these delays, with only mild residual delay over the lateral and inferior wall (*green* to *yellow*). (*Source:* Yu C, et al. A novel tool to assess systolic asynchrony and identify responders of cardiac resynchronization therapy by tissue synchronization imaging. J Am Coll Cardiol. 2005;45:677-84)

a number of models have been constructed to define dyssynchrony using variable numbers of myocardial segments. Several studies have demonstrated that TSI (including visual and quantitative parameters) is useful in predicting a response to CRT.[62-64]

STRAIN RATE IMAGING (SRI)

One of the major limitations of TDI is that myocardial velocities may be overestimated or underestimated by translational motion or tethering of the myocardium respectively.[65] Strain imaging overcomes this problem by measuring the actual extent of myocardial deformation in selected regions of the heart. In this manner, it can distinguish between passive motion and active contraction. Myocardial deformation occurs in three dimensions, and strain can therefore be assessed along each axis. Radial strain (RS) represents the myocardial thickening in a short-axis plane; circumferential strain (CS) represents myocardial shortening in a circumferential plane, and longitudinal strain (LS) represents the myocardial shortening in the long-axis plane.[66] Regional differences in strain along any of these axes, can be a marker of LV dyssynchrony. As with other echocardiographic techniques to evaluate dyssynchrony, a number of SRI-derived indices have been shown to predict reverse remodeling and response to CRT.[67-69]

SPECKLED TRACKING

The speckled tracking (ST) is another echocardiographic technique that takes advantage of acoustic markers produced by reflection, scattering and interference of the echo ultrasound beam to assess regional myocardial motion. Unlike TSI, which relies on tissue Doppler to assess myocardial strain, ST is not limited by angle dependence of the ultrasound transducer. Several studies have validated the used of speckled tracking measured LV dyssynchrony to predict response to CRT.[70-72]

THE PROSPECT TRIAL

One of the major limitations of the studies, such as the ones mentioned above, was that they were for the most part, confined to single centers and contained relatively few numbers of patients. The PROSPECT trial was designed to address these limitations. The PROSPECT was a nonrandomized observational study that sought to identify which of the previously published markers of dyssynchrony could predict response to CRT in a multicenter setting in three major regions (United States, Europe, Hong Kong).[32] A total number of 12 echocardiographic markers of dyssynchrony were evaluated in nearly 500 patients with blinded analysis of dyssynchrony in three core laboratories. Dyssynchrony markers were based on both conventional and tissue Doppler based methods, speckled tracking was not evaluated.

The results of PROSPECT raised several concerns with respect to previously published single-center experiences. The feasibility of image acquisition was a major limitation, particularly for TDI measures. Specifically, the percentage of individual parameters deemed interpretable by the core laboratories was between 37% and 82% for TDI-based tests. Intraoperator and interoperator reproducibility was also a major issue ranging from 3.8 to 24.3% and 6.5 to 72.1% respectively. Most disappointing was that no single parameter appeared to predict response to CRT effectively. Sensitivity for predicting improvement in the clinical composite endpoint ranged from 6 to 74% and specificity ranged from 35 to 92%. For all measured parameters, the area under the ROC curve to predict a positive response was less than or equal to 0.62.

Despite the results of PROSPECT, many investigators and clinicians continue to believe in the utility of dyssynchrony imaging for CRT. In PROSPECT, some investigators have raised concerns about site selection, lack of quality control, lack of adequate training, poor patient selection and poor image acquisition as the factors that might account for the discrepancies between its results and other previously published studies.[73,74] The role of echo-derived dyssynchrony imaging for CRT thus remains uncertain, and future studies will likely be performed to help elucidate this issue.

OTHER DYSSYNCHRONY IMAGING TECHNIQUES

In addition to two-dimensional echocardiography, a myriad of other imaging techniques have been utilized to assess dyssynchrony and/or predict response to CRT.

MAGNETIC RESONANCE IMAGING

The magnetic resonance imaging (MRI) is able to offer an integrated assessment of myocardial viability, function, dyssynchrony, anatomy and scar burden making it an attractive modality for patients in whom CRT is being considered. Advantages of CMR include high spatial resolution and

reproducibility, accurate assessment of cardiac chamber size and the ability to assess myocardial deformation in three dimensions. However, it is limited by high-cost, long acquisition times and, for the time being, incompatibility with implanted devices.

Three major CMR techniques have been used to assess LV dyssynchrony. The CMR myocardial tagging is similar to speckled tracking analysis whereby a grid is superimposed onto the myocardial image and myocardial strain is assessed via analysis of grid deformation. The CMR phase-contrast tissue velocity mapping (TVM) allows direct myocardial wall motion measurement similar to TDI (i.e. comparing velocity timing obtained in different regions of the myocardium). Unlike TDI, MR TVM is not limited by the acoustical windows of the chest and can acquire three-directional velocity information of the entire myocardium.[75] Displacement-encoded MRI, or DENSE, is a CMR technique that is similar to TVM. However, instead of coding for velocity, DENSE codes for myocardial displacement which are then used to calculate myocardial strain and dyssynchrony. While these MRI techniques are promising, there is currently little data to support their used in predicting response to CRT.

In addition to the quantification of strain, MRI is particularly useful in the assessment of myocardial scar via a technique known as delayed gadolinium enhancement. A high scar burden has been shown to correlate negatively with response to CRT.[76,77] The location of scar is also an important factor in considering CRT. Bleeker and his colleagues demonstrated that patients with ischemic cardiomyopathy, dyssynchrony and posterolateral scar as assessed by MRI do not respond well to CRT.[78]

NUCLEAR IMAGING

Equilibrium radionuclide angiography (ERNA) and gated SPECT myocardial perfusion imaging (MPI) have also been used to assess VV and LV. The ERNA derived phase image analysis, a functional method based on the first Fourier harmonic fit of the gated blood pool versus radioactivity curve, generates the parameters of amplitude (A) and phase angle (Ø). Amplitude (A) measures the magnitude of regional contraction and phase angle (Ø) represents the timing of regional contraction (Fig. 6). In a healthy heart, all segments of the myocardium should contract during the same phase angle. The mean and standard deviation of LV Ø have been used to characterize LV dyssynchrony[79] and has been used to predict changes in ejection fraction after CRT.[80] More recently, the synchrony (S) [efficiency of contraction in a region of interest (ROI)] and entropy (E) (disorder of contraction in a ROI) parameters have been developed and applied to planar ERNA as a tool for evaluation of LV dyssynchrony.[81] In one study, these parameters were shown to detect mechanical dyssynchrony with low interobserver and intraobserver variability.[82]

The role of ERNA or MPI dyssynchrony imaging represents a promising advance of a well-established myocardial imaging technology. Whether or not it will be useful in predicting response to CRT will need to be assessed in future studies. The role of nuclear imaging for evaluation of scar burden is somewhat better established. As with CMR, MPI has also been used to assess LV scar burden. Similar to MRI studies, scar burden as assessed by SPECT has been shown to correlate negatively with response to CRT.[83-85]

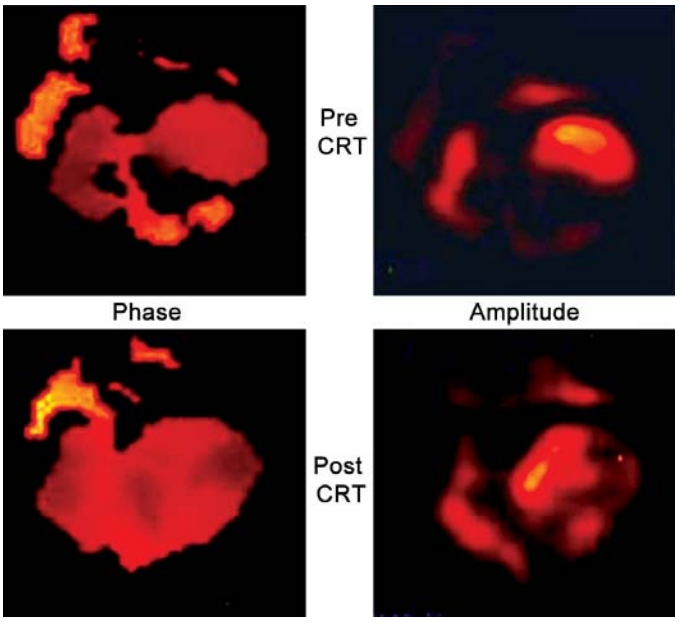


FIGURE 6: Equilibrium radionuclide angiogram (ERNA) images showing phase and amplitude analysis that are used to measure left ventricular dyssynchrony before and after cardiac resynchronization therapy (CRT). Phase analysis shows timing of regional contraction that shows apical dyssynchrony that corrects after CRT. Amplitude analysis reflects magnitude of regional contraction that shows improvement after CRT

REAL-TIME THREE-DIMENSIONAL ECHOCARDIOGRAPHY

The real-time three-dimensional echocardiography (RT3DE) has emerged as a new technique for assessment of LV dyssynchrony based on evaluation of LV regional volumetric changes.[86] This technique is accomplished by dividing the LV into 17 standard subvolumes and assessing the time for each segment to reach the minimum systolic volume (Tmsv). In a normally contracting heart the Tmsv should occur simultaneously for all myocardial segments. The standard deviation of 16 segments is used to create a dyssynchrony index (DI).[87] Preliminary data from a single center suggests that this technique may be used to predict response to CRT.[87] While RT3DE offers several advantages including accurate assessment of chamber size and volume, angle independence and semi-automated measurement, its application may be limited by translational artifacts and suboptimal image quality which may render the data unreadable.[88]

MULTIDETECTOR COMPUTED TOMOGRAPHY

Preliminary investigations have been performed utilizing computed tomography (CT) to assess LV dyssynchrony. Truong and his colleagues have derived several dyssynchrony indices with 64 slice CT using changes in wall thickness, wall motion and volume overtime.[89] The global LV dyssynchrony metric using changes in LV wall thickness overtime (average of the SD of 6 segments per slice, using all slices) had the best

reproducibility with high interobserver and intraobserver reproducibility. Compared to aged-matched controls, patients with systolic HF and wide QRS had a higher DI. This DI was also moderately well correlated with dyssynchrony as measured by 2D speckled tracking and RT3DE. As with MRI, CT assessment can provide additional information about the heart including its chamber size volumetric analysis, and contractile function. One of the unique features of CT is its ability to visualize CS anatomy, which could help operators to determine optimal lead location prior to implantation.

DYSSYNCHRONY SUMMARY

Despite extensive research and the multitude of imaging modalities established to assess myocardial dyssynchrony, its role in CRT remains uncertain. No single dyssynchrony parameter has been shown to conclusively predict response to CRT. While many of the above techniques appear promising, conclusive large-scale trials will need to be performed before dyssynchrony assessment can be incorporated into routine clinical practice. Accordingly, neither the ACC/AHA/HRS guidelines for device-based therapy of cardiac rhythm abnormalities nor the ACC/AHA guidelines for the diagnosis and management of HF recommend the use of dyssynchrony imaging to establish candidacy for CRT.[29,90]

LV LEAD PLACEMENT

The site of placement of the LV lead has also been shown to be an important determinant of the effects of CRT with demonstration of significantly better outcomes with lateral LV pacing as compared to anterior LV pacing.[16] Echocardiogram with TDI has been used to select sites of latest activation in the LV that will be ideal sites for placement of the LV lead.[91] Surgical LV lead placement should be considered when these areas of latest activation do not have a suitable CS branch vein that allows transvenous lead placement.[92-94] We have used multiple gated acquisition scan (MUGA) to identify areas of latest mechanical activation and shown significant improvement in clinical outcomes with imaging guided lead placement as compared to the traditional placement in the lateral LV.[95] Radiographic LV-RV interlead distance has also been shown to predict acute hemodynamic response to CRT as measured by a rise in dP/dt and this can be used to improve the success rate at the time of lead implantation.[96] Placement of the LV lead at areas of LV scarring is unlikely to show response to CRT and can lead to worsening of congestive heart failure (CHF) due to unopposed RV pacing[97] or worsening of ventricular tachycardia.[98] Imaging with PET or contrast enhanced cardiovascular magnetic resonance can identify areas of LV scar preoperatively.

CRT COMPLICATIONS

As with any implantable device there are a myriad of potential complications associated with CRT. In addition to standard device complications, such as infection and bleeding, there are several complications specific to CRT including: CS dissection and perforation, phrenic nerve stimulation and LV lead dislodgement. In major trials, LV lead dislodgement occurred in 4–6% of the patients.[10,18] The CS sinus dissection or perforation ranged from 0.3 to 4% and 0.8 to 2% respectively.[10,18,25] Management for CS dissection or perforation is usually conservative and, in most instances, CS cannulation can safely be performed several weeks later.

PHRENIC NERVE SIMULATION

The LV lead is frequently positioned in the region of the left phrenic nerve that may in turn lead to diaphragmatic stimulation. Although great care is taken to avoid phrenic nerve stimulation during implantation, subtle changes in lead position as well as postural changes can cause this complication at anytime postimplant. Phrenic nerve stimulation is often easy to recognize by observing the contractions of the abdomen during pacemaker output. Frequently, patients will complain of discomfort that occurs with certain positions or movements. It is sometimes helpful to ask a patient to recreate the setting in which they experience discomfort in order to make the diagnosis. A cardiologist or industry representative should be made immediately aware if the diagnosis of phrenic nerve stimulation is made. Although it is not life threatening, it can be the source of considerable discomfort for a patient. Frequently, a CRT device can be reprogrammed to eliminate phrenic nerve stimulation. At times, however, revision of the LV lead may be necessary.

LOSS OF CRT

As discussed above, it is essential to ensure maximum BiV pacing among patients with CRT devices. There are a number of settings in which maximum BiV pacing can be compromised (Table 2). It is important to recognize the loss of BiV capture in order to maximize the benefits of CRT.

CRT AND VENTRICULAR ARRHYTHMIAS

Several small studies have suggested that CRT may have a role in reducing the incidence of ventricular arrhythmias.[99-101] Although decreasing wall tension and favorable remodeling provide a biological basis for this hypothesis, CRT has not been formally tested in this manner. In many of the large randomized trials of CRT, the impact of CRT on the incidence of VT and

TABLE 2

Causes of loss of biventricular pacing

- Atrial undersensing can be caused by a variety of factors including sinus tachycardia with first-degree AV block, atrial fibrillation and lead dislodgement
- Fusion or pseudofusion (discussed above)
- Ventricular oversensing
- Atrial tachyarrhythmias with rapid ventricular conduction (frequently AF)
- Frequent ventricular ectopy
- Loss of LV capture due to LV pacing threshold increase
- Loss of LV capture due to LV lead dislodgement

VT storm was not systematically studied. However, meta-analysis of five major CRT trials revealed that sudden cardiac death was not significantly reduced by CRT when compared to optimal medical therapy.[102] In all but one of these trials, (CARE-HF) CRT, was not associated with a decreased risk of sudden death.

There is also concern that CRT has been associated with increases in ventricular arrhythmias. There are numerous reported cases of patients developing recurrent ventricular arrhythmias following implantation of a BiV device.[98,103-106] Various mechanisms have been proposed to explain CRT-associated ventricular arrhythmia including LV pacing in close proximity to scar, increases in the transmural dispersion of repolarization (which is proarrhythmic), and alteration of the wavefront of LV activation which is thought to facilitate re-entry.[106,107]

Nayak and his colleagues described a series of 8 out of 191 (4%) patients who developed VT storm (VTS) following BiV implantation.[106] Several observations, such as (1) VTS developed a mean of 16 ± 12.5 days after initiation of BVP, (2) VTS was refractory to intravenous antiarrhythmic medication and was managed by turning off LV pacing and/or radio-frequency catheter ablation and long-term oral antiarrhythmic therapy, (3) of the four patients who refused catheter ablation, three had cessation of VTS after turning off the LV lead; the fourth had the LV lead reprogrammed to a lower output resulting in considerable reduction in the burden of VT and (4) despite elimination of VT, the presence of VTS carried a poor prognosis in that all eight patients subsequently developed refractory CHF, were made in this single-center case-series.

Although reports such as these raise the possibility that CRT may facilitate VT in select patients, this concept has not been firmly established. Nonetheless, clinicians should consider this possibility in patients with BIV devices admitted for incessant VT refractory to antiarrhythmic therapy.

EMERGING CRT INDICATIONS

NARROW QRS

Although the benefits of CRT have been well established in patients with wide QRS duration, its role in patients with normal QRS is less clear. A number of small nonrandomized studies have been conducted which suggest that patients with narrow QRS and dyssynchrony benefit from CRT.[108-111] In addition, Jeevanantham and his colleagues performed a meta-analysis of nonrandomized narrow QRS CRT trials. Pooled data from three studies (totaling 98 patients) found that CRT was associated with improvements in NYHA, LVEF and 6-minute walking distance (6MWD).[112]

The role of CRT in narrow QRS patients was evaluated in a prospective randomized fashion in the RethinQ trial.[113] In this study, 172 patients with LVEF less than 35%, NHYA class III HF, QRS interval of less than 130 millisecond and evidence of mechanical dyssynchrony as measured by echocardiography were randomized to CRT + ICD or ICD-alone groups. No significant difference between these groups was found with respect to the primary endpoint of increase in peak oxygen consumption at 6 months. Additionally, no difference with respect of echocardiographic evidence of remodeling was observed between the two groups.

Despite these negative results, many clinicians and investigators continue to believe in the value of CRT in narrow QRS HF populations. Some of the criticisms of RethinQ, include, reliance on nonspecific dyssynchrony criteria (TDI-measured opposing wall delay greater than 65 millisecond, short follow-up time and a primary endpoint that was not studied in the major CRT trials. Further clinical trials are currently underway to determine whether alternative study designs may help to elucidate the discrepancies between RethinQ and previous observational studies among patients with HF and narrow QRS durations.[114]

ATRIAL FIBRILLATION

Multiple observational and at least one randomized trial have demonstrated benefit among patients who meet standard criteria for CRT and coexisting atrial fibrillation (AF).[115-118] In these trials, many of the enrolled patients had well-controlled ventricular rates, or else, had undergone prior AV nodal ablation. This underscores the challenges associated with the optimal delivery of BiV pacing in patients with AF. In AF, high ventricular rates may inhibit consistent BiV pacing. In addition, heart rate irregularity may result in fusion or pseudofusion thereby attenuating or eliminating the effects of BiV capture.

To overcome these challenges AV nodal ablation is increasingly utilized in patients with AF who meet criteria for CRT. Although this procedure renders a patient pacemaker-dependant and eliminates AV synchrony, it serves to regularize ventricular performance, and ensures 100% BiV pacing. The net result may be improvement in patient symptoms and beneficial remodeling in patients with HF. In one study, Gasparini and his colleagues prospectively evaluated 673 patients (162 in AF, 511 in sinus rhythm) with LVEF less than or equal to 35%, QRS greater than or equal to 120 millisecond, and NYHA greater than or equal to II.[119] Patients who were deemed to have inadequate BiV capture (arbitrarily determined to be < 85%) underwent AV nodal ablation. Both SR and AF groups showed significant and sustained improvements of all assessed parameters ($p < Û0.001$ for all parameters). However, within the AF group, only patients who underwent ablation showed a significant increase of ejection fraction ($p < 0.001$), reverse remodeling effect ($p < 0.001$) and improved exercise tolerance ($p < 0.001$); no improvements with respect to these parameters were observed in AF patients who did not undergo ablation. Although this strategy has not been evaluated in a randomized prospective fashion, a clinician should consider AV nodal ablation in AF patients with CRT devices, in whom consistent BIV capture cannot consistently be obtained or reliably assessed.

PACEMAKER DEPENDANT PATIENTS

It is well established that RV pacing is associated with hemodynamic derangement, the promotion of dyssynchrony and worsening of LV function, particularly among patients with decreased ejection fraction.[120-126] Early evidence that RV pacing may impact clinical endpoints came from analysis of the Mode

Selection Trial (MOST) a 6-year randomized trial of dual chamber rate adaptive pacemaker (DDDR) versus ventricular rate modulated pacing (VVIR) pacing in patients with sinus node dysfunction. Analysis of the trial suggested that the cumulative percent of ventricular paced beats (Cum%VP) was a strong predictor of HF hospitalization in both DDDR and VVIR modes.[125]

Corroborating evidence came from the dual chamber and VVI implantable defibrillator (DAVID) trial in which patients eligible for ICD were randomized to dual chamber universal, rate responsive (DDD/R) pacing at a lower rate of 70 or VVI, at a lower rate of 40 beats/min. The study was terminated prematurely due to an excess of HF and deaths in the DDD/R arm.[123] Subsequent analysis of the DAVID trial suggested that the lowest risk of HF worsening and death was seen in patients randomized to DDD/R with a low Cum%VP.[127]

The findings from these studies provided a therapeutic rational to investigate whether CRT may attenuate the negative impact of chronic long-term RV apical pacing. The Homburg Biventricular Pacing Evaluation (HOBIPACE) was a prospective randomized crossover study of patients with LV dysfunction and need for antibradycardiac pacing.[128] When compared with RV pacing, CRT was found to be superior to RV pacing as it induced reverse LV remodeling with significant reductions in LV end-diastolic and end-systolic volumes and an increase in ejection fraction. In addition, BiV pacing was found to impact favorably on the Minnesota living with HF score, NT-proBNP levels and peak oxygen consumption. The HOBIPACE was a small trial (30 patients) but served to reinforce the notion that RV pacing may particularly be detrimental to patients with pre-existing LV dysfunction.

The role of CRT among patients with normal EF and standard indications for pacing was tested in the pacing to avoid cardiac enlargement (PACE) trial.[129] A total of 177 patients with standard pacing indications in whom a BiV pacemaker was implanted were randomized to BiV pacing or RV apical pacing. The primary endpoints were LVEF and ESV at 12 months. In both groups, devices were programmed to ensure maximum pacing. During a follow-up period of 12 months, no effect on the primary endpoints was observed among those randomized to BiV pacing. However, there was a decline of 6.7 percentage points in LVEF and a 25% increase in left ventricular end-systolic volume in patients who were assigned to right ventricular pacing. The LVEF declined to less than 45% in 9% of the patients in the right-ventricular-pacing group.

While thought provoking, the results of PACE by no means suggest that all patients with pacing indications require a CRT device. First, roughly 40% of patients in each group had sinus node dysfunction. Since the study was designed to force RV pacing in the RV apical pacing group, native AV conduction would have been possible with alternative programming. In many patients, particularly those with sinus node dysfunction, RV pacing can be minimized by the use of extended AV delays, hysteresis and device algorithms that promote native AV conduction.

Second, there is a limited body of evidence that selective site right ventricular pacing (for example, from the RVOT) may be less detrimental than RV apical pacing.[130] It is possible that alternative RV pacing sites may sufficient to prevent adverse remodeling in properly selective patients. This could in theory obviate the need for CRT in patients with normal ejection fraction and AV nodal disease. However, larger clinical trials will need to be conducted to establish this as a viable pacing strategy.

Third, the clinical significance of the volumetric changes observed in the RV pacing group remains unknown. Although these changes are intuitively undesirable, they were not associated with concomitant reductions in 6-minute walking test, QOL or hospitalization for HF. It is possible that with longer follow-up duration, these parameters may have also been adversely affected.

Finally, only 9% of patients in the RV apical pacing group experienced significant reductions in LVEF (< 45%). This suggests that, at one year, the vast majority of patients with normal EF in whom antibradycardic pacing is indicated will not experience steep declines in their cardiac function with RV apical pacing. Accordingly, clinicians might consider initial implantation of an RV lead in these patients with the addition of an LV lead should a patient's EF decline with serial echocardiographic monitoring.

MINIMALLY SYMPTOMATIC HEART FAILURE

The beneficial effect of CRT on ventricular remodeling has prompted investigators to evaluate the role of CRT in patients with depressed ejection fraction and minimal symptoms (NYHA I-II). The resynchronization reverse remodeling in systolic left ventricular dysfunction (REVERSE) trial enrolled 610 patients with NYHA I or II HF, QRS greater than or equal to 120 millisecond and LVEF less than or equal to 40%.[131] All enrollees were implanted with CRT devices +/– ICD. Following implantation, patients were randomized in 2:1 fashion to CRT-on or CRT-off. At 12 months, there was no difference between these groups with respect to the trial's primary endpoint, a clinical composite that assessed worsening of HF through a number of measures including all-cause mortality, heart-failure hospitalizations, crossover due to worsening HF, NYHA class and the patient global assessment. The CRT was however shown to improve left ventricular end-systolic volumes (LVESV), left ventricular end-diastolic volumes (LVEDV) and LVEF.

A prospectively planned two-year follow-up of 262 European participants in REVERSE was also conducted. At two years, comparison of the CRT-on versus CRT-off groups demonstrated that a significantly higher percentage of patients in the latter group had a worsening of HF (34 vs 19% p = 0.01). Improvement in volumetric parameters persisted over this time period. In addition, there was a 12% absolute risk reduction in the time to first hospitalization or death, associated with CRT therapy (p = 0.003).

A similar hypothesis was tested in the MADIT-CRT trial.[132] In this study, 1,820 patients with ischemic or nonischemic cardiomyopathy, EF less than or equal to 30%, QRS greater than or equal to 130 millisecond and NYHA class I or II symptoms were randomly assigned to receive CRT + ICD or ICD alone. The primary end point was death from any cause or nonfatal heart-failure event (whichever came first). After a mean follow-up of 2.5 years, CRT therapy was associated with a significant 34% reduction in the risk of death or nonfatal HF

(p = 0.001). The difference between CRT and control groups was driven primarily by a reduced incidence of HF events among those randomized to CRT (23 vs 14% p < 0.001). As with many other CRT trials, CRT was associated with significant improvements in LVESV, LVEDV and EF.

The results of REVERSE and MADIT-CRT suggest that CRT may play a role in delaying HF progression in patients with minimal symptoms. Based on MADIT-CRT, FDA has recently been approved CRT therapy in patients with wide QRS, reduced ejection fraction and NYHA class I and II.

CRT FOR ACUTE DECOMPENSATED HEART FAILURE

Patients with systolic HF who are admitted to the ICU may be candidates for CTR. In these instances, patients who meet current guidelines for CRT implantation should be referred for further evaluation. In general, however, it is preferable to wait until a patient is stabilized, before CRT implantation is undertaken. Rarely, is CRT therapy required in an acute setting for patient stabilization. Although there is little evidence to guide the practice, many clinicians advocate acute implantation of CRT device for patients who meet criteria for implantation and cannot be weaned from inotropic therapies or else are responding poorly to aggressive HF management.[133,134] In this setting, there may be a role for acute CRT implantation as carefully selected patients may acutely respond with dramatic improvement in their clinical status. These cases should be evaluated on an individual basis in concert with consulting cardiologists, electrophysiologists or HF specialists.

SUMMARY

The advent of CRT has been an important development in the management of HF. The results of multiple large-scale clinical trials have consistently demonstrated its favorable impact on symptoms related to HF. In addition, there is mounting evidence that CRT is associated with mortality benefit. Current indications for CRT include patients with wide QRS and ejection fraction less than or equal to 35% with advanced HF despite optimal medical management. Around 30–40% of the patients who are candidates for CRT do not respond. This can be improved by optimizing the device, using imaging to select patients based on dyssynchrony and optimal LV lead placement. In the future, indications for BIV implantation may expand to include select patients with systolic HF and narrow QRS and patients with normal ejection fraction who require chronic RV pacing.

MODIFIED SUMMARY OF GUIDELINES (ACC/AHA/HRS GUIDELINES FOR DEVICE-BASED THERAPY, JACC. 2008;51:E1-62)

Modified by Kanu Chatterjee

Class I: Conditions for which there is evidence and/or general agreement that a given procedure/therapy is useful and effective.

Class II: Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of performing the procedure/therapy.

Class IIa: Weight of evidence/opinion is in favor of usefulness/efficacy.

Class IIb: Usefulness/efficacy is less well established by evidence/opinion.

Class III: Conditions for which there is evidence and/or general agreement that a procedure/therapy is not useful/effective and in some cases may be harmful.

Level A (highest): Derived from multiple randomized clinical trials.

Level B (intermediate): Data are on the basis of a limited number of randomized trials, nonrandomized studies or observational registries.

Level C (lowest): Primary basis for the recommendation was expert opinion.

RECOMMENDATIONS FOR PERMANENT PACING IN SINUS NODE DYSFUNCTION (SND)

Class I:

1. Permanent pacemaker implantation is indicated in symptomatic patients with symptomatic bradycardia including frequent symptomatic sinus pauses (Level of Evidence C).
2. Permanent pacemaker implantation is indicated for symptomatic chronotropic incompetence (Level of Evidence C).

Class IIa:

1. Permanent pacemaker implantation is reasonable for SND with heart rate less than 40/bpm, when a clear association between symptoms consistent with bradycardia and actual presence of bradycardia has not been documented (Level of Evidence C).
2. Permanent pacemaker implantation is reasonable in patients with unexplained syncope when SND is documented by electrophysiologic studies (Level of Evidence C).

Class IIb:
1. Permanent pacemaker therapy is reasonable in minimally symptomatic patients with chronic awake heart rate of less than 40/bpm (Level of Evidence C).

RECOMMENDATIONS FOR ACQUIRED ATRIOVENTRICULAR BLOCK IN ADULTS.

Class I:
1. Permanent pacemaker therapy is indicated in patients with third-degree and advanced second-degree AV block even in absence of symptoms (Level of Evidence C).
2. Permanent pacemaker therapy is indicated in patients with third-degree or advanced second-degree AV block in asymptomatic patients with documented period of asystole of 3 seconds or greater (Level of Evidence C).
3. Permanent pacemaker implantation is indicated in patients with third-degree or advanced second-degree AV block developing after AV nodal ablation (Level of Evidence C).
4. Permanent pacemaker therapy is indicated in postcardiac surgery AV block when AV block is unlikely to resolve (Level of Evidence C).
5. Permanent pacemaker treatment is indicated in patients with neuromuscular diseases (e.g. Duchane's and Baker's, limb girdle, peroneal muscular dystrophy) with third-degree or advanced second-degree AV block with or without symptoms (Level of Evidence B).
6. Permanent pacemaker therapy is indicated in symptomatic patients with any type of second degree AV block (Level of Evidence B).
7. Permanent pacemaker therapy is indicated in patients with systolic heart failure with third-degree or infranodal AV block in absence of symptoms related to heart block (Level of Evidence B).
8. Permanent pacemaker implantation is indicated in patients who develop second or third-degree AV block during exercise unrelated to myocardial ischemia (Level of Evidence C).

Class IIa:
1. Permanent pacemaker therapy is reasonable in asymptomatic patients with third-degree, or intra or infra Hisian AV block (Level of Evidence C).
2. Symptom limited exercise test at 3 to 6 weeks after discharge to assess prognosis, activity prescription or evaluation of medical therapy if early exercise test was submaximal.

RECOMMENDATIONS FOR PERMANENT PACING IN CHRONIC BIFASCICULAR BLOCK

Class I:
1. Permanent pacemaker therapy is indicated in patients with bifascicular block with advanced second-degree, intermittent third-degree or alternating bundle-branch block (Level of Evidence B).

Class IIa:
1. Permanent pacemaker implantation is reasonable in patients with bifascicular block with history of syncope when other causes have been excluded (Level of Evidence B).
2. Permanent pacemaker implantation is reasonable in patients with bifascicular block if HV interval is 100 ms or greater documented during electrophysiologic study (Level of Evidence B).

RECOMMENDATIONS FOR PERMANENT PACING AFTER THE ACUTE PHASE OF MYOCARDIAL INFARCTION

Class I:
1. Permanent pacemaker therapy is indicated in post-ST elevation myocardial infarction with intermittent or persistent third-degree, advanced second-degree infranodal AV block or alternating bundle-branch block (Level of Evidence B).
2. Permanent pacemaker therapy is indicated in symptomatic second-degree or third-degree AV block (Level of Evidence C).

RECOMMENDATIONS FOR PERMANENT PACING IN HYPERSENSITIVE CAROTID SINUS SYNDROME AND NEUROCARDIOGENIC SYNCOPE

Class I:
1. Permanent pacemaker implantation is indicated in patients with recurrent syncope due to hypersensitive carotid sinus syndrome with ventricular asystole of 3 seconds or longer (Level of Evidence C).

Class IIa:
1. Permanent pacing is reasonable in patient with hypersensitive carotid sinus syndrome with cardioinhibitory response of 3 seconds or longer without provocative events (Level of Evidence C).

Class IIb:
1. In patients with neurocardiogenic syncope permanent pacemaker therapy may be considered associated cardioinhibitory response occurring spontaneously or during tilt-table test (Level of Evidence B).

RECOMMENDATIONS FOR PACING AFTER CARDIAC TRANSPLANTATION

1. Permanent pacemaker implantation is indicated for inappropriate heart rate response and for Class I indications as in non transplant patients (Level of Evidence C).

Class IIb:
1. Permanent pacemaker therapy can be considered in postcardiac transplant patients with recurrent prolonged bradycardia or inappropriate heart rate response that limits rehabilitation (Level of Evidence C).

RECOMMENDATIONS FOR PACING TO PREVENT TACHYCARDIA

Class I:
1. Permanent pacemaker implantation is indicated for sustained pause-dependent ventricular tachycardia with or without QT prolongation (Level of Evidence C).

Class IIa:
1. Permanent pacemaker implantation is reasonable in high-risk patients with congenital Long QT syndrome (Level of Evidence B).

Class IIb:
1. Permanent pacing may be considered in patients with brady-tachy syndrome with recurrent atrial fibrillation (Level of Evidence B).
2. After discharge for activity counseling and/or exercise training as part of cardiac rehabilitation in patients who have undergone revascularization

Class IIb:
1. In patients with ECG abnormalities of LBBB, pre-excitation syndrome, left ventricular hypertrophy, digoxin therapy, greater than 1 mm resting ST depression. Electronically paced ventricular rhythm.
2. Periodic monitoring in patients who continue to participate in exercise training or cardiac rehabilitation.

Class III:
1. Severe comorbidity likely to limit life expectancy and/or candidacy for revascularization.
2. To evaluate patients with acute myocardial infarction with uncompensated heart failure, cardiac arrythmia or noncardiac conditions that limit the ability to exercise (Level of Evidence C).
3. Predischarge exercise test in patients who had already cardiac catheterization (Level of Evidence C).

ASYMPTOMATIC DIABETIC PATIENTS

Class IIa:
1. Evaluation of asymptomatic patients with diabetes who plan to do vigorous exercise (Level of Evidence C).

Class IIb:
1. Evaluation of patients with multiple risk factors as guide to risk-reduction therapy.
2. Evaluation of asymptomatic men older than 45 years or women older than 55 years who plan to do vigorous exercise or who are involved in an occupation in which exercise impairment may impact public safety or who are at high-risk for CAD.

Class III:
1. Routine screening of asymptomatic men or women.

PATIENTS WITH VALVULAR HEART DISEASE

Class I:
1. In patients with chronic aortic regurgitation for assessment of symptoms and functional capacity in whom it is difficult assess symptoms.

Class IIa:
1. In patients with chronic aortic regurgitation for evaluation of symptoms and functional capacity before participation in athletic activity.
2. In patients with chronic aortic regurgitation for assessment of prognosis before aortic valve replacement in asymptomatic or minimally symptomatic patients with left ventricular dysfunction.

Class IIb:
1. Evaluation of patients with valvular heart disease (see guide lines in valvular heart disease).

Class III:
1. For diagnosis of CAD in patients with moderate to severe valvular heart disease or with LBBB, electronically paced rhythm, pre-excitation syndrome or greater than 1 mm ST depression in the rest ECG.

PATIENTS WITH RHYTHM DISORDERS

Class I:
1. For identification of appropriate settings in patients with rate-adaptive pacemakers.
2. For evaluation of congenital complete heart block in patients considering increased physical activity or participation in competitive sports (Level of Evidence C).

Class IIa:
1. Evaluation of patients with known or suspected exercise-induced arrhythmias.
2. Evaluation medical, surgical or ablation therapy in patients with exercise-induced arrhythmias (including atrial fibrillation).

Class IIb:
1. Investigation of isolated ventricular ectopic beats in middle aged patients without other evidence of CAD.
2. For investigation of prolonged first-degree atrioventricular block or type I second degree Wenckebach, left bundle-branch block, right bundle-branch block or isolated ectopic beats in young persons considering participation in competitive sports (Level of Evidence C).

Class III:
1. Routine investigations of isolated ectopic beats in young patients.

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Chapter 41

Ambulatory Electrocardiographic Monitoring

Renee M Sullivan, Brian Olshansky, James B Martins, Alexander Mazur

"…orthodox electrocardiography will always have its uses in the measurement of established heart conditions, but it does not provide an accurate sampling of all-day heart activity any more than the analysis of a single rock provides an accurate sample of a mountain of ore."

Norman J. Holter[1]

Chapter Outline

- Holter Monitoring
- Event Recorders
- Mobile Cardiac Outpatient Telemetry
- Implantable Loop Recorders
- Key Considerations in Selecting a Monitoring Modality
- Guidelines

INTRODUCTION

Ambulatory electrocardiographic (AECG) monitoring, the recording of the electrocardiogram (ECG) over an extended period of time using a portable or implantable recording device, enables the clinician to study dynamic electrocardiographic changes during real-life activities. It is considered to be the cornerstone in the evaluation of patients with suspected cardiac arrhythmias.[2]

The AECG was championed by Norman J Holter in the late 1940s and was introduced into clinical practice in the early 1960s.[1] Early devices consisted of continuous single-lead ECG recordings on a magnetic tape with a storage capacity of only a few hours. The recorded data could be played back at an increased speed for manual review by an operator using a specific analyzer equipped with an oscilloscope. Technological advances in signal recording, processing and transmitting, as well as automatic data analysis, have significantly enhanced the diagnostic capabilities of the ambulatory monitors we use today.

With the advent of digital data acquisition and solid state memory technology, recording devices have been substantially downsized and are now capable of recording and storing high fidelity multichannel continuous electrocardiographic data over several days. Modern computer-based analysis systems use advanced diagnostic software algorithms that provide automatic quantification of a large amount of stored ECG data with calculation of multiple electrocardiographic parameters and generation of arrhythmia counters. In addition, areas of interest in the recordings that require operator review are automatically identified.

With the availability of event recorders that store only a few minutes of ECG when activated manually or automatically, based upon programmed parameters, and the capability of transmitting stored information over the phone, the period of monitoring has been extended to weeks and months. The implantable version of event recorders has further expanded the period of monitoring up to three years. More recently, the development of automatic arrhythmia detection algorithms, as well as wireless communication technology, has enabled continuous ambulatory monitoring with real-time data transfer and analysis. Currently available monitoring modalities include: continuous or Holter monitors, external event (postevent and loop) recorders, implantable loop recorders (ILRs), and mobile cardiac outpatient telemetry (MCOT) (Fig. 1 and Table 1).



FIGURE 1: Examples of current monitoring devices are pictured next to a quarter, shown as a reference for size. From left to right: an implantable loop recorder; a Holter monitor and an event monitor. This model of the event monitor may also be used as mobile cardiac outpatient telemetry when programmed as such

This chapter reviews the clinical utility and appropriate cost-effective selection of currently available monitoring modalities based on their advantages, limitations and diagnostic yields in specific populations of patients.

HOLTER MONITORING

Ambulatory Holter monitoring is accomplished with portable battery-operated devices that continuously record multiple

TABLE 1

Characteristics of monitoring modalities

	Recording type	*Monitoring period*	*Event activation*	*Transmission*	*Data analysis*
Holter monitor	Continuous, full disclosure	Typically 24–48 hours	Manual	Typically none	Delayed
Loop recorder	Intermittent pre-and post-event	Typically up to 30 days	Manual and automatic	Dial-in trans-telephonic	Delayed
Event recorder	Intermittent post-event		Manual	Dial-in trans-telephonic	Delayed
ILR	Intermittent	Up to 3 years	Manual and automatic	Dial-in trans-telephonic or wireless	Delayed
MCOT	Continuous, full disclosure	Individualized, up to 30 days	Manual and automatic	Automatic and dial-in wireless	Immediate

(Abbreviations: ILR: Implantable loop recorder; MCOT: Mobile cardiac outpatient telemetry)

electrocardiographic channels, typically over a 24–48 hours period. Some modern devices can store up to two weeks of continuous ECG data. Holter monitors generally record two to three ECG leads. Although devices that allow for the recording of up to 12 ECG leads are currently available, the clinical advantage of multichannel recordings is not well determined. Manually activated events are marked with timestamps which are linked to patient diaries in an attempt to correlate symptoms with an arrhythmia.

Automatic analysis of the full data set is performed using proprietary software, but a manual over read is generally completed to validate accuracy of the automatic arrhythmia diagnosis. The standard Holter monitor analysis summarizes heart rate trends, along with the presence and frequency of tachyarrhythmias and bradyarrhythmias, atrial and ventricular ectopy, as well as asystolic pauses. With the improved quality of acquired ECG signals in present day recorders, standard ECG measurements including PR and QT intervals, QRS width and variation in ST segments can be assessed accurately. The recorded ECG signals can also be used for more complex analyses including heart rate variability, signal averaged ECG, heart rate turbulence and T wave alternans.

Holter monitoring is generally utilized to detect a cause for symptoms and to diagnose rhythm disturbances that are expected to occur within a 24–48 hour monitoring period (Fig. 2 and Table 2). The major advantage of this modality is the continuous nature of the recording that provides "full disclosure" of the ECG during the monitoring period. This type of information is particularly useful for assessment of ventricular rate response in patients with atrial fibrillation or quantification of arrhythmia burden in patients with frequent ectopy.

Although an effective diagnostic modality in patients with daily symptoms, the diagnostic yield of a Holter monitor is likely to be low, as in the case of infrequent episodes of syncope or palpitations. Depending on patient selection and the length of monitoring, the likelihood of documenting cardiac rhythm during syncope is usually less than 20%; most of the captured events correlate with the absence of significant arrhythmia.[3-5] Patients with palpitations have a diagnosis secured by a Holter monitor more so than patients with syncope but only when the symptoms are frequent and occur during the recording.[6,7] The presence of an asymptomatic arrhythmia in patients with syncope or other symptoms should be interpreted with caution since it may have little clinical meaning. Rarely, an asymptomatic arrhythmia such as Mobitz II or complete atrial-



FIGURE 2: A 3-ECG channel Holter monitor recording obtained in a patient with recurrent palpitations and syncope. Note a 6-second sinus pause following termination of atrial fibrillation (arrow)

TABLE 2

Selection of monitoring modalities for common clinical indications

	Holter monitor	*Event monitor*		*Implantable loop recorder*	*Mobile cardiac outpatient telemetry*
		Looping	*Non-looping*		
Syncope					
≥ 1 episode/week	+				+
≥ 1 episode/month		+*			+
< 1 episode/month				+	
Palpitations					
≥ 1 episode/week	+		+		+
≥ 1 episode/month		+	+		+
< 1 episode/month			+	+	
Risk assessment (HCM, CAD, LQTS)	+	+*			
Atrial fibrillation					
Burden	+				+
Rate control	+	+*#			+
AAD monitoring		+*			+

* With auto-trigger capability
# With an automatic atrial fibrillation algorithm
Abbreviations: AAD: Antiarrhythmic drug; MCOT: Mobile cardiac outpatient telemetry; HCM: Hypertrophic cardiomyopathy; CAD: Coronary artery disease; LQTS: Long QT syndrome



FIGURE 3: Paroxysmal AV block recorded during an episode of dizziness in a young patient with recurrent exertional syncope. The patient has became asymptomatic following placement of a permanent pacemaker

ventricular block, prolonged sinus pauses, or significant QT interval prolongation, among others, may provide a diagnostic clue as to the cause of symptoms (Fig. 3). However, it is always critical to know whether an arrhythmia is temporally linked to a symptom or unnecessary therapy that may fail to provide benefit and cause harm. For instance, although sinus bradycardia may be documented during sleep, sinus bradycardia may not necessarily correlate with symptoms while the patient is awake.

In addition to its diagnostic indications, Holter monitoring may be useful as a screening tool in identifying patients at increased risk for sudden death. The presence of asymptomatic nonsustained ventricular tachycardia may aid in risk stratification in patients with hypertrophic cardiomyopathy or ischemic heart disease and impaired left systolic ventricular function.[8,9] Transient QT interval prolongation and macroscopic T wave alternans are recognized markers of risk for life-threatening ventricular arrhythmias in patients with long QT syndrome.[10] While possible to ascertain from high quality Holter monitor recordings, the clinical utility of heart rate variability, SAECG, heart rate turbulence, microscopic T wave alternans and other complex methods of analyzing continuous ECG recordings remains controversial.

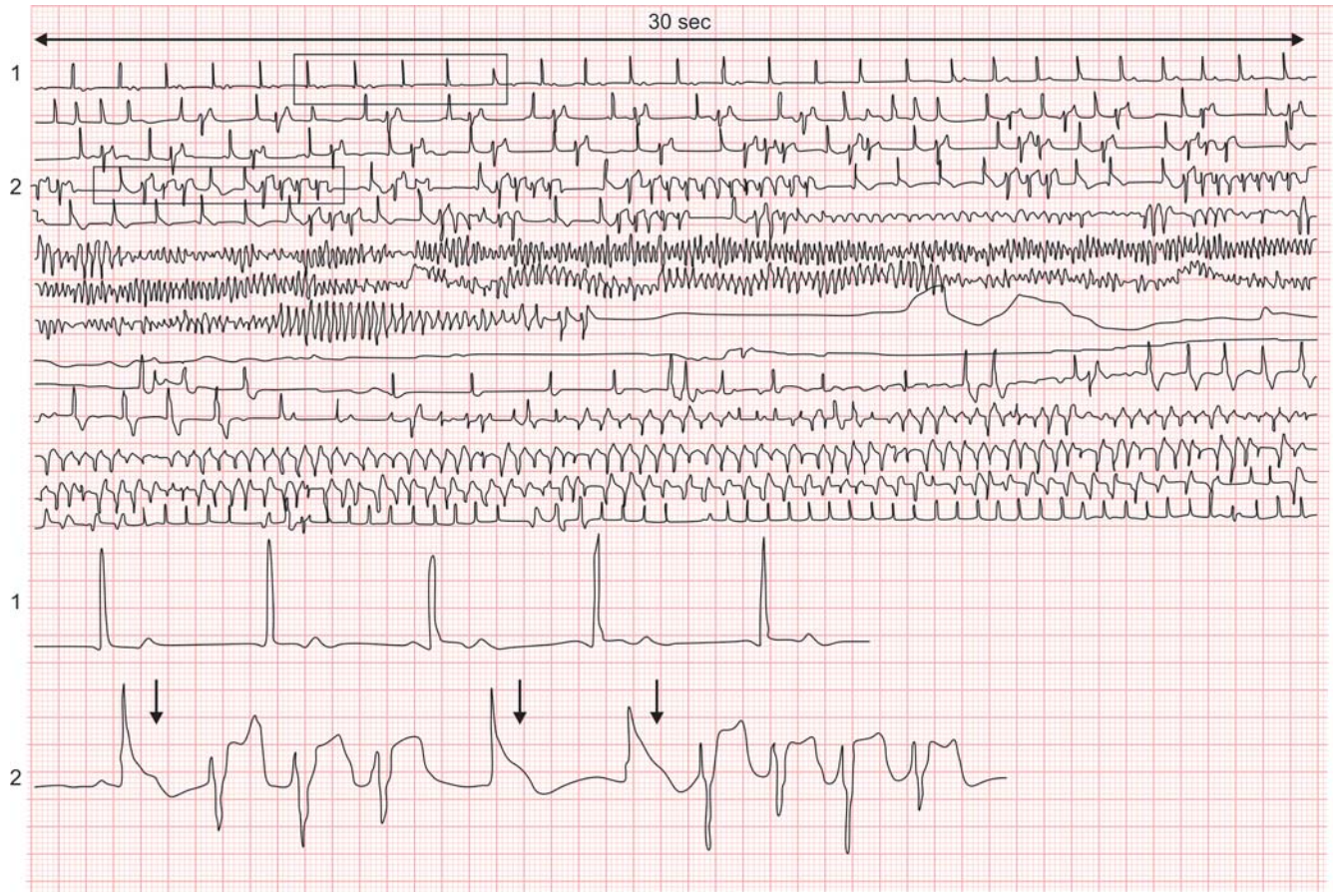


FIGURE 4: Continuous single channel Holter monitor ECG recorded during a prolonged syncopal spell in a 60-year-old patient with recurrent episodes of chest pressure and syncope. The bottom tracings (1 and 2) show selected portions of the ECG (boxes 1 and 2) in an expanded scale. Note transient ST-segment elevation (arrows, bottom tracing 2) followed by a 90-second episode of ventricular fibrillation and a 50-second asystolic pause. Coronary angiography showed mild (40%) narrowing of the right coronary artery

Holter monitoring has a limited role in assessing the efficacy and proarrhythmic response to antiarrhythmic medications due to the relatively short period of recording. Furthermore, conventional Holter recordings require off-line stored ECG processing and, therefore, do not provide immediate notification to the prescribing physician and patient about serious arrhythmic events. In this regard, the MCOT has recently emerged as a promising modality that permits extended periods of monitoring with automatic wireless transmission of arrhythmia events and real-time ECG analysis.[11] Short-term recording periods covered by conventional 24–48 hours Holter monitors are usually insufficient to quantify atrial fibrillation burden following initiation of antiarrhythmic therapy or a catheter ablation procedure.[12]

Detection of myocardial ischemia based upon variations in ST segments is another potential application of Holter monitoring. The ST segment changes on Holter recordings have been associated with adverse outcomes in patients with coronary artery disease in some series[13,14] but not in others.[15] Despite ongoing clinical interest in this area, the role of Holter monitoring in managing patients with coronary artery disease remains ill defined. This is at least in part due to the low specificity of ST segment changes on Holter recordings to predict ischemia as a number of technical and physiological factors may limit interpretation of the ST segment including body position, nonstandard lead position, medications and changes in autonomic tone. Rarely, Holter monitoring may be useful in the evaluation of patients with suspected variant angina (Fig. 4).

EVENT RECORDERS

Similar to Holter monitors, event recorders are used to correlate symptoms to arrhythmias but over longer periods of time, usually up to one month. Unlike continuous monitors, these devices have limited memory capacity and are capable of storing only short intervals of ECG recordings related to manually or automatically activated events and, therefore, do not provide "full disclosure" data. Data from event recorders are usually transmitted from a patient transtelephonically to a central location for interpretation and dispersal, by either internet transmission or facsimile, to the prescribing physician.

Event recorders are differentiated mainly by the presence or absence of the memory loop recording capability which allows for the storage of ECG recording immediately preceding a triggered event. A loop recorder continuously stores in internal loop memory several minutes of the most recent ECG by overwriting earlier data. Similarly to a Holter monitor, it is connected to the chest with leads and adhesive electrodes. When the patient develops symptoms and activates the device, pre-

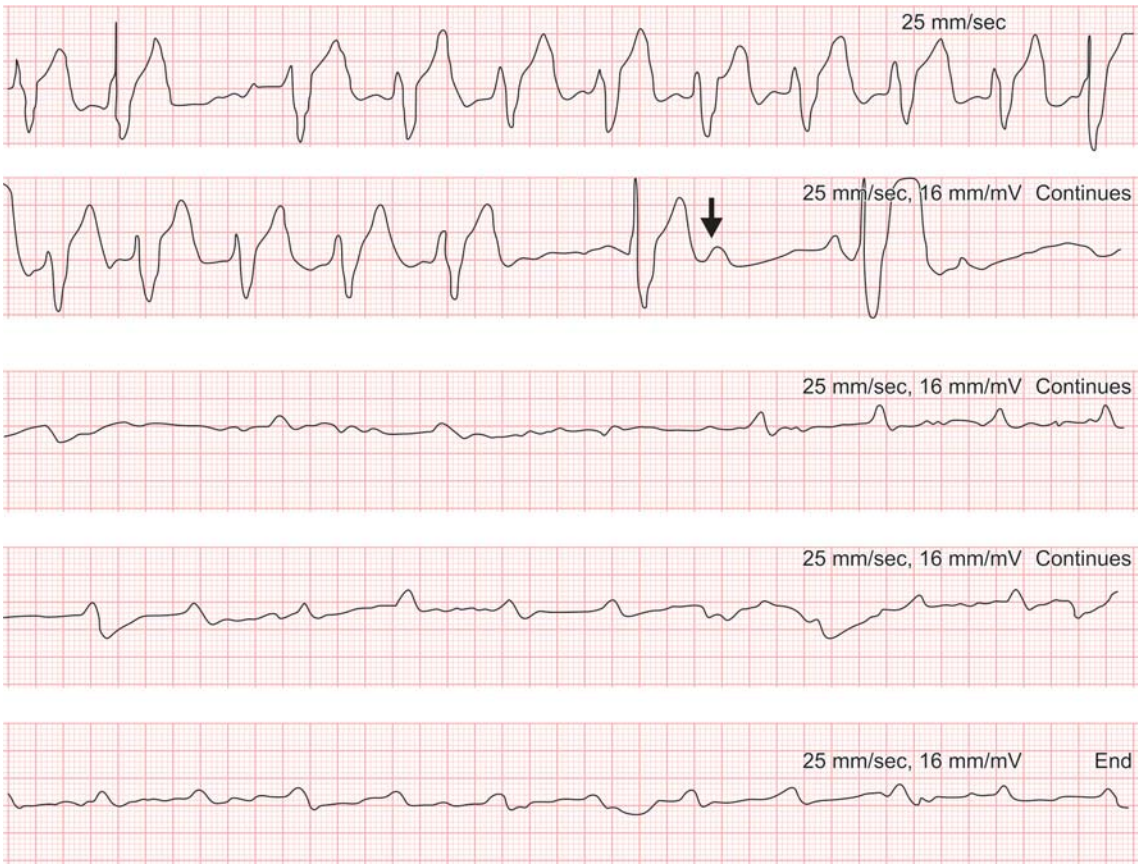


FIGURE 5: A continuous single channel recording automatically captured during an episode of syncope in a patient with recurrent palpitations and syncope. In this case, the patient was not able to activate the loop monitor manually. Note paroxysmal complete AV block with prolonged asystolic pause following termination of atrial fibrillation (arrow)

and postactivation ECG data are stored for several seconds to minutes depending on specific programmable recording time intervals. Some advanced loop monitors also have an auto-trigger capability based on specific algorithms that allow for automatic detection of slow, fast or irregular heart rates, as well as asystolic pauses. This feature is especially useful in the diagnosis of syncopal events when the patient is not able to manually activate the monitor or in the detection of asymptomatic arrhythmia (Fig. 5). It has been shown that the automatic arrhythmia detection capability improves the diagnostic yield of monitoring devices primarily by detecting asymptomatic arrhythmias.[16] A retrospective analysis of a large AECG database showed that clinically significant arrhythmias were detected in 36% of patients using auto-triggered loop recorders as compared to 17% and 6% using manually activated loop recorders and Holter monitors, respectively.[16] The relatively high diagnostic yield of auto-triggered recorders in this study was due to better documentation of asymptomatic atrial fibrillation or transient bradycardia.

"Non-looping" or postevent monitors do not have internal loop memory and record ECG only prospectively following manual activation by the patient. These small handheld or wrist worn monitors that have "built in" electrodes are applied directly to the skin for recording. Since no continuous application of adhesive electrodes is required, long-term compliance is usually better compared to loop recorders. Also, these monitors are ideal for use in patients with sensitivity or allergy to adhesives. However, given the technical aspects of the device, its clinical application is limited to situations when prompt activation of the device during symptoms is feasible. It is, therefore, not practical for patients with brief symptoms or syncope. Furthermore, lack of internal memory in these devices does not allow for the capturing of the ECG during the onset of arrhythmia, this information may be helpful in understanding the mechanism of some tachyarrhythmias. Finally, "non-looping" monitors do not provide information about asymptomatic arrhythmias. As mentioned earlier, in rare circumstances, detection of asymptomatic arrhythmias may help in guiding appropriate therapy in symptomatic patients. In addition, detection of asymptomatic recurrences plays an important role in assessing the efficacy of medical or interventional rhythm control strategies for atrial fibrillation.

Event recorders are useful in the diagnosis of symptoms (such as palpitations, syncope or pre-syncope) suspected to be directly caused by an arrhythmia that occur at least monthly (Table 2). Extended surveillance with event recorders provides higher diagnostic yield than conventional short-term Holter monitoring and allows symptom-ECG correlation in up to two-thirds of patients with frequent palpitations.[6,7] Similarly, loop recorders have been shown to be superior to Holter monitors in the evaluation of patients with frequent syncope (Fig. 5).[4] However, the relative diagnostic utility of these devices for evaluation of syncope as compared to palpitations is lower because of the unpredictable course of syncopal events.[17] The

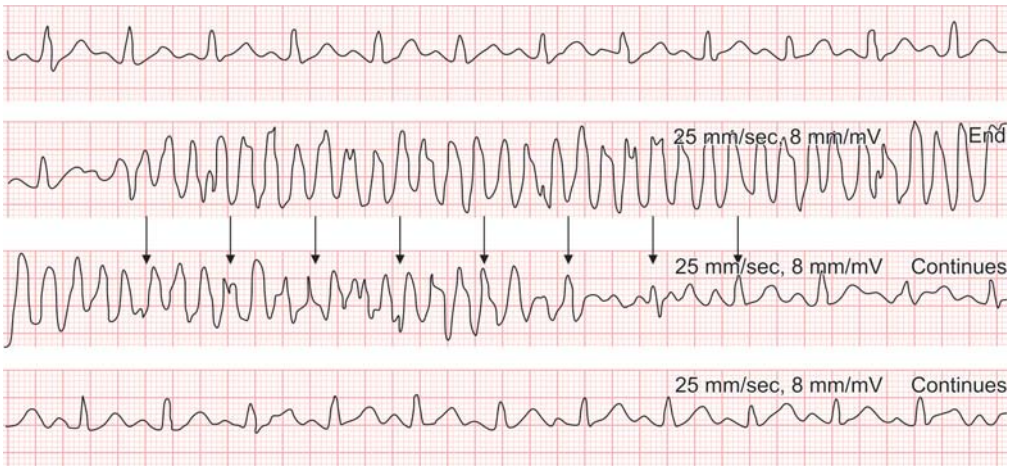


FIGURE 6: An automatically logged asymptomatic event consistent with recording artifact mimicking ventricular tachycardia. Note normal QRS complexes (arrows) "marching through" the artifacts

optimal duration of monitoring remains unclear. Although some studies suggest that 70–90% of arrhythmias are usually diagnosed within the first two weeks of surveillance,[7,18] the extent of the required monitoring period should be individualized depending on the type and frequency of symptoms.

Loop recorders with auto-trigger capability may be useful in the surveillance of patients undergoing medical therapy for arrhythmias or following catheter ablation procedures. In this regard, management of atrial fibrillation is one of the major applications for these devices, since they allow for the detection of asymptomatic recurrences. It is well recognized that atrial fibrillation recurrences are commonly asymptomatic, particularly following catheter ablation procedures.[19,20] Newer devices can detect atrial fibrillation automatically and display daily atrial fibrillation burden, although accuracy of this information needs further validation. However, this modality does not offer live monitoring with real-time data analysis and, therefore, may not be optimal for patients who are at high risk for serious proarrhythmia.

While event recorders have inherent advantages, they have limitations. Recorders without auto-trigger capability rely upon the patient to activate the device at the time of, or directly after, an episode. In one study, using patient activated loop recorders, one quarter of patients were unable to activate the device properly despite previous education and test transmissions.[4] Long-term compliance in wearing loop recorders is usually limited due to the need for application of adhesive electrodes.[5] As noted previously, patients with extremely rare symptoms may not be good candidates for external event recording. Correct interpretation of recording artifacts may be challenging when only a single lead ECG recording is available (Fig. 6).

MOBILE CARDIAC OUTPATIENT TELEMETRY

More recently, MCOT has been introduced into clinical practice. The devices used for MCOT are similar in size to conventional loop recorders and are capable of transmitting ECG data wirelessly, either directly or via a portable data manager (an external cellular telephone-sized device). Some providers use the same recorder which can be programmed either as a loop or MCOT monitor (Fig. 1). Potential advantages of MCOT over other modalities include continuous live ECG monitoring with automatic arrhythmia recognition and real-time ECG transmission to a central location that operates 24 hours a day and provides immediate notification of the ordering physician and patient about significant events based on prespecified notification criteria, in addition to daily summary reports. Since the ECG is transmitted continuously to a receiver system, there are practically no memory constraints and "full disclosure" data are available for analysis, including quantification of heart rate and arrhythmia burden.

Initial observational experience suggests that MCOT may offer an improved diagnostic yield in patients with symptoms concerning for arrhythmia and may also potentially be useful for outpatient initiation of antiarrhythmic medications, thereby obviating the need for hospitalization.[7,11] A randomized prospective evaluation of patients with symptoms suggestive of arrhythmia showed that symptom-ECG correlation could be obtained in 88% of patients randomized to MCOT, compared to 75% randomized to a patient activated loop recorder.[18] Higher diagnostic yield of MCOT in this study was due to detection of asymptomatic arrhythmia deemed to be clinically significant with atrial fibrillation and nonsustained ventricular tachycardia accounting for the majority of automatically captured events. However, outcome data show that asymptomatic arrhythmia could be used as a surrogate to guide appropriate therapy for symptomatic events are limited.[21]

Although there are potential advantages to this real-time approach to monitoring, more data are needed to define its role in the management of arrhythmia patients. The MCOT is a technologically and operationally demanding modality and, therefore, is substantially more expensive than conventional event recorders. The system requires not only well trained technical personnel but also a physician available 24 hours a day to manage large amounts of ECG data. It remains unclear whether or not this method can provide cost-effective benefit over older technologies, particularly auto-triggered loop recording.

IMPLANTABLE LOOP RECORDERS

Implantable loop recorders (ILRs) have extended diagnostic capabilities not afforded by external loop recorders and are generally indicated in patients with infrequent symptoms suspicious for cardiac arrhythmia. These small leadless devices are implanted subcutaneously, usually in the left pectoral area, and provide up to three years of continuous monitoring. They record a single bipolar ECG lead from a pair of electrodes embedded into the shell of the device. Despite relatively closely spaced electrodes, P waves and QRS complexes are generally visible. A subcutaneous wire antenna utilized in some new devices may improve quality of recording by providing more flexible electrode configurations and a larger inter-electrode distance.[22] Similar to external loop recorders, ILRs have limited memory capacity (42–48 minutes of compressed ECG signals) and store only short intervals (seconds to minutes) of both patient and automatically activated ECG recordings based on prespecified parameters. Stored data can be retrieved either manually during interrogation with a standard pacemaker programmer or remotely over the phone. Devices with wireless transmission capability (similar to MCOT) have recently become available,[22] although the clinical utility of live monitoring using ILRs has yet to be confirmed because of inherent problems with inappropriate sensing in these devices.

The longer periods of monitoring afforded by ILRs compared to external loop recorders allow for better correlation of events with arrhythmias in patients with rare but serious symptoms. The devices are usually well tolerated and there are no long-term compliance issues. Most data support their use in patients with recurrent unexplained syncope in whom a conventional invasive and noninvasive evaluation has been unrevealing. The reported diagnostic yield in symptom-ECG correlation is 30–88% depending on studied population of patients.[23-26] The diagnostic yield is directly proportional to the frequency of syncope while likelihood of the diagnosis of significant arrhythmia underlying syncopal events is higher in patients with structural heart disease and/or conduction abnormalities.[17] Some data suggest that selected patients with unexplained syncopal events clinically suspicious for arrhythmia may benefit from relatively early utilization of these devices before embarking on the conventional diagnostic, particularly invasive, techniques provided that cardiac conditions associated with high risk of life-threatening arrhythmia are carefully excluded.[27-29]

The ILRs play a relatively limited role in the evaluation of patients with palpitations as compared to syncope. Palpitations usually are a less severe symptom and are more likely to be diagnosed with external recorders or electrophysiologic testing.[17] In one study which randomized 50 patients with infrequent and sustained palpitations to either ILR or a conventional diagnostic approach including external monitoring and electrophysiology testing, the diagnostic yield of ILR was 73% compared to only 21% using the conventional strategy.[30] The ILR guided therapy yielded symptomatic benefit in the majority of patients.

Some observational data suggest that ILRs may be useful in guiding pacemaker therapy in patients with severe and frequent episodes of neurocardiogenic syncope caused by significant bradycardia.[29] However, prospective randomized studies are warranted before this approach can be adopted in routine clinical practice. The ILRs may potentially be helpful in establishing arrhythmic cause of recurrent nonaccidental falls,[31] as well as unexplained episodes of loss of consciousness.[32]

Other emerging areas of application for ILRs are risk stratification of patients with structural or primary arrhythmogenic cardiac conditions who are at high risk for sudden death (hypertrophic and right ventricular cardiomyopathies, myotonic dystrophy, long and short QT syndromes, Brugada syndrome, etc.) as well as long-term management of atrial fibrillation.[17] Automatic algorithms for the diagnosis of atrial fibrillation have been recently introduced, although accuracy of the derived information requires further validation.

With future advent of multiple physiological sensors (such as blood pressure, oxygen saturation, drug concentrations, etc.) implantable monitoring technology may become an invaluable tool in the management of a variety of cardiac and non-cardiac conditions.

Disadvantages of ILRs exist. The major issue remains inappropriate detection of arrhythmia episodes secondary to either undersensing, most commonly due to loss of electrode contact within the device pocket or oversensing due to "noise" (Fig. 7). This may compromise automatic arrhythmia detection either by undersensing of tachyarrhythmia episodes or by saturation of the device memory with inappropriately sensed ECG recordings and thereby precluding storage of true arrhythmia episodes. In a recent study that analyzed a large database of automatically stored ECGs by an ILR, inappropriately detected events were found in 71.9% of all recordings from 88.6% of patients.[33] An ILR is the most expensive of all available monitoring modalities, although some data suggest that it may be more cost effective compared to conventional diagnostic approaches in selected patients with rare, unexplained syncope.[34] The device requires surgical implantation with inherent risk of pocket complications.

KEY CONSIDERATIONS IN SELECTING A MONITORING MODALITY

- Major considerations in the selection of a monitoring modality are type and frequency of symptoms (Table 2). In patients with daily symptoms, a Holter monitor remains a preferred device. External event recorders are useful in patients with less frequent (but at least monthly) symptoms. An ILR is generally reserved for evaluation of rare symptoms, usually unexplained syncope, suggestive of an arrhythmic cause.
- In the case of syncope or brief palpitations, loop memory monitors that allow for capturing of ECG data preceding the activation are required. Recorders with auto-triggered capability or MCOT that do not rely solely on the patient's ability to activate the device during symptoms may help to better secure the diagnosis.
- For detection of asymptomatic arrhythmia recurrences or quantification of arrhythmia burden, as well as in patients who are not able to properly activate the device or transmit recorded ECG data, devices providing continuous, "full



FIGURE 7: An example of inappropriate automatic detection by an implantable loop recorder due to "noise" oversensing. Note normal QRS complexes (arrows) "marching through" nonphysiologic high frequency signals

disclosure", type of information (Holter monitor or MCOT) or event recorders with auto-triggered capability and special arrhythmia algorithms are the most appropriate choice.

- The MCOT offers continuous wireless live ECG monitoring with automatic arrhythmia recognition and immediate notification of the prescribing physician and patient regarding significant arrhythmia events.

(AAA/AHA GUIDELINES FOR AMBULATORY ELECTROCARDIOGRAPHY: EXECUTIVE SUMMARY AND RECOMMENDATIONS, CIRCULATION. 1999;100:886-93) MODIFIED SUMMARY OF GUIDELINES

Modified by Kanu Chatterjee

Class I: Conditions for which there is evidence and/or general agreement that a given procedure/therapy is useful and effective

Class II: Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of performing the procedure/therapy

Class IIa: Weight of evidence/opinion is in favor of usefulness/efficacy

Class IIb: Usefulness/efficacy is less well established by evidence/opinion

Class III: Conditions for which there is evidence and/ or general agreement that a procedure/therapy is not useful/effective and in some cases may be harmful

Level A (highest): Derived from multiple randomized clinical trials

Level B (intermediate): Data are on the basis of a limited number of randomized trials, nonrandomized studies or observational registries

Level C (lowest): Primary basis for the recommendation was expert opinion

INDICATIONS FOR AMBULATORY ELECTROCARDIOGRAPHY (AECG) TO ASSESS SYMPTOMS POSSIBLY RELATED TO RHYTHMIC DISTURBANCES

Class I:

1. Patients with unexplained syncope, presyncope or episodic dizziness
2. Patients with unexplained recurrent palpitation

Class IIb:
1. Patients with unexplained episodic shortness of breath, chest pain, or fatigue
2. Patients with neurological events when transient atrial fibrillation or flutter is suspected
3. Patients with persistent symptoms after non-arrhythmogenic cause of syncope, presyncope dizziness or palpitation have been detected and treated

Class III:
1. Patients with symptoms of syncope, presyncope episodic dizziness or palpitation in whom other causes have been established
2. Patients with cerebrovascular accidents without other evidence of arrhythmia

INDICATIONS FOR AECG ARRHYTHMIA DETECTION TO ASSESS RISK FOR FUTURE CARDIAC EVENTS IN PATIENTS WITHOUT SYMPTOMS FROM ARRHYTHMIA

Class I: None

Class IIb:
1. Post-MI patients with LV systolic dysfunction (ejection fraction of 40% or less)
2. Patients with congestive heart failure
3. Patients with idiopathic hypertrophic cardiomyopathy

Class III:
1. Patients who have sustained myocardial contusion
2. Systemic hypertensive patients with LV hypertrophy
3. Post-MI patients with normal LV function
4. Preoperative arrhythmia evaluation of patients for noncardiac surgery
5. Patients with sleep apnea
6. Patients with valvular heart disease

INDICATIONS FOR MEASUREMENT OF HEART RATE VARIABILITY (HRV) TO ASSESS RISK FOR FUTURE CARDIAC EVENTS IN PATIENTS WITHOUT SYMPTOMS FROM ARRHYTHMIA

Class I: None

Class IIb:
1. Post-MI patients with LV dysfunction
2. Patients with congestive heart failure
3. Patients with idiopathic hypertrophic cardiomyopathy

Class III:
1. Post-MI patients with normal LV function
2. Diabetic subjects to evaluate for diabetic neuropathy
3. Patients with rhythmic disturbances that preclude HRV analysis (i.e. atrial fibrillation)

INDICATIONS FOR AECG TO ASSESS ANTIARRHYTHMIC THERAPY

Class I: To assess antiarrhythmic drug response if required

Class IIa: To detect proarrhythmic response in patients at high risk

Class IIb:
1. To assess rate control during atrial fibrillation
2. To document recurrent or asymptomatic nonsustained arrhythmias in outpatients

INDICATIONS FOR AECG TO ASSESS PACEMAKER AND ICD FUNCTION

Class 1:
1. In patients with frequent palpitation, syncope, or presyncope to assess device malfunction
2. To assess the response to adjunctive pharmacotherapy

Class IIb:
1. Evaluation of device function immediately after implantation
2. Evaluation of the rate of supraventricular arrhythmias

Class III:
1. Assessment of device malfunction when it's diagnosis has been already established
2. For routine follow-up in asymptomatic patients

INDICATIONS FOR AECG FOR ISCHEMIA MONITORING

Class IIa: Patients with suspected variant angina

Class IIb:
1. Evaluation of patients with chest pain who cannot exercise
2. Preoperative evaluation for vascular surgery who cannot exercise
3. Patients with known CAD and atypical chest pain syndrome

Class III:
1. Initial evaluation of patients with chest pain who are able to exercise
2. Routine screening of asymptomatic subjects

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Chapter 42

Cardiac Arrest and Resuscitation

Christine Miyake, Richard E Kerber

Chapter Outline

- Overview or Background
  - Evolution of Cardiac Resuscitation
  - Cardiopulmonary Arrest
  - Emergency Medical Services
- Basic Life Support
  - Role of Bystanders
  - Emergency Medical Services Activation
  - Dispatcher Assisted Cardiopulmonary Resuscitation
  - Compression only Cardiopulmonary Resuscitation
  - Chest Compressions or Airway Management
  - Mechanical Devices for Cardiopulmonary Resuscitation
  - Use of Automatic External Defibrillators
  - Pacemaker or Automatic Implantable Cardioverter Defibrillator Patient in Cardiac Arrest
  - Complications of Cardiopulmonary Resuscitation
- Advanced Cardiac Life Support
  - Overview-Statistics of Success
  - Advanced Airway Management
  - Pharmaceutical Interventions
  - Defibrillation or Cardioversion
- Cessation of Resuscitation
- Post-resuscitation Care
  - Cardiopulmonary Support
  - Cardiac Interventions
  - Therapeutic Hypothermia

OVERVIEW OR BACKGROUND

Cardiopulmonary resuscitation (CPR) guidelines are continuously changing as new evidence and techniques are developed and researched. Despite these advances overall survival from sudden cardiac arrest remains low.[1] The return of spontaneous circulation (ROSC) is directly related to adequate coronary perfusion, while good clinical outcomes are more closely related to adequate vital organ perfusion during and immediately after resuscitation. This chapter covers the most recent understanding of blood flow, current emergency medical services (EMS) out of hospital resuscitation efforts, standard techniques of CPR, basic life support (BLS) and advanced life support (ALS) as well as post-resuscitative care. This chapter does not cover the details of pediatric resuscitation.

EVOLUTION OF CARDIAC RESUSCITATION

Cardiopulmonary resuscitation is a relatively new concept. The idea of artificial blood flow with artificial respirations as a means to restore life, after what appears to be death, was not a concept that came easily. It took many years of trial and error and research to develop the idea that blood can flow without opening the chest and directly massaging the heart. In the 1700s mouth-to-mouth resuscitation was recommended for drowning victims; however, there was no formal training for physicians or any type of EMS.[1] The Society for the Recovery of Drowned Persons became the first organization to deal with sudden and unexpected death; however, it was not until the 1950s that James Elam proved expired air was sufficient to maintain adequate oxygenation until blood flow was restored or other mechanical means of ventilation could be established.[1] In the late 1800s to early 1900s, external chest compressions were being used sporadically in humans with little scientific research or impact on survival rates. The first documented successful use of external chest compressions was reported by Dr George Crile in 1903.[1] After the landmark paper by Kouwenhoven and Jude in the 1960s, who showed adequate circulation could be achieved with closed chest cardiac massage, CPR guidelines were developed and the American Heart Association (AHA) started a program to train physicians and the general public in the techniques of closed-chest cardiac massage.[2] Prior to this landmark paper, it was believed that the only way to artificially circulate blood was to open the chest and perform direct cardiac massage. Since then the AHA has established the standards of care for CPR. The AHA re-evaluates its recommendations and updates the guidelines as new information and research become available.

The mechanism of forward blood flow during CPR has been the subject of much debate and research. There have been two proposed mechanisms most widely recognized: (1) the “thoracic pump model” and (2) the “cardiac pump model”. The thoracic pump model postulates that blood flows during closed chest cardiac massage, or CPR, due to an increase in intrathoracic vascular pressure that exceeds extrathoracic vascular pressures. This theory was postulated by Weale and Rothwell-Jackson in 1962. They showed almost equivalent increases in arterial and venous pressures in animals during closed chest CPR.[3] Blood flow is in the proper direction due to venous valves that prevent retrograde flow. The heart is essentially passive with the valves

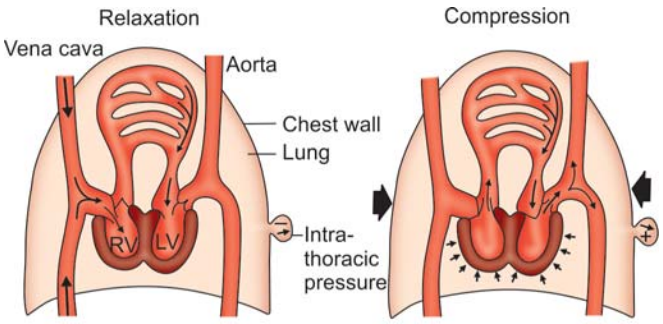


FIGURE 1: Cardiac pump model of cardiopulmonary resuscitaton. (*Source:* Modified from Luce JM, Cary JM, Ross BK, et al. New developments in cardiopulmonary resuscitation. JAMA. 1980;244:1366-70)

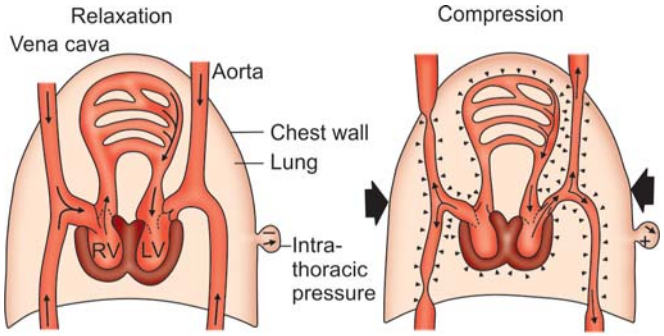


FIGURE 2: Thoracic pump model of cardiopulmonary resuscitation. (*Source:* Modified from Luce JM, Cary JM, Ross BK, et al. New developments in cardiopulmonary resuscitation. JAMA. 1980;244:1366-70)

remaining open due to equal pressure from all sides during compression (Fig. 1). The cardiac pump model, proposed by Kouwenhoven et al., states that flow occurs due to compression of the heart between the sternum and the spine.[2] Flow is maintained in the proper direction due to the mitral valve staying closed during systole or the compression phase. With release of the chest compression the heart expands, the mitral and tricuspid valves open and the heart fills with blood (Fig. 2). In 1993, Redberg et al. performed transesophageal echocardiography on 20 patients during resuscitation in an attempt to determine if cardiac size changed and if the mitral valve opened during diasystole or the release phase of CPR. They found a reduction of ventricular cavity size with compression and mitral valve opening during cardiac release, supporting the cardiac pump theory.[4] Multiple other studies have used ultrasound in an attempt to determine the mechanism of blood flow with mixed results. Studies done on animal models are difficult to extrapolate to humans and many of the human studies show conflicting results without much correlation with survival rates. Both mechanisms may occur, especially during prolonged resuscitation, when the myocardium becomes edematous and stiffer, which might make the heart less compressible favoring the thoracic pump mechanism. While it is still uncertain exactly which mechanism is correct or if it is a combination of both, it is known that the quality and rate of chest compression is extremely important for increasing rates of survival from sudden cardiac arrest.

Using electricity for cardioversion and defibrillation in order to terminate dysrhythmias has been used worldwide for many years. Its origins began in 1775 when Abildgaard demonstrated that stunned chickens can be revived by electrical shocks to the head and heart.[5] In 1899, Prevost and Batelli showed that dogs in ventricular fibrillation (VF) could be restored to a normal rhythm by electric shocks.[6] Then in the 1900s the Consolidated Edison Company of New York began funding research on the mechanisms and treatments of electrical accidents.[6] This allowed extensive research into the electrical mechanisms of heart function and, as a consequence, ways in which electricity can be used to restore proper function in the setting of electrical dysfunction. Human defibrillation began in an operating room in 1947 when Beck administered electrical shocks to the exposed heart (open chest defibrillation) to terminate VF.[7] The first closed chest defibrillation was not achieved until 1965 by Zoll et al.; prior to this a few successful attempts with direct cardiac defibrillation were reported.[8] After Kouwenhoven et al. developed closed-chest cardiac massage, the AHA started a program to train physicians with the techniques of advanced CPR that included CPR as well as electrical defibrillation.[2,6] Types of defibrillators and mechanism of defibrillation are discussed later in this chapter.

CARDIOPULMONARY ARREST

Sudden cardiac arrest is still a major public health problem and a leading cause of death in the United States. It is important when discussing resuscitation strategies from sudden cardiac arrest to define what is meant by “sudden”, “cardiac arrest” and “death”. The epidemiologic definition of “sudden” is usually defined by less than 1 hour from onset of symptoms to terminal clinical event which could include: death, loss of detectable pulse or cessation of breathing. This definition does not take into account unwitnessed events. The World Health organization has included in its definition of “sudden” unwitnessed deaths that occur less than 24 hours prior to discovery of the victim. “Death” is defined as an absolute irreversible event; this is a biologic, legal and literal definition. “Cardiac arrest” can be reversible and is defined as the cessation of pump function. If the patient is unable to be resuscitated or resuscitation is not performed then the event becomes irreversible and is considered sudden cardiac death. Cardiovascular collapse is defined as loss of effective blood flow either due to cardiac dysfunction or loss of vascular function.

Approximately 10% of all emergency department visits are cardiac related.[6] Cardiac causes are by far the most common cause of sudden cardiac arrest. Ventricular tachycardia (VT) and VF account for the vast majority of sudden death cases. Other causes of sudden death include intracranial hemorrhage, pulmonary embolism, drug overdose, lung disease, aortic dissection or rupture, trauma and drowning. Atherosclerotic disease is the leading cause of death in the United States and in addition it carries significant morbidity, disability and loss of productivity. Atherosclerotic disease is present to some extent in all adult patients, but genetic background and lifestyle risk factors, such as cigarette smoking, sedentary lifestyles and high fat diets, put patients at higher risk for developing significant atherosclerotic disease complications or death. The initiating event is usually injury to the vascular endothelium leading to

accumulation of macrophages and lipids at the site of injury. Plaque formation then occurs which can subsequently rupture leading to clot formation compromising blood flow through the arterial lumen. Decreased blood flow or complete occlusion leads to myocardial ischemia, hypoxia, acidosis and infarction. The consequences of arterial occlusion depend upon the availability of collateral blood flow and the size of the area of myocardium supplied by the occluded vessel. Risk factors for increasing plaque formation include: genetic predisposition, hypercholesterolemia, diabetes, hypertension, smoking, male gender and postmenopausal status in women.

The AHA estimates that there are 300,000 out of hospital cardiac arrests each year.[1] Unfortunately survival rates are extremely low. Of those that do survive, more than half have poor neurologic outcomes.[9] According to the AHA, an average of 31.4% of out of hospital cardiac arrest patients receive bystander CPR, of which 60% are treated by EMS.[1] Immediate CPR can substantially improve a victim's chance of survival. Increasing survival rates involves many factors including measuring outcomes and improving "weak links" in the chain of survival. The AHA uses four "links" in the "chain of survival" for victims of sudden cardiac arrest: (1) early recognition of the emergency and activation of emergency medical services; (2) early bystander CPR; (3) early defibrillation if indicated and (4) early ALS and post-resuscitative care. Quality rescuer education and frequency of retraining are also critical factors.

The cardiopulmonary resuscitation is highly accessible and requires little medical training and no equipment but out of hospital cardiac arrest survival rates remain low. Many studies have documented that only 15–30% of victims receive bystander CPR. The EMS often takes 6–7 minutes or longer to arrive at the scene; each minute that passes without blood flow to vital organs decreases the victims' chance of survival. Many theories have been proposed to explain the hesitation to perform CPR by bystanders even when they are trained. One explanation is the concern bystanders have performing mouth-to-mouth resuscitation. The complexity of the guidelines and instructional materials may prevent bystanders from performing CPR. The fear of poor performance or failure may also prevent many from even attempting. Legal liability is also a concern of many individuals because they may not be aware of "good Samaritan" laws that provide some protection for rescuers.

Every 5 years the AHA revises its guidelines for resuscitation care. The 2005 revision placed greater emphasis on compressions and de-emphasized ventilations. This change was studied after its initiation and found an increase in survival rates suggesting less interruption of chest compressions improves outcomes.[10,11] The bigger problem and concern was the need to increase bystander performed CPR. Given the concerns bystanders have of performing mouth-to-mouth resuscitation several studies were conducted to evaluate the outcome differences between compression only CPR and standard CPR with ventilations. Svensson et al. conducted a randomized prospective study comparing the two groups.[12] They found no significant difference in survival rates of compression only CPR and standard CPR for witnessed out of hospital cardiac arrest victims. This along with other studies prompted the AHA to change its recommendations for the 2010 guidelines to compression only CPR for witnessed out of hospital cardiac arrest victims. Two main conclusions can be currently drawn from these studies: (1) first and foremost CPR needs to be performed as quickly as possible and (2) quality compressions with minimal interruption need to occur. The 2010 AHA guidelines for pulseless arrest are discussed later in this chapter.

Implementation of new guidelines does improve outcomes; however, expediting guideline implementation is challenging. It can take several years for new guidelines to be implemented; barriers to implementation include: delays in instruction, technology upgrades, and difficulties with coordination of medical direction, government agencies and participation in research.

EMERGENCY MEDICAL SERVICES

The credit for developing the first EMS system seems to go to Napoleon's Surgeon-in-Chief, Barron Jean Larrey. He noted that wounded soldiers were left unattended until the fighting ceased, after which rescue teams would enter the battlefield and care for the wounded. He was convinced that if the wounded were attended to sooner, mortality rates would improve. He positioned medical transport teams closer to the battlefield to remove the injured soldiers. During the American Civil War the medical director of the Army of the Potomac, Jonathan Letterman, organized horse-drawn trains to rapidly remove wounded soldiers from the battlefield to field hospitals set-up nearby.[13]

During the first half of the 20th century most civilian transports were performed by morticians. There were no government regulations or financial support. The poor state of emergency medical response and treatment along with recommendations for improvement were first published by the National Safety Council's Traffic Conference after surveying several cities across the United States on how injuries from traffic accidents were handled.[14] In 1966, a second national survey by the National Academy of Sciences-National Research Council was used to complete the "White Paper" entitled Accidental Death and Disability: the Neglected Disease of Modern Society.[15] The issues brought forth in this paper along with public concern pushed congress to draft legislation that enabled the US Department of Transportation and the National Highway Traffic Safety Administration (NHTSA) to develop a national program to improve emergency medical care.[16] In 1973, the US Senate passed the EMS Systems Act which gave federal funding to improve regional EMS systems.[17] Currently all states have an administrative department that governs EMS activities and assists in the planning, licensing and development of standards of practice.

Each state is responsible to ensure that their citizens receive prompt emergency medical care. The National Highway Safety Administration has made recommendations and guidelines for the implementation of an EMS system and course curriculum training for care providers. At a minimum EMS, programs should have these ten components: (1) Regulation and Policy—this should include comprehensive legislation, regulations and operational policies and procedures to provide emergency medical and trauma care services; (2) Resource Management—the state should establish a central lead agency that identifies, categorizes and coordinates resources necessary for the overall system implementation and operation; (3) Human Resources

and Training—the EMS system must have trained persons to perform the required tasks, including first responders, emergency medical technicians (EMTs), communications, physicians, nurses, hospital administrators and planners; (4) Transportation—reliable and safe ambulance transportation is critical for an effective EMS system; (5) Facilities—proper facilities that are accessible are required to ensure high-quality care and these must be available in a timely manner. Hospital resources and capabilities need to be designated and known in advance and agreements need to be established between facilities to ensure patients receive treatment at the closest, most appropriate facility; (6) Communications—an effective communication system is needed to provide a means for persons to access resources, mobilize units, manage and coordinate those resources to provide care in a timely fashion; (7) Trauma Systems—a designated trauma system needs to be established to provide high quality, effective patient care; (8) Public Information and Education—public awareness and education of the EMS system is essential for proper access to occur; (9) Medical Direction—physician involvement is critical for a system to provide high quality and proper care. Physicians must delegate responsibilities to non-physician providers; protocols need to be developed, implemented and have continuous oversight with audits and evaluations. Immediate medical direction by a physician should be available at all times to ensure quality patient care and (10) Evaluation—evaluation is required to provide improvement in the system as new medical knowledge is obtained.[18] Table 1 summarizes all these ten components.

Not all EMS systems operate in similar fashion. System designs need to accommodate the needs of the local community or jurisdiction. The system may be served by a private or public agency, it may provide BLS services only or both BLS and ALS. Responses to 911 calls may be in the form of single-tiered, multi-tiered or first responder only. Currently not all systems incorporate record keeping, data collection or auditing programs. This puts these systems at a disadvantage due to their inability to improve patient care through changes in protocol, tracking those changes to ensure proper implementation and demonstrating a true impact on patient care.

TABLE 1

Components needed for EMS system operation

Regulation and policy	Legislation, regulations and operational policies and procedures
Resource management	Lead agency identifies categorizes and coordinates resources
Human resources and training	Trained persons to perform required tasks
Transportation	Reliable and safe ambulances
Facilities	Proper and accessible with known hospital capabilities
Communication	Communication system for resource allocation
Trauma system	Predetermined for timely access
Public information and education	Public awareness/education for proper utilization of resources
Medical direction	Physician directed protocols and oversight
Evaluation	Provide improvement and implementation of new medical knowledge

Public agencies are the responsibility of local governments; many of these systems use fire departments to provide EMS services. Providers are then cross trained as firefighter or paramedics. Some public EMS systems are separate entities referred to as municipal third-service systems. Some communities may combine public agencies such as EMS, fire and police services with one director or administrator. Funding public EMS systems may be tax based or a combination of use fees plus government funding. Medical oversight is usually provided by an appointed physician or medical control board.

Private agencies that provide EMS services may be locally owed, hospital based or operated by large corporations. Most private agencies are funded by user fees; some government subsidies may be provided; however, depending on the local needs and percent of uninsured population. Some systems have multiple agencies, public or private, providing services to the same area. These systems may have varying ways of allocating calls, such as rotational coverage or zone coverage.

Single-tier systems provide the same level of personnel and equipment irrelevant of call types, for example all BLS or all ALS. A multi-tiered system dispatches different levels, BLS or ALS depending on the nature of the call. Cost differences are debated and may depend on the community being served. It may prove to be cost effective to have a single ALS system providing consistent advanced care avoiding the potential to under-triage a call and send a lower BLS unit when an ALS unit is actually required. This can be difficult to fund as paramedics are more costly to staff than EMTs. First responders are usually part of any system and consist of police or firefighter who may arrive at the scene prior to the ambulance.

Individual states are responsible for drafting recognized provider levels, testing and recertification requirements. The NHTSA provides recommendations for a national standard curriculum. Basic provider levels include: First responder, emergency medical technician-basic (EMT-B), emergency medical technician-intermediate (EMT-I) and paramedic. The BLS and ALS refer to type of emergency care provided. The BLS or BLS services involve life-saving skills such as bag-valve-mask ventilation, oral and nasal airway use, CPR training, bleeding control techniques, basic fracture care or splinting and childbirth assistance. The use of an automated external defibrillator (AED) is also often included in BLS training. The ALS includes BLS training but also incorporates more advanced airways such as intubation, laryngeal mask airway (LMA) use and the use of rapid sequence intubation (RSI) medications. They also include cardiac medications for the resuscitation of cardiac arrest victims. Details about BLS and ALS are to be discussed later in this chapter.

First responder training is typically done for all personnel, such as firefighters and police officers, who might be the first to respond to an emergency. Many bystanders may also be first responder trained. First responders can provide limited life-saving procedures such as CPR, Heimlich maneuver, spinal immobilization and basic bleeding control measures. Most first responders receive 40 hours of didactic instruction and 16–36 hours required for refresher training as recommended by the NHTSA.[19]

TABLE 2

Summary of EMS provider levels

Training level	*Personnel*	*Skills*	*Education*
First responder	Personnel first on scene: Police/Firefighters/Bystanders	Limited life-saving procedures: CPR, Heimlich	40 hours didactic training
EMT-B	Minimum level of training to staff ambulance	First responder + immobilization techniques and use of oxygen, auto injection medications, albuterol	100–125 hours training including laboratory
EMT-I	EMT-B plus some advanced resuscitation techniques	EMT-B + LMA, IV line with fluid resuscitation, defibrillator use	300–400 hours training with clinical/field rotations
Paramedic	Most advanced prehospital training	EMT-I + ACLS, RSI, ECG interpretation, limited medication administration, IO	1100–1200 hours training: didactic + laboratory 250–300 hours clinical 250–300 hours field

The EMT-B is the minimal level of training required to staff an ambulance. It incorporates the skill of a first responder as well as some training in patient assessment, immobilization procedures and the use of oxygen administration. Depending on the state, some incorporate the use of life saving cardiac medications such as epinephrine given subcutaneously with auto injection, albuterol via nebulizer and intravenous (IV) fluids. The NHTSA recommends 100–125 hours of training that includes laboratory training.[20] The EMT-B usually also includes training in the use of AED.

Emergency Medical Technician-Intermediate (EMT-I) is trained in the skills of first responder and EMT-B plus more advanced techniques of care such as laryngeal mask airway, endotracheal intubation, IV line with fluid resuscitation and are trained in the use of a defibrillator. The EMT-I approaches the level of training of a paramedic but with less education and in most cases less cost. The NHTSA recommends 300–400 hours of initial education that combines classroom education as well as clinical training through hospital and field rotations.[21] Some states are removing the EMT-I level of training to simplify the training process.

Paramedics have the highest level of prehospital training. Their training includes all BLS training plus advanced cardiac life support (ACLS) training that includes the use of RSI medications, use of 12 lead ECG and its basic interpretation, defibrillator use, many medications including cardiac medications, pain medications and antiseizure medications. Paramedics are also trained in the use of alternative access lines such as the use of intraosseous access. Training also includes more advanced emergent delivery techniques such as neonatal resuscitation for emergency deliveries. The NHTSA recommends 1100–1200 hours of training that include 500–600 hours of classroom and laboratory time, 250–300 clinical hours in the hospital and 250–300 hours of field training.[22] All levels of training require some level of continuing medical education and refresher training. Table 2 summarizes prehospital personnel training levels.

BASIC LIFE SUPPORT

Basic life support is the first step and the foundation for saving lives from sudden cardiac arrest. It involves immediate recognition, activation of emergency response system, performing high-quality CPR and rapid defibrillation when appropriate.[23] The BLS also involves basic trauma and other medical techniques that have not been covered in this chapter. The more people who are trained in BLS the better survival rates can be since witnessed arrest victims would receive CPR sooner. It is not the intention of this chapter to provide complete instruction on the performance of CPR; interested individuals should seek a certified AHA BLS or ACLS classes for complete training and instruction.

ROLE OF BYSTANDERS

The role of bystanders in sudden cardiac arrest is extremely important in the "chain of survival". Bystanders can perform 3 of the 4 links in the chain of survival and greatly impact a victim's chance of survival with good neurologic outcome. Bystanders are important for recognition and EMS activation, perform immediate CPR and apply and use an AED for defibrillation. Kitamura et al.[24] conducted a prospective, observational study in Japan which evaluated the effects of nationwide dissemination of public-access AEDs on the rate of survival of out of hospital cardiac arrest victims. Nationwide access to AEDs resulted in earlier administration of shocks by laypersons and an increase in survival at one month with minimal neurologic impairment. The new 2010 AHA guidelines for BLS emphasize immediate chest compressions without delay for rescue breathing and application of an AED as soon as it is available.

EMERGENCY MEDICAL SERVICES ACTIVATION

Immediate activation of EMS is extremely important for the survival of sudden cardiac arrest victims. In many communities the time interval for EMS arrival is 7–8 minutes. This means that for the first several minutes the chances of survival for the victim is in the hands of bystanders. The sooner EMS can arrive at the scene the sooner victims can receive ACLS and post-resuscitative care. The BLS algorithm has been simplified: immediate activation of the emergency response system and initiate chest compressions for any unresponsive adult victim who is not breathing normally.[23] The previous recommendation of "Look, Listen and Feel" step was too time consuming and inconsistent between rescuers. Lay rescuers should not attempt

to check for a pulse as even trained healthcare providers often incorrectly assess the presence or absence of a pulse especially if blood pressure is extremely low.[23] Chest compression performed on a patient with a heart beat is rarely associated with significant injury.[25] Many arrest victims will have gasping respirations or appear to be having a seizure. Lay rescuers should be instructed to start CPR immediately on any unresponsive victim who appears to be struggling to breathe given the unusual presentations of sudden cardiac arrest.

DISPATCHER ASSISTED CARDIOPULMONARY RESUSCITATION

When dispatchers receive a 911 call of a witnessed sudden cardiac arrest they are encouraged to instruct the lay rescuer to perform "hands-only" (compression only) CPR. Compression only CPR is much easier to perform and prevents delays in providing chest compressions. Positioning the head, attaining a seal for mouth-to-mouth or assembling a bag mask can take time and as such this delay has been found to decrease overall survival rates. In 2005, the AHA published new guidelines for cardiac arrest victims in which chest compressions were emphasized before first defibrillation. Placing electrode pads and analyzing rhythm all take time during which the victim is not receiving CPR. It was believed that the lack of immediate chest compressions and the delay in CPR during the "3 stacked shocks" that were previously advised for cardiac arrest due to VF or unstable or pulseless VT was decreasing vital organ blood flow and contributing to poor outcomes. After implementation of the 2005 AHA guidelines multiple studies found significant improvement in survival rates.[10,26,27]

COMPRESSION ONLY CARDIOPULMONARY RESUSCITATION

Changing chest compression ratios, emphasizing more compressions and less ventilation was a controversial topic at the 2005 International Consensus Conference on Resuscitation and a major change to the AHA 2005 guidelines for CPR. Recent studies have demonstrated an increase in survival from out of hospital cardiac arrest resulting from improved quality of CPR, with adequate rate and depth and minimizing interruptions by avoiding excessive ventilations and "stacking shocks".[26-30] During the time between 2005 and 2010 the AHA has been studying ways to simplify CPR and increase its use by laypersons due to the fact that survival rates of out of hospital cardiac arrest remain low.[1] Compression only CPR for most adults for out of hospital cardiac arrest has been shown to achieve similar outcomes to those who receive standard CPR with rescue breathing.[12,31-34] Thus, bystanders are encouraged and directed by dispatch to perform compression only CPR until the arrival of EMS. Starting the procedure with compressions only eliminates the step that most laypersons have difficulty with: opening the airway and giving rescue breaths. However, children rarely arrest from a primary cardiac cause and thus for the pediatric cardiac arrest victim, rescue breathing may be much more important. Pediatric cardiac resuscitation has not been covered in this chapter.

CHEST COMPRESSIONS OR AIRWAY MANAGEMENT

The newest change to the AHA guidelines for CPR will be changing from "A-B-C" (airway, breathing, circulation) to "C-A-B" (chest compressions, airway, breathing).[23] The change will not be an easy one to make. Everyone who has ever learned CPR will have to be re-educated. The vast majority of sudden cardiac arrest patients arrest from VF or pulseless VT, and these patients have improved survival from immediate high quality CPR with early defibrillation.[23] When a collapse is witnessed by a lone rescuer the AHA now advises to confirm unresponsiveness, activate the emergency response system and then begin chest compressions with a rate of 100 per minute for adults with a depth of at least 2 inches, allowing complete recoil of the chest after each compression. Proper hand position is two fingerbreadths above the xiphoid-sternal notch. For the lay person it is easier to understand "center of the chest between the nipples". The first compression cycle should be 30 compressions in length. Early application of an AED or defibrillator should be done as soon as another rescuer is available. Ventilations should be given with 2 breaths after 30 compressions with minimal interruption of compressions. Bystander or dispatcher assisted CPR should be performed with compressions only if a barrier device is not available and there is concern about exposure. Once a "shockable" rhythm is identified and a defibrillator or AED has been applied a shock should be delivered. After the shock is delivered CPR should be started immediately without checking for a pulse or rhythm. After 2 minutes of CPR there should be a pause for a rhythm and pulse check. Healthcare providers should tailor the sequence of actions to the most likely cause of the arrest. In a known drowning, for example, conventional CPR with rescue breathing would be more important. Children and newborn infants are more likely to suffer a respiratory cause of arrest and would also benefit from the conventional A-B-C sequence of resuscitation. Children and infant CPR is performed slightly differently and is not covered in this chapter.

Rescue breathing should be performed with a head tilt chin lift maneuver or jaw thrust if trauma is suspected. A bag valve mask or other barrier should be used if available. More advanced airway techniques have been discussed below. Rescue breaths should be given quickly, minimizing interruption of chest compressions.

MECHANICAL DEVICES FOR CARDIOPULMONARY RESUSCITATION

Mechanical devices for adult CPR have been developed for several reasons. It is possible that mechanical devices may perform CPR better than standard CPR. Mechanical devices are also useful for long transports to prevent rescuer fatigue. The longer a rescuer performs CPR, the more the quality decreases as the rescuer becomes tired. Several studies have shown improved coronary perfusion pressures with mechanical devices. However no studies have shown improved survival with any mechanical device compared to standard CPR.[35-41] Decreased quality of chest compressions with time is however well recognized.[42] It is recommended that rescuers performing CPR

change often during the resuscitation and if a long transport is to occur a mechanical device should be considered to be used to prevent rescuer fatigue as well as free up the rescuer to perform other duties. More study is needed to effectively evaluate the use of mechanical CPR devices.

USE OF AUTOMATIC EXTERNAL DEFIBRILLATORS

Automatic external defibrillators are small, portable, battery operated devices that allow providers to defibrillate cardiac arrest victims without interpretation of an electrocardiographic waveform. Laypersons can use the device with minimal or no training, as audible and visual prompts are incorporated into the machine. It is well known that the earlier a victim is defibrillated the better chance of survival. Studies of placement of the devices where it was easily accessible have shown improvement in the survival rate of out of hospital cardiac arrest victims.[24] Most in-hospital defibrillators are now equipped with AED technology to help improve the time to first shock by allowing those untrained or uncertain to use the device.

When a victim is recognized and the emergency medical system is activated CPR should be started. Once the AED is available, the device should be placed by the patient's head for easy access and operation. The AED's power should be turned on which initiates a self check by the machine. The machine then instructs the user in its use. It will begin by advising to attach the electrode pads to the patient. There are pictures on the electrode pads for proper placement on the chest wall. The electrode pads should be placed on the right upper chest just below the clavicle and the left lower lateral chest below the nipple. The chest wall should be dry when the electrode pads are applied. The AED will then analyze the rhythm; some devices require a button to be pushed to analyze the rhythm. The CPR should continue uninterrupted as much as possible during set-up and application of the electrode pads. During analysis of the rhythm the patient should not be touched. The AED will then advise if a shock is indicated or if CPR should be continued. If shock is advised then the machine will indicate to "charge" then will wait for the user to push the "shock" button. Before the shock is initiated everyone must be clear of the patient. After the shock is initiated CPR should be started immediately and not be delayed to analyze the rhythm and check for a pulse. This is a deviation from past AHA guidelines and if the AED is old it may not be programmed appropriately, but CPR should be initiated after the shock in any case. If return of circulation occurs then airway or breathing assistance should be maintained until more definitive care arrives. The cycle of shock, 2 minutes of CPR then rhythm or pulse check should continue until advanced interventions are available.

PACEMAKER OR AUTOMATIC IMPLANTABLE CARDIOVERTER DEFIBRILLATOR PATIENT IN CARDIAC ARREST

If a patient has an implantable device such as a defibrillator or pacemaker, care should be taken to avoid placing electrode paddles or pads on the device; placement should be at least 1 inch away to avoid any potential artifact interference during rhythm analysis and potential damage to the device from defibrillation. There is little danger to a rescuer performing CPR from an implantable automatic internal defibrillator. If the defibrillator fires during CPR the rescuer may feel a slight electrical shock; however, it is not harmful. Pacemaker problems can occur from defibrillation or cardioverson, although this is rare, including damage to the circuitry resulting in complete dysfunction or inappropriate pacing or defibrillation. It is not necessary to turn off the devices during CPR; however, if it is indicated or to alleviate fears of the resuscitation team a circular magnet is needed. For an automatic implantable cardioverter defibrillator (AICD), the magnet is placed over the upper right-hand corner, if left in place for 30 seconds the AICD is turned off. The magnet is then removed. Placing the magnet back for 30 seconds will turn the AICD back on. If a magnet is placed on a pacemaker, it changes the pacemaker to a set predetermined rate in an asynchronous mode. It will pace at the predetermined rate without trying to sense an intrinsic rhythm or coordinate its pacing. All patients who present with a cardiac dysrhythmia and have a pacemaker or AICD in place should receive an interrogation of the device by a cardiologist, trained nurse or technician following the resuscitation. This can be helpful in determining the cause of the arrest as well as ensuring proper pacemaker or AICD function and reprogramming.

COMPLICATIONS OF CARDIOPULMONARY RESUSCITATION

Cardiopulmonary resuscitation is performed to save the life of the victim; however, it is not without complications. Resuscitation teams need to be aware of the potential complications in order to provide better care to a patient whose resuscitation is not going well or for those who deteriorate post-resuscitation. Many studies have been conducted in an attempt to determine the rate of complication from CPR. The most common complication found was sternal and rib fractures with a rate of 25–30%. Other complications include: anterior mediastinal hemorrhage, upper airway complications, abdominal organ injuries and lung injuries.[43-48]

Rib and sternal fractures are the most common complications of even well performed CPR.[45] The sternum may become separated from the ribs during the first several compression cycles and the anterior ribs during this time can be fractured. Most commonly this does not cause permanent problems for the patient but will be painful during recovery. Sometimes the fractured ribs can puncture or injure the lung leading to a tension pneumothorax. If a patient during resuscitation becomes difficult to bag it is important to consider pneumothorax as the cause. If a pneumothorax occurs this can quickly lead to tension for patients who are receiving positive pressure ventilation. Tension pneumothorax interferes with cardiac filling during diastole or the release phase of CPR and can lead to pulseless electrical activity (PEA). Providers need to decompress the chest quickly. To decompress the chest a chest tube needs to be placed, but this can take time during which the patient may continue to deteriorate. While obtaining the supplies and placing a chest tube a needle thoracotomy should be performed. This is performed by placing a large gauge (14-G is preferred) angio-catheter in the second intercostal space on the anterior chest in the midclavicular line. A rush of air should be heard releasing

the pressure on the heart allowing for proper filling. The needle can then be removed leaving the plastic catheter in place until a chest tube is in place. If a patient is very large with a thick chest wall a spinal needle may be used instead. While sternal and rib fractures are common complications of CPR they rarely cause any problems for the resuscitation. However, better CPR technique leads to a lower rate of complication.

During a resuscitation attempt many patients will develop gastric distention from either mouth-to-mouth or other rescue breathing prior to intubation. Patients may vomit from this gastric distention or from the resuscitation itself, which can lead to aspiration, especially before a definitive airway can be achieved. An endotracheal tube does not completely occlude the airway and fluid may still pass the endotracheal tube balloon; however, intubation does prevent large amounts of fluid and food particles from being aspirated. If aspiration occurs the patient is at risk for pneumonitis from the acidic contents.

Abdominal organ injury from CPR is not a common complication, but can occur. The most common organ injured is the liver; liver lacerations can occur due to fractured ribs and from CPR performed with the hands too low on the anterior chest. Splenic lacerations have also been known to occur. If a post-resuscitation patient becomes acutely hypotensive, one must consider liver or splenic lacerations as a potential source of hemorrhage. Bowel injury or perforation can also occur.

Fatal bleeding following CPR and the initiation of thrombolytic therapies is not a common complication. Even despite multiple rib fractures most patients do not suffer fatal hemorrhage.[49] Concern over the possible bleeding risks of thrombolytic agents should not preclude providers from thrombolysis following post-cardiac arrest if it is medically indicated for the treatment of acute coronary syndrome (ACS).

ADVANCED CARDIAC LIFE SUPPORT

OVERVIEW-STATISTICS OF SUCCESS

Advanced cardiac life support includes high quality BLS and interventions that can prevent cardiac arrest in the setting of ACSs, treat cardiac arrest and improve outcomes after the cardiac arrest patient is resuscitated. During any resuscitation the healthcare provider must recognize and treat reversible causes of cardiac arrest. The "4 Hs and 4 Ts" are known causes and possible complications of cardiac arrest. These are listed in Table 3. The new AHA 2010 guidelines for the "Chain of Survival" includes "Part 9: Post-Cardiac Arrest Care" emphasizing comprehensive multidisciplinary care beginning with the recognition of cardiac arrest and concludes with hospital discharge, but may carry beyond to prevent future cardiac complications.[23]

ADVANCED AIRWAY MANAGEMENT

The new 2010 AHA guidelines for ACLS have new recommendations for airway management that include: the use of quantitative waveform capnography for confirmation and continuous monitoring of endotracheal tube placement for adults, the use of supraglottic advanced airways as alternative to endotracheal intubation and they no longer recommend the routine use of cricoid pressure during airway management.[23]

TABLE 3

Reversible causes of cardiac arrest

Five Hs	*Five Ts*
Hypoxia	Toxins
Hypovolemia	Tamponade
Hydrogen ion (acidosis)	Tension pneumothorax
Hypokalemia/hyperkalemia	Thrombosis, pulmonary
Hypothermia	Thrombosis, coronary

(*Source:* Neumar RE, Ottto CS, Link MS, et al. Guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. Part 8: Adult advanced cardiovascular life support. Circulation. 2010;122(Suppl. 3):S729-67)

Endotracheal intubation is the recommended airway of choice for all patients needing invasive ventilation management or airway protection due to alteration in mentation, airway swelling or any other injuring that may compromise the upper airways. The possibility of spinal injury is a relative contraindication of direct laryngoscopy orotracheal intubation; however, if a patient requires endotracheal intubation for life-saving reasons then one must perform the procedure with as much spinal immobilization as possible without interfering with the intubation procedure. Interested individuals should seek a certified ACLS course for instruction on endotracheal intubation.

The difficult airway where intubation fails can be due to prominent upper incisors, inability to extend the neck, extremely large tongue, swelling, blood or secretions in the airway, small lower jaw, inability to completely open the mouth, tumors or any other unusual anatomy. Some patients despite normal-appearing anatomy without complicated history may pose an unexpected challenge to intubate. For those experienced and skilled in the practice of endotracheal intubation it is still the best airway; however, intubation is also a motor skill that requires practice and for those providers in the EMS system who may not be very experienced airway adjuncts are extremely important. Good bag-valve-mask (BVM) ventilation is the first technique and probably the most important to know. BVM, however, can cause gastric distention and does not protect the airway from aspiration. The most common adjunct supraglottic airways include the LMA, Combitube and King LT. An ideal airway should be rapidly and reliably inserted with minimal training, control ventilation, protect against aspiration and be able to be inserted with ongoing chest compressions. No one device provides all of these things but the LMA, Combitube and King LT are easy to use and found to be useful as adjunct airways for the inexperienced.[50] Multiple mannequin studies have found that most out of hospital providers prefer the King LT as easier and faster to insert.[51-54]

PHARMACEUTICAL INTERVENTIONS

Pharmaceutical interventions for cardiac arrest victims are a controversial subject. There is no evidence that any medications given during cardiac arrest that have lead to any improvement in survival to hospital discharge.[55,56] The most important factors in survival are high quality CPR and early defibrillation. When pharmaceutical therapies are to be used it is important to continue high quality CPR with minimal interruptions in

compressions for line placement and intubation. The medications used during CPR should assist in potentiating the return of circulation, enhance cardiac function, support blood pressure and shunt blood toward vital organs.[57] Drug therapy regimens should ultimately increase survival to discharge and not just increase initial resuscitation rates which may only result in unsalvageable patients with transient cardiac activity.[55,56] The AHA includes several medications in their Advanced Cardiovascular Life Support Pulseless Algorithm.

Epinephrine

Epinephrine is a mixed alpha and beta adrenergic receptor agonist. Alpha agonists are potent vasopressors and increase systemic vascular resistance which results in elevated aortic diastolic pressure which then increases coronary and carotid blood flow. However, epinephrine may increase myocardial workload and decrease endocardial perfusion, compromising cardiac tissue. The recommendation of the AHA is 1 mg of epinephrine on every 3–5 minutes for pulseless VT or VF and asystole. High-dose epinephrine does not enhance long-term outcome, can be detrimental and should not be used.[58]

Vasopressin

Vasopressin is a naturally occurring polypeptide produced from cells within the hypothalamus. When administered in pharmacologic dosages it acts as a peripheral vasoconstrictor. Vasopressin has also a longer half-life than epinephrine, about 10–20 minutes. Studies on the use of vasopressin in sudden cardiac arrest have not shown any greater benefit than epinephrine on long-term survival in sudden cardiac arrest.[59-63] If vasopressin is used, the AHA recommendation is 40 units IV in lieu of epinephrine for the first or second dose.

Lidocaine

Lidocaine increases uniformity of the action-potential duration and refractory period and can terminate reentrant rhythms. Lidocaine is given as a bolus of 1 mg/kg. The AHA recommends its administration after epinephrine, vasopressin and amiodarone have been tried. A second loading dose of 1 mg/kg can be given 10–15 minutes after the first one.

Amiodarone

Amiodarone is an antiarrhythmic agent that lengthens the cardiac action potential, prolongates refractoriness of the myocytes and decreases cardiac oxygen consumption. Amiodarone also improves cardiac pump performance, dilates coronary arteries, causes peripheral arterial vasodilatation and increases coronary blood supply. It does have the side effect of decreasing systemic vascular resistance and causing hypotension. The ALIVE trial showed significant improvement in terminating VF and increasing survival to hospital admission in the prehospital setting over the use of lidocaine; however, it is unclear if there is any long-term benefit from its use.[64,65] The AHA does have amiodarone in its guidelines for the use of refractory VF or VT in their pulseless arrest algorithm. The recommended dosing is 300 mg IV bolus with a second dose of 150 mg IV if needed.

Procainamide

Procainamide is a sodium channel-blocking antiarrhythmic medication that prolongs the refractory period and slows conduction through the myocardial conduction system. There are very few studies addressing the use of procainamide during pulseless cardiac arrest. Procainamide must be infused slowly; therefore, its practical use during cardiac arrest is limited. Procainamide must be avoided in patients with torsades de pointes. More study is needed to determine if procainamide has any long-term benefits for pulseless cardiac arrest. The AHA recommends procainamide for stable wide-QRS tachycardia but not for pulseless cardiac arrest.

Atropine

Atropine is a competitive antagonist of acetylcholine at muscarinic receptors. For cardiac arrest patients or those with symptomatic bradycardia, parasympathetic tone is increased due to vagal stimulation. Atropine blocks the depressant effect of the vagus nerve at the sinus and AV nodes. The AHA, however, has removed atropine from its 2010 guidelines for PEA or asystole ACLS Cardiac Arrest Algorithm due to a lack of any evidence showing therapeutic benefit.[66,67]

Magnesium Sulfate

If reversible causes of cardiac arrest are identified and treated patient outcomes improve. Magnesium deficiency can precipitate refractory VF. No prospective clinical trials have been published that show any change in long-term outcome from the routine use of magnesium in cardiac arrest patients except those with hypomagnesemia and patients in trosades de pointes. The recommended dose in cardiac arrest is 1–2 g diluted in 10 ml D5W given IV.

Calcium Chloride

Calcium chloride is not recommended for routine use in pulseless cardiac arrest unless there is an identifiable reason such as known hypocalcemia, hyperkalemia or calcium channel blocker toxicity. Increases in intracellular calcium potentiate myocardial ischemic injury. Canine myocardial cells were investigated and found to have increased uptake of calcium after myocardial ischemia followed by reperfusion, the mechanism of this uptake has not been established but could be a concern for ischemic cellular injury.[68] For hyperkalemia and calcium channel blocker overdose the recommended dosing is 500–1,000 mg IV.

Morphine and Oxygen

The new 2010 ACLS guidelines from the AHA do not recommend the routine administration of oxygen for all ACS patients. The recommendation is to use oxygen to keep saturations greater than 94%. For cardiac arrest patients, 100% oxygen should be used during resuscitation but weaned down in the post-resuscitation period. Morphine is indicated for ST elevation myocardial infarction and when a patient's chest pain is unresponsive to nitrates. Caution should be used when administering to unstable angina or non-ST elevation myocardial infarction patients.

DEFIBRILLATION OR CARDIOVERSION

Defibrillation is a procedure where controlled electrical energy is applied to the myocardium either through the chest wall or through directly on the heart and is designed to terminate an unstable or pulseless rhythm. Defibrillators are divided into two main types: (1) Manual and (2) Automatic. The AEDs were discussed earlier. Manual defibrillators require the provider to obtain and interpret an electrocardiogram and determine if: (1) defibrillation is necessary; (2) select an energy level and (3) decide if synchronization should be used. The goal of defibrillation is to uniformly depolarize a majority of the myocardium and terminate the abnormal dysrhythmia. Once electrical activity is reset and the myocardium regains its excitability, the SA node will presumptively reinitiate normal pacing and the myocardium can begin coordinated rhythmic contractions.

There are currently three basic theories of defibrillation. (1) The "critical mass" theory hypothesizes that the electrical current depolarizes a "critical mass" of myocardium and that the remaining myocardium that is not depolarized is inadequate to sustain the dysrhythmia. Zipes et al.[69] studied VF in dogs and found that successful defibrillation occurred most often when the electrodes were placed in the right ventricular apex and the posterior base of the left ventricle and least often when delivered between the two right ventricular electrodes;[69] (2) The theory of "upper limit of vulnerability" hypothesizes that the most important factor in defibrillation is achieving a critical current density throughout the ventricular myocardium that not only stops the fibrillation fronts but also does not reinitiate fibrillation by the same mechanism by which a shock during the vulnerable period of sinus or paced rhythm initiates fibrillation;[70] (3) It was found that the strength of shocks that stopped inducing VF were similar to the strength of shocks at the defibrillation threshold.[70] The theory of "extension of refractoriness" hypothesizes the shock prolongs the refractoriness in most of the myocardium so the fibrillation wavefronts cannot propagate.[71] Post-shock response durations, from shock to repolarization, were significantly longer in successful defibrillations than for unsuccessful defibrillation.[71] The "critical mass" theory may be important in both the "extension of refractoriness" and "upper limit of vulnerability" hypothesizes.

Defibrillators are classified by the type of waveforms they produce. Monophasic defibrillators send an electrical wave from one electrode to the other in only one direction. With biphasic defibrillators the electrode potential is reversed in midshock so the current reverses direction (Fig. 3). The waveform can also be classified by the way the current flows and terminates during the "discharge" period with respect to time on an x-y Cartesian plot—rapid or gradual at onset and termination. If the wave has a rapid rise to a peak and then a gradual decline to baseline it is considered a damped sinusoidal waveform. If the waveform has a rapid rise and then a rapid descent, it is considered a truncated waveform (Fig. 3). In 1962, Lown introduced the monophasic damped sinusoidal waveform for defibrillation and it remained the standard waveform for defibrillation for 30 years.[72] More recently studies have shown improved rates of terminating VF using biphasic truncated exponential (BTE) waveforms compared to monophasic damped sinusoidal waveforms. The BTE waveform also causes fewer post-shock

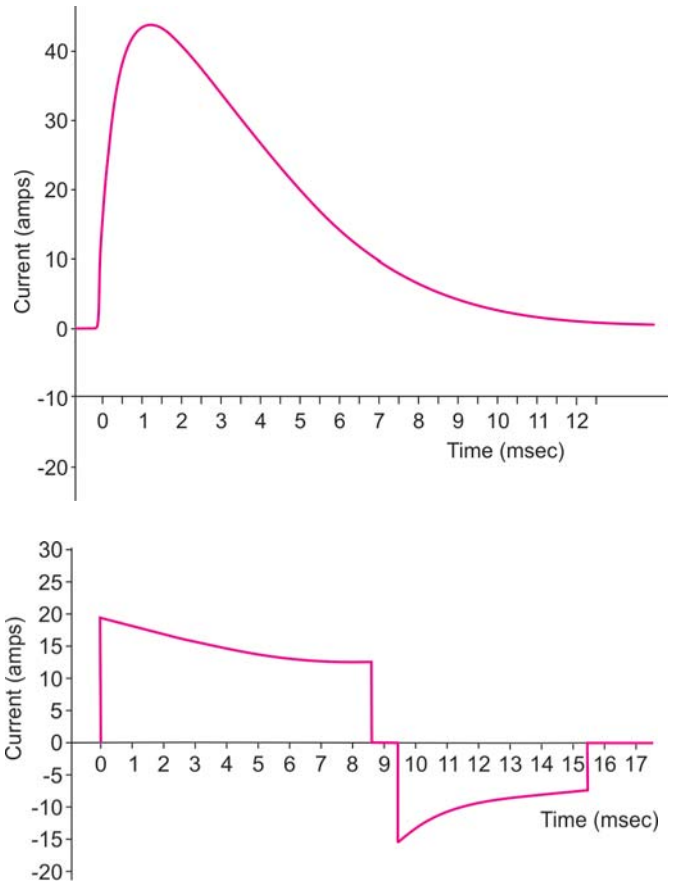


FIGURE 3: Monophasic vs Biphasic waveforms. The monophasic waveform is damped and the biphasic waveform is truncated. (*Source:* Modified from Deakin CD, Nolan JP, Sunde KJ, et al. European resuscitation council guidelines for resuscitation 2010 Section 3. Electrical therapies: automated external defibrillation, cardioversion and pacing. Resuscitation. 2010;81:1293-304)

arrhythmias with less myocardial damage.[73-78] The second phase of the biphasic shock also removes excess charge left on the myocardial cells after the first shock, a process called "charge burping".[79]

Biphasic defibrillators require lower energy levels to terminate VF or VT; the lower energy levels result in a decreased chance of myocardial damage and also allow smaller machines to be built. This technology has allowed portable battery operated AEDs to be developed and placed in public areas for use by lay rescuers. Public access to AEDs has increased survival rates for out of hospital cardiac arrest by decreasing time to first shock as discussed earlier in the chapter.[24,80]

Minimizing transthoracic impedance increases success rates of defibrillation. Paddle force, paddle orientation, a couplant, such as conductive gel use, shaving the chest and lung volumes, can all affect the transthoracic impedance. It is important that gel is applied when using hand-held paddles; without conductive gel the transthoracic impedance is extremely high resulting in poor current flow and decreased defibrillation success. Care must be taken not to smear the gel across the chest between the paddles as this could cause the current to flow through the low impedance path of the gel away from the heart.[81] Breast tissue can also increase impedance; therefore, the paddles or pads should be placed adjacent to or under the breast. Commercially

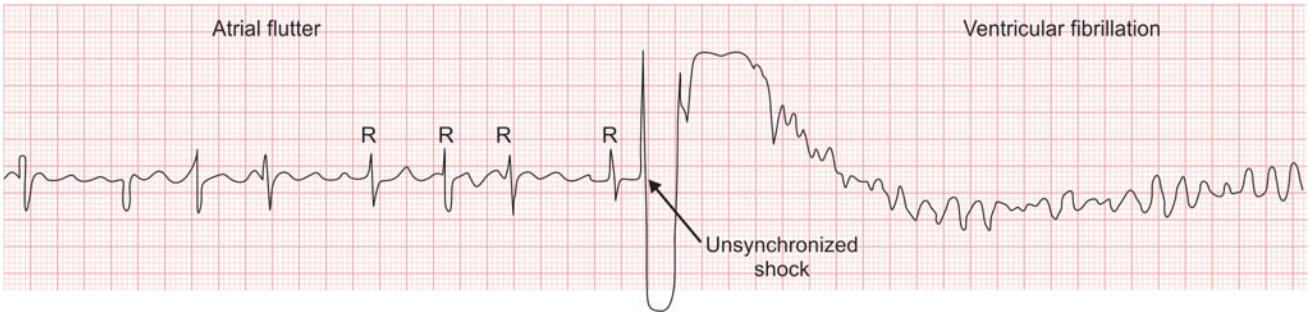


FIGURE 4: Induction of ventricular fibrillation by unsynchronized shock occurring on the vulnerable T-wave. (*Source:* Modified with permission from Kerber RE. Transchest cardioversion: Optimal technique. In Tacker WA (Ed). Defibrillation of the Heart. St Louis, USA: Mosby-Year Book; 1994. pp. 46-81)

available biphasic defibrillators are able to automatically adjust voltages and pulse duration to compensate for high or low transthoracic impedance. Monophasic defibrillators do not have this capability and result in considerable variability in delivered waveform depending on transthoracic impedance. "Smart" biphasic defibrillators can alter the waveform duration and/or voltage of the two pulses individually and instantaneously to optimize performance.

While defibrillation is a life-saving procedure it is not without risk. There are three basic risks: (1) risk to the patient; (2) risk to the user and (3) risk to equipment or environment. Care must be taken to minimize these risks.

Risk to the Patient

Defibrillators are equipped with "synchronization" mode which allows the user to avoid unintended delivery of a shock to the "T" wave of the ECG [which can induce VF, (Fig. 4)]. The user must be sure, when using a manual defibrillator, to appropriately use the synchronization for cardioversion of stable dysrhythmias but must avoid its use in unstable or pulseless rhythms, such as VF or polymorphic VT, where there will not be a discrete "R" wave to synchronize on and the device will not fire, thereby causing a delay until the synchronizer is disabled.

The energy level applied to the myocardium from defibrillation can cause damage manifest as myocardial necrosis and functional damage evident as atrioventricular conduction disturbances.[82] Chest wall impedance also posses challenges to delivery of safe defibrillation; high impedance results in a wide waveform with lower current, low impedance results in a narrow waveform with high current. Excessive current runs the risk of myocardial damage and low current may be inadequate to achieve defibrillation. As discussed earlier electrode orientation, electrode placement, chest hair and lung volumes can all affect impedance.

Incorrectly displayed asystole can occur when paddles or gel pads are used to display the ECG tracing due to electrical voltage "offset". This "false" asystole display can last long enough to mislead rescuers. If asystole is displayed it must be confirmed immediately by attaching the standard ECG electrodes; therefore, whenever possible gel pads or paddles should not be used for ECG display or monitoring.[83]

After transthoracic shocks first-degree skin burns are common.[84] Current flows preferentially to the edges of the electrodes increasing the thermal temperature causing skin burns mostly around the edges. New electrode pads are designed to decrease thermal temperatures at the contact site and therefore decrease skin burns.[85]

Risk to the Environment or Equipment

An increasing number of patients requiring CPR and defibrillation or cardioversion have implantable pacemakers or defibrillators. It is recommended that placement of paddles or pads are at least 12–15 cm from the device to help prevent damage to the implantable device. Although this risk is very low, it is possible that the electrical energy can be transferred down the lead wires damaging the wires and preventing proper defibrillation.[86-88]

Risks to the Rescuer

Risks to the rescuer during cardioversion or defibrillation are difficult to quantify. It is estimated that injury to paramedics was 1 per 1,700 without significant morbidity or mortality.[89] Recent clinical studies have measured current flow through rescuers who have deliberately placed themselves in the current pathway during cardioversion of atrial fibrillation; measured current flow through the rescuers was trivial and no injury occurred.[90] It has been suggested that the traditional admonition to "clear" the patient before delivering a defibrillating shock is therefore unnecessary, providing gloves are worn and self-adhesive paddles are used.[91] However the AHA recommends that all personnel stand clear during shock delivery. There is also no significant evidence documenting that performing CPR on a patient with an implantable cardiac defibrillator is harmful to the rescuer; therefore, CPR should be performed as usual but the device may be turned off as described earlier in the chapter when a magnet becomes available. The most common rescuer injuries are musculoskeletal related.

VF or VT-stable vs unstable: Ventricular fibrillation is always pulseless and, therefore, an unstable rhythm; CPR should be started immediately and defibrillation should be performed as soon as possible. The 2010 AHA guidelines recommend immediate CPR then defibrillation followed by more immediate CPR, minimizing pauses and "hands off" time. The monophasic energy recommendation is 360 J. Biphasic waveform defibrillator configurations differ among manufacturers and none have been directly compared to humans, therefore, the AHA

recommends using the manufacturer's recommendations for energy dose on biphasic machines. Since no optimal biphasic energy level has been determined the AHA does not make any definitive recommendation for the selected energy for subsequent biphasic defibrillation attempts. If subsequent shocks are required then the energy levels should be equivalent or higher than the first shock.

Ventricular tachycardia can be either unstable or stable. If the rhythm does not produce a blood pressure sufficient to maintain mentation then CPR should be started with defibrillation as soon as possible. If the patient with VT has a pulse with tolerable blood pressures then elective cardioversion is recommended, as soon as possible to prevent deterioration to a pulseless rhythm. Cardioversion is always performed using synchronized shocks, which avoids shock delivery during the relative refractory period of the cardiac cycle when the shock is most likely to induce VF. Monomorphic VT has been found to convert with lower energy and current during cardioversion than polymorphic VT which behaves more like VF.[92] Amiodarone administration for persistent VF or VT has been found to be relatively safe but ineffective for the acute termination of sustained VT.[93] Amiodarone is administered at a dose of 300 mg IV bolus.

Atrial fibrillation or supraventricular tachycardia: Atrial dysrhythmias and other tachycardias may require urgent cardioversion due to hypotension or pulmonary edema. Treatment of the cause of the arrhythmia may restore sinus rhythm or prevent recurrence. Causes include hyperthyroidism, pulmonary embolism, congestive heart failure and valve disorders. Table 4 lists some of the causes of wide and narrow tachycardia. Factors that may influence immediate and long-term success of cardioversion include the type of tachycardia, underlying cause of the dysrhythmia, and duration of the dysrhythmia. The AHA recommends initial biphasic energy doses of 120–200 J for atrial fibrillation; the monophasic energy dose should be 200 J. Atrial flutter and other supraventricular rhythms require less energy and a starting dose of 50–100 J of monophasic or biphasic with increasing step wise dosing is often sufficient. Synchronization is required for cardioversion. Table 4 summarizes classification of tachycardia.

TABLE 4

Classification of tachycardias

- Narrow–QRS-complex (SVT) tachycardias (QRS < 0.12 second), listed in order of frequency
  - Sinus tachycardia
  - Atrial fibrillation
  - Atrial flutter
  - AV nodal re-entry
  - Accessory pathway–mediated tachycardia
  - Atrial tachycardia
  - Multifocal atrial tachycardia (MAT)
  - Junctional tachycardia
- Wide–QRS-complex tachycardias (QRS ≥ 0.12 second)
  - Ventricular tachycardia (VT) and ventricular fibrillation (VF)
  - SVT with aberrant conduction
  - Pre-excitation tachycardias [Wolff-Parkinson-White (WPW) syndrome]
  - Ventricular paced rhythms

(*Source:* Neumar RW, Otto CS, Link MS, et al. American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. Part 8: Adult advanced cardiovascular life support. Circulation. 2010;122(Suppl. 3):S729-67)

Defibrillation or cardioversion in pacemaker or AICD patients: As described earlier in the chapter, defibrillation with pacemakers and AICDs in place pose little risk to the patient and the rescuer; however, some precautions are indicated. Placement of the pads or paddles should be in an anterior-posterior or anterior-lateral locations avoiding overlap with the device if at all possible. Delay in defibrillation should not occur due to an implantable device. Pacemaker spikes with unipolar pacing may confuse AED software and prevent VF from being recognized.[67] As soon as more advanced equipment and personnel are available the rhythm should be analyzed.

CESSATION OF RESUSCITATION

Termination of resuscitation is difficult for all providers of cardiac arrest patients but it can become especially difficult for emergency medical personnel in the prehospital setting. There are ethical, legal and cultural factors that need to be taken into consideration when deciding the need for termination of resuscitation. Initiation of resuscitation may conflict with a patient's desires or may not be in the best interest of the patient and in some instances resuscitation may not be the best use of limited resources. The public in general overestimates the probability of survival from cardiac arrest and even most physicians cannot accurately predict mortality rates of sudden cardiac arrest.

The 2010 AHA guidelines give some guidance for termination of resuscitation efforts in adults with out of hospital cardiac arrest. The AHA has developed the "BLS termination of resuscitation rule"; if all the following criteria are met then there is no indication for ambulance transport: (1) arrest was not witnessed by and EMS provider or first responder; (2) no ROSC after three complete rounds of CPR and AED analysis and (3) no AED shocks delivered. The "ALS termination of resuscitation rule" states if all the following criteria are met then termination of resuscitation before transport is indicated: (1) arrest not witnessed by anyone; (2) no bystander CPR provided; (3) no ROSC after complete ALS care in the field and (4) no shocks delivered. Implementation of these rules usually includes contacting the EMS medical control. EMS providers should be trained in sensitive communication with family members about outcomes. Collaboration with hospital EDs, medical coroner's office, online medical directors and the police are necessary. These rules have been validated for adult out of hospital cardiac arrest victims in multiple EMS settings across the United States, Canada and Europe.[67,94-96] Implementation of these rules reduces the rate of unnecessary hospital transports which can place providers and the public at risk from road traffic hazards, decrease unnecessary exposures from potential biohazards and decrease costs.

The decision to terminate resuscitative efforts is never an easy one. While guidelines are available, all providers including first responders, EMS personnel and physicians need to take into consideration many factors when deciding to terminate efforts. It is clear that resuscitation should not be started for

victims who have a valid do not resuscitate (DNR), newborn premature infants less than 23 weeks gestation and victims who present with obvious signs of death such as: rigor mortis, decapitation or dependent lavidity.

POST-RESUSCITATION CARE

Post-resuscitative care is a new section in the 2010 AHA guidelines for CPR. The goal is to emphasize an organized multidisciplinary program that focuses on optimizing neurologic, hemodynamic and metabolic function that may provide an increase in survival to hospital discharge.[67] Patients should be cared for in a multidisciplinary environment with angiography and interventional capabilities and a team capable of caring for patients with multiorgan dysfunction.

CARDIOPULMONARY SUPPORT

Once circulation is restored oxygen should be weaned down to lowest required to maintain oxygen greater than 94%, to avoid hyperoxia. The 2010 international consensus on CPR and ECC science with treatment recommendations found harmful effects of hyperoxia after ROSC.[67,97] An oxyhemoglobin of 100% can correspond to a PaO_2 anywhere between 80 and 500. With return of circulation a "post-arrest syndrome" often presents that requires proper inotropic support and monitoring. Standard vasopressor treatment is indicated to improve patient hemodynamics. Many patients will develop multisystem organ dysfunction and this must be anticipated and treated in a timely fashion.

CARDIAC INTERVENTIONS

The goal of interventions is to prevent further myocardial necrosis and left ventricular dysfunction leading to heart failure. Percutaneous coronary intervention (PCI) will provide patients with ST elevation myocardial infarction the most favorable outcomes, even in out of hospital cardiac arrest where overall survival remains low.[98-101] For those patients without obvious ST elevations an ischemic cardiac etiology may still be a reasonable assumption given the insensitivity or possible misleading electrocardiogram following cardiac arrest; more study is needed to determine if this subgroup of patients would benefit from intervention.[100] Patients should be transferred or taken from the scene to a facility that is capable of providing a comprehensive post-cardiac arrest treatment system of care that includes advanced cardiac interventions even if they have received thrombolytic therapy at a less capable institution. Early PCI following thrombolysis is associated with reduced recurrence of ischemia and reinfarction without increased risk of major hemorrhage.[102,103]

THERAPEUTIC HYPOTHERMIA

Predicting neurologic outcomes post-cardiac arrest is challenging. Therapeutically induced mild hypothermia after successful initial resuscitation has been studied and found to improve neurologic outcome in comatose cardiac arrest survivors and to decrease overall mortality.[104-107] Methods of inducing hypothermia to 33°C for 24 hours include: external ice, blankets through which cold water continuously circulates, cold IV saline and endovascular coils.[108,109] Interventions to rapidly reduce body temperature during CPR have been shown to improve defibrillation success and ROSC in animal models; however, limited clinical experience has been favorable.[110-113] Improving patients' final functional outcome also involves early recognition and treatment of treatable neurologic disorders such as seizures. Seizures may be difficult to diagnose in the hypothermia induced patient due to neuromuscular blockade use that is designed to prevent shivering. It is therefore important to have electroencephalographic monitoring during this coma induced state. To date there have not been any diagnostic evaluations or tools found that consistently predict neurologic outcome in post-cardiac arrest patients. There is limited evidence to guide clinical decisions and, therefore, best clinical judgment with family discussion should be used to make decisions regarding withdraw of life support.

SUMMARY

Cardiopulmonary resuscitation from sudden cardiac arrest is challenging. Since 1960, our impact on patient survival from out of hospital cardiac arrest has changed very little. What we do know is that high quality, minimally interrupted CPR that is started immediately upon recognition is extremely important for improving patient survival. Rate and depth of compressions is the key to high quality CPR. Providers who do not perform CPR often should have frequent retraining. The AHA guidelines for 2010 have been simplified to help improve compliance and to emphasize compressions over other interventions in the field to help improve the number of patients who receives bystander CPR; this includes compression only CPR for those who may be unwilling or unable to perform conventional CPR. Many fears that potential rescuers have may be alleviated with education and debriefing which may improve first responder or bystander initiation of resuscitation. Continuous evaluations and re-education should be implemented in all levels from the prehospital setting to hospital resuscitation teams, to improve resuscitation performance with an emphasis on CPR quality and team work. Continued research is required in all areas of resuscitation from prehospital to hospital discharge to improve survival and neurologic outcomes.

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Chapter 43

Risk Stratification for Sudden Cardiac Death

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Chapter Outline

- Healthy Athletes
- Brugada Syndrome
- Long QT Interval Syndrome
- Early Repolarization
- Short QT Syndrome
- Catecholamine Polymorphic Ventricular Tachycardia
- Wolff-Parkinson-White Syndrome
- Arrhythmogenic Right Ventricular Cardiomyopathy
- Hypertrophic Cardiomyopathy
- Marfan Syndrome
- Noncompaction
- Congenital Heart Disease
- Non-ischemic Cardiomyopathy
- Coronary Artery Disease

INTRODUCTION

Sudden death is overwhelmingly a cardiac etiology [sudden cardiac death (SCD)] defined as unexpected death occurring within one hour of symptoms.[1] The heart rhythm causing SCD is most frequently ventricular tachycardia (VT) or ventricular fibrillation (VF). Assessing risk is not trying to predict the future, but to plan for the possibility of this disaster with cost effective strategies; the most comprehensive discussion of individual assessment was published almost a decade ago and yet is still largely valid.[1] As Myerberg and Castellanos[2] have so aptly depicted this problem, the groups of patients where we think we know what to do to prevent SCD account for a small fraction of the total number; hence our need to continue looking to improve risk assessment. Our approach is to aid the clinician with the most recent scientifically based risk assessment to guide clinical judgment. The most frustrating aspects of this effort are that the first symptom of many entities may be SCD and that after a decade of reports little better risk assessment is available.

Many noninvasive as well as invasive procedures are available to help the clinician to evaluate the risk of SCD. A partial list includes signal averaged electrocardiogram (ECG), heart rate variability and turbulance, and T-wave alternans.[3] Unfortunately while these assessments have excellent basic background in theory, they do not pan out in studies of even the most common ischemic heart disease with congestive heart failure. However, we find studies revealing important simple clinical ways to help patients in specific categories. In general most SCDs involve patients with previous cardiac arrest or syncope or a family history of SCD.

HEALTHY ATHLETES

We start with those most healthy athletes which would apriori be the least likely to succumb to SCD. Surprisingly there was a 2.5-fold increase in SCD in an Italian athletic population, compared to non-athletes.[4] Some high profile deaths in professional sports have lead international groups to make recommendations which disagree.[5] The Bethesda conference recommends careful physical and history to include family occurrence of syncope and SCD. Symptoms of palpitations, syncope or seizure, especially during exercise, require further work up to identify the cause. Parenthetically, simple orthostatic dizziness due to vasodilatation is very common in elite athletes and needs to be separated from other symptoms. However, the European Society of Cardiology Consensus recommends routine ECGs, based on a reduction in SCD in athletes in Italy, but which is now reduced to the frequency observed in most other countries including the US.[6,7] However, this reduction was an uncontrolled observation.[8] Clearly standard evaluations based on good scientific criteria must be developed to protect athletes, without being overly invasive. Here we hope to give evidence based data that can inform all parties in this endeavor including the patient (athlete) and family.

Athletes may by virtue of their training actually develop a unique set of cardiac findings, different from untrained persons of the same age, which need to be appreciated as normal for sport. These include asymptomatic slower heart rates and second degree AV block at rest, but normal rate and rhythm with exercise.[9] Although we are only beginning to understand that ECG and echocardiographgic (ECHO) criteria may have to be altered in athletes such criteria change may depend on race.[10] A recent controlled study involving ECG screening in 510 athletes using ECHO as the standard increased specificity of screening from 5 to 10 of 11 documented ECHO abnormalities, but at the expense of increasing false positives from 5.5% to 16.9%. This study used standard ECG criteria published by European society of cardiology.[11] As expected such screening will significantly add to the cost of case finding.[12] One of six athletes would be expected to have an abnormal screening ECG,

but only about 1% of all would have a cardiac abnormality capable of causing SCD. Annual cost estimates for ECG screening and follow-up exceeded $126 million. False-positive ECGs accounted for 98.8% of follow-up costs. Similar evaluation schemes have been used for soccer with similar outcomes.[13] While 4.8% soccer players had potentially abnormal ECGs, only 1% had clearly abnormal evaluations preventing participation in the 2006 world cup.

Recently an international group recommended an entity specific ECG screening approach that may deal with the risk-cost ratio.[14] They made recommended limits on the ECG changes attributable to training in athletes, including incomplete right bundle branch block (RBBB), differentiating it from Brugada and early repolarization (pre-SCD findings, see below), eliminating incomplete RBBB as a risk factor. On the contrary ST sement depression, right atrial disease, ventricular hypertrophy, bundle branch block, QRS greater than 110 millisecond, QTc greater than 500 and lesser than 380 millisecond should prompt a further work up since these findings are not physiological in athletes. Thus the ECG will identify inherited electrical as well as structural heart diseases, which will apply to screening anyone with a family history of SCD including athletes.

BRUGADA SYNDROME

Electrocardiogram (ECG) screening has the potential for identification of electrical disorders which could lead to SCD, although there is not much evidence that athletes would be affected by these entities. Brugada syndrome is one such disorder;[15] it is an autosomal dominantly inherited disease producing a high-risk-associated ECG with a coved appearance of ST segment elevation (2 mm) in the right precordial leads; this pattern has (4.7-fold increase risk) predictive accuracy for SCD in meta analysis of 947 patients (Veltmann 09). However, in a patient with this ECG finding, syncope may predict SCD with a hazard ratio (HR) = 2.5–6.4 for SCD.[16] Males are 3.5 times at more risk than females and there is clustering of patients with the syndrome from South-east Asia. No other factors are reproducibly predictive including positive family history or abnormal EPS.[17]

LONG QT INTERVAL SYNDROME

Long QT interval syndrome has been well reviewed in general population[18] as well as in athletes. New data collectively suggest that the magnitude of the QT prolongation is highly predictive.[16] The younger age, the shorter the QT of risk, so in the first decade risk occurs at QTc > 500: HR = 2.12, the second decade QTc > 530: HR = 2.3. In adults the diagnosis is made with a QTc > 480, but the risk in adults is incrementally greater the larger the QTc: QTc 500–549: HR = 3.3 while QTc > 550: HR = 6.4. In children males are at higher risk, while after puberty females are at higher risk.[16] Genotyping, to confirm ECG types, may be abnormal in 70% of cases; some subtypes of LQT1, LQT2 and LQT3 may have more risk than others.[16] LQT1 should not compete particularly in swimming. Similar to Brugada, the addition of syncope to the QT increases risk of SCD to 2.7–18 times those without syncope. A recent report suggests that a simple standing QT measurement will confirm a diagnosis of long QT especially in LQT2 patients.[19] Therapy with ICD is indicated if symptoms cannot be controlled with beta blocker therapy and or cervicothoracic sympathectomy. ICD may be appropriate if there is a strong family history of SCD or inability to take beta blockers.[20]

EARLY REPOLARIZATION

Early repolarization on the ECG has been implicated in the etiology of SCD although the mechanism is unclear.[21] However, the occurrence of this finding in normal athletes with an apparently good prognosis make it a rather difficult risk assessment tool except perhaps when it is localized in the inferior leads in middle aged subjects.[22] Recently it is suggested that early repolarization localized to the lateral ECG leads is benign associated with athletic training, while localization to inferior leads is intermediate and localization to inferior, lateral and right precordial ECG is more high-risk for SCD.[23]

SHORT QT SYNDROME

Short QT syndrome[16] known only since 2000 has little patient data from which to guide assessment. Certainly a patient with QTc less than 350 and resuscitated SCD should have a defibrillator, but even syncope is not predictive of SCD unless in the presence of a markedly positive family history.

CATECHOLAMINE POLYMORPHIC VENTRICULAR TACHYCARDIA

Catecholamine polymorphic VT[16] is a well studied and strikingly reproducible syndrome of exercise facilitated VT with multiple morphologies associated with mutations in ryanodine (autosomal dominant) or calsequestrin (autosomal recessive). Exercise induced bidirectional ventricular ectopy and bidirectional VT makes the diagnosis and therapy with beta adrenergic blockers is indicated with ICD implantation if VT cannot be suppressed. Left upper thoracic chain sympathectomy may prevent ICD shocks. Genetic testing showing mutations in a family member are at risk of syncope and SCD, which may be prevented by beta blockers, has been shown to significantly reduce them. Flecainide may also be protective of VT. Family history of the syndrome does not predict SCD.

WOLFF-PARKINSON-WHITE SYNDROME

Pre-excitation of the ventricle by non-atrioventricular nodal structures when producing symptoms is called Wolff-Parkinson-White (WPW) syndrome. WPW is a well known entity found in 1% of individuals recently reviewed. It is clear that patients with rapid tachycardia symptoms need therapeutic ablation. However, the recommendation for ablation in order for asymptomatic persons with pre-excitation alone to participate in competitive athletics seems inappropriately invasive when the risk of pre-excitation alone is unclear. Prospective studies have not identified the presence of asymptomatic pre-excitation as a risk [24,25], although in children multiple pathways and rapidly conducting pathways (causing deterioration of supraventricular tachycardia to VT and VF) may suggest danger on follow-up.[26] Even electrophysiological study (EPS) identifying the functional

characteristics of rapidly conducting pathways do not predict the occurrence of SCD due to rarity of SCD (0.1%) in asymptomatic pre-excitation. Therefore, asymptomatic pre-excitation does not warrant EPS and ablation. Expert opinions on certain sports, such as sky-diving or occupations such as airline piloting suggest EPS and ablation for rapidly conducting pathways.

Electrical syndromes, however, do not account for most of sudden deaths in young people. In Italy, the top three causes of SCD in athletes were arrhythmogenic right ventricular cardiomyopathy (ARVC) (22%), coronary atherosclerosis (18%) and anomalous origin of a coronary artery (12%). In the US predominant structural cardiac abnormalities identified in the military population were coronary artery abnormalities (61%), myocarditis (20%) and hypertrophic cardiomyopathy (HCM) (13%). An anomalous coronary artery accounted for one-third (21 of 64 recruits) of the cases in this cohort, and, in each, the left coronary artery arose from the right sinus of Valsalva, coursing between the pulmonary artery and the aorta. So the populations are different. Recommendations include attention to young persons who complain of angina.

ARRHYTHMOGENIC RIGHT VENTRICULAR CARDIOMYOPATHY

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is an autosomal dominantly inherited disease involving molecular regulation of basic cell to cell adhesion, and production of fat, fibrous tissue and apoptosis, which results in VT and VF.[27] A specific list including major and minor criteria has been published including fibrofatty replacement of the RV, ECG depolarization (epsilon wave)/repolarization changes (with T-wave inversions in the right precordium), VT with a LBBBM and atrial fibrillation, and family history.[28,29] Of interest is the fact that the disease can be quiescent for years in youth but progresses to symptomatic disease with time. The highest risk occurs in patients having been resuscitated from SCD, with syncope at a young age or extreme involvement of the RV and LV. The primary prevention management of patients and their families is complex because of variable penetrance.[30] It was hoped that genetic testing would be an effective way to stratify risk. [31] Although eight causative genes have been identified, up to 50% of cases do not have genetic markers. Thus good clinical judgment is necessary since risk factors may be hidden, but progressive.[32,33] Since competitive sports may provoke VT/VF, exercise must be curtailed and beta blockers and sotalol may effectively prevent VT.

HYPERTROPHIC CARDIOMYOPATHY

Hypertrophic cardiomyopathy (HCM) is the most common cause of SCD in people in the US below the age of 25 years, particularly in athletes, with incidence of about 1%.[34] Clearly interdiction of competitive sports for such a patient would make the best sense. However, even though the arrhythmogenic substrate of myocardial disarray is clear, our ability to predict SCD is flawed due to apparent dormancy despite the presence of substrate. After years of attempts to prevent SCD with drugs although improving symptoms, it is concluded that this approach has never proved effective. Clearly a survivor of SCD can be treated with an ICD, but indications for primary prevention are not clear, particularly since 60% of ICD treated patient do not have VT/VF in 5 years after resuscitation from SCD.[29,35] Risk factors commonly cited have not been well proven until recently, particularly because the evidence was taken from "appropriate" ICD shocks, which are not the same as SCD (a VT which is shocked is only seconds long and may (had no ICD intervention taken place) have only been non-sustained and not cause syncope or SCD.[36] Syncope has clearly been shown on follow-up of untreated patients to predict SCD.[37] Combinations of studies taken together have recently suggested that the aforementioned risk stratification data may be true[38] including VT nonsustained: HR = 2.2–3.6 (95% confidence); syncope: HR = 0.97–4.4; extreme LVH (wall thickness > 3 cm): HR = 1.8–4.4; hypotension on exercise HR = 0.6–2.0 and family history of SCD = 1.2–1.4. Also combinations of risk factors produced a higher HR than individual ones. Aggravating factors including atrial fibrillation, ischemia, genotype and exercise do not show risk, but LVOT gradient may increase risk.

MARFAN SYNDROME

Marfan syndrome is a connective tissue disorder caused by mutations in genes encoding supporting scaffold for elastin. Its prevalence is between 1 in 5,000 or 10,000. It causes SCD, produced by aortic dissection, rupture and pericardial tamponade.[39] Risk stratification for this outcome is based on ECHO measurement of aortic root greater than 50–55 mm.[40] SCD without dissection are reported and ventricular arrhythmias are thought to be the cause;[41] mitral valve prolapse is a common component of Marfan's syndome but LV dilatation is the associated finding suggesting risk in Marfan's patients with ventricular ectopy and VT. Unfortunately LV dilatation is not commonly found in sporadic cases of SCD with only MVP studied at autopsy.[42] However, SD can occur without cardiac cause due to the elongated odontoid causing pressure on the cerebellum and medulla owing to alantoaxial hypermobility.[43]

NONCOMPACTION

Noncompaction of the left ventricle is a potentially arrhythmogenic condition diagnosable with ECHO which is presently not well understood. It is a cause of SCD which may be appropriately treated with ICD but follow-up shocks occur as frequently in primary as secondary prevention cases,[44] EPS does not predict ICD therapy for VT/VF. It is not clear which patients in absence of resuscitated VT/VF would benefit from ICD implantation.[20] There is simply no information to risk stratify this group at this time, since many patients with the disorder have a benign course.[45]

CONGENITAL HEART DISEASE

Congenital heart disease (CHD) afflicts approximately 75 of 1,000 live births. Significant advances in the treatment of CHD over past 50 years have allowed the majority of afflicted children to reach adulthood. The number of adults with CHD now exceeds that of children and is expected to increase with further advances.[46] SCD is the most common cause of death in these

patients, occurring usually by the third or forth decade of life. The incidence, estimated at 0.09% per year, represents up to a 100-fold increased risk compared to age matched controls.[47] SCD is especially likely in patients with repaired cyanotic and left heart obstructive lesions. In a recent report of over 8,000 patients with CHD, the majority of SCD occurred out of hospital (62%), at rest (only 7% SCD occurred during exercise), and demonstrated seasonal variation with the nadir occurring in summer (22%) and peak in the fall (33%).[48] Predictors of mortality in patients with CHD include New York Heart Association (NYHA) functional class greater than one, cyanosis, age (postsurgical repair) and complexity of malformations.[49,50] There are virtually no prospective or randomized clinical trials of risk stratification. Patients with CHD presenting with cardiac arrest, sustained symptomatic VT or syncope and have significant systemic ventricular dysfunction are stratified as high-risk and ICD therapy is generally recommended.[20] Three special groups are associated with the highest risk of SCD including patients treated with Mustard/Senning procedures, Fontan procedures and repaired tetralogy of Fallot (TOF).[51] In the latter incidence of SCD is approximately 0.15% per year, risk factors include QRS greater than 180 millisecond , older age at repair, transannular right ventricular outflow tract patch, left ventricular dysfunction, frequent ectopy and inducible sustained VT, with poor specificity. Although reduced left ventricular (EF < 35%) function is the strongest risk factor for SCD in ischemic heart disease (see below), there is debate as to whether such findings should be extended to patients with CHD.[52,53] Systemic ventricular dysfunction (such as in corrected transposition) has been demonstrated in numerous observational studies and registries to identify CHD patients at risk for SCD. Studies evaluating the efficacy of ICD therapy in CHD patients have usually been observational and retrospective.[54,55] Beyond secondary prevention scenarios risk stratification in the CHD population must be done on an individual basis combining available diagnostic data with sound clinical judgment and weighing the risk and benefits of a particular intervention.[56]

NON-ISCHEMIC CARDIOMYOPATHY

Non-ischemic cardiomyopathy (NICM) is the primary etiology in 10–15% of SCDs and accounts for the second largest number of SCDs from cardiac causes behind coronary artery disease (CAD).[57] NICM is characterized by biventricular dilatation and impaired ventricular contractility without CAD. Mortality rates in this patient population range from 12–13% at three years to 20% at five years.[29,58,59] Like ischemic heart disease, numerous diagnostic techniques exist to risk stratify without careful data to identify high-risk patients would benefit from existing interventions (ICDs); in fact the majority of the major primary prevention trials enrolling patients with NICM failed to demonstrate definitive benefit to ICD therapy.[59] The primary risk stratifying approach utilized was a combination of quantitative left ventricular function assessment and functional status based on NYHA functional class. Cardiomyopathy Trial (CAT), Amiodarone versus Implantable Cardioverter-defibrillator Study (AMIOVERT), Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) Trial and SCD in Heart Failure Trials (SCD-HEFT) failed to demonstrate significant mortality benefit of ICDs in patients with NICM.[59] The Comparison of Medical, Therapy, Pacing and Defibrillation in Heart Failure (COMPANION) did demonstrate benefit (significantly lower risk of death from any cause compared to medical therapy HR=0.5 P=0.015 but no significant benefit in the primary end point of the study which was a composite of death from any cause or hospitalization for any cause) of ICDs in patients with NICM treated with biventricular pacing.[60] However, the Cardiac resynchronization-Heart Failure (Care-HF) trial which enrolled 813 patients, a majority with NICM, EF < 35%, NYHA class III to IV, QRS > 149 or QRS 120–149 with evidence of dyssynchrony did demonstrate a significant benefit of CRT alone in decreasing mortality (36% $p < 0.003$) to the same extent as in the CRT-D arm of the COMPANION trial (36% $p < 0.003$).[61] Interestingly in Care-HF the presence of NICM predicted a better outcome. However, 36% of the deaths in the pacing only arm of the COMPANION trial were attributed to SCD similar to the 35% in the CRT arm CARE-HF trial; these deaths might have been prevented with an ICD.[62] A meta-analysis of the pooled data from the ICD trials (1854 patients) demonstrated 31% reduction in all cause mortality with ICD therapy compared to medical therapy.[63] Thus current guidelines recommend placement of ICDs in patients with NICM, EF less than 35% and NYHA Class II–III symptoms.[20] A number of noninvasive diagnostic methods for risk stratifying patients with NICM have recently been reviewed[64,65] with the exception of syncope, EF and NYHA functional class, no significant data exists for other methods of identifying patients that would benefit from available therapies.[65,66]

CORONARY ARTERY DISEASE

Coronary artery disease (CAD) accounts for (or is the underlying condition in) 65–80% of patients presenting with SCD. Depending on age group 13–50% of CAD deaths are SCD with coronary occlusion the most common.[57] In general the incidence of SCD in a population depends on the incidence of CAD.[57] In recent years, the steady decrease in mortality due to CAD has correlated with the decrease in SCD, although the prevalence of CAD has increased.[67] Medical therapy directed at treating CAD, in particular beta blockers and renin angiotensin system modifiers (ACE inhibitors ARBs, Aldosterone antagonist) have been demonstrated to decrease the incidence of SCD.[68] Traditional risk factors of CAD (HTN, DM, smoking, hypercholesterolemia) identify patients at risk for ischemic heart disease and hence SCD (with obesity, DM and smoking showing an increased proportion of deaths that are sudden).[29] However, these factors do not discriminate among CAD patients, those at high-risk.[69]

Risk stratification in patients immediately postmyocardial infarction is particularly difficult, especially in patients with impaired ventricular function.[29] These patients may have a particularly high-risk of SCD despite optimal medical therapy. To date no risk stratification strategy exists that utilizes invasive or noninvasive diagnostic testing that can identify patients that would benefit from advanced therapies (ICDs) within the first 40 days of infarction.[70] Both the Defibrillator in Acute

Myocardial Infarction Trial (DINAMIT) and the Immediate Risk-Stratification Improves Survival (IRIS) Trial failed to demonstrated any overall mortality benefit with ICD use.[70] Similarly in a substudy of the MADIT 2 Trial, no survival benefit was found in this population if the time interval from index infarct was within 18 months.[71] In the home use of external automated defibrillators for SCD trial (HAT) no mortality benefit was noted over conventional resuscitation methods in high-risk post-MI patients.[72] Current ICD guidelines reflect these results.[20]

The previously mentioned factors stratifying patients at high risk with NICM also identify CAD patients. So, NYHA functional class higher than 2, EF less than 35 and syncope identify patients who benefit from ICDs.[20] Unlike NICM, there may be utility of invasive electrophysiologic testing in patients with CAD. In the MUSTT and MADIT clinical trials sustained VT/VF during EPS, in addition to LV dysfunction (EF $\leq$ 40%) and presence of NSVT on ambulatory testing, identified patients that benefited from prophylactic ICD therapy.[20] In addition, invasive EP testing is recommended in patients with remote history of myocardial infarction and symptoms suggestive of VT, including palpitations syncope and presyncope.[29] If sustained VT/VF is induced then ICD therapy is usually recommended.[20] Although a positive EPS identifies patients with CAD at high-risk of SCD who benefit from advanced therapies a negative study in patients with severe LV dysfunction less than 30% does not necessarily indicate a good prognosis.[29,73]

Although LV function can identify patients at high-risk of sudden death it does not discriminate well between those at high-risk and those at low-risk of sudden death.[64] The risk of sudden death or cardiac arrest increased by 21% for every 5% decrease in left ventricular function. However, this is a U shaped relationship, in that as EF decreases deaths due to pump failure increase as arrhythmic deaths decrease.[64,74] Recently risk stratification test studied in the Cardiac Arrhythmias and Risk Stratification after Acute Myocardial Infarction (CARISMA) study and the Alternans Before Cardioverter Defibrillator (ABCD) trial were compared to a "coin toss" high-risk (heads) and low-risk (tails).[75] Compared to LVEF (NPV 94% PPV 9% HR 1.3) in CARISMA study population the coin toss performed only mildly worst (NPV 92% PPV 8%).[75,76] It was noted that the coin toss (HR 1 in both populations) has no role in risk stratification as net correct reclassification would always be zero. This comparison demonstrates the limitation of individual risk stratification test for SCD to adequately stratify patients. An alternative approach is a multi-tiered risk stratification strategy similar to that utilized by the SHAPE task force for atherosclerosis.[77,78] To date there have been no prospective studies utilizing such an approach.

SUMMARY

We have reviewed the available data on risk stratification in major entities encountered by clinicians. Generally good clinical judgment can be enhanced by the published knowledge; in addition to a history of SCD, symptoms of syncope or arrhythmogenic dizziness predict likely risk of SCD in most disorders. A family history of SCD may also inform such an evaluation. An ECG abnormality coupled with the above may focus additional evaluation such as exercise testing in appropriate patients. Documentation of structural heart disease by ECHO confirms risk in various population groups. Normal ECG and ECHO may exclude risk in many groups. Further research is needed to clarify the specific risk in more rare diseases. Unfortunately based on our experience with CAD, it is not likely we will find easy risk stratifiers in many disease states.

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Chapter 44

Cardiocerebral Resuscitation for Primary Cardiac Arrest

Jooby John, Gordon A Ewy

Chapter Outline

- Etiology and Pathophysiology of Cardiac Arrest
  - — Primary Cardiac Arrest in Children and Adolescents
  - — Pathophysiology of Primary Cardiac Arrest
  - — Coronary Perfusion Pressures during Resuscitation Efforts
  - — Assisted Ventilation in Primary Cardiac Arrest
  - — Not Following Guidelines for Primary Cardiac Arrest
  - — The Public Has Made Up Its Mind
  - — Increasing the Prevalence of Bystander Resuscitation Efforts
  - — Increasing the Ability to Promptly Identify Primary Cardiac Arrest
  - — The Three Phases of Ventricular Fibrillation (VF)
  - — Cardiocerebral Resuscitation: Prehospital Component
- Drug Therapy in Cardiac Resuscitation
- Cardiac Resuscitation Centers
  - — Therapeutic Mild Hypothermia
  - — Myocardial Ischemia Causing Cardiac Arrest
- Ending Resuscitative Efforts

INTRODUCTION

Out-of hospital cardiac arrest (OHCA) claims hundreds of thousands of lives each year.[1,2] Despite this enormous public health problem, and the promulgation of standards and guidelines, with also numerous updates of guidelines (Fig. 1), the aggregate survival rate of OHCA of 7.6% has not significantly changed in almost three decades.[3] Likewise there is little data to indicate that guidelines have improved in-hospital survival. A large medicare database of over 400,000 elderly patients revealed that even in-hospital survival after cardiopulmonary resuscitation (CPR) has been unchanged for the period from 1992 to 2005.[4]



FIGURE 1: Reported survival rates of out-of-hospital cardiac arrests 7.6% unchanged over the past 30 years

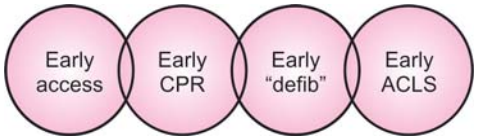


FIGURE 2: Cardiopulmonary resuscitation "chain of survival" (*Source:* Modified from Cummings, et al. Circulation. 1991;83:1832)

The major limitation of the chain of survival (Fig. 2) was the necessity for "early" initiation of each link.[5] However, in retrospect its failure to recognize that gasping was common during the first few minutes of primary cardiac arrest often prevented "early" recognition, its insistence on mouth-to-mouth ventilation as the initial intervention precluded most bystanders from providing "early" CPR, and many factors, including traffic congestion in larger cities, precluded "early" defibrillation. In addition, the prescription of endotracheal intubation as the initial step in advanced cardiac lift support (ACLS), and the use of automated external defibrillators for the proscribed "stacked" shocks further delayed or interrupted essential chest compressions; all contributed to poor survival rates.[6]

Survival was especially poor in large metropolitan cities. A 2005 report revealed a rate of neurologically intact survival from OHCA of 1.4% in Los Angeles, similar to survival rates previously reported from Chicago, New York City and Detroit.[7,8] Survival is better in areas where the incidence of bystander CPR is high and the emergency medical system (EMS) response times are short.[9] Unfortunately these "links" are rare, so new approaches were needed.

In this chapter we have discussed recent insights into the physiology of cardiac arrest and resuscitation and present a new approach to the management of cardiac arrest developed by our University of Arizona Sarver Heart Center Resuscitation Research Group, called Cardiocerebral Resuscitation (CCR) (Fig. 3). The CCR has been shown to markedly improve survival of patients with OHCA with survival rates of 38% or better in the subset of patients who have greatest chance of survival; those with witnessed arrest and a shockable rhythm (Fig. 4).[10-12]

ETIOLOGY AND PATHOPHYSIOLOGY OF CARDIAC ARREST

Cardiac arrest is either primary or secondary. The emphasis of this chapter is on primary cardiac arrest. The CCR is not recommended for arrests secondary to hypoxia from drowning or respiratory failure. However, it much be emphasized that not all cardiac arrest in individuals under the age of 18 years are respiratory.

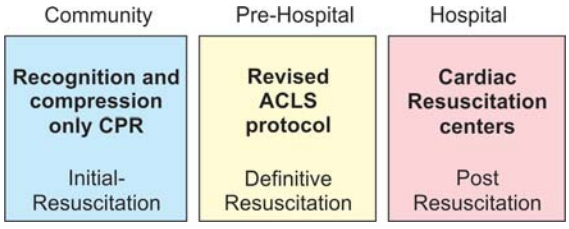


FIGURE 3: Cardiocerebral resuscitation "The New CPR" for primary cardiac arrest

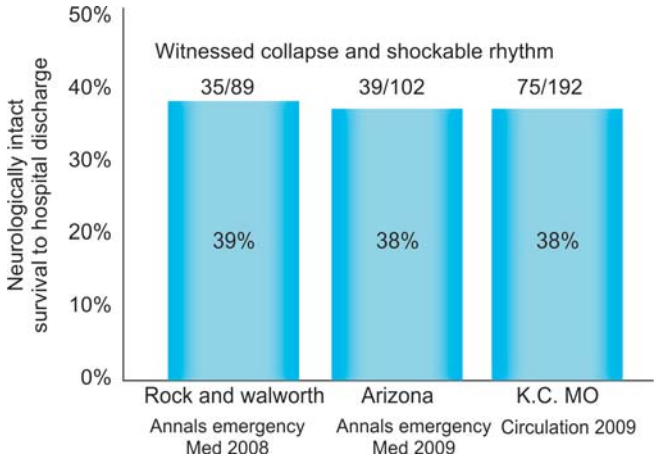


FIGURE 4: Cardiocerebral resuscitation for OHCA. Witnessed collapse and shockable rhythm

PRIMARY CARDIAC ARREST IN CHILDREN AND ADOLESCENTS

Respiratory arrests are the reason for the majority of cardiac arrests in children, and should be treated according to guidelines.[13] However, primary cardiac arrest also occurs in children and adolescents in the presence of diverse pathologies such as the prolonged QT syndrome, the cardiomyopathy of arrhythmogenic right ventricular dysplasia (ARVD), Brugada syndrome, anomalous coronary arteries or commotio cordis [where a blow to the precordium at the peak of the electrocardiographic T wave can result in ventricular fibrillation (VF)]. Accordingly, chest compression only (CCO) CPR is the best approach to bystander CPR in children and adolescence when the cardiac arrest is primary.

Primary cardiac arrest is recognized by an unexpected, witnessed (seen or heard) collapse in an individual who is not responsive. As emphasized in this chapter, many individuals with primary cardiac arrest continue to have spontaneous ventilation, and checking for the presence or absence of an arterial pulse by bystanders is no longer recommended.[13]

PATHOPHYSIOLOGY OF PRIMARY CARDIAC ARREST

One minute into persistent VF or pulseless VT, coronary blood flow comes to a standstill, and minutes later carotid blood flow (and therefore cerebral perfusion) becomes nil.[14] The ensuing equalization of systemic pressures in the arterial and venous beds takes place, resulting in the so-called "mean circulatory filling pressure" described by Guyton.[15] This shift in blood volume from higher pressure arterial system to the low pressure venous system results in "acute distension of the right ventricle" originally described by Professor Stig Steen in open chest swine.[16] This phenomenon is perhaps best illustrated by closed chest imaging techniques (Fig. 5).[17,18] The resultant pericardial restraint produces a constrictive pericardial condition, and even with defibrillation poor contractility occurs due to the lack of stretch of the myocardial fibers.[19] This sequence helps to explain why chest compressions (to decompress the heart to relieve pericardial

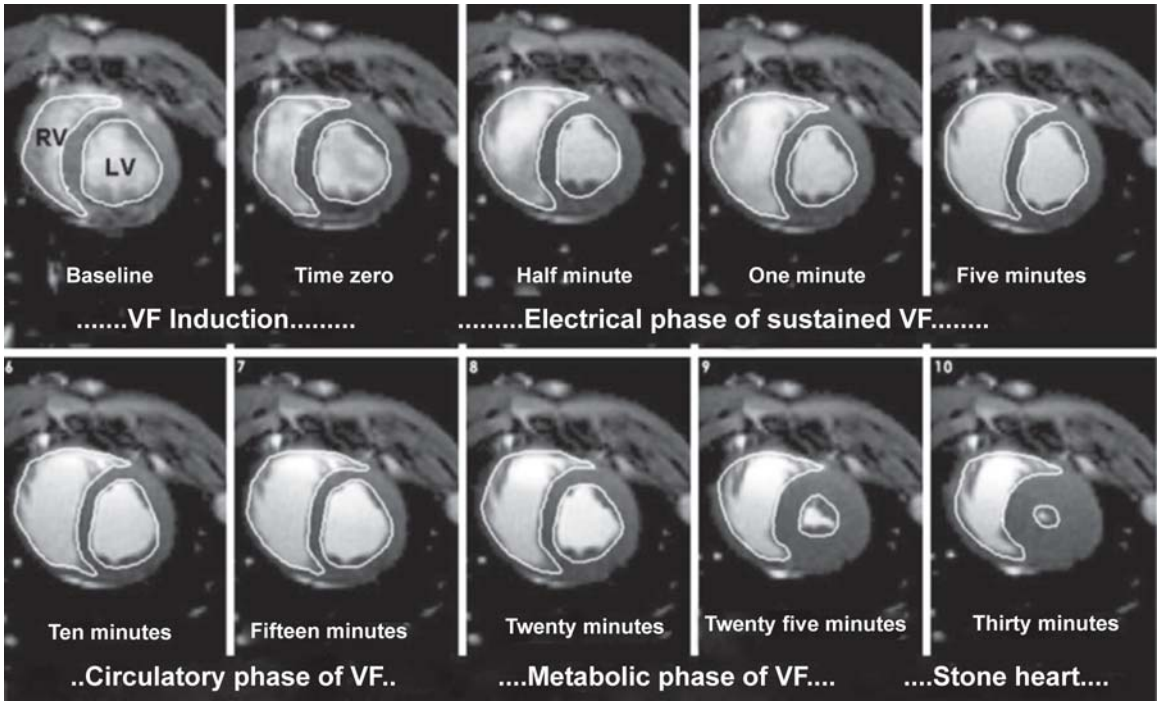


FIGURE 5: Development of the "Stone Heart" after prolonged VF (*Source:* Sorrell VL, Altbach MI, Kern KB, et al. Images in cardiovascular medicine. Continuous cardiac magnetic resonance imaging during untreated ventricular fibrillation. Circulation. 2005;111:e294)

restraint) are often necessary for successful generations of an arterial pressure following defibrillation.

Untreated VF results in a progressive decrease in left ventricular volumes until a state of extreme myocardial contraction develops (referred to as stone heart). This sequence has also been demonstrated by magnetic resonance imaging (MRI) in closed chest animal models of VF[17] (Fig. 5).

CORONARY PERFUSION PRESSURES DURING RESUSCITATION EFFORTS

Several observations lead the University of Arizona Sarver Heart Center Resuscitation Research Group almost two decades ago to advocate of CCO CPR. One of the most important was the observation during our early (1980s) experimental studies that survival from prolonged VF arrest was related to the coronary perfusion pressure (CPP) generated by chest compressions (Fig. 6).[20] The CPP is defined as the difference between the aortic and the right atrial pressures during the release phase "diastole" of closed chest cardiac compression (Fig. 7).[21] The CPP is the pressure gradient that is responsible for antegrade coronary flow. Similar to normal sinus rhythm where most blood flow through the coronary arteries occurs in diastole, during chest compressions for cardiac arrest, most coronary blood flow occurs during "compression diastole" or the release phase of chest compressions. During life the pressures in the myocardium, the ventricle and the aorta are similar during ventricular systole and therefore there is very little coronary blood flow. But during diastole, the aortic valve closes, the pressure is higher in the aorta than in the myocardium, and thus most of the coronary blood flow to the myocardium occurs during diastole. During chest compression for cardiac arrest, the pressure in the heart and aorta are similar. But during the release phase the aortic valve closes[22] and the pressure in the aorta is higher than the right atrium, so antegrade coronary blood flow occurs during the release phase of chest compressions. During cardiac arrest and resuscitation efforts, the amount of coronary flow is predominantly related to the amount of arterial pressure generated by chest compressions. We found that one had to generate a minimal CPP of 15 mm Hg for return of spontaneous circulation (ROSC) in our experimental studies.[20] Of interest is the fact that this was the same value found by Norman Paradis in his measurements during resuscitation efforts in man (Fig. 6).[21] Of note in their report there were no survivors![21]

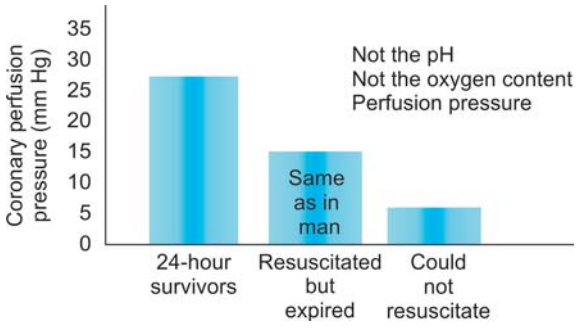


FIGURE 6: Survival from prolonged VF arrest in experimental studies was related to pressure generated by chest compressions. (*Source:* Kern, Ewy, Voorhees, Babbs, Tacker. Resuscitation. 1988;16:241-50; Paradis, et al. JAMA .1990;263:1106)

The CPP is built up slowly with the initiation of chest compressions during resuscitation efforts for cardiac arrest, such that the first few compressions often do not generate a significant CPP (Fig. 8). The CPP is a surrogate for myocardial cellular perfusion and has been shown to be a determinant of survival in prolonged VF.[20,23-25] Obviously to generate an adequate

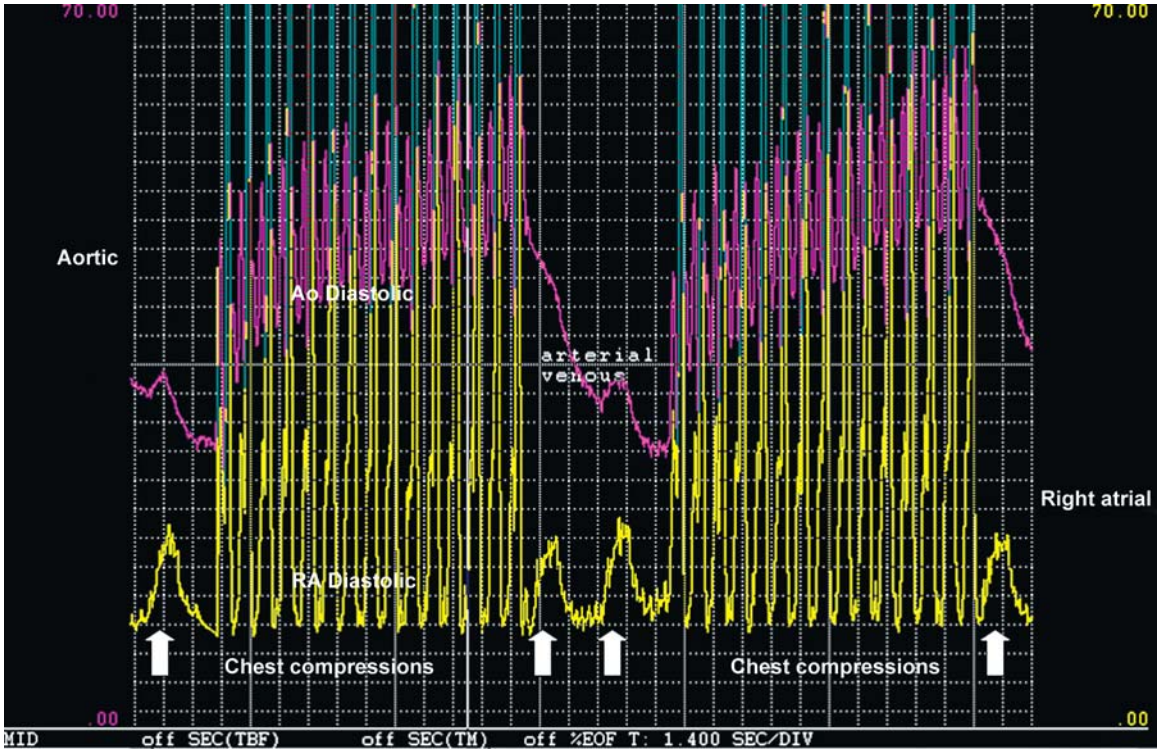


FIGURE 7: The difference between the aortic and the right atrial pressures during the released phase "diastole" of closed chest cardiac compression is termed as coronary perfusion pressure

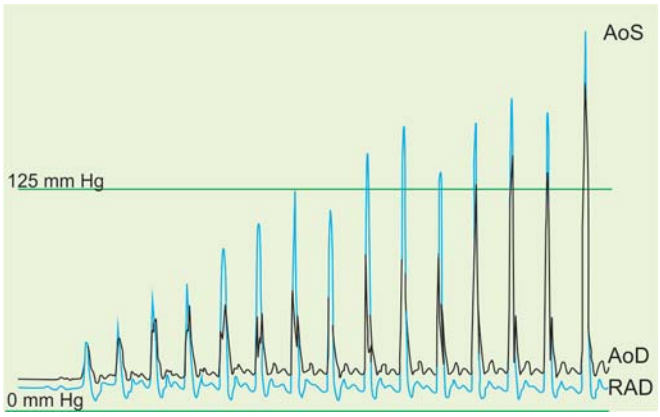


FIGURE 8: Simultaneous recording of aortic and right atrial pressures during first 15 external chest compressions in swine in cardiac arrest due to ventricular fibrillation. Note how initial compressions do not generate much of a pressure (*Source:* Modified from Ewy GA. Circulation. 2005;111:2134-42)

coronary perfusion pressure, one is usually generating an adequate cerebral perfusion pressure as the CPP produced during resuscitation efforts for cardiac arrest relates to neurologically intact survival as well. However, all who survive for 24 hours are not neurologically intact.[26]

When chest compressions are interrupted for even 4 seconds, the CPP decays and with it myocardial perfusion. The coronary perfusion gradient has to be re-established once again when compressions are restarted (Fig. 7). This is a key element in understanding why continuous chest compression (CCC) or CCO CPR results better survival. The CPP gradient, once established, is not interrupted and therefore cellular perfusion is maintained.[23,24,27]

ASSISTED VENTILATION IN PRIMARY CARDIAC ARREST

The technique of closed chest "cardiac massage" for cardiac arrest was first published in 1960 and, since the survival rate in this initial report was 70% (14/20), it quickly became the preferred technique for both in-hospital and prehospital treatment of cardiac arrest.[28] In their early teachings, the authors, Kouwenhoven, Knickerbocker and Jude said that, "assisted ventilation was not necessary as the victim gasped" during closed chest compression.[29] Seven of their initial 20 reported patients received chest-compression only without assisted ventilation.[28]

Nevertheless, influential individuals advocated bystander mouth-to-mouth assisted ventilations for cardiac as well as for respiratory arrests.[30,31] The possible justifications for this view were: (1) the emphasis of therapy for out-of-hospital arrests was historically based on the resuscitation of drowning victims; (2) it was thought that lay individuals could not reliably differentiate between respiratory and cardiac arrest; (3) gasping was not appreciated as a common event in primary cardiac arrest and (4) studies by Safer and his associates in volunteers given drugs to produce temporary paralysis showed that without assisted ventilation, their blood gases rapidly deteriorated.[31] Unfortunately it was not recognized that the explanation was that these subjects were not in cardiac arrest, and had normal cardiac outputs; therefore, their arterial blood quickly became unsaturated without assisted ventilation. In contrast, with sudden onset VF in primary cardiac arrest, the arterial blood is fully

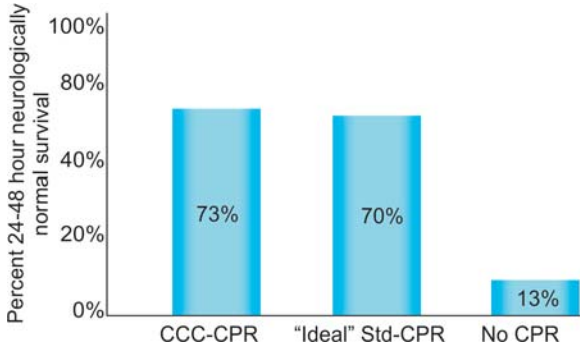


FIGURE 9: "CPR" for VF arrest, 6 different publications, in 169 non-paralyzed swine, between 1993 and 2002 (*Source:* University of Arizona Sarver Heart Center Resuscitation Research Group)

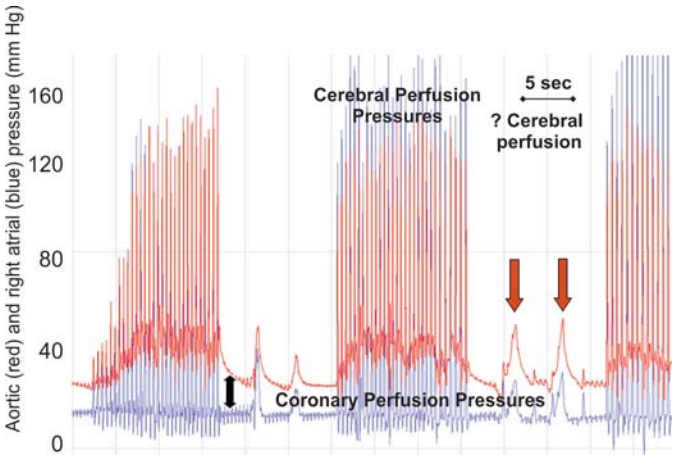


FIGURE 10: Hemodynamics of simulated single rescuer performing 30:2 compression: ventilations in experimental animal with realistic 16 sec. interruption of chest compressions for mouth-to-mouth ventilations

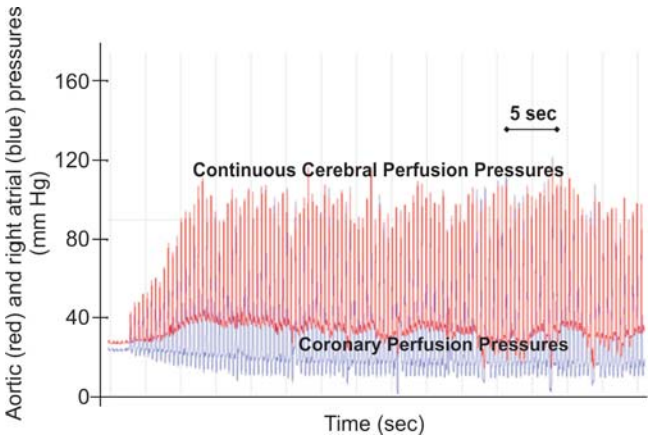


FIGURE 11: Hemodynamics of simulated single rescuer performing continuous chest compressions in experimental animal

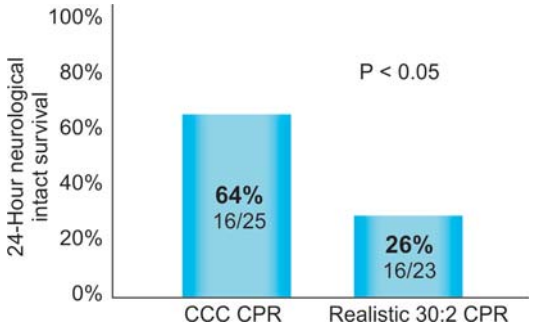


FIGURE 12: Survival following simulated single lay rescuer scenario of primary cardiac arrest (4–6 minutes untreated VF followed by bystander CPR; at 12 min, all received ACLS) (*Source:* Ewy GA, Zuercher M, Hilwig RW, et al. Circulation. 2007;116:2525)

oxygenated and remains so for several minutes, because it is not circulating. Nevertheless closed chest cardiac massage was merged with mouth-to-mouth to form what became known as cardiopulmonary resuscitation or CPR.[32]

By 1966, standardized methods of training and performance criteria for the administration of CPR had been advocated and published. A few years later the American Heart Association (AHA) adopted CPR as one of its main focus areas, developed standards for CPR and emergency cardiac care (ECC) and spearheaded a campaign to disseminate the techniques of CPR to the public and both CPR and ECC to professionals. Until the 2008 scientific advisory, all previous guidelines recommended mouth-to-mouth or so-called "rescue breathing" as the initial step for bystander initiated CPR.[33]

Years of defibrillation and resuscitation research led the senior author and his associates to advocate CCO CPR decades ago.[27,34-37] In our experimental laboratory, survival was better with CCO CPR than not doing anything until the simulated arrival of the paramedics and definite treatment. As our studies progressed, we were somewhat surprised to find that survival with CCO CPR was equivalent to "ideal" guidelines advocated CPR where each series of chest compressions were interrupted by 4 seconds to deliver the "two quick breaths" of "rescue breathing" (Fig. 9).[27,36]

In 2000, it was documented that recently certified lay individuals interrupted chest compressions for 16 seconds to deliver the two recommended "rescue breaths."[38] Subsequent experimental studies from our laboratories showed that survival was better with CCO CPR than with guidelines recommend CPR when each set of 15 compressions were interrupted a realistic 16 seconds to simulate the interruptions necessary for mouth-to-mouth ventilations.[24] Subsequently the AHA and International Liaison Committee on Resuscitation (ILCOR) changed the recommended compression to ventilation ratio to 30:2.[13] This recommendation was based on "consensus" as there was no data to support this recommendation. Accordingly, in our experimental laboratory, we then compared survival from simulated OHCA with CCO CPR and guidelines (30:2) CPR, and found that survival to be better with continuous chest compression CPR (Figs 10 to 12).[39] If lay individuals interrupted chest compressions an average of 16 seconds to provide the two recommended rescue breaths, could medical students who were younger provide these breaths quicker? How about the professionals, the paramedics? As shown in (Fig. 13) no one can provide mouth-to-mouth rescue breaths rapidly.[40,41]

NOT FOLLOWING GUIDELINES FOR PRIMARY CARDIAC ARREST

Years of defibrillation and resuscitation research and continuing analysis of the resuscitation literature and our failure to be able

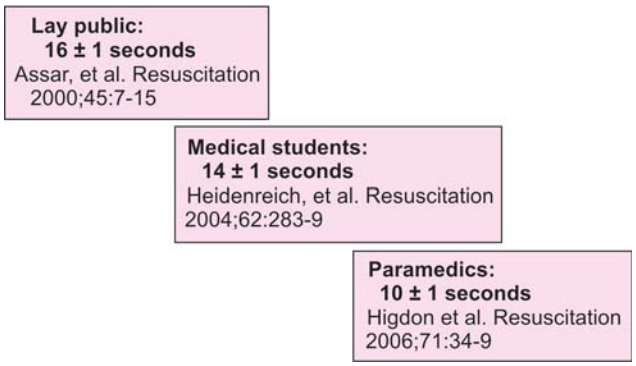


FIGURE 13: Interruptions of chest compressions by single rescuer CPR for guidelines recommended 2 quick mouth-to-mouth ventilations

to influence guidelines led the senior author to conclude in 2003 that we could no longer in good conscience follow the AHA and ILCOR guidelines of 2000.[36,37] We announced our intensions[37] and explained our approach[36,42] Our new approach was called CCR, due to its focus on the maintaining blood flow to the heart (cardio) and the brain (cerebral) during primary cardiac arrest by near continuous chest compressions prior to defibrillation, a necessary components of neurologically intact survival.[36] The CCR deemphasizes the early ventilation or "pulmonary" component of traditional CPR and attempts to minimize other possible detrimental aspects of positive pressure ventilation.[36]

The community (Fig. 3) component of CCR included CCO CPR. In 2003, CCO CPR was advocated in Tucson, AZ, with free training, local radio spots and newspaper interviews, and inserts into utility bills (Fig. 14). In 2004, with Dr Benjamin Bobrow and his statewide SHARE program a statewide effort was initiated in Arizona to encourage CCO CPR.[43] This was a multiple facet approach to training and information was dissemination in multiple venues that included websites (www.azshare.gov) and (www.heart.arizona.edu), celebrity endorsement, online video training, free in-person training in many setting and locations throughout the state, training kits sent to all 6–12th grade schools in Arizona, inserts mailed in utility bills (Fig. 15), tables set up at health and safety fairs by various departments (e.g. Fire, etc.), newspaper articles, editorials, local radio spots and interviews. To determine the effect of this effort, a statewide reporting system was developed.[44] In October 2008, the AHA published a science advisory, recommending CCO (Hands-Only CPR) for lay individuals untrained in CPR.[33]

Between 1 January 2005 and 31 December 2009 we analyzed the results of this five years effort, published as "chest compression-Only CPR by Lay Rescuers and Survival from Out-of-hospital cardiac arrest" in the Journal of the American Medical Association in 2010.[45] After excluding bystander CPR provided by health care professionals or arrests that occurred in a medical facility, 4,415 patients with OHCA were analyzed.[45] Survival to hospital discharge was 5.2% for no bystander CPR group, 7.8% for conventional CPR and 13.3% for CCO CPR (Fig. 16).[45] Survival to hospital discharge of those most likely to survive, those with witnessed arrest and a shockable rhythm on arrival of the Emergency medical services (EMS) personnel, was 17.6% in the no CPR group, 17.7% for conventional CPR

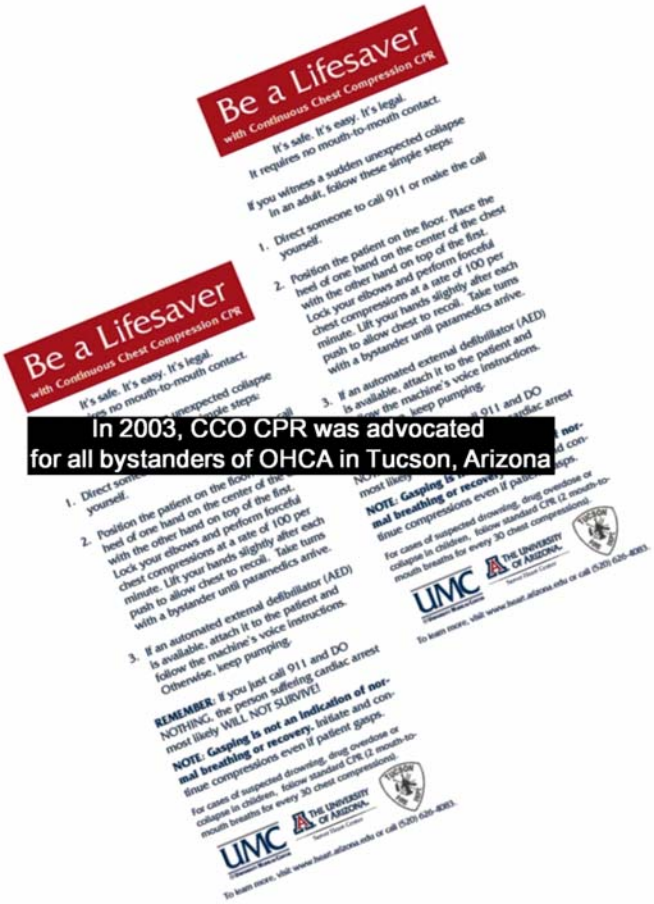


FIGURE 14: In 2003, CCO CPR was advocated for all bystanders of OHCA in Tucson, Arizona

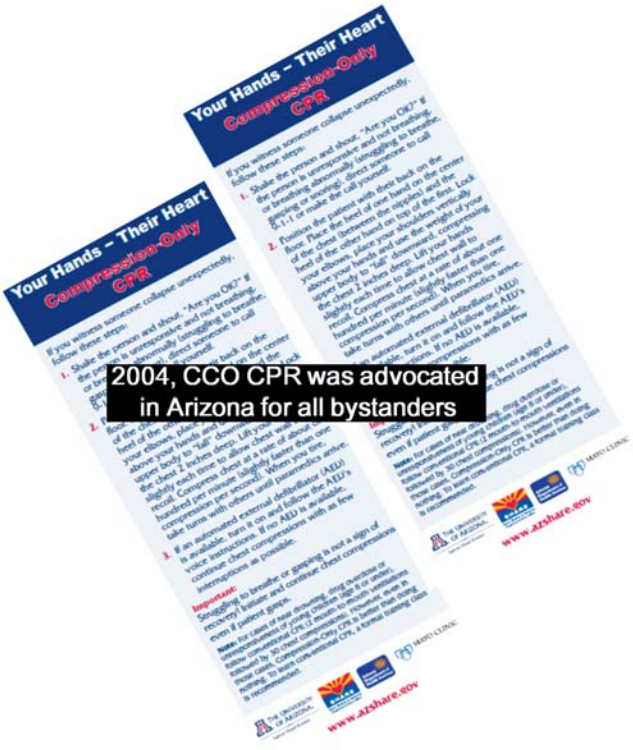


FIGURE 15: 2004, CCO CPR was advocated in Arizona for all bystanders

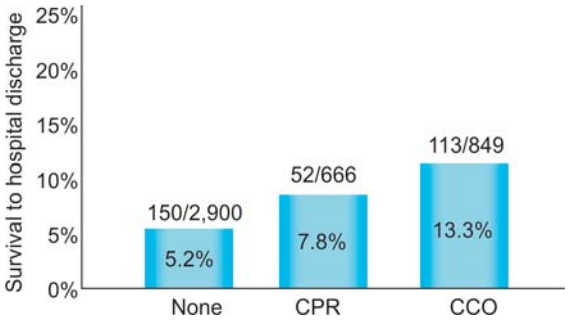


FIGURE 16: Effect of bystander CPR for OHCA on survival in Arizona (2005–2010) (*Source:* Modified from Bobrow, et al. JAMA. 2010)

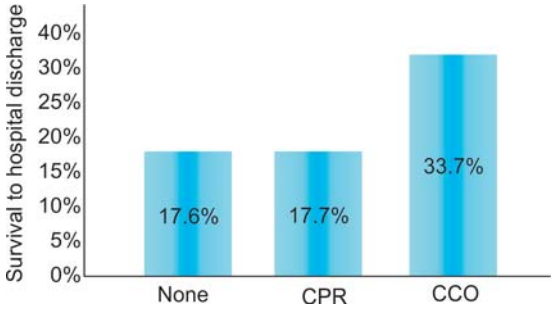


FIGURE 17: Bystander CPR for OHCA in Arizona (2005–2010) Witnessed/Shockable OHCA (*Source:* Modified from Bobrow, et al. JAMA. 2010)

and 33.7% for CCO CPR (Fig. 17).[45] There was no adverse effect of CCO CPR in the subgroup less likely to survive, witnessed arrest but without a shockable rhythm.[45]

This is the first prospective observational study to show that CCO CPR resulted in improved survival of patients with OHCA.[45] However, the first observational study to find that survival was better with lay individuals performing CCO CPR was the SOS-KANTO study which found that the survival of those individuals most likely to survive, witnessed arrest and a shockable rhythm was 11% for those receiving chest compressions plus mouth-to-mouth ventilations versus 19% for those receiving CCO (Fig. 18).[46] This study is of interest, for several reasons, including the fact that a bystander technique that had not been advocated nor taught was more effective than one that has been guidelines advocated for decades, and in which

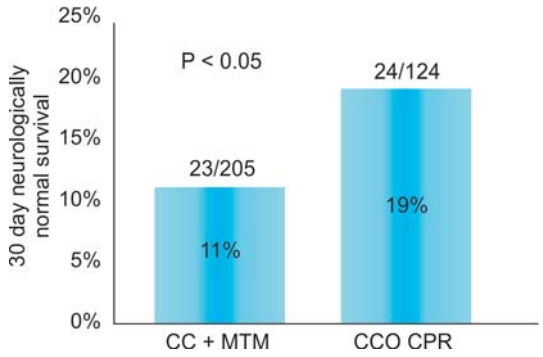


FIGURE 18: SOS-KANTO: Subset of patients with witnessed arrest and shockable rhythm (*Source:* Modified from Nagao et al. for the SOS-KANTO. The Lancet. 2007:369;920)

untold thousands of man-hours had been spent teaching and untold thousands of dollars spent advocating over the past several decades.

To date (2010), there are three reported randomized trials of dispatcher instructed CPR where one group was instructed in guidelines CPR of chest compressions plus mouth-to-mouth ventilations, and the other in CCO CPR. The first was by Hallstrom and his associates who reported in 2000 that the survival was 14.6% in those receiving chest compressions only CPR and 10.4% in those receiving instructions in chest compression and ventilations.[47] Since there were only 520 patients in the study, the difference were not significant and therefore the guidelines were not changed. However, this finding, published in 2000, encouraged the University of Arizona Sarver Heart Center Resuscitation Research Group in our decision in 2003 not to follow the AHA and ILCOR 2000 guidelines.

The other two recently reported studies of patients with OHCA, one from Sweden and the other from Seattle and London, both found no statistically difference in survival.[48,49] In the study from Sweden in which 620 patients received dispatch directed compression-only CPR and 656 received standard CPR, the survival was 8.7% compression-only and 7.0% for standard CPR. These authors concluded that overall "this study lends further support to the hypothesis that compression-only CPR, which is easier to learn and to perform, should be considered the preferred method for CPR for patients with cardiac arrest."[48]

Rea and his associates from Seattle also reported on dispatch directed chest compression alone (981patients) versus chest compression plus rescue breathing (960 patients) and found that survival to hospital discharge with favorable neurological outcome was 14.4% with chest compression alone and 11.5% in the CC plus rescue breathing group (p = 0.13).[49] However, their prespecified subgroup analysis showed a trend toward a higher proportion of patients survived to hospital discharge with chest compressions alone compared to chest compressions plus rescue breathing (15.5% vs 12.3%) and for those with a shockable rhythm 31.0% versus 25.7%.[49]

THE PUBLIC HAS MADE UP ITS MIND

In our statewide Arizona study, it was of interest to find that from 2005 to 2010, lay rescuer CPR only increased from 28.2% to 39.9% (Fig.19).[45] This was rather disappointing.

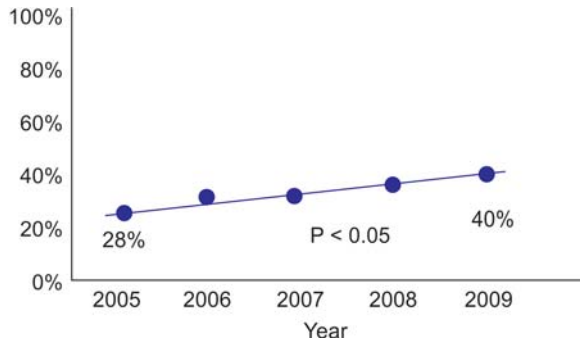


FIGURE 19: Incidence of bystander CPR for OHCA in Arizona (2005–2010) (*Source:* Modified from Bobrow, et al. JAMA. 2010)

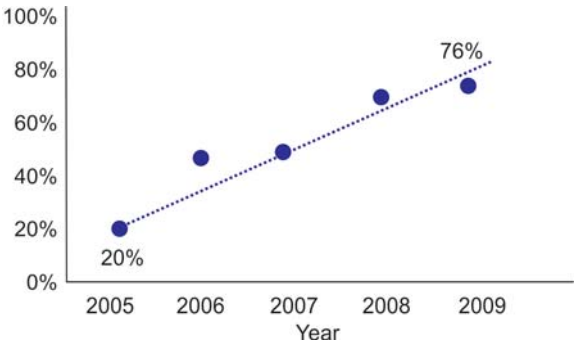


FIGURE 20: Bystander CPR for OHCA in Arizona (2005–2010): Percent of lay CPR providers who performed CCO-CPR (*Source:* Modified from Bobrow, et al. JAMA. 2010)

However, of those performing bystander CPR, the proportion of CPR that was CCO CPR increased from 19.6% to 75.9% (Fig. 20).[45] This indicates to us that the public has made up its mind. When encouraged they are much more likely to perform CCO CPR.

INCREASING THE PREVALENCE OF BYSTANDER RESUSCITATION EFFORTS

However, the fear or concern about mouth-to-mouth breathing is not the only reason a bystander may not initiate resuscitation efforts. We must address all of their concerns (Fig. 21) if we are to increase the prevalence of bystander resuscitation.[50]

INCREASING THE ABILITY TO PROMPTLY IDENTIFY PRIMARY CARDIAC ARREST

The prompt recognition of primary cardiac arrest is essential to any program to improve survival of patients with out-of-hospital cardiac arrest. The recommendation used by cardiocerebral resuscitation is the unexpected, witnessed (seen or heard) collapse in an individual who is not responsive. Note that this recommendation does not say anything about spontaneous ventilations. The reason for this is that one of the major impediments to the prompt recognition of primary cardiac arrest is the fact that subjects with cardiac arrest, rats, swine and humans have a high frequency of gasping after cardiac arrest (Fig. 22). Failure to recognize this fact delays the recognition of primary cardiac arrest (Fig. 23) lists the description of breathing abnormalities that have been described by witnesses of patients with cardiac arrest. Continued normal breathing for the first minute following cardiac arrest (Fig. 22) has only recently been observed in swine by the University of Arizona

• Fear/concern: mouth-to-mouth contact	~20%
• Fear/concern: harming person	~20%
• Fear/concern: legal consequences	~20%
• Fear/concern: not performing properly	~20%
• Physically unable to perform CPR	~20%

FIGURE 21: Is fear or concern about MTM contact the only deterrent to bystander CPR? (*Source:* Coons SJ, Guy MC. Resuscitation. 2009;80: 334-40) This study was designed and funded by the Sarver Heart Center University of Arizona College of Medicine and SHARE

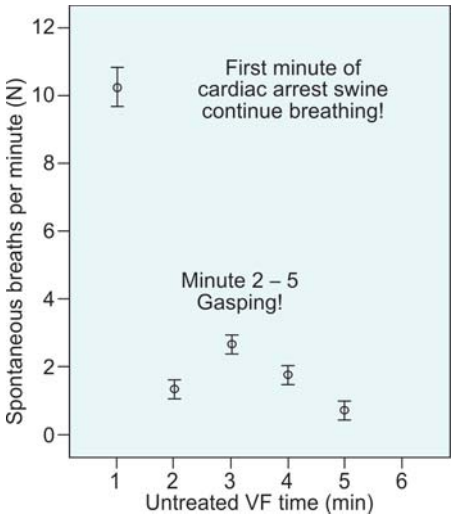


FIGURE 22: Recent unexpected finding (*Source:* Modified from Zuercher Ewy, Hillwig, et al. BioMedCentral Cardiovascular Disorders. 2010)

• Gasping	• Agonal breathing
• Snoring	• Barely breathing
• Gurgling	• Labored breathing
• Moaning	• Noisy breathing
• "Normal" breathing	• Heavy breathing
	• Abnormal breathing

FIGURE 23: Spontaneous ventilatory activity in patients with primary cardiac arrest

Sarver Heart Center Resuscitation Research Group.[51] However, gasping is well know and has been described in animals to begin during the second minute of VF arrest, and has a classical crescendo-decrescendo frequency pattern, of about 1,3,2,1 gasps per minutes (Fig. 22) and is no longer present six or more minutes after the onset of VF arrest, unless chest compressions provides enough blood flow to the brainstem to continue gasping.[52] Physician scientists refer to this phenomenon as gasping or agonal breathing, but lay people may refer to this phenomenon with other terms (Fig. 23).[53]

One of the reasons that assisted ventilation is often not necessary even during prolonged CCO CPR is that effective chest compression provides enough flood flow to the brainstem to maintain this primitive respiratory response.

THE THREE PHASES OF VENTRICULAR FIBRILLATION (VF)

To better understand some of the rationale for the second or pre-hospital phase of cardiocerebral resuscitation, one needs to appreciate not only the pathophysiology of cardiac arrest outlined above but also the electrophysiology of VF.

It has been known for decades that survival rates decrease by about 7–10% for every minute that a patient spends in untreated VF.[6] In the absence of chest compressions, after roughly 12 minutes, defibrillation for VF is rarely effective.[54] Our understanding of the therapy for VF was helped by the three-phase time sensitive concept of untreated VF, articulated by Weisfeldt and Becker in 2002 (Fig. 24).[54] This concept

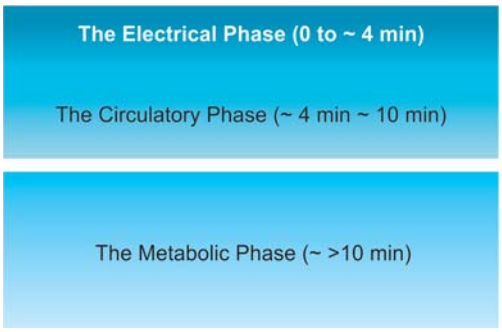


FIGURE 24: 3-Phase time-sensitive model of cardiac arrest due to ventricular fibrillation (*Source:* Modified from Weisfeldt ML, Becker LB. JAMA. 2002;288:3035-8)

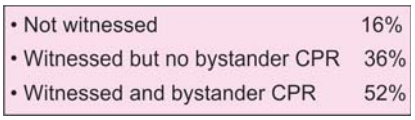


FIGURE 25: Prevalence of VF on arrival of EMS in out-of-hospital cardiac arrest in Arizona (*Source:* Data from 1,296 cardiac arrest in Arizona Voluntary reporting SHARE Program: Data collected October 2004 to April 2006 Bobrow, Clark, Ewy, Kern, Sanders)

divides VF into an electrical phase (around 0–4 minutes), circulatory phase (roughly 4–10 minutes) and a metabolic phase (> 10 minutes). This model helps us to understand why specific therapies need to be tailored to timelines.

Electrical Phase (0–4 minutes)

In this initial phase of VF, there is enough myocardial adenosine triphosphate (ATP) and other energy stores that defibrillation alone is adequate to restore a perfusing rhythm.[55] Patients defibrillated within seconds by an ICD or minutes by an AED often return to a perfusing stable rhythm since they are in the electrical phase of VF arrest. Chest compressions can prolong this so-called electrical phase of VF. As a prototype, the city of Seattle, WA, USA, has an average EMS response time of about 5 minutes, with a bystander CPR rate of over 60%. This translates into patients being defibrillated in the electrical phase and consequently having some of the best survival rates from OHCA anywhere in the United States.[9]

Circulatory Phase (4–10 minutes)

Conversely, once the markedly underperfused fibrillating ventricle uses up a significant portion of its energy stores, defibrillation, even if successful results in pulseless electrical activity (PEA) or asystole.[56] Prolonged untreated VF is manifested electrocardiographically by decreasing amplitude of the VF wave form with a transition to "fine" fibrillation waves on the electrocardiogram (ECG). Defibrillation in the absence of chest compressions is rarely successful in this phase of VF. However, if the CPP is re-established by chest compressions, the resultant perfusion of the myocardium allows the formation of new myocardial energy which makes the myocardium more responsive to defibrillation (Fig. 24) and less likely to deteriorate to PEA or asystole (Fig. 25). Thus chest compressions can prolong the electrical phase of VF.

Most OHCA patients are found in the circulatory phase of VF upon arrival of EMS personnel. For instance, the average time to response in the city of Tucson, Arizona, was 6 minutes 34 seconds[42], placing the patient precisely in the circulatory phase. A defibrillation first strategy in these patients is likely to result in a nonperfusing rhythm like PEA or asystole.[56] In this situation, preshock chest compressions have been demonstrated to increase the likelihood of successful defibrillation in a swine model.[57] A study from Seattle in humans showed increased survival when chest compressions were uniformly performed for 90 seconds prior to defibrillation.[58] In a similar study, Wik and his associates found survival to be improved with 3 minutes of chest compressions prior to defibrillation.[59] Based on these studies, for individuals encountered in the circulatory phase of untreated VF arrest, we prescribed, as part of cardiocerebral resuscitation, a period of 2 minutes of chest compressions prior to the first defibrillation attempt.[36] This was done first due to a compromise between the duration of chest compressions studied by Cobb et al. and by Wik et al. and because the senior author as well as we did not want the paramedics to use their watches to determine the duration of chest compressions prior to delivering the first shock. Two hundred chest compressions at 100 per minutes would be two minutes.[36] A recent report from the resuscitation outcomes consortium also confirmed improved survival in humans with preshock chest compressions, and interestingly they found that survival was greatest in the subgroup who received 2 minutes of chest compressions prior to the first attempted defibrillation.[60]

Metabolic Phase (> 10 minutes from Onset of Untreated Cardiac Arrest)

This third and terminal phase of untreated VF is universally associated with diminishing odds of successful defibrillation and neurologically intact survival. End organ damage has already set in with irreversible cellular impairment. Ischemic and reperfusion injuries are believed to predominate at this stage. Strategies that may delay the onset of irremediable damage during this phase of untreated VF include hypothermia.

CARDIOCEREBRAL RESUSCITATION; PREHOSPITAL COMPONENT

The initial approach to the prehospital component of CCR was implemented in Tucson, AZ, in late 2003 (Figs 26 to 28).[36,37,42] We announced our intensions and gave our rational for no longer following the National and International CPR and EMS guidelines (Fig. 29).[36,37] The CCR was predominantly based

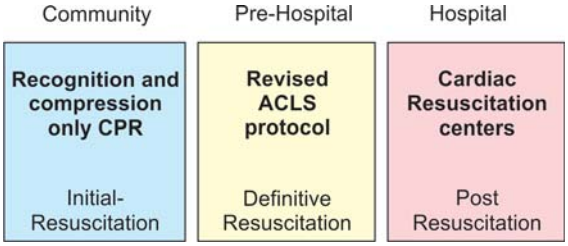


FIGURE 26: Cardiocerebral resuscitation "The New CPR" for primary cardiac arrest

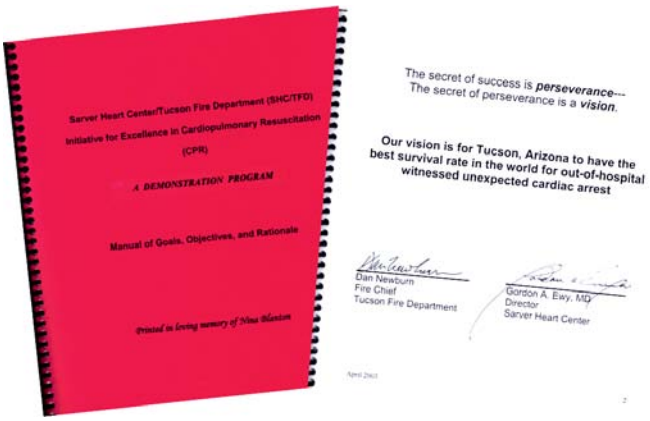


FIGURE 27: Manual of Goals, Objective, and Rationale

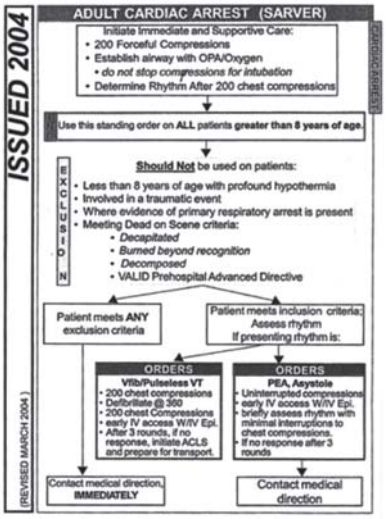


FIGURE 28: Tucson Fire Department

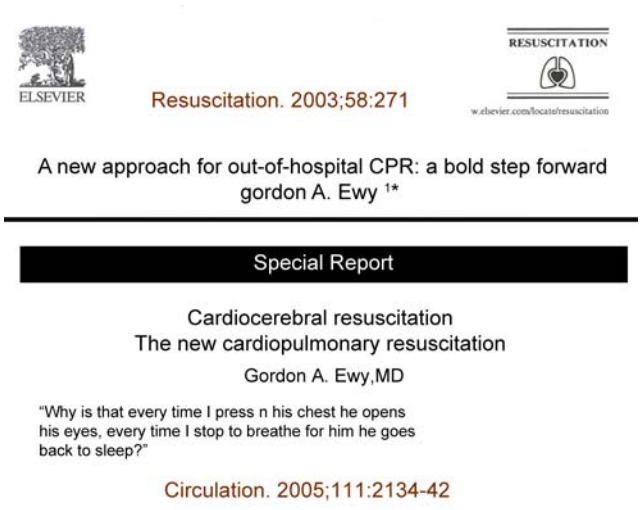


FIGURE 29: Sources of National and International CPR and EMS guidelines

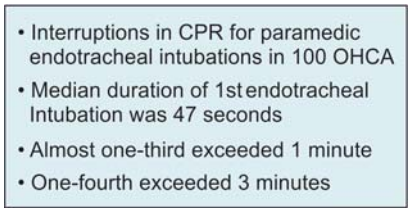


FIGURE 30: Interruptions of chest compressions for endotracheal intubation (*Source:* Modified from Wang, et al. Annals of Emergency Medicine. 2009;54:645)

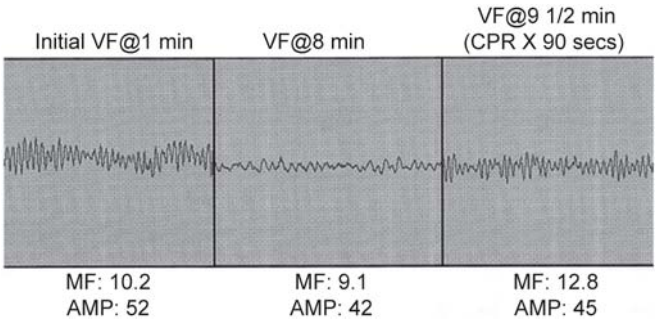


FIGURE 31: Untreated, the VF waveform decreased in amplitude with time. Following 90 seconds of chest compressions, the frequency and amplitude of the VF waveform increases

on our findings of the importance of uninterrupted chest compressions during cardiac arrest, and on ours or others findings that following the 2000 AHA and ILCOR guidelines, EMS paramedics/firefighters were performing chest compressions only half of the time while they were on the scene.[61,62]

We initially did not allow endotracheal intubation based our clinical observations that chest compressions were often interrupted for prolonged periods of time, even by well trained individuals attempting endotracheal intubation. This assumption proved to be correct as documented in a recent study by Wang and his associates (Fig. 30).[63]

We advocated chest compressions prior to defibrillation based on our experimental finding (Fig. 31),[64] and on the observations by Cobb et al. and Wik et al. that in patients with prolonged VF arrest, chest compressions prior to defibrillation improved survival.[58,59,65]

A single defibrillator shock was recommended based on the long interruptions of chest compressions for "stacked shocks". This approach also proved to be correct. Rae and his associates found increased survival in humans with single rather than stacked shocks, and subsequently this recommendation was made in the guidelines.[66]

In our experimental laboratory we found that chest compressions immediately after defibrillation shocks improved survival, and this approach was also subsequently advocated in 2005 guidelines.[13]

In 2004, the adverse affects of hyperventilation were reported by Aufderheide and his colleagues (Fig. 32). We had previously reported that during in-hospital cardiac arrests, physicians, in their excitement, were ventilating at an average rate of 37 per minute.[67] Aufderheide and his associates documented that paramedics were ventilating at this same rapid rate.[68] Accordingly we eliminated bag-mouth-ventilation and substituted "passive ventilation" as part of cardiocerebral resuscitation.[69,70] In 2004, after visiting us, Dr Mike Kellum and his associates instituted CCR (Fig. 33) in Rock and

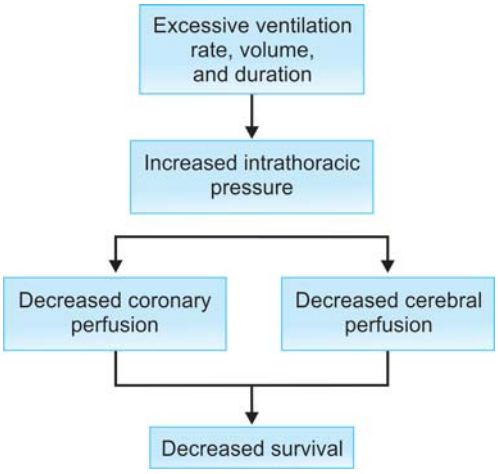


FIGURE 32: Consequence of excessive ventilation

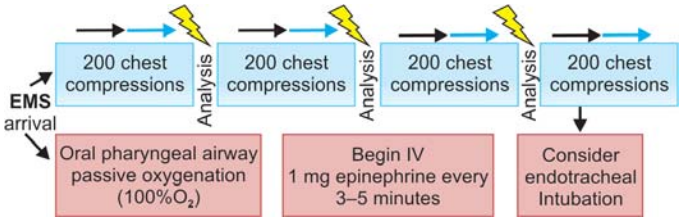


FIGURE 33: Cardiocerebral resuscitation. Goal: minimally interrupted chest compressions, avoiding hyperventilation, and early administration of epinephrine

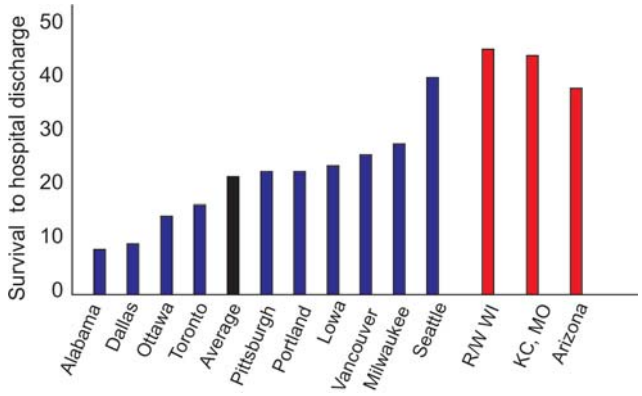


FIGURE 34: Survival to hospital discharge (%) of patients with VF arrest ROC 2005 Guidelines (all VF) vs cardiocerebral resuscitation (Witnessed VF)

Walworth Counties of Wisconsin.[10,36,71,72] The CCR (Figs 26 and 33), although advocating CCO CPR for bystanders, in the reports from Kellum et al. the intervention was essentially the "prehospital (Fig. 26) portion". Its initial component consisted of two hundred chest compressions. While this was being preformed, endotracheal intubation was not allowed, but rather an oral-pharyngeal airway, a non-rebreather mask, and high flow oxygen was administered.[72] A single shock was followed immediately by another 200 continuous chest compressions. After the single shock the EMS personnel were instructed not to feel for a pulse, nor evaluate the rhythm by looking at an ECG. These analyses were allowed, only after the first 400 chest compressions (4 minutes into ACLS). Equally important was the fact that only a single defibrillator shock, at maximal defibrillator output, was allowed.[10,36,72] Intravenous (IV) epinephrine was administered as soon as possible.[36,72]

In 2005, the rational for CCR was presented by the senior author to EMS medical directors in Arizona, and some chose to institute CCR in their cities. In part due to the enthusiasm of EMS personnel and in part in response to the statewide Save Hearts in Arizona Research and Education Program (SHARE) spearheaded by Dr Benjamin Bobrow, Director of the Arizona Department of Health Emergency Care and Trauma Service, CCR was expanded to a statewide effort.[11] In 2006, the senior author was invited to Kansas city, MO, to advocate cardiocerebral resuscitation.[12,73]

As shown in Figure 4, survival of the subset of patients more likely to survive, those with witnessed arrest and a shockable rhythm on arrival of EMS personnel, averaged 38% with CCR in all three of these areas. Then compared to arguably some of the better EMS systems in the United States and Canada, the resuscitation outcomes consortiums (ROC), survival with CCR was better than that advocated by the 2005 national and international guidelines for CPR and EMS care (Fig. 34).[1] There is a caveat with this comparison in that the results of CCR are for witnessed arrest and a shockable rhythm, whereas the results reported by ROC was for VF arrest.[1]

DRUG THERAPY IN CARDIAC RESUSCITATION

Epinephrine is a first line agent for a cardiac arrest and is used in all forms of cardiac arrest. Epinephrine causes immediate peripheral vasoconstriction by its α-adrenergic effect, and thereby during chest compressions for cardiac arrest, increases coronary and cerebral perfusion.[74-76] An IV epinephrine dose of 1 mg is administered ever 3–5 minutes till ROSC has been recommended. Since the time from onset of cardiac arrest to IV administration of epinephrine in the field is prolonged, there is a trend to the increasing use of intraosseous (IO) injections.

Vasopressin, which causes peripheral vasoconstriction through V1a receptors on vascular smooth muscle, is a more controversial drug. A large randomized trial of epinephrine or vasopressin showed no difference in survival between the two groups.[77] A 2005 meta analysis also failed to show any benefit of vasopressin over epinephrine.[78] Since the half-life of vasopressin is 10–20 minutes, it is administered as on one time 40U IV dose. Some have recommended epinephrine as the first vasopressor, followed by vasopressin as the second vasopressors in an effort to decrease the number of epinephrine doses.[10] Since it is the alpha adrenergic effect of epinephrine that is beneficial during resuscitation efforts, this approach could decrease the theoretical adverse effects of excessive beta adrenergic effects of frequent epinephrine doses. Others have recommended epinephrine alone, in efforts to simplify the regimen of EMS personnel. Experimental studies have suggested that vasopressin contributes to postresuscitation myocardial dysfunction, but not survival.[79]

Amiodarone and to a lesser extent lidocaine are antiarrhythmic drugs of choice for pulseless VT/VF, especially of presumed ischemic etiology. Amiodarone was superior to lidocaine in the ALIVE trial, and had been the recommended

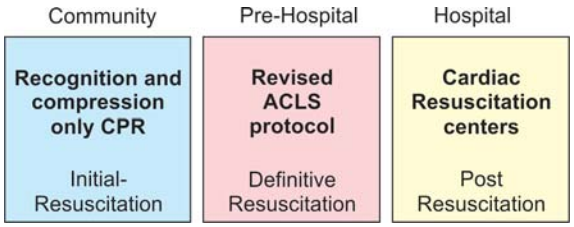


FIGURE 35: Cardiocerebral resuscitation "The New CPR" for primary cardiac arrest

first line antiarrhythmic agent for VF/VT arrest.[80,81] Amiodarone is administered as a single 300 mg IV push, followed by, if necessary, another 150 mg IV push.

The largest controlled trial (TROICA) of thrombolytics in cardiac arrest, involving 1,050 patients, was prematurely terminated due to a lack of benefit.[82]

For postresuscitation hypotension, dopamine should be considered. Intra-aortic balloon pumping was not found to be helpful in our experimental laboratory.[83]

CARDIAC RESUSCITATION CENTERS

A more recently advocated third component of CCR is Cardiac Resuscitation Centers (Fig. 35). Cardiac Resuscitations Centers are proposed to improve therapy of resuscitated but comatose patients following cardiac arrest. Although neurologic function after prolonged cardiac arrest is of major concern, there is almost always other organ dysfunction as well. In its 2008 consensus statement, ILCOR termed this as the "post cardiac arrest syndrome".[84]

The clinical manifestation of the post cardiac arrest syndrome can include hypoxic encephalopathy, myocardial dysfunction, aspiration pneumonia, ischemic gut injury, ischemic hepatopathy, renal dysfunction as well as peripheral limb ischemia. Generalized activation of immunological and coagulation cascades occur. Relative adrenal insufficiency,[85] glycemia,[86] and ventilator associated pneumonia are common. Seizures/myoclonus, consequent to hypoxic brain injury, is seen in up to 40% of resuscitated patient and should be treated promptly with anticonvulsants. Coronary flow reserve remains below normal for at least 4 hours in animal models (Fig. 36).

In Arizona, hospitals were encouraged to become designated as Cardiac Resuscitation Centers.[87] To be designated, a hospital has 24/7 capability for therapeutic hypothermia, early cardiac catheterization and indicated percutaneous intervention, glucose management protocols, provide hemodynamic optimization, prophylaxis therapy for stress ulcers, infection and venous thrombosis prophylaxis, and assessment for relative adrenal insufficiency, and be willing to submit their outcomes (which are subsequently not identified in statewide outcome reporting). In an effort to further improve survival from cardiac arrest, requirements for evidence based termination of resuscitation including at least a 72–hour moratorium for termination of care following therapeutic hypothermia, a protocol to address organ donation, and these hospitals are encouraged to have a community out-reach program to promote bystander CCO CPR for primary cardiac arrest.

In Arizona, the SHARE program has studied the impact of prehospital transport intervals on survival from OHCA and

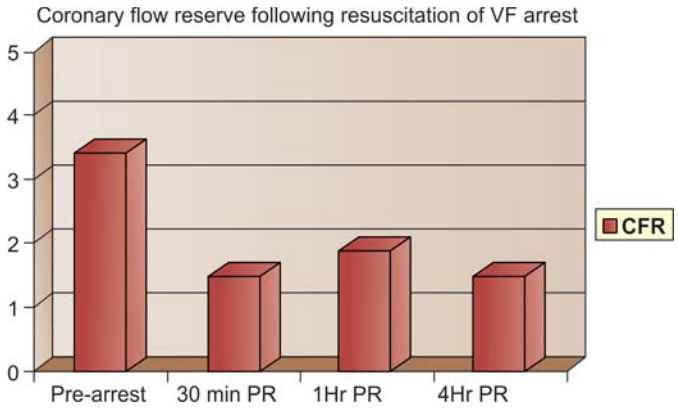


FIGURE 36: Coronary flow reserve (CFR) remained significantly below normal (ratio of 2:4) throughout the 4-hr postresuscitation period (*Source:* Modified from Kem KB, et al. Univ. AZ College Medicine)

found that bypassing a hospital to bring resuscitated but comatose patient to a Cardiac Resuscitation Center (provided the added transport time is < 15 minutes) is justifiable.[88]

Neurologically intact survival is the ultimate goal of resuscitation treatment strategies and is reflected in the inclusion of "cerebral" in "cardiocerebral resuscitation". Resuscitated patients require close monitoring in an intensive care unit setting as they are prone to repeat hemodynamic instability as well as recurrent cardiac arrhythmias.

THERAPEUTIC MILD HYPOTHERMIA

One of the most encouraging approaches to resuscitated cardiac arrest patients with coma is therapeutic controlled mild hypothermia [89.6–93.2°F (32–34°C)]. Two decisive randomized trials have established hypothermia as an integral part of postresuscitation care.[89,90] The hypothermia after cardiac arrest (HACA) study group performed the largest randomized clinical trial of hypothermia to date. Barnard et al. also studied adult patients with out-of-hospital cardiac arrest from VF. Hypothermia has been shown to be safe in patient with cardiogenic shock,[91] where the benefit appears to be even more robust. In 2007, a Norwegian report emphasized aggressive early hypothermia and early coronary angiography in patients who were comatose after OHCA, and demonstrated an increase in survival increased from 26% to 56% with the implementation of this protocol.[92] Based on randomized trial data, approximately 6 patients need to be treated with therapeutic hypothermia to gain one neurologically intact survivor.

The mechanism of action of hypothermia is unknown, but is thought to be related to its inhibitory effect on adverse enzymatic and chemical reactions that are initiated by the global ischemia. Continuous temperature monitoring is an essential part of therapeutic hypothermia as undershooting or overshooting can lead to malignant arrhythmias.[93] Transesophageal temperature monitoring is reported to be more reliable that urinary bladder monitoring.

Early institution of hypothermia in the field is recommended.[94] If available, the rapid administration of 2,000 ml of cold (4°C) normal saline is recommended.[95,96] If available, especially in hot environments, the application of ice packs to the groin, axilla and neck are considered.

The ILCOR, taking into account the increasing evidence, issued an advisory statement in 2003 recommending that unconscious adult patients with spontaneous circulation after out-of-hospital cardiac arrest should be cooled to 89.6–93.2°F (32–34°C) for 12–24 hours when the initial rhythm was VF. Similar recommendations were echoed in more recent guidelines.[13]

Electrolyte abnormalities, coagulation disturbances and alteration of drug metabolism have all been described as complications of therapeutic hypothermia. There is no data supporting one method of cooling over the other.

There are, at present, no reliable predictive tools that can be used in comatose patients to distinguish who will or will not wake up. The best prognostic sign postresuscitation recovery is the return of consciousness. Recent unpublished observation suggests that one should wait at least 72 hours after therapeutic hypothermia before making the decision to discontinue therapy.

MYOCARDIAL ISCHEMIA CAUSING CARDIAC ARREST

The recommendation for early catheterization and possible early percutaneous coronary intervention is based on the fact that about 50% of adult patients with VF arrest may have an acute myocardial infarction as the underlying etiology.[97] Unfortunately, in the postresuscitation state, neither clinical nor electrocardiographic findings are predictors of an acute coronary occlusion. In one study, 48% of patients who had no obvious noncardiac cause and had undergone coronary angiography after resuscitation from out-of-hospital cardiac arrest were found to have had an acute coronary occlusion.[98]

This has led to the concept of bundled postresuscitation care, with standardized protocol for patients with OHCA, including hypothermia and emergent coronary angiography.[87]

ENDING RESUSCITATIVE EFFORTS

For services delivering advanced cardiac life support in England, the Recognition of Life Extinct (ROLE) guidelines state that "resuscitation attempts should be terminated when the patient remains in asystole despite full advanced life support procedures for more than 20 minutes". The AHA guidelines state that "resuscitation efforts should be continued" until "reliable criteria indicating irreversible death are present".[99] Morrison et al. found that only 0.5% of arrest victims survived if: (1) there was no ROSC; (2) no shocks were administered; (3) the arrest was not witnessed by EMS personnel; (4) when response time greater than 8 minutes was retrospectively added to the prediction rule, the survival rate was 0.3% and (5) when not bystander witnessed no one survived.[100] However, practice patterns vary widely and no single consensus has been established as the gold standard for ending resuscitation efforts.

SUMMARY

The classic "chain of survival" identifies five fundamental links in resuscitation: early warning, early cardiopulmonary resuscitation by witnesses, early defibrillation, early advanced life support and care of the post-arrest patient. Despite all the advances, until recently there has only been a weak trend toward improved survival to hospital discharge.[3] The CCR is a new approach that has been shown to improve survival. It consists of a community approach, which emphasizes early recognition, including the frequency of gasping post witnessed cardiac arrest and early CCO CPR.[36] A Prehospital approach for primary cardiac arrest prohibits early endotracheal intubation, requires prompt initiation of minimally interrupted chest compressions before rhythm analysis or after an indicated single shock and the prompt administration of epinephrine.

The CCR now has human survival outcome data and will likely succeed traditional CPR as the preferred management of primary cardiac arrest.[10-12]

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Section 5

CORONARY HEART DISEASES

Chapter 45

Coronary Heart Disease: Risk Factors

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Chapter Outline

- CHD Screening and Prevention
- Clustering and Multiplicative Effects of Risk Factors
- CHD Risk Estimation
  - Framingham Risk Score (FRS)
  - European Risk Scores
  - Newer Risk Scores
- Measures to Evaluate Risk Prediction Models
- Traditional CHD Risk Factors
  - Non-Modifiable Risk Factors for CHD
  - Modifiable Risk Factors for CHD
- Emerging Risk Factors
  - High-sensitivity C-reactive Protein (hs-CRP)
  - Lipoprotein (a) [LP(a)]
  - Hyperhomocysteinemia
  - Lipoprotein-Associated Phospholipase A2 (LP-PLA2)
  - Apolipoprotein B
  - Fibrinogen and Other Hemostatic Factors
- Sub-Clinical Atherosclerosis
- Translating Risk Factor Screening into Event Reduction

INTRODUCTION

Cardiovascular disease (CVD) remains the leading cause of death in the United States and many other parts of the world and results in substantial disability and loss of productivity. Coronary heart disease (CHD) and stroke are the leading contributors to this heavy CVD burden. The exact mechanisms underlying development of CVD still remain to be fully described. However, through population-based studies starting in the 1940s and 1950s and intervention trials later, multiple risk factors for the development of CVD have been identified. The term 'risk factor' was in fact first used in the context of CHD.[1] A risk factor is any personal, environmental, psychosocial or genetic characteristic that gives an individual a higher likelihood of developing a particular disease. Even though the risk factor is a mere statistical association to an outcome, the current use of the term 'risk factor' often implies causalty. On the other hand, a 'risk marker' has association with a disease but a cause and effect relationship either does not exist or remains to be proven. These terms have evolved over the years and are non-uniformly used in the literature.

Cardiovascular disease risk factors are generally categorized into traditional/conventional and novel/emerging risk factors (Table 1). Risk factors can be inherited or acquired, some are modifiable and others are not. Risk factors may be defined dichotomously by their presence or absence or measured as a continuous variable.

The treatment of CVD risk factors has contributed to the fall in CVD mortality in the past 30 years, at least in developed countries.[2] At the same time, the prevalence of CVD and heart failure has increased due to higher survival rates and an aging population. More recent data suggest that we have reached a plateau in CVD mortality, which correlated with the obesity and physical inactivity epidemics. This highlights the challenge of CVD management: both identification and effective treatment of risk factors are required. Despite identification of patients at risk for CHD, significant gaps remain in implementing treatment. For instance, up to 15–20% of high risk patients discharged from the hospital, such as those with acute coronary syndrome, are not initiated on recommended combination therapy of aspirin, beta-blocker, statin and angiotensin

TABLE 1

Risk factors for cardiovascular disease

Traditional risk factors	
Modifiable	*Non-modifiable*
• Hypertension • Diabetes • Hyperlipidemia • Obesity • Tobacco use • Physical inactivity	• Age (male ≥ 45 years, female ≥ 55 years) • Gender • Family history of premature coronary artery disease*
Selected emerging risk factors • C-reactive protein • Small LDL particles • Lipoprotein(a) • Homocysteine • Lipoprotein-associated phospholipase A2 • Coagulation and hemostatic factors • Apolipoproteins A and B • White blood cell count	
(*Definite myocardial infarction or sudden death before 55 years of age in father or other male first-degree relative or before 65 years of age in mother or other female first-degree relative)	

TABLE 2

WHO principles for screening*

1. Condition screened should be an important health problem
2. There should be a suitable test for diagnosis
3. There should be an accepted treatment
4. Facilities for diagnosis and treatment should be available
5. The screening should be cost-effective
6. There should be a recognizable latent stage
7. The natural history should be adequately understood
8. Case finding should be a continuous process

(*Source:* Wilson JMG, Junger G. Principles and practice of screening for disease. Public Health Pap. Geneva: World Health Organization; 1968)

converting enzyme inhibitors. Fewer are referred to comprehensive risk reduction programs like cardiac rehabilitation suggesting that lifestyle risk factors are even less likely to be addressed.[3] As our quest for finding new risk factors and development of new therapeutic strategies is ongoing, we also have to devise ways to uniformly implement effective risk factor treatment.

CHD SCREENING AND PREVENTION

The high lifetime risk of CHD warrants population wide screening for prevention and treatment. The long lag time between the onset of atherosclerosis and its related morbidity and mortality allows for detection and early intervention. Screening involves routine evaluation of asymptomatic people. The widely accepted World Health Organization (WHO) criteria for screening of disease are summarized in Table 2. Screening should be cost-effective with the goal of detecting, not excluding, disease. Using established risk factors, a significant percentage of 'at risk' individuals can be screened as a target for preventive strategies.[4]

Three to five levels of prevention are described in the context of CVD (Table 3), often with dissimilar definition. The Centers for Disease Control and Prevention describe a simple classification with three levels of prevention.[5] Primordial prevention or health promotion targets the population without risk factors and aims to prevent the development of risk factors. The goal of primary prevention is to prevent the development of CVD in individuals with one or more risk factors. Secondary prevention involves patients with established clinical disease with the goal to prevent recurrent CVD events and their complications. A fourth level referred to as tertiary prevention targets late stages of the disease with the goal of restoration and rehabilitation.

TABLE 3

Levels of prevention in cardiovascular disease

1. Primordial prevention	Prevention of the risk factors for disease
2. Primary prevention	Reduction in incidence of disease
3. Secondary prevention	Reduction in the prevalence or consequence of disease
4. Tertiary prevention	Reductions in complications or disability, rehabilitation or restoration of function

CLUSTERING AND MULTIPLICATIVE EFFECTS OF RISK FACTORS

Initially, risk factors for CHD, such as diabetes, hypertension and hyperlipidemia, were targeted and treated individually. However, risk factors often occur in clusters and show a multiplicative effect rather than a simple additive effect. This has important implications for treatment. Most persons in a population have moderate elevation in multiple risk factors rather than an extremely high level of any single risk factor. Similarly, most cardiovascular events occur in individuals with mild to moderate abnormality in multiple risk factors. Targeting only high levels of individual risk factors will target only a small fraction of the population. Various expert groups stress the concept of 'comprehensive risk factor management'.

CHD RISK ESTIMATION

Despite our knowledge and understanding of many CHD risk factors, a clinical challenge is to effectively predict risk of CHD in individuals to allow appropriate and cost-effective treatment. Risk estimates are also used to raise awareness about CHD, determine population attributable risk to target specific public health measures, and to communicate risk to patients.

Coronary heart disease risk estimation measures the likelihood of a person developing a serious cardiovascular event over a specific follow-up time. Several multivariable models exist to predict the risk for future CHD and CVD (Table 4), many derived from the Framingham cohorts. Risk estimation results are critically dependent on the time frame of prediction. Earlier risk scores predicted short-term and medium-term risk of $\leq$ 10 years. More recently, long-term and lifetime risk estimation algorithms have been developed.[6,7] Risk estimation also depends on the endpoint chosen, for instance, CHD versus overall cardiovascular risk[8] and within CHD, 'hard events' such as myocardial infarction and CHD death or 'hard and soft endpoints' which also include angina pectoris and revascularization.

Refining and improving risk prediction is a major area of research in cardiovascular medicine. Key issues related to CVD risk estimation include the optimal time frame for risk assessment (short term, long term or lifetime), development of age-specific absolute risk models, defining cut offs for different risk categories, determining eligibility for pharmacological treatment, integration of imaging modalities to detect atherosclerosis and determining whether using a particular risk score will eventually result in better patient outcomes.

FRAMINGHAM RISK SCORE (FRS)

FRS and National Cholesterol Education Program's Third Adult Treatment Panel update (NCEP ATP III) are the most widely used risk scores (Table 4). FRS predicts the 10-year risk of CHD using a multivariable mathematical model of risk.[9] The calculator is available at: (http://www.framinghamheartstudy.org/risk/hrdcoronary.html). The NCEP ATP III risk assessment tool predicts the 10-year risk of hard CHD (myocardial infarction and coronary death).[10] The calculator is available at: (http://hp2010.nhlbihin.net/atpIII/calculator.asp?usertype=prof). Intensity of risk factor treatment is guided by the magnitude of absolute risk. Absolute risk is divided into three risk categories:

TABLE 4

Risk prediction scores for cardiovascular disease

Risk score (year)	*Study summary*	*Variables*	*End point*
Framingham Risk Score (1998)	5,209 men and women, ages 30–62 yrs Follow-up 10 yrs 10-year risk	Age, diabetes, smoking, hypertension, total cholesterol and LDL-C	All CHD
Framingham Risk Score for General Cardiovascular Disease (2008)	Men and women, ages 30–74 yrs without CVD at baseline Follow-up 12 yrs 10-year risk	Age, diabetes, smoking, treated and untreated systolic blood pressure, total cholesterol, HDL-C BMI replacing lipids in a simpler model	CVD (coronary death, myocardial infarction, coronary insufficiency, angina, ischemic stroke, hemorrhagic stroke, transient ischemic attack, peripheral artery disease, heart failure)
Reynolds Risk Score (2007)	24,558 women, age ≥ 45 yrs without CVD Median follow-up 10.2 yrs 10-year risk	Age, hemoglobin A_{1C}, smoking, systolic blood pressure, HDL-C, hs-CRP, total cholesterol, parental history of myocardial infarction at < 60 years	Global CVD (Composite end-point of cardiovascular death, myocardial infarction, ischemic stroke and coronary revascularization)
Reynolds Risk Score, men (2008)	10,724 men, ages 50–80 yrs 10-year risk	Age, hemoglobin A_{1C}, smoking, systolic blood pressure, HDL-C, hs-CRP, total cholesterol, parental history of myocardial infarction at < 60 years	Global CVD (Composite end-point of cardiovascular death, myocardial infarction, ischemic stroke and coronary revascularization)
Third Report of NCEP Adult Treatment Panel (2002, Update 2004)	Uses Framingham Risk Score 10-year risk	Variables same as Framingham risk score. Diabetes is considered a CVD equivalent	Hard CHD (CHD death and non-fatal myocardial infarction)
SCORE (2003)	205, 178 persons, ages 45–64 yrs 10-year risk	Age, cholesterol, smoking, systolic blood pressure Individuals with > 5% 10-year risk are defined as high risk	CVD death
QRISK (2007)	Derivation cohort 1.28 million patients, age 35–74 yrs. Median follow-up 6.5 years 10-year risk	Age, body mass index, ratio of total cholesterol to HDL-cholesterol, family history of premature cardiovascular disease, smoking, systolic blood pressure, deprivation score	CVD (myocardial infarction, ischemic stroke, transient ischemic attack and coronary heart disease)
Prospective cardiovascular Münster (PROCAM) (2002)	5,389 men, age 35–65 yrs 10-year follow-up	Age, LDL-C, smoking, HDL-C, systolic blood pressure, family history of premature myocardial infarction, diabetes mellitus, triglycerides Score 0 to > 60 with score > 53 defined as high risk (> 20% 10-year risk of cardiac event)	Hard CHD (sudden cardiac death or a definite fatal or nonfatal myocardial infarction)
Rasmussen Score (2003)	396 individuals	Blood pressure, N terminal proBNP, electrocardiogram, carotid intima-media thickness, microalbuminuria, treadmill exercise blood pressure, left ventricular ultrasound left ventricular mass index, small and large artery elasticity, optic fundoscopy for retinal vasculature	

(Abbreviations: CVD: Cardiovascular disease; CHD: Coronary heart disease; LDL-C: Low density cholesterol; HDL-C: High density cholesterol; hs-CRP: High-sensitivity C-reactive protein; NCEP: National cholesterol education program)

high, intermediate and low risk (Table 5). High risk individuals include those with established CHD, diabetes, stroke, peripheral vascular disease or with multiple risk factors without established CHD, but a10-year risk of CHD events greater than or equal to 20%. Certain individuals are considered 'very high-risk' and, according to the NCEP ATP III update,[11] they should be the target of more intensive lipid lowering therapy. This group includes individuals with established CVD in the presence of multiple major risk factors, especially if uncontrolled, or patients with acute coronary syndromes.

The FRS predicts major CHD events well in different populations.[12] Limitations of FRS are that it was developed exclusively in Caucasians. FRS does not include family history, obesity and psychosocial factors, which are important risk factors for CVD. FRS calculates only CHD risk and not the complete risk of other CVD processes including stroke, heart failure and peripheral vascular disease. The data used in the original Framingham Heart Study precede the obesity and physical inactivity epidemic. FRS is heavily influenced by age[13] and gender. For instance, most non-smoking men less than

TABLE 5

Risk categories for 10-year risk of coronary heart disease

Risk category definition	
High risk	CHD or CHD risk equivalent* or ≥ 2 risk factors† and 10-year predicted risk of ≥ 20%
Moderately high risk	≥ 2 Risk factors and 10-year predicted risk of 10–20%
Moderate risk	≥ 2 Risk factors and 10-year predicted risk of ≥ 10%
Low risk	0–1 Risk factor

*Peripheral arterial disease, diabetes mellitus; †Risk factors include cigarette smoking, hypertension (blood pressure ≥ 140/90 mm Hg or on antihypertensive medication), low high-density lipoprotein cholesterol (< 40 mg/dL), family history of premature CHD (CHD in male first-degree relative < 55 years of age; CHD in female first-degree relative < 65 years of age) and age (men ≥ 45 years; women ≥ 55 years)

45 years and almost all women less than 65 years of age have a 10-year risk of less than 10%. Despite some limitations, FRS is the most widely used and validated risk assessment tool and is able to provide remarkably good discrimination for the majority of individuals.[14]

EUROPEAN RISK SCORES

Since FRS is based on a North American sample, in Europe different risk scores were established including the Systematic Coronary Risk Evaluation (SCORE) project and the QRESEARCH cardiovascular RISK algorithm (QRISK). The SCORE[15] has been adopted by the Joint European Societies' guidelines on CVD prevention. The SCORE risk prediction system uses only fatal CVD as the outcome measure. The risk chart provides more detail for middle-aged persons in whom the risk changes with age. Separate charts are available for higher and lower risk areas in Europe. Individuals with a 10-year risk of CVD death of 5% or more are considered at an '*increased risk*' and qualify for intensive risk factor management.[16] A newer, computer-based tool for total risk estimation, which operates using the SCORE data, is called the HEARTSCORE (http://www.heartscore.org/eu/high/Pages/Welcome.aspx). The QRISK[17] algorithm was developed using the QRESEARCH database. The QRISK score includes family history of premature CHD, body mass index (BMI) and social deprivation that are not part of the FRS. A 2008 update (QRISK 2 score) contains additional variables including renal disease, atrial fibrillation and rheumatoid arthritis.[18]

NEWER RISK SCORES

Newer risk scores were developed in an attempt to overcome limitations of FRS and to incorporate emerging risk factors for CVD. A risk score's ability to reclassify patients at intermediate risk for CHD into higher risk for more aggressive management or lower risk categories for reassurance may clinically be useful. Some risk factor algorithms have eliminated laboratory based testing to reduce cost and increase availability, in particular to the primary care physicians, who are generally the first contact for the majority of the low-to-intermediate risk population.

The Reynolds risk score[19] for women was developed in 24,558 women from the Women's Health Study. In addition to traditional subject-reported risk factors, it incorporates family history of myocardial infarction, high-sensitivity C-reactive protein (hs-CRP) and hemoglobin A_{1C}. In the original study, Reynolds risk score was able to reclassify 40–50% of intermediate risk women into higher or lower risk categories. Later, a Reynolds risk score for men was developed in a cohort of 10,724 men from the Physicians Health Study II. This risk score reclassified 18% of men into a higher or lower risk category.[20] The risk calculator is available at http://www.reynoldsriskscore.org.

A general CVD risk prediction model was developed by D'Agostino et al.[8] using the original and offspring cohorts of the Framingham study. The risk estimation is for all CVD events compared to only CHD events in FRS. The investigators formulated two separate risk scoring models: one based on standard risk factors including laboratory variables and another using only non-laboratory based clinical variables. This risk assessment tool also presents the concept of 'vascular age' of an individual. Vascular age is the chronological age with optimal risk factors that gives the same predicted risk as that of the individual whose risk is being estimated. Currently, there are no established cut-offs for what is considered high risk when using global risk score. Published studies have used a 10-year risk of a CVD event of greater than 20% as the cut-off. To overcome the limitation of short-term risk prediction, recently, long-term and lifetime risk estimation algorithms have been developed.[7] Lifetime risk estimation may be useful for younger patients who have low short-term risk but high lifetime risk. In fact, data from the National Health and Nutrition Examination Survey 2003 to 2006 suggest that over 50% of US adults with a low 10-year risk have a high lifetime risk of CVD.[21] Initiating earlier treatment may result in substantial benefit over the life of these individuals but also potentially exposes them to long-term pharmacological therapy, of which the safety and cost-effectiveness is not fully established.

In contrast to the traditional approach of identifying risk factors for CVD, others have proposed direct assessment of the presence and severity of atherosclerosis/vascular disease. Cohn et al. developed the Rasmussen score[22] based on ten parameters including imaging modalities such as echocardiogram and carotid ultrasound. Similarly, the Screening for Heart Attack Prevention and Education (SHAPE) Task Force issued a consensus statement recommending that all asymptomatic men (45–75 years) and women (55–75 years) with a 10-year risk of CHD greater than 5% should undergo noninvasive imaging to detect subclinical CHD.[23] The SHAPE task force II is currently working to update to these guidelines.

MEASURES TO EVALUATE RISK PREDICTION MODELS

Several metrics exist to help clinicians evaluate the performance and utility of risk prediction scores including discrimination, calibration and reclassification.[24] Discrimination is the ability of a model to separate those with or without disease. The C statistic or area under the receiver operating characteristic (ROC) curve is widely used to report the discrimination ability of a

risk score. It indicates the probability of a randomly selected case having a higher score than a noncase. For instance, a C statistic of 0.80 predicts that a patient with disease will have a higher score compared to a healthy patient 80% of the time. 1.0 is perfect discrimination and 0.5 is random chance. A C statistic greater than 0.70 is considered an acceptable level of discrimination. The C statistic does not quantitate the difference of risk between the case and the noncase. Large odds ratios or relative risks are required to achieve an acceptable C statistic score.

Calibration of a test determines its ability to accurately predict the absolute level of risk by comparing the predicted to the observed event rate. A good model will have an observed event rate close to the predicted rate. A test may have good discrimination but poor calibration. Generally, a model cannot have a perfect discrimination and be perfectly calibrated at the same time.

Other measures include likelihood ratio tests and Bayes information criterion which are sensitive assessments, used as initial measures to ascertain the global fit of the model.[25] These assess the ability of a score to predict disease incidence better than by chance alone. A penalty is paid for the number of variables included. A risk score's ability to reclassify individuals from one risk category to another is also used to evaluate the utility of the model. Both the net reclassification improvement (NRI) (difference between appropriate reclassification and inappropriate reclassification) and how much the individual moved in order to be reclassified (termed the integrative discrimination index or IDI) are important when using reclassification.

TRADITIONAL CHD RISK FACTORS

NON-MODIFIABLE RISK FACTORS FOR CHD

Certain risk factors for CHD are non-modifiable including age, male gender and family history of CHD. Although these risk factors are non-modifiable, they are an essential part of the risk prediction algorithms and identification of patients at higher risk for CHD events. Based on the Framingham Heart Study and NCEP ATP III recommendations, a positive family history of premature CHD is defined as a coronary event in parents before age 55 years in men and 65 years in women. Parental CHD, on an average, doubles the risk of CHD in an adult offspring. CVD in siblings also increases the risk of incident CVD even after adjustment for traditional risk factors and parental history of CVD. Compared to parental CVD, sibling CVD is reported to be a stronger predictor of CVD.[26] The reported variability in risk with family history of CVD is possibly due to recall bias, difference in family size and referral bias.[26]

MODIFIABLE RISK FACTORS FOR CHD

Lifestyle Risk Factors

Lifestyle risk factors including physical inactivity, diet and psychosocial factors are established risk factors for CHD and carry considerable public health importance as targets for intervention. In the INTERHEART study,[27] healthy lifestyle behavior including eating fruits and vegetables, exercising regularly and avoiding smoking led to 80% lower relative risk for myocardial infarction.

Smoking: Cigarette smoking is an important risk factor not only for CVD but also due to its impact on non-cardiovascular morbidity and mortality. It is the single most important preventable cause of disease and early death.[28] Smoking is a major public health threat in low-to-middle income countries where CVD is already on the rise.

Cigarette smoking has several detrimental effects on the cardiovascular system including increase in heart rate and blood pressure, increased thrombogenesis, endothelial dysfunction, increased plaque instability and less favorable effects on lipids. These processes lead to a proinflammatory state and atherosclerosis. Cigarette smoking also decreases high density lipoprotein cholesterol (HDL-C) levels. These effects are directly proportional to the amount of tobacco smoked. There is no evidence that using filters or other barriers reduces the risk. Smoking cigars and pipe raises the risk of CHD, as does passive smoking. It is unclear if decreasing, but not quitting, tobacco use provides any benefit or not.[29] Quitting smoking both for asymptomatic persons and those with established CVD is an extremely effective preventive measure for decreasing CVD mortality. Past smokers continue to reduce their risk over 10 years and eventually reach that of a non-smoker. For secondary prevention, patients who quit smoking decrease their risk of recurrent myocardial infarction by 50%.[30] Patients who quit smoking after coronary artery bypass have better survival and lower rates of angina and hospital admissions compared to patients who continue to smoke.[31]

In the clinical setting, it is important that every patient undergoes a full assessment of smoking status. This includes amount, type and duration of cigarette smoking, any other tobacco products used, social and family environment and reason for smoking. Physicians should assess the patient's knowledge about specific harmful effects of smoking on the cardiovascular system. Practitioners can use the clinical practice guidelines issued by the US Department of Health and Human Services to effectively intervene on tobacco users. The five steps recommended for intervention, referred to as the 5As, are summarized in Table 6. It is important to continue to address

TABLE 6

The 5As for intervention for tobacco dependence*

1. *Ask about tobacco use*	Identify and document tobacco use status for every patient at every visit
2. *Advise to quit*	In a clear, strong and personalized manner urge every tobacco user to quit
3. *Assess willingness to make a quit attempt*	Is the tobacco user willing to make a quit attempt at this time?
4. *Assist in quit attempt*	For the patient willing to make a quit attempt, use counseling and pharmacotherapy to help him or her quit
5. *Arrange follow-up*	Schedule follow-up contact, preferably within the first week after the quit date

(*Fiore et al. Treating Tobacco Use and Dependence: Clinical Practice Guideline. Rockville, MD: US Dept of Health and Human Services; 2000)

smoking cessation at every visit. Physicians can also use the opportunity at the time of an acute myocardial infarction to provide smoking cessation counseling, as patients are more likely to be motivated to quit. Multiple options exist to help with smoking cessation including providing self-help materials to patients,[32] behavioral counseling[33] and group therapy. Support from spouse and family may also be important. Data regarding acupuncture and hypnotherapy for smoking cessation is inconsistent and these are not currently recommended. Physicians should be aware of different pharmacological therapy options available including several nicotine preparations, the anti-depressant drug bupropion and the more recently introduced medication vareniciline. In most patients, smoking cessation is associated with only mild weight gain. Any deleterious effects of even modest-to-major weight gain are likely minor compared to the harmful effects of continued smoking.[34] At a public health and policy level, restricting smoking in public places and at work, limiting tobacco advertising and promotion, and preventing tobacco sales to minors are some of the ways by which tobacco use can be decreased.

Physical inactivity: Physical activity is any bodily movement that expends energy. It is generally measured by self-reporting or occasionally by activity monitors. Cardiorespiratory fitness is a physiological characteristic of a person measured by exercise testing. Regular physical activity improves cardiorespiratory fitness. Any planned physical activity with the intent of improving one's health or fitness is considered exercise. It is important to note that not all physical activity is exercise.

Physical inactivity is an important and increasingly common lifestyle factor contributing to the global burden of CVD. Data from several lines of investigation link physical inactivity to CHD morbidity and mortality. Physical inactivity and excess caloric intake have greatly contributed to the global obesity epidemic. Physical activity exerts multiple cardiovascular benefits including decreased risk of developing hypertension, insulin resistance, and dyslipidemia and beneficial effects on endothelial function and thrombogenesis. The minimum recommended level of physical activity includes moderate intensity exercise for 30 minutes on at least 5 days of the week. The daily 30 minutes can be accumulated in as little as 10-minute sessions and may include walking, cycling, gardening, elliptical, swimming, recreational sports, etc. There are no recommendations for the maximum amount of physical activity and the 'optimal' level likely varies among different individuals and the endpoint desired (metabolic change vs peak fitness). Nearly half of the population fails to meet even the recommended minimum physical activity.[35] The small amount of excess risk reported with vigorous physical activity is negligible compared to the beneficial effects of regular physical activity. In patients with established CHD, physical activity and cardiac rehabilitation decrease risk of future coronary events and mortality.[36]

Guidelines to help physicians evaluate physical activity level and counsel appropriately have been published.[37] Physicians should assess the level of physical activity (both leisure time and at work) for all patients. Physical activity can be measured by recall questionnaire, diary or using a pedometer. Exercise prescriptions can provide more specific instructions to help with compliance. Referral to exercise programs or rehabilitation centers should be made as appropriate.

Nutrition: Diet is an important risk factor for CVD and also directly influences multiple CVD risk factors. Several dietary factors including the intake of fruits, vegetables, fatty acids, fiber, alcohol, excess salt and the ratio of carbohydrates, fat and lipids have been studied in relation to CHD risk (Table 7). Both epidemiological studies and intervention trials have demonstrated the importance of a balanced diet for CHD prevention.

Dietary lipids have an important role in the formation of atheromatous plaque. Diets, high in saturated and trans-fatty acids, are linked to higher rates of CHD.[38] Saturated fatty acids increase low density lipoprotein cholesterol (LDL-C) concentration. The principal source of saturated fatty acids is animal products and some commercially prepared meals. Consumption of polyunsaturated fatty acids decreases LDL-C. Primary food sources of polyunsaturated fatty acids include vegetable oil, soya bean and rapeseed. Eicosapentaenoic acids (EPA) and docosahexaenoic acids (DHA) are members of the n-3 fatty acid group derived from fish oil. Intake of EPA and DHA reduces plasma triglycerides, increases HDL-C and has beneficial effects on the cardiovascular system. Multiple proposed mechanisms for the benefit of fish consumption and omega-3 fatty acids include anti-inflammatory, antiarrhythmic and antithrombotic effects.[39] Guidelines recommend less than 30% of total calories from dietary fat and less than 7% from saturated fats.[40,41] Dietary primary prevention trials show benefit of reduced saturated fatty acid intake and increase in polyunsaturated fat intake on clinical cardiovascular endpoints.[42] Such dietary data should not be extrapolated to include intake of corresponding supplements.

High sodium intake is linked to hypertension, CHD and death. Current recommendations for the general population are to consume less than 5–6 gm of salt daily (equivalent of roughly 2,000–2,400 mg of sodium).[41,43] A diet rich in fiber and natural products, fruits and vegetables decreases risk of CHD.[38] The idea of combining foods or different diets, a portfolio, to achieve cholesterol control was suggested in the 1990s. The dietary portfolio contains four main elements including soy, nuts, viscous fibers and plant sterols and has been shown to reduce cholesterol.[44]

Nutrition is often neglected when counseling about CVD prevention and treatment. Health care providers quote lack of time and knowledge as barriers to successful nutrition counseling. Misleading information from the media is compounded by the lack of clinical trials. Despite patient counseling, the results are often disappointing in bringing substantial change in nutrition habits. In general, a cardioprotective or healthy diet is well balanced and includes different food sources. It should include the recommended amounts of fatty acids and sodium. The diet should be rich in fruits, vegetables, whole grains and high fiber foods. Fish should be consumed at least twice weekly.[40] A balanced diet also helps to maintain a healthy body weight. Consultation with a dietitian should be sought whenever available.

Obesity: Obesity is an independent risk factor for CVD and increases mortality. Obesity is also associated with multiple other

TABLE 7

Select studies involving dietary interventions and cardiovascular outcomes

Reference, Year, Study design, Duration (N)	*Study population*	*Intervention*	*Outcome*	*Results*
Dasinger ML, et al. Comparison of Atkins, Ornish, Weight Watchers and Zone diets for weight loss and heart disease risk reduction, 2005, RCT, 12 months (N = 160)	160 adults aged 22–72 yrs	Assigned to Atkins, Zone, Weight Watchers or Ornish diets	1 year changes in baseline weight and cardiac risk factors, and self-selected dietary adherence rates per self-report	Modest weight loss and reduction in total/HDL-C, C reactive protein, insulin without any significant difference among different diets
Howard BV, et al. Low fat dietary pattern and risk of cardiovascular disease, 2006, RCT, 8.1 yrs (N = 48,835)	48,835 post-menopausal women aged 50–79 yrs	Assigned to reduced fat, high fruits, vegetables and grains group or a comparison group	Fatal and nonfatal CHD, fatal and nonfatal stroke, and CVD (composite of CHD and stroke)	No difference in CVD, CHD or stroke
Hooper L, et al. Dietary fat intake and prevention cardiovascular disease: Systematic review, 2001, Meta-analysis, at least 6 months of follow-up	27 studies (30,902 persons years of observation) included	Advice about reducing or modifying dietary fat intake	Total and cardiovascular mortality and cardiovascular morbidity	Small reduction in total mortality 0.98; 95% confidence of interval 0.86–1.12) and cardiovascular mortality (0.91; 0.77–1.07). Cardiovascular events reduced by 16% (0.84; 0.72–0.99)
Hooper L, et al. Omega 3 fatty acids for prevention and treatment of cardiovascular disease, 2004, meta-analysis of RCTs and cohort studies, follow-up for at least 6 months, (N = 36,913)	36,913 participants from 48 RCTs and 41 cohort studies	Dietary or supplemental omega 3 fatty acids	Total mortality, cardiovascular events or cancers	No reduction in end point in persons taking additional omega 3 fats
de Lorgeril M, et al. Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction: Final report of the Lyon Diet Heart Study, 1999, RCT, 5 yrs (N = 423)	423 patients with CHD	Mediterranean diet versus western prudent	Composite endpoints of cardiac death and nonfatal myocardial infarction. Additional endpoints also included (unstable angina, stroke, heart failure, pulmonary or peripheral embolism	Significant reduction in composite end point (risk ratio 0.28, 0.015–0.53)
Sacks FM, et al. Effects on blood pressure of reduced dietary sodium and the dietary approaches to stop hypertension (DASH) Diet, 2001, RCT, 5 yrs (N = 412)	412 participants	Comparing DASH diet (rich in vegetables, fruits and low-fat dairy products) to typical western diet	Reduction in blood pressure	DASH diet with a low sodium level led to a mean systolic blood pressure reduction of 7.1 mm Hg in participants without hypertension, and 11.5 mm Hg in participants with hypertension
Liu S, et al. Fruit and vegetable intake and risk of cardiovascular disease: The Women's Health Study, 2000, Prospective observational, 5 yrs (N = 39,876)	39,876 female health professionals without CVD or cancer	Assessing fruit and vegetable intake	Nonfatal myocardial infarction, stroke, percutaneous transluminal coronary angioplasty, coronary artery bypass graft or death due to CVD	Significant inverse association between fruit and vegetable intake and CVD risk. Compared to median serving of 2.6/day the relative risk in those consuming 10.2 servings/day was 0.68 (0.51, 0.92; P = 0.01).
Tuttle KR, et al. Comparison of low-fat versus Mediterranean-style dietary intervention after first myocardial infarction (from The Heart Institute of Spokane Diet Intervention and Evaluation Trial), 2008, RCT, 46 months (N = 202)	202 patients with CHD	Comparison of Mediterranean diet, low fat diet and controls	Reduction in cardiovascular event and morality after first myocardial infarction	Primary outcome did not differ between Mediterranean and low fat diets but was significantly lower in either diet compared to the usual diet with adjusted odd ratio of 0.28 (0.13–0.63, p = 0.002)
Swain JF, et al. Characteristics of the diet patterns tested in the optimal macronutrient intake trial to prevent heart disease (OmniHeart): options for a heart-healthy diet, 2008, RCT, 19 weeks (N = 164)	164 participants with prehypertension and hypertension	Comparison of carbohydrate rich, high protein and high fat diet	Estimated cardiovascular risk	All three diets reduced blood pressure, total and low-density lipoprotein cholesterol levels, and estimated CHD risk

(Abbreviations: RCT: Randomized controlled trial; CHD: Coronary heart disease; CVD: Cardiovascular disease; HDL-C: High density lipoprotein cholesterol)

TABLE 8

Effects of obesity on different organ systems and diseases

- Increase heart rate, blood volume and cardiac output
- Left ventricular hypertrophy
- Diastolic dysfunction
- Obesity cardiomyopathy and congestive heart failure
- Arrhythmias
- Venous stasis and insufficiency
- Pulmonary thromboembolism
- Endothelial dysfunction
- Hypertension
- Dyslipidemia
- Insulin resistance
- Proinflammatory state
- Sleep apnea
- Pulmonary hypertension
- Stroke
- Coronary heart disease

CVD risk factors (Table 8), which in turn adversely affects the heart.[45] Obesity has reached epidemic proportions in many industrialized countries and its prevalence continues to increase, posing a major global health problem. Prevalence of childhood and adolescent obesity is also on the rise. Sedentary lifestyle, ease of access to food, increase in portion size and caloric intake are important reasons for the current obesity epidemic. Genetic factors and certain other environmental factors also predispose some individuals to excess weight.

Mechanisms by which obesity is associated with CVD are not completely understood. Adipocytes act as an endocrine organ and may play a central role in the pathogenesis through the release of adipocytokines. The role of different fat depots is also under active research. Several measures exist to define obesity, the commonest being BMI. The BMI is calculated as weight (kg)/height (m^2). Obesity is defined as BMI of greater than or equal to 30 (Table 9). Other indexes of obesity include waist circumference and waist-hip ratio, increases in which are also linked to adverse cardiovascular outcomes. Different cut-offs for abnormal waist circumferences according to ethnicity are summarized in Table 10. Both BMI and waist circumference should be recorded for overall risk assessment and tracked over time as a vital sign.

Weight loss can prevent and improve obesity related risk factors and CVD. Interventions for weight management include dietary changes, increased physical activity, pharmacological therapy and surgical treatment. A weight reducing diet combined with exercise can result in significant weight loss.[46] Reduction in calorie intake, regardless of the proportion of macronutrients (fats, proteins or carbohydrates), results in clinically meaningful weight loss.[47]

TABLE 9

Classification of obesity by body mass index

Body mass index (kg/m^2)	
• Underweight	< 18.5
• Normal	18.5–24.9
• Overweight	25.0–29.9
• Obesity Class	
— I	30.0–34.9
— II	35.0–39.9
— III	≥ 40

TABLE 10

Ethnic specific values for abnormal waist circumference

Ethnic group/region	*Waist circumference*	
North America	Male	≥ 102 cm
	Female	≥ 88 cm
Europe	Male	≥ 94 cm
	Female	≥ 80 cm
South Asians	Male	≥ 90 cm
	Female	≥ 80 cm
Chinese	Male	≥ 90 cm
	Female	≥ 80 cm
Japanese	Male	≥ 90 cm
	Female	≥ 90 cm
South and Central America	Use South Asian recommendations	
Middle East (Arab) and Eastern Mediterranean	Use European recommendations	

Despite great interest in pharmacotherapy for obesity, its clinical use is limited by modest weight loss, high relapse rate and side effects of the medications. Fenfluramine and dexfenfluramine were withdrawn due to their adverse effects on heart valves. Orlistat, a gastrointestinal lipase inhibitor, induces weight loss by decreasing fat absorption.[48] It is FDA approved and is available also for over the counter use for weight loss. Common side effects include oily stools, diarrhea and gas. Rimonabant, a selective cannabinoid-1 receptor blocker, improved weight and cardiovascular risk factors,[49] but was not approved in the United States over concerns about psychiatric side effects and did not reduce cardiovascular events in one large clinical trial.[50]

Surgical treatment for obesity includes various malabsorptive or restrictive procedures. In patients who have failed an adequate diet and exercise program, with severe obesity (BMI ≥ 40) or medically complicated obesity with a BMI greater than or equal to 35, bariatric surgery may be considered.[51,52] Long-term follow-up of patients after bariatric surgery continues to show weight loss, improvement in CVD risk factors and lower mortality.[53]

Psychosocial factors: Several psychosocial factors are associated with increased risk of CVD including depression, stress, anxiety, social isolation, lack of social support and stress at work.[54] In a meta-analysis, depression was shown to increase the risk of CHD by 64%.[55] In the MRFIT study greater depressive symptoms were associated with increased 18-year mortality.[56] Depression especially after coronary events is not only common but also increases the incidence of recurrent coronary event by threefold.[57] Lower socioeconomic class and adverse events in life are also associated with CVD. Poor socio-economic status is linked to increased risk of CHD through multiple mechanisms including unhealthy diet, lack of access to health care, excessive stress and tobacco use.

Type A behavior with associated hostility and anger raises the risk of CHD.[58] Social isolation and lack of social support

may increase the risk of CHD by 2–3 fold in men and 3–5 fold in women.[59] Marital discord worsens prognosis in acute coronary syndrome. Psychosocial risk factors tend to cluster in the same individuals and groups; for instance, job stress is linked to depression, hostility, anger and social isolation. This compounds the risk of CVD.

Psychosocial factors raise the risk of CVD through several mechanisms including greater likelihood of unhealthy behaviors such as smoking, alcohol and drug use and increased calorie intake and direct physiologic effects such as increased platelet activation and increase in inflammatory cytokines[60] and neuroendocrine reactivity[61] to stress.

Management of psychosocial risk factors is challenging in part due to the difficulty in defining an individual's level of risk and in part due to complex treatment. Moreover, the influence of these factors in any individual may change over time. Few trials show benefits of behavioral intervention on CVD risk or outcomes. Meditation decreases blood pressure and carotid artery intimal thickness in men. Extended cardiac rehabilitation (stress management combined with physical training and cooking sessions) improved depression, anxiety and quality of life at one year in patients with CHD.[62] In the Recurrent Coronary Prevention Project, behavioral counseling resulted in reduced type A behavior and decrease in cardiac risk.[63] Behavioral treatment in The Enhancing Recovery in Coronary Heart Disease (ENRICHD) trial reduced depression and social isolation in post-MI patients, but did not improve survival.[64] To reduce psychosocial risk factors, emphasis needs to be placed on modifying stress, improving quality of life and recognizing and treating depression and other mood disorders.

Hypertension

Hypertension defined as a blood pressure of greater than or equal to 140/90 mm Hg is a major risk factor for CVD. In fact, there is a strong, graded relationship between blood pressure and fatal coronary events: risk doubles for every 20 mm Hg increase in systolic blood pressure or 10 mm Hg increase in diastolic blood pressure. Various mechanisms by which hypertension leads to coronary events include hemodynamic stress on blood vessels and heart, increased myocardial oxygen demand, diminished coronary blood flow and impaired endothelial function. Several trials have shown reduction in cardiovascular morbidity and mortality by reduction in blood pressure.[65]

The seventh report of the Joint National Committee (JNC) on prevention, detection, evaluation, and treatment of high blood pressure recommends a treatment goal of less than 140/90 mm Hg for all individuals, however, in patients with CHD, renal insufficiency, congestive heart failure, peripheral vascular disease and diabetes a stricter goal of less than 130/80 mm Hg is recommended.[66] Treatment of pre-hypertension (blood pressure 120–139/80–89 mm Hg) with Candesartan reduced the risk of incident hypertension in the TROPHY trial.[67] Whether lowering of blood pressure to 'normal' (< 120/80 mm Hg) is beneficial is not clear. The next JNC guidelines are expected to be released in 2012.

Nonpharmacological interventions such as dietary modification,[68] moderation of alcohol consumption, smoking cessation, increasing physical activity and weight loss improve blood pressure and are recommended for any level of hypertension. Multiple drug classes exist to treat hypertension including beta blockers, calcium channel blockers, diuretics, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, renin inhibitors, vasodilators and centrally acting agents. First-line therapy is usually tailored to drug availability, cost, comorbid medical conditions and side effect profile of medications. Blood pressure lowering is more important than the choice of drug class. In a meta-analysis of 29 randomized controlled trials,[69] Turnbull et al. found that there were no significant differences in the primary endpoint of major cardiovascular events between regimens based on angiotensin converting enzyme inhibitors, calcium antagonists, diuretics or beta-blockers.

Hyperlipidemia

There is a strong positive association between total cholesterol and LDL-C and CVD risk. Elevated triglycerides and low HDL-C are also independent risk factors for CVD. Individuals with severely elevated levels of LDL-C due to genetic abnormalities show premature atherosclerosis. Conversely, individuals with certain loss of function variants of the PCSK9 gene, who have moderate life-long reduction in LDL-C, have up to 88% reduction in risk of CHD.[70] Different mechanisms by which LDL-C increases CHD include delivery of cholesterol to blood vessels, proinflammatory properties, role in plaque formation and plaque instability. High levels of HDL-C convey reduced risk of CHD. HDL-C exerts its protective effects on the cardiovascular system through numerous mechanisms including reverse cholesterol transport, antioxidant properties, inhibition of apoptosis and dysfunction of endothelial cells and inhibition of LDL oxidation.[71] Low HDL-C and elevated triglycerides frequently occur with the presence of small dense LDL particles. This pattern of dyslipidemia is referred to as diabetic or atherogenic dyslipidemia.

Elevated LDL-C is the primary target for therapy and reduction in LDL-C substantially reduces CHD risk. In patients with elevated triglycerides (≥ 200 mg/dL), non-HDL-C (total cholesterol minus HDL-C) is a secondary target for therapy due to a strong association with CHD risk.[72] Non-HDL-C highly correlates with levels of apolipoprotein B which is the major apolipoprotein of all major atherogenic lipoproteins. The non-HDL-C treatment goal is 30 mg/dL higher than LDL-C.

Lifestyle changes are important for management of hyperlipidemia including reduction in intake of saturated fats and cholesterol, increasing fiber intake, increasing physical activity and weight reduction. Pharmacological therapy is required to treat hyperlipidemia in many patients. The availability of HMG-CoA reductase inhibitors (statins) has revolutionized treatment for both primary and secondary prevention of CVD. Multiple large randomized controlled clinical trials have shown benefits of using statins for treatment of hyperlipidemia with an estimated 20–40% reduction in major cardiovascular events and mortality.[73] The reduction in risk for an individual depends both on their initial overall risk for CVD as well as the degree of elevation in cholesterol, in particular

LDL-C. Statins are usually first-line agents but combination therapy is sometimes required when LDL-C elevation is pronounced or multiple lipid abnormalities are present. Available agents include bile acid sequestrants, nicotinic acid, fibrates, ezetimibe or high doses of EPA/DHA. For low HDL-C, after controlling LDL-C and instituting lifestyle changes, niacin or fibrates can be used. Caution should be used when combining fibrate therapy with statins as it increases the risk of myopathy. Markedly elevated triglyceride levels (> 500 mg/dl) should be treated to prevent pancreatitis. The next NCEP guidelines are expected to be released in 2012.

Diabetes Mellitus

Diabetes is a strong and independent risk factor for CVD. Whether diabetes confers a risk of events similar to that of established CHD is controversial,[74,75] but current guidelines consider diabetes a CHD equivalent. Mechanisms by which diabetes causes CHD include increase in platelet aggregability, increase in inflammatory mediators, impaired endothelial function, dyslipidemia, increase in highly small, dense highly atherogenic LDL-C, among others.

Intensive glycemic control (hemoglobin A_{1C} ~7%) prevents microvascular complications but the impact on macrovascular complications including cardiovascular events is less well established. Recent large trials including the ACCORD[76] and ADVANCE[77] failed to show benefit of tighter control of diabetes (Hemoglobin A_{1C} < 6–6.5%) compared to usual glycemic control (Hemoglobin A_{1C} 7–7.9%) on major cardiovascular events. The American Diabetes Association and other major societies recommend a target Hemoglobin A_{1C} goal of less than 7%.[78]

Lifestyle interventions for prevention and treatment of diabetes are well established and are the recommended initial strategy.[79,80] Several different classes of drugs exist for treatment of diabetes the details of which are beyond the scope of this chapter.

Alcohol

Numerous prospective studies have suggested an inverse relation between moderate alcohol consumption (1–2 drinks per day) and CHD.[81] Mechanisms by which alcohol may exert beneficial effects on CHD include antioxidant effects, increase in HDL-C and antithrombotic action.[82] It is unclear if any particular type of alcoholic beverage is more protective. At the same time, alcohol use is associated with several health problems including cardiomyopathy, sudden cardiac death, cardiac arrhythmias, hypertension and stroke. Alcohol is an addictive substance and abuse of it remains a major public health problem.

Due to limitations of observational data, lack of clinical trials and the health hazards associated with its use, alcohol intake is not recommended as a cardioprotective strategy.[83] For patients with current or past abuse, systemic diseases including hepatic or cardiac problems, it is best to advise against alcohol use. On a case-by-case basis, for individuals who drink, 1–2 drinks per day for men and 1 drink for women is acceptable to advise.

EMERGING RISK FACTORS

More than a hundred non-traditional or emerging risk factors have been reported.[84] Whether they independently predict risk of CHD or add incremental information to existing risk factors continues to generate controversy and poses an obstacle to their incorporation into risk assessment and routine clinical practice. For a risk factor to be accurate and effective in predicting risk, it must meet certain criteria: It must have a strong, consistent association with the disease in a dose-response manner that is biologically plausible. It should be measured easily with acceptable reference values. It should be an independent predictor of major CHD events. It should reclassify a substantial number of individuals who were previously stratified by traditional risk factors and the results should be generalizable to different population groups.[14] Before a novel risk factor or marker is incorporated into guidelines, its predictive value must be tested in multiple ways in different populations.

A recent US Preventive Services Task Force Recommendation Statement concludes that the current evidence is insufficient to assess the balance of benefits and harms of using non-traditional risk factors for screening asymptomatic men and women.[14,85] Similarly, NCEP ATP III guidelines do not recommend routine use of emerging risk factors for risk assessment.

The emerging risk factors include both laboratory-based tests for biomarkers of atherosclerosis and noninvasive imaging modalities for detecting atherosclerosis. Some of the more commonly used emergent risk factors will briefly be reviewed.

HIGH-SENSITIVITY C-REACTIVE PROTEIN (hs-CRP)

hs-CRP has been extensively studied to help in risk stratification for CHD events. CRP is an acute phase reactant that is made by the liver. Inflammatory conditions result in a rise in CRP levels. Several CVD risk factors are also associated with higher levels of CRP. For cardiovascular risk prediction, an hs-CRP assay exists with levels less than 1.0 mg/L considered low risk, between 1.0–3.0 as intermediate risk and greater than 3.0 as high risk. hs-CRP independently predicts coronary events,[86] however, the risk is modest with about 1.5 times elevated risk of coronary events in patients with CRP greater than 2.0, after adjustment for traditional CHD risk factors.[87] The American Heart Association and Centers for Disease Control and Prevention endorse using hs-CRP as an optional test to help with further classification in particular of those patients who are at intermediate risk by FRS (Class IIa).[88]

Weight loss, physical activity, smoking cessation, cholesterol therapy with statins and niacin all decrease hs-CRP levels. In a subgroup of the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/Tex-CAPS) study Ridker et al.[89] showed that participants with LDL-C below and hs-CRP above the median benefited from lovastatin therapy [relative risk, 0.58 (0.34, 0.98)] in contrast to those participants with both LDL-C and hs-CRP below the median whose coronary events were not reduced [relative risk, 1.08 (0.56–2.08)]. Results from the randomized controlled JUPITER trial[90] suggest that hs-CRP

could be used to select patients (women ≥ 60 years, men ≥ 50 years) for primary prevention with statins. For secondary prevention, a sub-analysis from the PROVE IT study showed that lowering hs-CRP in patients with acute coronary syndrome with statins resulted in lower risk of future coronary events.[91]

LIPOPROTEIN (A) [LP(A)]

Lp(a) consists of an LDL particle linked to an apo A polypeptide chain. Levels of Lp(a) are genetically determined. There are no observed gender differences but racial differences exist. Whether Lp(a) is causally linked to CHD remains controversial.[92] A recent study using genetic data suggested causal relation of elevated Lp(a) to myocardial infarction.[93]

The European Atherosclerosis Society recommends screening for Lp(a) in patients at intermediate or high risk for CHD.[94] Levels of Lp(a) less than 50 mg/dL were recommended as the treatment goal using niacin, while acknowledging that randomized controlled trials are lacking. A North American panel endorsed testing for Lp(a) in patients who are moderate to high risk according to FRS, and decreasing the LDL-C treatment goal by 30 mg/dL in patients with high levels of Lp(a) (> 200 ng/mL).[95]

HYPERHOMOCYSTEINEMIA

Homocysteine is an intermediary product of methionine metabolism. Homocysteine can cause endothelial dysfunction and result in a procoagulant state. Many cross-sectional and prospective observational studies report a positive association between homocysteine levels and CVD. Untreated patients who are homozygous for homocystinuria have serum homocysteine concentrations five times above normal and increased risk of vascular events.

Dietary intake of folate, vitamin B6 and B12 affect homocysteine levels. Despite observational data linking homocysteine to CVD, multiple randomized controlled trials using supplementation with vitamin B12 and folic acid showed no reduction in the risk of major cardiovascular events in patients with or without preexisting vascular disease.[96,97] The 2007 American Heart Association guidelines for prevention of CVD in women recommend against using folic acid supplementation, with or without B6 and B12 for CVD prevention.[98]

LIPOPROTEIN-ASSOCIATED PHOSPHOLIPASE A2 (LP-PLA2)

Lp-PLA2 is an enzyme expressed by inflammatory cells in atherosclerotic plaques. In observational and epidemiological studies, Lp-PLA2 was modestly associated with an increased risk of CHD.[99] There is an approximately 10% increase in coronary events per one standard deviation higher Lp-PLA2 activity and mass. In one study[100] Lp-PLA2 increased the ROC curve minimally suggesting some clinical improvement in risk discrimination. Even though the FDA has approved a test for Lp-PLA2 for CHD, there is no trial evidence to date that Lp-PLA2 modification changes risk. A randomized controlled trial (STABILITY) involving the Lp-PLA2 inhibitor darapladib is expected to be reported in late 2012.

TABLE 11

Hemostatic factors associated with cardiovascular disease

- Fibrinogen
- Fibrin D-dimer
- Factor VII
- Factor VIII
- Plasminogen activator inhibitor
- Tissue plasminogen activator
- von Willebrand factor antigen
- Activated partial thromboplastin time
- Thrombin-antithrombin
- Activated protein C ratio

APOLIPOPROTEIN B

Apoliporotein B (Apo B) is a structural component of several lipoprotein particles which are atherogenic. Standardized assays for measurement of Apo B are available. Apo B is associated with increased risk of CHD.[101] Whether Apo B measurement predicts CHD risk beyond commonly assessed risk factors in the FRS is uncertain.[102]

Plasma Apo B levels may be useful as a treatment target. A target value of less than 85 mg/dL for patients at high risk for CHD is proposed by the Canadian Cardiovascular Society.[103] American Association of Clinical Chemistry recommends a treatment goal of less than 80 mg/dL in patients whose target LDL-C by NCEP ATPIII guidelines is less than 100 mg/dL.[104]

FIBRINOGEN AND OTHER HEMOSTATIC FACTORS

Several hemostatic factors involved in coagulation and fibrinolysis are associated with increased risk of CHD[105] (Table 11). Fibrinogen levels in the upper third of the control distribution are associated with a 2.0–2.5 times excess risk of future CVD.[106] The current assays are not standardized and whether fibrinogen and other hemostatic factors add to traditional risk factors is unclear. Physical activity can decrease levels of fibrinogen but there is no evidence from randomized trials that fibrinogen modification by lifestyle or pharmacological therapy decreases CHD events.

SUB-CLINICAL ATHEROSCLEROSIS

Detecting sub-clinical atherosclerosis with noninvasive imaging modalities has generated great interest. This is distinct from the general 'risk factor' concept. Whether early detection of atherosclerosis should lead to modification in therapy and whether such modification in therapy offers clinical benefit is not clear.

The presence of calcium in coronary arteries correlates with atherosclerosis and is measured using cardiac tomographic imaging. Coronary artery calcium (CAC) score, which quantifies the extent of coronary calcium, is reported as percentiles of calcification according to age and sex. A 'negative' test has a CAC score of 0 and is associated with a low risk of subsequent coronary events. Numerous studies show that CAC testing is an independent predictor of coronary events in both men and

women, from multiple racial and ethnic groups.[107,108] CAC score has high sensitivity and negative predictive value for angiographically obstructive CAD but its positive predictive value is low.[24] To date, it is unclear whether CAC testing should lead to change in therapy if that results in a favorable impact on clinical outcomes. Cost and radiation exposure also limit widespread CAC screening. CAC score may be used in select intermediate risk patients for further risk stratification.

Vascular intimal thickening is one of the earliest changes of atherosclerosis. Carotid arteries can easily be visualized because of their location and using ultrasound techniques the intima-media thickness can be determined noninvasively, without exposure to radiation. Increased carotid intima-media thickness is an independent predictor of cardiovascular risk.[109] Carotid intima-media thickness also correlates with multiple CVD risk factors.[110] Statin treatment decreases Carotid intima-media thickness. There is lack of consensus on examination techniques and reference standards for quantifying intima-media thickness.[85] Recently, the American Society of Echocardiography published a consensus statement proposing standardization of imaging and measurement protocols.[111] Correct patient selection, assessment of clinical benefit of treatment and lack of outcome data limits widespread use at present.

Ankle brachial index is a noninvasive test to diagnose and assess the severity of peripheral vascular disease. It is the ratio of systolic blood pressure in the ankle, measured at the level of the posterior tibial or dorsalis pedis artery, to that of the brachial artery. A lower value of ankle brachial index is not only an indicator for the severity of peripheral vascular disease but also correlates independently with major coronary events and stroke.[112,113] When used in conjunction with FRS, a low ankle brachial index ($\leq$ 0.90) approximately doubled the risk of cardiovascular events and death.[114]

At a population level, the best approach currently is probably to use the traditional risk factors for CHD screening. It is generally agreed that the established risk factors for CHD have very good ability to discriminate those at risk for CHD and account for over 90% of population attributable risk.[27] We need to ensure that the traditional risk factors and risk prediction tools are applied routinely in clinical practice. At the same time, clinicians should be aware of the emerging risk factors and may use their clinical judgment to use additional screening modalities to better gauge an individual patient's risk.

TRANSLATING RISK FACTOR SCREENING INTO EVENT REDUCTION

It is our responsibility to fully implement strategies to ensure that any risk factors identified are fully treated. Barriers to such implementation exist at the physician, patient, system and societal level.[115] Physicians can, through better communication and education, ensure better adherence to risk factor reduction strategies. Specific verbal and written instructions and prompt follow-up can help increase adherence. Monitoring progress goals and providing feedback can help patients stay on track, particularly with lifestyle modifications. There should be open communication between the specialists and primary care physicians. Enabling easy access to electronic medical records from index hospitalization as well as specialist visits should help primary care physicians to deliver risk factor reduction treatment on a long-term basis.

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Chapter 46

Changing Focus in Global Burden of Cardiovascular Diseases

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Chapter Outline

- CVD in High Income Countries
- Low and Middle Income Countries
- Risk Factors
- Global Response for Combating CVD

INTRODUCTION

Cardiovascular diseases (CVD), such as coronary heart disease (CHD) and stroke, are the most important causes of mortality and morbidity worldwide. Globally the burden of these diseases has shifted from high to middle and presently to low income countries. These diseases peaked in high income countries of Western Europe and North America in the middle of last century and have been declining there ever since. A decline is also observed, albeit at a lower pace, in many middle income countries in Eastern Europe and South America. However, in almost all low income countries of Asia, Central and South America and Africa, these diseases are increasing. In terms of absolute numbers the patients with these diseases are many times more in low income countries, such as China, India, Pakistan and Bangladesh, as compared to all other regions of the globe. This article summarizes burden of CVD, especially CHD, in high income countries and increasing burden of these diseases in middle and low income countries. We also enumerate the reasons for decline in mortality and morbidity from CVD in high income countries. Also suggested are policy actions and clinical measures for preventing and controlling these diseases in low income countries, the new focus in global CVD epidemiology.

CVD IN HIGH INCOME COUNTRIES

Globally, there is an uneven distribution of CVD mortality (Fig. 1). The lowest age-adjusted mortality rates are in the industrialized high income countries whereas the highest rates today are found in Eastern Europe and a number of low and middle income countries. For example, age-standardized mortality rates for CVD are in excess of 500 per 100,000 in Russia and Egypt; between 400 and 450 for South Africa, India, Pakistan and Saudi Arabia; and around 300 for Brazil and China. This is in contrast to rates between 100 and 200 per 100,000 for Australia, Japan, France and the United States. About 15% of world population lives in high income countries that include the United States, Canada, Australia, New Zealand, Western European countries in the European Union and Japan. The

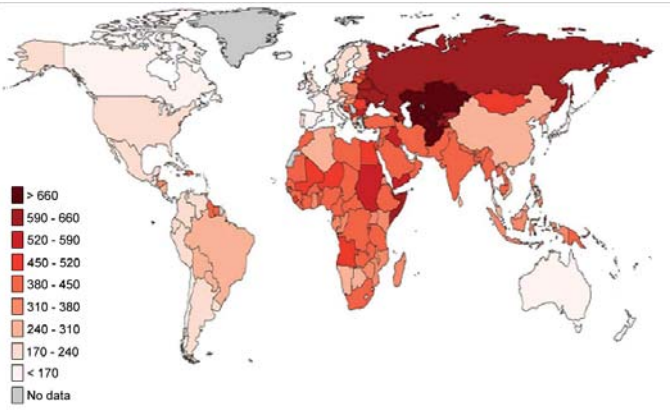


FIGURE 1: Cardiovascular mortality patterns in different countries. There is substantial variation in age-adjusted mortality rates. (*Source:* US Institute of Medicine Report, 2010)

epidemic of CVD has reached mature levels in these countries. Majority of CVD events occur in men and women greater than 70 years of age, there is low premature mortality and low morbidity. In the United States there has been a gradual decline in mortality from all forms of CVD, CHD and strokes, beginning 1970s (Fig. 2).

Examination of CHD mortality trends across countries reveals considerable variability in the shape and magnitude of CHD epidemics since the 1950s. Trends are not consistent even among countries or within the same geographic region. In general, the disease and mortality incidence increased, peaked and then fell significantly in many countries (Fig. 2). There are rising patterns, where rates have steadily increased indicating an ongoing epidemic; and a flat pattern, where CHD mortality rates have remained relatively low and stable. The rise-and-fall pattern is most notable in high income Anglo-Celtic, Nordic and Western European countries as well as in the United States and Australia. In these countries, CHD mortality rates peaked in the 1960s or early 1970s and have since fallen precipitously by an average of about 50%. The rising pattern of CHD is most notable in Eastern European and former Soviet countries, where

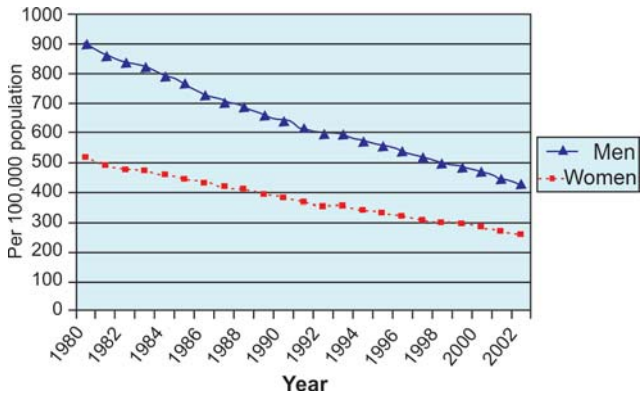


FIGURE 2: Declining mortality from coronary heart disease in USA. Trends in age-adjusted mortality rates for adults less than 35 years (*Source:* Modified from Ford, Capewell. J Am Coll Cardiol. 2007;50:2128-32)

mortality rates have continued to increase at an alarming pace and where the highest mortality rates ever recorded are currently being observed. Although data on CVD mortality trends in low income countries are scarce, an increasing trend, which is similar to the rising pattern in Eastern European nations, is observed in many of these countries such as China and India. By contrast, CHD mortality rates in Japan and several European Mediterranean countries have remained relatively low, following the flat pattern. Epidemiological transition, which is change in disease profile with societal changes, is responsible for changing disease patterns. Initially defined as changing disease profiles with aging and modernization, this is now considered a dynamic process with five distinct phases. These phases of epidemiological transition are shown in Table 1.

The theory of epidemiological transition was initially described by Omran. He described a progressive state of transition in evolution of communicable diseases in populations and hypothesized that the non-communicable disease epidemic also follows a similar trend. He postulated that in the initial phase, characterized by poverty, the diseases are related mainly to undernutrition and infection and death occurs at younger ages (Fig. 3A). With socioeconomic progress the diseases patterns change and infections are replaced with degenerative diseases. Gillum in early 1990s modified this schema after study of hypertension and stroke among the blacks in USA. He postulated that in a population initial lifestyle changes associated with affluence lead to increase in salt and fat intake leading to epidemic of hypertension, hypercholesterolemia and later to CVD. More socioeconomic evolution leads to positive changes in lifestyle with control of smoking, high blood pressure and cholesterol levels. This is associated with decline in CVD (Fig. 3B). The present phase in developed countries is characterized by massive increases in obesity and the metabolic syndrome that is poised to lead to a second wave of CVD epidemic (Fig. 3C). Recent studies have shown that despite increasing obesity, the metabolic syndrome and diabetes in developed countries the cardiovascular mortality has continued to decline due to greater decline in smoking and better control of hypertension and hypercholesterolemia (Fig. 3D).

TABLE 1

Epidemiological transition in disease patterns with societal progress and aging

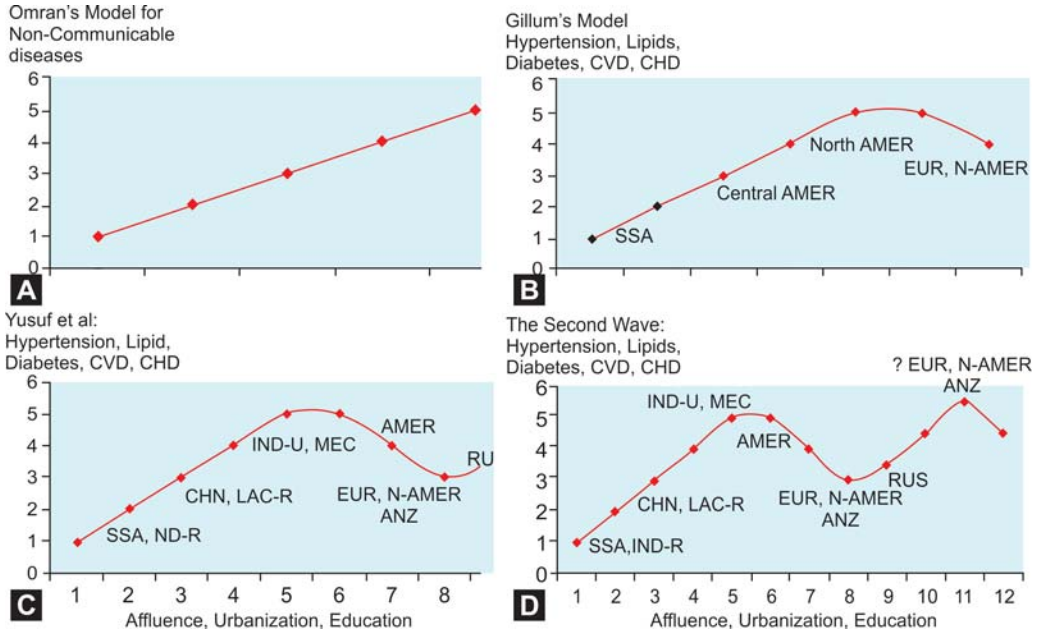
Stage of transition	*Societal development*	*Disease patterns*
Stage I	Stage of pestilence and famine, < 10% urban	Infection and undernutrition related diseases
Stage II	Stage of early development, 10–30% urban	Receding infective pandemics and emerging lifestyle habits
Stage III	Increasing urbanization and migration, 30–50% urban	Degenerative and lifestyle diseases
Stage IV	Stabilized population, > 50–60% urban	Age of delayed degenerative diseases
Stage V	Stage of social and economic upheavals in a stabilized population, > 60% urban	Increasing stress and lifestyle related diseases

The decline in CVD mortality in high income European and North American countries has followed two phases. The first phase of decline from 1970 to 1990s was due to population based measures for risk factor control initiated by changes in policies on smoking, substitution of vegetable oils for animal fats and physical activity promotion. The second phase of decline from 1990s to date is ascribed to better management of risk factors and acute CVD syndromes and short-term as well as long-term use of evidence based pharmacotherapies and coronary interventions or coronary bypass surgeries. Public healthcare financing and strengthening of primary, secondary and tertiary care are important in this regard. Influence of policy changes on CVD mortality in different countries is summarized in Table 2. It is observed that in countries where population based tobacco control policies, salt and fat control strategies and focused control of multiple CVD risk factors (mainly hypertension and hypercholesterolemia) by physicians have been actively pursued there has been a significant decline in CVD incidence varying from 50% to 90% over a 25–30 year period. In middle income countries of Eastern Europe where such initiatives were delayed there has been a lesser decline (20–40%).

LOW AND MIDDLE INCOME COUNTRIES

Researchers project that by 2030 non-communicable diseases will account for more than two-thirds of deaths worldwide; CVD alone will be responsible for more deaths in low income countries than infectious diseases (including HIV/AIDS, tuberculosis and malaria), maternal and perinatal conditions and nutritional disorders combined. Thus, CVD is today the largest single contributor to global mortality and will continue to dominate mortality trends in the future. Global deaths from non-communicable and CVD will continue to rise over the next 10 years, with sub-Saharan Africa expected to see the highest relative increase.

World Health Organization (WHO) estimates that chronic diseases—mainly cardiovascular disease, cancer, chronic respiratory diseases and diabetes—cause more than 60% of all deaths. In absolute terms it has been estimated that, in 2005, the total number of CVD deaths (mainly CHD, stroke and



FIGURES 3A TO D: Models of epidemiological transition and CVD mortality in different countries. (A) In the initial phase the chronic non-communicable diseases are considered a continuum and it is projected to progressively increase with increasing civilization. With socioeconomic progress the diseases patterns change and infections are replaced with degenerative diseases; (B) Gillum postulated that in a population initial lifestyle changes associated with affluence lead to increase in salt and fat intake leading to epidemic of hypertension, hypercholesterolemia and later to cardiovascular diseases. More socioeconomic evolution leads to positive changes in lifestyle with control of smoking, high blood pressure and cholesterol levels. This is associated with decline in cardiovascular diseases. The present phase in high income countries is characterized by massive increases in obesity and the metabolic syndrome that is poised to lead to a second wave of CVD epidemic; (C and D) Recent studies have shown that despite increasing obesity, the metabolic syndrome and diabetes in developed countries the cardiovascular mortality has continued to decline due to greater decline in smoking and better control of hypertension and hypercholesterolemia. (Abbreviations: SSA: Sub-Saharan Africa; AMER: Americas; EUR: Europe; CHN: China; IND: India; RUS: Russia; ANZ: Australia-New Zealand; U: Urban; R: Rural)

rheumatic heart disease) had increased globally to 17.5 million from 14.4 million in 1990. Of these, 7.6 million were attributed to CHD and 5.7 million to stroke. More than 80% of the deaths occurred in low and middle income countries. It was also estimated that there will be about 20 million CVD deaths in 2015, accounting for 31% of all deaths worldwide. This increase in CVD is due to a number of causes which include the following: (i) conquest of deaths in childhood and infancy from nutritional deficiencies and infection; (ii) urbanization with increasing levels of obesity; (iii) increasing longevity of the population so that a higher proportion of individuals reaches the age when they are subject to chronic diseases and (iv) increasing use of tobacco worldwide. In most countries in the world other than those in the West, the burden of disease is still due to a combination of infections and nutritional disorders as well as those due to chronic diseases. This double burden of disease poses a challenge that is not only medical and epidemiological, but also social and political.

Disease burden in a given country can be estimated using a variety of processes including national vital registration systems using physician certified cause-of-death data, sample registration surveys using trained enumerators and verbal autopsy instruments, epidemiological assessment using prevalence and incidence data and estimates derived from empirical modeling. Presently in most of the low and middle income countries global trends in CVD are based on models that use country-specific data from a diverse range of developed and developing countries including those of the European Union, Saudi Arabia, Pakistan, South Africa, China, Indonesia, Mexico, India and the United States. Over the past decade, the quality and availability of country-specific data on CVD risks, incidence and mortality has increased. What emerges are nationally derived data on risks and CVD outcomes. Therefore, in many developing countries, the lack of country-specific data on risks and CVD outcomes is less of an impediment to policy development and action. Nonetheless, before beginning a discussion of CVD trends and risk factor incidence around the world and in specific countries and regions, it is important to note several persistent limitations with the available data. Although, many countries have established health surveillance systems with death registration data, the quality of the data collected varies substantially across countries.

Mortality rates generally appear to be most closely linked to a country's stage of epidemiological transition. Epidemiological transition, a concept first proposed by Omran in the 1970s, refers to the changes in the predominant forms of disease and mortality burdening a population that occurs as its economy and health system develops as described above (Table 1, Figs 3A to D). In underdeveloped countries at the early stages of epidemiological transition, infectious diseases predominate, but as the economy, development status and health systems of these countries improve, the population moves to a later stage of epidemiological transition and chronic non-communicable diseases become the predominant causes of death and disease.

Although this general pattern connecting trends in causes of mortality and stage of development can be observed, it is

TABLE 2

Changes in policy and practice in European, North American and other countries that led to decline in CVD mortality

Country	*Political agenda*		*Risk factor prevention*			*Better risk factor and disease management*				*Decline in CVD mortality*	
	Strengthening of healthcare systems for acute and chronic CVD care	Public healthcare financing and insurance	Tobacco control policies	Food-modification initiatives	Physical activity promotion	Chronic diseases/ CVD focused physician education	Aggressive population based pharma-cological risk factor control	CVD focused primary care	CVD focused secondary/ tertiary care	Period evaluated	Percent change
Western Europe	++++	++++	+++	++	++	++++	++	+++	+++	1970-2000	(-) 40-45%
Finland	++++	++++	+++	++	+++	++++	++	+++	+++	1972-2007	(-) 75-80%
Germany	++++	++++	+++	++	+++	++++	++	+++	+++	1980-2000	(-) 39-50%
Spain	++++	++++	+++	+++	+++	++++	++	+++	+++	1970-2000	(-) 48-50%
England	++++	++++	+++	++	++	++++	+++	++++	+++	1984-2004	(-) 48-52%
Australia	++++	++++	+++	++	++	++++	+++	++++	+++	1968-2000	(-) 83%
USA	+++	++	++	++	++	++++	++++	+++	++++	1970-2000	(-) 60%
Russia	++	+++	++	+	+	++ +	++	++	+++	1970-2000	(-) 10%
Eastern Europe	++	++	++	++	++	+++	++	++	++	1985-2000	(-) 16%
China	+	+++	+	++	++	++	+	+	++	1985-2004	(+) 27-50%
India	+	+	++	0	0	+	0	0	+++	No data	—

Scale of 0 to 4+.

difficult to make generalized observations about CHD mortality trends for most low and middle income regions. This is due to limited trending data from many low and middle income countries as well as considerable country-to-country variability within regions. The data are strongest from Latin America, where several countries, such as Argentina, Brazil, Chile and Cuba, have experienced decline in CHD mortality rates in the past several decades. However, with the exception of Argentina, where rates declined by more than 60% between 1970 and 2000, the declines have generally occurred more recently (in the 1980s and 1990s) and have been less dramatic (between 20% and 45%) than those in high income countries. By contrast, the epidemic in Mexico appears to be worsening, with CHD mortality rates increasing by more than 90% between 1970 and 2000. Mortality rates in Peru have remained relatively low, following the flat pattern. In Asia, some high income countries, such as Singapore, have followed the rise-and-fall pattern, while CHD deaths in other countries (such as the Philippines, urban China and India) appear to be rising. Although trending data for most of Africa is not available, it has been reported that mortality rates for CVD and diabetes are rising in South Africa.

Because there can be so much variability in the nature of CVD epidemics within regions it is concluded that the most prudent strategy when grouping countries in similar epidemiological situations is to group according to CVD mortality pattern rather than by geographic region (Fig. 4). In India and China, the two major countries of the world, there is variable nature of epidemiological transition in different geographic regions. In rural areas of these countries infectious diseases are still predominant causes of deaths while in urban regions chronic non-communicable diseases predominate. The epidemic of CVD and CHD may have evolved in some highly developed social and ethnic groups in these countries which is similar to the countries of North America and West Europe.

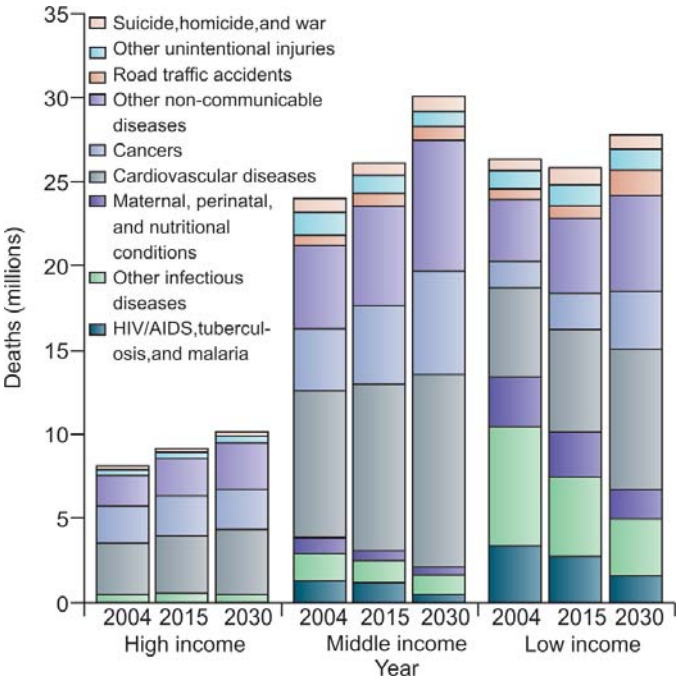


FIGURE 4: Trends in mortality from cardiovascular and other diseases in high, middle and low income countries. (*Source:* Modified from World Health Report, WHO, 2008)

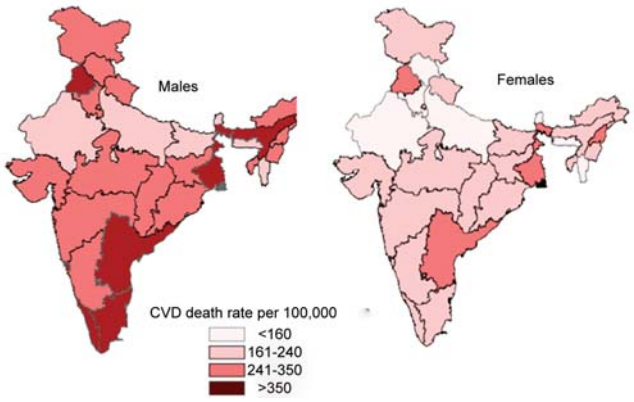


FIGURE 5: Geographic variation in cardiovascular mortality in different states of India in men and women according to Million Death Study in India (2009)

The geographic heterogeneity of CVD mortality rates in India and China are shown in Figures 5 and 6. In India, reliable mortality data using vital registration systems do not exist and there is paucity of data from other national sources. Mortality data from Registrar General of India prior to 1998 were poorly compiled and obtained from predominantly rural populations where vital registration varied from 5% to 15%. The first phase of the Million Death Study has reported mortality statistics from all Indian states using National Sample Registration System units. Causes of deaths in more than 113,000 subjects from about 1.1 million homes were analyzed using a validated verbal autopsy instrument. CVD were the single largest cause of deaths in men (20.3%) as well as women (16.9%) and led to 1.7–2.0 million deaths annually. The prospective phase of this study shall provide more information about trends in mortality from various causes. More robust vital registration systems need to be developed in India. Similar trends in CVD mortality are predicted from other countries of South Asia.

In China it has been observed that CVD are major causes of mortality (stroke and CHD in that order). Using Markov model and InterASIA study data the future risk factor trends in China were projected based on prior trends. CVD (CHD and stroke) in adults ages 35–84 years was projected from 2010 to 2030 and with risk factor levels held constant, projected annual

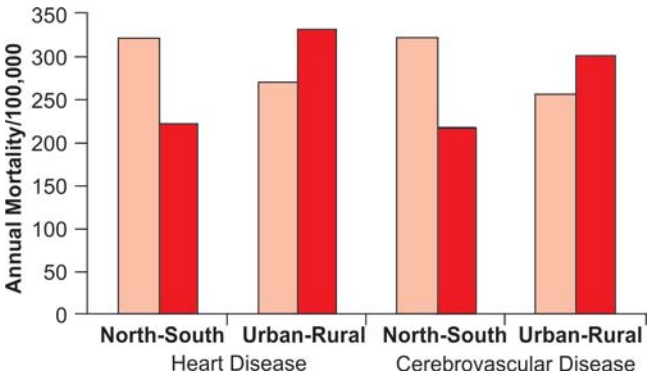


FIGURE 6: Variation in cardiovascular mortality in northern vs southern and urban vs rural regions of China. (*Source:* Modified from He et al. N Engl J Med. 2005;353:1124-34)

cardiovascular events increased by greater than 50% between 2010 and 2030 based on population aging and growth alone. Projected trends in blood pressure, total cholesterol, diabetes (increases) and active smoking (decline) would increase annual CVD events by an additional 23%, an increase of approximately 21.3 million cardiovascular events and 7.7 million cardiovascular deaths over 2010 to 2030. Aggressively reducing active smoking in Chinese men to 20% prevalence in 2020 and 10% prevalence in 2030 or reducing mean systolic blood pressure by 3.8 mm Hg in men and women would counteract adverse trends in other risk factors by preventing cardiovascular events and 2.9–5.7 million total deaths over two decades. It has been concluded that aging and population growth will increase cardiovascular disease by more than a half over the coming 20 years and projected unfavorable trends in blood pressure, total cholesterol, diabetes and body mass index may accelerate the epidemic.

The evolving epidemic of CVD in low and middle income countries and increasing burden of these diseases threatens to overwhelm their strapped health systems and cripple their fragile economies. CVD accounts for large burden from chronic diseases in low and middle income countries. This is especially true in urban centers of countries, such as China and India, where CVD is now the leading cause of disability. Increasing disability adjusted life years (DALYs) lost from CVD has been projected by WHO (Table 3). Hospital-based statistics have revealed an increasing burden of CVD patients (acute CHD and stroke) in low and middle income countries. WHO has predicted that DALYs lost from CVD as well as CHD shall double in both men and women in India. Another method to assess the burden of disease is analysis of CHD and stroke prevalence studies. In India, it has been reported that CHD diagnosed using history and ECG changes trebled in both urban and rural adults from mid-1960s to 2000s to 10% and 5% respectively. Similar trends are observed for stroke prevalence. There are no long-term prospective CHD incidence data. Stroke incidence registries using population-based surveillance have reported that annual incidence of strokes is increasing in these countries especially China (Fig. 7). Cross sectional studies provide only limited information of burden of diseases but can provide empirical assessment regarding increasing trends but have multiple limitations. There is need for properly designed prospective studies in different countries to correctly identify trends in incidence of CVD.

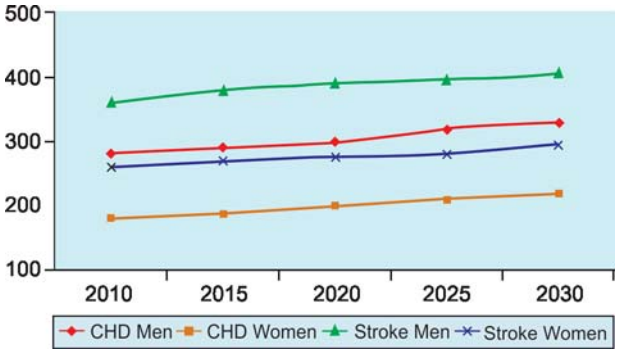


FIGURE 7: Projections for crude event rates (per 100,000) of CHD and hemorrhagic stroke in Chinese men and women ages 35–84 years projected from 2010 to 2030. (*Source:* Modified from Moran et al. Circ Cardiovasc Qual Outcomes. 2010;3:243-52)

RISK FACTORS

Risk factors for CVD have been extensively studied in developed countries. Multiple prospective studies have reported that smoking, high LDL cholesterol, low HDL cholesterol, hypertension and type 2 diabetes are major proximate risk factors. All these are caused by abnormal lifestyles characterized by sedentary habits, over-nutrition and stress. Scientific articles from the 1970s and 1980s suggest hypertension, cholesterol, poor nutrition, obesity, smoking, physical inactivity and psychosocial stress as the leading factors contributing to CVD and CHD. Tobacco use has been the most reliably documented and historical trends in CVD mortality and tobacco use in the United States from 1900 to 1990 closely mirror each other, with both rates increasing through the 1950s, followed by a precipitous fall beginning in the 1960s. There is a strong epidemiological, experimental, clinical and randomized trial evidence of support for some other risk factors such as high LDL cholesterol, low HDL cholesterol and hypertension, and control of them. In the United Kingdom, a 38 year follow-up of men showed that baseline differences in tobacco use, high blood pressure and cholesterol were associated with a 10- to 15-year shorter life expectancy from age 50. This study has significance for developing countries since many of the baseline levels of risk common in the late 1960s in the United Kingdom are the norm in many developing countries today.

The increase in CHD and stroke in low and middle income countries is largely an urban phenomenon and only now a rapid rise in rural population has been reported. There are no prospective studies from these countries that have identified risk factors of importance in either urban or rural populations. The case-control INTERHEART study conducted in 52 countries worldwide, with a large representation from low income countries, reported that standard risk factors, such as smoking,

TABLE 3

DALYs lost due to cardiovascular disease in low and middle income countries (in millions)

	1990	*2002*	*2005*	*2015*	*2020*	*2030*
China	22.9	25.4	25.4	25.5	26.1	27.1
India	23.4	30.7	32.2	35.2	37.4	41.6
Sub-Saharan Africa	11.6	11.7	12.7	16.1	17.97	22.8
Latin America/Caribbean	7.8	8.6	9.1	10.3	10.91	12.1

TABLE 4

Population attributable risks (%) of various cardiovascular risk factors for CHD and stroke in INTERHEART and INTERSTROKE studies

Risk factor	*INTERHEART (acute myocardial infarction)*	*INTERSTROKE (thrombotic or hemorrhagic strokes)*
Apolipoprotein A/B ratio	49.2	24.9
Hypertension	17.9	34.6
Smoking	35.7	18.9
Diabetes	9.9	5.0
High waist-hip ratio	20.1	26.5
Psychosocial stress	32.5	9.8
Regular physical activity	12.2	28.5
Diet	13.7	18.8
Alcohol intake	6.7	3.8
Cardiac causes	—	6.7

abnormal lipids, hypertension, diabetes, high waist-hip ratio, sedentary lifestyle, psychosocial stress and lack of consumption of fruits and vegetables, explained more than 90% of acute CHD events. Preliminary data from the INTERSTROKE study reported that these risk factors explained more than 90% of thrombotic and hemorrhagic strokes. However, population attributable risks are different for CHD and stroke (Table 4). There are only a few prospective studies that provide more direct insight into the causes of recent increase in CVD incidence and mortality in low and middle income countries. For example, in a study on the rise of CHD mortality in Beijing from 1984 to 1990, it was reported that blood lipid increase were the largest contributor—responsible for 77% of increased CHD mortality. Another likely contributor is a rise in smoking. There has been a steady rise in global cigarette consumption since the 1970s, which is expected to continue over the next decade if current trends continue.

An emerging body of evidence suggests that rapid dietary changes associated with nutritional transition, along with a decrease in levels of physical activity in many rapidly urbanizing societies, also may play a particularly important role in the rise of CVD observed in developing countries. The nutritional transition currently occurring in many low and middle income countries has created a new phenomenon in which it is not uncommon to see both undernutrition and obesity coexist in the same population. Epidemiological evidence suggests that dietary changes associated with the nutritional transition, specifically the increasing consumption of energy-dense diets high in unhealthy fats, oils, sodium and sugars, have contributed to an increase in CVD incidence in low and middle income countries. It is now clear that both smoking as well as obesity reduce life span by 10 years and cause equal CVD risk (Fig. 7).

Traditionally, monitoring of dietary consumption trends in low and middle income countries has been difficult due to poor availability of quality data. The Food and Agricultural Organization (FAO) of the United Nations examines trends in the amounts of various foods that are produced, which can serve as a rough proxy for consumption. This measure usually overestimates consumption, but trends remain valid indicators of the broad changes underway. FAO data indicate that the total kilocalorie intake per capita per day in many low and middle income countries as well as the consumption of animal products and some tropical oils (e.g. palm oil)—major sources of saturated fat—have been increasing.

Multiple epidemiological studies to identify prevalence of CHD and stroke risk factors have been performed in different low and middle income countries. Although many studies suffer from multiple biases inherent to population based prevalence studies, large regional studies, have provided important information. Tobacco production as well as consumption has been increasing rapidly in China and India. Prevalence of hypertension defined using earlier and more recent criteria has increased in both urban and rural populations and presently in urban adult subjects, it is prevalent in 25–40%. Lipids levels are increasing and serial studies from a north India city reported increasing mean levels of total, LDL and non-HDL cholesterol and triglycerides and decreasing HDL cholesterol. Although there are large regional variations in prevalence of diabetes, it has more than quadrupled in the last 20 years in urban as well as rural areas. Studies have reported increasing obesity as well as truncal obesity, increasing sedentary lifestyle and psychosocial stress. Trends in major CVD risk factors (smoking, obesity, hypertension, dyslipidemia and diabetes) in India are shown in Figures 8 and 9.

Social determinants of CVD have been inadequately studied in low income countries. There are multiple determinants that include the social gradient, stress, early life events, social exclusion, work conditions, unemployment, lack of social support, addiction including alcohol, tobacco use and smoking, food quality, lack of urban transport and illiteracy and low educational status. All these determinants have been extensively studied in high income countries where a direct correlation of CVD and risk factors with increasing levels of these determinants has been found. Low income countries suffer from social inequality and one of the highest income differentials within the countries are found in India and China. The inequality index (Gini coefficient of economists) is low in high income countries, such as Sweden, Norway and countries of West Europe, and is very high in Central and South American, East and South Asian and African countries (Fig. 10). The inequality is also increasing in these countries. All these countries also have a huge burden of cardiovascular risk factors and CVD.

GLOBAL RESPONSE FOR COMBATING CVD

Tackling the global epidemic of CVD needs policies that combine sound knowledge of prevention and good clinical care and also deal with the allocation of resources for both individual level and community level preventive strategies. The former involves dealing with high-risk individuals through appropriate medical and therapeutic interventions. The latter involves societal level changes including laws that curb the use of tobacco and strategies that promote physical activities and appropriate nutrition. Prevention and control from all types of CVD including CHD is a three pronged process:

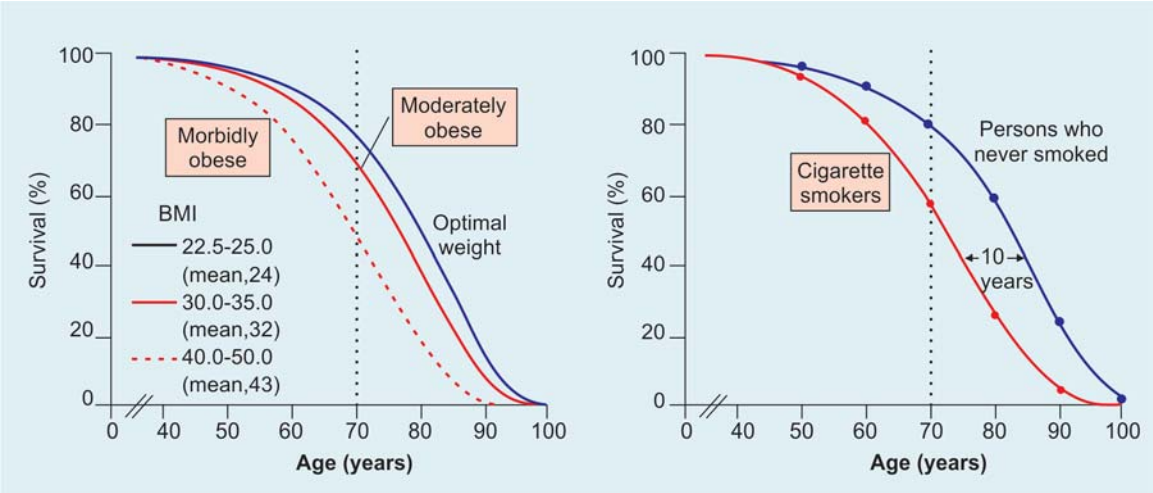


FIGURE 8: Influence of obesity and smoking on survival. (*Source:* Modified from Peto and Jha. N Engl J Med. 2010;362:855-7)

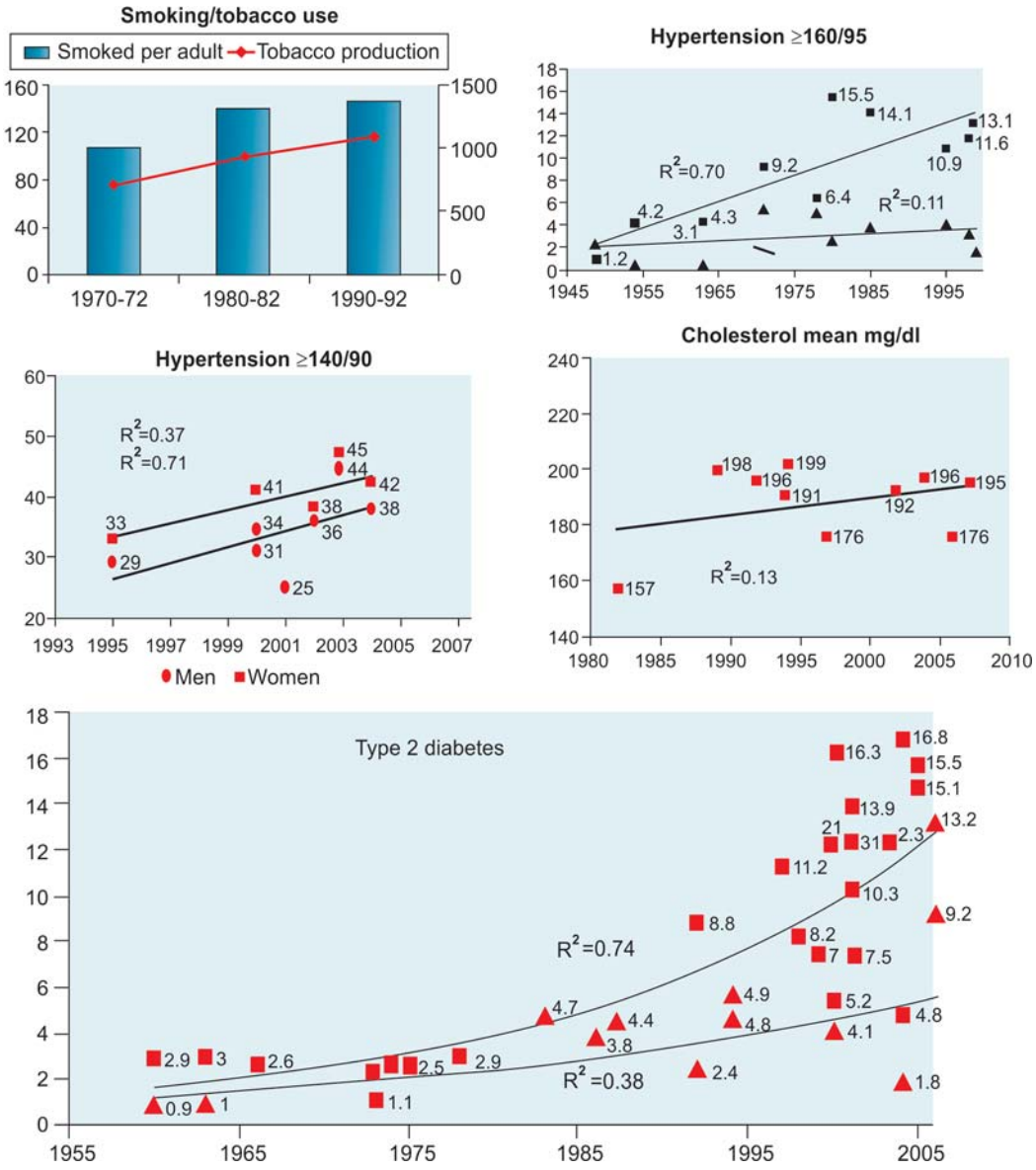


FIGURE 9: Secular trends in prevalence of major coronary risk factors in India. All the four major risk factors: smoking, hypertension, hypercholesterolemia and diabetes show a significant increase, both in urban (square marker) and rural (triangular marker) populations

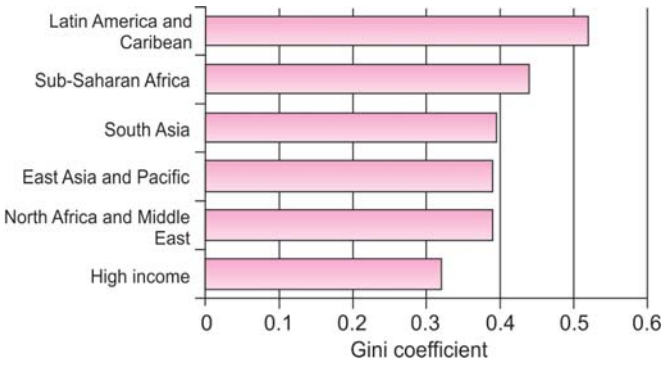


FIGURE 10: Inequality index (Gini coefficient) by region in 2004 (*Source:* Modified from The Economist 2010)

- Primordial prevention, i.e. prevention of occurrence of proximate CVD risk factors by lifestyle changes that involve control of three major risk factor determinants (smoking and tobacco use, physical inactivity and poor quality diet).
- Primary prevention, which is focused on control of proximate risk factors, dyslipidemia, hypertension and diabetes, using lifestyle changes and pharmacological measures.
- Secondary prevention, i.e. prevention of occurrence of second CVD event in patients with established CHD and stroke using lifestyle changes and evidence based pharmacotherapies and cardiovascular interventions.

Progression of CVD is a continuum and prevention extends across all stages of the diseases. Propensity to development of risk factors is either genetic or begins in early antenatal and postnatal period, risk behaviors start in early adolescence and young adulthood, risk factors commence in young to middle ages and depending on accumulation of risks the disease manifests in middle age in low income countries and at an older age in high income countries. The prevention continuum extends across all phases of disease. Social determinants of CVD, such as social organization, early life events, life course social gradient and hierarchy, unemployment, work environment, transport, social support and cohesion, food, poverty and social exclusion and low literacy, influence individual health behaviors and influence primordial, primary as well as secondary prevention. Primary prevention is focused on control of risk factors using both population-based and clinic-based control strategies while secondary prevention strategies involve acute and long-term disease management including lifestyle changes, revascularization and pharmacotherapy.

The decline in mortality from CVD in high income countries is almost all due to population wide decrease in risk factors, better risk factor management and better disease management strategies. Primordial prevention is focused on decreasing risk factor load in the population using strategies for increasing awareness and access through education regarding smoking and tobacco cessation, dietary modulation (low fat and high fruit and vegetables intake) and increased physical activity. It also involves addressing the social determinants of health through improvement in daily living conditions, fair distribution of power, money and resources and continuous upgradation of knowledge, monitoring and skills. Primary prevention is directed towards control of CVD risk factors, such as smoking, hypertension, high LDL cholesterol, low HDL cholesterol, metabolic syndrome and diabetes, so that onset of manifestation of CVD is avoided or delayed. Secondary prevention is use of lifestyle changes, risk factor control and pharmacological strategies in patients with established CVD (CHD, stroke and others) and tertiary prevention is use of advanced techniques, such as coronary interventions and bypass surgery, in addition to secondary prevention strategies in patients with established disease.

Prevention can also be seen as a pyramid with greatest focus on tackling social determinants of health, policies directed to smoking control, promotion of healthy diet and enhancement of physical activity. These issues along with better health insurance and public healthcare financing are also important. In developing countries the medical curriculum has to be extensively revised to focus on CVD. Conventional primary and secondary prevention which involve control of risk factors and better disease management also contribute to CVD mortality decline.

Approaches must be comprehensive and integrated which means investing in and combining measures that reduce the risks associated with poverty and implementing strategies that take a holistic and preventative approach. The evidence shows that the majority of CVD can be prevented by addressing risk factors like unhealthy diet, physical inactivity, alcoholism and tobacco use at policy, population and individual levels. Those that are non-preventable can be treated with essential medicines. While medicines, such as aspirin, penicillin and insulin, to control diseases and morphine to relieve pain have been on the WHO essential medicines list for years, the reality is that they remain beyond the reach of many. Funding models for HIV/AIDS, tuberculosis and malaria should be expanded to allow for the provision of essential medicines for CVD. Strategies for prevention include effective national CVD control program with financial and management support, risk factor control programs on smoking cessation, enhanced physical activity, dietary modulation and better risk factor and disease management.

A 10-point policy and clinical initiative that combines strategies of primordial, primary and secondary prevention and can be implemented in low and middle income countries is hereby suggested. The policies should focus on (i) improvement in socioeconomic status and literacy; (ii) implementation of national CVD control program; (iii) adequate healthcare financing and public health insurance for preventive and curative treatment; (iv) change in educational curriculum with focus on CVD; (v) smoking and tobacco control program; (vi) promotion of healthy diet with legislative control of saturated fats, trans fats, salt and alcohol and promotion of fruits and vegetables; (vii) increased physical activity through better urban planning, worksite and school-based interventions; (viii) aggressive primary prevention for control of smoking, hypertension, dyslipidemia and diabetes; (ix) implementation of evidence based acute care and (x) effective long-term care for secondary prevention.

CONCLUSION

Cardiovascular diseases are major pubic health problems worldwide. The diseases peaked in mid 1970s in high income

countries and age-adjusted mortality is declining in these countries since then. On the other hand the epidemic is increasing in low income countries and is established in middle income countries. Standard cardiovascular risk factors that are rampant worldwide are important in genesis of the disease. The risk factors include societal factors, primordial lifestyle factors (smoking, poor diet and physical inactivity) and primary proximate risk factors (smoking, hypertension, lipid abnormalities and diabetes). The reasons for rise and fall in CVD in high income countries have been well documented and include prevention and control of risk factors, better medical management of acute CVD events, better long term care and judicious use of advanced interventional techniques. On the other hand in low income countries rapid increase in urbanization and affluence is fuelling the increase in risk factors and increase in CVD mortality and morbidity. Tackling the epidemic of CVD in low and middle income countries is a global priority and needs policy response from governments and clinical response from medical institutions and physicians.

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Chapter 47

Evaluation of Chest Pain

Kirsten E Fleischmann, Raveen Pal

Chapter Outline

- Scope
- History
- Differential Diagnosis
- Patient's Description
  - Location
  - Radiation
  - Quality
  - Intensity
  - Associated Symptoms
  - Onset of Pain
  - Duration
  - Alleviating and Aggravating Factors
- Angina
- Past Medical History
- Physical Examination
- Investigations
  - Chest X-ray
  - ECG
  - Laboratory Investigations
- Estimation of Risk
- Diagnostic Testing
  - Treadmill Exercise Stress Testing
  - Stress Testing with Myocardial Imaging
  - Stress Myocardial Perfusion Imaging
  - Positron Emission Tomographic Perfusion Imaging
  - Stress Testing with Echocardiogram Imaging
  - Comparison of MPI to Stress Echo
  - Noninvasive Computed Tomographic Angiography
  - Invasive Coronary Angiography
- Guidelines

SCOPE

Chest pain is a common presenting symptom for patients visiting family physicians, general internists, cardiologists and emergency physicians. In 2009, there were 8 million visits to the emergency room alone due to chest pain.[1] Although chest pain is most often benign,[2] it may represent the symptoms of a life threatening process, such as myocardial infarction (MI) or aortic dissection, so a low threshold for prompt investigation is prudent. Indeed, heart disease is the leading cause of death in the United States. In 2009, an estimated 785,000 had a new heart attack, while approximately 470,000 had a recurrent heart attack.[3] This high incidence has resulted in the development of programs directed to both the general public and the general medical practitioners to promote awareness of the signs and symptoms of heart disease and the indications for further investigation of chest pain. Fortunately, through increased awareness and improved therapies, mortality from heart disease has decreased steadily in the last few decades.[4]

This chapter reviews the history and differential diagnosis of chest pain, the physical findings associated with cardiac ischemic pain and the role of various investigations in the further investigation and management of chest pain.

HISTORY

Chest pain has an extensive differential diagnosis, so the clinical history is critical in establishing the pre-test probability of any given diagnosis and to guide subsequent test decisions. Testing then refines this risk further into a post-test risk. Finally, the history is an important part of the physician patient interaction that helps patients to establish trust and provides the physician with important social information about the patient that may impact their management.

DIFFERENTIAL DIAGNOSIS

Chest pain has an extensive differential diagnosis. It may be useful to think of the differential diagnosis of chest pain by system (Table 1).

The first step in the management of chest pain is to rule out an immediate life threatening cause. Once stable vitals have been established and if the patient is not in extremis, it is reasonable to proceed with a more detailed history and physical examination, helping to differentiate among the various etiologies. The history includes the description of the pain itself and the patient's medical history and risk factors.

TABLE 1

Differential diagnosis of chest pain by system

- Cardiac
  - Angina
  - MI
  - Pericarditis/Myocarditis
  - Aortic dissection
- Musculoskeletal
- Gastrointestinal
  - Esophageal spasm
  - Reflux
  - Cholecystitis
  - Pancreatitis
- Pulmonary
  - Pulmonary embolus
  - Pneumothorax
  - Pneumonia
  - Pulmonary hypertension
- Neuropathic
  - Shingles
  - Costochondritis
  - Cervical spine
- Psychiatric

PATIENT'S DESCRIPTION

Description of patient's presenting symptoms should include details of location, radiation, quality, intensity, onset, duration, and exacerbating and alleviating factors.

LOCATION

Location of pain (retrosternal, epigastric, shoulder) can be useful to determine the source. A discrete location of pain, especially if reproducible with palpation, makes a musculoskeletal origin more likely. Epigastric pain more commonly has a gastrointestinal (GI) etiology, although ischemia, particularly in the inferior distribution, can sometimes mimic GI symptoms. Pain that follows a nerve distribution may be attributable to shingles. In general, location of pain is a poor discriminator.[5]

RADIATION

Radiation of pain to the jaw, neck, shoulders, arms or back can be useful in assessing the likely cause of chest pain. Pain radiating to the jaws or neck or arms is classically associated with cardiac ischemia. Radiation to the back is classically associated with aortic dissection. This feature can be used to rule in cardiac ischemia with a greater likelihood.[6]

QUALITY

Description of chest pain by the patient can be helpful. Angina may be described in many ways. However, most often it is described as a dull ache, squeezing or heaviness. Pain that is sharp or stabbing in nature is less likely to be ischemic in origin. Pain that is referred to as burning is more suggestive of a GI etiology. Classically, the pain of aortic dissection has been described as a tearing sensation. These various descriptors can help raise or lower suspicion for various causes of pain.

INTENSITY

Pain severity is typically graded on a scale of 1 to 10. However, recent data suggest that pain due to myocardial ischemia has a wide range of intensities and that severity is not useful to discriminate source of chest discomfort.[7] Thus, pain severity is most useful to grade relief from pain or change from previous episodes.

ASSOCIATED SYMPTOMS

Shortness of breath, diaphoresis, nausea and dizziness are symptoms that often accompany cardiac ischemia.

ONSET OF PAIN

Sudden onset versus gradual onset is a useful differentiating feature. Aortic dissection and pulmonary embolism tend to have sudden onsets. More gradual and escalating pain is more typical of cardiac ischemia. Cardiac ischemic pain tends to occur with activity. Also, cardiac pain has been reported to occur more frequently in the morning when sympathetic tone is highest.

DURATION

The length of symptoms is a useful piece of information. Pain that is brief and sharp, and conversely pain that is prolonged and unremitting for days, are both less likely to be ischemic in origin.

ALLEVIATING AND AGGRAVATING FACTORS

Pain with a pleuritic component that worsens with position or with respiration suggests a pericardial or respiratory etiology. Pain that worsens following meals, or at night after lying down, and is relieved with oral antacid preparations, suggests a GI etiology. Pain that is exacerbated by exertion or strong emotion is more typical of cardiac ischemia. While it is classically taught that pain relieved with nitroglycerin is suggestive of cardiac ischemia, it can also be esophageal in origin, limiting its usefulness as a distinguishing feature.[8]

It is important to recognize that, while pain descriptors make various etiologies of pain more or less likely, there is no perfect discriminator. Various studies have shown a wide range of likelihood ratios for different symptoms and signs.[9,10] Furthermore, elderly,[11] female[12,13] and diabetic[14] patients have been found to have more atypical symptoms. Thus, while the medical history can help to narrow the differential diagnosis and determine the next most appropriate steps in management, no one symptom is definitive.

ANGINA

Angina is a medical term derived from the classical Greek word "ankhon" meaning to strangle or choke. Angina pectoris is chest pain due to lack of blood flow to the heart, or cardiac ischemia. The first ischemic chest pain was described by Heberden in 1798; a painful sensation in the chest accompanied by a strangling sensation. This description remains largely unchanged today. Angina is still classically described as a dull, heavy, pressure-like sensation in the retrosternal area. Since angina is caused by inadequate blood flow to the myocardium, which is

innervated by the vagus nerve, there is a visceral nature to the pain that does not allow clear localization. It is broadly localized to the central chest area. Occasionally, patients will make a fist on top of their retrosternal area; this has been given the moniker the Levine sign, and may be associated with ischemia. Pain can radiate to the jaw, neck or shoulders. The intensity varies quite significantly and lasts for a few minutes to half an hour. (Please see the section "History").

Angina is due to a fixed coronary artery stenosis, less commonly dynamic coronary artery stenosis and spasm or small vessel disease, that does not allow adequate blood flow, and thus oxygen delivery, to the myocardium. Therefore, it is usually brought on by exercise, emotional exertion, or even after large meals; states that result in increased heart rate (HR) and/or blood pressure (BP) and, therefore, have increased myocardial oxygen demands. Coronary blood flow is increased during exercise, but oxygen extraction is not, since it is already at maximal levels. Therefore, oxygen delivery to the myocardium is directly proportional to vessel size. If there is a fixed coronary artery stenosis that limits blood flow, it, in effect, limits oxygen delivery to the myocardium. Thus, in states requiring increased myocardial oxygen, there is an imbalance between oxygen delivery and demand.

Double product (HR times BP) is an indirect marker of myocardial oxygen consumption in patients with fixed coronary stenosis, because it incorporates two variables that affect oxygen consumption. First, the systolic pressure developed by the ventricular wall (Laplace's law tension = pressure x radius/wall thickness) and second, the HR which determines diastolic filling time, during which the majority of coronary blood flow occurs. Since the degree of stenosis determines the amount of blood flow, the amount of physical activity that elicits angina appears to be related to the severity of stenosis rather than the number of stenoses.

Diurnal variation in angina has been reported. It can sometimes be reported consistently with sleep. It is speculated that this is due to the increased venous return to the heart in the supine position, which results in increased LV size, and therefore LV wall tension (Laplace's law), resulting in increased oxygen demand. Angina can also classically be reported as a morning phenomenon. It is thought that this is related to increased sympathetic activity following waking which results in increased HR and BP. These variables together result in increased oxygen demand with less delivery, resulting in angina. Angina is classically relieved with rest or the use of sublingual nitroglycerin. Nitroglycerin relaxes the vascular tone resulting in dilation of coronary vasculature, resulting in increased flow to the myocardium. This, at least temporarily, alleviates the oxygen delivery imbalance and relieves pain. It also decreases myocardial oxygen demand resulting from decreased left ventricular (LV) end-diastolic volume.

Diamond and Forrester [15] developed a simple classification scheme to determine the pre-test likelihood that a patient's pain was cardiac ischemic in origin. Patient's age and sex was recorded and their symptoms were divided into typical, atypical, non-cardiac and asymptomatic. Typical angina (definite) was described as: (1) substernal chest discomfort with a characteristic quality and duration; (2) provoked by exertion or emotional stress and (3) relieved by rest or NTG. Atypical angina (probable) met two of the above characteristics, and so-called noncardiac chest pain met one or none of the typical anginal characteristics. Based on age, gender and symptom description, the pre-test likelihood of angina was determined. This system continues to provide a rapid and reasonably reliable estimate of the likelihood that a patient's symptoms are reflective of coronary artery disease (CAD).

PAST MEDICAL HISTORY

Once the chest pain description has been clearly classified, risk factors for the development of CAD should be determined. Large population studies, like Framingham, followed participants prospectively and determined their risk of developing CAD depending on their medical conditions. From this cohort study, currently established cardiac risk factors include age, cigarette smoking, hyperlipidemia, diabetes and hypertension.[16,17] These clinical features are incorporated into a risk score (Fig. 1) that determines if a patient is at low (< 10%), intermediate (10% to < 20%) or high (≥ 20%) risk for the development of atherosclerosis over the next 10 years.[18] In addition, pre-established histories of kidney disease and coronary vascular, cerebrovascular or peripheral vascular disease are high-risk indicators. An alternate, revised risk score is the Reynolds risk score. This score incorporates all of the Framingham risk factors, but adds family history of CAD and requires a high sensitivity CRP determination.[19]

While risk factors increase the risk of underlying CAD, they have not been shown to predict whether an individual presentation of chest pain is or is not cardiac ischemic in origin.[20-22] A classic history, ECG finding and/or biomarker findings supersede clinical risk factor prediction.

PHYSICAL EXAMINATION

Following a history, the next step is to incorporate the patient's physical examination findings into a clinical decision making process. The physical examination starts with a general assessment of appearance. It is important to observe if the patient is in distress, diaphoretic, working hard to breath, pale or cyanotic. Concurrently vital signs, such as HR, BP and rhythm, should be recorded. Normal sinus rhythm is regular and between 60 and 100 beats per minute. The BP should be performed in both arms to detect discrepancies that may heighten suspicion for dissection or peripheral vascular disease. Respiratory rate and oxygen saturation should all be done routinely. An anatomical approach with review of the patient's head and neck area may reveal signs of hypercholesterolemia—specifically arcus senilis in patients under 50, xanthelasma and xanthomas in the feet. A fundoscopic exam may reveal signs of longstanding hypertension (pruning of arterioles distally, arteriovenous nicking, flame-shaped hemorrhages, optic head edema) or diabetes (hard exudates, microaneurysms, retinopathy).

A complete cardiovascular examination including inspection, palpation and auscultation should be completed. The carotid pulsation is palpated for volume and contour. Then all of the peripheral pulses (brachial, radial, renal, femoral, popliteal and dorsalis pedis) are palpated and areas overlying the carotid and femoral pulses auscultated for bruits. The jugular venous pressure (JVP) is examined for height and contour.

Step 1

Age		
Years	LDL pts	Chol pts
30–34	–1	[–1]
35–39	0	[0]
40–44	1	[1]
45–49	2	[2]
50–54	3	[3]
55–59	4	[4]
60–64	5	[5]
65–69	6	[6]
70–74	7	[7]

Step 2

LDL-C		
(mg/dl)	(mmol/L)	LDL pts
< 100	< 2.59	-3
100-129	2.60-3.36	0
130-159	3.37-4.14	0
160-190	4.15-4.92	1
≥ 190	≥ 4.92	2

Cholesterol		
(mg/dl)	(mmol/L)	Chol pts
< 160	< 4.14	[-3]
160-199	4.15-5.17	[0]
200-239	5.18-6.21	[1]
240-279	6.22-7.24	[2]
≥ 280	≥ 7.25	[3]

Step 3

HDL-C			
(mg/dl)	(mmol/L)	LDL pts	Chol pts
< 35	< 0.90	2	[2]
35-44	0.91-1.16	1	[1]
45-49	1.17-1.29	0	[0]
50-59	1.30-1.55	0	[0]
≥ 60	≥ 1.56	-1	[-2]

Step 4

Blood pressure					
Systolic (mm Hg)	Diastolic (mm Hg)				
	< 80	80-84	85-89	90-99	≥ 100
< 120	0 [0] pts				
120-129		0 [0] pts			
130-139			1 [1] pts		
140-159				2 [2] pts	
≥ 160					3 [3] pts

Note: When systolic and diastolic pressures provide different estimates for point scores, use the higher number

Step 5

Diabetes		
	LDL pts	Chol pts
No	0	[0]
Yes	2	[2]

Step 6

Smoker		
	LDL pts	Chol pts
No	0	[0]
Yes	2	[2]

(Sum from steps 1-6)

Step 7

Adding up the points	
Age	_____
LDL-C or Chol	_____
HDL-C	
Blood pressure	_____
Diabetes	_____
Smoker	_____
Point total	_____

Key	
Color	Relative risk
Green	Very low
White	Low
Yellow	Moderate
Rose	High
Red	Very high

(Determine CHD risk from point total)

Step 8

CHD Risk			
LDL Pts total	10 Yr CHD Risk	Chol Pts Total	10 Yr CHD Risk
< -3	1%		
-2	2%		
-1	2%	[< -1]	[2%]
0	3%	[0]	[3%]
1	4%	[1]	[3%]
2	4%	[2]	[4%]
3	6%	[3]	[5%]
4	7%	[4]	[7%]
5	9%	[5]	[8%]
6	11%	[6]	[10%]
7	14%	[7]	[13%]
8	18%	[8]	[16%]
9	22%	[9]	[20%]
10	27%	[10]	[25%]
11	33%	[11]	[31%]
12	40%	[12]	[37%]
13	47%	[13]	[45%]
≥ 14	≥ 56%	[≥ 14]	[≥ 53%]

(compare to average person your age)

Step 9

Comparative Risk			
Age (years)	Average 10 Yr CHD Risk	Average Hard* 10 Yr CHD Risk	Low** 10 Yr CHD Risk
30-34	3%	1%	2%
35-39	5%	4%	3%
40-44	7%	4%	4%
45-49	11%	8%	4%
50-54	14%	10%	6%
55-59	16%	13%	7%
60-64	21%	20%	9%
65-69	25%	22%	11%
70-74	30%	25%	14%

* Hard CHD events exclude angina pectoris

** Low risk was calculated for a person the same age, optimal blood pressure, LDL-C 100-129 mg/dl or cholesterol 160-199 mg/dl, HDL-C 45 mg/dl for men or 55 mg/dl for women, non-smoker, no diabetes

Risk estimates were derived from the experience of the Framingham Heart Study, a predominantly Caucasian population in Massachusetts, USA

FIGURE 1: Framingham risk score calculation. (*Source:* Wilson, et al. Circulation. 1998;97:1837-47)

Auscultation of the patient with chest pain usually reveals normal sounding first and second heart sounds. The S2 may demonstrate paradoxical splitting during active myocardial ischemia for the same reason as a left bundle branch block (LBBB); the delayed LV ejection time due to dysfunctional myocardium results in a later aortic component resulting in lack of splitting or paradoxical splitting of S2. The S3 can be heard, if there is associated heart failure, due to rapid and high volume LV filling. Actively ischemic myocardium also has decreased ventricular compliance, resulting in an audible S4.

Auscultation for systolic and diastolic murmurs is important in the aortic, tricuspid, pulmonic and mitral areas. The most common murmur heard in patients with CAD is one of mild mitral regurgitation due to ischemia and papillary muscle dysfunction. In particular, the murmurs secondary to acute complications of MIs, including acute mitral regurgitation, ventricular septal defect and free wall rupture, are important to seek. Also, the murmur of aortic regurgitation, which may suggest an aortic dissection, is important to rule out and may be accentuated by auscultation at end expiration with the patient sitting forward. Finally, the discovery of a pericardial rub may lend support to an alternate diagnosis of chest pain namely pericarditis.

The respiratory exam is an important part of a chest pain examination. There may be crepitations or crackles heard in the lower lung fields or throughout the lung fields depending on the degree of edema present. Crepitations localized to one focal area with evidence of consolidation may be more representative of an infectious process such as pneumonia. Active wheeze may represent bronchoconstriction, although pulmonary edema can present with wheezing as well. Finally an examination of the abdomen, searching for liver capsule tenderness, abdominal aorta size and epigastric pain on palpation should be completed (please see the section "Physical Examination").

Most commonly, the physical exam of a patient with stable CAD is quite benign. In the routine investigation of chest pain,

the physical exam is most important in ruling out an imminent life threatening cause requiring immediate investigation or intervention.

INVESTIGATIONS

CHEST X-RAY

The chest radiograph is a routine diagnostic test in the assessment of patients with chest pain. The cardiac silhouette may be enlarged due to LV chamber enlargement, resulting in a high cardiac:thoracic (C:T) ratio. Longstanding hypertension or LV dysfunction can lead to left atrial enlargement, suggested by flattening of the left heart border, splaying of the left and right bronchus, or by a double right heart border. The right ventricle (RV) may also be enlarged due to infarction, volume overload or pulmonary hypertension and is marked by loss of the retrosternal airspace in the lateral projection. Right atrial enlargement is seen by a prominent right heart border.[23] Aortic arch, aortic valve and mitral valve calcification can be viewed on plain radiographs and are associated with increased risk of atherosclerosis.[24] Coronary artery calcification is difficult to visualize on plain radiographs, but if present is also a high risk indicator of coronary atherosclerosis. There may be signs of congestive heart failure; plethoric pulmonary arteries, peribronchiolar cuffing, interstitial edema, Kerley B lines and blunting of the costophrenic angles with pleural effusions. There may be signs of pulmonary hypertension, prominent pulmonary arteries with rapid pruning, with right atrial and/or RV enlargement.

Chest radiograph is most commonly normal in a patient with anginal chest pain, but may be helpful in identifying a non-cardiac diagnosis or to diagnose complications of acute cardiac ischemia. In patients with aortic dissection, there may be a wide mediastinum, pericardial effusion or displacement of calcium from the soft tissue border of the aorta. In pulmonary embolus, there may be RV and pulmonary artery enlargement, a Westermark sign (a zone of avascular tissue), or Hampton's hump (wedge-shaped density along the periphery consistent with infarction).[25] Clear signs of an infiltrative process, a pneumothorax or a mediastinal mass may also help to direct the diagnosis.

ECG

The resting electrocardiogram (ECG) is normal in up to half of individuals who present with undifferentiated chest pain. A normal ECG is very useful in reducing the probability of acute coronary syndromes (ACS).[26,27] However, a retrospective series of patients presenting to an outpatient cardiology clinic for evaluation of recent chest pain showed that up to 30% of patients ultimately diagnosed with unstable angina (UA) had a normal ECG.[28]

An abnormal ECG may reveal the presence of Q waves suggesting a previous MI. However, it is important to note that prior MI may not result in the presence of a Q wave and that the presence of Q waves is not pathognomic of infarction, particularly if seen in leads III, V1 and V2.

Changes in the ST segment are important to pursue. Elevation of more than 1 mm in two or more consecutive leads is highly concerning for acute transmural infarction and requires immediate evalution for possible intervention. ST flattening and ST depression are also commonly witnessed and are also highly suggestive of ischemia. The only changes seen on an ECG may be T wave flattening or inversion. Deep symmetric T wave inversion in the anterior precordial leads is referred to as Wellen's sign, a marker of LAD territory ischemia. The presence of ST elevation, Q waves, ST depression, T wave inversion or new conduction defects all significantly increase the risk of chest pain being cardiac ischemic in origin.[27,29]

Comparison with a prior ECG and serial ECGs are very helpful in the interpretation of ECG changes. Patients may have longstanding non-specific ST segment flattening. The presence of the same findings during an episode of chest pain in a patient with a previously normal ECG is far more concerning. Subtle ECG changes which are transient during an episode of chest discomfort are highly suspicious for cardiac ischemic changes. Finally alternate causes of ST and T waves changes, such as pericarditis, metabolic states, digitalis effect or hypertrophic cardiomyopathy, should always be considered.

LABORATORY INVESTIGATIONS

Laboratory biomarkers can be useful for determining diagnosis as well as prognosis in cardiac disease. In addition to this, biomarkers help to identify the subset of patients most likely to benefit from more aggressive therapeutic interventions. As myocardium becomes ischemic and necrotic, the myocardial cell membrane integrity is compromised resulting in leakage of intracellular enzymes. While there are multiple enzymes (myoglobin, creatine kinase, troponins) that are specific to muscle cell compromise, there are only a few enzymes, such as troponins T and I, that are specific to cardiac muscle cells. The presence of these enzymes in the blood stream implies loss of specifically cardiac muscle.

Creatine kinase (CK) has multiple isoforms such as MM, BB and MB. The MB form is most concentrated in cardiac muscle. In the past, unfractionated CK or CK-MB were the primary cardiac markers used in the evaluation of ACS. The CK-MB is limited by its specificity since it can also be released by strain or damage to skeletal muscles and it is occasionally present in normal healthy individuals.[30] Troponin detection is the current key tool in the diagnosis of MI. The troponin complex is composed of Troponin T, I and C. The Troponin I (TnI) and Troponin T (TnT) of cardiac myofibrils are distinct from those of skeletal muscles. Therefore, if cardiac myofibrils undergo damage, cardiac-specific TnI or TnT is released into the bloodstream.[31] Troponins have both greater specificity and greater sensitivity for small amounts of cardiac damage than CK-MB.[32] Troponin elevation without CK-MB elevation has been found to be associated with evidence of focal myocardial necrosis. One study estimated that 30% of patients who presented with rest pain, and without ECG changes, would have been diagnosed as having UA rather than non ST elevation myocardial infarction (NSTEMI), based on CK-MB alone versus TnI or TnT. It is important to distinguish between detection of myocardial damage and the cause of myocardial damage. While myocardial strain or damage can be inferred by the release of TnI or TnT into the bloodstream, myocardial strain can be secondary to many causes other than ACS and underlying

CAD. Congestive heart failure, chronic kidney disease, LV hypertrophy and extreme exercise are all common alternate explanations for an elevated troponin. Elevated levels of TnI or TnT also provide useful prognostic information. Patients with elevated levels of TnI or TnT are at increased risk of death, irrespective of whether the troponin elevation is identified as having a cardiac cause or not.[33,34] When elevated troponin is due to CAD, the amount of troponin released is related to the amount of damaged myocardium. Larger amounts of troponin release are associated with increased risk of death.[35,36] Troponin elevation can also help to identify the subset of patients presenting with ACS who will benefit from GpIIb/IIIa inhibitor treatment[37] and LMWH treatment.[38] Only patients who were biomarker positive showed a lower risk of death or MI when treated with these more aggressive medications. Cardiac biomarkers have varying kinetics with respect to their release into the bloodstream and, thus, their availability to detection. Therefore, it is critical to correlate the presence or absence of a particular biomarker in the blood stream with the onset of the patient's symptoms. While myoglobin is the earliest detectable biomarker, its lack of specificity limits its utility. CK is present in the bloodstream as quickly as 2–4 hours after the onset of damage. As compared with troponins, CK levels peak more quickly (24 hours) and clear much more quickly. Troponins are typically not present until 6 hours after the onset of damage, they take 5–7 days to peak and can persist for 10–14 days. These timelines are important in determining presence of damage and whether or not recurrence of pain is associated with recurrence of damage. Thus, if troponin is negative immediately after, or within the first 6 hours after, an episode of pain, it must be repeated, so that it is being measured at least 8–10 hours after pain in order to ensure that it is in fact negative. Furthermore, it is important to understand that troponin levels may be persistently elevated after an episode of cardiac damage. Thus, if a patient has an MI on day one and then experiences more pain on day 5, a single elevated troponin may simply represent residual biomarker from the incident MI, not a recurrent MI. If serial troponin levels are increasing, however, this would be consistent with a recurrent ischemic event.

ESTIMATION OF RISK

As aforementioned, the Framingham and Reynolds risk scores are population based risk scores that predict an individual's risk of having a heart disease event in the longer term.

However, other scores have been developed that address the more acute risk of adverse events in patients with ACS. Risk of death or other adverse outcome based on initial presentation has been assessed in multiple large trials. The thrombolysis in myocardial infarction (TIMI) risk score is one score that assesses 7 aspects of the history and physical examination to predict the risk of adverse outcome. Age more than 64 years, greater than 3 CAD risk factors (family history, hypertension, increased cholesterol, diabetes, smoking), known CAD (stenosis > 50%), aspirin use in the last 7 days, recent (< 24 hours) severe angina, increased cardiac markers and ST deviation on ECG greater than or equal to 0.5 mm are each assigned a single point. The risk of death, MI or urgent revascularization by 14 days based on this score ranges from 5% to 41%.[39]

Another score, the Grace risk score, derived from a population with undifferentiated chest pain, incorporates age, HR, systolic BP, Killip class (degree of pulmonary edema/shock), presence of ST deviation on ECG, cardiac arrest, creatinine and elevated cardiac biomarkers to predict in-hospital mortality. It has been shown to be predictive of both shorter (30 days) and longer term (1 year) mortality.[40]

One limitation of these scores is that they have been derived from trial populations that tend to exclude very high and very low risk patients. So, their application to all patients is unclear. Also, known high-risk indicators, such as kidney dysfunction, are not included since these patients tend to be excluded from the clinical trials from which these scores are derived. Finally, regression models used to derive these prediction scores can result in statistical significance, but not necessarily clinical meaning.

Thus, while these scores can be used to determine, how aggressively a patient should be treated with medications and interventions, clinical judgment must always be factored in.

DIAGNOSTIC TESTING

Several testing modalities are available to help determine whether an individual patient's chest pain is due to CAD or ischemia. The main distinction among testing modalities is functional versus anatomic testing. Functional tests investigate the effect of stress on the myocardium, while anatomic tests image the coronary arteries that provide blood flow to the myocardium. Functional tests generally employ stress in the form of exercise (treadmill or bicycle) or pharmaceutical agents (dipyridamole, dobutamine and adenosine). There are many combinations of these stress and imaging modalities. The most commonly applied stress test is the treadmill electrocardiogram test (ETT), which involves stress in the form of ambulation and electrocardiography as the main assessment tool. It is important to understand that each test has its own sensitivity and specificity for the detection of CAD. Thus, depending on the pre-test likelihood of a patient's having CAD, a test will further increase or decrease that probability.

The choice of stress test often relates to patient factors that make either a test inappropriate or uninterpretable. For example, treadmill stress testing is generally inappropriate in a person unable to exercise, or with ACS, unstable arrhythmia, symptomatic heart failure, acute aortic dissection, acute pericarditis/myocarditis, or acute pulmonary embolism. Additional relative contraindications include known left main disease, uncontrolled systolic hypertension at rest, severe aortic stenosis or dynamic LV outflow obstruction, high-grade atrioventricular block, and severe peripheral vascular disease. Testing would be uninterpretable in someone with resting ECG abnormalities (ST-T shift, LBBB, digitalis effect, accessory pathways, paced rhythm) that interfere with assessment for ischemia, and limited exercise capacity or beta-blocker use may blunt the ability to elevate HR to diagnostic level and therefore reduce sensitivity.

If a patient is unable to exercise, a pharmaceutical agent can be used to simulate exercise. The most common agents used are dipyridamole, adenosine and dobutamine. These agents are mostly used in conjunction with nuclear perfusion imaging, although echocardiography has also been performed.

Dobutamine is a positive inotrope that increases both the HR and the strength of contraction, resulting in ischemia if a stenosis is present. It is most commonly paired with echocardiography. The choice of a pharmaceutical agent is also affected by the patient's clinical factors. Dipyridamole can worsen bronchospasm and heart block, while dobutamine can cause or exacerbate paroxysmal arrhythmia. LBBB and paced rhythms can cause significant artifact in nuclear perfusion images and abnormal septal motion in dobutamine stress echocardiograms, but are still considered preferable to exercise electrocardiogram alone. Differences in cost, local availability and local expertise may also drive testing decisions.[41]

TREADMILL EXERCISE STRESS TESTING

An ETT involves ambulation on a treadmill according to a specified protocol. The most common is the Bruce protocol that involves an increase in speed and inclines every 3 minutes.[42,43] The test is continued until the patient fatigues, the target HR (85% of peak HR) is achieved, or concerning symptomatic, electrocardiographic or hemodynamic changes are noted.

It is imperative to consider the pre-test probability of CAD in the patient prior to the application of a stress test. In a classic study of patients with a wide range of pre-test likelihoods of CAD (7–87%) based on chest pain description, a positive ETT only increased the pre-test risk by 6–20% and a negative ETT decreased the post-test risk by only 2–28%.[44] This is in part due to limitations in the diagnostic performance of ETT. A large meta-analysis of ETT, in comparison to angiography as the gold standard, showed a wide variation in the sensitivity and specificity of ETT. These researchers found that the mean sensitivity was 68% ± 16%; range, 23–100% and mean specificity, 77% ± 17%; range, 17–100%). When the analysis was restricted to those patients who agreed to both tests prior to either examination, the sensitivity was 50% and the specificity was 90%.[45] In a more recent study of ETT, the sensitivity of treadmill exercise testing alone was 45%, with a specificity of 85%.[46] However, in populations with a low pre-test likelihood of CAD, the specificity of ST-segment depression for detecting CAD decreased to the range of only 60%. Specificity can be increased by increasing the amount of ST segment depression required for a positive study from 1 mm to 2 mm. However this comes at the risk of decreased sensitivity.

The ETT can also be used to provide prognostic information with the calculation of a Duke treadmill score. This score incorporates total exercise time, degree of ST segment deviation and presence/absence of anginal symptoms to predict risk of future cardiac events and death. This score can also be used to diagnostically predict the likelihood of CV disease. Patients with high-risk scores (< -11) were associated with a 74% chance of 3 vessel or left main disease. However use of the score does not improve the sensitivity of the test.[47]

These studies all highlight the limitations of ETT and the need for judicious application of the test to the appropriate population and the need for clinical correlation. If the history of chest discomfort is non-anginal in nature, but an ETT is ordered, there is an approximately 40% chance that it will be falsely positive resulting in further unnecessary testing. Alternatively, if the history is very suggestive of anginal discomfort, but the ETT is negative, further testing may still be warranted.

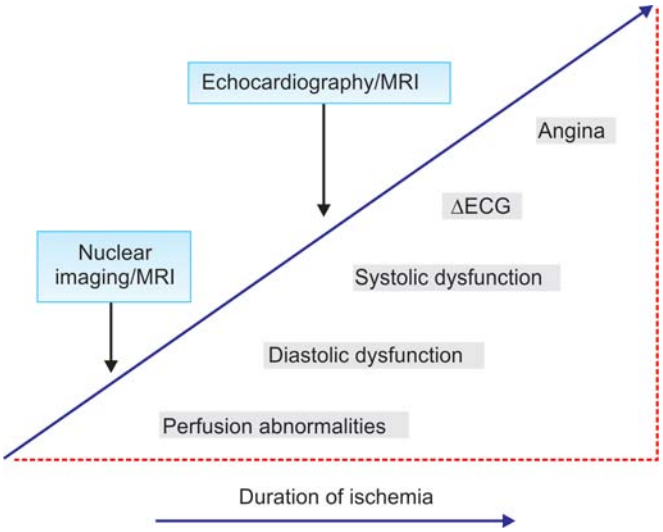


FIGURE 2: Diagrammatic representation of the ischemic cascade with increasing time from onset of ischemia (as with increasing heart rate and BP with exercise stress). Regional hypoperfusion (that can be detected by nuclear imaging) occurs early, followed by diastolic and systolic functional abnormalities (that can be detected by echocardiography), culminating with ECG changes of ischemia and angina. (*Source:* Schuiff JD, Shaw LJ, Wijns W, et al. Cardiac imaging in coronary artery disease: differing modalities. Heart. 2005;91:1110-7)

STRESS TESTING WITH MYOCARDIAL IMAGING

The addition of myocardial imaging increases the sensitivity and specificity to ETT alone. This increased accuracy is due to the changes seen in the ischemic cascade. As exercise progresses, a supply demand mismatch develops. The myocardium requires increased oxygen supply, but myocardial blood flow (supply) is limited, presumably due to a coronary artery stenosis. This decrease in myocardial perfusion is followed by diastolic and then systolic changes. Finally, electrocardiographic changes and symptoms occur (Fig. 2). The earliest change in decreased myocardial perfusion can be detected by the nuclear perfusion imaging.

In addition to adding an imaging modality, exercise can be simulated by pharmaceutical means. Pharmaceutical stress tests are always conducted with myocardial imaging as well as ECG monitoring due to the poor diagnostic performance of pharmacologic stress ECG alone.

STRESS MYOCARDIAL PERFUSION IMAGING

Single photon emission computed tomography (SPECT) utilizes a nuclear tracer, delivered intravenously, to image perfusion of the myocardium. Images are taken of the myocardium at rest and following stress (exercise or vasodilator). Rest and stress images are compared to each other to detect areas of reversible defects, indicating areas of ischemia.

In a pooled analysis of 44 studies, exercise SPECT had a sensitivity of 87% (95% CI, 86–88%) but a specificity of only 64% (95% CI, 60–68%) (i.e. more false positives).[48] The incremental improvement in test performance over exercise ECG was 1.49. In another study of 33 pooled results, the sensitivity for detecting CAD (≥ 50% stenosis) averaged 87% and specificity, derived from patients referred for cardiac catheterization who had normal angiograms, averaged 73%. In

addition, the normalcy rate, or the percentage of patients with normal results who had less than 5% chance of disease, was 91%. This means 91% of patients with a low pre-test probability of disease (< 5%) had normal SPECTs. Normalcy rate reduces the referral bias inherent in specificity determinations that use a negative coronary angiogram as gold standard. The diagnostic performance of pharmacologic vasodilator (dipyridamole or adenosine) stress imaging tests were comparable to those of exercise stress imaging with a sensitivity of 89% and specificity of 75%.[49] The sensitivity (85%) and specificity (72%) of dobutamine stress myocardial perfusion imaging (MPI) for diagnosis of CAD in a study of 13 pooled results was also similar. The reported sensitivity and specificity for CAD detection by exercise, dipyridamole and dobutamine myocardial perfusion imaging are comparable.

Stress myocardial imaging has several advantages; it does not necessarily require myocardium to become ischemic since it detects differential perfusion to produce an abnormal result. Stress data can be obtained at peak stress rather than immediately post exercise, if a pharmacological stress is used. It also allows determination of the location and the extent of CAD. The disadvantages are that only LV volumes and ejection fraction can be obtained and no other cardiac structures are assessed. The imaging protocols are longer and take multiple sessions for rest and peak imaging. Radioactive tracers are employed with the inherent risks of radiation exposure. There can be false positives due to attenuation from diaphragmatic or breast tissue in addition to artifactual defects due to LBBB, and false positives due to overlap with liver or gut uptake of tracer and spatial resolution is low. Finally, defects are seen in comparison to normally perfused myocardium; therefore, balanced ischemia or diffusely reduced blood flow can result in relatively normal appearing scans which can "miss" significant underlying CAD.

POSITRON EMISSION TOMOGRAPHIC PERFUSION IMAGING

Positron emission tomographic (PET) perfusion imaging is an alternative to SPECT imaging. PET perfusion imaging involves the administration of Rubidium (Rb-82) and of a glucose analog, fluorine-18-deoxyglucose (FDG). The Rb-82 distributes in perfused vascular spaces while FDG is metabolized by viable tissue. Rb-82 has a very short half-life (78 seconds) and must be generated just prior to administration. The stress must be in the form of a vasodilator. In a pooled analysis comparing PET to SPECT, the sensitivity and specificity of Rb-82 PET for detection of CAD are 91% and 90% respectively compared to 83% and 72%.[50] The diagnostic accuracy of PET was 89% versus 79% with SPECT.[51]

There are a number of advantages of PET relative to SPECT. Some of these include:

- Attenuation correction is more easily performed.
- PET has higher spatial and contrast resolution, which potentially yields better specificity and improved multivessel disease identification, with determination of perfusion and viability simultaneously.
- PET can quantify myocardial blood flow in ml/min/g, so that coronary flow reserve can be assessed. This permits better identification of diffuse CAD since tracer uptake can be homogeneous, reflective of balanced ischemia.

There are important limitations to PET as well. Given the short half-life, only vasodilator stress can be used. In addition, a generator is required as well as a PET scanner making it an expensive and less commonly available test.

STRESS TESTING WITH ECHOCARDIOGRAM IMAGING

Echocardiography is a versatile tool that can be used with treadmill, bicycle or arm ergonometer and dipyridamole, adenosine or dobutamine stress modalities. The addition of echocardiography to an exercise stress protocol increases both sensitivity and specificity.[48] If pharmaceutical stress is used in conjunction with echocardiography, dobutamine has the best combination of sensitivity and specificity compared with dipyridamole and adenosine echocardiography or SPECT (Table 2).[52]

There are many advantages to stress echocardiography. It is non-invasive, inexpensive, portable, and does not involve the use of radioactive tracers. It can also be used to define structural heart disease that may provide alternative explanations for symptoms. Stress echocardiography's limitations are that the endocardium can be difficult to visualize, peak images are

TABLE 2

Weighted mean sensitivities and specificities of stress studies

Pharmacologic test	*Studies*	*Subjects*	*Mean age (y)*	*CAD (%)*	*MI (%)*	*Men (%)*	*Sensitivity (% [95% CI])*	*Specificity (% [95% CI])*
Adenosine echocardiography	6	516	65	73	31	71	72 (62–79)	91 (88–93)
Adenosine SPECT	9	1,207	63	80	17	59	90 (89–92)	75 (70–79)
Dipyridamole echocardiography	20	1,835	56	67	15	72	70 (66–74)	93 (90–95)
Dipyridamole SPECT	21	1,464	60	71	31	77	89 (84–93)	65 (54–74)
Dobutamine echocardiography*	40	4,097	59	70	26	66	80 (77–83)	84 (80–86)
Dobutamine SPECT	14	1,066	58	66	9	63	82 (77–87)	75 (70–79)
Total	120†	10,817						

*One dobutamine echocardiographic study not included here because only multivessel disease was examined.
†Total number of tests exceeds the number of studies reviewed because some studies examined more than one pharmacologic test.
(*Source:* Kim C, et al. Pharmacologic stress testing for coronary disease diagnosis: a meta-analysis. Am Heart J. 2001;142:934-44)

difficult to acquire due to rapid breathing and cardiac motion, a truly ischemic response resulting in abnormal wall motion is required for detection of ischemia, quality of imaging is operator dependent, and finally there is significant inter-observer variability in interpretation depending on reader experience.[53] Some of the current limitations of stress echocardiography are being addressed with the use of contrast and the advent of three-dimensional imaging. Intravenous (IV) contrast administration has been shown to improve endocardial border recognition, making previously non-diagnostic images interpretable.[54,55] In addition, three-dimensional echocardiography has made image acquisition less angle dependent and made assessment more reproducible and accurate.[56,57]

COMPARISON OF MPI TO STRESS ECHO

Most studies compare two or, at most, three tests to each other. No study has compared all possible diagnostic tests in the same population. One cost-effectiveness study compared ETT, SPECT, planar thallium imaging, dobutamine stress echocardiography (DSE) and PET. This study showed that while SPECT had higher sensitivity, DSE had higher specificity. In this analysis, due to its higher specificity, stress echo was the most cost effective test. The non-invasive test with the highest sensitivity and specificity was PET and it was cost-effective (Table 3).[58]

Another pooled analysis, comparing stress myocardial perfusion imaging to stress echocardiography had similar findings; that myocardial perfusion imaging offered higher sensitivity (84% vs 80%), but specificity was lower (77% vs 86%) than stress echocardiography. However, using normalcy rate as a substitute for specificity, resulted in a false-positive rate of only 10%.[59] The largest meta-analysis of 44 studies compared these modalities and found that comparing exercise echocardiogram performance to exercise SPECT, the exercise echocardiogram was associated with better discriminatory power (1.18; 95% CI, 0.71–1.65), when adjusted for age, publication year, and a setting including known CAD. The incremental improvement in performance over exercise stress was greater for echo (3.43; 95% CI, 2.74–4.11) than for SPECT (1.49; 95% CI 0.91-2.08).[48]

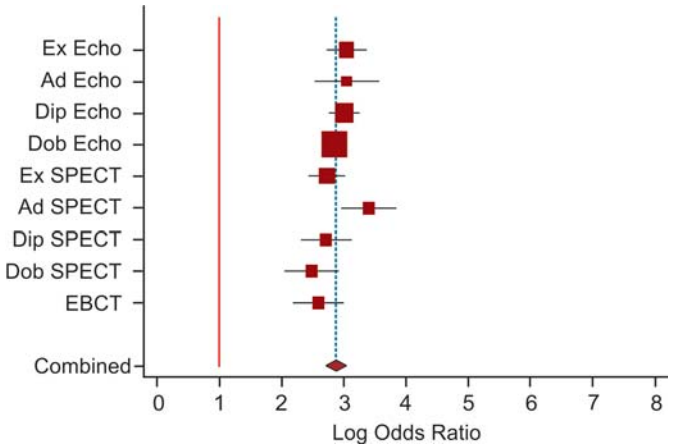


FIGURE 3: Log odds of various stress test modalities. (*Source:* Heijenbrok-kal MH, Fleischmann KE, Hunink MG. Stress echocardiography, stress single-photon-emission computed tomography and electron beam computed tomography for the assessment of coronary artery disease: a meta-analysis of diagnostic performance. Am Heart J. 2007;154:415-23)

Clearly, the addition of an imaging component, either nuclear perfusion or echocardiography, to ETT confers greater sensitivity and specificity to ETT alone (Fig. 3). The application of nuclear perfusion imaging versus stress echo, however, depends on pre-test probability, patient factors, local availability, expertise and cost.

All these various studies demonstrate similar themes. The addition of an imaging component to any form of stress increases the sensitivity and specificity of that test. Overall, stress echocardiography tends toward increased specificity, while stress nuclear imaging may tend toward increased sensitivity.

TABLE 3

Pooled sensitivities and specifities of noninvasive tests

Diagnostic test	*Sensitivity (Range)**	*Specificity (Range)**	*Studies (n)*	*Patients (n)`*	*Patients with Coronary Disease (%)*	*Sensitivity for Left Main or Three-Vessel Disease*	*Studies (n)*	*Patients (n)*
Planar thallium imaging	0.79 (0.70–0.94)	0.73 (0.43–0.97)	6	510	66	0.93	2	72
Single-photon emission computed tomography	0.88 (0.73–0.98)	0.77 (0.53–0.96)	8	628	70	0.98	3	92
Echocardiography†	0.76 (0.40–1.00)	0.88 (0.80–0.95)	10	1174	64	0.94	4	115
Positron emission tomography	0.91 (0.69–1.00)	0.82 (0.73–0.88)	3	206	68	Not available		
Exercise electrocardiography‡	0.68	0.77	132	24074	66	0.86	48	

*Range of sensitivity and specificity reported in individual studies
†Test characteristics for echocardiography are based on pooled studies of dobutamine, dipyridamole, and exercise as stressors. Pooling only studies that used dobutamine as a stressor gave similar results, with a sensitivity of 0.76 and a specificity of 0.87 for all coronary disease
‡Sensitivity of exercise electrocardiography for detection of all coronary artery disease is based on a meta-analysis that included 144 studies for estimates of sensitivity and 132 studies for specificity. Exercise electrocardiography results for sensitivity in left main and three-vessel disease were based on another meta-analysis. No studies of positron emission tomography reported sensitivity for left main and three-vessel disease.
(*Source:* Garber AM, Solomon NA. Cost-effectiveness of alternative test strategies for the diagnosis of coronary artery disease. Ann Intern Med. 1999;130:719-28)

However, various forms of stress imaging tests have generally similar diagnostic log odds ratios and overall diagnostic performance.[60] While PET has improved sensitivity and specificity over both stress echocardiography and stress nuclear, the cost and lack of availability limits its use.

NONINVASIVE COMPUTED TOMOGRAPHIC ANGIOGRAPHY

Computed tomographic angiography (CTA) is a promising technology that allows direct visualization of coronary arteries without an invasive procedure. Intravenous contrast is delivered through a peripheral IV and images are rapidly acquired within a 10 second breath-hold.

The original CTA scanners were electron beam CTs (EBCT), which still have the advantage of superior temporal resolution, but have quite limited spatial resolution. Currently CTA is performed by multi-detector CT (MDCT) scanners which are capable of a high degree of both spatial and temporal resolution. A 64 detector array is the current standard allowing a 0.5 mm discrimination.

There have been three recent trials assessing the accuracy and precision of 64-MDCT in relation to invasive angiography. Core-64 studied 291 patients undergoing both CTA and invasive coronary angiography. In comparison to invasive coronary angiography, CTA had a sensitivity of 85% and specificity of 90%, resulting in a PPV = 91% and NPV = 83%.[61] Another study found that in 230 patients having both procedures there was a sensitivity of 95%, and a specificity of 83%. The positive and negative predictive values were 64% and 99% respectively.[62] The third large trial comparing the diagnostic accuracy of CTA to invasive coronary angiography found a similar sensitivity of 99%, but a much lower specificity of only 64%, resulting in an NPV of 97% and a PPV of 86%.[63] These studies all demonstrate that the main utility of CTA is its negative predictive value in ruling out obstructive CAD in symptomatic low- to intermediate-risk patients.

In addition to its diagnostic use, CTA also has incremental prognostic value, beyond standard risk factors, in assessing future risk of coronary events or death.[64-66] However, whether CTA should be used to narrow risk stratification and whether any additional testing is cost-effective in routine use are currently unclear.

The advantage that CTA provides is an anatomical picture without requiring an invasive procedure with its small but definite risks of vascular access complication, stroke, arrhythmia, ischemia or death. It is useful for detecting coronary anomalies, assessing patency of coronary artery bypass grafts, and ruling out CAD in symptomatic patients with low to intermediate risk of CAD and equivocal stress test results.[67]

Computed tomographic angiography has shown promising results in the triage of patients with chest pain in the emergency department,[68,69] as a first test in the investigation of chest pain,[70,71] and as compared to invasive catheterization in patients with low pre-test probability of CAD.[72] CTA has also been compared to MPI as a first test in the detection of coronary disease. It has been shown to be more diagnostic and more economical in small, single-center, non-randomized studies.[68,71] However, the positive predictive value of CTA is low resulting in potentially unnecessary invasive angiograms in low-risk populations. Therefore, the appropriate use of CTA in the diagnosis of CAD is not yet established and is undergoing evaluation.[73,74]

INVASIVE CORONARY ANGIOGRAPHY

The current gold standard for the detection of CAD is invasive coronary angiography. In the event that the clinical history is highly suspicious for ischemic pain, and non-invasive tests are negative or equivocal, the definitive test is a coronary angiogram. It is also the test of first choice in situations where pre-test likelihood is high and in most cases of ACS.[41]

The limitations of invasive coronary angiography are that it is invasive and therefore carries various risks, although small, of vascular access complications, heart attack, arrhythmia, stroke and death. It requires a dedicated facility and is costly. It requires the use of intra-arterial contrast and radiation with their respective side effects. Finally, it does not provide information with respect to the functional significance of visual coronary stenosis, which is especially important for lesions of borderline severity, although the addition of fractional flow reserve assessment can be helpful in this regard. The advantages are that it provides a definitive diagnosis[75] and it allows for a therapeutic intervention to be carried out within the diagnostic procedure.[76] It should be recognized that definitive diagnosis of CAD with invasive angiography is limited to epicardial vessel disease. There are a minority of patients with clearly ischemic symptoms and no epicardial vessel disease, who may have small vessel disease.[77] Thus, even with the gold standard in the diagnosis of CAD, clinical context must be considered.

SUMMARY

In summary, the evaluation and management of patients with chest pain is not always straightforward. Initial evaluation includes a thorough medical history incorporated with physical exam findings. Biomarker evaluation helps to risk stratify patients into low, intermediate or high-risk categories. This risk stratification process determines the most appropriate further testing to be conducted and results should be interpreted in the context of the individual patient's risk.

MODIFIED SUMMARIES OF GUIDELINES
(Testing of Low-risk Patients Presenting to the Emergency Department with Chest Pain. A Scientific Statement from the American Heart Association. Circulation 2010;122:756-76)

Kanu Chatterjee

THE MAGNITUDE OF THE PROBLEM

There are more than 8 million visits to emergency department (ED) annually for chest pain or other symptoms suggesting myocardial ischemia. This is the second most frequent cause of ED visits in adults.

Less than 5% of patients presenting with chest pain have ST-segment elevation myocardial infarction (STEMI). Approximately 25% of patients have non-ST-segment elevation acute coronary syndrome (NSTEMI/UA).

HIGH LIKELIHOOD OF ACS

- History—Accelerating tempo of ischemic symptoms in preceding 48 hours
- Character of pain—Prolonged ongoing (> 20 min) rest pain
- Clinical findings—Hemodynamic pulmonary edema, new or worsening mitral regurgitation, S3 or new/worsening rales, hypotension, bradycardia, tachycardia, age greater than 75 years
- ECG—ST-segment changes greater than 0.05 mV, new or presumed new bundle-branch block, sustained ventricular tachycardia
- Cardiac markers—Elevated troponin.

INTERMEDIATE LIKELIHOOD OF ACS

- History—Prior MI or cerebrovascular disease, or CABG; prior aspirin use
- Character of pain—Prolonged (> 20 min) rest angina now resolved with moderate or high likelihood of CAD, rest angina (< 20 min or relieved with rest or nitroglycerin)
- Clinical findings—Greater than 70 years
- ECG—T-wave inversions greater than 0.2 mV, pathologic Q waves
- Cardiac markers—Normal troponin.

LOW LIKELIHOOD OF ACS

- Character of pain—New-onset or progressive Canadian Cardiovascular System III or IV angina during the past 2 weeks without prolonged (> 20 min) rest pain but with moderate or high likelihood of CAD
- ECG—Normal or unchanged ECG during an episode of chest pain
- Cardiac markers—Normal troponin.

CARDIAC CAUSES OF ACUTE CHEST PAIN

Cardiovascular Causes of Chest Pain

Angina

- Location: Usually substernal, can be epigastric, intercapular, shoulders, frequently difficult to localize (localize—finger sign)
- Quality: Pressure, heaviness, squeezing, indigestion
- Radiation: One or both the arms, upper back, neck, epigastrium, shoulder, lower jaw (not upper jaw or head, lower back, lower abdomen or lower extremity)
- Duration: 1-10 minutes (not a few seconds or hours)
- Aggravating or relieving factors: Exercise, cold weather, emotional stress heavy meals; heavy meals, relieved by rest or nitroglycerin (not diagnostic)
- Associated symptoms or signs: Dyspnea, S4, MR murmur

Pericarditis

Physical examination:
- Pericardial rub

Diagnostic tests:
- ECG
- TTE if necessary

Acute Aortic Dissection

Physical examination:
- Auscultation for AR
- Findings for tamponade

Diagnostic tests:
- ECG
- Chest X-ray
- CT, MRI, TEE

Pulmonary Embolism

Physical examination:
- Findings for right heart failure
- Pulmonary hypertension
- Pleural rub

Diagnostic tests:
- ECG
- Chest X-ray
- Dimers
- CT
- V/Q scan

NONCARDIAC CAUSES OF ACUTE CHEST PAIN

- Gastrointestinal—Esophageal reflux, peptic ulcer biliary disease, pancreatitis
- Musculoskeletal—Costochondritis, cervical disk disease
- Psychological—Anxiety, depression

CONFIRMATORY TEST SELECTION IN ACCELERATED DIAGNOSTIC PROTOCOLS

- Exercise Treadmill Testing
- Myocardial imaging—Pharmacologic stress nuclear perfusion imaging, positron emission tomography, stress echocardiography
- Computed tomography coronary angiography.
- Magnetic resonance imaging.

FOLLOW-UP OF PATIENTS WITH NEGATIVE CHEST PAIN UNIT EVALUATIONS

All patients should be followed in the cardiology clinic for appropriate investigations and treatments.

MODIFIED SUMMARY OF GUIDELINES
ACC/AHA 2007 Guidelines on Perioperative Cardiovascular Evaluation and Care for Non Cardiac Surgery Circulation 2007;1971-96)

Kanu Chatterjee

Class I: Conditions for which there is evidence and/or general agreement that a given procedure or treatment is useful and effective.

Class II: Conditions for which there is conflicting evidence and/or divergence of opinion about the usefulness/efficacy of a procedure or treatment.

Class IIa: Weight of evidence/opinion is in favor of usefulness/efficacy.

Class IIb: Usefulness/efficacy is well established by evidence/opinion.

Class III: Conditions for which there is evidence and/or general agreement that the procedure/treatment is not useful/effective and in some cases may be harmful.

Level of evidence A: The presence of multiple randomized clinical trials.

Level of evidence B: The presence of a single randomized trial or nonrandomized studies.

Level of evidence C: Expert consensus.

High-risk procedure (e.g. Aortic aneurysm surgery).

Intermediate-risk procedure (e.g. Carotid surgery).

Low-risk procedure (e.g. Cataract surgery).

PREOPERATIVE NONINVASIVE EVALUATION OF LEFT VENTRICULAR FUNCTION

Class IIa:
- Patients with dyspnea (level of evidence: C)
- Patients with current or prior heart failure (level of evidence: C)

Class IIb:
- Reassessment of left ventricular function in clinically stable patients in whom the diagnosis is not well established (level of evidence: C)

Class III:
- Routine perioperative evaluation of left ventricular function (level of evidence: B)

PREOPERATIVE RESTING 12-LEAD ECG

Class I:
- Patients with at least one clinical risk factor (level of evidence: B)
- Patients with known coronary artery disease, peripheral arterial disease
- Cerebrovascular disease who are undergoing intermediate-risk surgical procedures (level of evidence: C)

Class IIa:
- Patients with no clinical risk factors undergoing vascular surgical procedures (level of evidence: B)

Class IIb:
- In patients with at least one clinical risk factor who are undergoing intermediate-risk operative procedures (level of evidence: B)

Class III:
- Asymptomatic patients undergoing low-risk surgical procedures (level of evidence: B)

RECOMMENDATIONS FOR NONINVASIVE STRESS TESTING BEFORE NONCARDIAC SURGERY

Class I:
- Patients with active cardiac conditions (level of evidence: B)

Class IIa:
- Recommended in patients with 3 or more clinical risk factors and poor functional capacity who require vascular surgery (level of evidence: B)

Class IIb:
- In patients with at least 1 or 2 clinical risk factors and poor functional capacity who require intermediate-risk noncardiac surgery (level of evidence: B)
- In patients with at least 1 or 2 clinical risk factors and good functional capacity who are undergoing vascular surgery (level of evidence: B)

Class III:
- In patients with no clinical risk factors undergoing intermediate-risk noncardiac surgery (level of evidence: C)
- In patients undergoing low-risk noncardiac surgery (level of evidence: C)

RECOMMENDATIONS FOR PREOPERATIVE CORONARY REVASCULARIZATION WITH CORONARY ARTERY BYPASS GRAFTING OR PERCUTANEOUS CORONARY INTERVENTION

Class I:
- In patients with stable angina who have significant left coronary artery stenosis (level of evidence: A)
- In patients with stable angina who have 3-vessel disease (level of evidence: A)
- In patients with stable angina who have 2-vessel disease (level of evidence: A)
- In patients with high-risk unstable angina or non-ST-segment elevation myocardial infarction (level of evidence: A)
- In patients with acute ST-elevation MI (level of evidence: A)

Class IIa:
- Patients in whom percutaneous intervention (PCI) is appropriate for relief of cardiac symptoms and who need elective noncardiac surgery (level of evidence: B)
- It is reasonable to continue aspirin if it is at all possible in patients who had drug-eluting coronary artery stents who require urgent surgical procedures

Class IIb:
- In patients the usefulness of coronary revascularization is not well established (level of evidence: C)
- In patients the usefulness of coronary revascularization is not well established for low-risk ischemic patients with an abnormal dobutamine stress echocardiogram (level of evidence: B)

Class III:
- Routine prophylactic coronary revascularization in patients with stable coronary artery disease (level of evidence: B)
- Elective noncardiac surgery is not recommended within 4"6 weeks in patients receiving bare-metal stents or within 12 months in patients receiving drug-eluting stents in whom aspirin or clopidogrel will need to be discontinued (level of evidence: B)
- Elective noncardiac surgery is not recommended within 4 weeks of coronary revascularization with balloon angioplasty (level of evidence: B)

RECOMMENDATIONS FOR BETA-BLOCKER MEDICAL THERAPY

Class I:
- Beta blockers should be continued if the patients had been on beta blocker therapy (level of evidence: C)
- Beta blockers should be given in the high-risk patients (level of evidence: B)

Class IIa:
- Beta blockers are recommended in patients with suspected or established coronary artery disease (level of evidence: B)
- Beta blockers are probably recommended for patients in whom preoperative assessment for vascular surgery identifies high cardiac risk, as defined by more than one clinical risk factor(level of evidence: B)
- Beta blockers are probably recommended in whom preoperative assessment identifies coronary heart disease or high cardiac risk as identified by the presence of more than one clinical risk factor (level of evidence: B)

Class IIb:
- The usefulness of beta blockers is uncertain for patients who are undergoing either intermediate-risk procedures or vascular surgery in whom preoperative assessment identifies a single clinical risk factor (level of evidence: C)
- The usefulness of beta blockers is uncertain in patients undergoing vascular surgery with no clinical risk factors who are not currently taking beta blockers (level of evidence: B)

Class III:
- Beta blockers should not be given in patients undergoing surgery who have absolute contraindications to beta blockers (level of evidence: C)

RECOMMENDATIONS FOR STATIN THERAPY

Class I:
- For patients currently taking statins and scheduled for noncardiac surgery statins should be continued (level of evidence: B)

Class IIa:
- For patients undergoing vascular surgery with or without clinical risk factors, statin use is reasonable (level of evidence: C)

Class IIb:
- For patients with at least one clinical risk factor who are undergoing intermediate-risk procedures (level of evidence: C)

RECOMMENDATIONS FOR ALPHA-2 AGONISTS

Class IIb:
- Alpha-2 agonists for perioperative control of hypertension may be considered for patients with known CAD or at least one clinical risk factor who are undergoing surgery (level of evidence: B)

Class III:
- Alpha-2 agonists should not be given to patients undergoing surgery who have contraindications for alpha-2 agonists

RECOMMENDATIONS FOR PREOPERATIVE INTENSIVE CARE MONITORING

Class IIb:
- Should be restricted to a very few patients who are unstable and who have multiple comorbid conditions (level of evidence: B)

RECOMMENDATIONS FOR USE OF VOLATILE ANESTHETIC AGENTS

Class IIa:
- May be useful in stable patients at risk of myocardial ischemia (level of evidence: B)

RECOMMENDATIONS FOR PROPHYLACTIC INTRAOPERATIVE NITROGLYCERIN

Class IIb:
- The usefulness of intraoperative nitroglycerin to prevent myocardial ischemia has not been established. It should be used with caution as vasodilatation and hypotension may occur (level of evidence: C)

RECOMMENDATIONS FOR USE OF TRANSESOPHAGEAL ECHOCARDIOGRAPHY (TEE)

Class IIa:
- The emergency use of TEE is reasonable to determine the cause of persistent hemodynamic abnormality (level of evidence: C)

RECOMMENDATIONS FOR MAINTENANCE OF BODY TEMPERATURE

Class I:
- Maintenance of normothermia is indicated during most procedures except in patients with mild hypothermia is indicated (e.g. during high aortic cross-clamping) (level of evidence: B)

RECOMMENDATIONS FOR PERIOPERATIVE CONTROL OF BLOOD GLUCOSE CONCENTRATION

Class IIa:
- It is reasonable to control blood sugar in diabetics or in patients with acute hyperglycemia during high-risk surgical procedures

Class IIb:
- The usefulness of strict control of blood glucose remains in uncertain in patients who are not planned to be in intensive care units (level of evidence: C)

RECOMMENDATIONS FOR PERIOPERATIVE USE OF PULMONARY ARTERY CATHETERS

Class IIb:
- May be reasonable in patients at risk for major hemodynamic disturbances during high-risk noncardiac surgical procedures (e.g. liver transplantation) provided proper interpretations of hemodynamics can be made by persons with the knowledge of hemodynamics (level of evidence: B)

Class III:
- Routine use of pulmonary artery catheters for noncardiac surgical procedures (level of evidence: A)

RECOMMENDATIONS FOR INTRAOPERATIVE AND POSTOPERATIVE USE OF ST-SEGMENT MONITORING

Class IIa:
- To monitor for myocardial ischemia in patients with known CAD or those undergoing vascular surgery (level of evidence: B)

Class IIb:
- In patients with single or multiple risk factors for CAD (level of evidence: B)

RECOMMENDATIONS FOR SURVEILLANCE FOR PERIOPERATIVE MI

Class I:
- Postoperative troponin measurement is recommended in patients with ECG changes or chest pain typical of acute coronary syndrome (level of evidence: C)

Class IIb:
- Routine measurement of postoperative troponin is not well established in clinically stable patients who had vascular and intermediate-risk surgery (level of evidence: C)

Class III:
- Postoperative measurement of troponin is not recommended in asymptomatic stable patients who had high-risk surgery (level of evidence: C)

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Chapter 48

Acute Coronary Syndrome I (Unstable Angina and Non-ST-Segment Elevation Myocardial Infarction): Diagnosis and Early Treatment

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Chapter Outline

- Pathophysiology
  - Etiology
  - Vulnerable Plaque
  - Systemic Factors (Vulnerable Patient)
  - Role of Platelets and Coagulation System
- Clinical Features
  - Physical Examination
  - Electrocardiogram
  - Biomarkers
- Risk Stratification—Putting it All Together to Determine the Optimal Treatment Strategy
  - History
  - Electrocardiogram
  - Cardiac Biomarkers
- Early Medical Therapy
  - General Measures
  - Nitrates
  - Morphine
  - Beta Blockers
  - Calcium Channel Blockers
  - Antiplatelet Agents
  - Antithrombotic Agents
- Early Invasive or Initial Conservative Strategy
- Revascularization

INTRODUCTION

Each year, more than 1.3 million patients are admitted to hospitals throughout the United States with an acute coronary syndrome (ACS); unstable angina (UA) and non-ST-elevation myocardial infarction (NSTEMI) account for 60–70% of all those admissions.[1] Recognizing that everyone with an ACS is not admitted to a hospital, one can appreciate the magnitude of this problem.

The UA/NSTEMI constitutes a subset of the clinical syndrome of ACS that is usually, but not always, caused by atherosclerotic coronary artery disease (CAD). In the spectrum of ACS, UA/NSTEMI is defined by an accelerated or unstable clinical syndrome consistent with angina, with electrocardiographic changes consistent with ischemia and/or positive biomarkers of necrosis (e.g. troponin), in the absence of ST-segment elevation.

PATHOPHYSIOLOGY

ETIOLOGY

The physiology of myocardial ischemia is simply an imbalance between coronary supply and myocardial demand. Any factor leading to decreased flow or increased demand may offset this delicate balance of supply and demand, and result in myocardial ischemia.

Although chronic stable angina is most commonly secondary to an obstructive coronary stenosis that has developed over years, ACS on the other hand occurs due to an acute event that is most commonly associated with a morphologic change in a previously nonobstructive plaque. This event is usually a result of the abrupt development of plaque rupture or erosion at an unstable plaque with resultant thrombus formation. This occurs through a series of events related to innate plaque characteristics and/or external factors. Consequently, plaque composition rather than degree of luminal stenosis is the major predisposing factor.

Less commonly, acute ischemic events (i.e. ACS) may be precipitated in patients with chronic stable angina by an increase in myocardial workload (increased demand). These may include but are not limited to hemodynamic stress imposed by surgery, hypoxia, anemia, significant hypertension, tachycardia, hyperthyroidism, etc. In this case, the treatment must focus on what is driving the increased in myocardial work. The ACS can also occur in the setting of coronary vasospasm. Coronary vasospasm may occur in the large epicardial vessels, in which case there is generally nonobstructive CAD at the site of the spasm, or in the microcirculation (with angiographically normal epicardial vessels). The spasm may be precipitated by the presence of superimposing environmental triggers such as medications (e.g. vasoconstrictors, triptans, etc.), illicit drugs (e.g. cocaine, methamphetamines, etc.), or may occur in a patient who has an underlying vasoactive disorder (Raynaud's phenomenon or migraine headaches) or endothelial dysfunction. These episodes may have a circadian pattern, occurring commonly in the early morning hours, are more likely in smokers and, although seen commonly at rest, may be precipitated by exercise (although not reproducibly so, as is the case in chronic stable CAD), or even hyperventilation. Finally,

progressive atherosclerosis may lead to acceleration in coronary ischemic symptoms, although this is less common, and may be most commonly seen with coronary stent restenosis.

VULNERABLE PLAQUE

Despite a common pathophysiologic pathway, atherosclerotic lesions are heterogeneous in their risk for rupture. The lesions that are at highest risk for rupture are referred to as unstable or vulnerable plaques. These typically consist of a large lipid laden core (> 40% of the total plaque volume),[2] a thin fibrous cap, with a dense infiltration of monocytes and macrophages, with abundant production of matrix metalloproteinases, a loss of smooth muscle cells and a decrease in stabilizing collagen. These characteristics make them more prone to rupture when compared to the fibrous, collagen-rich plaques. Since these plaques are generally not flow limiting, they may escape identification by stress testing and even angiography as at times the vessel will remodel in a positive way and maintain the lumen size. Once plaque disruption occurs, the highly thrombogenic, lipid-rich core is exposed and thrombogenic tissue factors and vasoconstrictors are released into the local circulation. This is followed by activation and aggregations of platelets with formation of a thrombus at the site of rupture. This may lead to various degrees of acute narrowing of the vessel lumen. In patients with UA/NSTEMI, this process falls short of complete vessel occlusion but results in ischemia to the distal territory that is manifested by new (or a change in) symptoms, ischemic electrocardiographic changes and/or biomarker elevation. It has been estimated that up to 75% of vulnerable lesions resulting in ACS and sudden cardiac death are secondary to plaque rupture; the remaining lesions have plaque erosion as the precipitating event.[2]

Multiple lines of evidence suggest that the "culprit" lesion responsible for ACS is frequently nonobstructive prior to the rupture. Data from the Coronary Artery Surgery Study (CASS) evaluated progression of disease among non-bypassed arteries. They found that lesions with greatest severity of stenosis had a higher likelihood of progression to occlusion compared to nonobstructive lesions. However, given that there were many more nonobstructive lesions within an individual's coronary artery tree, the majority of coronary occlusions at follow-up were accounted for by lesions that were nonobstructive at baseline.[3,4] Furthermore, studies have also shown that many patients with ACS do not have an acute collateral filling of the infarct related artery suggesting that the acute event occurred in a lesion that was not previously hemodynamically significant.[5]

SYSTEMIC FACTORS (VULNERABLE PATIENT)

The predisposition to plaque rupture and, thus, the development of ACS and sudden cardiac death may not solely be a manifestation of the plaque itself; other "systemic" factors play an important role. The systemic inflammatory response, changes in local shear stress (sudden and abrupt changes in blood velocity), or chronic and recurrent changes in shear stress may result in fatigue of the fibrous cap leading to rupture.[6] Prothrombotic states (e.g. transient hypercoagulability from smoking, dehydration, infection, cocaine, malignancy, etc.) could facilitate progression of thrombosis once the plaque has eroded/ruptured.[7] One study showed that the levels of neutrophil myeloperoxidase (a marker of inflammation) were significantly increased in both right and left coronary arteries and the femoral artery in patients with ACS compared to stable angina, or variant angina.[8] In addition, this elevation was independent of site of the culprit lesion. Finally, it is now a well-recognized phenomenon that patients presenting with ACS may have more than one "culprit lesion".[9] In these patients and others seen in routine practice, there is a lesion that appears to be causing the clinical syndrome of ACS, based on degree of obstruction or electrocardiogram (ECG) changes (the "culprit lesion"). In addition, the patient will have one or more lesions that appear irregular, ulcerated, hazy and/or thrombotic suggesting an active, acute process. Multiple active lesions in a single individual suggest a systemic impact. Thus, systemic factors are important, perhaps equally so, in determining the individual's predisposition to acute changes in plaques that herald the onset of ACS.

Finally, histologic evaluation supports that the progression of atherosclerosis, perhaps at an accelerated rate, may be subsequent to healing of previously ruptured plaques. The acute event of rupture of the plaque may have had no clinically apparent impact, but the healing of these may result in more rapid luminal narrowing.[10] This suggests that the rupture of the atherosclerotic plaque, in and of itself, may be insufficient to lead to ACS.

Atherosclerosis with positive remodeling maintains lumen patency despite, at times, significant plaque burden. Coronary angiography is, therefore, inherently limited in its ability to estimate atherosclerotic burden in the setting of positive remodeling which preserves a normal lumen diameter. Extensive plaque may be visualized by intravascular ultrasound, CT angiography, or postmortem examination in these patients, that is not apparent, or underestimated by coronary angiography. Newer technologies including intravascular ultrasound with virtual histology, optical coherence tomography (OCT), angioscopy, thermography, positron emission tomography (PET) and magnetic resonance imaging (MRI) are being studied to help us identify the "vulnerable plaque" in the potentially vulnerable patient. Until then, our ability to prevent ACS altogether remains limited.

ROLE OF PLATELETS AND COAGULATION SYSTEM

Platelets play a central role in vascular hemostasis and thrombosis, and our understanding of the mechanisms involved in platelet activation (Fig. 1A), aggregation and its integration with the coagulation cascade (Fig. 1B) has paved the way for the development of several new and investigational drugs that target some key pathways. While an extensive review of the different mechanisms involved in platelet response to vascular injury is outside the scope of this chapter, a brief overview is warranted.

Plaque disruption exposes subendothelial collagen, and platelets adhere to the exposed collagen via surface glycoprotein receptors. This interaction is mediated by von Willebrand factor

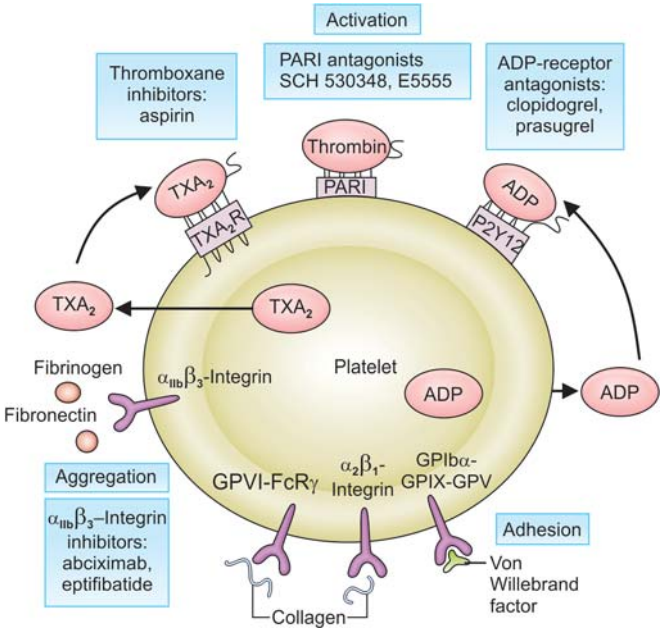


FIGURE 1A: Platelet surface receptors and targets of antiplatelet therapy. (*Source:* Modified from Mackman N. Triggers, targets and treatments for thrombosis. Nature. 2008;451:914-8[9])

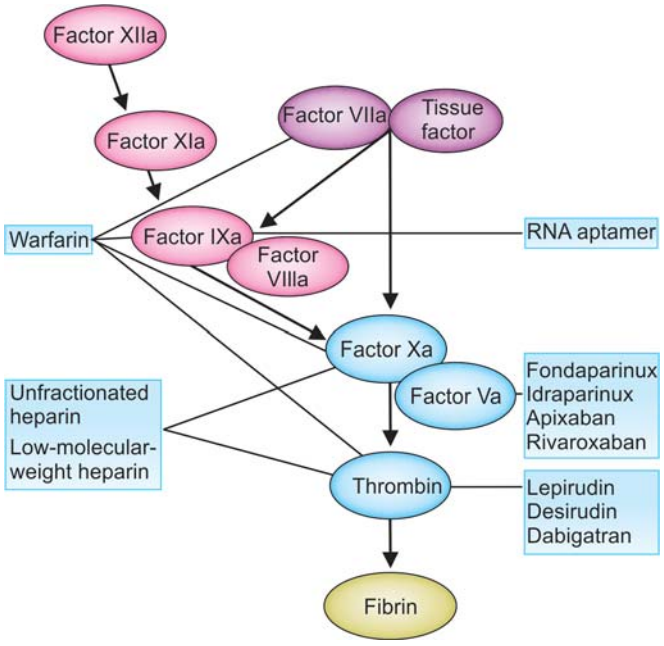


FIGURE 1B: The coagulation pathway and targets of anticoagulation medications. (*Source:* Modified from Mackman N. Triggers, targets and treatments for thrombosis. Nature. 2008;451:914-8[9])

(vWF) and results in adhesion to the subendothelium. Simultaneously, release of tissue factor activates the coagulation cascade with production of thrombin. Thrombin is a very potent activator of human platelets and initiates platelet activation via interaction of proteinase activator receptor 1 (PAR 1) and proteinase activator receptor 4 (PAR 4). A number of intracellular events are triggered that result in platelet activation and degranulation. Platelet granules release among other substances ADP, which is an agonist on two important receptors; the P2Y1 and P2Y12 receptors. This amplifies the platelet activation response by a positive feedback mechanism. The latter receptor is the target of clopidogrel, prasugrel and ticagrelor. In addition, activation of platelets leads to influx of calcium in the cytosol which activates phospholipase A_2; this enzyme releases phospholipids, which leads to the formation of thromboxane A_2 (TXA_2) via the cyclooxygenase (COX) pathway. Aspirin inhibits this activation pathway. The downstream action of platelet activation is a marked increased surface expression of glycoprotein IIb/IIIa which through the binding with fibrinogen, resulting in platelet aggregation and the development of a platelet rich hemostatic plug. The different glycoprotein IIb/IIIa inhibitors exert their antiplatelet action by inhibiting this binding. Thereby, the rupture of an unstable plaque may lead to abrupt change in coronary luminal area by the aggressive development of a platelet-rich thrombus. Within this pathway, there are multiple sites of potential inhibition that are targets of the medications considered to be standard of care in the treatment of patients with ACS.

CLINICAL FEATURES

Anginal chest pain is the cardinal symptom of ischemic coronary disease. The pain is typically described as deep or poorly localized pain that is reproducibly associated with physical exertion or emotional stress, and is promptly relieved with rest or nitroglycerin. It may radiate to the jaw, neck, back or arm(s) and may be associated with shortness of breath, nausea, lightheadedness or diaphoresis. In patients with UA/NSTEMI, episodes of angina may be severe or prolonged, may be provoked by minimal exertion or may even occur at rest. Many patients do not describe angina as "chest pain" but may describe it as a discomfort; this distinction may be important while interviewing patients as they may deny having pain, but will admit to having discomfort. This pain/discomfort is typically not localized, but rather, is diffuse and in most cases not severe. Others may have no chest discomfort at all and may only experience pain in jaw, neck, arm, shoulder, back or epigastrium. Occasionally, patients may present without any discomfort, instead they may experience unexplained shortness of breath, diaphoresis, nausea, lightheadedness or even syncope as their presenting symptom.[11-13] Such atypical presentations may account for about one-third of all patients who present to the hospital with an ACS.[14] Atypical symptoms are particularly common among the elderly, women, diabetics and patients with heart failure. It is important to recognize that the term "atypical" refers only to the reality that the symptoms are not classical/typical, but does not exclude the diagnosis of ischemia as the etiology of these symptoms. Finally, the angina symptoms may not be relieved with, only partially relieved with, or relieved with rapid recurrence, with rest or nitroglycerin.

In comparison, features that are generally not characteristic of acute myocardial ischemia include: (1) Pleuritic chest pain; (2) Pain localized at the tip of the finger particularly over the left ventricular (LV) apex or costochondral junction; (3) Pain reproduced with movement or palpation and (4) Pain lasting for a few seconds. Although these four types of chest discomfort are not generally ischemic in origin, there is no single characteristic that clearly defines, or excludes the diagnosis of ACS.

The relief of chest pain with nitroglycerin does not always predict CAD as the cause. In a study, up to 41% of patients without CAD had relief of chest pain with nitroglycerin.[15] Due to its effect on smooth muscle relaxation, nitroglycerin may relieve chest pain that may be on account of esophageal spasm, etc. At the same time, relief of chest pain with a "GI cocktail" does not preclude the diagnosis of CAD either.

Finally, knowledge of a patient's risk factors is very important in determining the pretest probability of ACS. Information regarding presence of known CAD, peripheral arterial disease (PAD), hypertension, diabetes, hyperlipidemia, tobacco use, obesity, physical inactivity and/or a family history of premature cardiovascular disease as well as other non-traditional risk factors (e.g. connective tissue diseases, renal failure, etc.) must be sought.[16-18] At least one traditional risk factor is present in as many as 90% of patients with a coronary event.

PHYSICAL EXAMINATION

A normal physical examination is common in patients with ACS and does not exclude this diagnosis. More importantly, findings on the physical examination can help to assess the hemodynamic impact of the ischemic insult. The signs and symptoms, such as cool, clammy skin, diaphoresis, sinus tachycardia, significant bradycardia, S3 or S4, mitral regurgitation murmur and bibasilar rales, may herald the onset of cardiogenic shock even before the development of frank hypotension. Such patients are at a high risk and may require urgent coronary angiography and admission to a coronary intensive care unit (CICU). The physical examination may also be useful in identifying the precipitating causes such as anemia, thyrotoxicosis, uncontrolled blood pressure, and may also helpful in identifying important comorbid conditions (e.g. lung disease, malignancy, etc.) that influence medical decision-making. Occasionally, physical findings might suggest an alternative diagnosis, such as aortic dissection, pericarditis, cholecystitis, etc. and therefore the importance of physical examination cannot be overemphasized.

ELECTROCARDIOGRAM

A 12-lead electrocardiogram (ECG) is an integral part of the initial evaluation of a patient with ACS. In addition to identifying candidates for reperfusion (e.g. STEMI patients), it also provides prognostic information.[19] It is, therefore, a powerful tool in the evaluation and the treatment of patients with possible ACS and should be obtained in all patients with chest pain or angina equivalent, within 10 minutes of arrival to the hospital.

Typical ECG findings that are consistent with ischemia in patients with UA/NSTEMI include the presence of ST-segment depression (at least 0.5 mm in at least two contiguous leads), transient ST changes or presence of T wave inversions. However, up to 20% of patients with an NSTEMI, confirmed by cardiac enzymes, have no diagnostic ischemic ECG changes. While isolated T wave inversion is nonspecific, the finding of symmetric deep T wave inversion (> 2 mm) in multiple precordial leads is usually associated with severe critical stenosis of the proximal left anterior descending artery (Wellen's syndrome) (Fig. 2).[20] Such patients should be promptly referred for cardiac consultation, and early coronary angiography. An ECG finding with ST depression less than 0.5 mm is less specific for the diagnosis of ACS. A normal ECG decreases but does not eliminate the possibility of ACS. Approximately up to 4% of patients with chest pain and a normal ECG are later diagnosed with UA/NSTEMI.[21] It is well known that infarcts in the distribution of the left circumflex coronary artery can be electrocardiographically silent on the standard 12-lead ECG. In these situations, posterior leads (V7–V9) may help to uncover ischemia involving the posterior wall. In some patients, the ECG changes may be dynamic. Therefore the finding of a normal initial ECG in a patient where the clinical suspicion is high should always prompt serial ECG evaluation (along with cardiac biomarker testing), especially if the ECG was obtained after the symptoms have resolved.

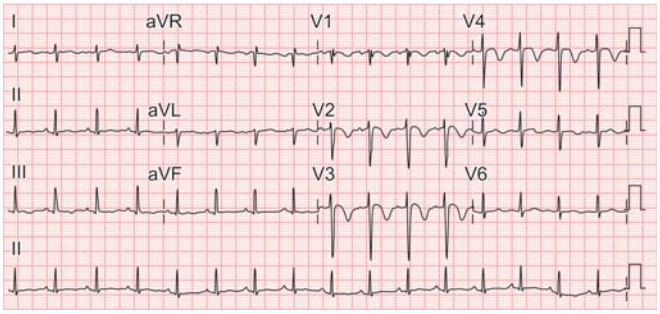


FIGURE 2: Symmetric deep T wave inversions involving multiple precordial leads (Wellen's syndrome). This patient had a 90% stenosis in his proximal left anterior descending artery stenosis. (*Source:* Modified from Rhinehardt J, Brady WJ, Perron AD, et al. Electrocardiographic manifestations of Wellen's syndrome. Am J Emerg Med. 2002;20: 638-43)

It is always helpful to compare a current ECG with a previous one, if available, to note subtle changes, or pseudo-normalization (the change from a previously inverted T wave to now a normal appearing upright T wave). Also, development of ischemic changes, while a patient is experiencing chest discomfort, which resolve if the patient becomes asymptomatic, is highly suggestive of cardiac ischemia and increases the likelihood of underlying significant CAD.

BIOMARKERS

Creatinine Kinase

Creatinine kinase (CK) has been the most commonly used biochemical markers among patients with ACS worldwide. The MB isoenzyme has greater specificity for myocardial tissue compared to total CK (which may be elevated in neurological or skeletal muscle disorders as well). The CK-MB levels peak at 10–18 hours after injury and usually remain elevated up to 72 hours after which they return to baseline (Fig. 3). Due to its shorter half-life, CK and CK-MB elevation is particularly useful in detecting episodes of reinfarction. It should be remembered that CK is cleared by the kidneys and thus may be chronically elevated in renal failure in patients and may not be indicative of an acute myocardial infarction (AMI).

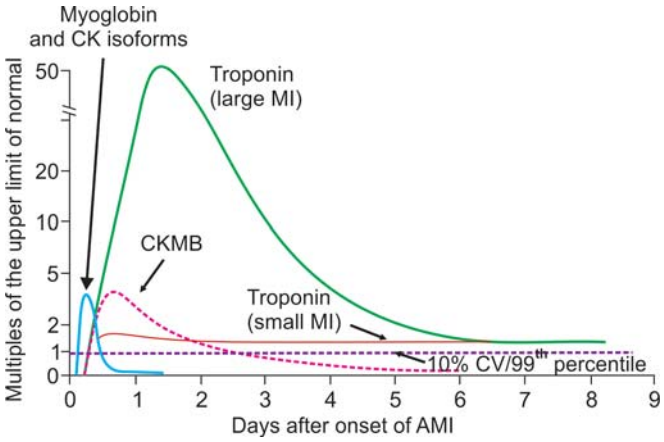


FIGURE 3: Timing of release of various biomarkers after acute ischemic myocardial infarction. (*Source:* Modified from Kumar, et al. Acute coronary syndromes: diagnosis and management, Part 1. Mayo Clin Proc. 2009;84(10):917-38)

Troponin

Cardiac troponins have gained widespread acceptance, and have largely replaced CK-MB as the biomarkers of choice for detecting myocardial injury. This is due to their high sensitivity and specificity to the heart muscle as well as the commercial availability of a rapid, inexpensive and reproducible test. Troponin is a multimer that is composed of three subunits: (1) Troponin (Tn) T, (2) Tn I and (3) Tn C. Only Tn T and Tn I are commercially available as diagnostic tests. Since normal individuals should not have any detectable levels, levels higher than 99th percentile of a normal population of subjects are used as a cutoff for troponin elevation.

Troponin levels do not increase until at least 6 hours after the onset of the infarct; therefore, a negative test during this period should be repeated after a period of 4–6 hours (Fig. 3). Also, the longer half-life of troponin (5–14 days) limits its usefulness in detecting reinfarction. In these situations, CKD and CK-MB are more reliable.

Among patients with symptoms consistent with UA, the presence of troponin elevation identifies patients with NSTEMI. It is estimated that up to 25% of patients with UA who have normal CK-MB levels would be classified as having NSTEMI based on troponin assay.[22] It must be emphasized, however, that the availability of an easy to order test should not replace clinical judgment. Troponins are specific markers of myocardial injury, but they do not automatically imply ischemia as the cause of injury (e.g. myocarditis, heart failure, cardiac contusion, etc.).[23] Therefore one must interpret the results of biomarker elevation in the context of the clinical syndrome.

RISK STRATIFICATION—PUTTING IT ALL TOGETHER TO DETERMINE THE OPTIMAL TREATMENT STRATEGY

Patients presenting with chest pain or angina equivalent, consistent with possible UA/NSTEMI are heterogeneous in terms of their risk of mortality. Therefore, appropriate risk stratification is of paramount importance.

Early risk assessment must be twofold. Firstly, one must determine the likelihood that the clinical syndrome is related to coronary ischemia and evaluate whether the course of symptoms are accelerated. This is performed by a focused history assessing whether the clinical presentation is consistent with angina. In order to do so, one must understand the clinical characteristics that are typical of angina (described previously) and be aware of the potential for atypical presentations of angina. In addition, one must consider the overall risk factors that the individual patient will have CAD by assessing patient's risk factors (known CAD, PAD, hypertension, diabetes, hyperlipidemia, smoking, family history of premature CAD, obesity, physical inactivity, chronic renal failure and the presence of a connective tissue disease or rheumatoid arthritis).[16-18,24] Next, one must consider findings on the ECG and available laboratory testing. Finally, one must consider the likelihood of alternative diagnoses.

Based upon this, a patient may be classified into one of the following groups:

- Definite ACS (clinical symptoms consistent with angina, and electrocardiogram (ECG) changes consistent with ischemia and/or positive troponin, or patients with known stable angina with acceleration in the pattern of the angina).
- Possible ACS (clinical symptoms consistent with angina, but lack of ECG changes or positive troponin).
- Stable angina (clinical symptoms consistent with angina, without a pattern of acceleration or instability).
- Noncardiac chest pain (clinical symptoms that are not consistent with angina and lack of ECG changes or positive troponins, especially with a documented noncardiac cause).

Patients with definite ACS require hospitalization and further evaluation and treatment as described here. Patients with possible ACS require further evaluation in a monitored setting such as a chest pain observation unit or a monitored telemetry unit. In the chest pain observation unit, ECG and cardiac markers are repeated after 3–8 hours (pending institutional protocol and the time elapsed from the onset of discomfort) and if negative the patient will undergo a provocative (stress) or anatomic (CT) test to assess coronary ischemia as the etiology of the syndrome. If the evaluation is negative, the patient may be discharged with recommendations for risk factor modification as appropriate and follow-up as necessary. Patients with a presumed diagnosis of noncardiac chest must have an evaluation to determine other life-threatening noncoronary diagnoses (e.g. pulmonary embolism, aortic dissection, pneumonia, etc.). Of course, the identification of a noncardiac cause should prompt appropriate treatment. If any of the tests suggests the diagnosis of ACS, the patient will be admitted for further evaluation and therapy. Patients with stable angina may be discharged home with increased medical therapy to follow-up as an outpatient.

Second, one must perform early risk stratification in those patients with possible/definite ACS to tailor treatment intensity according to patient's risk for early morbidity and mortality. The estimation of risk in ACS involves incorporating information from several prognostic variables which include history, physical findings, ECG changes and troponin, and is further discussed below.

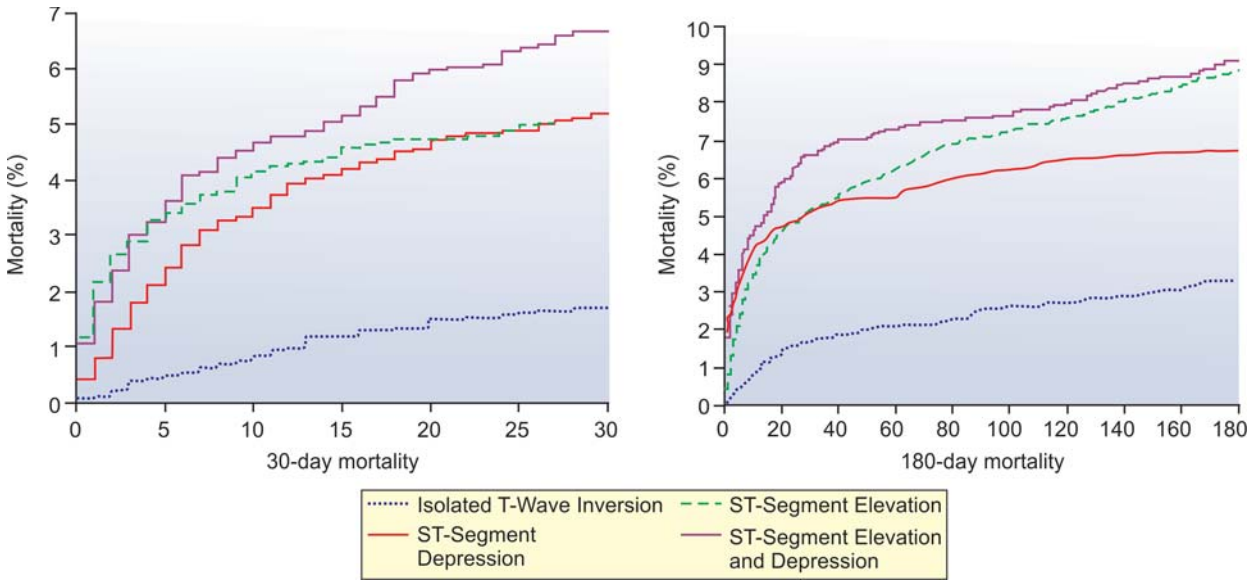


FIGURE 4: Risk of 30-day and 180-day mortality according to ECG changes at presentation in patients with NSTEMI. (*Source:* Modified from Savonitto S et al. Admission ECG changes and the impact on 30- and 180-day mortality. JAMA. 1999;281:707-13)

HISTORY

The risk for short-term and long-term mortality increases with advancing age among patients with UA/NSTEMI.[25] Prior history of CAD increases the likelihood of obstructive and multivessel CAD. While traditional risk factors are important in assessing the likelihood of ACS as discussed above, they are less important in predicting short-term mortality except history of diabetes[26] and/or extra cardiac PAD,[27] both of which increase the short-term risk. Similarly, patients who present with hemodynamic compromise (advanced Killip Class) have a significantly higher risk of death and should be treated with aggressive use of antithrombotics and early use of invasive angiography.[28]

ELECTROCARDIOGRAM

Multiple studies have shown that the electrocardiogram (ECG) provides valuable prognostic information among patients with ACS. The patient with ACS and an ECG showing dynamic ST segment changes or left bundle branch block (LBBB) have the highest risk of death while patients with isolated T wave inversions or normal ECG have a lower risk of death. This association is independent of the remaining clinical findings and the patient risk factors (Fig. 4).[29,30] The association of Wellen's T waves with critical proximal left anterior descending artery stenosis has been previously discussed. These patients if left untreated are at a high risk for developing extensive anterior wall myocardial infarction, significant morbidity and death. Once recognized, urgent coronary angiography should be pursued in these patients.[20]

CARDIAC BIOMARKERS

Elevation in troponin is a strong predictor of short-term mortality with a gradient of risk according to the level of troponin

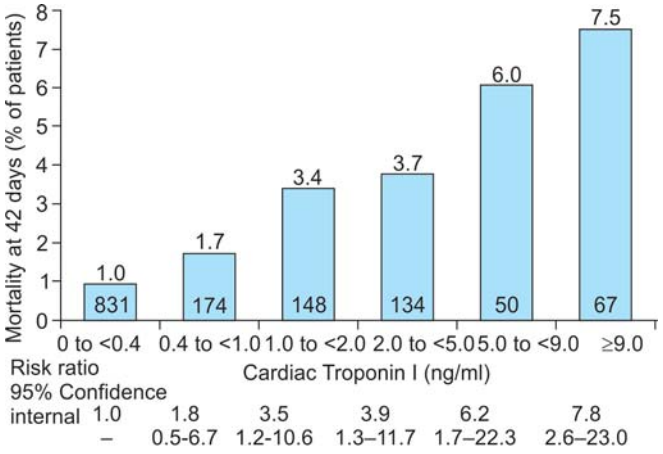
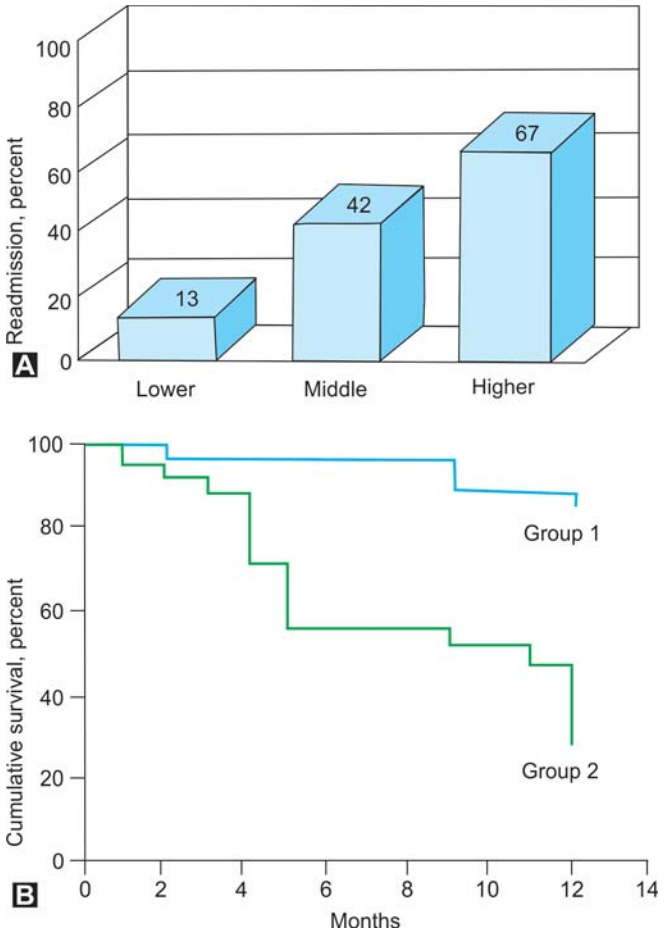


FIGURE 5: Mortality rates at 42 days according to the level of cardiac troponin I. (*Source:* Modified from Antman EM, Tanasijevic MJ, Thompson B, et al. Cardiac-specific troponin I levels to predict the risk of mortality in patients with acute coronary syndromes. N Engl J Med. 1996;335:1342-9)

elevation (Fig. 5),[22] and it is incorporated into all of the risk prediction tools that are currently available. Therefore, the utility of the test is not just limited to diagnosis; an elevated troponin level implies a worse prognosis regardless of etiology, even among those patients later identified to have no epicardial CAD.[31,32] Thus, troponin elevation is considered as an important marker of risk and identifies patients who may be candidates for more aggressive treatment (see risk stratification below).

During the past decade, inflammation has been recognized to play an important role in the pathogenesis of ACS. Consequently, attention has been focused on biomarkers of inflammation, of which C-reactive protein (CRP) is the most widely studied. Elevated CRP detected by a high sensitivity assay (hs-CRP) has been strongly associated with increased risk



FIGURES 6A AND B: The incidence of readmission for unstable angina or myocardial infarction during follow-up correlates with the serum concentration of CRP measured at discharge in patients with unstable angina. (A) Patients in upper tertile of serum CRP (≥ 0.87 mg/dL) had significantly more events during follow-up than patients in the middle (0.26–0.86 mg/dL) or lower (≤ 0.25 mg/dL) tertiles. (B) The 1-year survival free of readmission for myocardial infarction or unstable angina was lower in patients with increased serum CRP at discharge compared to those with normal levels. (*Source:* Modified from Biasucci LM, Liuzzo G, Grillo RL, et al. Elevated levels of C-reactive protein at discharge in patients with unstable angina predict recurrent instability. Circulation. 1999;99:855-60)

TABLE 1

TIMI risk score

• Age > 65 years • Chest pain in previous 24 hours • Three major risk factors (diabetes, hypertension, hyperlipidemia, family history of ischemic heart disease and current smoking) • Aspirin use in last 7 days • Known coronary stenosis > 50% • ST segment deviation > 0.5 mm or new left bundle branch block on initial ECG • Elevated troponin level
(Score: One point is awarded for each parameter)

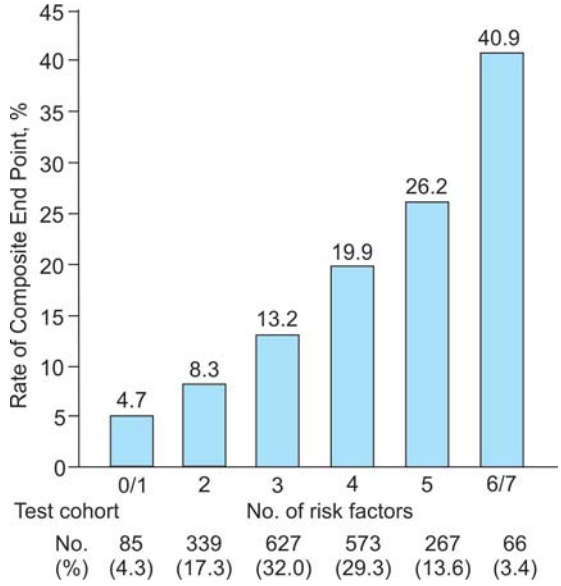


FIGURE 7: Rates of mortality, myocardial infarction, severe recurrent myocardial ischemia that prompted urgent revascularization according to TIMI risk score. (*Source:* Modified from Antman EM, Cohen M, Bernink PJ, et al. The TIMI risk score for unstable angina/non-ST elevation MI: a method for prognostication and therapeutic decision-making. JAMA. 2000;284:835-42)

of short-term mortality, and identifies patients with normal troponin levels who are at an increased risk of death and recurrent ischemic events (e.g. recurrent ischemia/hospitalization, reinfarction and death) (Figs 6A and B).[33,34] Similarly, elevated levels of B-type natriuretic peptide (BNP) have also been shown to provide powerful prognostic information across the entire spectrum of ACS for both short-term and long-term mortality in a number of studies.[35,36]

Since multiple variables are predictive of risk in UA/NSTEMI patients, several groups have developed comprehensive multivariable risk models that incorporate information from several predictor variables into a score for the purpose of determining intensity of initial treatment and prognosis. The most commonly used risk score in the United States is the thrombolysis in myocardial infarction (TIMI) risk score, which incorporates information from seven variables (Table 1).[37] The TIMI risk score enables identification of high-risk patients that are at increased risk of death, and recurrent myocardial infarction (MI) and thus would benefit from aggressive therapies and early invasive treatment (Fig. 7). Other risk scores, such as the GRACE and PURSUIT are also available, and may be better at predicting mortality, but are more complex.[38,39]

EARLY MEDICAL THERAPY

The following section discusses early medical therapy in patients with ACS with special emphasis on UA/NSTEMI. At the end of each section, recommendations from the American College of Cardiology (ACC) and the American Heart Association (AHA) 2007 guidelines, and the more recent 2011 focused updates on the management of patients with UA/NSTEMI are included wherever appropriate.[40,41] Indications for use are divided into Class I (should be performed/administered), Class II (reasonable to or may consider performing/administering) and

Class III (should NOT perform/administer due to the lack of benefit and/or potential for harm). The reader is directed to the guidelines for a detailed discussion and the reasoning for these recommendations.

GENERAL MEASURES

Based on the risk of future events, patients with a presumed diagnosis of UA/NSTEMI may be admitted to a coronary care unit (high risk), a telemetry unit (intermediate or low risk) or may be managed in a chest pain observation unit (low risk). Continuous telemetry monitoring should be available to detect dysrhythmias.

Even though not rigorously studied, oxygen supplementation is frequently used to provide adequate supply of oxygen, especially to the patients with oxygen saturations of 90% or below. The patients should be on bed rest during the early evaluation process.

The American College of Cardiology (ACC)/American Heart Association (AHA) guidelines recommend:

Class I

- *Bed rest and continuous ECG monitoring during the initial evaluation.*
- *Supplemental oxygen if arterial saturation is less than 90%, for patient with respiratory distress or patient who are at high risk for the development of hypoxemia.*

NITRATES

These agents are donors of nitric oxide (NO), which causes activation of cyclic guanylyl cyclase pathway resulting in an increase in intracellular cyclic guanosine monophosphate (cGMP). This leads to vasodilation, primarily in the venous bed with decrease in venous return and cardiac preload. Additional mechanisms include coronary vasodilation and improvement in blood flow to ischemic areas. Finally, a reduction in platelet aggregation has also been proposed as a potentially beneficial mechanism.[42]

Patients with ACS should receive a sublingual nitroglycerin (0.4 mg) or a buccal spray which may be repeated every 5 minutes for a total of 3 doses. If pain persists, then intravenous nitroglycerin should be initiated at a dose of 10 microgram/minute and rapidly titrated up (every 3–5 minutes) to achieve pain relief or until relative hypotension develops. There is no absolute maximum dose of nitroglycerin, although doses above 200 microgram/minute have not generally been shown to provide additional benefit. Nitrates should not be used in patients who have recently ingested type 5 phosphodiesterase inhibitors (e.g. sildenafil, tadalafil, etc.) as it may result in dangerous and reportedly fatal hypotension. Men and patients with known pulmonary hypertension should be questioned regarding recent use of these agents. Once the acute pain episode has resolved oral or, less commonly, topical nitrates may be used to prevent recurrences of symptomatic ischemic episodes. It must be remembered that patients should ultimately have a nitrate free period of at least 8–10 hours to prevent the development of tachyphylaxis, but generally in the first 24 hours after presentation, nitroglycerin may be continued for pain relief and prevention.

Evidence for the effect of nitrates in reducing long-term mortality is generally lacking.[43,44] Therefore, the primary role of chronic nitrates in ACS patients is relief of pain acutely in patients who have angina that is refractory to other effective medications (e.g. aspirin, clopidogrel, β-blockers, etc.).

The American College of Cardiology (ACC)/American Heart Association (AHA) guidelines recommend:

Class I

- *Sublingual nitroglycerin every 5 minutes for 3 doses to relieve symptoms.*
- *Intravenous nitroglycerin for up to 48 hours in patients with refractory symptoms of ischemia, or heart failure or continued hypertension despite medical therapy, provided use of nitroglycerin does not preclude the use of other mortality-reducing agents (β-blockers or ACE inhibitors).*

Class III

Use of nitrates should be avoided in:

- *Systolic pressure less than 90 mm Hg or a 30 mm Hg drop from baseline.*
- *Significant bradycardia or tachycardia in absence of heart failure.*
- *Suspected right ventricular infarction.*
- *Patient has taken a phosphodiesterase inhibitor for erectile dysfunction in previous 24 hours for sildenafil or 48 hours for tadalafil.*

MORPHINE

Morphine sulfate used in a dose of 1–4 mg intravenously is a useful adjunctive therapy for pain relief among patients with ACS. In addition to its potent analgesic effect, morphine results in venodilation and reduction in cardiac preload—this effect is particularly beneficial in patients with pulmonary edema. In addition, due to its anxiolytic effect, it helps to relieve agitation and has a calming effect in such patients; therefore, decreasing their myocardial oxygen demand. Some patients may develop hypotension which generally responds to supine positioning and/or volume challenge. Rarely, respiratory depression may develop that responds to reversal with naloxone.

The American College of Cardiology (ACC)/American Heart Association (AHA) guidelines recommend:

Class IIA

- *Morphine sulfate may be used for symptom control in addition to other medical therapy for ischemia.*

BETA BLOCKERS

These drugs act by blocking the effect of catecholamines on β1-receptors of the heart which results in slowing of the heart rate, and reduction of contractility thereby reducing myocardial oxygen consumption. Slowing of the heart rate is beneficial as it helps in prolonging diastole thereby improving coronary perfusion.

In the absence of contraindications, patients with ACS should be treated with β-blockers at initial presentation. Oral dosing is appropriate although it is reasonable to use intravenous dosing in patients who are persistently hypertensive. Contraindications to the use of β-blockers include: (1) Signs of heart failure; (2) Evidence of low-output state; (3) Increased risk for cardiogenic shock and (4) Other relative contraindications (first degree AV block with PR interval > 0.24 seconds, any 2nd or 3rd degree AV block, reactive airway disease or active asthma). A history of chronic obstructive pulmonary disease (COPD) should not preclude use of β-blockers; however, one should select a short-acting agent that is cardioselective (e.g. metoprolol).

While the use of β-blockers acutely in ACS is widespread, the data supporting this practice are based on older trials.[45,46] In the modern era, role of β-blockers in ACS was studied in the clopidogrel and metoprolol in myocardial infarction trial/second chinese cardiac study (COMMIT/CCS-2) trial. This large trial (45,852 patients with AMI with a majority of patients with STEMI) found no difference in the risk of a composite outcome of death, reinfarction, shock or cardiac arrest among patients treated with early metoprolol (intravenous up to 15 mg followed by 200 mg daily) compared to placebo for a period of 30 days. While risk of reinfarction and ventricular fibrillation was significantly lower with β-blockers; this was counterbalanced with a significantly increased risk of cardiogenic shock.[47] Based on this trial, caution must be exercised in the use of intravenous β-blockers acutely in the setting of an AMI particularly in patients with decompensated heart failure or who are at high risk of developing cardiogenic shock.

The American College of Cardiology (ACC)/American Heart Association (AHA) guidelines recommend:

Class I

- *Oral β-blockers be given in the first 24 hours after presentation if no contraindication are present.*
- *Intravenous β-blockers be considered only in patients without heart failure, evidence of low cardiac output state, relative contraindications (asthma and heart block) or multiple risk factors for development of cardiogenic shock (age > 70 years, systolic blood pressure of < 120 mm Hg, sinus rhythm with heart rates > 110 or < 60, and prolonged time from onset of ischemia to presentation).*

CALCIUM CHANNEL BLOCKERS

These drugs inhibit the inward flux of calcium via L-type calcium channels and thus inhibit both myocardial and vascular smooth muscle contraction. Agents in this class have diverse effects—the dihydropyridines (nifedipine and amlodipine) predominantly cause vasodilation by relaxation of vascular smooth muscle; the non-dihydropyridines (verapamil and diltiazem) have additional predominant negative inotropic and chronotropic actions. Calcium channel blockers that slow the heart rate may be used for the relief of angina in patients with angina refractory to nitrates and β-blockers, in patients with contraindications to β-blockers, in those with vasospastic angina, or in those with hypertension. The side effects include bradycardia, worsening of heart block, hypotension and heart failure respectively.

Both diltiazem[48] and verapamil[49] have been studied in the setting of AMI and have been shown to reduce recurrent MI and death. Importantly though, both agents were associated with an increase in the risk of death among patients with AMI and LV systolic dysfunction or congestive heart failure (CHF) and, therefore, should not be used in these patients.[50] Nifedipine, which is a predominant vasodilator and does not lower the heart rate (but may cause a reflex tachycardia), is also associated with increased mortality in the absence of β-blockade and should not be used in patients with ACS.[51] The newer agents (amlodipine and felodipine) have not been directly studied in UA/NSTEMI patients, but have otherwise been found to be safe in patients with CAD and LV dysfunction.[52,53] Amlodipine and felodipine may be used as additional agents for blood pressure control in the subacute and chronic stages of the treatment.

Overall, the role of calcium channel blockers is primarily for symptomatic relief when β-blockers cannot be used or for the treatment of hypertension or persistent symptoms despite maximal therapy with β-blockers and nitrates. One must use caution when combining high doses of β-blockers with calcium channel blockers due to the risk of sinus node and AV block, and depression of LV function.

The American College of Cardiology (ACC)/American Heart Association (AHA) guidelines recommend:

Class I

- *Non-dihydropyridine agents may be considered if persistent ischemia and no contraindications (heart failure) despite maximal dosing of nitrates and β-blocker.*

Class III

- *Avoid immediate release dihydropyridine calcium channel blockers in absence of a β-blocker.*

ANTIPLATELET AGENTS

Potent antiplatelet therapy is the cornerstone of management of UA/NSTEMI given what has been previously described regarding the central role of platelets/thrombus in the pathophysiology of ACS.

Aspirin

For more than 50 years, aspirin has been the cornerstone of antiplatelet therapy and occupies a prominent role even today. It irreversibly acetylates the platelet enzyme COX-1 and thus prevents the generation of TXA2 from arachidonic acid thereby blocking the activation of platelets (Fig. 1). Aspirin is rapidly absorbed in the buccal mucosa (when chewed) and the stomach and the small intestine, achieving platelet inhibition within 15–60 minutes.[54] Even though aspirin chemically has a short plasma half-life, the antiplatelet action lasts for the lifetime of the platelet (7–10 days), due to irreversible inhibition of COX-1 enzyme.

To date, there have been four large-scale randomized trials that have demonstrated greater than 50% reduction in the risk of recurrent MI or death in patients with UA/NSTEMI.[55-58] The benefit begins as early as the first day of treatment. An initial dose of 162–325 mg daily followed by 75–162 mg daily for secondary prevention is recommended. However, considerable controversy surrounds the optimal dose of aspirin for long-term use in patients for secondary prevention. This controversy is mainly engendered by observational studies that have suggested no difference in efficacy in death or MI prevention, but a higher risk of bleeding with higher doses (> 200 mg) of aspirin.[59,60] To address this, a large randomized trial to examine clinical outcomes in more than 25,000 ACS patients referred for an invasive strategy who were randomized to aspirin at a dose of 300–325 mg versus 75–100 mg was recently completed. The trial did not show any difference in clinical efficacy endpoint or the risk of major bleeding between the two aspirin groups.[61] Thus, all UA/NSTEMI patients should receive aspirin as soon as possible after hospital presentation and this should be continued indefinitely.

The concept of "aspirin resistance" has emerged in the past decade. Based on small studies, 2–8% of patients have a limited antiplatelet effect (as assessed by in vitro platelet function studies) despite being on aspirin therapy. Two recently published meta-analyses showed a strong association with laboratory defined aspirin resistance and a higher risk of recurrent cardiovascular events in these patients.[62,63] Limitations of these meta-analyses include varied prevalence of aspirin resistance, small sample size of included studies, inability to account for noncompliance and possibly publication bias. Increasing the dose of aspirin from 81 mg to 325 mg may result in more complete antiplatelet response in these patients.[64] Routine monitoring of platelet function and adjustment of aspirin dose based on test results maybe an effective strategy that has not been evaluated in larger trials. Consideration of aspirin resistance should be given to any patient presenting with stent thrombosis.

The American College of Cardiology (ACC)/American Heart Association (AHA) guidelines recommend:

Class I

- *Aspirin (dose of 162–325 mg) should be given as soon as possible to all patients without a contraindication (allergy or active bleeding), and continued indefinitely.*

Adenosine Dinucleotide Phosphate Receptor Antagonists

The adenosine dinucleotide phosphate (ADP) is an important platelet agonist which exerts its action by binding to the P2Y12 receptors on the surface of the platelets (Fig. 1). The result of ADP signaling through the P2Y12 receptor pathway is the amplification of degranulation and ultimately platelet aggregation.[65] This is achieved by enhanced surface expression and affinity of platelet glycoprotein IIb/IIIa protein which interacts with fibrinogen and vWF to result in platelet aggregation. Consequently, several drugs have been developed that target the inhibition of this pathway.

Clopidogrel

It is a thienopyridine that causes irreversible inhibition of the P2Y12 receptor and thus prevents ADP binding to its molecular target on the platelet surface. Clopidogrel is a prodrug and requires metabolic activation by cytochrome P450s to its active metabolite. Clopidogrel has largely replaced ticlopidine (the first agent in this class, now rarely used) as the latter was associated with an increased risk of hematologic complications such as neutropenia and thrombotic thrombocytopenic purpura.[66]

The landmark clopidogrel in unstable angina to prevent recurrent events (CURE) trial showed that clopidogrel in addition to aspirin, heparin and other standard therapy was beneficial in preventing death, MI or stroke in UA/NSTEMI patients.[67] The benefit occurred as early as 24 hours and continued for up to 1 year in the study. Although clopidogrel is indicated in patients who are treated with stents,[68] the vast majority of patients in the CURE trial were not treated with stents, suggesting that clopidogrel results in a significant reduction in ischemic endpoints among patients with UA/NSTEMI regardless of treatment strategy (i.e. invasive vs conservative).[69,70] More recently, a higher loading dose of clopidogrel (600 mg) followed by a maintenance dose of 150 mg daily for 6 days and then 75 mg daily was compared to standard dose (loading dose 300 mg followed by 75 mg daily) in a large multinational trial involving high-risk ACS patients. While the overall trial results did not show a significant reduction in the combined endpoint of cardiovascular death, MI or stroke at 30 days, the subgroup of patients who underwent percutaneous coronary intervention (PCI) and received higher dose clopidogrel had lower rates of the primary outcome and stent thrombosis; this benefit was largely offset by increased risk of bleeding.[61]

Bleeding risk: Not surprisingly, antiplatelet inhibition with clopidogrel is associated with an increased risk of major bleeding. This is of particular concern among patients who are identified as candidates for bypass surgery. In the CURE trial, the increased coronary artery bypass grafting (CABG) related bleeding risk was only confined to those patients who did not discontinue clopidogrel for at least 5 days; bleeding was not increased among those who discontinued clopidogrel for greater than 5 days. Therefore, it is recommended that clopidogrel be discontinued at least 5 days before planned/elective surgery, if possible. After bypass surgery, clopidogrel should be resumed whenever feasible and continued for a period of up to 1 year. To avoid delaying surgery in a patient who may have multivessel or left main disease, some physicians withhold clopidogrel treatment acutely in an ACS patient until coronary anatomy is defined.[71] While this delayed approach avoids the increased bleeding risk in approximately 10% of patients with UA/NSTEMI who undergo CABG, it deprives all patients of the significant benefit from ischemic events or death that early initiation of clopidogrel affords.[69,70] It has been suggested that for every 1,000 UA/NSTEMI patients who are treated with early clopidogrel, 10–12 deaths, MIs or stroke would be prevented compared to delayed use, at the cost of 1 excess major bleeding (CABG-related) assuming that all clopidogrel treated patients

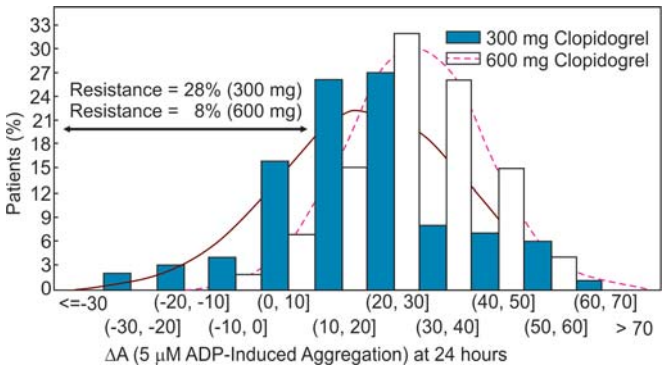


FIGURE 8: Distribution of ADP-induced platelet aggregation at 24 hours according to 300 mg and 600 mg of clopidogrel loading dose. (*Source:* Modified from Gurbel PA, Bliden KP, Hayes KM, et al. The relation of dosing to clopidogrel responsiveness and the incidence of high post-treatment platelet aggregation in patients undergoing coronary stenting. J Am Coll Cardiol. 2005;45:1392-6)

continued the drug until surgery.[72] Thus the risk-benefit ratio favors early use of clopidogrel in most patients.

Clopidogrel Resistance

The antiplatelet response of clopidogrel shows considerable interindividual variability (Fig. 8).[73] This may be overcome by higher loading doses.[74] The variability in response is clinically relevant—patients who achieve lower platelet inhibition on clopidogrel (hyporesponders) have been shown to have an increased risk for adverse cardiac events including death in multiple studies.[75,76] This is of particular concern among patients treated with stents where clopidogrel hyporesponsiveness may be associated with increased risk of developing stent thrombosis. It is well established that stent thrombosis leads to significant morbidity (e.g. recurrent MI, rehospitalization, etc.) and mortality (at least 30–40% risk of death), and thus all measures should be taken to avoid it.[77,78]

Clopidogrel is a prodrug that undergoes enzymatic conversion to its metabolically active form by the cytochrome P450 family of enzymes. As a result, polymorphism of the cytochrome P450 enzymes explain much of the observed variability in clopidogrel response in populations.[79-82] Most of the evidence points toward CYP2C19*2 allele, a loss of function allele, that results in reduced activity of the enzyme and lower antiplatelet effect of clopidogrel. Polymorphisms in the CYP2C19 gene are quite common and are reported in approximately 30% of whites, 40% of blacks and over 55% of east Asians.[83] Likewise inhibitors of cytochrome P450 enzymes (e.g. omeprazole)[84] have been suggested to cause reduced antiplatelet activity among clopidogrel treated patients; however, the impact of this finding on clinical outcomes remains uncertain.[85]

At this time, genetic testing is being evaluated as a strategy to identify patients with clopidogrel resistance as is the use of platelet function assays in guiding treatment strategy (higher dose of clopidogrel vs prasugrel). There is no definitive data at this time to suggest population-wide screening of the genetic polymorphism, or evaluation of platelet reactivity. As well, the effect of the combination of clopidogrel and proton pump inhibitors on clopidogrel effect is under investigation.

The American College of Cardiology (ACC)/American Heart Association (AHA) guidelines recommend:

Class I

Clopidogrel loading dose (at least 300 mg) with continued daily dosing (75 mg daily) should be administered:

- *As alternative antiplatelet therapy for patients intolerant/allergic to aspirin.*
- *As 2nd antiplatelet therapy in patients on aspirin with planned initial conservative approach for at least 1 month, and preferably 1 year.*
- *As 2nd antiplatelet agent in patients on aspirin in medium to high-risk patients with planned early invasive approach for at least 1 month, and preferably 1 year.*

Class IIb

- *Patients with definite UA/NSTEMI and undergoing PCI, a loading dose of clopidogrel 600 mg followed by a higher maintenance dose of 150 mg daily for 6 days, and then 75 mg daily may be reasonable in patients who are not at a high risk of bleeding.*
- *Clopidogrel may be considered beyond 15 months in patients receiving drug-eluting stents.*

PLATELET FUNCTION AND GENETIC TESTING

Class IIb

- Platelet function testing to determine platelet inhibitory response in patients with UA/NSTEMI (or, after ACS and PCI) on thienopyridine therapy may be considered if results of testing may alter management.
- Genotyping for a CYP2C19 loss of function variant in patients with UA/NSTEMI (or, after ACS and with PCI) on clopidogrel therapy might be considered if results of testing may alter management.

Newer Antiplatelet Agents

Prasugrel: Variability in the dose response of standard dose clopidogrel has led to an interest in the development of newer agents. Prasugrel is an oral thienopyridine drug and is less dependent on the cytochrome P450 enzymes for metabolic activation. After a loading dose of 60 mg, prasugrel reaches peak action within 30 minutes. Compared to clopidogrel (75 mg), prasugrel (10 mg) achieves more rapid and complete platelet inhibition with significantly less interindividual variability in its response; this is partly due to lesser dependence on the cytochrome P450 enzymes for metabolic activation.[86]

The clinical efficacy of prasugrel was studied in the TRITON-TIMI trial.[87] In this study, treatment with prasugrel (60 mg loading dose followed by 10 mg maintenance dose) was compared to clopidogrel (300 mg loading dose followed by 75 mg maintenance dose) in 13,608 high-risk ACS patients

(10,074 patients with UA/NSTEMI). Prasugrel treatment was associated with a significant reduction in the primary endpoint of death from cardiovascular causes, nonfatal MI or nonfatal stroke when compared to standard dose clopidogrel (9.9% vs 12.1%, p < 0.001). However, this was at the cost of a significantly increased risk of major bleeding (2.4% vs 1.8%, *P* value = 0.03) and life threatening bleeding (1.4% vs 0.9%, *P* value = 0.01) among prasugrel treated patients. As a result, overall mortality was not different in between the two groups at 15 months. Post-hoc analysis revealed that patients with prior stroke or transient ischemic attack (TIA) had net harm on prasugrel, while those 75 years or older and also those with body weight less than 60 kg did not have a net benefit on prasugrel.

Given the greater potency and lesser interindividual variability on inhibition of platelet function, prasugrel is a reasonable alternative in patients with recurrent events on clopidogrel therapy (clopidogrel hyporesponders). There are currently no systematic data on resistance to prasugrel or its clinical impact. While a case report of a patient who had persistently high on-treatment platelet reactivity to prasugrel is described, the clinical significance of this finding was not conclusively demonstrated.[88]

Prasugrel was recently approved by the FDA with a warning against its use in patient's age greater than 75 years, body weight less than 60 kg and prior history of TIA or stroke.

The American College of Cardiology (ACC)/American Heart Association (AHA) guidelines recommend:

Class I

Prasugrel loading dose (60 mg) followed by a maintenance dose (10 mg) should be given:

- *As 2nd antiplatelet agent in patients on aspirin in medium to high-risk patients with planned early invasive approach for at least 1 month and preferably 1 year.*
- *Prasugrel 60 mg loading dose promptly upon presentation in patients with UA/NSTEMI for whom PCI is planned, before definition of coronary anatomy if both the risk for bleeding is low and the need for CABG is considered unlikely.*

Class IIb

- *Prasugrel may be considered beyond 15 months in patients receiving drug-eluting stents.*

Class III

Prasugrel should be avoided in patients with:

- *Prior history of TIA or stroke, for whom PCI is planned.*

Ticagrelor: Ticagrelor is a non-thienopyridine, directly acting oral ADP receptor antagonist that reversibly binds to the P2Y12 receptor, with a stronger and more rapid antiplatelet effect than clopidogrel.[89] Unlike prasugrel and clopidogrel, it does not require metabolic activation, and its effect is reversed within 12–24 hours of drug discontinuation.

In the recently published study of platelet inhibition and patient outcomes (PLATO) trial, treatment with ticagrelor (180 mg loading dose, followed by 90 mg twice daily maintenance dose) was associated with a 16% relative reduction in the risk of cardiovascular events when compared to standard dose clopidogrel in high-risk ACS patients without a significantly increased risk of major bleeding. Even though the trial was not powered for mortality, patients randomized to ticagrelor also had a lower risk of all cause mortality (4.5% vs 5.9%, p < 0.001). An increased risk of dyspnea and bradycardia was noted among ticagrelor treated patients, which has been attributed to its modulation of adenosine receptors.[90]

At the time of writing of this chapter, the FDA has not approved ticagrelor for use in ACS.

Glycoprotein IIb/IIIa inhibitors: These medications block the final common pathway of platelet activation and aggregation and thereby prevent platelet aggregation initiated from a variety of stimuli (Fig. 1). Drugs which are currently available include: (1) Abciximab: a recombinant murine monoclonal antibody against the human GP IIb/IIIa receptor. Abciximab binds to this receptor tightly and inhibits platelet aggregation for days after the drug infusion is discontinued. (2) Eptifibatide: a cyclic peptide inhibitor with a rapid onset and short half-life (1–2.5 hours). Therefore it requires a continuous infusion for sustained response. (3) Tirofiban: a non-peptide Gp IIb/IIIa antagonist with a half-life of 4 hours.

The role of Gp IIb/IIIa inhibitors in the contemporary management of UA/NSTEMI continues to evolve. Numerous studies have shown that glycoprotein IIb/IIIa inhibitors reduce the risk of periprocedural MI, recurrent ischemia and death when used in patients with ACS.[91-95] This benefit reached statistical significance due predominantly to reduction in recurrent ischemic events. This has been confirmed in a large meta-analysis of all contemporary studies.[96] This benefit is particularly seen in higher risk patients, e.g. troponin positive patients,[97,98] those with dynamic ST changes or recurrent angina,[91] diabetic patients[99] or those with TIMI risk-score greater than 4.[37] In addition, in high-risk patients, the benefit seems to be present even in a subset of those patients who have been pretreated with clopidogrel and are given the medication as an adjunct during PCI.[92] In contrast, low-risk patients or those who are treated with an initial conservative strategy derive a very modest benefit with these drugs which may be counterbalanced by a significantly increased risk of major and life threatening bleeding.[96] Consequently, careful patient selection is important in identifying those who have the greatest likelihood for benefit.

Optimal timing of Gp IIb/IIIa inhibition continues to remain uncertain. Traditionally, two treatment strategies have been advocated: (1) Use as adjunctive therapy in the catheterization lab at the time of PCI or (2) As upstream therapy early in the course of ACS. While earlier studies have suggested a benefit of upstream therapy before PCI in these patients, these studies were performed in the era when clopidogrel was not widely used and rates of early angiography and revascularization were low. More recent data from two large randomized studies (ACUITY and EARLY-ACS) have not shown any benefit of routine upstream use of eptifibatide compared to delayed provisional use at the time of angiography in these patients,

thus arguing that for most patients adjunctive use at the time of PCI may be most appropriate.[100,101]

Currently, all three agents have been approved for use as adjunctive PCI therapy; however, only eptifibatide and tirofiban have been approved for use as upstream therapy. This is because in a large trial of upstream therapy, abciximab was associated with no benefit and a trend toward harm.[93] Concomitant use of aspirin and heparin is recommended with glycoprotein IIb/IIIa inhibitors. Since bleeding risk may be substantial with combination therapies and is frequently due to excess dosing,[102] careful attention should be paid when using these drugs especially in patients who are at a heightened risk of bleeding (e.g. elderly, patients with renal disease, patients with small BMI, etc.). Thrombocytopenia occurs in about 0.5% of patients treated with glycoprotein IIb/IIIa inhibitors necessitating the need for platelet monitoring. This routinely resolves after cessation of therapy.

The American College of Cardiology (ACC)/American Heart Association (AHA) guidelines recommend:

Use of a Gp IIb/IIIa receptor inhibitor (in addition to aspirin) in patients with UA/NSTEMI when:

Class I

- *Medium- to high-risk patients in whom an initial invasive strategy is planned either upstream or at the time of PCI (alternative to thienopyridines, preferred agents: eptifibatide or tirofiban).*
- *An initial conservative strategy is planned, but patient develops recurrent ischemia, heart failure or significant arrhythmias prior to the patient having urgent diagnostic angiography (alternative to clopidogrel).*

Class IIa

- *Patients in whom an initial conservative strategy is planned and who have recurrent discomfort with aspirin, clopidogrel and anticoagulants.*
- *Patient in whom PCI is planned, glycoprotein IIb/IIIa inhibitors may be started particularly in high-risk patients (e.g. troponin positive).*
- *Patients in whom PCI is planned, it is reasonable to omit glycoprotein IIb/IIIa drugs when bivalirudin is selected and at least 300 mg of clopidogrel has been administered at least 6 hours prior.*

Class IIb

- *Upstream therapy in high-risk patients already receiving aspirin and clopidogrel in whom an initial invasive strategy is planned (troponin positive, diabetes or significant ST segment depression) and who do not have a high risk of bleeding.*

Class III

Avoidance of the upstream use of Gp IIb/IIIa inhibitors:

- *Upstream use of abciximab in patients in whom coronary intervention in not planned.*
- *Low-risk patients (TIMI risk score < 2) or those at high risk of bleeding already receiving aspirin and clopidogrel.*

In addition to the medications that inhibit platelet activation and aggregation, medications that inhibit the coagulation cascade remain an important part of the treatment armamentarium.

Heparin

Unfractionated heparin (UFH) is the most commonly used medication in the setting of ACS. It is a glycosaminoglycan with polysaccharide side chains of varying lengths. It binds to antithrombin which results in a conformational change in the latter, thereby inactivating factor IIa (thrombin) and Xa. In clinical practice, only one-third of a given dose of heparin binds to antithrombin. Heparin also binds to several other plasma proteins which results in variability of dose response. Therefore, the anticoagulant effect of heparin should be closely monitored by measurement of activated partial thromboplastin time (APTT). The variability in action, need for close monitoring and the potential for heparin-induced thrombocytopenia makes heparin a suboptimal antithrombotic medication.

In a meta-analysis of patients with UA/NSTEMI, treatment with heparin was associated with a non-significant 33% relative reduction in the composite outcome of death or MI.[103]

Low-Molecular Weight Heparin

Low-molecular weight heparins (LMWH) are derived from heparin by chemical modification of the polysaccharide side chains. Enoxaparin is the most widely used LMWH in the United States. Compared to UFH, it is a more potent anti-Xa agent which inhibits generation of thrombin more effectively. Also, its greater bioavailability and lower plasma protein binding allows for a convenient subcutaneous dosing and predictable dose response and therefore does not require routine monitoring of anticoagulant effect. Anticoagulant activity of LMWH drugs cannot be reliably monitored using the APTT. Rather, it requires the measurement of anti-Xa activity and these assays are not as widely available. The standard dose of 1 mg/kg subcutaneous twice daily provides effective anticoagulant effect. The incidence of heparin induced thrombocytopenia is significantly lower compared to the UFH. Since LMWH are cleared by the kidney, the dose should be adjusted or altogether avoided in patients with renal dysfunction depending on their glomerular filtration rate. Also, dose response may be unpredictable in morbidly obese patients and therefore enoxaparin should generally be avoided in these patients.

Two early studies[104,105] compared enoxaparin to UFH in UA/NSTEMI patients and both found that enoxaparin was superior with a lower risk of death, MI or recurrent angina. The overall benefit was slightly offset with a slightly higher risk of bleeding with enoxaparin. In more recent studies,[106,107] which enrolled a higher risk group of patients showed that enoxaparin was noninferior but not superior to UFH. These divergent findings are likely due to more widespread use of additional antiplatelet drugs (clopidogrel, and/or Gp IIb/IIIa) and greater use of early invasive approach in the more recent studies. In fact, studies suggest that UA/NSTEMI patients undergoing initially conservative management derived much greater benefit with enoxaparin when compared to the UFH. In contrast, in patients

who underwent an early invasive approach, the results were very similar between the UFH and the enoxaparin group.[108] The greater bleeding associated with enoxaparin has been suggested as a possible explanation. This finding along with the complexity of monitoring the level of anticoagulant activity in the catheterization lab has prevented the widespread adoption of enoxaparin for adjunctive therapy at the time of PCI.

Fondaparinux

Fondaparinux is a synthetic pentasaccharide. It is an anti-Xa agent and does not have any direct effect on thrombin. This drug has predictable metabolism and can be conveniently dosed once a day by subcutaneous injection without any need for monitoring.

A large study comparing fondaparinux 2.5 mg/day to enoxaparin 1 mg/kg twice a day found the two medications to be similar with respect to the primary efficacy endpoint (death, MI, refractory ischemia—5.9% with fondaparinux vs 5.8% with enoxaparin at day 9) with a nearly 50% lower risk of bleeding in the fondaparinux group.[109] This translated into an overall lower 30-day mortality rate in the fondaparinux treated patients in this trial (2.9% vs 3.5%, p = 0.02). However, inclusion of patients with elevated creatinine and use of supplemental UFH may have resulted in greater bleeding in enoxaparin treated group, and biased the results in favor of fondaparinux. Also, fondaparinux was associated with a significantly higher risk of acute thrombosis in those undergoing PCI. Due to these concerns, the use of fondaparinux among ACS patients is not widespread.

Direct Thrombin Inhibitors

Bivalirudin: Bivaliridin is a synthetic analog derived from hirudin. It has direct action on thrombin, and therefore differs from heparin in that it does not require a cofactor (antithrombin) for its action. It directly inactivates thrombin including clot-bound thrombin. It also does not bind any plasma proteins and therefore has predictable pharmacokinetics. It does not result in complications such as thrombocytopenia.

The REPLACE-2 trial studied bivalirudin monotherapy in patients undergoing elective PCI compared to UFH and eptifibatide and found similar rates of ischemic events and death with significantly lower rates of bleeding in the bivalirudin treated patients.[110] Although this was a PCI trial, between 40% and 45% of patients had UA or MI as indication for the PCI. Subsequently, the ACUITY trial evaluated bivalirudin therapy in moderate- to high-risk UA/NSTEMI patients undergoing early invasive treatment. The trial had a complex design, but the principal findings of this trial were that bivalirudin monotherapy was not inferior to combination therapy with glycoprotein IIb/IIIa inhibitor with UFH, enoxaparin or bivalirudin for the prevention of major adverse cardiovascular events. At the same time, bivalirudin monotherapy was associated with a nearly 50% lower risk of bleeding.[100] Cost-effectiveness studies have found that despite higher medication costs, bivalirudin alone is cost-saving when compared to heparin and eptifibatide in moderate to high-risk NSTEMI patients.[111]

The American College of Cardiology (ACC)/American Heart Association (AHA) guidelines recommend:

Class I

Anticoagulation therapy in addition to antiplatelet therapy in patients with UA/NSTEMI as soon as possible with:

- *Enoxaparin or unfractionated heparin, or consider bivalirudin or fondaparinux in patients with a planned invasive strategy.*
- *Enoxaparin or fondaparinux in patients with a planned conservative strategy with fondaparinux being the preferred agent in patients with an increased risk of bleeding.*
- *Discontinue anticoagulant after PCI with uncomplicated procedures.*

Warfarin

Several studies have examined the role of warfarin in combination with aspirin in patients with ACS.[112,113] More recent studies have suggested a benefit of carefully monitored oral warfarin at a goal INR of 2.0–2.5 along with aspirin in reducing the combined endpoint of death, MI or stroke.[113] However, the contemporary role of warfarin is limited given the established role of clopidogrel in these patients particularly in those who receive PCI with a coronary stent. In the patient without a coronary stent, who may have another indication for warfarin, the combination of aspirin and warfarin may be preferable. The "triple" antithrombotic therapy (e.g. aspirin, clopidogrel and warfarin) has not been prospectively studied, and is likely to be associated with a greater risk of bleeding. This is not an infrequent consideration in a patient who receives a coronary stent, and also has another strong indication to be on warfarin (e.g. atrial fibrillation with a high CHADS2 score, or mechanical valve). Guidelines recommend using low dose of aspirin (75–162 mg aspirin), close monitoring of INR to a goal of 2.0–2.5, and use of clopidogrel for the shortest recommended duration based on type of stent (Class IIb).

The American College of Cardiology (ACC)/American Heart Association (AHA) guidelines recommend:

Class IIb

- *When triple-combination therapy is necessary based on clear clinical indications, consider using low dose of aspirin (75–162 mg aspirin), close monitoring and careful regulation of INR to a goal of 2.0–3.0, and use of clopidogrel for the shortest recommended duration based on type of stent.*

EARLY INVASIVE OR INITIAL CONSERVATIVE STRATEGY

An early invasive strategy involves performing coronary angiography within the first 24–48 hours of admission with the intent of performing revascularization with PCI or CABG, as appropriate. An initial conservative strategy involves initial medical management as outlined below with coronary angiography reserved for patients who have recurrent ischemia or a high-risk stress test despite medical therapy.

A number of randomized trials have compared early invasive strategy to an initial conservative strategy and the results have been mixed.[114-120] In a meta-analysis of contemporary trials, an early invasive strategy was associated with a 25% lower risk of death compared to initial conservative strategy.[121,122] A consistent finding in studies is that an early invasive strategy affords greatest benefit in high-risk patients especially those with elevated troponin, ST-segment deviation or higher TIMI risk score (> 3). While a study examining gender differences in treatment benefit suggested that low-risk women with UA/NSTEMI (negative biomarkers cardiac necrosis) may be potentially harmed with an early invasive strategy.[123] A heterogeneous study population with different standard medical regimens and a varied proportion of patient's actually undergoing revascularization in each group are important limitations of this study. It is clear that additional investigations to further clarify the gender differences in outcomes with different treatment strategies are warranted.

The specific issues regarding PCI in patients with ACS, particularly those with NSTEMI are: (1) The use of bare metal versus drug eluting stent at the time of PCI, and (2) The timing of angiography and intervention. The data on safety and efficacy of drug eluting stents versus bare metal stents for this population (UA/NSTEMI) are somewhat sparse, are mostly based on registry data (not randomized trials) and are conflicting. Presently there is no clear contraindication for either, but further randomized trials are recommended.[124,125]

Recent studies have addressed the issue of optimal timing of PCI in UA/NSTEMI patients, specifically the role of early intervention. The timing of intervention in acute coronary syndrome (TIMACS) study showed that early intervention within 24 hours (median time, 14 hours) did not result in a reduction in risk of death, recurrent MI or stroke in the first 6 months) when compared to delayed intervention more than 36 hours (median time, 50 hours). The subgroup analyses suggested a benefit of early intervention among high-risk patients (GRACE risk score > 140).[126] A second study compared very early intervention (within 6 hours) versus prolonged medical treatment or "cooling off" for 3–5 days with aspirin, heparin, clopidogrel and tirofiban among patients with chest discomfort and ischemic ECG changes and/or positive biomarkers. The study found no difference in events between these groups.[118] Lastly, a French study examined a strategy of planned immediate intervention (median time from randomization to sheath insertion was 70 minutes) versus a planned delayed intervention strategy (median time, 21 hours) and found no difference in the primary endpoint of peak troponin elevation, or in the secondary endpoint of death, MI or urgent revascularization within 30 days.[127] Thus, existing data do not support a strategy for immediate intervention for patients with UA/NSTEMI (unlike that for STEMI). At the same time, there is no inherent benefit in delaying revascularization with PCI after a "cooling off" period. The data suggest that the patient should be taken, in a timely manner, to the cardiac catheterization lab for angiography and planned intervention as deemed medically appropriate.

The American College of Cardiology (ACC)/American Heart Association (AHA) guidelines recommend:

Class I

- *An early invasive strategy in patients with refractory angina, or hemodynamic or electrically instability.*
- *An early invasive strategy in patients who have been stabilized with medical therapy, who are without comorbidities or contraindications to angiography or coronary intervention, and who have an increased risk of future events.*

Class IIa

- *Early invasive strategy (within 12–24 hours of admission) over a delayed invasive strategy for initially stabilized high-risk patients with UA/NSTEMI. For patients not at high risk, a delayed invasive approach is reasonable.*

Class IIb

- *An initial conservative strategy in patients at increased risk of future events (high risk) stabilized with medical therapy, who are without comorbidities or contraindications to angiography or coronary intervention, based on physician and patient preference.*
- *An early invasive strategy in patients with chronic renal failure, specifically with Stage II or Stage III CKD—there is not enough data for recommendations for more advanced stages of CKD.*

Class III

Avoidance of an early invasive strategy in patients with:

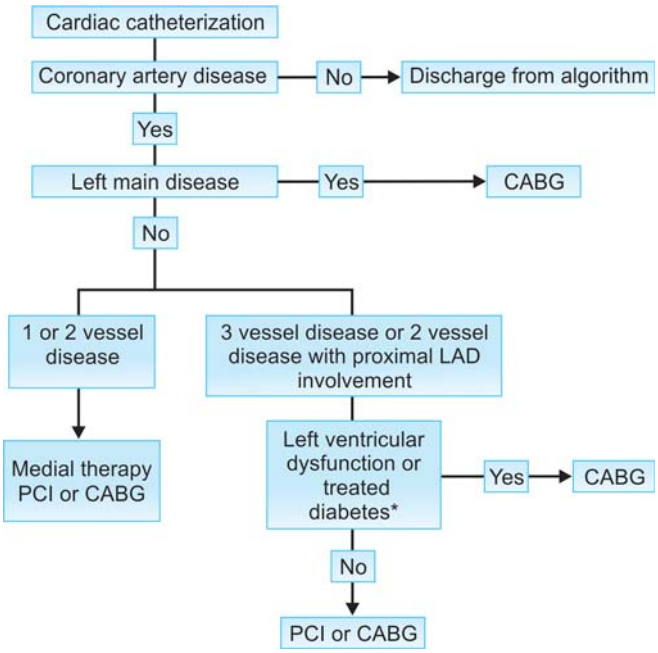
- *Extensive comorbities in whom the risk of revascularization outweigh the benefits.*
- *Acute chest discomfort and a low likelihood of ACS.*
- *No plan to consent for revascularization regardless of the findings on angiography.*

REVASCULARIZATION

Revascularization in patients with UA/NSTEMI may improve symptoms, quality of life, reduce ischemic complications or improve survival depending on the clinical circumstance. The need for revascularization depends on several factors which include patient age and more importantly functional status, serious comorbidities, expected survival, coronary anatomy, LV function and V, viability and severity of symptoms. Available alternatives for revascularization include PCI and CABG. The choice of revascularization strategy for patients with coronary disease has been a moving target with ongoing advances in technology, and the indications may continue to evolve.

In general, the indications for revascularization (and for CABG vs PCI) for patients with UA/NSTEMI are similar to those in patients with stable angina, with the exception of patients who may be candidates for CABG, based on anatomy, but has urgent/emergent need for infarct-related artery (IRA) revascularization for poor TIMI flow or threatened closure of

FLOW CHART 1: Revascularization strategy in UA/NSTEMI[2]



**There is conflicting information about these patients. Most consider CABG to be preferable to PCI*

(*Source:* Modified from Anderson JL, Adams CD, Antman EM, et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2007;116:e148-304)

the vessel. In this instance, PCI of the IRA to stabilize the patient, with subsequent consideration of further need for revascularization, should be performed. The high-risk patients with left main (> 50%) or three vessel disease, two-vessel disease with proximal LAD stenosis, diabetics with multivessel disease, and multivessel disease with LV dysfunction are better suited for CABG provided surgery can be performed with an acceptable risk (Flow chart 1).[128,129] An important issue that frequently influences timing of bypass surgery in these patients is the use of thienopyridines which increase the risk of CABG-related bleeding. Therefore, these drugs should be discontinued to allow for dissipation of the antiplatelet effect (clopidogrel 5 days, prasugrel 7 days) in an elective setting. However, clinical judgment should be exercised in making this decision in more emergent case (e.g. severe left main disease or recurrent ischemia) where the need for urgent revascularization may outweigh the risks of bleeding. Finally, while some studies have suggested an increased risk in CABG-related mortality in the first 3–5 days after an MI, recent data from the National Cardiovascular Data Registry found no difference in mortality in UA/NSTEMI patients undergoing early (within 48 hours) versus late CABG (after 48 hours). Thus, delaying surgery might increase resource use without improving outcomes.[130]

For other high-risk patients with less severe CAD, PCI may be an appropriate alternative to surgical revascularization particularly if the lesions are amenable to PCI. The angiographic success rate of PCI is generally more than 95%; further reduction in acute ischemic complications may be achieved with adjunctive use of glycoprotein IIb/IIIa inhibitors, clopidogrel and/or other antithrombotic drugs. Among low-risk patients, survival benefit with revascularization is less apparent from the available data and medical therapy alone may be appropriate. In such patients, revascularization may be considered for the treatment of symptoms that are refractory to optimal medical therapy, and for improvement in quality of life. It must be remembered that the modest benefit with revascularization in these patients must be counterbalanced with procedural risk.

The American College of Cardiology (ACC)/American Heart Association (AHA) guidelines recommend:

Class I

- *Early invasive strategy with angiography and PCI within 12–24 hours of admission.*
- *Early invasive PCI strategy in high-risk patients without serious comorbidity and who have amenable lesions for PCI.*
- *The PCI or CABG in patients with 1 or 2 vessel CAD with or without proximal LAD but with a large viable at-risk territory.*
- *The PCI or CABG in patients with multivessel CAD and suitable anatomy with normal LV function and no diabetes.*

Class II

PCI in patients with:

- *Vein graft lesions who are poor candidates for reoperation.*
- *Left main stenosis (> 50%) in patients who are not CABG candidates or who require emergent intervention for hemodynamic instability.*
- *No high-risk features who have single vessel CAD, or patients with multivessel CAD who have at least one lesion to be dilated with decreased likelihood of success.*
- *Considered in patients with two or three vessel disease amenable to percutaneous intervention with proximal LAD disease who have neither treated diabetes nor decreased LV systolic function.*

PCI or CABG in patients with:

- *One or two vessel CAD with or without proximal LAD stenosis but with moderate-sized viable at-risk territory.*
- *One vessel CAD with significant proximal LAD stenosis.*

Class III

PCI in patients with:

- *One or two vessel CAD without proximal LAD stenosis, with no ischemic symptoms or evidence of ischemia on stress testing.*

PCI in patients without high-risk features, in absence of a trial of medical therapy, and with:

- *Small sized at-risk territory.*
- *Lesions with low likelihood of success in treatment.*
- *High procedural risk of morbidity or mortality.*
- *Lesions that are not hemodynamically significant (< 50%).*
- *Significant left main CAD and are candidates for CABG.*
- *Stable patient with persistent occlusion of infarct-related artery.*

The American College of Cardiology (ACC)/American Heart Association (AHA) guidelines recommend:

Class I

CABG in patients with:

- *Significant left main CAD (> 50%).*
- *Three vessel CAD, especially patients with LVEF less than 50%.*
- *Two vessel CAD with significant proximal LAD stenosis and either LVEF less than 50% or ischemia on stress testing.*
- *Poor or no options for PCI who have ongoing ischemia refractory to medical therapy.*
- *UA/NSTEMI patients on thienopyridines, in whom CABG is planned and can be delayed, thienopyridines should be discontinued to allow dissipation of the antiplatelet effect (clopidogrel 5 days, prasugrel 7 days) unless the need for revascularization and the net effect of thienopyridines outweighs the risk of bleeding.*

Class II

CABG in patients with:

- *Multivessel disease who have diabetes and who will have an internal mammary graft during CABG.*
- *Single or two-vessel CAD, without proximal LAD stenosis, but with a modest sized at-risk territory and PCI option is poor and not possible.*
- *Need for repeat CABG when there are multiple vein graft stenosis and the graft to the LAD has a significant stenosis.*

Class III

CABG in patients with:

- *Single or two-vessel CAD without proximal LAD stenosis, with no ischemic symptoms or evidence of ischemia on stress testing.*

SUMMARY AND CONCLUSIONS

Over the past few years, there has been a tremendous growth in our understanding of the biology of atherosclerosis and the mechanisms that lead to ACS, one of the most dreaded consequences of coronary atherosclerosis. At the same time, important breakthroughs have emerged with development of new medications and treatment protocols that have improved patient outcomes. Diagnosis of ACS hinges on a careful assessment which includes a detailed history, physical examination, ECG and levels of cardiac biomarkers. The initial management of ACS includes initial medical stabilization with relief of pain, dual antiplatelet and antithrombotic therapy with consideration for early invasive treatment and revascularization. Early risk stratification is a very important tool that allows identification of patients who are at a high risk for short-term mortality; these patients benefit the most from aggressive management including thienopyridines, glycoprotein IIb/IIIa inhibitors and early invasive treatment. Revascularization should be considered in high-risk patients, and the choice of revascularization strategy and its timing depends on a patient's clinical condition, coronary anatomy and associated comorbidities.

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Chapter 49

Acute Coronary Syndrome II (ST-Elevation Myocardial Infarction and Post Myocardial Infarction): Complications and Care

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Chapter Outline

- Pathophysiology
- Clinical Presentation
  - Prehospital Assessment
  - Emergency Room Evaluation
- Reperfusion
  - Thrombolysis
  - Primary Coronary Intervention
- Early Medical Therapy
  - General Measures
  - Nitrates
  - Morphine
  - Antiplatelet Agents
  - Anticoagulation
  - Beta Blockers
- Post Myocardial Infarction Care
  - Assessment of Left Ventricular Ejection Fraction
  - Stress Testing Prior to Discharge
  - Coronary Angiography and Revascularization
- Complications
  - Right Ventricular Infarction
  - Heart Failure or Cardiogenic Shock and Mechanical Complications after a Myocardial Infarction
  - Dysrhythmias
  - Recurrent Chest Discomfort
- Special Considerations
  - Diabetes
  - Women
  - Elderly
  - Acute Coronary Syndrome with Cocaine (and Methamphetamine) Use
  - Post Myocardial Infarction Depression
  - Survivors of Out of Hospital Cardiac Arrest
- Continued Medical Therapy for Patients with a Myocardial Infarction
  - Inhibition of the Renin-Angiotensin-Aldosterone Axis
  - Lipid Management
  - Glucose Management
  - Smoking Cessation
- Discharge
  - Cardiac Rehabilitation and Secondary Prevention of Coronary Heart Disease for Patients with Myocardial Infarction

INTRODUCTION

Nearly 400,000 patients suffer from an ST-elevation myocardial Infarction (STEMI) every year in the United States.[1] It is a life-threatening event and a true medical emergency.[1] The risk of morbidity and mortality associated with STEMI increases with greater amount of myocardium at risk, delay in reperfusion, lack of collaterals to the infarct related artery (IRA), previous cardiovascular disease co-morbidities (e.g. diabetes, renal failure, etc.) and abnormal thrombolysis in myocardial infarction (TIMI) flow postreperfusion. It is estimated that at least 15% of patients, with a confirmed myocardial infarction (MI), die acutely and that 70% of these deaths occur prior to arrival at a hospital.[1] Based on 2006 data, 181,000 people in the United States died of STEMI. Among survivors, it is estimated that the average MI results in 15 years of life lost.[1]

The time from onset of symptoms to reperfusion is an extremely important factor on overall mortality (Fig. 1).[2,3] The success of restoration of normal flow in the IRA after primary percutaneous intervention was directly related to the ischemic time (i.e. symptom onset to initial balloon).[2] The relative risk of death increased by 1.075 for every 30-minute increase in symptom onset to balloon time.[2] Therefore, we must not only treat STEMI patients rapidly and appropriately when they arrive at our facilities, but we must also educate all patients on the signs and symptoms of an MI and the urgency of seeking medical treatment. In addition, patients must be educated to utilize the emergency medical transport system, instead of utilizing private transportation to the emergency facility. This allows for the prehospital treatment protocols that have been developed and utilized within communities to be effective in facilitating rapid reperfusion.

The reader should compare and contrast the evaluation and management of STEMI patients with UA/NSTEMI patients described in the Chapter 48. At the end of each section, recommendations from the American College of Cardiology (ACC) and the American Heart Association (AHA) 2004 guidelines[4] for the management of patients with STEMI, and

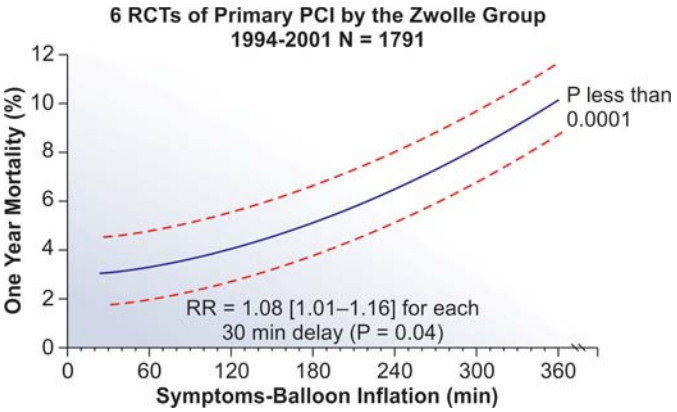


FIGURE 1: Symptom onset to balloon time and mortality in primary PCI for ST-elevation myocardial infarction. The relationship between time-to-treatment and 1 year mortality, as continuous functions, was assessed using a quadratic regression model. The dotted lines represent 95% confidence intervals of the predicted mortality. (Abbreviations: RCT: Randomized controlled trial; PCI: Percutaneous coronary intervention) (*Source:* Modified from DuLuca G, Suryapranate H, Ottervanger JP, et al. Time delay to treatments and mortality in primary angioplasty for acute myocardial infarction: every minute of delay counts. Circulation. 2004;109:1223-5)

the focused updates in 2007 and 2009[5,6] are included wherever appropriate. In addition, reference is also made to respective 2007 guidelines[7] for UA/NSTEMI and the 2011 focused update[8] wherever appropriate. Indications for use are divided into Class I (should be performed or administered), Class II (reasonable or may consider performing or administering) and Class III (should not perform or administer due to the lack of benefit and/or potential for harm). The reader is directed to the guidelines for a detailed discussion and the reasoning for these recommendations.

PATHOPHYSIOLOGY

The pathophysiology of STEMI is most commonly associated with acute rupture of a vulnerable plaque. This has been discussed in detail in Chapter 48 "Acute Coronary Syndrome I: Unstable Angina and Non-ST Segment Elevation Myocardial Infarction". Patients who present with UA/NSTEMI do not, in general, have sustained thrombotic vessel occlusion secondary to this plaque rupture. When this sustained occlusion occurs, STEMI results and the treatment strategy is focused on restoring flow as rapidly as possible as discussed later.

STENT THROMBOSIS

With the advent of stenting, particularly drug-eluting stent use, a second major etiology of STEMI, is stent thrombosis. The pathophysiology of early (within 24 hours of the procedure) stent thrombosis is related to mechanical complications, such as edge dissection or malapposition or under sizing of the stent, decreased flow in the target vessel at procedure end, or physical aspects of the vessel including visible thrombus during the procedure, intermediate lesions (50–70%) distal to the treated lesion, and stents placed at a bifurcation. After any coronary intervention, one must also be aware of potential for acute coronary syndrome (ACS), secondary to procedural complications due to mechanical trauma at the site of treatment as well as remote to the treated site (e.g, guide catheter or wire trauma). For early postcoronary intervention patients who develop STEMI, the interventional center must have a protocol for rapid assessment and immediate return to the catheterization laboratory for rapid restoration of flow.

The risk, of stent thrombosis continues after the initial periprocedural time period. Registry data with follow-up mean of 30 months demonstrated that 2.1% of patients presented with confirmed stent thrombosis. The risk of stent thrombosis decreases over time with 32% occurring within 24 hours, 41.2% occurring after 24 hours, but within 30 days, 13.3% at 31days to 1 year, 13.5% were beyond 1 year. This registry suggested no difference in numbers of stent thrombosis in bare metal stents compared to drug eluting stents.[9] With bare metal stenting, the risk of stent thrombosis is elevated above the long-term baseline for up to 1 month, but for drug eluting stents, this time of increased risk may be to 1 year and perhaps beyond.

The majority of subacute stent thromboses occur in patients who discontinue the necessary dual antiplatelet therapy early. Therefore, patients with stenting in the previous year, who present with STEMI in the territory of the previously treated vessel, must be questioned about compliance with their antiplatelet regimen. This questioning has direct impact on procedural strategies (if repeat stenting is necessary), and post interventional antiplatelet therapy.

In addition, characteristics of the patient (including prothrombotic states, the presence of malignancy, etc.) may significantly increase the risk.[9] Finally, aspirin and/or clopidogrel resistance may increase the risk of stent thrombosis.[10-13] Again, differentiation between noncompliance and resistance is very important in the management of patients. Data regarding resistance to antiplatelet therapy, particularly clopidogrel, including recent identification of genetic mutations in the cytochrome P450 pathway (CYP2C19 loss of function alleles), have been implicated in the increased risk of cardiovascular events and stent thrombosis in compliant patients.[14] This has been thoroughly discussed in Chapter 48 "Acute Coronary Syndrome I: Unstable Angina and Non-ST Segment Elevation Myocardial Infarction".

COCAINE OR METHAMPHETAMINE

Cocaine or methamphetamine-associated STEMI must be considered in all patients. Although, it may be more common to see illicit-drug associated cardiovascular events in younger patients, one must have a suspicion in all patients and take a careful history regarding cocaine or methamphetamine use. Urine toxicology testing must be considered especially patients with few or no risk factors for coronary artery disease (CAD). Most events occur early, but the illicit-drug may be a factor up to a few days after use. The ST-elevation may be a result of coronary vasoconstriction, commonly diffuse, without obstructive CAD, obstructive CAD related to repeated use and/or risk factors for CAD with or without plaque rupture, or related to myopericarditis related to the illicit-drug use. Patients using illicit-drugs may have other associated cardiovascular effects including dysrhythmia, aortic dissection, or stroke.

Other etiologies of STEMI include vasospasm, thromboemboli (originating from a mechanical valve, the left atrium in a patient with atrial fibrillation, left ventricular (LV)

thrombus, etc.) and stent restenosis with or without associated thrombus.

CLINICAL PRESENTATION

Patients with diagnosis of STEMI will present with symptoms consistent with ACS (see Chapter 48 "Acute Coronary Syndrome I: Unstable Angina and Non-ST Segment Elevation Myocardial Infarction"). Those with STEMI, though, have a higher likelihood of early complications including hemodynamic instability and shock, atrial and ventricular dysrhythmias and sudden cardiac death. Therefore, early evaluation including prehospital evaluation and timely determination of optimal reperfusion is essential.

PREHOSPITAL ASSESSMENT

The development of community or regional based STEMI protocols between emergency medical services (EMS), emergency rooms and the interventional cardiology catheterization labs is critical for optimal treatment of STEMI. The advent of systems that allow for high quality digital transmission of a 12-lead electrocardiogram (ECG) from the field facilitates early recognition of STEMI and infield treatment including thrombolysis. When a STEMI patient is to be transported to a facility with capability to perform primary angioplasty [percutaneous coronary intervention (PCI) center], activation of the cardiac catheterization laboratory team while the patient is in the field, decreases time to reperfusion and improves likelihood of TIMI III flow in the IRA.[15,16] This decrease in time leads to equalization of door to balloon (D2B) times between normal working hours and after hours or weekends when the interventional team may not be onsite. Thus, early in field activation of the interventional laboratory team allows for an overall decrease in D2B times and an improvement in patient outcomes.[15,16]

Alternatively, if the patient is not near a PCI center, a determination of need for full-dose thrombolysis can be performed by qualified physicians at the accepting facility after the checklist of contraindications is reviewed by EMS paramedics. When this thrombolytic therapy is given in the field, the time to therapy can be decreased by up to 40% depending on the location of the patient and time to the accepting facility.[17] Thrombolysis in the field, though, requires advanced training, clear protocols and ongoing quality assessment which limit the ability for this to be widespread.

It is also important to recognize that if primary angioplasty or stenting is to be performed, transport of the patient directly to a PCI center is optimal, even if it results in bypassing a non-PCI center.[18] Recent statewide protocols have been changed, including in the predominantly rural state of Iowa, to bypass small critical access hospitals and take the patient directly to a PCI center. This decreases overall transport time to the PCI center by eliminating time spent transporting the patient to and having the patient evaluated at a hospital that is not able to perform primary PCI and in many instances does not have a STEMI protocol to optimize D2B times. This direct transport to a PCI center improves time to reperfusion and thus improves outcomes.

The American College of Cardiology (ACC)/American Heart Association (AHA) guidelines recommend:

Class I

Community based programs be developed and instituted to include:

- *Quality focused multidisciplinary teams (personnel from EMS and hospitals including PCI centers and non-PCI centers)*
- *Prehospital identification and activation protocols*
- *PCI center protocols for STEMI*
- *Non-PCI center protocols for transfer of STEMI patients.*

Class II

Prehospital thrombolysis protocols be established and utilized if:

- *Either physician or full-time paramedics with ECG interpretation training are present in ambulance, and who work with dedicated hospital based STEMI program with ongoing continual quality improvement.*

EMERGENCY ROOM EVALUATION

It is expected that when a patient presents to a facility with chest pain, or other symptoms consistent with MI, that an ECG be performed and read by a qualified physician as soon as possible, but always within 10 minutes of arriving at that facility. If the electrocardiogram (ECG) is not diagnostic but the clinical scenario is consistent, the ECG must be repeated in no more than 10 minutes to assess for changes or evolution. If EKG is consistent with a STEMI (Figs 2 to 14) then, reperfusion must be the primary focus. A brief and rapid clinical evaluation for contraindications to reperfusion therapies and identification of other medical disorders, (particularly aortic dissection with compromise of a coronary artery resulting in STEMI) must be performed. In addition, it is prudent to evaluate the patient for emergency PCI, by rapidly assessing anticoagulation status, any history of contrast allergy and potential vascular access. This evaluation should not delay the reperfusion course. If the patient is not in a PCI Center, arrangements for transfer and/or consideration of thrombolysis should begin immediately.

The American College of Cardiology (ACC)/American Heart Association (AHA) guidelines recommend:

Class I

- *Hospitals should establish multidisciplinary teams with protocols for rapid triage and delivery of therapy including determination and delivery of reperfusion strategy*
- *The ECG within 10 minutes of arrival, with repeat in 5–10 minutes if ongoing symptoms and initial ECG is not diagnostic of STEMI*
- *Emergency room provider must rapidly obtain a focused history and physical examination to evaluate likelihood of STEMI and contraindications to reperfusion strategies.*

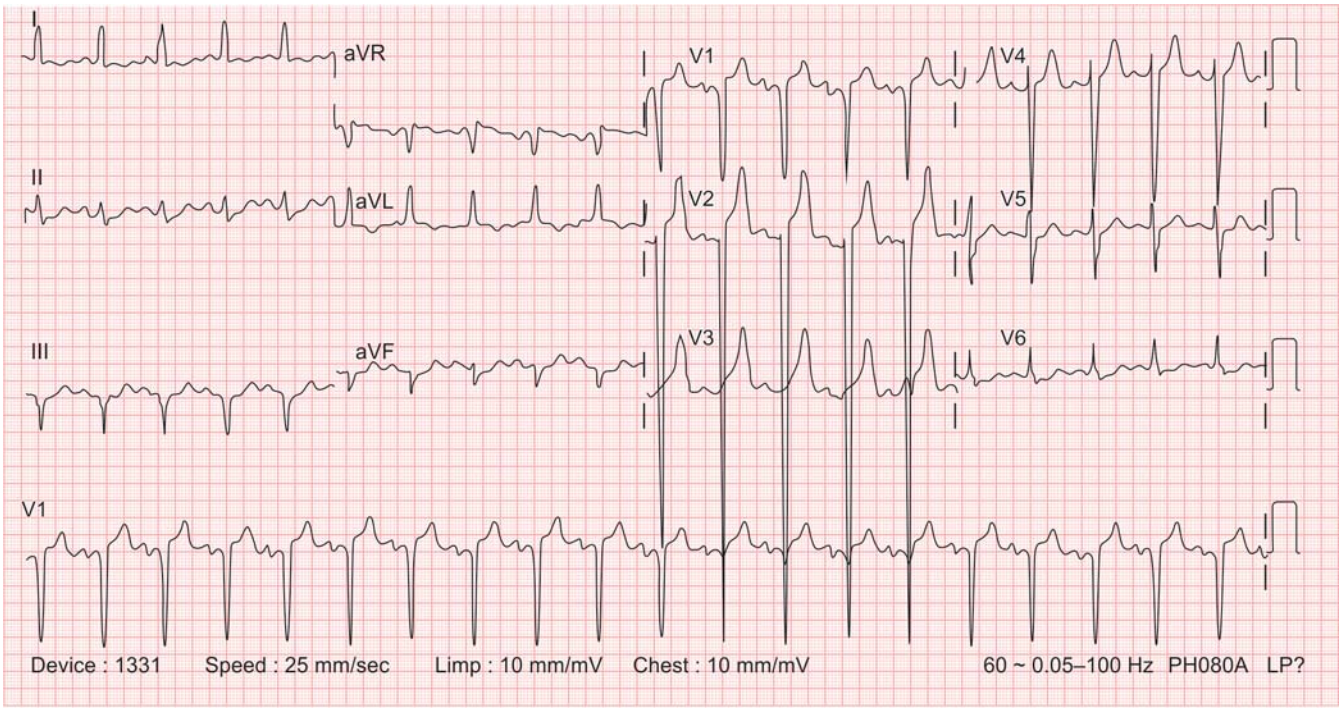


FIGURE 2: A 65-year-old patient who was in hospital undergoing evaluation for chest discomfort, developed recurrent chest pain and ECG was done within minutes. Patient has baseline j-point elevation in the anterior precordium likely due to LVH, but T waves are markedly different from previous and are tall and peaked consistent with hyper acute T waves. Note also the beginnings of subtle ST abnormalities in the inferior and lateral leads (V6 and aVF). Patient was taken to cardiac catheterization lab and had a thrombotic occlusion of the proximal left anterior descending (LAD) coronary artery

Electrocardiogram

The ECG is the essential tool in the assessment and risk stratification of patients presenting with chest pain.[19] The presence of ST-elevation on ECG denotes STEMI in greater than 80% of patients and can assist in the localization of the MI into anterior, inferior (with or without posterior and/or right ventricular (RV) involvement) and lateral.[20] The remaining 20% of patients with apparent ST-elevation may have: vasospasm, myopericarditis, takotsubo cardiomyopathy, LV hypertrophy and/or hypertrophic cardiomyopathy, ventricular preexcitation (Wolff-Parkinson-White syndrome) hyperkalemia, or a normal variant. It must be recognized that the clinical picture is very important in determining etiology of the ST-elevation, particularly when the ECG is not classic for STEMI (shape of ST segments, lack of reciprocal changes, etc.).

The first change in the ECG that occurs during vessel occlusion is upright, peaked and symmetric T waves (commonly referred to as hyper acute).[21] The duration of this change, in the presence of persistent occlusion, is short (in minutes) and, therefore, is rarely seen clinically.[22] If present, subtle reciprocal abnormalities may be seen increasing the suspicion for acute myocardial infarction (AMI) (Fig. 2). The subsequent evolution is to the development of ST-elevation. The shape of the ST-segment (coving or straightening of the segment compared to a normal concave upward segment), and the presence of reciprocal changes (ST-depressions) in the leads opposite the ST-elevation are strongly supportive of STEMI as the etiology of the ST-elevation.

The presence of ST-elevation in V1–V3 signifies anteroseptal STEMI or if involving V4, V5 and V6, anterolateral STEMI resulting from occlusion of the LAD coronary artery. Presence of ST-elevation in aVL suggests involvement of a high diagonal and thus a proximal LAD occlusion. In either case, the diagnosis of STEMI is supported by ST-depressions in II, III and aVF (reciprocal changes). In a patient with a large LAD that "wraps" around the apex of the heart and supplies a significant portion of the inferior wall, or with occlusion of the left main coronary artery, one may see ST-elevation in II, III and aVF as well (Figs 3 and 4).

The presence of ST-elevation in V5, V6 and I and aVL suggests a high lateral MI and may signify occlusion of a large ramus intermedius, very proximal obtuse marginal from the left circumflex or early diagonal coronary artery from the left anterior descending coronary artery (Fig. 5).

The ST-elevation in II, III and aVF signifies inferior MI (Fig. 6). In inferior STEMI, reciprocal changes (ST-depressions) can be seen in I, aVL and V1–V3. The presence of ST-elevation in III greater than in II suggests right coronary artery (RCA) occlusion versus occlusion of a dominant left circumflex coronary artery (LCX). The determination of RCA versus LCX involvement is important to the cardiac interventionalist in preparing the procedural protocol in the catheterization lab, but is also very important to the treating physician in that only with RCA occlusion can one potentially have coexistence of RVMI (Fig. 7). In addition, the presence of ST-elevation of at least 1 mm in V1 suggests that this occlusion is in the proximal RCA and thus, involves the right ventricle.[23] A more complex

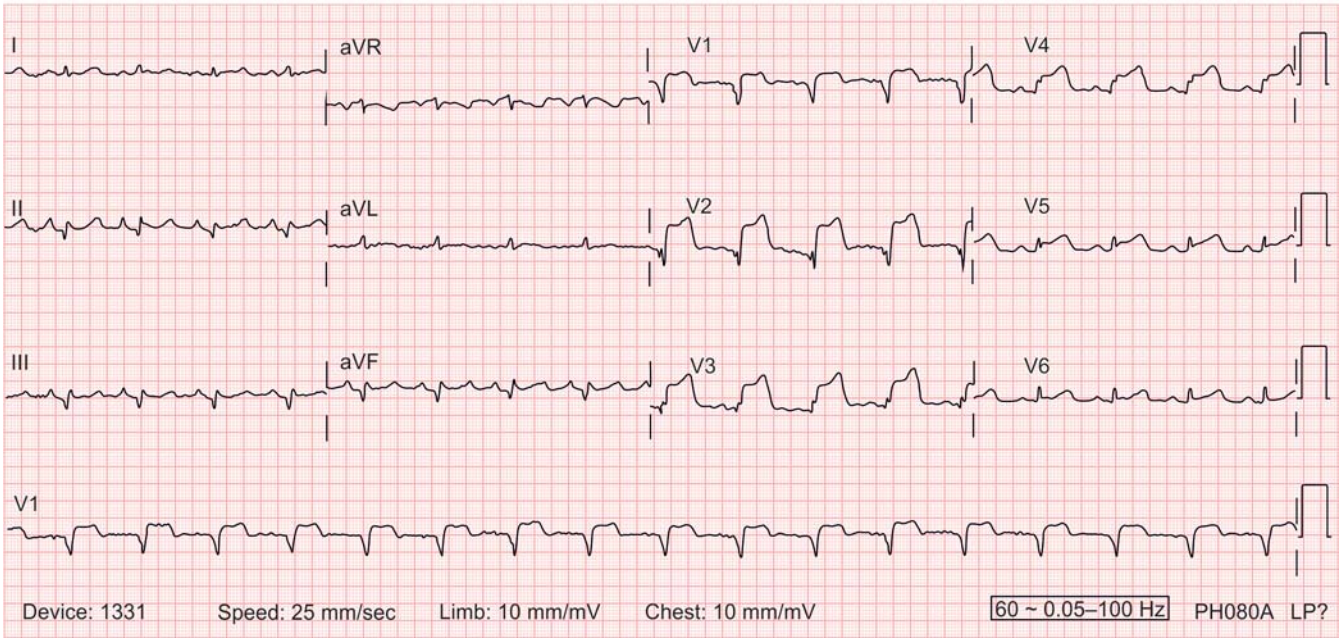


FIGURE 3: A 56-year-old patient with drug eluting stent to mid left anterior descending coronary artery that wrapped around the apex and supplied the inferior wall, one week prior who presented now after cardiac arrest. Note the shape and extent of the ST-elevation in all the precordial leads, but not in I, or aVL; this consistent with mid LAD occlusion. In addition, there are no reciprocal changes, but the shape of the ST segments is quite consistent with injury, and the clinical scenario consistent with STEMI. Coronary angiography showed stent thrombosis and patient was noted to have been noncompliant with dual antiplatelet therapy prior to this event

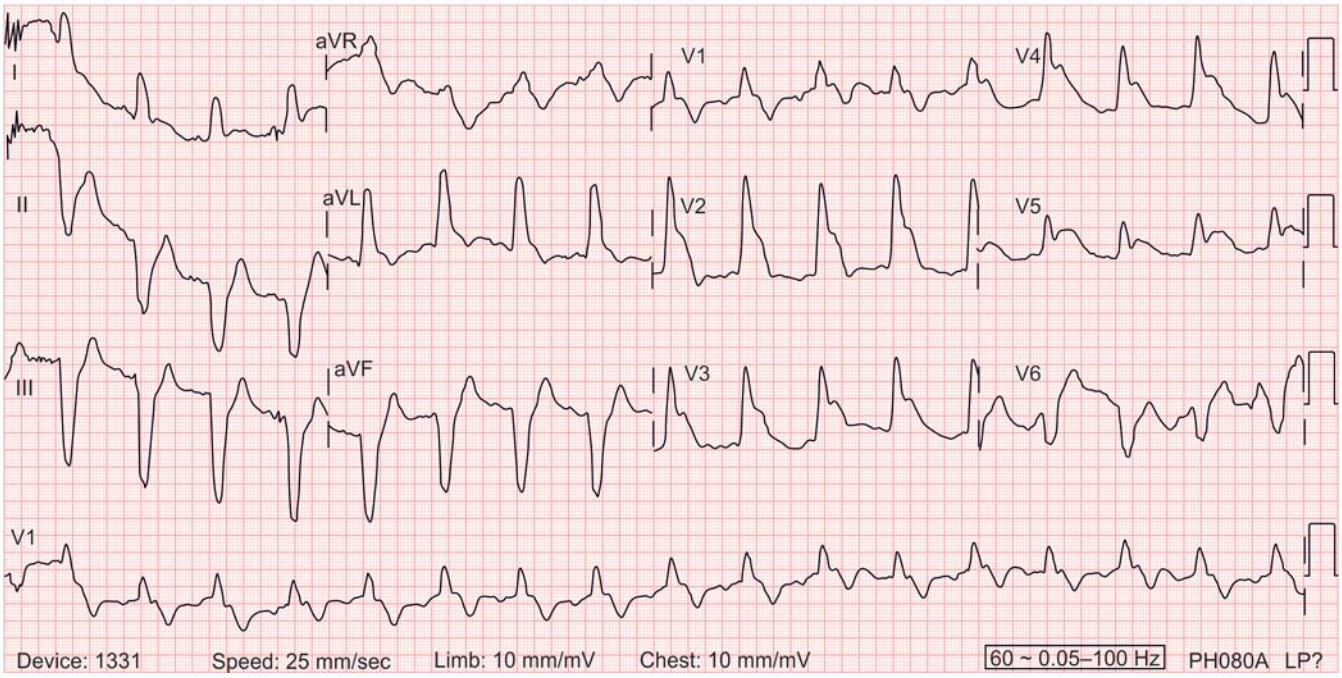


FIGURE 4: A 46-year-old patient presented with chest pain, became hemodynamically unstable and progressed to cardiac arrest. The ECG was obtained just prior to arrest; note the diffuse ST-elevation in the presence of an RBBB. Note the lack of expected ST-segments (discordant to the QRS), in the precordial leads with the RBBB. Coronary angiography showed left main coronary artery occlusion

algorithm exists to assist in differentiating the culprit artery in inferior MI.[24] Finally, the presence of RV infarction can be identified with high accuracy by obtaining right sided ECG leads in which the precordial leads V3–V6 are placed in the same interspace positions, but to the right of the sternum, mirroring their normal position. The presence of at least 1 mm of ST-elevation in lead V4R signifies RVMI.[25] The identification of RVMI is imperative as the medical treatment as well as the prognostic significance of RVMI differs from the general population of STEMI patients, as has been discussed later.

True posterior wall MI (without inferior involvement) is challenging to diagnose on ECG as these patients may present

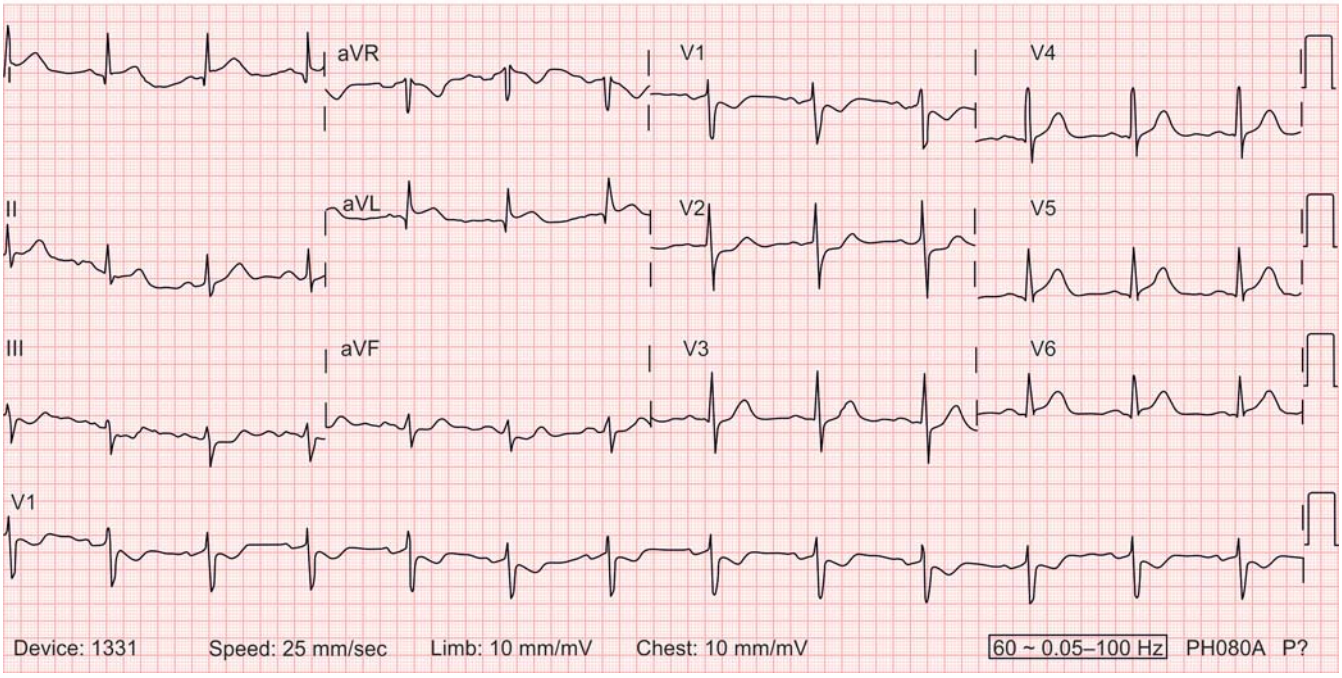


FIGURE 5: A 71-year-old patient presented with chest and jaw pain. Note ST-elevation in V5, V6, I and aVL with reciprocal changes is most prominent in V1 and V2. Coronary angiography showed 99% thrombotic lesion in large ramus intermedius

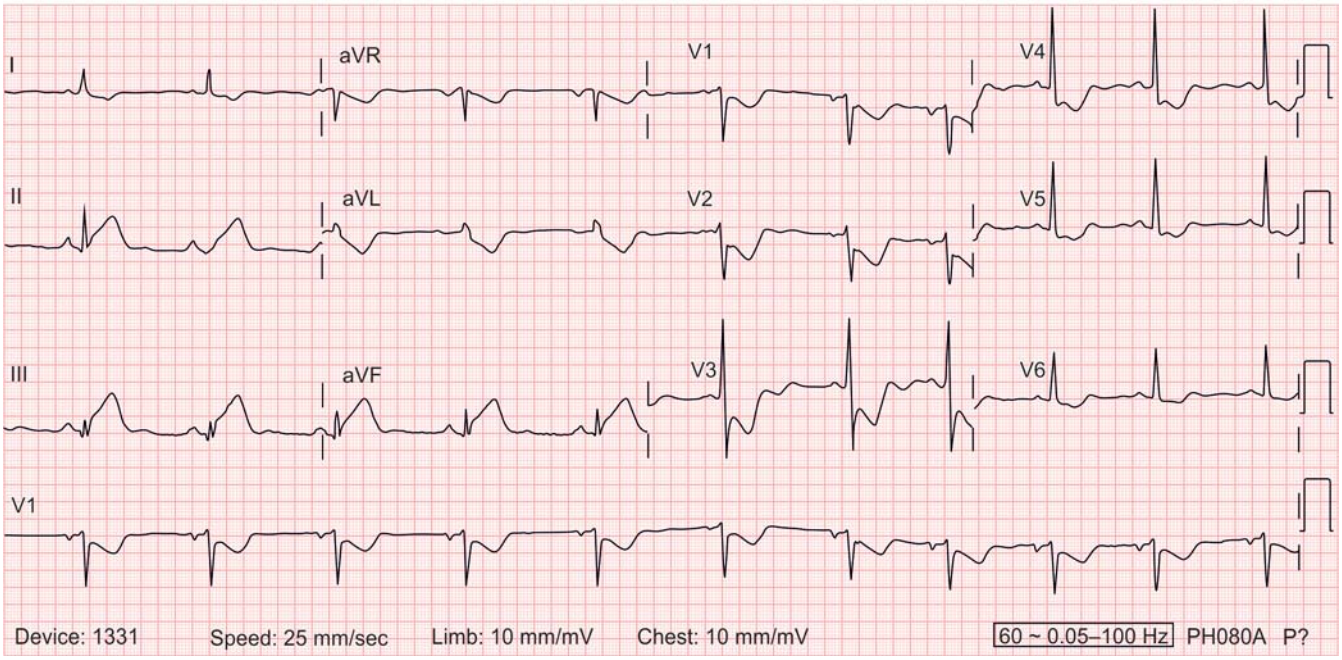


FIGURE 6: A 76-year-old patient presents with chest pain radiating to left arm with diaphoresis and shortness of breath. Note ST-elevations of similar magnitude in II and III, and significant ST-depressions throughout the precordial leads that are likely reciprocal, but may be manifestation of posterior STEMI or remote ischemia given the patients left main coronary artery lesion. Coronary angiogram showed occlusion on distal RCA with 65% left main coronary artery lesion

with ST-depressions in leads V1–V3 that are mirror images of the ST-elevations posteriorly (Fig. 8) or may present with no ECG changes (Fig. 9). There may be occlusion of the mid to distal LCX, or of a large posterolateral branch of the circumflex or the RCA that is electrocardiographically silent on the standard 12-lead ECG. Therefore, true posterior wall infarction should be considered in all patients who present with ongoing chest discomfort and persistent ST-depressions in these V1–V3, or no ECG changes at all. One should consider posterior infarction in any patient with typical angina, a normal ECG and persistent chest discomfort despite optimal medical therapy. To better assess, one can obtain posterior ECG leads by placing leads V7, V8 and V9 in the 5th interspace posteriorly around the chest. The presence of ST-elevations in these leads assists in the

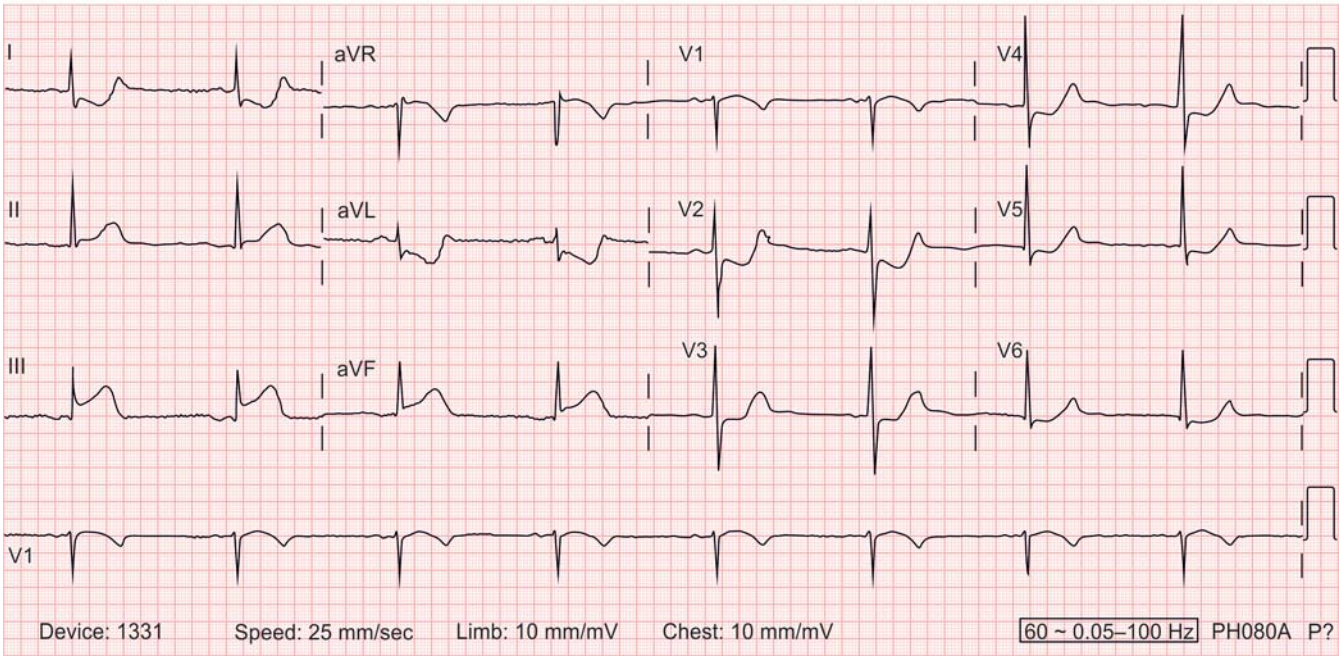


FIGURE 7: A 52-year-old patient presented with chest pain and shortness of breath. He developed hypotension and bradycardia after nitroglycerin was administered; this required IV fluid bolus and initiation of dopamine. Note sinus bradycardia with ST-elevation in III of greater magnitude than in II, lack of ST-depression in V1 and reciprocal changes in I and aVL. Clinical scenario, angiogram and EKG are consistent with and inferoposterior STEMI with RV infarction. Coronary angiography showed thrombotic occlusion of the proximal right coronary artery. Patient developed significant RV dysfunction post MI

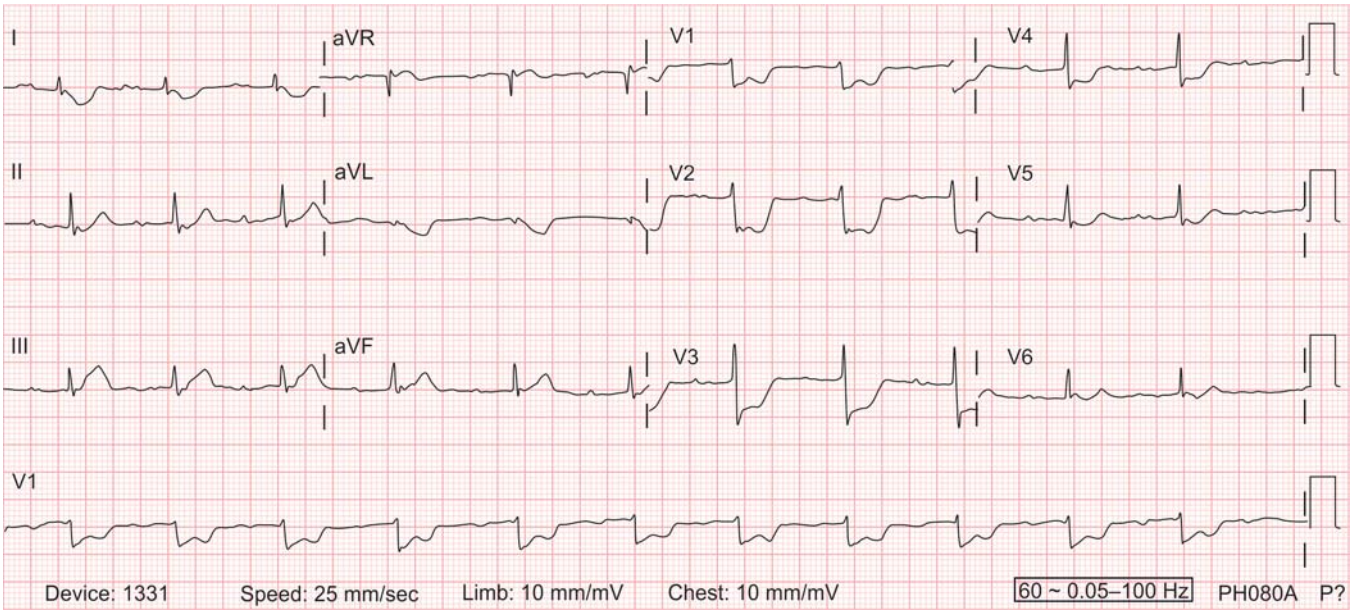


FIGURE 8: A 43-year-old patient presented with chest tightness and left neck pain. Shortly after presentation became unstable with hypotension and respiratory failure. Note significant ST-depressions in the anterior leads that, in this case, signify a true posterior infarct. In light of the patient's instability, the diagnosis was readily made (versus consideration of anterior ischemia) and posterior leads were not obtained. Coronary angiogram showed thrombotic occlusion at the origin of the left circumflex coronary artery with thrombus extending into, but not obstructing the left main coronary artery

diagnosis of posterior STEMI and allows for the physician to initiate a reperfusion strategy. As well, assessment with a transthoracic echocardiogram looking for a new wall motion abnormality may assist in determining need for immediate reperfusion.

In the presence of a right bundle branch block (RBBB) ST-elevation is identifiable (Fig. 4). In the presence of a left bundle branch block (LBBB) (Fig. 10), STEMI diagnosis is more complex. First, the presence of a new or presumed LBBB in the clinical scenario of ongoing symptoms of ACS should

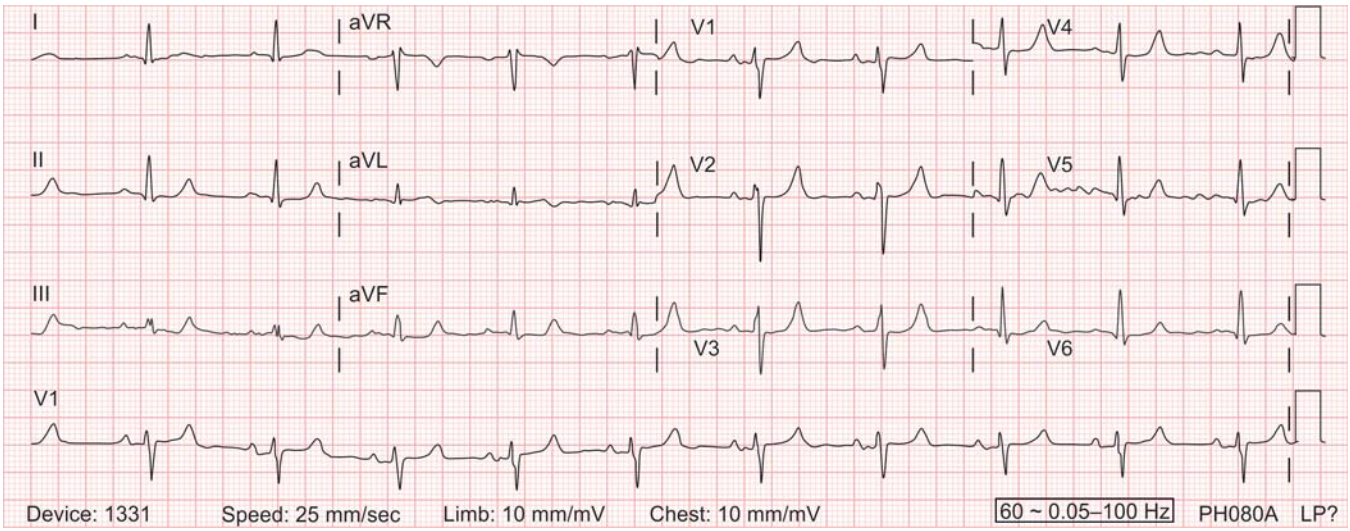


FIGURE 9: A 43-year-old patient post-remote coronary artery bypass graft (CABG) presented with ongoing chest discomfort that was not responsive to nitroglycerin at high doses, in addition to standard medical therapy. Note ECG without significant ST abnormality, in this case, consistent with the potentially electrically silent posterolateral wall MI. Coronary angiogram showed previously known right posterior descending coronary artery occlusion, with new mid RCA occlusion, supplying only the right posterolateral coronary artery myocardial territory

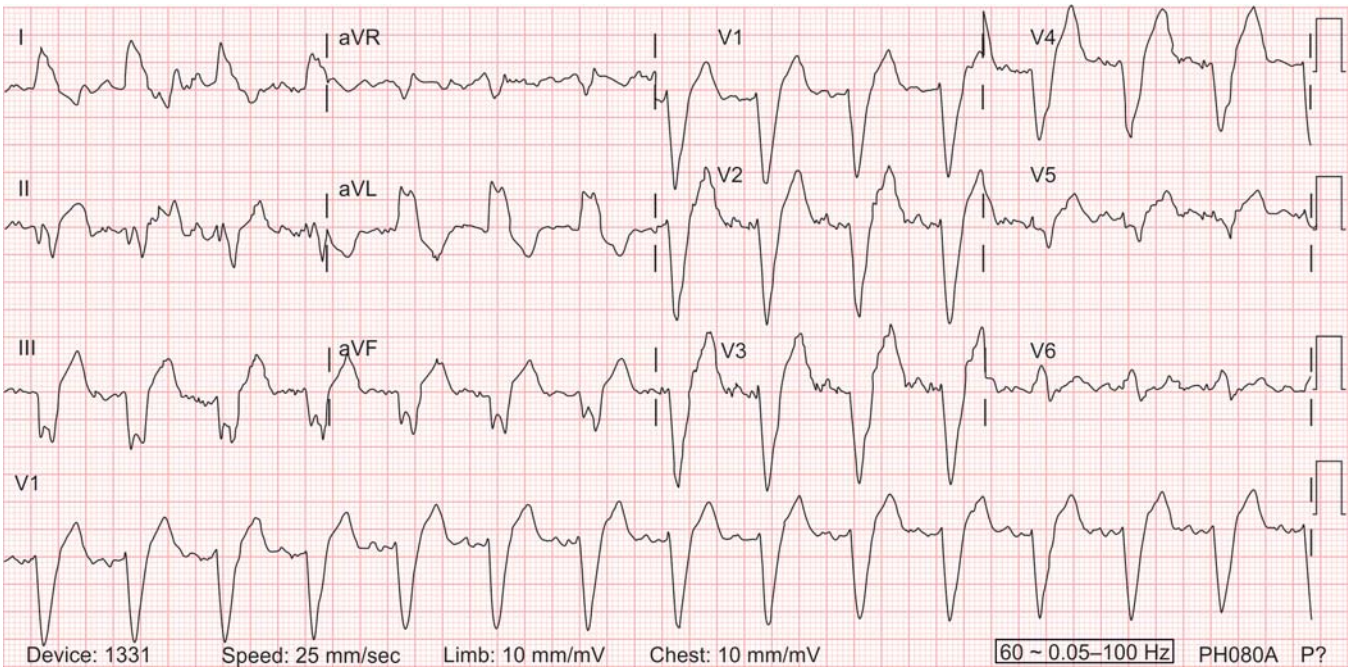


FIGURE 10: A 51-year-old patient presents with chest pain and new LBBB (compared to ECG 4 months prior). Note LBBB, new, with no other criteria for STEMI. Coronary angiography showed no culprit vessel for STEMI. The troponins were negative on serial examination. Despite the fact that this patient did not have STEMI, the emergent coronary angiogram was the correct diagnostic evaluation in the given clinical scenario

prompt strong and rapid consideration of vessel occlusion or MI (STEMI-equivalent). This patient should be considered for reperfusion therapy. In a patient with a known LBBB, there are diagnostic criteria for acute STEMI: greater than or equal to 1 mm of ST-elevation that is concordant (in the same direction as the QRS), greater than or equal to 1 mm ST-depression in lead V1, V2 or V3, and greater than or equal to 5 mm ST-elevation that is discordant (opposite direction of the QRS). The presence of any degree of ST-elevation that is concordant is not found with an LBBB; therefore, this criterion is highly specific for the diagnosis of acute MI in the presence of an LBBB, but it is not necessary. The presence of ST-depressions in the precordial leads should as well be considered a specific marker of MI in the patient with an LBBB. The presence of discordant ST-elevation should significantly raise the physician's suspicion, but one may consider confirmatory evaluation (i.e. transthoracic echocardiogram, etc.)[26]

One should not be "distracted by the obvious and remarkable abnormality" of ST-elevation when reading the ECG. The rapid recognition of STEMI is laudable and necessary, but the entire ECG must be interpreted in order that the patient should be cared for optimally. Learners should develop an organized

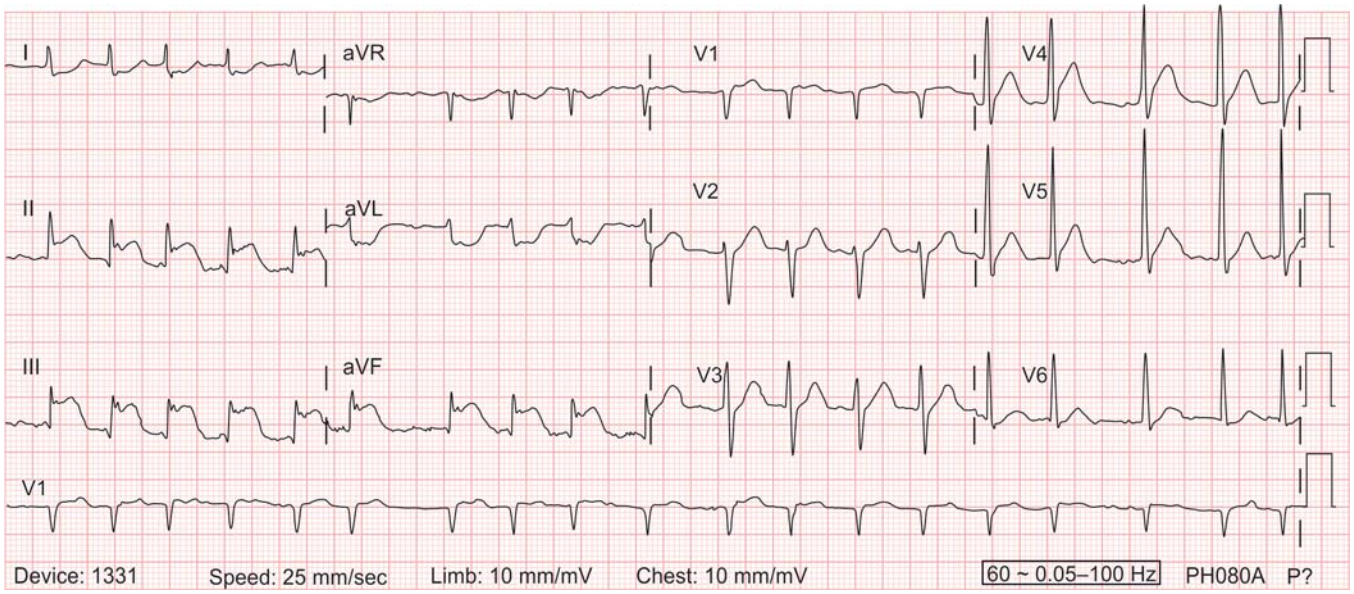


FIGURE 11: A 48-year-old patient presented with chest pain. An ECG shows atrial fibrillation with rapid ventricular response, with inferior ST-elevations and is consistent with RV involvement given the ST-elevations greater in III than II, and the lack of ST depression in V1. Coronary angiography was attempted with failure to engage the coronary arteries due to aortic dissection with involvement of the right coronary ostium resulting in inferior STEMI. After dissection was repaired, and coronary artery bypass graft (CABG) performed to the distal RCA, patient had significant RV dysfunction resulting in cardiogenic shock, requiring right ventricular assist device placement

system for reading the ECG beginning with the rhythm and continuing through the assessment of the QT interval. If one does not, the potential for this "distraction" exists, and will prompt the reader to miss other important aspects of the ECG, particularly the rhythm (Fig. 11). In the setting of AMI, sinus bradycardia, advance heart block and atrial and ventricular dysrhythmias may exist that require identification and at times specific treatment. In addition, the presence of accelerated idioventricular rhythm may signal reperfusion.

Finally, the reader must understand the evolution of the ECG in the hours and days after MI. Acutely after reperfusion, the ST-segments will return to or toward normal, and the T waves may initially appear normalized. In the following hours, the T waves will invert and may appear biphasic (Figs 12 to 14). These QRS and T wave changes are a part of the typical evolutionary process of the ECG after MI and should not be interpreted as a clinical change, in the absence of symptoms. If symptoms are present, these, usually marked abnormalities, will inhibit electrocardiographic evaluation to varying degrees.

Persistent ST elevation and the development of Q waves in the infarcted territory signals significant myocardial necrosis. ST-elevations that persist for days to weeks may signal the

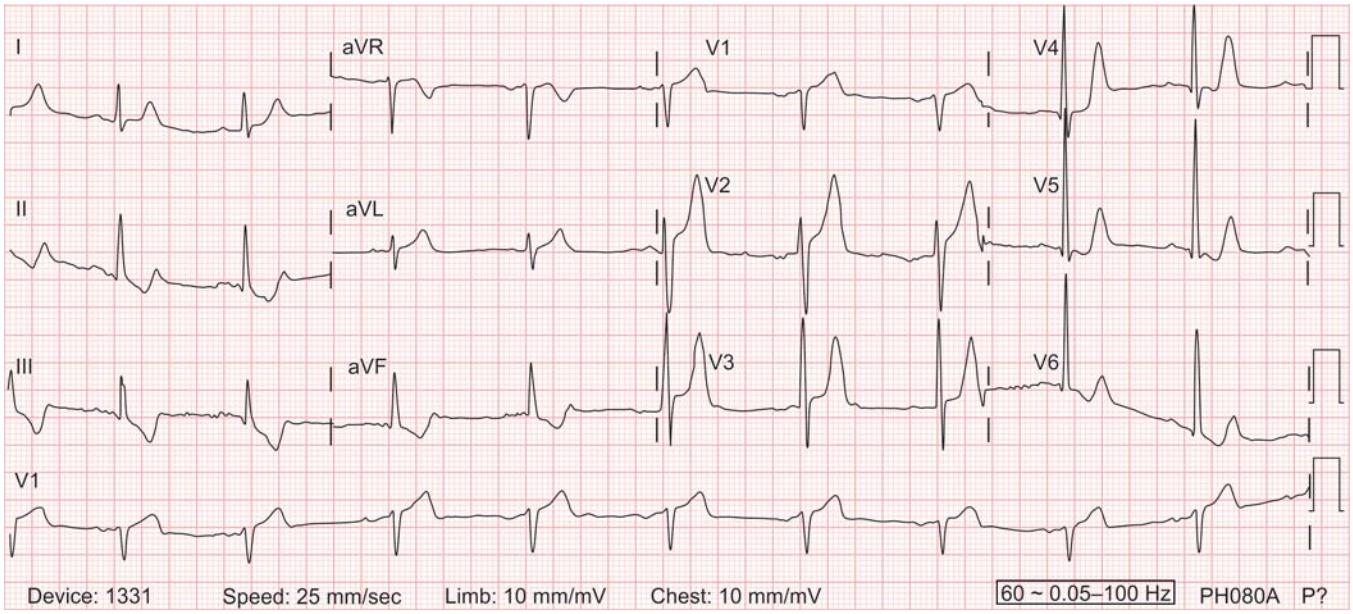


FIGURE 12: The figure demonstrates tall peaked T waves with associated ST-elevation in the anterior leads, and reciprocal depressions in the inferior leads. Coronary angiography done rapidly after onset of symptoms, showed 99% proximal left anterior descending coronary artery

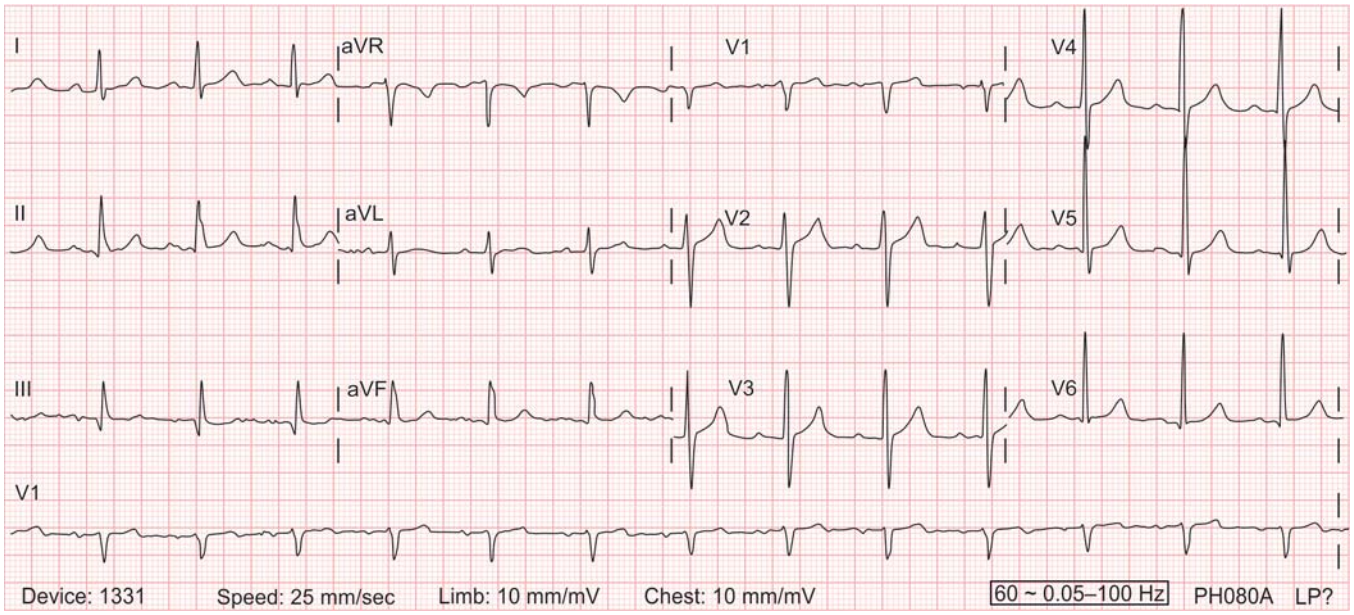


FIGURE 13: This figure is immediately after successful stenting of the lesion. Note normalization of the ST-segments and T waves

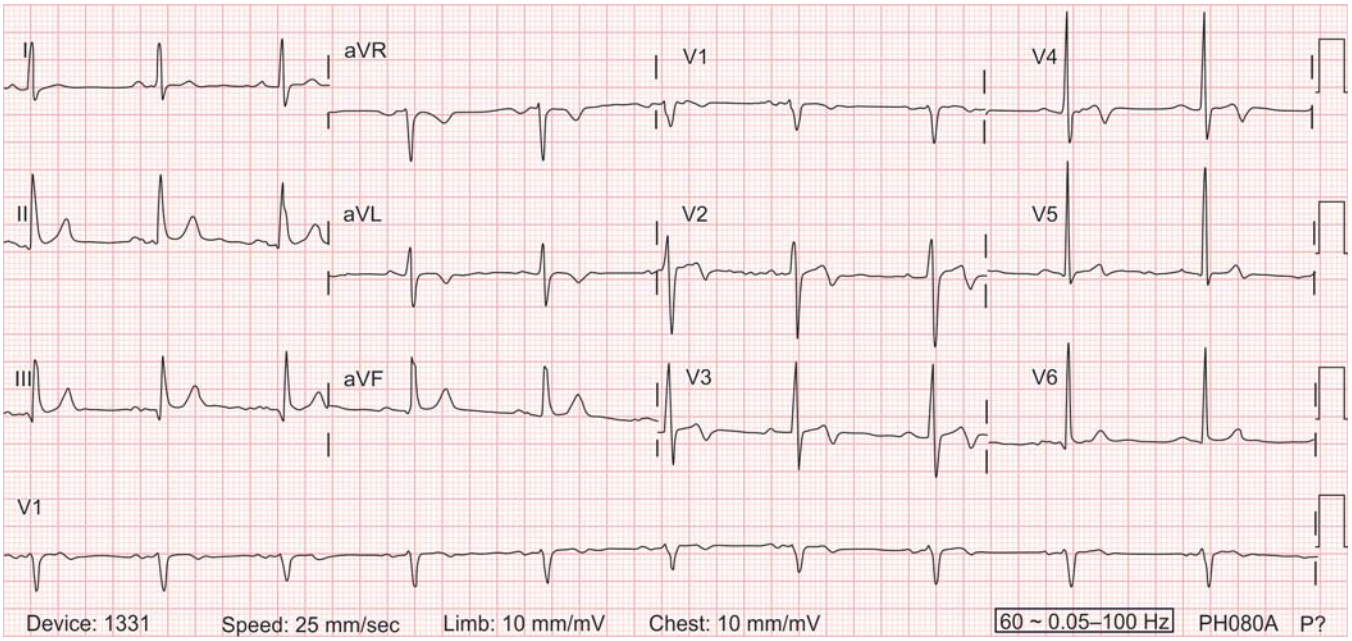


FIGURE 14: The figure demonstrates evolutionary changes in the anterior precordium. The patient was asymptomatic and these changes were not related to recurrent ischemia but were normal evolution after anterior MI

development of a ventricular aneurysm, defining nonviable myocardium. The lack of Q waves is in general a testament to early reperfusion and myocardial salvage.

Other Early Diagnostic Evaluation

Further evaluation with laboratory studies, portable chest X-ray, echocardiography, etc. should be done, if they do not delay reperfusion and if there is a clear clinical indication (evaluation for aortic dissection, etc.). Laboratory studies sent on arrival to the emergency room are helpful in assessing electrolytes (particularly potassium), renal function, hemoglobin, platelets and coagulation status. Urine toxicology screen should be considered on all patients, particularly those with few or no risk factors for CAD; this can be done after reperfusion. Biomarkers should be sent, but the reader must remember that elevation in the biomarker takes time (see the chapter "Acute Coronary Syndrome I: Unstable Angina and Non-ST Segment Elevation Myocardial Infarction") and a normal initial troponin in a patient with is quite common. The lack of elevation in troponin at presentation should not alter the physicians plan for reperfusion therapy in the early presenters. Portable chest X-ray (CXR) should be used to evaluate other etiologies of chest discomfort, such as aortic dissection, or when the diagnosis of STEMI is unclear. It is unnecessary to obtain a CXR to diagnose pulmonary edema, as this will be evident on examination.

A bedside echocardiogram is helpful in patients in which the diagnosis is unclear or there is concern that anterior ST-depressions are a marker of posterior wall infarction.

The American College of Cardiology (ACC)/American Heart Association (AHA) guidelines recommend:

Class I

- *Laboratory examinations should be performed but should not delay delivery of reperfusion therapy*
- *Troponin should be used as the optimal biomarker:*
  - *Abnormal cardiac biomarkers should not be necessary to proceed with reperfusion therapy*
  - *Portable chest X-ray should be performed as possible, but should not delay reperfusion therapy unless the physician suspects a clinical condition (i.e. aortic dissection) that would be a contraindication for reperfusion*
  - *Imaging of the aorta via transthoracic or transesophageal echocardiography, chest CT or MRI should be performed if there is significant concern for aortic dissection as etiology of syndrome.*

REPERFUSION

Reperfusion is the primary treatment of patients who present with STEMI. Medical therapy should be instituted as a reperfusion strategy is being put in place. The decision to perform primary PCI or administer a thrombolytic agent must be made and carried out rapidly in order to salvage as much myocardium as possible, and therefore prevent morbidity and mortality. Institutional protocols should be in place to allow for this decision to be made rapidly by the treating physician. These protocols must take into consideration the availability of each strategy and the estimated time to delivery of the appropriate care. The standard of care is D2B (patient arrival to first balloon inflation in the catheterization laboratory) of less than 90 minutes and door to needle (patient arrival to administration of thrombolytic agent) of less than 30 minutes. Again, although these times are standards of care, the physician must aim for these times to be as low as is possible. Presently the time begins with the patient's entry to the emergency room. Ideally this "door" time should begin with first medical contact (i.e. paramedic, etc.). Protocols should be continually reviewed and include discussion between local paramedics, emergency room physicians and the interventional cardiologists regarding potential to eliminate delays in delivery of each patient's appropriate reperfusion strategy and thus to optimize time to reperfusion.

The following is a discussion of the data to support each strategy, thrombolysis versus primary PCI. Although there are situations in which emergency coronary artery bypass graft (CABG) is the optimal reperfusion strategy in certain individual patients, these are rare. The time necessary to mobilize the operating room and reperfuse the patient is always excessive. Emergency CABG should be considered only in patients with critical left main CAD who have reperfused at the time of angiography (done with intent to perform PCI) and continue to demonstrate hemodynamic stability, or in patients with a large at-risk territory in whom PCI was attempted and is unsuccessful. Again, these scenarios are rare.

From this discussion, the physician should recognize the indications and contraindications to each strategy and be able to determine the most appropriate therapy for each individual patient based on the time from onset of symptoms, specific patient clinical status and contraindications, and the time to availability of primary PCI (within a PCI center vs need for transport and the time this will require).

THROMBOLYSIS

Available thrombolytics approved for use in STEMI have included: Streptokinase, Alteplase, Reteplase and Tenecteplase (TNK).

1. Streptokinase is a naturally occurring polypeptide obtained from the culture of group C beta hemolytic *Streptococcus*. It binds to plasminogen creating an active complex and thereby facilitates the transformation of plasminogen to plasmin resulting in fibrinolysis and proteolysis. It is therefore not specific to fibrin cleavage. It is antigenic and although significant allergic reactions are rare, repeat administration, even years after initial administration, increases the risk of serious allergic reaction. Approximately up to 10% may develop a rash and patients may develop hypotension during infusion. The half-life is 80 minutes.[27]
2. Alteplase is a reproduction of a naturally occurring tissue plasminogen activator (tPA) that is manufactured by recombinant technology. It is fibrin specific (does not have proteolytic effects) and the bound alteplase or fibrin compound has a high affinity for plasminogen. It does not have the side effect of hypotension, and allergic reactions are rare. The half-life is short (3–4 minutes). The use of IV heparin with alteplase during STEMI results in increased patency and less reocclusion.[27]
3. Reteplase is a recombinant plasminogen activator (rPA) that has less affinity for fibrin and a longer half-life than alteplase.[27]
4. Tenecteplase (TNK-tPA) is a genetically engineered plasminogen activator. The half-life is longer allowing for single bolus dosing which is advantageous in STEMI. In addition, it has less clinical intracranial bleeding than alteplase, though has been shown to have equal efficacy with respect to major adverse cardiac endpoints.[27,28] Therefore, TNK is preferred based on its equal efficacy, and decreased risk of intracranial hemorrhage. In the United States, TNK is the most widely used lytic agent for STEMI today. Comparison and contrast of these four agents are provided in Table 1.[4]

FACILITATED PERCUTANEOUS CORONARY INTERVENTION

Facilitated percutaneous coronary intervention (PCI) (upstream administration of partial dose GpIIb/IIIa inhibitor or full or partial dose thrombolytic or a combination thereof with plan for emergent PCI), in ambulance or at a non-PCI center prior to transfer for planned immediate PCI, has not been shown to improve mortality and in many instances led to increased

TABLE 1

Comparison of approved thrombolytic agents

	Streptokinase	*Alteplase*	*Reteplase*	*Tenecteplase*
Dose	1.5 MU over 30–60 minutes	Up to 100 mg in 90 minutes (weight based)	10 U × 2 each 30–50 mg over 2 minutes	Weight based
Bolus administration	No	No	Yes	Yes
Antigenic	Yes	No	No	No
Allergic reactions	Yes (hypotension)	No	No	No
Systemic fibrinogen depletion	Marked	Mild	Moderate	Minimal
~ 90 minutes patency rate	50%	75%	75%	75%
%TIMI 3 flow at 90 minutes	32	54	60	63
Approximate cost per dose (2004)	$613	$2974	$2750	$2833 for 50 mg (US$)

(*Source:* ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction. Circulation. 2004;110:588-636)

morbidity (increased need for revascularization, increased reinfarction rates and increased major bleeding complications).[29,30] Although the strategy would seem helpful in improving vessel patency, and some studies have shown this to be true (infarct-related artery patency is improved with some protocols), this has not been translated to a decrease in major adverse cardiovascular events (MACE).[31-34] Facilitated PCI for STEMI cannot be recommended.

The American College of Cardiology (ACC)/American Heart Association (AHA) guidelines 2009 update removed the recommendation regarding facilitated PCI given the lack of convincing benefit.

Full Dose Thrombolytic Agent

Full dose thrombolytic as primary reperfusion therapy has been shown to improve mortality in patients with STEMI, compared to standard medical therapy. Both Second International Study of Infarct Survival (ISIS-2) (comparing the addition of streptokinase to aspirin vs placebo)[35] and Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI)[36] showed that streptokinase was effective in reducing the incidence of death. In addition, ISIS-2 showed benefit in the addition of aspirin to streptokinase in the reduction in reinfarction, stroke and death.[35] Further studies have shown that accelerated dose alteplase (t-PA) had a greater benefit than streptokinase.[37] This study also showed that the administration of IV heparin was superior to subcutaneous heparin with alteplase. Notably the reduction of events with t-PA over streptokinase (death or disabling stroke), although significant, was just 1%. Given the cost difference between streptokinase and t-PA and this apparent small benefit, this study launched significant discussion regarding the cost or benefit of the use of accelerated t-PA over streptokinase, the financial impact this would have on hospitals, particularly smaller hospitals.

Secondly, data from this study[37] showed the greatest benefit in patients who are less than 75 years of age and also with an anterior infarction. A meta-analysis of large thrombolytic trials[38] further characterized that there was an overall 18% reduction in 35 days mortality with thrombolysis (with the benefit being

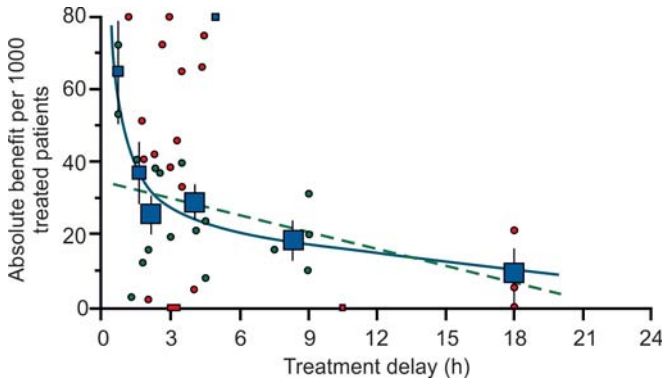


FIGURE 15: Absolute 35 days mortality reduction versus treatment delay: small closed dots—information from trials included in FTT analysis; open dots—information from additional trials; small squares—data beyond scale of x/y cross. The linear (34·7–1·6x) and non-linear (19·4–0·6x+29·3x–1) regression lines are fitted within these data, weighed by inverse of the variance of the absolute benefit in each datapoint. The four black squares: average effects in six time-to-treatment groups (areas of squares are inversely proportional to variance of absolute benefit described). (*Source:* Modified from Boersma E, Maas ACP, Deckers JW, et al. Early thrombolytic treatment in acute myocardial infarction: reappraisal of the golden hour. Lancet. 1996;348:771-5)

seen between 2–35 days, due to an excess number of deaths in the treatment arm in days 0 and 1). This benefit was seen in patients with STEMI and LBBB but not MI with EKG showing ST depressions. In patients with anterior STEMI versus inferior STEMI, the relative risk reduction was not different, but given the higher overall risk of the anterior STEMI patients, the absolute benefit was greater in patients presenting with anterior ST-elevation. Patients had a gradual decrease in benefit of thrombolysis with time from onset of symptoms, with the greatest benefit from delivery of drug within the first hour and a non-statistically significant benefit of only 1% overall when medication was administered greater than 12 hours from time of onset of symptoms.[38] This absolute mortality reduction over time has been confirmed (Figs 15 to 17).[39] Therefore, in patients who present to a non-PCI center with STEMI in the first hour after onset of symptoms (commonly referred to as the "golden hour"), strong consideration should be given to the

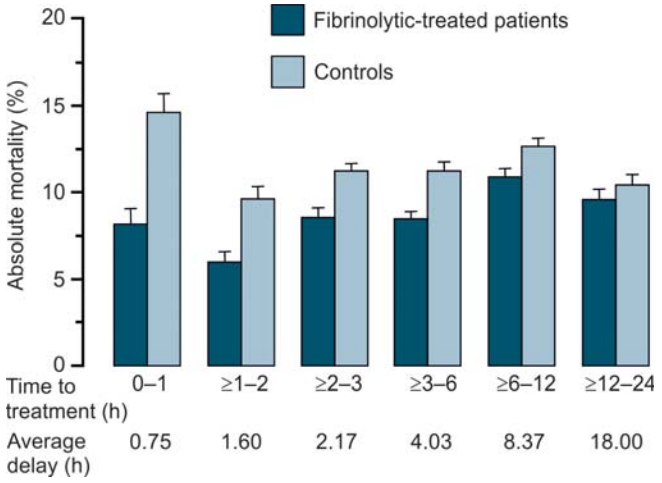


FIGURE 16: Mortality at 35 days among fibrinolytic-treated and control patients, according to treatment delay. (*Source:* Modified from Boersma E, Maas ACP, Deckers JW, et al. Early thrombolytic treatment in acute myocardial infarction: reappraisal of the golden hour. Lancet. 1996;348: 771-5)

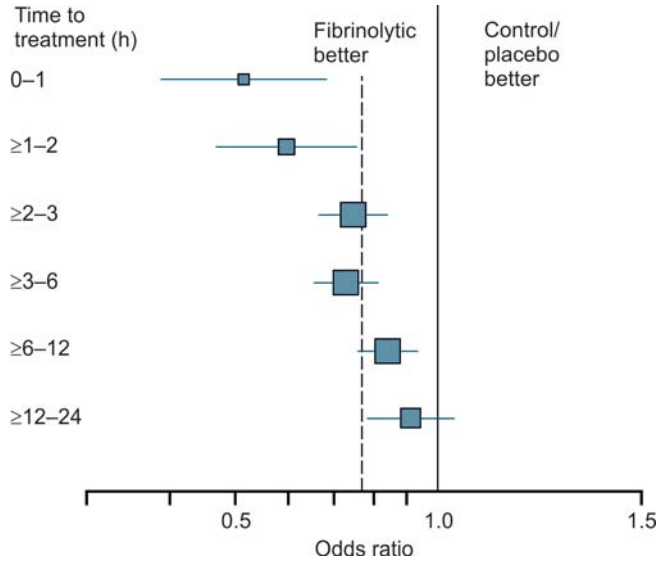


FIGURE 17: Proportional effect of fibrinolytic therapy on 35 days mortality according to treatment delay. (*Source:* Modified from Boersma E, Maas ACP, Deckers JW, et al. Early thrombolytic treatment in acute myocardial infarction: reappraisal of the golden hour. Lancet. 1996;348:771-5)

administration of thrombolytic for maximal myocardial salvage. The older patients had a higher overall mortality with STEMI and also had greatest risk of therapy. Therefore, although there was a trend to greater mortality reduction in the young, the absolute mortality reductions were similar for young and old. For multiple populations, men and women, diabetics and non-diabetics, young and old, anterior versus inferior STEMI, there was an absolute risk reduction with lysis compared to standard medical therapy.[38]

Established contraindications are noted in Table 2.[4] All patients, being considered for the use of thrombolysis for reperfusion in STEMI, should be evaluated for the presence of contraindications and thus the risk or benefit of this therapy should be determined.

TABLE 2

Contraindications and cautions for fibrinolysis in ST-elevation myocardial infarction

Absolute contraindications
- Any prior ICH
- Known structural cerebral vascular lesion (e.g. arteriovenous malformation)
- Known malignant intracranial neoplasm (primary or metastatic)
- Ischemic stroke within 3 months
- Suspected aortic dissection
- Active bleeding or bleeding diathesis (excluding menses)
- Significant closed-head or facial trauma within 3 months

Relative contraindications
- History of chronic, severe, poorly controlled hypertension
- Severe uncontrolled hypertension on presentation (SBP >180 mm Hg or DBP > 110 mm Hg)†
- History of prior ischemic stroke greater than 3 months
- History of dementia, or known intracranial pathology not covered in contraindications
- Traumatic or prolonged (> 10 minutes) CPR or major surgery (< 3 weeks)
- Recent (within 2–4 weeks) internal bleeding
- Noncompressible vascular punctures
- For streptokinase: prior exposure (> 5 days ago) or prior allergic reaction to these agents
- Pregnancy
- Active peptic ulcer
- Current use of anticoagulants: the higher the INR, the higher the risk of bleeding

(Abbriviations: ICH: Intracranial Hemorrhage; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; CPR: Cardiopulmonary Resuscitation; INR: International Normalized Ratio; MI: Myocardial Infarction)
†Could be an absolute contraindication in low-risk patients with MI
(*Source:* Modified from ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction. Circulation. 2004;110: 588-636)

The American College of Cardiology (ACC)/American Heart Association (AHA) guidelines recommend:

Class I

Thrombolysis should be considered in patients with STEMI (or LBBB) without contraindications, who:
- *Present within 12 hours of onset of symptoms and*
- *Are at a non-PCI center when transfer to a PCI center will result in greater than 90 minutes from first medical contact, or have a greater than 60 minutes probable difference between initiation of thrombolytic and angioplasty at a PCI center*

Class II

Thrombolysis (with stipulations as above) when:
- *True posterior infarct is likely*
- *Patient presents in 12–24 hours after onset of symptoms, but with persistent symptoms and ECG consistent with STEMI*

Class III

Avoid thrombolytics:

- *When patient presents in greater than 24 hours after STEMI and has no ischemic symptoms*
- *Patient has only ST depressions on ECG, and no evidence of true posterior infarct.*

Clinically, reperfusion after administration of thrombolytic is demonstrated when the patient has some or all of the following characteristics: resolution of ischemic symptoms, improvement in ST elevation by at least 50% and the presence of a notable reperfusion rhythm (accelerated idioventricular rhythm). Angiographically, reperfusion is noted with reestablishment of TIMI 3 (normal) flow in the IRA. Angiographically, failure of thrombolysis occurs in nearly 40% of patients treated with thrombolytics (i.e. ~ 60% of patients have TIMI 3 flow in the infarct-related artery at 90 minutes).[40] In addition, it is clear that reperfusion (defined as improvement in ST-elevation), leads to improved mortality in the first 30 days.[41] Therefore, if reperfusion does not occur, it is essential that this be recognized by the physician and that continued efforts to attain normal flow in the IRA be instituted.

Rescue PCI is superior to both conservative medical therapy and repeat thrombolysis in patients who fail thrombolysis (with failure defined as reduction of < 50% of the ST elevation at 90 minutes).[42] In contrast to previous trials, stents were used more commonly as part of rescue PCI strategy. Furthermore, decision to perform PCI was not based solely on lack of TIMI3 flow; degree of residual stenosis was also considered consistent with modern clinical practice.[42] Given this data, it is recommended that high-risk patients who present to a non-PCI center, and receive thrombolytic therapy, be considered for transport as soon as possible to the nearest PCI center in order that, if necessary, they may receive rescue PCI with stenting of the IRA, in a timely manner. The high-risk patients are defined as: extensive ST elevation, anterior STEMI, new LBBB, previous MI, Killip class greater than 2, previous EF less than or equal to 35%,[43] or inferior STEMI with systolic blood pressure less than 100 mm Hg, heart rate more than 100 bpm, or greater than 2 mm ST depression, or at least 1 mm ST elevation in right sided lead V4 (indicative of RV involvement).[44]

The American College of Cardiology (ACC)/American Heart Association (AHA) guidelines recommend:

Class I

- *Transfer of high-risk patients, extensive ST elevation, anterior STEMI, new LBBB, previous MI, Killip class greater than 2, previous EF less than or equal to 35%, or inferior STEMI with systolic blood pressure less than 100 mm Hg, heart rate more than 100 bpm, or greater than 2 mm ST depression, or at least 1 mm ST elevation in right sided lead V4 indication RV involvement. From a non-PCI center to the nearest PCI center immediately after thrombolysis*
- *Consideration of transfer, as soon as possible, in patients who have received thrombolysis and are not at high risk to the nearest PCI center after thrombolysis for PCI as needed*
- *Coronary angiography with intent to perform revascularization be performed in patients after treatment with thrombolysis who have:*
  - *Cardiogenic shock and who are reasonable candidates for revascularization (Class I if age ≤ 75, and Class II if age > 75)*
  - *Severe congestive heart failure (CHF) or pulmonary edema*
  - *Hemodynamically significant dysrhythmias*
  - *Hemodynamic or electrical instability*
  - *Persistent ischemic type symptoms*
  - *Failure of lysis and large myocardium at risk, anterior STEMI, or*
  - *Inferior STEMI with evidence of RV involvement*

Class III

- *Avoid planned (in absence of the above clinical parameters) immediate PCI in patients having received full dose thrombolytics*

Elective Angiography and PCI after Successful Thrombolysis

In patients with apparent reperfusion after thrombolysis for STEMI, the consideration of invasive angiography and revascularization is based on the clinical features of the patient. Patients who develop recurrent ischemic symptoms or threatened reocclusion of the vessel have an increased mortality both at 30 days and at 2 years. During hospitalization PCI has been shown to decrease recurrent MI and 2 year mortality.[45] Patients who develop shock, severe CHF, including pulmonary edema, or hemodynamically significant ventricular dysrhythmias during hospitalization should be considered for invasive angiography, and revascularization by PCI or coronary artery bypass grafting as appropriate.

Elective angiography and PCI in patients receiving thrombolysis have been studied with variable results. The TRANSFER AMI trial[44] studied high-risk patients with STEMI, receiving TNK within 2 hours of symptom onset, with transfer to a PCI center for planned elective PCI within 6 hours. Mean time to angiography was 3 hours in the invasive group and 33 hours in the medical therapy group. The primary endpoint of death, reinfarction, CHF, severe recurrent ischemia and shock was significantly less in the invasive group with no significant difference in bleeding. The majority of this benefit was in recurrent ischemia and infarct. The GRACIA-1 trial[46] studied patients who presented with STEMI, received thrombolysis, and were not at high risk, in contrast to the previous trial. They showed that in the invasive group (with angiography at 6–24 hours after lysis) patients had less need for revascularization and hospitalization, but primary endpoints at 30 days were similar. At 1 year the combined event rate of death and nonfatal reinfarction was statistically significant in favor of the invasive approach, but the majority of this was due to reinfarction. In addition, they found no increase in bleeding events and showed a significantly decreased length of stay (LOS) at the time of the initial event. Therefore, elective PCI, after apparent successful thrombolysis, is reasonable in that there is no increase in cardiac events or in bleeding, and it may decrease the index hospitalization LOS and prevent recurrent hospitalizations due to recurrent ischemia or reinfarction.

The issue of late (24 hours to 30 days) elective PCI of a persistently occluded IRA has been addressed.[47] There is no data to suggest a benefit of this approach, in absence of symptoms.

The American College of Cardiology (ACC)/American Heart Association (AHA) guidelines recommend:

Class IIb

- *Elective coronary angiography with the intent to perform PCI in STEMI patients (who have received successful thrombolysis) in the absence of high-risk features noted above*
- *The PCI of a lesion, that is hemodynamically significant, but not 100% occluded, within 24 hours after STEMI*

Class III

- *There is no indication for PCI of an occluded IRA for 24 hours or more after STEMI in a patient without symptoms, hemodynamic or electrical instability, or evidence of severe ischemia.*

PRIMARY CORONARY INTERVENTION

Reperfusion (vessel patency) can be accomplished at higher rates with primary coronary intervention than with thrombolysis in patients presenting with STEMI. Studies have shown that the majority of patients are candidates for this reperfusion strategy, and it is superior to full dose thrombolysis with statistically significant decrease in rates of death, nonfatal MI and stroke.[48,49] In addition to improved rates of reperfusion, this strategy also offers the ability to risk stratify patients by evaluation of the remainder of the coronary anatomy, thus allowing for optimal treatment post MI and allows for evaluation of hemodynamics and cardiac filling pressures as needed. Finally patients who have cardiogenic shock have the greatest benefit from primary coronary intervention versus thrombolysis.[50]

Today coronary intervention is done with the great majority of patients receiving coronary stents, not just angioplasty alone. Available data shows that primary coronary stenting is superior to primary coronary angioplasty in patients with STEMI with decreased major adverse cardiac events at 30 and 180 days.[51,52] The greatest benefit was in recurrent ischemia and need for revascularization. The previously discussed meta-analysis showing benefit from PCI compared to thrombolysis also demonstrated that the benefit of PCI with stents versus thrombolysis (compared to primary coronary angioplasty) was maintained (Fig. 18).[49]

It should be noted that this data is valid only in centers with experienced interventionalists and laboratories with protocols maintaining D2B times as short as possible (and always less than 90 minutes). Patients who present to a PCI center with STEMI, in absence of contraindications should undergo emergency angiography with intent to perform PCI, unless there are extenuating circumstances that will not allow for the patient to have a D2B time of less than 90 minutes. In patients who present to a non-PCI center, the choice of thrombolysis versus transfer of patients for PCI becomes more complex. Studies have been performed to assess the impact of transfer on outcomes. These studies suggest that transfer of patients for PCI with arrival at the PCI center within 90–120 minutes of arrival at the transferring center has statistical benefit in the primary endpoint of death, reinfarction and stroke.[53-55] The greatest benefit of timely transfer for primary PCI over thrombolytics was in achieving lower rates of reinfarction.[53] At the same time, ensuring timely reperfusion in patients undergoing transfer to a PCI center requires substantial investment in developing sophisticated systems of care and treatment protocols which may not be feasible for all hospitals and communities.[53]

The American College of Cardiology (ACC)/American Heart Association (AHA) guidelines recommend:

Class I

- *The STEMI patients undergo PCI (when presenting to a capable PCI-center) within 90 minutes from first medical contact*
- *The STEMI patients presenting to a PCI center without the capability for expert, prompt intervention with primary PCI within 90 minutes of first medical contact should receive thrombolytic therapy unless contraindicated*
- *The STEMI patients presenting to a center without PCI capability and who cannot be transferred to a PCI center and undergo PCI within 90 minutes of first medical contact should receive thrombolytic therapy within 30 minutes of hospital presentation unless contraindicated.*

EARLY MEDICAL THERAPY

GENERAL MEASURES

As reperfusion therapy is being arranged, medical therapy must be initiated; this medical therapy mirrors that has been discussed for UA/NSTEMI in the chapter "Acute Coronary Syndrome I: Unstable Angina and Non-ST Segment Elevation Myocardial Infarction". Oxygen should be administered. Patients should be placed on continuous telemetry and all transport must be monitored with a defibrillator and emergency medications immediately available. As soon as STEMI is diagnosed, in a PCI center, preparation must be made for emergency transport into the cardiac catheterization laboratory.

The American College of Cardiology (ACC)/American Heart Association (AHA) guidelines recommend:

Class I

- *Supplemental oxygen should be given to patients with desaturation below 90%*

Class II

- *It is reasonable to consider supplemental oxygen to all STEMI patients for first 6 hours.*

NITRATES

In order to decrease the vasoconstriction which is associated with STEMI, nitroglycerin (SL and IV as necessary) should be given. Care should be taken in the STEMI patient as abrupt changes in hemodynamics may occur. In addition, the reader

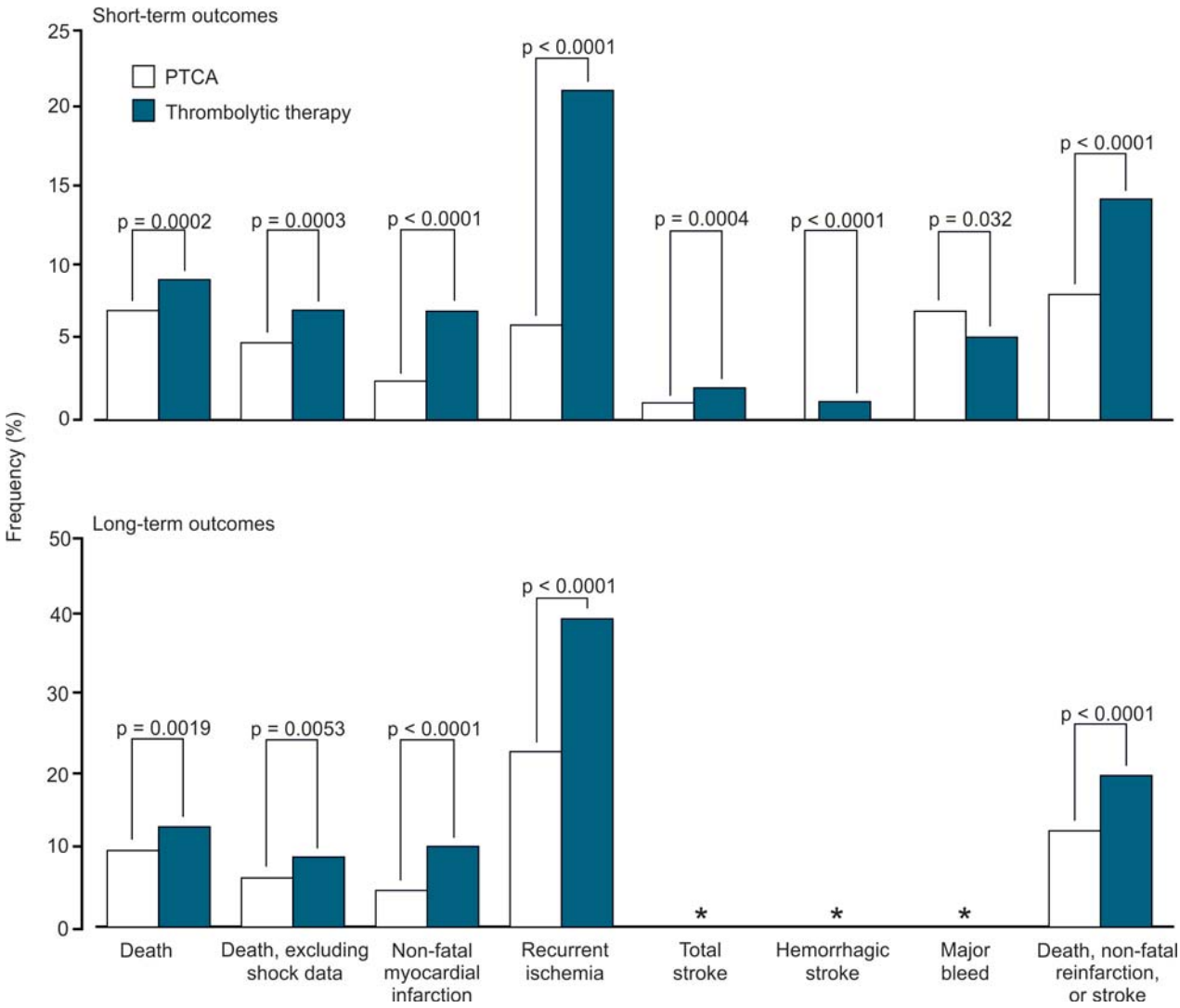


FIGURE 18: Percutaneous coronary intervention (PCI) versus fibrinolysis for ST-elevation myocardial infarction (STEMI). The short-term (4–6 weeks) and long-term outcomes for the various endpoints shown are plotted for patients with STEMI randomized to PCI or fibrinolysis for reperfusion in 23 trials (N = 7739) (*Source:* Modified from Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomized trials. Lancet. 2003;361:13-20)

should be well aware of the potential hypotension and hemodynamic collapse that may occur in a patient with a RV infarction who receives nitroglycerin and avoid the use of nitrates in these patients.

The American College of Cardiology (ACC)/American Heart Association (AHA) guidelines recommend:

Class I

- *Nitroglycerin 0.4 mg sl every 5 minutes for 3 doses and then consider IV nitroglycerin for ongoing ischemic symptoms, hypertension or for management of pulmonary congestion*

Class III

- *Nitrates should be avoided in patients with:*
  - *Systolic blood pressure less than 90 mm Hg or more than 30 mm Hg below baseline*
  - *Severe bradycardia (< 50 bpm)*
  - *Tachycardia (> 100 bpm)*
  - *Suspected RV infarction*
  - *Use of type 5 phosphodiesterase inhibitors in last 24–48 hours*

Note: The guideline notes that these are used in men for erectile dysfunction, but the reader should be aware of the increasing use of sildenafil for patients with pulmonary hypertension.

MORPHINE

Morphine can serve as analgesia and thereby decreases the generalized anxiety and apprehension that is common in STEMI patients. One must be aware of the potential for hypotension associated with morphine dosing, and be aware of potential treatment of this with placing the patient supine and potentially raising the lower extremities to improve venous return and administering a fluid bolus (neither to be performed in the patient with pulmonary edema). Morphine will also have a positive

effect on patients presenting with STEMI and pulmonary edema to decrease venous return and improve respiratory status.

The uses of nonsteroidal anti-inflammatory agents for analgesia are to be avoided.

The American College of Cardiology (ACC)/American Heart Association (AHA) guidelines recommend:

Class I

- *Administration of morphine sulfate 2–4 mg IV with repeated dosing of 2–8 mg every 5–15 minutes as needed*
- *Discontinue all nonaspirin NSAID agents*

Class III

- *Avoid all nonaspirin NSAID agents.*

ANTIPLATELET AGENTS

If not already given, the patient must receive aspirin therapy at a dose of 162–325 mg, chewed. The importance of aspirin cannot be underestimated, and therefore, if the physician is not certain that aspirin has been taken by the patient at home, or was given in the ambulance, it should be given without delay.

Thienopyridines are effective in decreasing MACE in patients presenting with STEMI as is seen in patients with UA/NSTEMI. The COMMIT-CCS trial showed that a combination of aspirin 162 mg daily and clopidogrel 75 mg daily was superior to aspirin alone in prevention of death, re-infarction and stroke in patients with acute MI (majority of the treated patients had STEMI). This benefit was seen regardless of reperfusion strategy (thrombolysis or primary PCI). Notably the risks of major bleeding and cerebral bleeding were not statistically different between the two groups.[56] The CLARITY-TIMI 28 trial randomized patients with STEMI who underwent reperfusion with thrombolytics to clopidogrel (loading dose 300 mg followed by 75 mg daily) or placebo. All patients received aspirin. The trial showed a significant reduction in the primary endpoint of death, recurrent MI and occluded artery on angiogram, without a significant increase in bleeding. Additionally, there was a reduction in the need for urgent revascularization.[57] Based on these studies, it is recommended to administer clopidogrel at arrival to all STEMI patients who are 75 years old or younger.

A discussion of clopidogrel resistance can be found in the Chapter 48 "Acute Coronary Syndrome I: Unstable Angina and Non-ST Segment Elevation Myocardial Infarction". Also included in that chapter was a discussion of reluctance of some physicians to administer clopidogrel to MI patients until coronary anatomy is defined. Although clopidogrel does increase the risk of bleeding should a patient need to undergo CABG emergently, that scenario is becoming increasingly rare given the advances in modern interventional techniques and the rapidity with which reperfusion can be achieved with PCI compared to CABG. Therefore, we recommend pre-treatment of all STEMI patients with clopidogrel if no contraindications exist.

The TRITON-TIMI 38 trial[58] studied patients with ACS randomized to prasugrel (60 mg load, then 10 mg daily) or clopidogrel (300 mg load, then 75 mg daily). All patients received standard medical therapy. Reperfusion strategies in the subgroup of STEMI patients included primary PCI or thrombolysis followed by later secondary elective PCI 12 hours to 14 days later). In the STEMI subgroup who received prasugrel, there was a significant reduction in the primary event of cardiovascular death, nonfatal MI and nonfatal stroke, and in the secondary endpoint of cardiovascular death, MI and need for urgent target vessel revascularization at 30 days with persistence to 15 months. The rate of stent thrombosis was decreased with prasugrel. Prasugrel is therefore quite attractive for use in STEMI patients as it has faster onset of action, and in the STEMI subgroup there was no increase in bleeding compared to clopidogrel.

The American College of Cardiology (ACC)/American Heart Association (AHA) guidelines recommend:

Class I

- *Clopidogrel loading dose of 300–600 mg as early as possible, before or at PCI*
- *Prasugrel 60 mg as soon as possible for primary PCI*
- *Discontinuation of clopidogrel for 5 days and prasugrel for 7 days prior to elective CABG*

Class III

- *Avoidance of prasugrel in STEMI patients undergoing primary PCI who have a history of a stroke or transient ischemic attack (TIA).*

Unlike in the UA/NSTEMI patient, the benefit of upstream glycoprotein IIb/IIIA inhibitors has not definitively been demonstrated. These may be useful as adjunctive therapy during primary PCI for STEMI, although the most recent studies in which patients received dual oral antiplatelet therapy are small and fail to show a significant benefit. One study, HORIZONS AMI suggested a potentially increased incidence of net clinical events (particularly a higher risk of bleeding) when glycoprotein IIb/IIIa receptor blockers with heparin or bivalirudin was compared to bivalirudin alone.[59]

The American College of Cardiology (ACC)/American Heart Association (AHA) guidelines recommend:

Class II

- *Administration of glycoprotein IIb/IIIa receptor blockers (abciximab or eptifibatide) at the time of primary PCI in selected patients with STEMI*
- *Administration of glycoprotein IIb/IIIa receptor blockers as a part of preparatory medication regimen in STEMI patients being taken to the cardiac cath lab is of uncertain benefit.*

ANTICOAGULATION

Anticoagulation therapy should be administered in all STEMI patients who are without absolute contraindication. The choice of anticoagulant may be, in part, based on the reperfusion strategy, but in all cases full systemic anticoagulation with either unfractionated heparin or low molecular weight heparin or bivalirudin is beneficial.[59] Anticoagulation should continue for

48 hours in patients treated with thrombolysis. In patients who undergo primary PCI, anticoagulation may be discontinued after the procedure, unless there is another indication (i.e. intra-aortic balloon pump, LV thrombus, mechanical valve, etc.). Data for bivalirudin suggests that it be used predominantly in the catheterization laboratory during PCI.

The American College of Cardiology (ACC)/American Heart Association (AHA) guidelines recommend:

Class I

- *All STEMI patients receive, in addition to aspirin and a thienopyridine:*
  - *Unfractionated heparin upstream and during primary PCI or*
  - *Bivalirudin during primary PCI either alone, or after the use of heparin prior to arriving in the catheterization lab*

Class II

- *Bivalirudin for patients undergoing primary PCI for STEMI who have a high risk of bleeding.*

BETA BLOCKERS

Beta blockers should be given orally, with reservation of IV beta blockade for hypertensive or tachycardic patients with ongoing chest pain. Based on the COMMIT study, IV beta blockade should be avoided in patients at high risk for cardiogenic shock, those with systolic blood pressures below 105 mm Hg, and those who are more than 75 years old, due to a higher risk of hypotension and increased mortality.[5,60] In the case of a patient with suspected cocaine- or methamphetamine-associated STEMI, one should not use beta blockers as there is a physiologic concern about unopposed alpha constriction and worsening of the clinical scenario.

The American College of Cardiology (ACC)/American Heart Association (AHA) guidelines recommend:

Class I

- *Oral beta blockers be administered within the first 24 hours after STEMI in patients without:*
  - *Congestive heart failure*
  - *Evidence of poor cardiac index*
  - *Increased risk for cardiogenic shock, defined as an increased number of these risk factors: age more than 70 years old, systolic pressure less than 120 mm Hg, heart rate more than 100 or less than 60 bpm or prolonged ischemic time.*
  - *Heart block (PR > 240 ms or second or third degree AV block)*
  - *Active asthma or known significant reactive airway disease*
  - *If not given in the first 24 hours, that oral beta blockers be considered for secondary prevention*
  - *Patients with moderate or severe LV dysfunction receive beta blockers as secondary prevention*

Class II

- *Intravenous (IV) beta blockers in hypertensive patients with no contraindications above*

Class III

Avoid IV beta blockers in patients with:

- *Acute congestive heart failure*
- *Evidence of poor cardiac index*
- *Increased risk for cardiogenic shock, age more than 70 years old, systolic pressure less than 120 mm Hg, heart rate more than 100 or less than 60 bpm or prolonged ischemic time*
- *Heart block (PR > 240 ms or second or third degree AV block)*
- *Active asthma or known significant reactive airway disease.*

POST MYOCARDIAL INFARCTION CARE

ASSESSMENT OF LEFT VENTRICULAR EJECTION FRACTION

All patients following an MI must have assessment of LV ejection fraction (LVEF). This not only guides medical therapy but also provides prognostic information. It has long been known that decreased LVEF post MI and increased end systolic volume are markers for increased risk of development of CHF and death.[61-63] Abnormal LVEF (< 40%) portends an overall poor prognosis in the post MI patient (Fig. 19).[62] In addition, when comparing multiple variables and prognosis, decreased EF is the single most significant predictor of mortality. The presence of multivessel disease and the development of clinical heart failure, as well, did increase the likelihood of mortality, although to a lesser degree (Fig. 20).[63]

The choice of imaging modalities available today to assess EF, include: left ventriculography, transthoracic echocardiography, radionuclide imaging, CT and magnetic resonance imaging (MRI). Each modality offers additional information that may be helpful to the clinician and each is limited by patient-specific factors. Left ventriculography done at the time of coronary angiography offers the additional measurement of LV end diastolic pressure, assessment of mitral regurgitation and assessment for ventricular septal defect, location and relative size. It is limited by the need for radiation, iodinated contrast (important considerations in the presence of decompensated heart failure and/or with renal insufficiency) and inability to visualize wall motion in all territories (unless biplane capabilities are available or a second contrast injection is performed).

Echocardiography offers the ability to not only assess the LVEF but also to assess for wall motion abnormalities in all territories, detects LV thrombus, ventricular septal defect, noninvasive estimate of pulmonary artery pressures, RV systolic function, pericardial effusion and importantly to assess for preexisting or post MI valvular abnormalities. Echocardiographic imaging is limited at times by the patient's body habitus (obesity, large breasts, etc.), and in patients with significant obstructive lung disease. In addition, the assessment of EF is to some extent subjective.

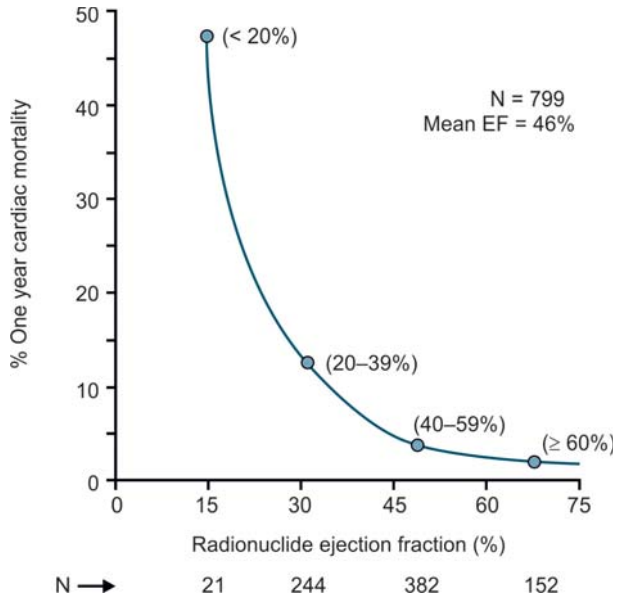


FIGURE 19: One year cardiac mortality rate in four categories of radionuclide ejection fraction (EF) determined before discharge. (*Source:* Modified from The Multicenter Postinfarction Research Group. Risk stratification and survival after myocardial infarction. N Engl J Med. 1983;309(6):331-6)

Radionuclide ventriculography offers a more objective LVEF and right ventricular ejection fraction (RVEF) assessment and can assess wall motion in all territories. It does not provide additional data, and is limited by the radiation exposure to the patient.

Cardiac MRI, done in facilities with expertise, offers the ability to assess wall motion, LVEF and RVEF (and is now the gold standard for EF assessment). Precise evaluation of VSD and other structural abnormalities (including assessment of aortic disease, pericardial disease, LV mass and LV thrombus) can be performed with cardiac MRI. Of great value, is the potential to assess the infarct zone (versus peri-infarct), the amount of scar (versus viability) and presence of inflammation and infiltration. However, MRI is the optimal test for these assessments. The MRI test is limited in patients with metal implants, patients who have significant claustrophobia (in whom sedation is a poor option or in patients who will require high levels of sedation to overcome the claustrophobic symptoms, thus inhibiting the necessary breath hold for the test) and in patients who have renal insufficiency who require IV gadolinium for assessment of LV structure (viability, infiltration, inflammation, etc.). Therefore, the physician must choose the optimal study for each patient with the goal to first assess EF and then to assess other clinical parameters as deemed most necessary.

The American College of Cardiology (ACC)/American Heart Association (AHA) guidelines recommend:

Class I

- *The LVEF assessment in all STEMI/NSTEMI patients*
- *A noninvasive assessment of EF in patients who are not scheduled to undergo left ventriculography*

STRESS TESTING PRIOR TO DISCHARGE

Stress testing should be considered to assess areas of at-risk myocardium in the patient who has received successful thrombolysis, who presented late with presumed completed infarct and did not receive reperfusion therapy, who presented with ACS non-STEMI who has been chosen for a conservative medical therapy approach and in the patient who has an indeterminate lesion noted on coronary angiography during the index hospitalization. The choice of stress testing includes exercise treadmill testing with or without imaging (echocardiography or nuclear perfusion) or chemical stress testing with dobutamine or dipyridamole/adenosine/regadenosine (depending on the institutional practice) with echocardiography or nuclear perfusion. In depth descriptions of these tests can be found in the chapter on Stress Testing and will not be reviewed here. It should be noted, although, that if a patient has an interpretable ECG and are able to undergo exercise testing, this

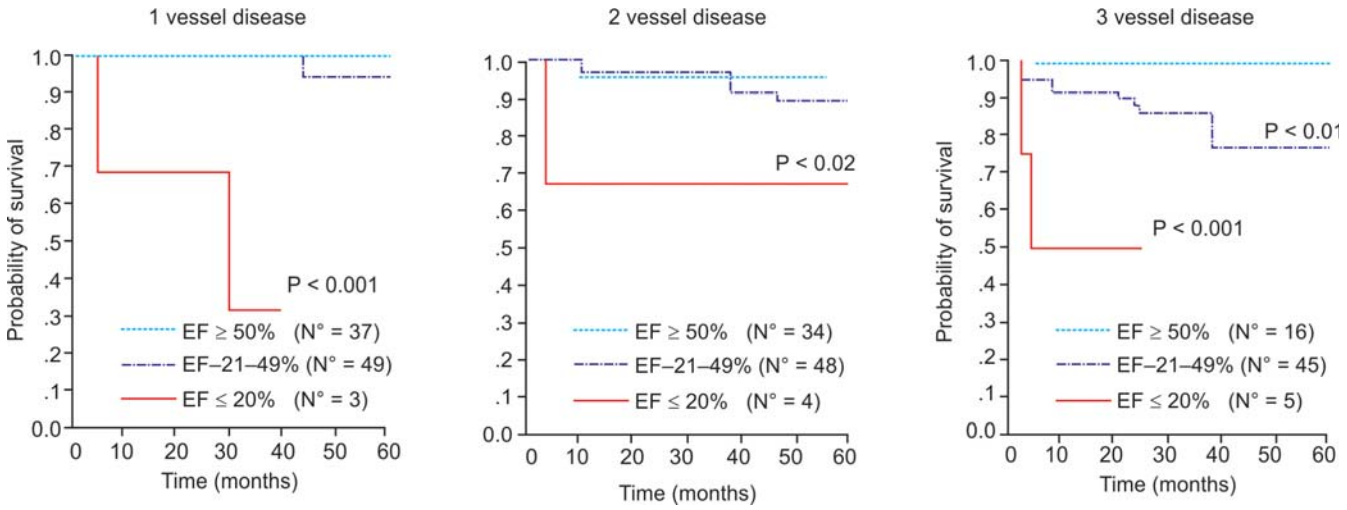


FIGURE 20: Kaplan-Meier survival curves of patients with 1-vessel, 2-vessel and 3-vessel disease, stratified according to ejection fraction (EF). Caution should be taken with interpretation of the class of patients with EF less than 20% due to the very small numbers in these groups. (*Source:* Modified from Sanz G, Castañer A, Betriu A, et al. Determinants of prognosis in survivors of myocardial infarction: a prospective clinical angiographic study. N Engl J Med. 1982;306(18):1065-70)

should be preferred to chemical stress as it provides information regarding heart rate and blood pressure response, and peak exercise workload that is important for the treating physician.

The American College of Cardiology (ACC)/American Heart Association (AHA) guidelines recommend:

Class I

- *Exercise testing in:*
  - *Low-risk patients with ACS (this does not include patients with ECG changes or positive biomarkers)*
  - *Intermediate risk patients with ACS (this may include patients with an abnormal resting ECG or a slight increase in troponins) who have been without ischemia (at rest or with low-level activity) or heart failure within the preceding 12–24 hours*
  - *The STEMI patients in hospital or early post discharge who have not during the index hospitalization and have no plan to proceed directly to coronary angiography and intervention, and are without high-risk features*

Class III

- *Avoid stress testing in STEMI patients who have not undergone reperfusion within 2–3 days of STEMI*
- *Post MI patients who have unstable post-infarction angina, decompensated heart failure, ventricular dysrhythmias, or other absolute contraindications to stress testing*
- *Patients who have planned coronary angiography pending*

CORONARY ANGIOGRAPHY AND REVASCULARIZATION

In patients who present with ACS, the decision for emergent and early angiography and intervention has been discussed in this chapter as well as in Chapter 48 "Acute Coronary Syndrome I: Unstable Angina and Non-ST Segment Elevation Myocardial Infarction". In patients who have not undergone early angiography, the need for angiography and possible intervention prior to discharge must be addressed. The potential contraindications should be evaluated and considered, including the patient's willingness to consent to both coronary angiography and potential revascularization. If no absolute or limiting relative contraindications exist, the following patients should be considered appropriate. In patients who present without STEMI, if any high-risk feature is identified on presentation, including accelerated or rest anginal symptoms, evidence of heart failure or hemodynamic instability, dynamic ECG changes or positive biomarkers for MI, one should strongly consider coronary angiography. In patients who have recurrent ischemic symptoms in hospital, particularly those who have angina at rest or are refractory to medical therapy, or those with post-infarction angina, coronary angiography is indicated. Patients with a decrease in EF or those with evidence of heart failure during hospitalization should undergo angiography. In addition, in patients who have undergone stress testing, a positive test with a significant amount of at-risk myocardium should prompt angiography. In addition, the previously reviewed indications for STEMI patients post lysis.

The American College of Cardiology (ACC)/American Heart Association (AHA) guidelines recommend:

Class I

- *Prompt angiography in patients with ACS (NSTEMI) who have failed intensive medical treatment*
- *Coronary angiography in STEMI patients with:*
  - *Recurrent myocardial ischemia*
  - *Intermediate or high-risk features on stress testing*
  - *Before surgical treatment of a mechanical complication of MI (acute MR, VSD or LV aneurysm repair) in a hemodynamically stable patient*
  - *Hemodynamic instability*
  - *Heart failure during hospitalization, but with normal EF*
- *PCI in patients with any high-risk features (recurrent angina, elevated cardiac biomarkers for infarction, new ST depressions, symptoms of heart failure, high-risk findings on stress testing, hemodynamic instability, ventricular dysrhythmias, PCI within preceding 6 months, prior CABG, high-risk score on presentation, or decreased LVEF) if lesion amenable and no contraindication*
- *PCI (or CABG) as indicated based on lesion morphology and patient characteristics as per the guidelines for PCI or CABG*

Class II

- *Early angiography (within 12–24 hours from admission) in initially stabilized high-risk patient with UA/NSTEMI*
- *Coronary angiography in STEMI patients with:*
  - *Patients who have STEMI suspected to not be secondary to CAD (i.e. emboli, spasm, etc.)*
  - *Diabetes, decreased EF (or ≤ 40%, heart failure, history of PCI or CABG, or ventricular dysrhythmia)*
  - *As a routine strategy post-successful thrombolysis*
- *PCI of left main stenosis greater than 50% in patients who are not eligible for CABG (or who require PCI emergently due to hemodynamic compromise)*
- *PCI in a patient with a hemodynamically significant lesion greater than 24 hours after STEMI as a part of an invasive approach (in a patient who has had successful lysis)*
  - *Chapter 48 stent or drug*

Class III

- *Coronary angiography in patients who are not candidates for revascularization*
- *Non-LAD lesion PCI or CABG in patients with no current symptoms (or symptoms that are unlikely to be secondary to ischemia) and no inducible ischemia on stress testing*
- *PCI in patients with no high-risk features, no trial of medical therapy and:*
  - *A small at-risk territory on stress testing*
  - *Likelihood of successful PCI is low in the lesion to be treated*
  - *Procedural morbidity or mortality is excessively high*
  - *No lesions greater than 50% stenosed (with exception on LM stenosis who are not eligible for CABG)*
  - *Stable post-NSTEMI patients with a persistently occluded infarct related vessel*

Patients who require revascularization, should undergo this without avoidable delay (although there is a lack of data to suggest urgent coronary angiography in stable ACS, non-STEMI patients).[64] The exception to this is in the patient who requires nonurgent CABG who has been given clopidogrel or prasugrel (see section on thienopyridines), who has acutely reversible renal failure,[65] and who has had STEMI in which consideration of 3–7 days delay to CABG is recommended.[66] There is an increase in hospital mortality early after MI in patients undergoing CABG with mortality rates of 11.8% if within 6 hours, 9.5% between 6 hours and 1 day and 2.8% after 1 day. Patients with a transmural MI had a higher mortality up to 7 days post MI. Therefore, nonurgent CABG should be delayed for 5–7 days after clopidogrel or prasugrel respectively, until renal function improves and for up to 7 days in STEMI patients.

The physician should recognize that although the bleeding risk in patients on clopidogrel and prasugrel is increased, there is no data to suggest that aspirin should be held at the time of CABG. As a matter of fact administration of aspirin in the patient's undergoing CABG is a Class I indication. Therefore, aspirin should be continued without interruption in all patients undergoing CABG.

The American College of Cardiology (ACC)/American Heart Association (AHA) guidelines recommend:

Class I

- *Aspirin should not be withheld prior to CABG*
- *Elective CABG should be delayed for 5 days in patients on clopidogrel and 7 days in patients on prasugrel*
- *In STEMI patients, CABG mortality is increased in the first 3–7 days after infarct*
- *The Risk/Benefit ratio must be assessed (presence or lack of symptoms, hemodynamic stability, presences of dysrhythmias and extent of MI and likelihood of recovery in short-term with medical therapy):*
  - *Stable patients with normal EF may undergo CABG within several days of infarct*
  - *If critical anatomy does not exist consideration of CABG may be done after the index hospitalization*

COMPLICATIONS

RIGHT VENTRICULAR INFARCTION

The involvement of the right ventricle in patients presenting with inferior wall STEMI portends a poor prognosis.[25] Data suggests that in hospital mortality is increased from 5% (without RV infarct) to 31% (with RV infarct). In addition, the major complications of cardiogenic shock, high-grade AV block (both transient and requiring permanent pacemaker placement) and ventricular dysrhythmias, increased from 28% to 64% respectively.[25] The identification of RV infarction is critical in the care of the patient with an inferior wall MI and therefore the presenting ECG should be scrutinized for the criteria noted previously. In addition, the use of a right-sided ECG is strongly encouraged. These patients are not only at higher risk but also are much more sensitive to optimal cardiac preload. Therefore, optimizing volume status and consideration of IV fluid challenge should be performed. One should avoid the use of nitroglycerin in patients with suspected or diagnosed RV infarction. These patients not uncommonly will require inotropic support (dobutamine or epinephrine infusion preferred) and therefore one should be very cautious with beta blockers in these patients as administration may precipitate hemodynamic collapse.

The American College of Cardiology (ACC)/American Heart Association (AHA) guidelines recommend:

Class I

- *Right sided ECG in patients presenting with inferior STEMI and hemodynamic compromise*
- *Patient with STEMI and RV infarction/ischemia have therapy with:*
  - *Early reperfusion*
  - *Correction of bradycardia and AV block*
  - *Optimal RV preloading conditions, consider IV fluid challenge*
  - *Optimal RV afterload (i.e. treatment of LV dysfunction)*
  - *Inotropic support as necessary*

Class II

- *Up to 4 weeks delay to CABG in patient with RV dysfunction*

HEART FAILURE OR CARDIOGENIC SHOCK AND MECHANICAL COMPLICATIONS AFTER A MYOCARDIAL INFARCTION

The incidence of heart failure and frank shock is increased in patients presenting with STEMI, but is certainly a complication of NSTEMI as well. Patients with MI complicated by heart failure have a high mortality, approaching 50% in some studies. Patients with heart failure should have aggressive treatment of ischemia or infarct. As already described, patients with cardiogenic shock achieve greater benefit with primary PCI compared to thrombolysis.[50] As noted in the previous section, RV infarct or failure can be the etiology of heart failure and shock, and should be considered in all patients with shock and inferior wall MI. Assessment of LVEF early in treatment is necessary to determine if the clinical heart failure is secondary to systolic or diastolic dysfunction and to guide both medical and revascularization therapy.

In addition to severe LV or RV dysfunction as etiology of heart failure or shock, the physician should be aware of the mechanical complications of MI and the expected timing of these. Although these are thoroughly covered elsewhere in this text and the reader is encouraged to read this chapter; briefly the three major complications resulting in hemodynamic compromise and collapse include acute papillary muscle rupture resulting in acute mitral regurgitation, acute ventricular septal rupture and LV free wall rupture. These complications require emergent evaluation and treatment, with surgery being the mainstay of treatment in all patients. In preparation for surgical intervention, patients with acute mitral regurgitation or ventricular septal defect may benefit from intra-aortic balloon pump (IABP) support. The patient with ventricular free wall rupture has an extremely high mortality, but may benefit from emergent pericardiocentesis to decrease the hemodynamic

impact of the elevated pericardial pressures, as the operating team or room is being mobilized.

Supplemental oxygen, morphine, nitrates and diuresis may improve symptomatic pulmonary edema. Beta blockers should be avoided early in acute heart failure complicating MI. The use of a pulmonary artery catheter may help to guide medical therapy. An IABP may be necessary in patients with refractory heart failure or shock. More aggressive support may be required with LV assist devices, including Impella, TandemHeart and implantable left ventricular assist device (LVAD). Ultimately the patient who has refractory heart failure may need consideration of heart transplantation.

The American College of Cardiology (ACC)/American Heart Association (AHA) guidelines recommend:

Class I

- *For post MI heart failure:*
  - *Oxygen supplementation if oxygen saturation is less than 90%*
  - *Morphine sulfate for patients with pulmonary congestion*
  - *Nitrates for patients with pulmonary congestion unless systolic blood pressure is 30 mm Hg below baseline or less than 100 mm Hg*
  - *Diuretic for patients with pulmonary congestion and volume overload*
  - *Beta blockers should be considered at low dose with gradual titration upwards prior to discharge*
  - *Aldosterone blockers should be considered in patients without contraindication*
  - *Transthoracic echocardiogram should be performed urgently to assess LV and RV systolic function and exclude mechanical complications of MI*
- *Intra-aortic balloon counterpulsation if:*
  - *Cardiogenic shock is not readily reversed with medical therapy or revascularization*
  - *Patient has low cardiac output state*
  - *Recurrent ischemia refractory to medical therapy and hemodynamic instability, poor LVEF, or a large at-risk territory of myocardium. Consideration should be given to urgent revascularization in these patients*
- *Early revascularization for STEMI patients in the age of less than 75 years old who:*
  - *Develop shock within 36 hours of STEMI*
  - *Are suitable for revascularization that can be accomplished within 18 hours and*
  - *Do not have contraindication or reason not to pursue revascularization (i.e. Patient wishes, futility, etc.)*

Class II

- *Pulmonary artery catheter placement:*
  - *To guide therapy of STEMI patients with cardiogenic shock*
  - *In STEMI patients with hypotension unresponsive to IV fluid challenge*
  - *When mechanical complication of MI are suspected*
- *Early revascularization for STEMI patients in the age of 75 years old or more who:*
  - *Develop shock within 36 hours of STEMI*
  - *Are suitable for revascularization that can be accomplished within 18 hours and*
  - *Do not have contraindication or reason not to pursue revascularization (i.e. Patient wishes, futility, etc.)*

DYSRHYTHMIAS

In the early phase of STEMI (first 24–48 hours), ventricular dysrhythmias can occur related to the ischemic event. The patient should be supported during this time with the main goal being reperfusion, normalization of electrolytes and treatment of any heart failure. Cardioversion should be performed if the patient has ventricular fibrillation (VF), sustained and hemodynamically significant ventricular tachycardia (VT), or VT associated with angina or pulmonary edema. Recurrence may require antiarrhythmic therapy with IV amiodarone or IABP placement. The reader should recognize the benefit of IABP for the treatment of refractory ventricular dysrhythmias. Treatment of premature ventricular complexes or nonsustained ventricular tachycardia (NSVT) is not recommended unless there is impact on hemodynamics. In the absence of significant heart failure, up titration of beta blockers may improve ventricular ectopy.

Sustained ventricular dysrhythmias that occur after 48 hours (without recurrent ischemia/infarct, decompensated CHF or other precipitant), in general, require long-term therapy including but not necessarily limited to internal cardioverter/defibrillator placement (ICD). These patients may require antiarrhythmic medication to prevent repetitive ICD discharges.

The American College of Cardiology (ACC)/American Heart Association (AHA) guidelines recommend:

Class I

- *Cardioversion for VF, polymorphic VT or monomorphic VT without pulse, or associated with angina, pulmonary edema or hypotension and*
- *Amiodarone 150 mg bolus over 10 minutes with repeat as needed and consideration of full loading dose of 1 mg/minute over 6 hours and then 0.5 mg/minute over 18 hours, not to exceed 2.2 g in 24 hours for patients with monomorphic VT associated with angina, pulmonary edema or hypotension*
- *ICD may be considered in patients with VF or hemodynamically significant VT greater than 48 hours after STEMI provided that this is not felt to be secondary to recurrent ischemia or reinfarction*

Class II

- *Amiodarone 300 mg IV bolus over 10 minutes be considered when VF or pulseless VT is refractory to cardioversion, in preparation for repeat cardioversion*
- *Correction of electrolyte abnormalities (goal potassium > 4.0 mEq/L and magnesium > 2.0 mg/dL) to prevent further VT/VF*
- *ICD placement in patient with LVEF of 30% or less and with STEMI greater than 1 month prior and last revascularization greater than 90 days prior*

Class III

- *Avoidance of routine prophylactic antiarrhythmic medications for:*
  - *All STEMI patients undergoing thrombolysis*
  - *Suppression of ectopy or NSVT*
  - *Accelerated idioventricular rhythms*
- *Avoid of ICD in patients with early VT/VF (< 48 hours), or who have an LVEF greater than 40% at 1 month post MI.*

As previously mentioned, particularly with patients with inferior MI (with or without RV infarction), bradycardia and heart block may complicate the MI and require permanent pacemaker placement. Transient bradycardia or heart block should be treated supportively, and may require short-term temporary transvenous pacemaker placement if hemodynamically significant.

The American College of Cardiology (ACC)/American Heart Association (AHA) guidelines recommend:

Class I

- *Temporary pacemaker placement for medically refractory symptomatic sinus bradycardia, sinus bradycardia with heart rate less than 40 bpm associated with hypotension or sinus pause of greater than 3 seconds*
- *Consideration of permanent pacemaker placement for sinus node dysfunction should follow ACC/AHA guidelines for pacemaker placement*
- *Permanent pacemaker placement for:*
  - *Second degree AV block (below the His-Purkinje system) with bilateral bundle branch block*
  - *Third degree block within or below the His-Purkinje system*
- *All patients requiring permanent pacemaker placement post MI should be assessed for indications for ICD implantation*

Class II

- *Permanent pacemaker placement for persistent second or third degree AV block at the level of the AV node*

Class III

- *Avoid permanent pacemaker placement for:*
  - *First degree AV block in the presence of bundle branch block*
  - *Transient AV block*
  - *New left anterior fascicular block.*

Other dysrhythmias may occur during the index hospitalization for STEMI, including atrial fibrillation, atrial flutter or SVT. These should be treated appropriately with consideration of cardioversion early given the more tenuous status of these patients. In patients with heart failure and atrial fibrillation or flutter, consideration should be given to the use of digoxin for ventricular rate control.

RECURRENT CHEST DISCOMFORT

The reader should be aware of potential etiologies of recurrent chest discomfort post MI. Recurrent ischemia or infarction must always be a consideration. The ECG evaluation during symptoms and monitoring of cardiac biomarkers of necrosis should be used for diagnosis of recurrent ischemia or reinfarction. Unfortunately each of these presents a difficulty. Not uncommonly patients have a persistently abnormal ECG, or an ECG consistent with evolution of infarct, limiting the ability to confidently assess for acute or dynamic changes. In addition, the longer half-life of troponin prevents accurate determination of reinfarction in the first 10–14 days after MI; therefore, creatine kinase (CK and CK MB) which rises and falls more rapidly may be needed. Stress testing may be appropriate, if not previously performed and repetition of coronary angiography may be necessary to assess patency of stented vessels.

Post MI pericarditis may occur early after MI (within the first 4 days) or late, generally after discharge (Dressler's syndrome). It is diagnosed by characteristic pain, a pericardial rub on auscultation, ECG changes (which may be obscured in the early post MI period), presence of a small effusion on echocardiography and improvement with anti-inflammatory agents. Early pericarditis is associated with late index presentation, longer ischemic times prior to reperfusion, larger infarct and failed PCI.[67] Despite the fact that this association exists, the presence of early pericarditis alone does not seem to have any implications on short- or long-term prognosis.[67] Late pericarditis or Dressler's syndrome is very uncommon today given the improved success with reperfusion therapies.

Pericarditis may be treated with higher dose of aspirin or indomethacin. Colchicine is another option, as is the use of steroids, although steroids are not preferred in the early post MI period due to potential inhibition of the normal scarring that occurs in the infarcted zone. This decrease in appropriate scar formation at the site of the infarct can potentially increase the risk of myocardial rupture.

As patients are hospitalized for ACS, and thus are immobile, they are at increased risk for deep venous thrombosis (DVT) and pulmonary embolism. Patients with a prolonged hospital course (particularly those with CHF), patients with heparin-induced thrombocytopenia and thrombosis, or other hypercoagulable states should be anticoagulated to prevent DVT. Pulmonary embolism should be considered in all patients with pleuritic-type chest discomfort, shortness of breath that is unexplained, or sudden hemodynamic change not associated with a cardiovascular change. Treatment should proceed with full anticoagulation if not contraindicated.

SPECIAL CONSIDERATIONS

DIABETES

The diabetic population is unique with respect to ACS and have been shown to have worse short-term and long-term outcomes after an MI compared to non-diabetics. It is also known that they require more aggressive efforts at primary and secondary prevention. In addition, hyperglycemia during hospitalization

has been associated with worse outcomes. Although the 2004 guidelines recommended aggressive glucose control with IV insulin to normalize blood glucose as a Class I indication, that recommendation has been downgraded to a Class II indication based on a recent study showing higher mortality in aggressively treated patients.[5,6]

The American College of Cardiology (ACC)/American Heart Association (AHA) guidelines recommend:

Class II

- *Use of an insulin-based regimen to achieve and maintain glucose levels less than 180 mg/dL, while avoiding hypoglycemia.*

WOMEN

In general, women present with ACS at an older age than men and have the potential to have a more atypical presentation. They should be treated in similar manner to their male counterparts in the setting of ACS. Many of the early trials for ACS did not include a significant percentage of women. There is no clear data, that MI therapy should be significantly different for women than for men, except for the discontinuation of hormone replacement therapy. Due to the smaller body size of women, there may be increased risk of bleeding with standard dosing of antiplatelet medications and anticoagulants. This should be considered when treating the female patient.

The American College of Cardiology (ACC)/American Heart Association (AHA) guidelines recommend:

Class I

- *Women with ACS:*
  - *Should be managed similarly as men*
  - *May need dose adjustment for antiplatelet and anticoagulation therapy based on smaller body surface area*
  - *Have similar indications for noninvasive testing (and similar prognostic value if imaging is used) compared to men*
  - *Are recommended for early invasive strategy if at high risk*
  - *Are recommended for conservative medical strategy if at low risk*
  - *Should not have initiation of, and should have discontinuation of previously prescribed, hormone replacement therapy after an MI.*

ELDERLY

Patients should not have care withheld or altered based on age alone. The recommendations made in this chapter and in the guidelines, in certain areas, are based on data from studies that suggested either a decreased benefit or an increased risk in patients who are elderly. The premorbid functional class of the patient, as well as their associated comorbidities should guide therapy to a greater degree than age alone.

ACUTE CORONARY SYNDROME WITH COCAINE (AND METHAMPHETAMINE) USE

Cocaine as an etiology of ACS has been discussed earlier in this chapter. As the pathophysiology of cocaine induced ischemia or infarct may not be related to obstructive CAD, its management is somewhat different. Coronary vasodilators are the mainstay of therapy. However, the potential unopposed alpha constriction that may occur when beta blockers are given is a concern. Finally, although patients with cocaine use may have risk factors for CAD and develop a ruptured plaque to cause ACS, a significant portion do not have ACS secondary to platelet aggregation or thrombus formation. Therefore, the previous discussions regarding invasive approach to UA/NSTEMI and the use of antiplatelet medications, anticoagulants and thrombolytics may be less applicable in this population. Finally, methamphetamine use is on the rise and, although is not addressed directly in the guidelines, one may consider applying a similar approach in these patients as well.

The American College of Cardiology (ACC)/American Heart Association (AHA) guidelines recommend:

Class I

- *Use of nitroglycerin and calcium channel blockers for the patients with ischemic-type chest discomfort and ST-depressions after cocaine use*
- *Immediate coronary angiography with intent to perform primary PCI as necessary, should be performed if ST-elevation persists after coronary vasodilators*
- *Thrombolytics should be considered in the above patient if coronary angiography is not possible*

Class II

- *Nitroglycerin or calcium channel blockers in patients after cocaine use, with ischemic-type chest discomfort with no or minimal ECG changes*
- *Coronary angiography in patients after cocaine use if persistent ischemic-type chest discomfort and ST-depressions or isolated T wave inversions and lack of response to nitroglycerin or calcium channel blockers*
- *Management of ACS patients after the use of methamphetamines be similar to patients after cocaine use*
- *Use of combined alpha and beta blocking agents (labetalol) for patients with hypertension or sinus tachycardia, after the administration of nitroglycerin and/or calcium channel blockers*

Class III

- *Coronary angiography in patients after using cocaine who presented with chest discomfort and have no ST-segment or T-wave changes on ECG, negative biomarkers for necrosis and a negative stress test*

POST MYOCARDIAL INFARCTION DEPRESSION

Patients with depression after MI have a significantly worse prognosis compare to those who do not. Specifically, there is an increased risk of mortality at 6 months. This impact on

prognosis is equivalent to the impact of high Killip class or previous MI.[68] In addition, mortality at 4 months was elevated even in patients with mild depression and the increase in mortality correlated with the degree of depression.[69,70]

Interestingly, the impact of depression seems to be solely related to mortality, not to the frequency of recurrent events. In addition, there does not appear to be a definitive study showing that medical treatment of the depression has a favorable impact.[71] Therefore, the physician should recognize the potential increase in incidence of depression in the patient post MI, and the increase in mortality associated with this diagnosis. Routine assessment of patients for the symptoms of depression should be a part of post MI care, both before and after discharge. Given that there is presently no data that treatment is either beneficial or harmful, medical therapy and counseling should be recommended as with any other patient with depression.

SURVIVORS OF OUT OF HOSPITAL CARDIAC ARREST

Out of hospital cardiac arrest is a complication of acute MI and, unlike in-hospital arrest, the prognosis is very poor with less than 10% rates of survival to discharge with any meaningul neurologic function.[72] Neurologic prognosis is worse if arrest is unwitnessed, occurs at home (versus in a public place), results in increased time to resuscitation, as well as in patients with advanced age and the initial rhythm of asystole or PEA compared to VF or VT. The cause of death is less commonly due to cardiogenic shock or recurrent dysrhythmias and more commonly related to complications of the anoxic brain injury (anoxic encephalopathy, sepsis, ventilator associated pneumonia, multiorgan failure, etc.). Thus prevention of brain injury has to be a focus of care for post MI patients who arrest prior to arrival at the hospital. The mainstay of this care today is induced therapeutic hypothermia. Patients are intentionally cooled to 32–34°C for 12–24 hours. In order to accomplish this, the patients must be paralyzed and sedated. Commercially available systems are available, and cold saline infusion is delivered to accomplish cooling. Two large randomized trials studied the use of therapeutic hypothermia in patients who were successfully resuscitated with out of hospital cardiac arrest due to VF and were comatose on arrival to the hospital. Both studies showed a significant improvement in survival and favorable neurologic outcome at the time of discharge.[73,74] Notably, in practice, patients who undergo cooling have a higher likelihood of hemodynamic and electric instability. These must be treated supportively with some tolerance of mild perturbations and then the addition of medications and occasionally IABP. There is an increased risk of coagulopathy. This should be considered in the patient who is at higher risk of bleeding due to thrombocytopenia, elevated INR or active bleeding. The American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science, published within the last few months, clearly recommends consideration of therapeutic hypothermia in comatose patients presenting after cardiac arrest. This recommendation is made with recognition that although there is apparent benefit, the specifics of timing, duration and optimal patient selection require further study.[75]

CONTINUED MEDICAL THERAPY FOR PATIENTS WITH A MYOCARDIAL INFARCTION

INHIBITION OF THE RENIN-ANGIOTENSIN-ALDOSTERONE AXIS

Angiotensin converting enzyme (ACE) inhibitors have been thoroughly studied in patients with heart failure.[76-79] The data show that they are indicated and beneficial in patients post MI who have a decreased LV systolic function (defined as LVEF $\geq$ 40%), or who have chronic kidney disease, diabetes or hypertension. The guidelines recommend against the routine use of IV ACE inhibitors, except in refractory hypertension.

Angiotensin receptor blockers should be considered in patients who are intolerant to ACE inhibitors (i.e. cough, angioedema, etc.) and have either a decrease in LVEF or who have hypertension requiring treatment, or as a primary option (versus ACE inhibitors) in these patients.[79-81]

Blood pressure reduction with the medications (beta blockers, nitrates, ACE inhibitors or angiotensin receptor blockers as first line, calcium channel blockers and thiazides as second line, etc.) and lifestyle changes to include diet (including reduction in sodium intake), exercise and weight reduction in attempt to attain ideal body weight should be a part of the patients discharge planning. The goal of blood pressure is less than 140/90 (with more stringent goal of < 130/80 blood pressure in patients with diabetes mellitus or chronic kidney disease).

The use of an aldosterone antagonist has been well established in heart failure[82] and has been shown to improve mortality and morbidity in patients who have had an AMI complicated by LV systolic dysfunction and heart failure.[83] Therefore, patients with decreased LVEF ($\geq$ 40%) and who do not have significant decrease in renal function or elevation in potassium, who are post MI should be considered for initiation of eplerenone 25 mg daily in the beginning on 3–14 days and titrated up to 50 mg as tolerated.

The American College of Cardiology (ACC)/American Heart Association (AHA) guidelines recommend:

Class I

- *ACE inhibitors should be administered to post MI patients with:*
  - *An EF less than or equal to 40%*
  - *Diabetes*
  - *Hypertension (Goal of <140/90 blood pressure in general and < 130/80 blood pressure in patients with chronic kidney disease or diabetes mellitus)*
  - *Chronic kidney disease*
  - *Increased risk for the recurrence of cardiovascular events (i.e. continued elevated risk due to poorly controlled risk factors)*[84]
  - *Normal EF with risk factors under control, at the discretion of the physician and patient (reasonable to administer)*
- *Angiotensin receptor blocker should be administered to post MI patients with:*

- *— The LVEF less than or equal to 40% who are intolerant to ACE inhibitor*
- *— Hypertension who are ACEI in tolerant*
- *— Systolic dysfunction who are already on ACE inhibitor*
- *Aldosterone receptor blocker should be administered to post MI patients with:*
  - *— The LVEF less than or equal to 40% and either diabetes or heart failure, but without significant renal dysfunction (Creatinine < 2.5 mg/dL in men and 2.0 mg/dL in women)*

Class III

- *The IV ACE inhibitor use in patient with MI due to the risk of hypotension (may be considered to control refractory hypertension)*

LIPID MANAGEMENT

Although there is a clear benefit from several medications we prescribe for patients with cardiovascular disease, as providers, we must remember that the "prescription" of a heart healthy diet combined with a regular exercise program is highly beneficial to and essential for our patients. The diet has been shown, by itself and with exercise to lower low density lipoprotein (LDL) cholesterol, decrease progression of CAD (and potentially lead to regression) and reduce cardiovascular events.[85-88] However, the majority of CAD patients, are not able to either follow these stringent diets or intense physical exercise regimens and are unable to attain their lipid goal with these lifestyle changes alone. Patients with recent ACS have the lowest target LDL, at less than 70 mg/dL, which is extremely difficult to achieve for most of the patients, without medications.[89,90]

It is clear from multiple studies that lipid lowering with 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG CoA) reductase inhibitors (statins) prevents cardiovascular events both primarily (prior to first event) and secondarily (after diagnosis of atherosclerotic cardiovascular disease).[91-93] Early and aggressive use of statins (atorvastatin 80 mg daily) decreases risk in the early (as early as 16 weeks post ACS)[94-96] and late period post MI (after 4 months with simvastatin 40 mg up titrated to 80 mg/dL at 1 month).[97] These benefits remain long term.[98]

Reduction in LDL is important for reducing progression of atherosclerosis over long term. However, the relatively early benefit with statins as noted in major trials suggests that additional mechanisms besides LDL lowering may be involved. In fact, multiple "pleiotropic" effects of statins have been studied. These effects include: stabilization of the vulnerable plaque, improvement in endothelial function, decrease in inflammation both in the plaque itself (less macrophages and decreased metalloproteinase production by macrophages and decreased cell death within the plaque) and systemically (by decreasing expression of chemokines and inflammatory cytokines, lowering of clinical markers of inflammation—highly sensitive C-reactive protein) and decreased thrombogenesis.[99]

Full fasting lipid panel should be measured as soon as possible after admission. It must be recognized by the physician that LDL cholesterol decreases, significantly, after MI and to a lesser extent with unstable angina. This decreased level will underestimate true baseline level and the needed reduction based on diet, exercise and medication. The absolute decrease in any given patient is variable, but the decrease itself is generally significant and can approach 50%.[100]

It is recommended that a statin medication be initiated in patients who have no contraindication, early after the diagnosis of ACS (as early as day 1), and no later than at the time of discharge. In addition to the early effects of statins, the initiation of this medication at the time of the ACS event, improves long-term compliance.[101]

Niacin has been shown to decrease the risk of recurrent nonfatal MI in patients with a previous history of MI,[102] and is a consideration in the statin intolerant patient. The AIM-HIGH trial, which is presently ongoing, will look at patients with optimal LDL levels on a statin, plus placebo versus extended release niacin.[103]

Omega 3 fatty acids are beneficial in lowering triglycerides and thus raising HDL, both as an increase in dietary intake and as a supplement. The supplemental use of omega 3 fatty acids has been shown to prevent sudden cardiac death in patients with previous MI.[104] The addition of omega 3 fatty acids should be considered in patients post MI with elevated triglycerides.

The American College of Cardiology (ACC)/American Heart Association (AHA) guidelines recommend:

Class I

- *Assessment of lipids within 24 hours of presentation and initiation of medications prior to discharge*
- *Dietary changes (education) to reduce intake of saturated fats (< 7% of calories), trans fats and cholesterol (< 200 mg/dL)*
- *Promote daily physical activity and weight management*
- *The HMG CoA reductase inhibitors, in absence of contraindications:*
  - *— In UA/NSTEMI, regardless of baseline*
  - *— In UA/NSTEMI/STEMI patients with LDL greater than 100 mg/dL (it is reasonable to use medications to achieve LDL < 70 mg/dL—Class II)*
- *Treatment of triglycerides, if between 200 and 499 mg/dL, and non-HDL (total cholesterol minus HDL) if greater than 130 mg/dL is reasonable*
- *Treatment of triglycerides if greater than 500 mg/dL with fibrates or niacin should be a first priority*

Class II

- *Increase dietary intake of omega 3 fatty acids or supplement (up to 1 g/dL if triglycerides are normal, 4 g/dL if triglycerides are elevated)*
- *Addition of niacin or fibrates (beware of increased incidence of side effects with combination therapy) to treat low HDL (< 40 mg/dL) or elevated triglycerides (> 200 mg/dL) after LDL lowering therapy is instituted.*

GLUCOSE MANAGEMENT

It is well established that diabetics have an increased risk of cardiovascular events. Unfortunately, to date, there have not been any definitive randomized trials to show that intensive glucose control in established diabetics has a benefit on reduction in major adverse cardiovascular events. On the

contrary, the ACCORD study was stopped prematurely due to an excess mortality in the intensive treatment group.[105]

The United Kingdom Prospective Diabetes study, in contrast, looked at new diabetics and assigned them to conventional therapy, (diet alone) versus an intensive glucose control arm with sulfonylurea or insulin. Findings from this study showed that intensive treatment of type 2 diabetes with a sulfonylurea or insulin resulted in a lower incidence of microvascular complications (e.g., neuropathy, retinopathy, and nephropathy) without a significant reduction in macrovascular events (e.g., myocardial infarction). Aggressive control of blood pressure on the other hand was shown to have a beneficial impact on the risk of macrovascular complications. In the subgroup of patients treated with metformin however, notable reduction in the risk of microvascular and macrovascular complications was noted.[106]

Based on this data, one should consider aggressive glucose control in new diabetics, but recognize that intensive control in long-term diabetics may have a negative impact on cardiovascular events and mortality. More data is clearly necessary to determine optimal level of glycemic control and the type of therapy to be used in patients with long-term diabetes.

Finally, it is clear that aggressive risk modification should occur in patients with diabetes particularly with blood pressure and lipid management.[107,108]

The American College of Cardiology (ACC)/American Heart Association (AHA) guidelines recommend:

Class I

- *Initiate lifestyle modification and pharmacotherapy with goal of near normal HbA1c*
- *Aggressive modification of other risk factors (weight loss, exercise, blood pressure control, lipid management, etc.)*
- *Care coordination for management of diabetes with primary care physician or endocrinologist*

SMOKING CESSATION

Continued tobacco smoking in patients with CAD significantly increases the risk of reinfarcton and death.[109] Compliance with smoking cessation increases when initiated at the time of an event (MI or CABG).[110] Smoking cessation decreased the relative risk of mortality by 36% and significantly decreased the risk of nonfatal cardiac events, in a meta-analysis of studies performed in patients with previous cardiovascular events.[111] The relative risk of death is decreased by half in women smokers who quit compared to those who continued to smoke, and these curves begin to separate within the first year. The incidence of reinfarction trended toward a decrease, but this was not statistically significant in this study.[112]

Secondhand or passive smoke increases the risk of developing CAD, cardiovascular events and cardiovascular mortality, and should be avoided.[113] Patients and their family members (particularly the spouse and other smokers residing in the same residence) should be counseled on the deleterious effects of secondhand smoke and on the inability of the patient to discontinue smoking in the presence of ongoing smokers. Given the multiple bans on smoking in the community, the likelihood of the patient encountering with unavoidable smoking in the workplace has decreased.

Smoking cessation is a difficult task for most of the patients. It is a duty of the caregiver (physician, nurse and cardiac rehabilitation specialist) to discuss with the patient about the negative impacts of smoking on his or her cardiovascular and overall health. The patient must first recognize these impacts and understand the necessity of smoking cessation. Counseling is a mainstay of smoking cessation. This should occur at multiple levels, including prior to and also after discharge. Successful discontinuation of tobacco use is dependent on the patient making a determination that cessation is necessary. The direct discussion between patient and physician is a first step in the patient making a determination of need to quit and this counseling increases the likelihood of cessation.[114] Ongoing counseling will occur in cardiac rehabilitation and is also available via telephone and internet through the "QUITNOW" program. The patients should be encouraged to utilize these resources.

The addition of pharmacotherapy to counseling is beneficial. Adding nicotine replacement therapy has been shown to increase the likelihood of cessation.[114] Nicotine replacement therapy is clearly safe in patients with stable angina and considered safe in patients after ACS (safer than continued smoking), particularly if revascularized.[115] Patients should be counseled on the avoidance of combining nicotine replacement therapy with continued active smoking.

Bupropion is at least as effective as nicotine replacement therapy in smoking cessation.[116,117] Consideration may be given to combined therapy, in some patients, although there was not a statistically significant difference when compared to bupropion alone. The smoker should be encouraged to choose a "quit date" and then to begin the bupropion 1 week prior at a dose of 150 mg/dL for 3 days, then 150 mg twice per day for at least 12 weeks and up to 6 months. There is efficacy data for the single daily 150 mg dose in some studies and therefore it can be considered as an option. Bupropion can decrease seizure threshold and thus should not be given in patients with a seizure disorder.[118]

Varenicline is a partial agonist of the nicotinic acetylcholine receptor and thus decreases the withdrawal symptoms.[27] Varenicline has been compared to bupropion in randomized controlled trials and it is superior to use both for short-term and long-term smoking cessation.[119,120] There have been reported cases of suicidal ideation and/or new aggressive or erratic behaviors in patients taking varenicline. The FDA therefore has issued a warning that varenicline may increase the risk of serious neuropsychiatric symptoms in patients. Physicians should assess the risk or benefit of this therapy, use caution in prescribing and educate patients and their families regarding symptoms that should prompt discontinuation of the medication and when to seek medical evaluation (including changes in behavior, aggression, decreased mood or increased anxiety or agitation, or suicidal ideation).

Small studies have suggested the increased efficacy and safety of combined varenicline and bupropion, as well as varenicline with nicotine replacement.[121,122] One should consider reserving this therapy for patients with low risk of side effects and continued interest in cessation despite lack of success with either medication alone.

The American College of Cardiology (ACC)/American Heart Association (AHA) guidelines recommend:

Class I

- *Smoking cessation and avoidance of environmental smoke at home and work with a stepwise strategy:*
  - *Ask the patient about exposure (smoking and exposure to secondhand smoke)*
  - *Advise counsel regarding cessation of smoking and avoidance of secondhand smoke*
  - *Assess willingness to quit, and barriers (including smokers in environment) and continually asses success rate at follow-up visits*
  - *Assist with pharmacologic agents as necessary*
  - *Arrange follow-up and cardiac rehabilitation*

DISCHARGE

Optimal length of stay for a patient with an MI is dependent on the patient's clinical status, the need for monitoring and completion of the evaluation. Although length of stay has progressively decreased over time, ultimately there will be a point at which it cannot decrease further or patient safety will be impacted. Low-risk patients (defined as patients age < 70 years old who were without heart failure, major dysrhythmias, three-vessel CAD, or need for IABP and with EF > 45%, a successful PCI and CK/MB-fraction values < two times the upper limit of the reference value at the discharge) were discharged in 48–72 hours after admission without significant morbidity or mortality at 6 weeks (0% mortality and 0.6% morbidity), or 6 months (0.5% mortality and 2% morbidity).[123] Notably, at least in this study, the risk stratification is not impacted by the patients original presentation, particularly whether the patient presents with NSTEMI or STEMI. Patients with a complicated course will require longer stay. Predischarge planning should occur early in the hospital stay in order for the patient to be ready for discharge as early as their medical condition allows. The average length of stay for a patient with MI is 3–5 days.

NITRATES

Although there is no data to show a mortality benefit in patients treated with nitrates chronically, it is important that all patients with CAD have rescue nitroglycerin available to them. This can be delivered in tablet (sublingual) or spray form. Patients should be given a prescription at discharge and be educated on its use. The standard instructions are to use nitroglycerin at the onset of angina, and repeat in every 5 minutes as needed. The patient should be instructed to call 911 if requiring a third dose. It is important that patients understand the indications for use, and be educated on "their angina" as many patients will have either atypical angina, or have difficulty in differentiating angina from other chest or epigastric symptoms. In addition, it is appropriate to educate the patient on the side effects, including hypotension (instructing patients to sit or lie down when taking nitroglycerin, if possible) and the potential for headache and to let them know about the serious interaction with type 5 phosphodiesterase inhibitors.

The American College of Cardiology (ACC)/American Heart Association (AHA) guidelines recommend:

Class I

- *The use of nitrates to limit ischemic symptoms.*

CARDIAC REHABILITATION AND SECONDARY PREVENTION OF CORONARY HEART DISEASE FOR PATIENTS WITH MYOCARDIAL INFARCTION

Over the past two decades, there has been tremendous progress in pharmacological therapies, sophisticated technology-based diagnostic and therapeutic procedures for the treatment of cardiovascular diseases. As survival from acute events has improved, a greater number of men and women with prevalent cardiovascular disease are at increased risk for future events and thus, may suffer significant physical and psychological disability. Secondary prevention strategies focused on lifestyle modification, diet, exercise and medical therapy are an integral part of disease management and have been discussed. Cardiac rehabilitation is a very important (and underutilized) multidisciplinary intervention that provides comprehensive services focused on exercise training and important life style modifications for a patient with cardiovascular disease. It helps to limit the functional and psychological impact of the illness and to prevent future events.

Cardiac rehabilitation can begin as soon as an eligible inpatient stabilizes after AMI, PCI, CABG surgery, valve surgery, heart transplant or acute coronary syndrome. Inpatient rehabilitation, known as Phase I, is intended to prevent deconditioning from hospitalization, ready the patient for referral to an outpatient cardiac rehabilitation program, assess for activity tolerance, prescribe activity for the period immediately following hospital discharge, and begin patient teaching for secondary prevention.

Outpatient cardiac rehabilitation, also known as Phase II, is a standard of care following MI, PCI, CABG surgery, valve surgery, heart transplant, and for those with stable angina. It is designed to limit the physiological and psychological effects of MI, reduce the risk of sudden cardiac death and reinfarction, control cardiac symptoms, stabilize or reverse the atherosclerotic process, and enhance patients' psychosocial and vocational status.[124,125] Secondary prevention, essential in contemporary care of patients with heart disease, is a key element of cardiac rehabilitation.[126]

Phase II cardiac rehabilitation begins with referral into a program as soon as possible post MI, followed by baseline patient assessment, including exercise, nutritional and psychosocial assessments. Patients are then provided appropriate individualized nutritional counseling, aggressive risk factor management, psychosocial intervention as needed, and monitored exercise training by a qualified multidisciplinary team, typically composed of experienced registered nurses, exercise physiologists, physical therapists, a registered dietitian and psychologist or social worker. Patients are strongly encouraged to attend several sessions (up to 36 and sometimes more), the number of which is determined by complications, risk category and progress in meeting goals. Medicare, medicaid

and most private insurance companies reimburse for Phase II cardiac rehabilitation. Some insurance plans have recently implemented co-payments that have made CR prohibitively expensive. However, many Medicare patients carry supplemental insurance that assist with co-payments that have recently risen substantially since 2010.

The benefits of Phase II cardiac rehabilitation are impressive, multifaceted and interrelated, and are attained by implementing the following components:

- *Exercise training*: Supervised monitored exercise is carried out in a group setting (typically no more than 4 patients per staff member) after individual exercise assessment. The exercise prescription, recommended by the staff and approved by the physician, includes aerobic and strength training with various modes of exercise equipment based on the patient's goals and abilities. The initial exercise assessment is comprised of an exercise test not to exceed 70% of age-predicted maximum heart rate for the post MI patient, 85% for the non-MI patient, or a rating of perceived exertion (RPE) of 14 (Borg 6–20 scale), absence of angina or ECG signs of ischemia and arrhythmias. From that initial assessment, the exercise prescription is written considering heart rate parameters, avoidance of angina and/or ECG signs of ischemia and RPE. On the first evaluation, patients achieve a peak level of anywhere between 1.6 and 13.5 METs* (METs are estimated metabolic equivalent units where 1 MET = oxygen consumption of 3.5 ml/kg/minute), depending on age, physical conditioning prior to the event and severity of cardiac diagnosis. Patients then progress by gradually increasing the aerobic exercise duration (up to 60 minutes) as well as the workload. Typically patients are able to begin aerobic training at 50% or more of their peak MET level on admission. The typical patient is training at the level at which they tested on admission at least by mid-point in the program. Aerobic training includes exercise on treadmills, bicycles, elliptical trainers, arm ergometers and other modes. Strength training begins as soon as possible in Phase II based on the patient's diagnosis, surgical status (and clearance from surgeon) and blood pressure response to exercise.

  The exercise training increases a patient's peak oxygen uptake by 11–36%, with the greatest improvement in the most deconditioned individuals.[124,126,127] At the University of Iowa CHAMPS (cardiac rehabilitation program) the final exercise evaluation showed a mean improvement in estimated METs of 53%†, (range 2.2–21.5 METs).

  In addition, exercise increases high density lipoprotein, lowers triglycerides, and helps with weight loss and blood pressure control. Specifically designed exercise programs enable patients to safely return to occupational demands as well as attain recreational goals.
- *Nutritional counseling*: For most patients, lipid management, blood pressure lowering and weight control are important goals. Baseline data are collected concerning usual caloric intake, saturated and trans fat consumption, eating habits, fruits and vegetables consumption, carbohydrate and alcohol consumption. Patient-specific goals are delineated.
- *Weight management*: Not only is obesity an independent risk factor for cardiovascular disease, it adversely impacts other risk factors.[128] Calculation of the body mass index, measurement of the waist circumference, frequent body weights and patient history help the dietitian establish short-term and long-term goals appropriate for the patient and specific risk factors.
- *Blood pressure (BP) management*: Resting, orthostatic and exercise BPs are routinely and regularly obtained in cardiac rehabilitation programs. Weight management, sodium restriction when indicated, other dietary interventions, and exercise all work to lower the BP. Optimal blood pressure is accomplished through these lifestyle changes, in conjunction with interaction with the physician for optimal medical therapy.
- *Lipid management*: Dietary counseling aimed at specific lipid and/or blood glucose abnormalities are provided, followed and coordinated with the patient's physician. This allows the patient to reach lipid goals with lifestyle alteration and medical management.
- *Diabetes management*: Diabetes mellitus is an independent risk factor for cardiovascular disease. Management of the diabetic patient in terms of exercise and diet are imperative for secondary prevention. Self-monitoring skills are taught as well as practiced and take on special significance for the insulin-dependent patient on a diet and exercise regimen. For example, patients are taught how to recognize hypoglycemia and ways to avoid this during exercise. In addition, they are taught ideal blood sugar control based on individual pathology, exercise intensity, body weight loss and medications.
- *Tobacco cessation*: Current smoking, smokeless tobacco and secondhand smoke are addressed with appropriate cessation interventions. Relapse prevention is taught and patient follow-up is implemented.
- *Psychosocial intervention*: Depression and hostility, common in patients with MI, have been shown to increase the risk of coronary heart disease as well as impede recovery. Participation in Phase II cardiac rehabilitation has been shown to markedly improve these profiles[129] through counseling and exercise. Compared with older (mean ± SD age 75 ± 3 years) patients, young (mean ± SD age, 48 ± 6 years) patients have been shown to have higher scores for anxiety and hostility and slightly more depression symptoms. Following phase II cardiac rehabilitation, younger patients have shown markedly improved scores for depression, anxiety and hostility.[130] At the University of Iowa CHAMPS, the 9-Symptom Checklist is used to assess depression on admission and discharge. From July 2000 through November 2010, 1,170 patients took the admission 9-Symptom Checklist for a mean score of 6.53. The 701 patients took the test at the time of discharge with a mean score of 3.48. Patients with scores of 6 or more, which may indicate other

*Based on data compiled at the University of Iowa CHAMPS Phase II cardiac rehabilitation from 2000 to 2010, n = 1,123)
†Matched pairs analysis of 704 consecutive patients who finished Phase II cardiac rehabilitation from 2000 to 2010 showed a mean difference of 2.84 METs from first test (mean 5.28 METs) to final test (mean 8.12 METs)

depressive syndrome, who took the admission and discharge assessment (n = 283) demonstrated significant improvement with a mean admission score of 10.71 to a mean discharge score of 5.75. It is important to note that this occurred without the use of antidepressant medications.

After completion of Phase II cardiac rehabilitation, patients are urged to enter maintenance programs, also known as Phases III and IV, for long-term risk factor modification. These programs are typically not covered by insurance and have less staff supervision. The ECG monitoring is not done routinely, and the staff to patient ratio is higher than in Phase II.

Advantages of Cardic Rehabilitation

Meta-analyses of randomized controlled trials of exercise-based rehabilitation for patients with coronary heart disease have confirmed numerous benefits. Compared with usual care, cardiac rehabilitation was associated with a reduction of all-cause mortality [odds ratio (OR) = 0.80; 95% confidence interval (CI): 0.68–0.93] as well as cardiac mortality [OR = 0.74; 95% CI: 0.61–0.96]. In addition, lipids and smoking cessation were positively impacted with greater reductions in total cholesterol, triglycerides and reduction of systolic blood pressure (weighted mean difference, -3.2 mm Hg; 95% CI: -5.4 to -0.9 mm Hg).[131]

Patients age of 65 years and/or older benefit from a strong dose-response relationship between the number of sessions and positive long-term outcomes at 4 years. Those who completed 36 sessions had lower death and MI rates than those who completed fewer sessions.[132] Specifically, patients who attended 36 sessions had a 14%, 22%, and 47% lower risk of death compated to those who attended 24 sessions, 12 sessions and only 1 session, respectively.[132] The beneficial impact of cardiac rehabilitation on the incidence of new MI was also similar.[132] In addition, studies have demonstrated a clear cost-effectiveness ratio for cardiac rehabilitation programs for the post MI patient.[133-135]

Utilization of Cardiac Rehabilitation in the United States

With such impressive outcomes, the expectation is that participation in cardiac rehabilitation would be high. However, this is not the case. The use of cardiac rehabilitation is relatively low among Medicare beneficiaries. An analysis of 267,427 beneficiaries 65 years of age or older revealed that overall, cardiac rehabilitation was utilized by only 13.9% of patients hospitalized for AMI and 31% of patients who underwent coronary artery bypass graft surgery. The use of cardiac rehabilitation varied from 6.6% in Idaho to the highest rates of 53.5%, 48.9% and 46.5% in Nebraska, South Dakota, and Iowa respectively with the highest rates clustered in the northern central states of the United States.[136]

At University of Iowa, cardiac rehabilitation is a standing order following MI, PCI, CABG, and valve surgery. Since its inception in 1990, the program has enjoyed among the highest referral and participation rates in the United States. The development of a culture of cardiac rehabilitation as an integral part of the cardiac patient's care, fosters these high referral and participation rates. It is clear that hospitals and physician practices should embrace the "culture of cardiac rehab" to best serve their cardiac patients.

With decreases in mortality, morbidity and cardiac risk factors enjoyed by patients who complete cardiac rehabilitation, analyses suggest that greater utilization of cardiac rehabilitation in the United States would be highly cost-effective.[137,138] It has been proposed that referral to and completion of cardiac rehabilitation be included as a quality indicator for organizations such as the ACC, the AHA, the Agency for Health Care Research and Quality, the National Committee for Quality Assurance and the Joint Commission on Accreditation of Health Care Organizations as a way to increase the use of cardiac rehabilitation.[136]

Predischarge Education

Education must occur before discharge regarding importance of recurrence of symptoms, diet, exercise, smoking cessation, medication compliance and continuing cardiac rehabilitation as an outpatient. The patient must have a follow-up appointment scheduled prior to discharge. The timing of this appointment depends on the medical stability of the patient and can vary 1–6 weeks after discharge. The patient should clearly understand how to contact someone in the healthcare team (who will continue long-term follow-up with the patient) if there are questions, concerns or symptoms after discharge.

The physician should understand that the patient will have many questions regarding resumption of normal daily activity after ACS. In the patient with an uncomplicated course, activities of daily living (showering, dressing, normal walking, etc.) should be resumed immediately dictated by symptoms. Driving can be resumed within 1 week, with this limitation being predominantly related to concern for complications from femoral access for PCI.

Returning to normal sexual activity is anxiety provoking for the patient and should be discussed prior to discharge. This is, of course, a topic that the patient may not be comfortable bringing to the attention of the physician. Therefore, it should be normal practice for the physician, nurse and/or rehab specialist to discuss prior to discharge. Sexual activity may resume within 1–2 weeks after discharge in a symptoms limited approach, or be addressed during the early course of phase II CR in the patient with concerns or with decreased functional capacity.

Return to work is a decision to be made by the treating physician (in consultation with the patient's cardiac rehabilitation specialist) and should be based on the overall clinical status of the patient (lack symptoms of ischemia, heart failure or dysrhythmia), the patient's premorbid functional status and the physical nature of the patient's job. It is reasonable to consider return to work within 2 weeks in the low-risk post MI patient (age < 70 years old, normal EF and optimal revascularization),[139] specifically those who are able to exercise to more than 7 METs on a symptom limited exercise treadmill test.[140] This study also suggested that patients with an EF less than 40% who were able to exercise to 7 METs without symptoms or ECG changes, and did not have any evidence of electrical instability could return to normal activities, including work at 2 weeks.[140]

This time frame also allows for the patients to begin cardiac rehabilitation in order to assess their overall function status and

anginal symptoms with activity. In the patients who are at low risk and have a sedentary and low stress job, it may be reasonable to return to work after the first rehabilitation session. In a patient with a high physical workload, or high stress job, one should consider longer convalescence, focused education regarding stress reduction, and a "back to work evaluation" that is tailored to the patient's myocardial work demands (lifting, etc.). Data suggests that older age, manual labor jobs, unmarried status (poor social network) and the presence of anxiety and depression, but not necessarily the severity of the event, may increase the likelihood of a patient not returning to work after MI.[141,142]

SUMMARY

In summary, STEMI is a life-threatening event and a true medical emergency. It is important that physicians and patients alike recognize that time is muscle. Patients should be educated regarding symptoms, and the necessity to utilize the emergency medical transport system (911), if they have accelerated or rest symptoms that are consistent with an MI. At the time of arrival, the team must be prepared to rapidly evaluate the patient and make quick decisions regarding reperfusion. Protocols should be in place, and routinely reviewed, as this is an area of medicine where we as clinicians can make a great difference in the outcome of these patients. One must remain vigilant to recognize and manage complications especially with an acute change in patient's clinical status. Risk factors for recurrence of future cardiovascular events must be recognized during hospitalization and every effort should be made towards ameliorating that risk. Recommendations should include lifestyle modification (diet, physical activity, smoking cessation), and medications to treat hypertension, hyperlipidemia, diabetes as well as the sequelae of the current insult (heart failure). Finally, we must prepare our patients to adapt to this changing event. Cardiac rehabilitation program is an important multi-disciplinary intervention focused on exercise training, and lifestyle modification that can have a significant impact in returning patients back to a normal life and positively impact their outcomes.

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Chapter 50

Management of Patients with Chronic Coronary Artery Disease and Stable Angina

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Chapter Outline

- Current Therapeutic Approaches for Stable Angina
- Antianginal Drug Therapy
  - Nitrates
  - Beta-blockers
  - Calcium Channel Blockers
- Newer Antianginal Drugs
  - Ranolazine
  - Ivabradine
- Combination Therapy
- Other Drugs in Patients with Stable Angina and Chronic CAD
  - Angiotensin Converting Enzyme Inhibitors
  - Lipid Lowering Therapy
- Role of Myocardial Revascularization
- Comparison of Revascularization with Pharmacological Antianginal Therapy
- Medical Therapy versus Percutaneous Revascularization or Strategies Comparing Invasive versus Optimal Medical Therapy
- Guidelines

INTRODUCTION

Ischemic heart disease (IHD), usually due to underling coronary artery disease (CAD), remains the leading cause of mortality in the United States and in developed countries.[1,2] In many patients with IHD, stable angina seems to be the initial clinical manifestation. Additionally, many patients who survive a nonfatal acute coronary syndrome (ACS), such as unstable angina or an acute myocardial infarction (MI), go onto experience anginal symptoms after such an acute event.[3] It can be estimated that there are 30 cases of stable angina for every patient with MI who is hospitalized.[1] This estimate, however, does not include patients who do not seek medical attention for their chest pain or whose chest pain has a noncardiac cause. Overall, it is estimated that more than 10 million Americans suffer from stable angina. Stable angina is important not only because of its high prevalence, but also because of its associated morbidity and mortality.

In many patients, anginal symptoms could be disabling and frightening, and present a challenge for the clinician on a frequent basis. Effective treatment for symptom control in patients with chronic stable angina is an essential therapeutic goal to improve quality of life and clinical outcomes. Angina occurs, whenever there is myocardial ischemia due to an imbalance between myocardial perfusion and myocardial oxygen demand. In most patients myocardial ischemia occurs due to a flow limiting coronary stenotic lesion secondary to atherosclerotic process. However, it is important to recognize that although the high grade stenotic lesions are responsible for the impaired coronary blood flow, it is the less stenotic (< 50% stenosis), so-called, "vulnerable" plaques that seem to be responsible for most cases of ACS. Therefore, the treatment of patients with chronic stable angina should not only aim at relief of symptoms by correcting the imbalance between myocardial oxygen demand and supply, but it should also be directed towards stabilization of the vulnerable plaque to reduce the risk of future coronary events.

There two major goals of therapy in patients with chronic stable angina: relief of symptoms and reduction in cardiac morbidity and mortality. There are multiple medical and revascularization modalities available for treatment of anginal symptoms, however, recent data suggest that current therapies are not universally effective in controlling symptoms and most do not reduce cardiovascular events. For example, studies have shown that despite optimal revascularization many patients continue to experience anginal symptoms and as many as two-thirds of the patients might require one or more antianginal drugs.[1,3] It is also known that persistence of symptoms in patients with stable angina is associated with impaired quality of life.[4] Additionally, despite a strong push for routine revascularization in most patients with stable angina, there is little evidence that such strategy improves survival in patients with stable CAD.

CURRENT THERAPEUTIC APPROACHES FOR STABLE ANGINA

There are multiple therapeutic modalities currently available for treatment of anginal symptoms in patients with stable CAD. These include antianginal drugs and myocardial revascularization procedures. Until recently, the antianginal drug therapy primarily consisted of nitrates, beta-blockers and calcium channel blockers (CCB). Although antianginal drug therapy is effective in most patients, it is not infrequent that many patients

are subjected to percutaneous or surgical revascularization. In the following section, we will discuss currently available treatment modalities for stable angina, and examine their effectiveness in controlling symptoms as well as their impact on cardiovascular outcomes.

ANTIANGINAL DRUG THERAPY

Several antianginal agents primarily nitrates, beta-blockers and CCB (Table 1) have been used in the management of symptoms in patients with chronic CAD and stable angina pectoris.[1,2,5-7] Although these drugs have been found to be effective antianginal agents, there is lack of data on the effect of such therapies on clinical outcomes including MI and death in patients with chronic CAD and stable angina.[1,5,6] Despite the popularity of nitrates and beta-blockers in patient with angina, these drugs have not been evaluated in prospective randomized clinical trials regarding their impact on hard clinical end points such as myocardial infarction and cardiac death.

NITRATES

Nitrates exert their beneficial effects primarily by venodilatation resulting in venous pooling of blood, which reduces ventricular volume and cardiac work and chamber size (Table 1). Nitrates are also systemic as well as coronary arterial vasodilators; however, to what extent these effects account for their antianginal efficacy is not well established (except in patients with coronary artery spasm). It is well established that sublingual nitroglycerine is the most effective therapy for relief of anginal symptoms and all patients with anginal symptoms should be given sublingual nitroglycerin. The long acting nitrates are often prescribed as prophylactic antianginal drugs and are particularly effective in patients who are nitrate responders. However, because of the problem of nitrate tolerance during long term therapy, it is essential to use eccentric dosing scheme which provides a minimum of 10–12 hours nitrate free interval.[1,5,6] Although effective in symptom control, nitrate therapy has not been evaluated regarding impact on cardiovascular outcomes. Some of the important side effects/limitations of nitrates and other antianginal drugs in the treatment of stable angina are shown in Table 2.

BETA-BLOCKERS

Beta-blockers have been found to be effective antianginal therapy by increasing exercise tolerance and decreasing the frequency and severity of anginal episodes.[1,2,5,6,8] Beta-blockers exert their effects through a reduction in myocardial oxygen demand which includes a decrease in ventricular inotropy, decreased heart rate and a decrease in the maximal velocity of myocardial fiber shortening. Therapy with beta-blockers has been associated with a reduced risk of death (sudden and non-sudden) and reduced risk of MI in patients who survived an acute MI. However, it is not known whether similar benefit would occur in stable angina patients without prior MI.

TABLE 1

Pharmacologic actions of antianginal drugs

Class	*Heart rate*	*Arterial pressure*	*Venous return*	*Myocardial contractility*	*Coronary flow*
β-blockers	↓	↓	↔	↓	↔
DHP CCB	↑*	↓	↔	↓	↑
Non-DHP CCB	↓	↓	↔	↓	↑
Long acting nitrates	↑/↔	↓	↓	↔	↑
Ranolazine†	↔	↔	↔	↔	↔

*Except amlodipine
†Late Na + channel blocker
(Abbreviations: ↓: Decrease, ↔: No effect; ↑: Increase

TABLE 2

Side effects, precautions and contraindications of antianginal drugs

	Beta-blockers	*Nitrates*	*Calcium channel blockers*	*Ranolazine*
Side effects	• Hypotension • Syncope • Sexual dysfunction • Fatigue • Depression	• Hypotension • Syncope • Headache • Tolerance	• Hypotension • Flushing • Dizziness • Edema • Fatigue	• Dizziness • Headache • Constipation • Nausea
Precautions/ contraindications	• Bradycardia • AV conduction problems • Sick sinus syndrome • Peripheral vascular disease • COPD	• Left ventricular outflow tract obstruction • Erectile dysfunction (concomitant use of PDE5 inhibitors)	• Bradycardia • AV conduction problems • Sick sinus syndrome • Heart failure • LV dysfunction	• Use with QT prolonging drugs • Significant liver disease • Contraindicated with strong CYP3A4 inhibitors (ketoconazole, clarithromycin, or nelfinavir) and CYP3A inducers (rifampin, phenobarb)

Although no prospective, randomized controlled trial (RCT) has evaluated the effect of therapy with beta-blocker(s) on clinical outcomes in patients with chronic CAD and stable angina, there is limited data available regarding the impact of beta-blocker therapy on clinical outcomes in asymptomatic, or minimally symptomatic patients with CAD. The atenolol silent ischemia study (ASIST)[9] evaluated the effects of atenolol on clinical outcomes and ischemia during daily life in patients with documented CAD who were asymptomatic, or minimally symptomatic [Canadian cardiac society classification (CCS) class I or II). Compared to placebo, treatment with atenolol was associated with a significantly lower risk (11.1% vs 25.3%, respectively) of the primary combined end point that included death, resuscitation from ventricular tachycardia/fibrillation (VT/VF), nonfatal MI, hospitalization for unstable angina, aggravation of angina requiring known antianginal therapy, or need for myocardial revascularization during the follow-up period of 12 months. There was no difference between the treatment groups on the incidence of individual hard end points such as death and nonfatal MI most likely due to a lack of power to identify significant differences. Table 2 illustrates some of the limitations/side effects of beta-blocker therapy in the treatment of stable angina.

CALCIUM CHANNEL BLOCKERS

Calcium channel blockers (CCB) are potent coronary and systemic arterial vasodilators, and these agents reduce blood pressure as well as cardiac contractility. CCBs have been shown to increase coronary blood flow and are highly effective antianginal agents in patients with coronary artery spasm. CCBs have become popular in treatment of patients with angina primarily because of the relatively lower incidence of side effects. However, like other antianginal drugs, their impact on cardiovascular outcomes in patients with stable CAD and angina has not been systematically evaluated in RCT. There is limited information available from the "a coronary disease trial investigating outcome with nifedipine gastrointestinal therapeutic system" (ACTION) study,[10] which evaluated the effects of the long acting CCB nifedipine (nifedipine GITS) on the combined end point defined as death, acute MI, refractory angina, congestive heart failure, nonfatal stroke, or need for peripheral arterial revascularization in patients with stable symptomatic CAD. Compared to placebo, therapy with nifedipine GITS was associated with similar rates of the combined primary end point, as well as the individual end points of death, MI and stroke. Therapy with nifedipine GITS was associated with a small, but statistically significant, reduction in the "softer" end points of need for coronary angiography and need for coronary artery bypass graft surgery (CABGS). The important side effects and limitation of CCB are shown in Table 2.

NEWER ANTIANGINAL DRUGS

Although there has been lack of development of newer antianginal drugs during the past 25 years, recently several new drugs with unique mechanism of action have been introduced for treatment of patients with stable angina. In the following section, we will discuss two of these agents that have recently become available or about to become available to the clinician for the treatment of patients with stable angina.

RANOLAZINE

Ranolazine is the newest drug recently approved by the Food and Drug Administration (FDA) for use in the initial or supplementary treatment of patient with chronic angina.[11,12] Although the precise mechanism of ranolazine is not established, it is thought to be related to selective late sodium channel blockade. The findings from clinical trials that have evaluated ranolazine suggest that its antianginal effect is different than that of currently available conventional antianginal medications, as it is neither a coronary vasodilator, nor it is associated with reduction in hemodynamic parameters (e.g. heart rate, blood pressure, preload and inotropy) (Table 1).[13-15]

Several clinical trials have evaluated the antianginal efficacy of ranolazine in patients with confirmed diagnosis of CAD and inducible ischemia on treadmill exercise test. These trials have demonstrated that ranolazine used either as monotherapy, or as an add-on therapy to traditional antianginal drugs, including beta-blocker, CCB or nitrates, improves not only anginal symptoms, but also associated with improved performance during exercise testing. Based on the results of these trials ranolazine was initially approved for clinical use only in patients who had persistent anginal symptoms despite use of traditional antianginal drugs. This limited indication was primarily due to the concern about its safety related to the prolongation of the QT interval. However, this limited indication has now been expanded to unrestricted use of ranolazine in all patients with stable angina. This was possible primarily because of the safety of ranolazine demonstrated in a large cohort of high risk patients with ACS enrolled in the metabolic efficiency with ranolazine for less ischemia in non-ST-elevation acute coronary syndromes (MERLIN)-TIMI 36 study.[11,12]

The MERLIN trial also provided additional data regarding the antianginal efficacy of ranolazine. In the analysis of the pre-specified group of patients with history of chronic angina before an ACS,[12] in the MERLIN-TIMI 36 study, the long term effects of ranolazine on modification of antianginal therapy as well as improvement in the exercise duration during a stress test performed at the 8 months follow-up period was evaluated. Compared to patients on placebo, treatment with ranolazine was associated with: a significant improvement in anginal symptoms, need for additional antianginal drugs and longer exercise duration. Additionally, in this cohort of patients with prior history of angina, ranolazine was associated with a significantly lower risk of the primary combined end point at the 1 month follow-up (23.3% vs 19.8%, respectively P = 0.039) and at 12 months (29.4% vs 25.2%, respectively P = 0.017). This risk reduction was primarily due to a reduction in the rate of recurrent ischemia at 1 month (17.2% vs 13.7%, respectively P = 0.015) and at 12 months (21.1% vs 16.5%, respectively P = 0.002). However, at 12 months treatment with ranolazine did not significantly reduce the risk of CV death or MI (12.5% vs 11.9%, respectively).[11,12]

The findings from the available studies indicate that ranolazine is a safe and well tolerated antianginal medication. Ranolazine is effective in patients who continue to experience angina despite optimized treatment with other conventional antianginal agents. Ranolazine can also be safely used in patients with compromised hemodynamic parameters (e.g. baseline bradycardia and/or risk of developing significant hypotension). Furthermore, ranolazine can be used safely in patients with

diabetes, COPD, LV dysfunction/heart failure and in those patients requiring Phosphodiesterase-5 inhibitor such as Sildenafil. Compared to other antianginal drugs, ranolazine has fewer side effects (Table 2).

IVABRADINE

Ivabradine is a newer drug that has been evaluated in patients with chronic CAD and stable angina (BEAUTIFUL. Lancet. 2008;372(9641):807-16). Ivabradine is a specific inhibitor of the I-f channels in the sinoatrial node. As a result, it is considered a pure heart rate lowering agent in patients with sinus rhythm. Ivabradine does not seem to have an effect on blood pressure, myocardial inotropy, intracardiac conduction, or ventricular repolarization (BEAUTIFUL. Lancet. 2008;372(9641):807-16). Ivabradine is an agent that seems effective in reducing myocardial ischemia, and in controlling symptoms in patients with chronic stable angina pectoris who are in sinus rhythm primarily by reducing heart rate. There have been several clinical trials that have evaluated the role of ivabradine as monotherapy, as well as an add-on therapy, and have shown its effectiveness in controlling anginal symptoms as well as increasing the exercise performance. In addition, the data from a large randomized clinical trial in patients with stable CAD and LV systolic dysfunction showed that treatment with ivabradine was associated with reduced incidence of CAD related outcomes in the subgroup of patients with resting heart rate 70 bpm or greater.[16]

COMBINATION THERAPY

Combination therapy is often necessary for adequate symptom control in many patients with stable angina. It is important to realize that the best combination therapy is the one that provides maximum symptoms relief with relatively few adverse effects. In general, combination therapy should utilize a beta-blocker with nitrate, or CCB based on patient's underlying comorbid conditions. Such combination may allow the clinician to use lower doses of each agent to achieve symptom control with minimal side effects. Additionally, several studies have shown effectiveness of ranolazine when added to standard therapy with beta-blockers, CCB and nitrates. Ranolazine has been particularly found to be quite useful in patients who remain symptomatic despite optimal doses of older established antianginal drugs. However, there has not been a systematic evaluation of combination therapy on hard clinical end points in patients with stable angina.

OTHER DRUGS IN PATIENTS WITH STABLE ANGINA AND CHRONIC CAD

ANGIOTENSIN CONVERTING ENZYME INHIBITORS

Because of the well demonstrated vasculoprotective effects of angiotensin converting enzyme inhibitors (ACEI), two recent studies evaluated their effects in patients with stable CAD or diabetes, and at least one other cardiovascular factor.[17,18] The heart outcomes prevention evaluation (HOPE) trial[17] evaluated the effect of ramipril 10 mg daily in a high risk population characterized by patients with history of CAD, stroke, peripheral vascular disease, or diabetes, and at least one other cardiovascular risk factor (hypertension, elevated total cholesterol levels, low high-density lipoprotein cholesterol levels, cigarette smoking or documented microalbuminuria). These patients had no prior history of heart failure and had no evidence of depressed LV systolic function. Compared to placebo, treatment with the ACEI was associated with a significantly lower absolute risk (17.8% vs 14%, respectively) of experiencing the composite end point (MI, stroke or CV death) as well as a significantly lower risk of each individual end point.[17] Secondary end points were death from any cause, admission to hospital for congestive heart failure, or unstable angina, complications related to diabetes and cardiovascular revascularization.[17] Compared to placebo, the ramipril arm underwent significantly fewer cardiovascular revascularizations (18.3% vs 16%, P = 0.002) and experienced fewer complications related to diabetes (7.6% vs 6.4%, P = 0.03). The incidence of other secondary end points was similar between the groups.

The European trial on reduction of cardiac events with perindopril in stable coronary artery disease (EUROPA) study[18] evaluated the effect of another ACEI, perindopril, on clinical outcomes in patients with stable CAD and angina. In this study, compared to placebo, the therapy with perindopril resulted in a relatively small but significantly lower risk (9.9% vs 8%, respectively) of the composite end point (NFMI, CV death, or resuscitated arrest). Of the individual end points only the risk of NFMI was significantly lower during therapy with perindopril.

A meta-analysis of six studies,[19] including the HOPE and the EUROPA, evaluated the effect of ACEI therapy in patients with CAD, and preserved LV systolic function. The findings from this meta-analysis revealed that, compared to placebo, therapy with an ACEI was associated with a modest, statistically significant favorable effect resulting in reduced rates of CV death, all cause mortality and nonfatal MI.

Based on the findings of these two trials and the findings of the recent meta-analysis, an ACEI should be considered in stable patients who are considered to be at high risk of cardiovascular events, and in patients with stable CAD and angina pectoris.

LIPID LOWERING THERAPY

A number of studies during the last two decades have shown that lipid lowering therapy with statins not only reduces the risk of major acute coronary events (MACE) but it also reduces the need for revascularization as well as decreases the signs and symptoms of myocardial ischemia in patients with angina pectoris.[20-24]

The atorvastatin versus revascularization treatment (AVERT)[22] trial was a randomized study that evaluated the impact of lipid lowering therapy on outcomes in patients, with stable CAD and angina, who received atorvastatin and compared them to patients who underwent percutaneous myocardial revascularization with or without stent implantation. Treatment with atorvastatin 80 mg daily was associated with a lower risk of the primary composite end point defined as at least one of the following: death from cardiac causes, resuscitation after cardiac arrest, nonfatal MI, cerebrovascular accident, CABGS, angioplasty, and worsening angina with objective evidence resulting in hospitalization. There was no difference between the treatment groups in rates of cardiac death, nonfatal MI, or

need for CABGS. It is important to note that, as expected, treatment with percutaneous coronary angioplasty (PTCA) was associated with significantly greater improvement in the severity of anginal symptoms as assessed by CCS. The quality of the AVERT study was not as robust compared to the previous trials, since it was conducted in an unmasked manner and was unclear if randomization was concealed.

Recently, several clinical trials have specifically evaluated the role of lipid lowering therapy with a statin as anti-ischemic therapy in patients with stable CAD. The Scandinavian simvastatin survival study (4S)[25] is one of the earlier studies that revealed the potential antianginal property of statin therapy. In this trial, 4444 patients with dyslipidemia and coronary heart disease (CHD) were randomized to receive treatment with placebo, or simvastatin during a period of 5.4 years. In a post hoc analysis, treatment with simvastatin, compared to placebo, was associated with a 26% reduction in new angina, or worsening angina, and a 37% reduction in the need to undergo revascularization. Furthermore, the simvastatin group treated with simvastatin, experienced a significant reduction in the risk of new or worsening intermittent claudication.

There is evidence from clinical assessment which suggests that the anti-ischemic efficacy of statins is comparable to that of the more established pharmacological antianginal medications. The double-blind atorvastatin amlodipine (DUAAL) trial [26] compared the anti-ischemic effects of atorvastatin with that of the CCB amlodipine. After treatment for 24 weeks, both treatments resulted in a similar significant reduction in myocardial ischemia detected during ambulatory electrocardiography (AECG) and exercise testing. The marked decrease in the frequency of angina and the use of nitroglycerin was seen during treatment with amlodipine, which was equivalent to the effect seen during the treatment with atorvastatin. These findings lead to the conclusion that atorvastatin was a similar antianginal agent as amlodipine.[26]

In addition, there is evidence in the medical literature showing a favorable influence of statins on myocardial ischemia in patients with CHD. The vascular basis for the treatment of myocardial ischemia study[23] of patients with dyslipidemia, stable CHD and documented ischemia on stress testing or on AECG showed that 12 months of treatment with a statin using either intensive or moderate dosing strategies led to a significant reduction in the duration of ischemia and on the frequency of anginal episodes. Statin therapy also resulted in a significant improvement in exercise duration prior to onset of ischemia on the ECG.

Another major clinical trial, the study assessing goals in the elderly (SAGE)[27] compared intensive (atorvastatin 80 mg daily) to moderate (pravastatin 40 mg daily) statin therapy in nearly 900 patients with CHF and at least one documented episode of myocardial ischemia on AECG. After 1 year of follow-up, the trial demonstrated that statin therapy, using either intensive or moderate dosing strategies, was associated with a significant 37% reduction in the total duration of myocardial ischemia on AECG, a benefit that was evident as early as 3 months into the study. Similar to the findings in the Vascular Basis Study, there was no significant difference between treatment groups in the total duration of ischemia despite a greater cholesterol reduction in those who received intensive statin therapy[27]. However, a trend towards fewer occurrences of major adverse cardiac events was also seen in the intensive lipid-lowering arm. Remarkably, high-dose atorvastatin was associated with a significant 77% reduction in total mortality. These findings suggest that the magnitude of LDL lowering that seems effective in the stabilization of vulnerable plaque and in the reduction of adverse clinical events may show a continuous relationship. When taken in context of the clinical outcomes utilizing revascularization and aggressive drug evaluation (COURAGE) trial[28] the results of these studies suggest that treatment with a statin in patients with chronic stable angina not only reduces the risk of future coronary events, but such therapy also has the potential of reducing myocardial ischemia and the associated symptoms. Therefore, it is recommended that all patients with chronic, stable angina should be treated with a statin to a goal of reducing LDL-C less than 70 mg/dl.

ROLE OF MYOCARDIAL REVASCULARIZATION

Myocardial revascularization (revascularization) has been evaluated and compared to medical treatments in patients with chronic stable angina. Revascularization includes CABGS and PTCA with or without stent deployment [percutaneous revascularization (PCI)]. Although revascularization provides relief of anginal symptoms, it seems to abolish anginal episodes in a minority of patients. A significant proportion of patients will continue to experience anginal symptoms after revascularization. Furthermore, revascularization procedures are often performed in asymptomatic patients with the intent of reducing the incidence of coronary events and cardiac death in patients with stable CAD. However, little data exists to support such benefit.

COMPARISON OF REVASCULARIZATION WITH PHARMACOLOGICAL ANTIANGINAL THERAPY

During the past four decades several studies[28-52] have compared the impact of pharmacological antianginal therapy versus revascularization in patients with chronic CAD and stable angina. In general, the results of these studies have shown that revascularization is usually more effective in symptom control compared to the conventional antianginal drug therapy. However, it is important to note that since the earlier time when many of the previous trials were conducted, the medical therapy of patients with stable angina has improved considerably with the routine use of beta-blockers, antiplatelet agents, ACEI and lipid lowering therapy particularly with statins, and as such the result of those earlier trials might not be applicable and pertinent today. A number of recent trials using these drugs have shown that medical therapy may be as effective as revascularization in controlling symptoms and, when aggressive risk factor modification is implemented, such strategy is also effective in reducing the risk of future coronary events in patients with chronic CAD and stable angina.[29,51,52] In the following section we will first review the results of the earlier randomized clinical trials with myocardial revascularization and then discuss the recently completed trials that compared the contemporary medical therapy (including comprehensive and aggressive risk factor modification) with the state-of-the-art revascularization procedure in stable CAD patients.

Three of the earlier major randomized CABGS studies: the VA cooperative study of surgery for coronary arterial occlusive disease (VACSS),[29-35] the European coronary surgery study (ECSS),[36-41] and the National Heart, Lung, and Blood Institute coronary artery surgery study (CASS)[42-46] were conducted on patients with angina and stable CAD. The CASS trial also included a group of post MI asymptomatic patients.

In these initial CABGS trials, all randomized patients continued to receive medical measures as needed to assist with control of anginal symptoms. In the VACSS, ECSS, and CASS studies, structured antianginal therapies were not provided, dosages were not controlled, and medical treatment was provided according to individual clinical practice patterns, thereby making the comparisons between pharmacological therapy and revascularization less meaningful. The VACSS and CASS trials included short and long acting nitrates as well as propranolol as antianginal agents. In the ECSS antianginal therapy was left to the clinical judgment of the care provider. Also, in all three trials, management of coronary risk factors was suggested but not enforced.

Applying an intention-to-treat (ITT) analysis approach, the VACSS, ECSS and CASS trials revealed similar mortality rates between the patients randomized to undergo CABGS, and the patients randomized to receive pharmacological antianginal therapy.[32,37,44-46] Only the ECSS showed that during long term follow-up there was a small, but statistically significant improvement in mortality rate with CABGS compared to medical therapy at some points in time.[37] The rates of MI in these trials were similar between the patients who underwent CABGS, compared to patient who did not undergo CABGS.[35,41,43] Surprisingly, the VACSS study reported a small, but statistically significant, increase in the incidence of nonfatal MI among patients who underwent CABGS compared to patients randomized to receive medical therapy.[35]

Each of these trials identified, on post hoc analyses, high risk subgroups that include patients with left main coronary (LMC) artery involvement,[30,31] patients with three-vessel CAD[36] and impaired LV function,[30,31] patients with p-LAD greater than 75% stenosis as a part of two-vessel or three-vessel CAD,[36] and patients with three-vessel CAD and LVEF less than 50%.[42,43]

The first official report by the VACSS described outcomes on the relatively small (n = 113) subgroup of patients with involvement of the LMC.[30] Although compared to medical therapy, CABGS was associated with a significant lower mortality risk (29.3% vs 7.1%, respectively) by 36 months of follow-up the mortality difference between the two groups was not statistically significant. The loss of significance is likely related to the initial small size of the subgroup and to progressive reduction in the size of the subgroup due to mortality during follow-up. In a subsequent report,[33] patients were further sub-grouped into those with a LMC showing a 50–75% stenosis (n = 47) and those with a LMC stenosis greater than 75% (n = 44). The subgroup with a LMC showing a 50–75% stenosis revealed no difference in mortality between the CABGS and no CABGS arms. However, the sub-analysis of the 44 patients with a LMC showing greater than 75% stenosis revealed a statistically significant reduction (17% vs 52%, respectively) in mortality among CABGS patients compared to patients randomized to medical therapy. Based on the findings from these small subgroups,[30,33] a recommendation to offer CABGS was issued for patients receiving medical therapy. Subsequently, it became standard clinical practice to perform CABGS in patients with LMC showing greater than 50% stenosis. Since these results were published, no further attempts have been made to confirm, in a prospective randomized trial, the results of the VACSS in the subgroup of patients with involvement of the LMC. Interestingly, in the ECSS trial the post hoc analysis of the subgroup with LMC involvement revealed no difference in mortality between the CABGS and the no CABGS arms.[37]

In a different report, the VACSS evaluated another subgroup, this time without LMC involvement. This was the subgroup with three-vessel CAD plus impaired LV function.[35] In this angiographic high risk subgroup, compared to the medical therapy arm, CABGS improved survival up to 132 months of follow-up, after which this difference disappeared.

The ECSS evaluated the subgroups with two-vessel and three-vessel CAD.[36,38-40] In the subgroup with two-vessel CAD, there was no difference in mortality between the CABGS and medical therapy groups.[36,38-40] However, in the subgroup with three-vessel CAD, there was a statistically significant difference in survival favoring the CABGS group.[37] Further sub-analyses of the two-vessel CAD subgroup was carried out to separate the patients into those with either greater than or equal to 50% stenosis of the proximal LAD (p-LAD) and those without p-LAD involvement (< 50% stenosis) of the p-LAD.[39] This analysis revealed that in patients with two-vessel CAD plus p-LAD involvement CABGS, compared to medical therapy, was associated with a relatively small, but statistically significant, reduced mortality rate. When the sub-analysis was carried out with the p-LAD showing either greater than or equal to 75% stenosis, therapy with CABGS, compared to medical therapy, was associated with an even smaller, but statistically significant, improved survival.[41] Following these sub-analyses, the subgroup with p-LAD involvement (≥ 50% stenosis) and presence of two-vessel or three-vessel CAD was evaluated.[37] This sub-analysis revealed that CABGS, compared to medical therapy, was associated with a significantly lower mortality rate. Based of this sub-analysis,[37] patients with p-LAD involvement were identified as a high risk subgroup that appeared to derive benefit from therapy with CABGS.

In contrast, in the CASS trial, analysis of the subgroup with LAD involvement (≥ 70% stenosis in its proximal, mid, or distal sections) revealed no difference in mortality rates between patients randomized to undergo CABGS, and those randomized to medical therapy.[45] Additionally, in the CASS study CABGS compared to medical therapy was associated with improved survival in the subgroup with LVEF less than 50% as well as in the subgroup with LVEF less than 50% plus three-vessel involvement. In these two subgroups, the improved survival with CABGS became statistically significant at 84 months follow-up [44,45]. However, the analysis at 120 months in the subgroup with LVEF less than 50% plus three-vessel involvement, the survival benefit of CABGS was not significant anymore. Except for these findings, there was no difference in mortality between the treatment arms in patients sub-grouped by 1v, 2v or 3v involvement.[44,46] Based on these findings patients with LVEF less than 50% plus three-vessel involvement were identified as a high risk subgroup that appeared to benefit from therapy with CABGS.

Based on the angiographic profiles considered to confer higher risk to the various subgroups in the VACSS, ECSS and CASS studies, recommendations for treatment with CABGS were put into practice guidelines for patients with chronic CAD and stable angina who met a similar high risk angiographic criteria. Of the several subgroups identified by angiography as being at high risk, only the subgroup with p-LAD involvement was subsequently evaluated in a prospective manner in the medicine, angioplasty or surgery study (MASS-1).[47,48]

MEDICAL THERAPY VERSUS PERCUTANEOUS REVASCULARIZATION OR STRATEGIES COMPARING INVASIVE VERSUS OPTIMAL MEDICAL THERAPY

Several studies have evaluated the role of CABGS, PTCA/PCI, or medical treatment in patients with stable CAD. These include the asymptomatic cardiac ischemia pilot (ACIP),[31,32] the MASS trials,[47,48,51] the COURAGE trial[28] and the bypass angioplasty revascularization investigation 2 diabetes (BARI 2D) trial.[52]

The ACIP study[49,50] evaluated the effects of medical or revascularization (PTCA or CABGS) treatment strategies in patients with stable angiographic CAD (≥ 50% stenosis) with or without angina, myocardial ischemia on AECG, and evidence of ischemia on an exercise treadmill test or pharmaceutical stress perfusion study. In this complex, partly blinded study, the three treatment strategies were angina-guided medical therapy; angina-guided plus AECG ischemia-guided medical therapy; and myocardial revascularization of major coronary arteries. Use of one or more unblinded antianginal medication(s) for control of symptoms was necessary in 77%, 70% and 39% of the treatment arms respectively. The primary end point was complete suppression of ischemia on 48 hours AECG. Secondary clinical outcomes at 12 months included death, MI, cardiac arrest, unstable angina, sustained ventricular tachycardia and congestive heart failure. Compared to the medical therapy arms, myocardial revascularization was associated with a significantly greater proportion of patients free of ischemia on AECG. However, compared to the medical therapy arms, revascularization therapy was associated with a similar risk of MI or stroke. Compared to angina-guided medical therapy only, revascularization was associated with a significantly lower mortality rate (4.4% vs 0.0%, respectively). Although, mortality rates were similar between the two medical treatment arms and between the revascularization and angina-guided plus AECG-guided medical therapy (1.6%).[49,50]

The MASS trial compared the effect of these therapies in patients with proximal-LAD (MASS-1)[47,48] and in patients with multi-vessel CAD (MASS-2).[51] In the MASS trials, all patients were placed on an optimal medical regimen that included: nitrates, aspirin, beta-blockers, CCB, ACEI, or a combination of these drugs. In addition, a statin along with a low-fat diet was provided on an individual basis.[47,48,51]

In the prospective MASS-1 trial [47,48] in patients with p-LAD involvement (≥ 80% stenosis) compared to PTCA and medical therapy, CABGS was associated with a modest benefit on the combined outcome that consisted of cardiac death, MI, or angina requiring revascularization (the benefit was predominantly related to a reduced frequent need for subsequent revascularization).[47,48] It is important to note that compared to CABGS, medical therapy was associated with a similar reduction in the risk of hard events (mortality or MI). Treatment with PTCA appeared to be an inferior option compared to the other treatment strategies.

In the MASS-2 trial[51] of patients with stable multi-vessel CAD, there was no difference in mortality between the medical therapy, medical therapy plus PTCA, and medical therapy plus CABGS groups. The group treated with medical therapy plus CABGS had the best outcome for the primary end point that consisted of cardiac death, Q-wave MI, or anginal symptoms requiring revascularization. The group with medical therapy plus PTCA appeared to have the worse outcome due to increased risk of MI as well as higher mortality.

Only a few trials have carefully examined the strategy of initial angiography/revascularization versus medical therapy in patients with stable CAD and angina pectoris.[53-58] The trial of invasive versus medical therapy in elderly patients (TIME)[55,56] with chronic symptomatic coronary-artery disease was a prospective, randomized, multi-center study in patients aged 75 years or more with angina CCS class II or more despite treatment with either two or more antianginal drugs. This study compared the invasive strategy of left-heart catheterization followed by either PCI or CABGS, with a strategy of optimized medical therapy with aimed at increase in the number of antianginal drugs and their doses to reduce anginal pain as much as possible. Additionally, antiplatelet agents and lipid-lowering drugs were advised. Compared to optimum medical therapy, the invasive strategy was associated with a lower risk of admission for ACS that required revascularization. However, compared to optimum medical therapy, the invasive strategy was associated with a similar risk of the hard end point of death or MI.

The second randomized intervention treatment of angina (RITA-2) trial[57,58] was designed to compare the effects of initial strategies of coronary angioplasty or conservative (medical) care over a follow-up of 5 years or more. Compared to medical treatment for symptom relief, treatment with PTCA was associated with similar risk of the primary combined end point (death or definite MI) or secondary hard end point (death). The pattern of unstable angina was similar in both groups. Although both groups remained symptomatic, an early intervention with PTCA was associated with greater, albeit temporary, symptomatic improvement in angina.

The COURAGE trial compared the clinical efficacy of PCI plus optimal medical therapy (OMT) versus OMT alone in patients with stable CAD.[28] OMT consisted of therapy with a beta-blocker and, when needed, diltiazem and aggressive management of risk factors for CAD. During the median follow-up of 55 months the OMT and the OMT plus PCI groups had similar rates of the primary combined (death and nonfatal MI) outcome (18.5% vs 19.0%, respectively) (Fig. 1). As expected a significantly greater proportion of patients in the PCI group were angina-free at 12 months (57% vs 50%, respectively, P = 0.005), however, this benefit was lost at 3 years (59% vs 56%, respectively) (Fig. 2).[59]

The BARI 2D trial[52] in patients with diabetes, CAD, and classic angina compared the effects of prompt revascularization by discretionary CABGS or PCI to medical therapy alone on clinical outcomes. During the 5-year follow-up there was no difference between the medical therapy and revascularization

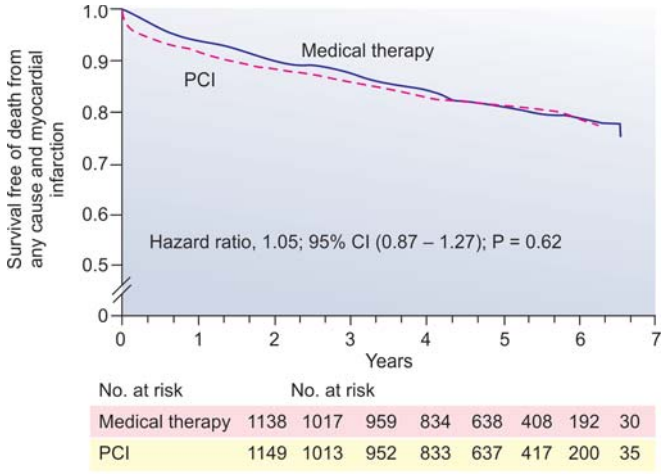


FIGURE 1: The estimated 4.6 year rate of the composite primary outcome of death from any cause and nonfatal myocardial infarction was 19.0% in the PCI group and 18.5% in the medical therapy group. (*Source:* Modified from reference 28, with permission)

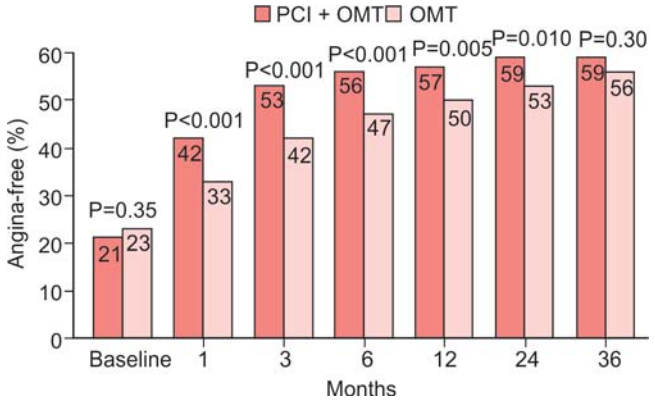
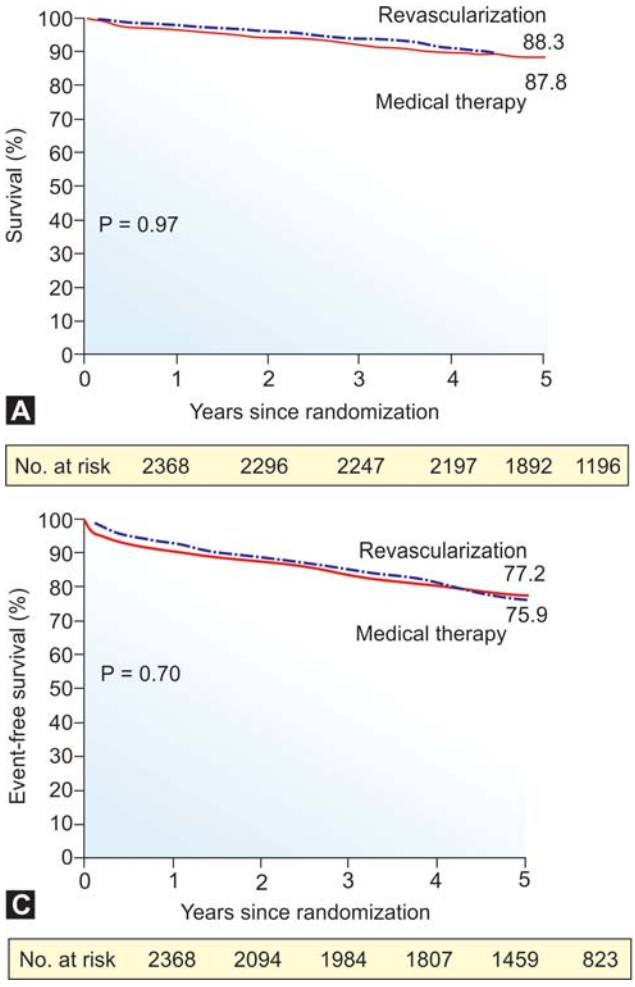
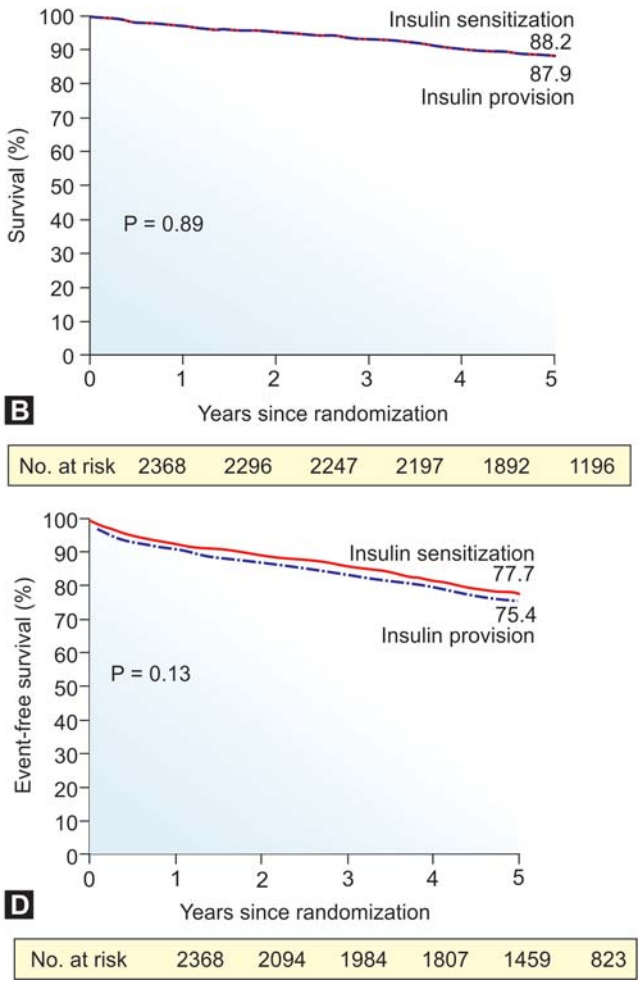


FIGURE 2: Freedom from angina over time as assessed with the angina-frequency scale of the Seattle angina questionnaire, according to treatment group. (Abbreviations: OMT: Optimal medical therapy; PCI: Percutaneous coronary intervention). (*Source:* Modified from reference 59, with perission)

groups on the risk (13.5% vs 13.2%, respectively) of the primary outcome (all cause-death), or the risk of MI (11.6% vs 10.0%, respectively), or the risk of stroke (2.8% vs 2.6%, respectively) (Figs 3A to D).

The above discussion of the early revascularization trials as well as the recent revascularization trials in patients with stable CAD have provided data that confirm the impression that, compared to medical treatment, revascularization has resulted





FIGURES 3A TO D: Rates of survival and freedom from major cardiovascular events. (A) There was no significant difference in rates of survival between the revascularization group and the medical therapy group and (B) between the insulin sensitization group and the insulin-provision group. (C) The rates of major cardiovascular events (death, myocardial infarction, or stroke) also did not differ significantly between the revascularization group and the medical therapy group or (D) between the insulin sensitization group and the insulin provision group. (*Source:* Modified from reference 52, with permission)

in similar rates of hard clinical outcomes in the main groups. The consistent benefit of revascularization, compared to medical treatment, appears to be a more striking, albeit temporary, improvement in anginal discomfort.

CONCLUSION

There are many therapeutic options available for the treatment of anginal symptoms in patients with stable CAD. These options include nitrates, beta-blockers, CCB, and ranolazine. Although combination therapy is often necessary for symptomatic relief, there has been no evaluation of the effects of combination antianginal therapy on hard clinical end points in such patients. Recent trials have shown that medical therapy is as effective as revascularization in controlling symptoms and, along with aggressive risk factor modification, is highly effective in reducing the risk of future coronary events. There is need for more definitive outcomes studies which examine the role of existing therapies (including aggressive and comprehensive risk factor modification), and newer antianginal agents with the state-of-the-art revascularization procedure in high risk patients with stable CAD and chronic angina.

GUIDELINES

ACC/AHA/ACP-ASIM GUIDELINES FOR THE MANAGEMENT OF PATIENTS WITH CHRONIC STABLE ANGINA: EXECUTIVE SUMMARY AND RECOMMENDATIONS CIRCULATION 1999; 99:2829-48

Kanu Chatterjee

Class I: Conditions for which there is evidence and /or general agreement that a given procedure or treatment is useful and effective.

Class II: Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment.

Class IIa: Weight of evidence/opinion is in favor of usefulness/efficacy.

Class IIb: Usefulness/efficacy is less well established by evidence/opinion.

Class III: Conditions for which there is evidence and/or general agreement that the procedure/treatment is not useful/effective and in some cases may be harmful.

Level of Evidence A: The presence of multiple randomized clinical trials.

Level of Evidence B: The presence of a single randomized trial or nonrandomized studies.

Level of Evidence C: Expert consensus.

RECOMMENDATIONS FOR PHARMACOTHERAPY TO PREVENT MI AND REDUCE SYMPTOMS

Class I

1. Aspirin in the absence of contraindications (Level of Evidence A).
2. Beta-blockers as initial therapy in absence of contraindications in patients with prior MI (Level of Evidence A).
3. Beta-blockers as initial therapy in absence of contraindications in patients without prior MI (Level of Evidence B).
4. Heart rate regulating calcium channel antagonists and/or long-acting nitrates as initial therapy when beta-blockers are contraindicated (Level of Evidence B).
5. Heart rate regulating calcium channel antagonists and/or long-acting nitrates in combination with beta-blockers when initial treatment with beta-blockers is not successful (Level of Evidence B).
6. Heart rate regulating calcium antagonists and/or long-acting nitrates as a substitute for beta-blockers if initial treatment with beta-blockers leads to unacceptable side effects (Level of Evidence C).
7. Sublingual nitroglycerin or nitroglycerin spray for the immediate relief of angina (Level of Evidence C).
8. Lipid-lowering therapy in patients with documented or suspected CAD and LDL cholesterol > 130 mg/dl with a target LDL of < 100 mg/dl (Level of Evidence A).

Class IIa

1. Clopidogrel when aspirin is absolutely contraindicated (Level of Evidence B).
2. Long-acting heart rate regulating calcium channel blocking agents instead of beta-blockers as initial therapy (Level of Evidence B).
3. Lipid-lowering therapy in patients with documented or suspected CAD and LDL cholesterol between 100 and 129 mg /dl, with a target of 100 mg/dl (Level of Evidence B).

Class IIb

1. Low-intensity anticoagulation with warfarin in addition to aspirin (Level of Evidence B).

Class III

1. Dipyridamole (Level of Evidence B).
2. Chelation therapy (Level of Evidence B).

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Chapter 51

Variant Angina

Reza Ardehali, John Speer Schroeder

Chapter Outline

- Incidence and Predisposing Risk Factors
- Pathophysiology
- Clinical Presentation
- Diagnosis
  - History and Physical Examination
  - Noninvasive Studies
  - Coronary Arteriography
  - Provocative Testing
- Differential Diagnosis
- Management
  - Medical Therapy
  - Surgical and Percutaneous Intervention
- Natural History and Prognosis

INTRODUCTION

The term "variant angina" was coined by Prinzmetal in 1959 when he and his co-workers published a description of three patients that varied from traditional exertional or Heberden's angina.[1,2] The prime "variant" features were typical of angina pectoris except that it occurred at rest or during sleep rather than during exertion and an electrocardiogram (ECG) during an episode of chest pain showed ST segment elevation suggestive of an acute myocardial infarction (MI) rather than ST segment depression. However, resolution of the pain by sublingual nitroglycerine spontaneously resulted in resolution of the abnormal ST segment elevation. The authors proposed that this syndrome was most likely due to temporary occlusion of a large diseased coronary artery, due to local spasm or an intermittent "increased tonus".

Previous observers have also commented on the possibility of spasm of coronary artery causing or contributing to the angina pectoris syndrome. Osler observed that angina pectoris was associated with changes in the arterial wall that were organic or functional.[3] Then, in 1941, Wilson and Johnston reported a patient with ST segment elevation in ECG leads II, III and AVF during spontaneous episodes of chest pain and observed that the attendant myocardial ischemia is due to a change in caliber of coronary arteries affected, rather than an increase in work of the heart.[4]

Variant angina pectoris was considered a relatively rare problem until the advent of coronary arteriography in the early 1970s, when it was observed that as many as 10% of patients with rest or unstable angina have a normal or relatively normal coronary arteriogram.[5] The initial work of Prinzmetal was supported by MacAlpin and his colleagues who reported angiographic findings in 20 patients of variant angina.[6] Subsequently, the introduction of a provocative test for Prinzmetal's angina allowed more precise definition, characterization and understanding of the syndrome.[7] Many of Prinzmetal's theories about the pathophysiology of variant angina have turned out to be remarkably perceptive.

This chapter focuses on variant angina rather than discuss the multiple angina syndrome in which coronary artery spasm may play a role, such as cardiac syndrome X, coronary microvascular disease, inherited thrombophilia or cocaine use.

INCIDENCE AND PREDISPOSING RISK FACTORS

Between 10% and 30% of patients who undergo coronary angiogram are found to have arteriographically normal coronary arteries.[8,9] Despite a normal angiogram, the presence of angina and ischemic ECG findings suggests a cardiac origin for chest pain. It is difficult to identify the precise incidence of variant angina, as different authorities have used different diagnostic tests and criteria to define it. There may also be racial variations in incidence. Large studies from France and North America have found an incidence of 12.3% and 4% positive ergonovine testing,[10,11] whereas a smaller Japanese group reported an incidence of 32.3% using intracoronary acetylcholine.[12] The variability in these reports highlights the differences between patient populations. Although no definitive risk factors have yet been identified, several studies have suggested a number of genetic and environmental risk factors that predispose people to coronary spasm and variant angina (Table 1).[13]

TABLE 1

Predisposing factors

• Racial predisposition
• Age and sex
• Cigarette smoking
• Insulin resistance
• Hormonal variation
• Classic coronary artery disease risk factors

PATHOPHYSIOLOGY

The original hypothesis by Prinzmetal and his colleagues that stated angina is induced by a transient increase in coronary vasomotor tone has been convincingly confirmed by angiographic studies. In contrast to exertion-induced angina pectoris in which the pain and myocardial ischemia reflect an inadequate increase in coronary blood flow through the diseased coronary vessel as myocardial work and oxygen demand increase, variant angina occurs due to a transient reduction in coronary flow. This reduction in flow due to a decrement in vessel diameter can be abrupt and transient causing myocardial ischemia angina symptoms. Although this etiology has been proposed for many years, and repeatedly demonstrated experimentally, the first patient with documented spontaneous coronary spasm during coronary arteriography was reported by Oliva and his co-workers in 1973.[14] Since that time, numerous investigators have observed and reported focal coronary artery spasm occurring either spontaneously or after provocation during coronary arteriography.[15,16] There is little doubt that this focal spasm is responsible for the reduction in coronary flow and causes transient transmural myocardial ischemia, resulting the chest pain or variant angina. The coronary spasm tends to be focal and frequently occurs at an area of atherosclerosis plaque or abnormality in the vessel. MacAlpin and his associates have reported that the focal spasm tends to occur in the same area on repeated occasions and in an area of atherosclerotic plaque during both spontaneous and provoked spasm.[17] The spasm can occur in any of the coronary arteries, although the right coronary artery and, to a lesser degree, the left anterior descending coronary artery are the ones most commonly involved. Patients with very severe coronary artery spasm have been observed to have spasm in more than one vessel or for the spasm to involve a greater length of the vessel. Incomplete occlusion of the vessel has been observed repeatedly. This may cause nontransmural myocardial ischemia in the area supplied by the vessel, resulting ST segment depression or even silent ischemia in these patients. It is believed, however, that this nontransmural ischemia is simply part of the spectrum of coronary artery spasm and that causes for occasionally incomplete spasm are the same as those for complete occlusion of a vessel.

Stress cardiomyopathy or takotsubo cardiomyopathy is a disorder associated with transient left ventricular dysfunction that occurs usually after a stressful event in patients who may or may not have atherosclerotic disease. Several studies have suggested that coronary vasospasm can lead to left ventricular wall-motion abnormalities resembling those in stress-cardiomyopathy.[18,19] It has been shown that substantially elevated plasma catecholamine levels is seen in stress cardiomyopathy.[20,21] This observation could be particularly relevant in inducing coronary vasospasm. However, whether there is a direct cause-effect relationship between coronary vasospasm and stress-cardiomyopathy remains unknown. Furthermore, global coronary vasospasm cannot explain the common variant of stress-cardiomyopathy, which mainly involves apical ballooning with basal sparing.

There are three questions regarding the pathophysiology of coronary artery spasm:

1. Why does the spasm tend to occur in a localized area of the vessel?
2. What initiates or precipitates the spasm?
3. What are the underlying molecular mechanisms?

First, the fact that spasm tends to occur in areas of abnormality or atherosclerotic plaques suggests a local hyperreactivity in the wall of the coronary artery. It has been observed that patients with variant angina tend to have recurrent episodes in the same location, suggesting that this is a local abnormality or hyperreactivity to some vasoconstrictive influence rather than to a generalized hyperreactivity or abnormality in the innervation or level of sympathetic tone of coronary vessels. Ginsburg and his co-workers have reported that in human coronary arteries, areas containing atherosclerotic plaques tend to be more reactive to some vasoconstrictive influences such as histamine in comparison to areas that are not involved with the atherosclerotic process.[22] These studies have been confirmed by other investigators and suggest that a local abnormality may be responsible for the spasm. In addition, it has been recognized that varying provocative agents can precipitate coronary artery spasm in an individual patient. This would suggest that it is not the agent but an abnormality in vasoreactivity in the area where the spasm occurs which is responsible for the spasm and the clinical symptoms.

Second, what are the precipitating causes of this focal spasm in an area of local increased vasoreactivity? Many hypotheses have been proposed including increased vagal tone during sleep. This hypothesis has been supported by the use of methacholine inducing coronary spasm in some reports.[23,24] However, the mechanism for the actual vasoconstrictor triggering of the focal spasm during this period is not understood. Other authors have proposed that the focal spasm occurs at times of increased vagal tone when there is unopposed withdrawal of sympathetic tone such as during sleep or after exercise. Other hypotheses have centered around the general or local release of vasoconstrictive substances such as thromboxane A_2 or sympathomimetic amines; however, these theories would not explain the focality of the spasm.

It is most likely that two circumstances are required to have typical variant angina. One is a local hyperreactivity of a segment of coronary artery, and the other is abnormal release or triggering of the vasoconstrictive influence.

CLINICAL PRESENTATION

The typical patient with variant angina reports recurrent episodes of angina pectoris that are typical in their character, distribution and responsiveness to nitroglycerine. They tend to be younger compared to those with classic stable or unstable angina secondary to atherosclerotic disease. The pain is substernal, with a tight, constricting pressure sensation in the chest that may radiate into the neck, jaw, teeth or inner aspect of the left and/or right arm. Occasionally, patients report the pain occurring predominantly in the jaw or arm with minimal or no chest pain. The pain typically awakens the patients at night or in the early morning hours and can be very severe. Other episodes may occur after arising in the early morning or at other times of the day during rest. In addition to the unprovoked episodes, approximately 50% of patients also report at least some

angina related to physical exertion or excitement, but these episodes may occur after cessation of the activity rather than at its peak. Although the circadian nature of the attacks usually remains similar for a given patient, the frequency and severity of the episodes tend to be highly variable and cyclical. Many patients report general worsening of their symptoms during periods of emotional stress in their lives.

The angina usually resolves spontaneously after a few minutes but may last much longer. Response to sublingual nitroglycerine tends to be excellent; in fact, the diagnosis should be questioned if there is not a rapid response to either oral or sublingual nitrates. Patients may complain of anxiety or shortness of breath during the angina if the pain is prolonged and causes transient left ventricular dysfunction and pulmonary venous congestion. In fact, transient left ventricular apical ballooning (LVAB) cardiomyopathy, which leads to severe myocardial dysfunction may occur in the presence of normal coronary arteries on angiography. A recent report demonstrated reproduction of LVAB and coronary spasm in the catheterization laboratory during acetylcholine testing.[25]

In addition to a careful history and characterization of the pain, one should look for other features of the variant angina syndrome and for manifestation of other vasospastic phenomena. Most patients present between ages of 35–50 years. There is a female predominance and a frequent smoking history, and most patients acknowledge stress or tension either in their personal life or job. There is frequently a history of migraine headache in the patient or his/her family. Complaints of Raynaud's phenomenon are common, and some patients simply complain that their hands and feet have been cold all of their lives.

A high index of suspicion for variant angina is important since these patients may themselves attribute their chest pains to nerves and unless the diagnosis of variant angina is being considered many of these patients are diagnosed as having psychogenic chest pain. The report that the chest pain awakens them from sleep is one of the most important clues that this is a medical problem rather than a psychological one.

DIAGNOSIS

HISTORY AND PHYSICAL EXAMINATION

The hallmark of a patient with variant angina is the history of spontaneous or unprovoked episodes of typical angina pectoris. At times when the patient is not having variant angina, examination is usually normal or unrelated to variant angina syndrome. During an episode of pain, the patient may manifest symptoms of pain, sweating, tachycardia or increased blood pressure in response to the pain. Ventricular arrhythmias are common. The patient with right coronary spasm may have varying degrees of atrioventricular (AV) block. More severe or prolonged episodes of myocardial ischemia may result in manifestations of left ventricular dysfunction, such as an S_3 or S_4 gallop rhythm, bibasilar rales or pulmonary congestion or a transient murmur of mitral insufficiency due to ischemic papillary muscle dysfunction. The diagnosis, however, although suspected on the basis of history and physical examination must be confirmed on the ECG and preferably during coronary arteriography.

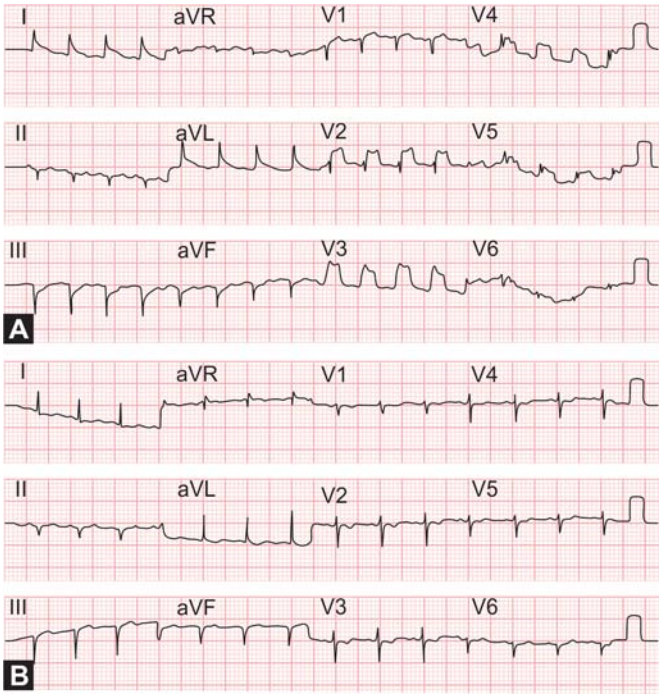
Laboratory Findings

It is not easy to distinguish variant angina from coronary artery disease due to atherosclerosis based on laboratory data. Since coronary spasms may cause transient occlusion of the vessel, prolonged episodes of myocardial ischemia may lead to release of cardiac biomarkers. Recent studies have demonstrated elevated levels of circulating inflammatory cells, including white blood cells (WBC) and monocytes, as well as high levels of plasma *C-reactive protein* (CRP) and *interleukin-6 (*IL-6) among patients with variant angina.[26,27]

NONINVASIVE STUDIES

ECG Studies

To establish the diagnosis of typical variant angina, it is essential to observe transient ST segment elevation on an ECG during an episode of spontaneous angina pectoris. The ECG abnormalities occur in the areas supplied by the artery that is undergoing coronary spasm and is transiently occluded. The ST segment elevation can be either minimal or at times very dramatic, nearly obscuring the QRS complex and appearing to be the initial ECG manifestation of an acute transmural MI (Figs 1A and B). However, the ST segment elevation resolves with the administration of sublingual nitroglycerin. It is not unusual to see ventricular arrhythmias or even ventricular tachycardia or complete heart block during an episode of severe coronary artery spasm. Since the episodes of pain tend to occur at night and spontaneously, it may be difficult to record an ECG during a severe episode of pain. There are several alternative approaches to this in order to establish a diagnosis.



FIGURES 1A AND B: Marked ST segment elevation in the anterior leads of a 12-lead ECG during angina caused by spasm of the left anterior descending artery induced by 0.1 mg ergonovine maleate (A) and after nitroglycerin (B). (*Source:* Modified from Schroeder JS (Ed). Invasive Cardiology. Philadelphia, FA Daving, 1984. pp. 83-96)

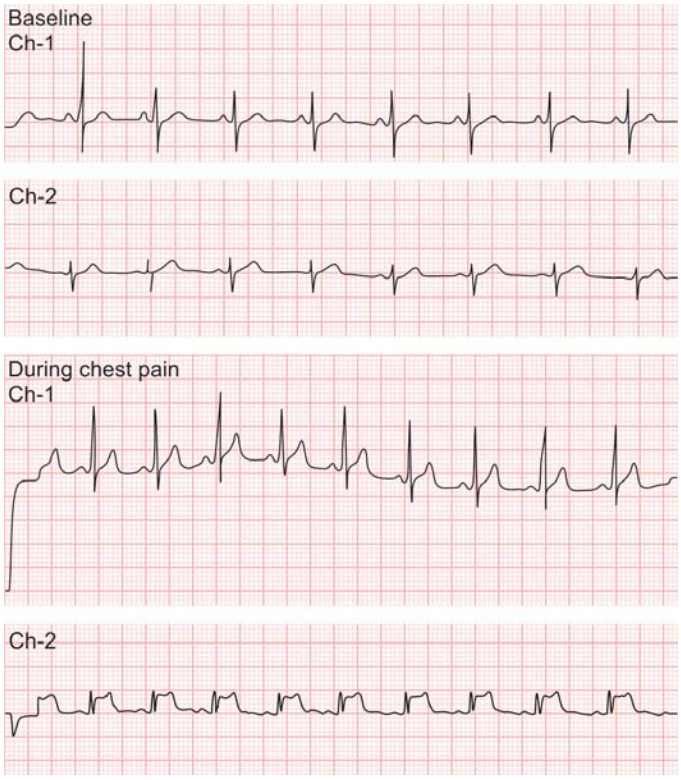


FIGURE 2: Two-channel ambulatory ECG recordings during pain-free period (upper panel) and during angina (lower panel). (*Source:* Modified from Schroeder JS (Ed). Invasive Cardiology. Philadelphia, FA Daving, 1984. pp. 83-96)

Ambulatory ECG Monitoring

If the patient is having frequent or daily episodes of chest pain, ambulatory ECG recordings may be effective in establishing the diagnosis. A two-channel recorder with sufficiently low frequency response to detect 0.1 mV changes is essential. By recording two channels, that is, one inferior and one anterior lead, ST segment elevation reflecting spasm of either the right or left anterior descending coronary artery may be observed (Fig. 2). In addition, patients who complain of syncope or palpitation may have arrhythmias or heart block documented during chest pain as well (Fig. 3).



FIGURE 3: Computer printout of Holter ECG recording showing transient second-degree heart block. (*Source:* Modified from Ginsburg R, Schroeder JS, Harrison DC. Coronary artery spasm: pathophysiology, clinical presentations diagnostic approaches and rational treatment. West J Med 1982;136:398)

At other times, patients may have minimal or no chest pain during the episode reflecting silent ischemia as detected on the ECG. In these patients there may be episodes of transient ST segment depression or even occasionally ST segment elevation that are brief and so do not come to clinical attention or result in complaints of angina. In order to establish a diagnosis of variant angina, it is preferable to have at least one episode of ST segment elevation in association with a complaint of or observed chest pain.

Self-Initiated Transtelephonic ECG Monitoring

Since many patients with angina have infrequent or unpredictable chest pain that is not suitable for diagnosis by ambulatory ECG monitoring, several studies have reported the use of transtelephonic transmission of an ECG during symptomatic chest pain.[28-30] Here, a transtelephonic device, such as cardiobeeper (Survival Technology) or cardiophone (Nihon Kohden), can be used to transmit one or two leads of an ECG during chest pain.[29,30] The episode can either be stored on certain units for subsequent transmission or be transmitted by telephone directly during chest pain and recorded for subsequent analysis. It is essential that a baseline transmission be taken for comparison owing to the highly variable nature of ST segment shifts. This system is quite helpful when it is positive, particularly if ST segment elevation is observed (Fig. 4). However, due to the single lead nature of the transmission system and the difficulty in ascertaining how severe the symptomatic episode of chest pain was, a negative test does not rule out a diagnosis of variant angina.

In-Hospital ECG Recording

Despite multiple attempts some patients elude establishment of a diagnosis of variant angina as outpatient because of the difficulty in obtaining a suitable ECG during chest pain. In these patients, it may be feasible to establish the diagnosis by hospitalizing the patient and attaching a 12-lead ECG to monitor the patient overnight. The patient can be instructed to push the record button if chest pain occurs in order to record a 12-lead ECG before nitroglycerine is administered or before the pain resolves spontaneously. This approach does not require support

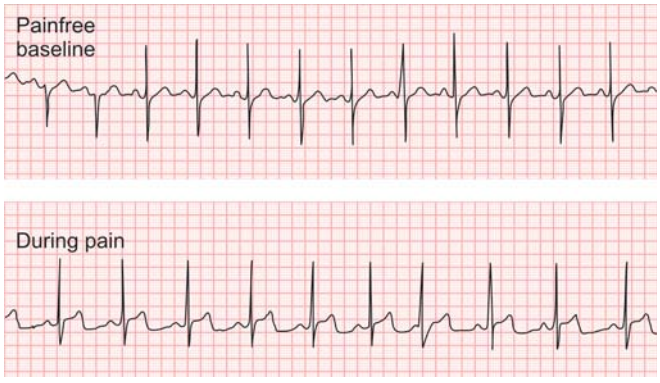


FIGURE 4: ST segment elevation compared with baseline, documented by transtelephonic ECG transmission during chest pain. (*Source:* Modified from Schroeder JS (Ed). Invasive Cardiology. Philadelphia, FA Daving, 1984. pp. 83-96)

from other medical personnel or the availability of a telephone, and it can be useful in the difficult-to-diagnose patient.

Treadmill Exercise Testing

Although the typical patient with variant angina who has relatively normal coronary arteries will have a negative treadmill exercise test and no exertional evidence of chest pain, there are several subgroups of patients who may have abnormalities during exercise testing. One group of patients may have coronary artery spasm that occurs shortly after cessation of exercise. The typical patient does very well during the treadmill test and has relatively normal exercise tolerance in the absence of any ST segment abnormalities. Once exercise has stopped, the onset of variant angina is noted within the first 5 minutes and at this time ST segment elevation is present. For this reason the ECG leads should be left on patient for at least 10 minutes post exercise. Another group of patients may have coronary artery spasm superimposed on a severely occlusive atherosclerotic lesion. These patients typically complain of effort-induced angina as well and can be identified by detecting either ST segment depression during low level exercise testing or poor exercise tolerance or even exercise-induced hypotension. It is essential that these patients who have ST segment depression plus a history of unprovoked and spontaneous angina undergo coronary arteriography to rule out severe proximal occlusive coronary artery disease.

Radionucleotide Scintigraphy

Several studies have demonstrated the utility of perfusion scintigraphy in detecting variant angina. Single-photon computed tomography (SPECT) and ^{123}I-β-methyl-*p*-iodophenyl pentadecanoic acid (BMIPP) and ^{123}I-metaiodobenzylguanidine (MIBG) scintigraphy have been used as non-invasive techniques to determine the presence and location of coronary spasm.[31,32] Furthermore, ^{13}N-ammonia positron emission tomography (PET) is an accurate method for myocardial blood flow quantification and presence of microvasculature defect.[33] Clinical utility of these tests need to be confirmed by larger studies.

CORONARY ARTERIOGRAPHY

Since unprovoked angina may be the first manifestation of unstable angina reflecting an extremely severe proximal coronary artery occlusion or early thrombotic occlusion, it is generally recommended that all patients with rest or unprovoked angina undergo coronary arteriography. This study allows definition of the severity of the coronary artery disease and assists in separating the severe occlusive coronary patient who may require angioplasty or surgery from the patient with variant angina who has normal coronary arteries and will respond to medical therapy.

Unless the patient gives a history suggestive of severe occlusive coronary disease, that is, either progressively severe effort angina or risk factors of coronary disease suggesting that this may not be variant angina, it is important to stop all anti-anginal medications for at least 24 hours prior to coronary arteriography. Nitroglycerine can be used for treatment of spontaneous episodes of pain until 1 hour prior to the procedure. It is particularly important that all long-acting nitrates and transcutaneously applied nitrates, such as nitrate patches and calcium antagonists, be stopped. If the patient is having frequent episodes of pain, this should be done in the hospital under close medical observation.

Routine coronary arteriography is first accomplished to determine whether the patient has severe coronary artery disease and unstable angina or he has mild disease or completely normal vessels and, therefore, falls into the suspect variant angina group. Occasionally a patient will have a spontaneous episode of angina during the arteriogram and documentation of complete or incomplete focal spasm associated with the patient's typical chest pain will help establish the diagnosis. It is helpful to apply radiolucent electrode pads on the chest wall for a complete 12-lead ECG prior to start of arteriogram if variant angina is suspected. A three-channel 12-lead ECG machine can then be attached, and if the patient has angina or has complaints that suggest angina during the arteriogram, ST segment changes can be documented on the ECG. In most cases the patient will not have a spontaneous episode of chest pain, and after documentation of non-occlusive coronary disease or normal coronary arteries, it may be necessary to proceed with provocative testing (Fig. 1).

PROVOCATIVE TESTINGS

Intravenous administration of ergonovine was commonly used to provoke coronary arterial spasm in cardiac catheterization laboratory. However, due to several reports of irreversible coronary spasm and arrhythmias induced by ergonovine, many centers use methacholine as their standard provocative testing. The mechanism by which methacholine may precipitate coronary spasm is not clearly understood. One theory is that spasm results from direct stimulation of cholinergic muscarinic receptors on peripheral vascular smooth muscle, which then results in an abrupt fall in blood pressure with reflex-mediated increase in sympathetic tone. Compared to ergonovine, which acts through serotogenic receptors, the duration of acetylcholine effects is significantly shorter which makes it more attractive agent to use.

A common protocol used by many centers is summarized below.[34] It is essential to anticipate the need for acetylcholine testing so that informed consent, cessation of anti-anginal medication, and proper preparation of the patient can be accomplished prior to documentation of normal coronary vessel or insufficient coronary disease to explain the patient's rest angina. The sequential protocol includes injection of acetylcholine chloride in incremental doses of 20, 50 and 80 mg in 10 ml normal saline into the right coronary artery and 20, 50 and 100 mg into the left coronary artery over 20 seconds with at least a 3-minute interval between each injection. Patients are asked to report any chest pain graded on a scale of 1–10. A standard 12-lead ECG must record every 30 seconds. One minute after each injection, or when chest pain or significant ischemic ST changes appear, coronary arteriogram are obtained.

DIFFERENTIAL DIAGNOSIS

The most important group of patients to consider in the differential diagnosis at the time that a patient presents with

TABLE 2

Clinical characteristics of angina subtypes

	Stable	*Unstable*	*Variant*
Chest pain			
Character	Typical	Typical	Typical
Onset	Exertion	Rest/Exertion	Rest
ECG during	ST depression	ST depression	ST elevation
Pain		Occasional ST	Occasional ST
Elevation depression arteriography	Coronary CAD	Severe CAD	Normal or mild CAD

(Abbreviation: CAD: Coronary artery disease)

rest or nocturnal chest pain is those with unstable or crescendo angina due to severe underlying coronary artery disease (Table 2). Although most of these patients will have a history of known coronary artery disease or effort angina in the past, a few patients will present de novo with this syndrome. Factors that will be helpful in evaluating this patient are the presence of coronary artery disease risk factors, presence of an old MI on ECG, and persistent ECG evidence of ischemia, which would suggest a persistent occlusion or partial occlusion rather than a transient occlusion due to coronary spasm. In patients who have not had previous coronary arteriography, it is essential to proceed with this evaluation to rule out tight occlusion or preinfarction angina.

Most troublesome is the patient who develops typical chest pain in response to acetylcholine testing but does not have demonstrable significant focal spasm on coronary arteriography or major ST-segment changes on ECG. The pathophysiology of chest pain in many of these patients is poorly understood. Esophageal spasm has been proposed as a cause, although results of studies with acetylcholine provocation during esophageal manometry have been difficult to interpret. These patients may have spasm of intramural vessels or have small vessel coronary disease due to endothelial dysfunction that is poorly understood at this time.

Finally, it is important to remember that the coronary spasm generally responds extremely well to either sublingual or intravenous nitroglycerine. In the patient with persistent ST-segment elevation, the early phase of acute MI must be considered and ruled out.

MANAGEMENT

MEDICAL THERAPY

Acute treatment of the chest pain episode is generally sublingual nitroglycerine. This is highly effective treatment, which almost always reverses the spasm. In fact, the diagnosis of transient coronary spasm should be questioned if there is not an excellent response to the nitroglycerine. Other sublingual nitrate preparations may be useful as well in terminating the acute attack.

Long-acting oral nitrates have long been used for prophylaxis in patients with variant angina.[35] Oral agents, such as isosorbide dinitrate, extended release form and nitroglycerine paste, have all been reported to be effective. The primary limiting factor with use of prophylactic nitrate therapy is the suspected development of tolerance in these patients, although it has been poorly documented in long-term clinical trials. Another limiting factor is the fact that many patients require high doses of nitrates for prophylaxis, which may lead to a significant frequency of adverse side effects, particularly headache and hypotension at a dose level that will prevent the spontaneous episodes of chest pain and angina. Controlled trials of nitrate efficacy for prophylaxis have been limited. Hirai and his colleagues demonstrated that simultaneous administration of an angiotensin II and type 1 receptor blockers suppressed the development of nitrate tolerance during transdermal nitroglycerine therapy.[36] They suggested that increased oxidative stress induced by activation of angiotensin II may be important in the development of nitrate tolerance. Hill and his co-workers reported on a double-blind randomized crossover comparison of nifedipine versus isosorbide dinitrate in 19 patients with variant angina.[37] There was a 72% decrease in angina frequency during nifedipine therapy and a 63% decrease during isosorbide dinitrate therapy compared with placebo. The authors concluded that the two agents were approximately equally effective in this particular trial. Intravenous administration of isosorbide dinitrate at a dose of 1.25–5.0 mg/hr has been reported to be effective in patients in whom oral agents did not control recurrent episodes of angina. In addition, sodium nitroprusside has been reported to be effective, but the adverse side effects of hypotension must be monitored carefully in this patient group.

Alpha-adrenergic blockers, such as phenoxybenzamine or phentolamine, have also been reported to be effective in preventing repeated episode of coronary artery spasm in variant angina patients.[35] The mechanism proposed is simply blockade of coronary artery α-receptors, resulting in prevention of focal spasm. Although these agents have been reported to be effective, it was common to have to achieve doses that cause significant orthostatic hypotension before they were effective in preventing episodes of coronary spasm. For this reason, these treatments have generally been abandoned with the advent of demonstrated excellent efficacy of the calcium blockers.

Treatment of Arrhythmias

Patients may either develop heart block due to spasm of the right coronary artery or ventricular arrhythmias, including sustained ventricular tachycardia, due to spasm of the right,

circumflex or left anterior descending coronary arteries. These arrhythmias generally occur in the setting of either myocardial ischemia or reperfusion when the spasm is broken or resolves spontaneously. For this reason antiarrhythmic drugs are not very effective and treatment should be directed at the treatment or prevention of the focal coronary spasm. Patients who have episodes of second- or third-degree heart block and syncope who have not responded to prophylactic therapy with calcium blockers will benefit from a demand pacemaker. Additionally, patients with ischemia associated ventricular fibrillation, who continue to have ischemia despite treatment, should receive an implantable cardioverter-defibrillator.[38]

Calcium Antagonists

Calcium channel blockers have dramatically improved the success of therapy and most likely improved the long-term prognosis for patients with variant angina. The calcium antagonists block the influx of ionized calcium via slow channels during the plateau phase of action potential. This blocking action is more potent at the calcium channel of the vascular smooth muscle cells than of the myocardial cells. This differential effect allows relaxation of vascular smooth muscle at therapeutic concentrations of the drug, which results in minimal negative inotropic activity. The calcium antagonists, therefore, cause a decrease in coronary vascular tone and reactivity, which results in increase in coronary flow. These agents also appear to block the abnormal hyperreactivity or spasm of coronary vessels, which is the cause of variant angina. Clinical trials with calcium antagonists have conclusively shown marked reduction in angina frequency during therapy with calcium antagonists.

Diltiazam, nifedipine and verapamil are all effective for prophylaxis in variant angina. These agents have been proven efficacious in double-blind randomized clinical trials with 50–70% reduction in angina frequency and nitroglycerine consumption compared with a placebo control. Endo and his colleagues first reported, in 1975, that diltiazam was effective for prophylaxis of variant angina.[39] After initial experience with this agent in Japan, subsequent studies in the United States have confirmed that diltiazam is not only efficacious but also safe for short- and long-term efficacy in variant angina. Rosenthal and his co-workers reported on a total of 13 patients with documented coronary spasm and variant angina who completed a prospective randomized dose-finding crossover study of diltiazam, 120 mg/day and 240 mg/day, versus placebo, each given for a 2-week period.[40] The 240 mg/day dose of diltiazam resulted in a decrease in pain of 79% to 50% (P = 0.03) and a significant decrease in angina frequency from 1.6 to 0.4 episodes per day, with similar reductions in nitroglycerine consumption. There was no evidence for a rebound phenomenon when the diltiazam was abruptly changed to placebo, and there were no significant adverse side effects. These findings were confirmed by other investigators, including Pepine and his colleagues, who studied a similar group of patients in whom 64% had either complete or partial resolution of their angina during therapy with diltiazam.[41] Diltiazam has also been shown to be effective for long-term treatment of these patients without evidence of either tolerance or rebound. Rosenthal and his co-workers reported later reported on the long-term efficacy of diltiazam in 16 patients with clinical variant angina.[42] This 44 weeks study involved eleven 28-day cycles with one random placebo period during the first five cycles and one during the last six cycles. There was a 73% decrease in angina frequency in phase I and a 55% decrease compared with placebo in phase II. In addition, marked disease attenuation was noted. Thus, diltiazam is effective as long-term therapy without evidence of drug tolerance developing.

Open-label experience with the patients who have been on diltiazam shows similar results. We first reported on 36 patients who were followed in the Stanford coronary artery spasm clinic for 6 months or more.[43] During a mean of 7.5 months of diltiazam therapy, angina frequency was reduced from 21.5 to 1.3 attacks per week on either 240 mg or 360 mg of diltiazam daily (Fig. 5). Pain break-through occurred a mean of 1.7 times during the 17.5-month follow-up and tended to be a short duration and related to episodes of stress in patient's life. Six patients had trace to 1+ pedal edema, but no other adverse side effects were reported. Thus, diltiazam appears to be effective for short- and long-term prophylaxis for variant angina.

Nifedipine for prophylaxis of Printzmetal's variant angina was first reported by Hosoda and his associates in 1975.[44] These uncontrolled studies reported a dramatic reduction in angina frequency. Testing of this agent in the United States was first reported by Antman and his colleagues in 1980.[45] In an open-label study of 127 patients with documented coronary spasm and variant angina, doses of 40–160 mg/day resulted in a 63% of patients being completely relieved by of their angina. Furthermore, a total of 87% of patients had 50% or more reduction in the frequency of angina. The authors reported that approximately 5% of patients had to terminate therapy due to adverse side effects. Although few controlled studies of this agent have been reported, it is clear that this is a highly effective

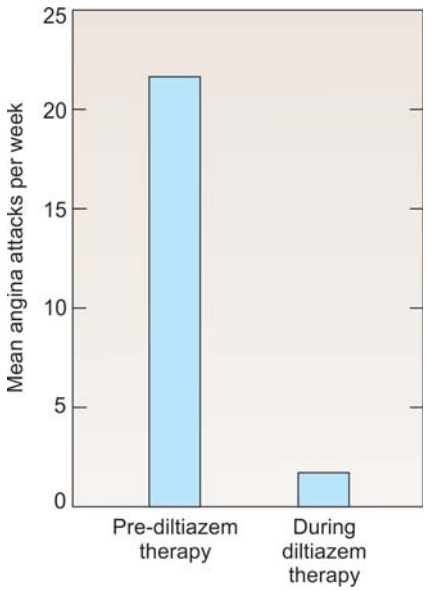


FIGURE 5: Response of 36 patients with angina due to documented coronary arterial spasm during medical therapy with long-acting nitrates (pre-diltiazem) and after therapy with 240 to 360 mg/day of diltiazem. (*Source:* Modified from Schroeder JS, Lamb IH, Ginsberg R et al, Diltiazem for long-term therapy of coronary arterial spasm. Am J Cardiol. 1982;49:533).

drug for prophylaxis of variant angina. It has also been demonstrated in the cardiac catheterization laboratory to block spasm during provocation with ergonovine maleate. With regard to long-term responses, Hill and his co-workers reported on 26 patients who had angina due to coronary spasm who completed a crossover study comparing nifedipine with isosorbide dinitrate.[46] Of the 18 patients who had a short-term beneficial response to nifedipine, 14 were followed for an average of 9.4 months on long-term nifedipine therapy. Overall, 80% of patients had a 50% or more decrease in angina frequency. Three patients did have a marked increase in angina at 9, 14 and 3 months after initiation of therapy, requiring hospitalization. In addition, nifedipine was discontinued in two patients and the dose was decreased in three additional patients due to significant adverse side effects. The authors reported that adverse effects were common, but reduction of dosing usually diminished the unwanted effects of the drug.

Verapamil has also been reported to be effective in carefully controlled randomized trials. Johnson and his colleagues reported on the prophylactic use of verapamil in 16 patients with variant angina over a 9-month period.[47] During the treatment period with verapamil, the angina frequency decreased from 12.6 to 1.7 pain episodes per week with similar decreases in nitroglycerine consumption. Holter monitoring showed marked reduction in episodes of ST-segment deviation from 33.1 to 7.1 deviations per week while on active therapy.[48] The authors concluded that verapamil was an effective drug for therapy of variant angina, but it should be noted that 14 of the 16 patients were also receiving oral isosorbide dinitrate, mean dose 105 mg/day, with a range of 120–200 mg given in four to six divided doses.

There have been very few comparative studies of the efficacy of calcium blockers for treatment of variant angina. The only study that has attempted to compare these agents was a survey of 11 cardiology institutes in Japan where investigators were asked to comment on their impression of the efficacy of nifedipine, diltiazam and verapamil.[49] Efficacy rates were assessed at 94% for nifedipine, 90.8% for diltiazam and 85.7% for verapamil. These agents also tended to be more effective in patients with normal or near normal coronary arteries rather than in patients with coronary disease. It is interesting, however, that verapamil was reported as markedly effective in only 10.7% of patients compared with 80.5% for diltiazam and 77.2% nifedipine. The authors also reported that in 15 patients on a combination of nifedipine and diltiazam that 73.3% had a markedly effective response.

Other studies have attempted to compare calcium antagonists with long-acting nitrates. Ginsburg and his co-workers reported on 12 patients who were entered into a randomized double-blind study comparing nifedipine, mean dose 82 mg/day, with isosorbide dinitrate, mean dose 66 mg/day. Treatment of the 12 patients resulted in a total of 161 patients-days that were available for analysis.[50] During baseline there was an average 1.1 angina attacks per day on placebo, which fell to 0.28 per day during nifedipine treatment and to 0.39 per day during isosorbide dinitrate treatment (Fig. 6). There is no statistical difference between these two responses. A number of adverse side effects occurred with headache being the most prominent during isosorbide dinitrate treatment in 81%

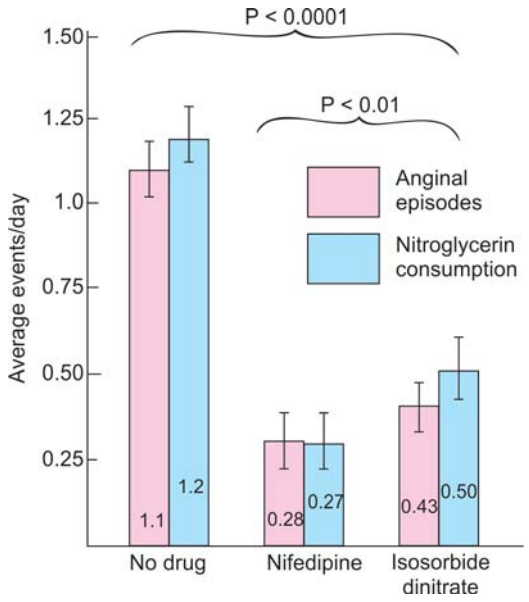


FIGURE 6: Comparison of nifedipine versus isosorbide dinitrate drug efficacy in variant angina therapy in terms of reduction of anginal episodes and sublingual nitroglycerin consumption. (*Source:* Modified from Ginsburg R, Lamb IH, Schroeder JS, et al. Randomized double-blind comparison of nifedipine and isosorbide dinitrate therapy in variant angina pectoris due to coronary arrtery spasm. Am J Heart J. 1982;103:44.)

of patients and dependent edema occurring in 33% patients during nifedipine treatment. Significant adverse side effects requiring cessation of therapy occurred in two patients on nifedipine and in three patients on isosorbide dinitrate. The authors concluded that both these agents were effective but that nifedipine was preferred by majority of patients. Ascherman and his colleagues reported on a randomized double-blind comparison of nifedipine and isosorbide in patients with variant angina.[51] Seventeen patients with documented variant angina were randomized to 20 mg/day of nifedipine versus 120 mg/day of isosorbide dinitrate. The design included a placebo-run-in period and two 6-weeks crossover period of treatment. They demonstrated that mean frequency of angina decreased from 43 attacks per week during placebo period to 4 per week with isosorbide dinitrate and 8 with nifedipine. They also concluded both nifedipine and isosorbide dinitrate in their slow release formulation are effective in the treatment of variant angina.

Patients who are refractory to treatment with oral calcium channel blockers will respond to intravenous isosorbide dinitrate or intravenous nitroglycerine. However, in the medically refractory patient, consideration should be given to combining diltiazam and nifedipine, gradually increasing the combined dose to limit adverse effects.

Beta-blockers have been reported to occasionally be detrimental or to aggravate variant angina. Robertson and his colleagues reported that both 160 mg and 640 mg propranolol per day were associated with significantly prolonged angina episodes compared with findings in control groups.[52] Tilmant studied 11 patients on placebo, diltiazam, propranolol or a combination.[53] Propranolol resulted in increased frequency and duration of angina attacks, but when diltiazam was added, this adverse effect disappeared. Therefore, β-blockers are generally not recommended for the patients with variant angina, although

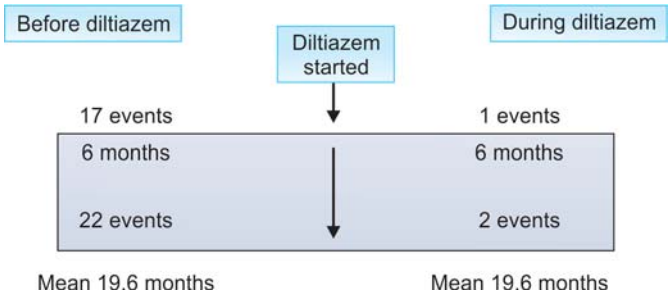


FIGURE 7: Total cardiovascular events (myocardial infarction, sudden death, or hospitalization to rule out myocardial infarction) in 43 patients with documented coronary artery spasm. Events are noted for the 6 months immediately before and after initiation of diltiazem therapy, as well as during the mean 19.6 months before and after initiation of diltiazem therapy. (*Source:* Modified from Schroeder JS, Lamb IH, Bristow MR, et al. Prevention of cardiovascular events in variant angina by long-term diltiazem therapy. J Am Coll Cardiol, 1983;1:1507)

they can be used for demand-related angina in the setting of occlusive coronary artery disease if calcium antagonists are given concurrently.

Is there any evidence that long-term use of calcium antagonists may affect the long-term prognosis of these patients? We previously reported on 43 patients with variant angina and compared their cardiovascular event rate after beginning diltiazam therapy with that at an equal time prior to therapy.[54] Cardiovascular events defined as MI, sudden death and hospitalization for prolonged angina were decreased significantly during both the 6 and mean 19.6 months of therapy compared with a similar period prior to the initiation of therapy. When the data were analyzed by the binomial principle, 22 events occurred during the 19.6 months before therapy and 2 events on therapy (Fig. 7). No patient died during the follow-up period, and there were reports of a dramatic decrease in angina frequency of approximately 94%. Although this was a retrospective study, the marked reduction in events during drug therapy suggested a protective effect and these patients benefit from long-term therapy from this drug. Due to the marked improvement in angina symptoms, it is sometimes difficult to assess how long the patients should be treated with calcium antagonists. Most authors recommend that the patients be treated at least 1 year with gradual reduction in calcium antagonist therapy after that if the patient remains pain free. We have found that flares in angina frequency occur at times of emotional stress and the patients may need increases in their dosing.

SURGICAL AND PERCUTANEOUS INTERVENTION

Although the calcium antagonists are highly effective for prophylaxis in this patient group, an occasional patient has severe unrelenting spasm despite maximal medical therapy. Some authors have reported coronary bypass grafting in such patients with the hypothesis that the graft can bypass the area of focal spasm and result in sufficient perfusion even when spasm occurs.[55] However, those patients who have severe coronary spasm may have a more diffuse process. Subsequent reports indicate that the spasm may involve or propagate distal to the area of the insertion of the bypass graft, and this approach is generally no longer applied in this patient group. Nordstrom and his co-workers reported on persistence of chest pain despite coronary bypass grafts and a relatively high occlusion rate or postoperative infarction rate.[56] Due to the possibility of sympathetic nervous system-induced spasm, plexectomy at the time of aortocoronary bypass grafting has been reported in an effort to more completely denervate the vessel.[57] Although many of these patients seem to improve, it has been difficult to assess short- and long-term efficacy of these procedures. Prior to the introduction of calcium antagonists, Clark and his colleagues reported on four patients who underwent cardiac denervation because of unrelenting coronary spasm with myocardial ischemia and/or ventricular arrhythmias.[58] Two of their four patients die, but the two survivors did have good short-term relief of the coronary spasm.

Percutaneous transluminal coronary angioplasty (PTCA) has also been proposed as effective therapy for variant angina.[59] However, the success rate for PTCA in variant angina has been variable. As Gruntzig stated "coronary spasm and balloons do not mix".[60] The reason is obvious; if an artery is spastic in one location, manipulation of that artery may lead to more intense spasms. The advent of stents offered a more ideal approach. Corcos and his co-workers reported on 21 patients with variant angina of whom 17 also had effort-induced angina.[61] All patients had single-vessel disease with 60–95% stenotic lesions present. Angioplasty was successful in 19 patients, but only 8 remained free of angina. The restenosis rate appeared to be higher in those patients who had calcium antagonists discontinued after the procedure (80%) compared with those who continued the drug (21%). During a mean follow-up of 33 months, 20 patients were free of angina with 75% of all anti-anginal medications. Therefore, where there is a fixed stenotic coronary lesion related to focal coronary spasm, angioplasty and calcium antagonists may be effective therapies. Martí and his co-workers reported on 22 patients with documented variant angina, 5 who were refractory to pharmacologic treatment and underwent PTCA.[62] Of the 5 patients, the investigators observed coronary spasm recurrence proximal or distal to the stent in 4 patients (2 during the stent implantation procedure and the other 2 in the coronary care unit within 48 hours post procedure). Three patients required additional stenting and the fourth patient improved with pharmacologic treatment. The authors concluded that although PTCA may be an alternative therapy for patients with recurrent variant angina refractory to medical treatment, spasm recurrence in other segments of the treated vessel is common and immediate and continued surveillance is important.

NATURAL HISTORY AND PROGNOSIS

The long-term outlook for patients with variant angina has been reported as quite variable, most likely because of differences in the degree of underlying coronary disease and the advent of calcium channel blockers as the cornerstone of medical therapy. Severi reported on 138 patients with variant angina who were followed for up to 8 years.[63] Only 9 of 107 patients had normal coronary arteries, and the majority had greater than 50% stenosis of at least one major vessel. Coronary vasospasm was demonstrated in only 37 of the patients at the time of coronary arteriography. They reported that 28 patients had an acute MI

and 5 patients died within 1 month of hospital admission. The authors then followed the 133 remaining patients, of whom 120 were treated medically and 13 surgically. In the medically treated group, 7 patients died during the follow-up period and symptoms generally became less frequent and severe. Over 50% of patients remained asymptomatic for at least 12 months by the end of year 4. The author noted a general correlation between the severity of the underlying coronary disease and the poor prognosis.

The prognosis of patients with variant angina in the absence of significant coronary artery disease appears to be relatively good.[64] Bory and his colleagues studied 277 successive patients with coronary spasm and normal or near normal coronary arteries for a median follow-up of 7.5 years.[65] While they reported that recurrent angina was common (39%), cardiac death and MI were relatively infrequent and occurred in only 3.6% and 6.5% respectively.

The prognosis of variant angina in patients with multivessel spasm is believed to be poor. Onaka and his colleagues evaluated the clinical manifestation of ischemic episodes in patients with variant angina and normal coronary arteries.[66] They concluded that anginal attacks due to sequential and simultaneous multivessel spasm were more dangerous than those involving single-vessel spasms. The observed pattern of spasm in patients with multivessel involvement included:

- Migratory spasm, which is spasm at a different site on different occasions,
- Spasm that sequentially affected two different sites, and
- Simultaneous spasm at more than one site.

In conclusion, variant angina is characterized by considerable variability of symptoms and response to treatment. Spontaneous remission is frequent outcome in many patients, but numerous studies have convincingly demonstrated that patients with variant angina and no or mild coronary disease do extremely well if they have long-term therapy with a calcium channel blocker. For this reason, we recommend that patients continue medication for at least 1–2 years and then that it be tapered slowly and that medication be added at any time that there is a recurrence of symptoms.

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Chapter 52

Cardiogenic Shock in Acute Coronary Syndromes

Sanjay K Shah, Eugen Ivan, Andrew D Michaels

Chapter Outline

- Incidence
- Mortality
- Predictors of Cardiogenic Shock
- Pathophysiology
- Pathology
- Other Cardiac Causes of Cardiogenic Shock
  - Right Ventricular Infarction
  - Ventricular Septal Rupture
  - Cardiac Rupture
  - Mitral Regurgitation
- Diagnostic Evaluation
- Medical Management
- Mechanical Support
  - Intra-aortic Balloon Pump
  - Left Ventricular Assist Device
  - TandemHeart
  - Impella
- Revascularization

INTRODUCTION

Cardiogenic shock, a syndrome of organ hypoperfusion secondary to cardiac failure, complicates ST-segment elevation myocardial infarction (STEMI) in 5–8% of cases.[1] Although less common, cardiogenic shock complicates 2.9% cases of non-ST elevation myocardial infarction and 2.1% of those with unstable angina.[2] Hemodynamic features of this syndrome include hypotension, reduced cardiac output and elevated right- or left-sided filling pressures (Table 1). Pre-shock or shock with end-organ hypoperfusion may be manifest as decreased urine output (oliguria), mental obtundation and/or cool extremities. Although shock is usually caused by left ventricular (LV) pump dysfunction secondary to a large area of LV ischemia or infarction, there is increasing data that neurohormonal or systemic inflammatory response syndrome (SIRS) may be a causative mechanism of shock in acute coronary syndromes (ACS). Other clinical entities must be considered when evaluating shock in the setting of ACS. Mechanical complications of myocardial infarction that can cause shock include right ventricular (RV) infarction, cardiac tamponade secondary to free wall rupture, papillary muscle ischemia or infarction and ventricular septal defect. Additionally, entities that may mimic ACS and present with shock should be considered. Takotsubo cardiomyopathy, acute myopericarditis, hypertrophic cardiomyopathy and acute aortic dissection can present with ST-segment elevation in the absence of significant coronary artery disease.[1]

INCIDENCE

Historically, cardiogenic shock was reported to occur in 7.5% of patients who presented with acute myocardial infarction.[3] More recent observational studies from the 1990s indicate that the incidence of cardiogenic shock in acute myocardial infarction is roughly 6%.[4] Patients who develop cardiogenic shock are more likely be older and have had a history of myocardial infarction, ischemic heart disease, prior coronary artery bypass graft (CABG) surgery, stroke, diabetes, heart failure, anterior infarction location and bundle branch block.[5,6] Indeed, 48% had significant left anterior descending disease in the Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock (SHOCK) trial.[7] Patients who develop cardiogenic shock have a higher prevalence of underlying three-vessel disease or left main disease.[8]

MORTALITY

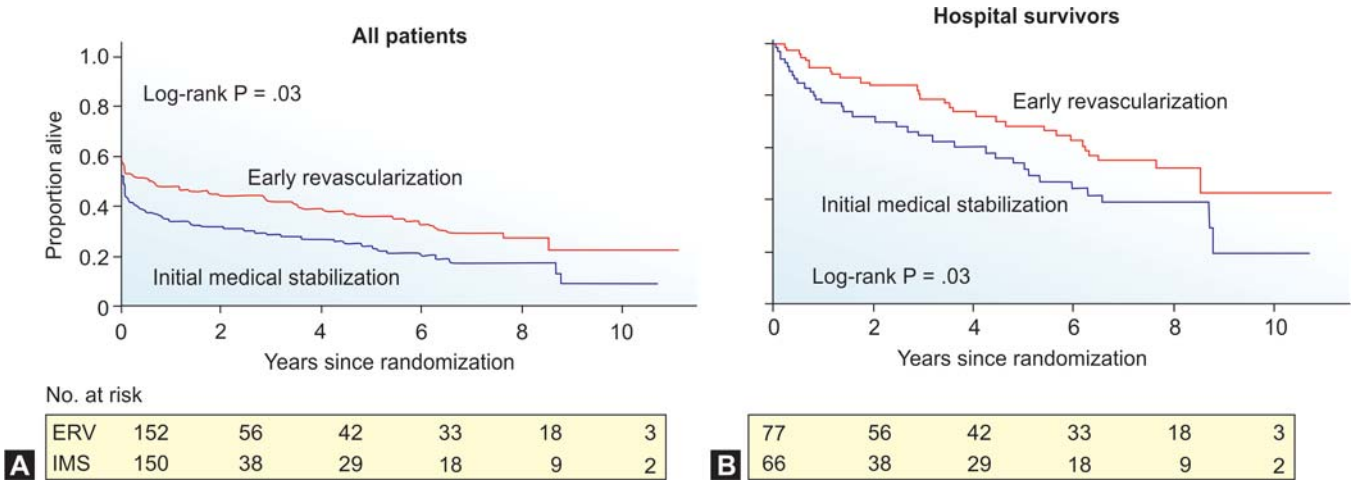
Prior to the routine use of thrombolytics and percutaneous coronary intervention (PCI) in the setting of STEMI, the in-hospital mortality rate for myocardial infarction complicated by

TABLE 1

Clinical and hemodynamic features of cardiogenic shock

Clinical
- Hypotension: Systolic blood pressure ≤ 90 mm Hg
- Impaired organ perfusion: Oliguria, cold clammy skin, mental obtundation

Hemodynamics
- Systolic blood pressure ≤ 90 mm Hg
- Cardiac index ≤ 2.2 l/min/m^2
- Primary LV failure: Pulmonary capillary wedge pressure ≥ 18 mm Hg with right atrial pressure lower than pulmonary capillary wedge pressure
- Primary RV failure: Right atrial pressure ≥ 15 mm Hg with pulmonary capillary wedge pressure less than right atrial pressure



FIGURES 1A AND B: Kaplan-Meier long-term survival of all patients and those surviving to hospital discharge from the SHOCK trial[12] (*Source*: Hochman JS, Sleeper LA, Webb JG, et al. Early revascularization and long-term survival in cardiogenic shock complicating acute myocardial infarction. JAMA. 2006;295:2511-5)

cardiogenic shock was 70–80%.[3] A more recent analysis of the National Registry of Myocardial Infarction database showed a progressive decline in in-hospital mortality (from 60.3% to 47.9% during 1994–2004) in association with increased use of primary PCI for patients with STEMI complicated by cardiogenic shock.[9] Similar improvements in in-hospital mortality were noted in a Swiss observational study.[10] Similar trends in decreased mortality were noted in analysis of the long-term outcomes of the SHOCK trial, a trial that compared initial medical stabilization to early revascularization. At 1 year, survival was lower for those treated with intensive medical therapy (46.7%) compared to those treated with early revascularization (33.3%).[11] Similarly, a follow-up analysis at 6 years of the SHOCK trial showed advantages in survival in the total cohort (32.8% vs 19.6%) and among those who were alive at hospital discharge (62.4% vs 44.4%) for those randomized to the early revascularization group compared with those randomized to the intensive medical therapy group (Figs 1A and B).[12]

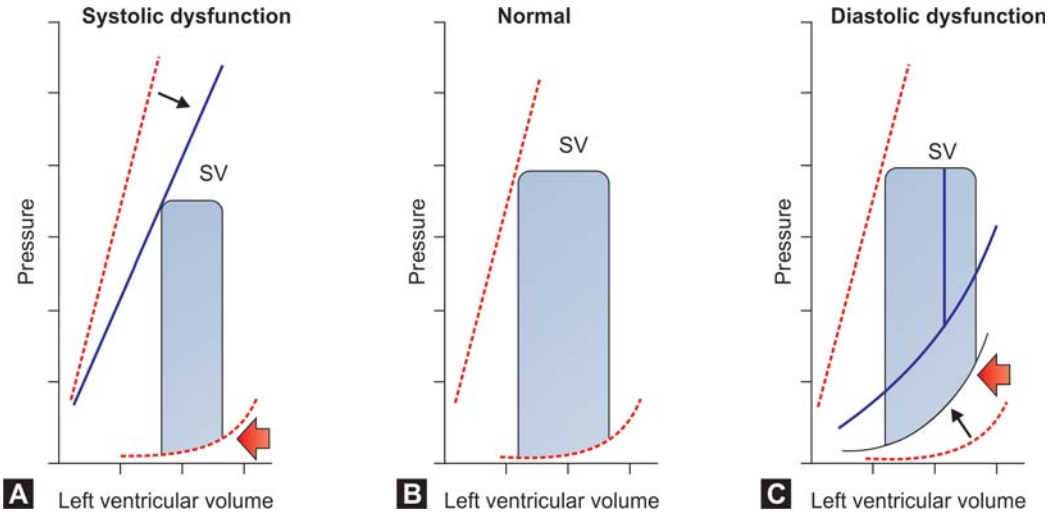
PREDICTORS OF CARDIOGENIC SHOCK

Predictors of short-term mortality from cardiogenic shock include advanced age, male gender, Killip class, low systolic blood pressure, anterior location of infarction, increased heart rate, pre-existing cardiac risk factors, prior infarction or angina and previous CABG.[13] In the GUSTO-1 study, age was the greatest predictor of 30-day mortality. For every 10-year increase in age, there was a 47% greater risk of developing shock.[13,14] In an analysis of the TRIUMPH data, creatinine clearance, systolic blood pressure and number of vasopressors were significant predictors of mortality at 30 days in those who underwent successful PCI.[15] In addition, several studies have shown that PCI and glycoprotein IIb/IIIa inhibitor use were associated with decreased mortality.[16,17] In a substudy of the SHOCK trial, three-vessel disease was associated with worse outcome, as was the presence of the left main or saphenous vein graft as the infarct related artery.[18] If the infarct related artery was the left circumflex or the left anterior descending, this was associated with an intermediate mortality, and the right coronary artery was associated with the best outcome.[8] In a 6-year follow-up of the SHOCK trial, an initial medical stabilization strategy, reduced LV ejection fraction, advanced age and increased serum creatinine were associated with long-term mortality.[12]

PATHOPHYSIOLOGY

The primary cause of cardiogenic shock in ACS is LV dysfunction secondary to infarction and ischemia. Patients with predominantly diastolic dysfunction from ischemia may present with cardiogenic shock. When ischemia or infarction affects a large portion of the LV myocardium, stroke volume and consequently cardiac output decrease. With impairment in the pumping function of the left ventricle, tachycardia ensues to try to maintain cardiac output. However, due to inability to maintain cardiac output, hypotension ensues. In addition, LV filling pressures increase due to pump failure (Figs 2A to C). These compensatory mechanisms beget further ischemia as tachycardia decreases the diastolic filling of the coronary arteries, while hypotension and increased LV filling pressures decrease coronary perfusion pressure, which causes further ischemia leading to a downward spiral. Previous studies suggested that cardiogenic shock ensued when 40–50% of the LV myocardium was infarcted.[19] However, the average ejection fraction in the SHOCK trial was roughly 30%.[20] Although this was measured during the patient's acute presentation when the patients were often on inotropes or had intra-aortic balloon pump (IABP) support, this did not differ significantly from the ejection fraction measured 2 weeks following the incident event. In addition, in the SHOCK trial there was improved ejection fraction in survivors, suggesting that at least part of the myocardium was ischemic and not infarcted.[21]

In addition to the hemodynamic effects of shock, decreased cardiac output stimulates increased sympathetic discharge. In addition, hypotension stimulates the release of renin and angiotensin. Catecholamine stimulation leads to tachycardia and increased systemic vascular resistance. While preserving cardiac output by inotropy, and increasing coronary blood flow by increased systemic vascular resistance, this comes at the cost of increased afterload. Similarly, the renin angiotension system



FIGURES 2A TO C: Schematic pressure-volume loops illustrate the mechanisms for increased LV diastolic pressure and lower cardiac output in systolic and diastolic dysfunction: (A) in cardiogenic shock patients with systolic dysfunction; (B) contractility is reduced compared to normals and (C) cardiogenic shock patients with diastolic dysfunction, the major mechanism of increased diastolic filling pressure is increased ventricular stiffness resulting in an upward and leftward shift in the end-diastolic pressure-volume relationship (*Source*: Chatterjee K, McGlothlin D, Michaels A. Analytic reviews: Cardiogenic shock with preserved systolic function: A reminder. J Intensive Care Med. 2008;23:355-66)

causes deleterious affects by increasing systemic vascular resistance and by fluid retention, further compromising coronary blood flow and increasing filling pressures. These compensatory mechanisms exacerbate the physiology by increasing fluid retention and biventricular filling pressures, causing increased heart rate and systemic vascular resistance, further leading to worsening of the clinical picture.[1]

Through these mechanisms, it would be expected that cardiogenic shock would be invariably associated with a high systemic vascular resistance. This, however, is not the case; there is growing data that the cause of cardiogenic shock complicating acute myocardial infarction is multifactorial, including a syndrome of SIRS with accompanied leukocytosis, fever and reduced systemic vascular resistance (Fig. 3). In the SHOCK trial, 18% manifested signs of SIRS. This group had a median SVR that was within the normal range. Of this group, 74% were culture positive.[22] It has been postulated that passive venous congestion of the gut causes bacterial translocation, which leads to SIRS. One study revealed that a majority of patients with cardiogenic shock had elevated levels of procalcitonin, a marker of an infective process.[23] In addition, TNF-α and IL-6 have been shown to be elevated in patients with acute myocardial infarction who develop shock while in the hospital. These markers, which have cardiodepressant properties, have been shown to be predictive of death and shock.[24] Additionally, nitric oxide (NO) and inducible nitric oxide synthase (iNOS) may be related to SIRS. iNOS and NO are increased in myocardial infarction.[25] NO may lead to excessive vasodilation and contribute to SIRS and consequently to shock. Although trials of the iNOS inhibitor L-MMMA showed no mortality benefit in the setting of cardiogenic shock, there was a significant increase in blood pressure shortly after infusion compared with placebo, suggesting a possible role of iNOS in the development of cardiogenic shock.[26,27]

PATHOLOGY

Pathologic cardiac examinations of patients who died of cardiogenic shock reveal areas of infarct expansion and extension. Infarct expansion occurs to areas of the noninfarcted ventricle after a large infarct, often after extensive anterior infarction. This may occur due to mechanical effects or due to shock with further coronary ischemia in remote areas. Often the most susceptible areas are "watershed" areas adjacent to area of necrosis. One landmark autopsy study revealed that infarct extension occurred in 18 of 22 autopsies analyzed.[19] In addition, there is infarct extension due to reocclusion of patent arteries, propagation of intracoronary thrombi, or from ischemia secondary to cardiogenic shock itself.[28,29]

OTHER CARDIAC CAUSES OF CARDIOGENIC SHOCK

The evaluation of cardiogenic shock in ACS involves exclusion of other cardiac causes of shock in the setting of ACS, including RV infarction, ventricular septal rupture (VSR), ischemic mitral regurgitation and cardiac rupture.

RIGHT VENTRICULAR INFARCTION

Right ventricular infarction may cause cardiogenic shock. Most commonly associated with inferior myocardial infarction, isolated RV infarction occurs in roughly 5% of cases of cardiogenic shock. Mortality in the SHOCK registry was only slightly lower in those with cardiogenic shock from RV versus LV failure.[30] There is typically RV volume overload with decreased LV preload. LV volume is not only decreased due to decreased RV function, but due to a shift of the interventricular septum to the LV from RV volume overload and increased end diastolic pressure.[31]

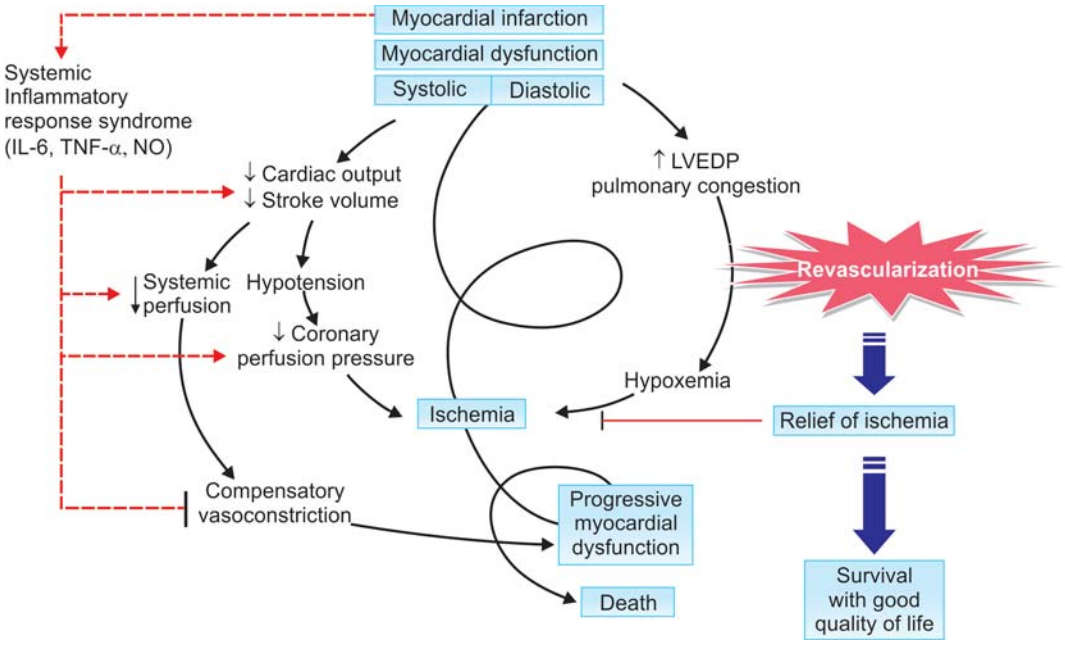


FIGURE 3: The current concept of cardiogenic shock pathophysiology. The classic description of cardiogenic shock pathogenesis is shown in black. Myocardial injury causes systolic and diastolic dysfunction. A decrease in cardiac output leads to a decrease in systemic and coronary perfusion. This exacerbates ischemia causes cell death in the infarct border zone and the remote zone of myocardium. Inadequate systemic perfusion triggers reflex vasoconstriction, which is usually insufficient. Systemic inflammation may play a role in limiting the peripheral vascular compensatory response and may contribute to myocardial dysfunction. Whether inflammation plays a causal role or is only an epiphenomenon remains unclear. Revascularization leads to relief of ischemia. It has not been possible to demonstrate an increase in cardiac output or ejection fraction as the mechanism of benefit of revascularization; however, revascularization does significantly increase the likelihood of survival with good quality of life (Abbreviations: IL-6-Interleukin-6; TNF-α: Tumor necrosis factor-α; LVEDP: LV end-diastolic pressure)[1] (*Source*: Reynolds HR, Hochman JS. Cardiogenic shock: Current concepts and improving outcomes. Circulation. 2008;117:686-97)

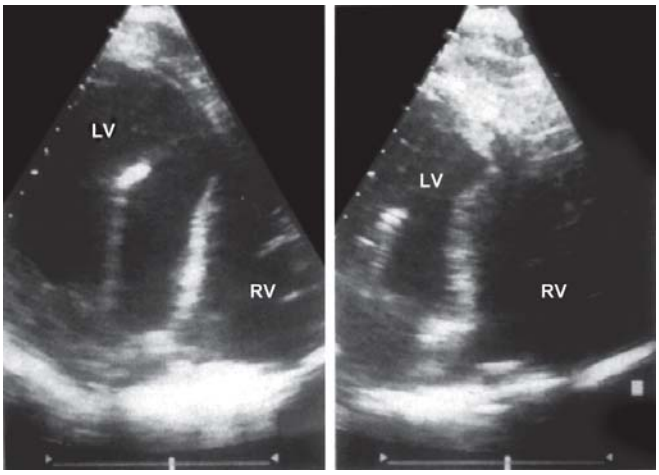


FIGURE 4: Transthoracic two-dimensional echocardiograms from a dog model of RV infarction. Before infarction, both LV and RV volumes were normal (left panel). After infarction, the right ventricle is dilated, while the LV end-diastolic volume is decreased. Leftward diastolic shift of the interventricular septum is evident (Abbreviations: RV: Right ventricle; LV: Left ventricle)[33] (*Source*: Modified from Chatterjee K, McGlothlin D, Michaels A. Analytic reviews: Cardiogenic shock with preserved systolic function: A reminder. J Intensive Care Med. 2008;23:355-66)

Historically, treatment has been volume resuscitation; however, this may impair LV filling. Ideally, RV diastolic pressures should be maintained between 10 mm Hg and 14 mm Hg to maintain RV stroke index.[32] The clinical presentation shows features of cardiogenic shock, evidence of right heart failure and the absence of pulmonary congestion. Elevated jugular venous pressure with a positive Kussmaul's sign, clear lungs, an RV S3 gallop and lack of increased intensity of P2, suggest RV infarct as the diagnosis. There is usually inferior ST elevation and elevation in V1 and V3R–V4R. Echocardiography usually reveals RV hypokinesis with dilatation, with relatively preserved LV ejection fraction **(**Fig 4). Treatment involves opening the infarct related artery and supportive medical measures.[33]

VENTRICULAR SEPTAL RUPTURE

Ventricular septal rupture is a rare complication of acute myocardial infarction, occurring in 0.2% of patients in the GUSTO-1 cohort.[34] Risk factors for development of a post-MI VSD include older age, female sex, absence of previous angina or infarction, late time to revascularization and systemic hypertension. VSDs occur with either anterior or inferior myocardial infarctions. VSDs associated with anterior infarction are usually apical in location, whereas those associated with inferior infarction are in the basal septum (Fig. 5). Rupture can occur within the first 24 hours in large infarctions associated with intramural hematomas, or 3–5 days later due to coagulation necrosis.[35] Usually patients present with cardiogenic shock and biventricular failure with a loud holosystolic murmur that is heard best at the lower left sternal border often associated with a thrill. The defect can be diagnosed with echocardiography, ventriculography or catheterization to document a left-to-right shunt in the right ventricle (Fig. 6).[36]

Previously, this defect was surgically closed via patch closure. However recent series have used a technique of surgical exclusion with improved outcomes.[37] Percutaneous closure has been attempted with mixed results.[38]

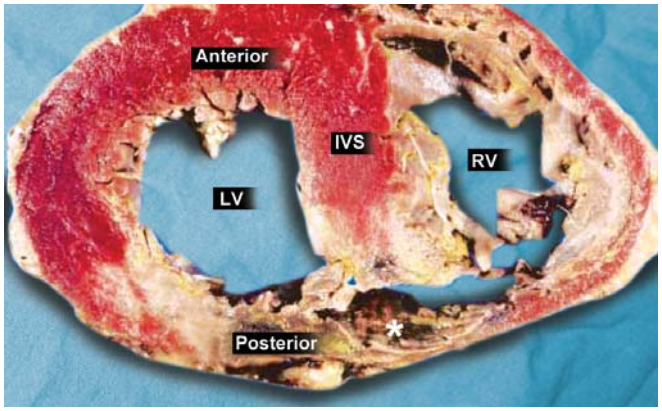


FIGURE 5: Gross findings from a patient with a posterior ventricular septal defect. There is an infarction involving the basal inferior septum, the basal posteroinferior wall, and the right ventricle. The ventricular septal rupture (star) is complex, with an irregular tract at the junction of the inferior wall and the interventricular septum[35] (Abbreviations: RV: Right ventricle; IVS: Interventricular septum) (*Source*: Modified from Birnbaum Y, Fishbein MC, Blanche C, et al. Ventricular septal rupture after acute myocardial infarction. N Engl J Med. 2002;347:1426-32)

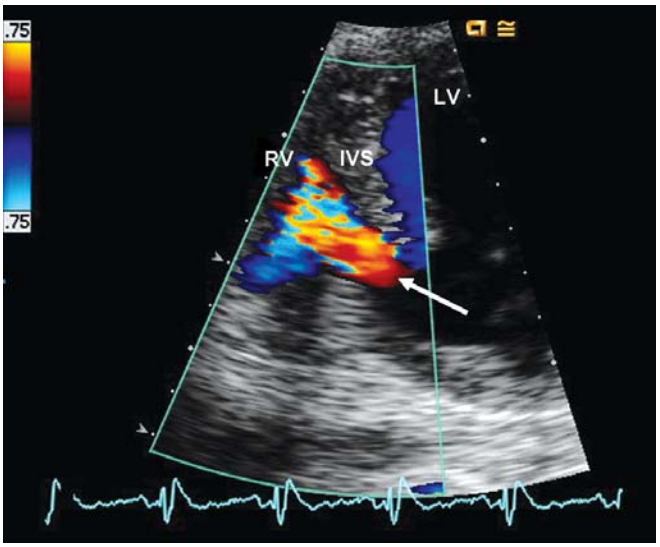


FIGURE 6: Doppler echocardiography demonstrating a post-MI ventricular septal defect with left-to-right flow (arrow) (Abbreviations: LV: Left ventricle; IVS: Interventricular septum; RV: Right ventricle)

CARDIAC RUPTURE

Cardiac rupture occurs in less than 1% of patients who present with acute myocardial infarction (Fig. 7). Cardiac rupture usually involves the anterior or lateral walls. Risk factors for cardiac rupture include female sex, advanced age and systemic hypertension.[39] Cardiac rupture usually occurs in patients without previous myocardial infarction who suffer a transmural infarct. Often, the time to reperfusion therapy is very long. It rarely occurs in patients who have well collateralized or thickened ventricles.[40] Cardiac rupture usually occurs in the first 5 days after myocardial infarction but can occur up to 3 weeks after infarction.[41] It is preceded by infarct expansion, with thinning of the necrotic area.[42] Rupture can occur from a tear in the wall, or it can occur from a dissecting hematoma.[41]

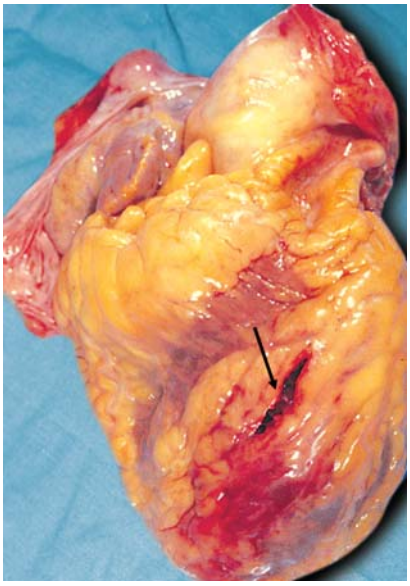


FIGURE 7: Cardiac rupture syndromes complicating ST-elevation myocardial infarction STEMI. Anterior myocardial rupture in an acute infarct (arrow), resulting in death from tamponade (*Source*: Modified from Schoen FJ. The heart. In: Kumar V, Abbas AK, Fausto N (Eds). Robbins and Cotran Pathologic Basis of Disease, 7th edn. Philadelphia: Saunders; 2005)

Rupture usually leads to hemopericardium and death from cardiac tamponade. However there is spectrum of presentations depending on whether or not the rupture is contained. Patients can present with "pericardial" pain, nausea, hypotension and nonspecific symptoms.[43] This is usually followed by pulseless electrical activity and death. Rupture can be diagnosed by transthoracic echocardiography.[44] Survival depends on recognition of tamponade, prompt pericardiocentesis and immediate surgical repair. Medical stabilization includes intravenous resuscitation, vasopressor or inotropic support and IABP support prior to surgical repair.[41,43,45]

MITRAL REGURGITATION

Acute severe mitral regurgitation from severe papillary dysfunction or papillary muscle rupture is a rare, life-threatening complication of acute myocardial infarction (Figs 8 and 9). This complication usually affects the posteromedial papillary muscle, which has its sole blood supply from the posterior descending artery. The anterolateral papillary muscle usually has dual blood supply from the left circumflex and left anterior descending.[36] Usually occurring 2–7 days postinfarction, most patients have relatively modest sized areas of infarction with poor collaterals.[46] Sudden onset of severe mitral regurgitation is associated with decreased forward output and stroke volume, increased pulmonary venous congestion, pulmonary edema and signs of hypoperfusion. On examination, patients have a new holosystolic murmur, often with an associated palpable and audible S3 and S4. The murmur may not extend to the second heart sound due to reduction of regurgitation in late systole because of rapid equalization of LV and left atrial pressures. Echocardiography usually confirms the diagnosis. Pulmonary artery catheterization reveals a large V wave in the pulmonary capillary wedge tracing. Definitive surgical treatment with mitral repair or replacement should be performed. Prior to surgical treatment, vasodilators

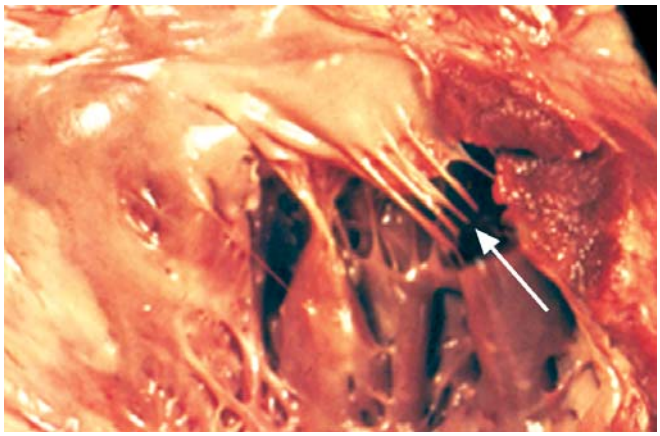


FIGURE 8: Complete rupture of a necrotic papillary muscle (arrow) in a post-infarction patient

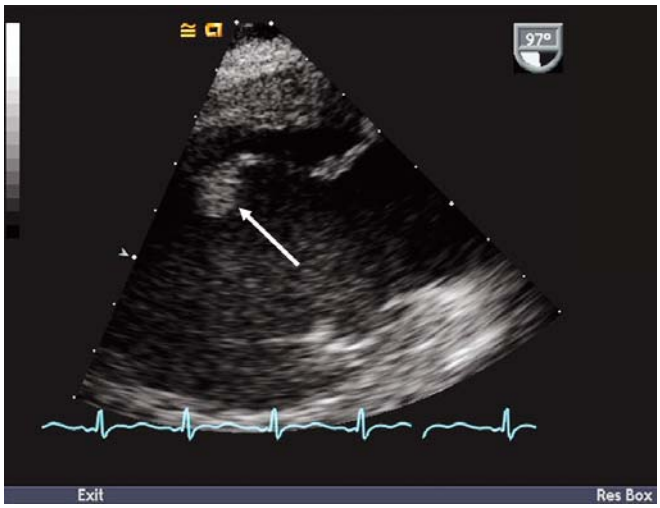


FIGURE 9: Two-dimensional echocardiography illustrates rupture of the posteromedial papillary muscle (arrow) in a patient presenting in cardiogenic shock from acute severe mitral regurgitation

can be used to stabilize the patient. Intravenous sodium nitroprusside can produce dramatic hemodynamic improvement.[33] Vasopressors should be avoided as they increase the regurgitant volume and further impair forward cardiac output. In severe hemodynamic compromise, IABP is indicated to improve cardiac output, decrease regurgitant volume and preserve coronary perfusion.[45]

DIAGNOSTIC EVALUATION

Cardiogenic shock can often be suspected by the presence of signs of shock in the setting of acute myocardial infarction (Table 1). Further testing should be performed to confirm the diagnosis of cardiogenic shock given that there is considerable overlap with other causes of shock. Echocardiography is an invaluable tool for evaluating biventricular dysfunction and excluding mechanical complications of myocardial infarction as a cause of cardiogenic shock. However image quality can be suboptimal due to mechanical ventilation, body habitus, chest deformities or positioning. Pulmonary artery catheterization is often useful, especially in patients who do not have prompt recovery from a shock state with reperfusion to guide further therapy. Invasive arterial monitoring is essential to guide further therapy.[45]

In addition to a diagnostic tool, echocardiography can be used as a tool to prognosticate patients. In a substudy of the SHOCK trial, echocardiography was performed on 169 subjects. The only echocardiographic variables predictive of mortality were ejection fraction and mitral regurgitation.[21] Those that were alive at 1 year had a mean ejection fraction of 34% versus 28% in those that died. For those with an ejection fraction less than 28%, mortality at 1 year was 24% compared to 56% with an ejection fraction greater than or equal to 28%. Similarly, those with no or mild mitral regurgitation had improved survival compared to those with more significant regurgitation.[21]

MEDICAL MANAGEMENT

The mainstay of medical management for cardiogenic shock includes inotropic and vasopressor agents.[45,46] Although dopamine and dobutamine improve the hemodynamics acutely in cardiogenic shock, there is no data to suggest that they improve survival. These agents increase myocardial oxygen demand, which may worsen supply-demand mismatch in an already failing heart. Although norepinephrine is often a second-line agent given its potent alpha effects, it is useful in patients who have a normal systemic vascular resistance in cardiogenic shock. Recent data suggest that the role of dopamine may need to be reconsidered as there is evidence that treatment with dopamine increases short-term mortality in comparison with those treated with norepinephrine.[47] Pure alpha agents are contraindicated in cardiogenic shock as they increase afterload and further depress cardiac output. Vasodilators may be useful in preshock states; however, they are not recommended as lone agents once shock has ensued as they can lead to further hypotension, thus decreasing coronary blood flow.[48] Vasodilators may be useful when used together with IABP or inotropes; however, there are no trials that have evaluated this strategy. Loop diuretics should be used when there is pulmonary congestion.

MECHANICAL SUPPORT

Considering the profound hemodynamic alterations that are germane to cardiogenic shock, adjunctive mechanical circulatory support is often needed.[1] Several devices are available for mechanical circulatory support in cardiogenic shock. They include IABP, TandemHeart (CardiacAssist, Inc., Pittsburgh, PA), Impella (Abiomed, Inc., Danvers, MA) and surgically implanted left ventricular assist devices (LVAD). While there are significant differences between the mode of action, hemodynamic support and available literature concerning each device, the common objective is maintenance of adequate blood pressure, tissue perfusion and oxygenation. Although not intended to be an exhaustive review of all modalities historically used for mechanical circulatory support, this section will highlight current devices that are most frequently employed in this clinical situation, their indications, limitations and future trends. Devices have been discussed in chronological order of their development.

INTRA-AORTIC BALLOON PUMP

The IABP was developed by a team led by Dr Adrian Kantrowitz. The first clinical implant was performed at Maimonides Hospital, Brooklyn, New York in October 1967 for a 48-year-old woman who was in cardiogenic shock unresponsive to traditional therapy.[49] An IABP was inserted by a cut-down of the left femoral artery. Pumping was performed for approximately 6 hours. Shock reversed and the patient was subsequently discharged home.

The size of the original balloon catheter was 15 French, but eventually 7–9 French balloons were developed. The balloon was initially inserted through a surgical cut-down of the femoral artery, requiring a second operation for removal of the balloon catheter. Since 1979, percutaneous placement of the balloon has been adopted using the Seldinger technique. Sequential design improvements have led to a decrease in device diameter (and therefore smaller sheaths are required for insertion, reducing vascular complications), more precise algorithms for triggering, requiring less user input and adjustments and fiber-optic sensors, which allow more precise waveform detection.

Intra-aortic balloon pump (IABP) has become the most common method of mechanical cardiac assistance in ACS today. It is commonly inserted via a transfemoral approach, with the tip placed in the descending aorta, just distal to the left subclavian artery, using fluoroscopic landmarks and with the distal end of the balloon superior to the ostia of the renal arteries. This is most commonly accomplished in the cardiac catheterization laboratory, but successful insertion of the pump may be performed at the bedside (generally in the intensive care unit) and in the operating room. Inflation and deflation are synchronized to the patient's cardiac cycle. Inflation occurs at the onset of diastole, resulting in proximal and distal displacement of blood volume in the aorta. Deflation occurs just prior to the onset of systole, resulting in reduced LV afterload. Advantages of the IABP include widespread availability and ease of use, as well as familiarity with its mode of action in most catheterization labs and intensive care units.

Use of an IABP improves coronary and peripheral perfusion during diastolic balloon inflation, and augments LV performance during systolic balloon deflation with an acute decrease in afterload. Accurate timing of inflation and deflation provides optimal support.

Contraindications for IABP insertion include severe aortic insufficiency, aortic dissection and severe peripheral vascular disease. Complications associated with IABP have decreased in the modern era, likely due to miniaturization of the device. In the largest series, the overall and major complication rates were 7.2% and 2.8% respectively.[50] Risk factors for complications include female sex, small body size and peripheral vascular disease.

Despite over four decades of use, high-quality scientific evidence supporting clinical use of intra-aortic balloon counterpulsation from randomized clinical trials still lags behind its widespread clinical adoption. To date, there are no randomized clinical trials of IABP performed specifically for STEMI complicated by cardiogenic shock, and only a few (relatively small) randomized clinical trials have studied IABP therapy in STEMI. The American College of Cardiology and American Heart Association STEMI guidelines list IABP therapy in cardiogenic shock as a class IB recommendation.[51] The European Society of Cardiology STEMI guidelines also strongly recommend supportive treatment with an IABP in cardiogenic shock patients (Table 2).[52]

TABLE 2

ACC/AHA recommendations for cardiogenic shock*

Class 1A: Primary percutaneous coronary intervention (PCI) is recommended for patients < 75 years, with ST elevation or LBBB or who develop shock within 36 hours of MI and are suitable for revascularization that can be performed within 18 hours of shock.
Class 1.1a: Primary PCI is reasonable for selected patients 75 years or older with ST elevation or LBBB or who develop shock within 36 hours of MI and are suitable for revascularization that can be performed within 18 hours of shock.
Class 1A: Intra-aortic ballon pulsation when cardiogenic shock is not quickly reversed with pharmacologic therapy.
*ACC/AHA Revision of Guidelines for the management of STEMI. Circulation. 2004;110.

Although widely adopted by the clinical community and endorsed by official guidelines, the efficacy of IABP use in cardiogenic shock has come under significant scrutiny lately. A recent systematic review and meta-analysis from 2009 challenged established guidelines, and found that there is insufficient evidence endorsing the current guideline recommendation for the use of IABP therapy in the setting of STEMI complicated by cardiogenic shock.[53] Two separate meta-analyses were performed, the first including seven randomized trials comprising 1,009 patients with STEMI, and the second including nine cohort studies of STEMI patients with cardiogenic shock (n = 10,529). IABP showed neither a 30-day survival benefit nor improved LV ejection fraction, while being associated with significantly higher stroke and bleeding rates. In patients treated with thrombolysis, IABP was associated with an 18% [95% confidence interval (CI), 16–20%; p = 0.0001] decrease in 30-day mortality, but the effect was confounded due to significantly higher revascularization rates in IABP patients compared to patients without support. However, in patients treated with primary PCI, IABP was associated with a 6% (95% CI, 3–10%; p = 0.0008) increase in 30-day mortality. The authors concluded that the pooled randomized data do not support IABP use in patients with high-risk STEMI. The meta-analysis of cohort studies in the setting of STEMI complicated by cardiogenic shock supported IABP therapy adjunctive to thrombolysis. In contrast, the observational data did not support IABP therapy adjunctive to primary PCI. All available observational data concerning IABP therapy in the setting of cardiogenic shock is importantly hampered by bias and confounding.

LEFT VENTRICULAR ASSIST DEVICE

Surgically implanted left ventricular assist devices (LVADs) are another option for mechanical support in cardiogenic shock patients. Manufactured by a variety of companies, these devices remove blood through a cannula placed at the LV apex and return blood to the ascending aorta. These devices have extensively been used for other indications, such as bridge-to-transplant,

post-cardiac surgery recovery and as destination therapy in patients with severe heart failure who are not candidates for transplantation. LVADs provide significant augmentation of cardiac output with preload reduction. In cardiogenic shock patients, surgically implanted LVADs have generally been used as a bridge to cardiac transplantation. In the largest reported LVAD series to date, 74% of 49 patients survived to transplantation, and 87% of transplanted patients survived to hospital discharge after receiving a variety of surgical LVADs.[54]

However they are not widely used in cardiogenic shock due to their lack of availability at many institutions (even those providing primary PCI) as well as the logistical challenges involved in assembling an operating team and room in a short time frame.

TANDEMHEART

TandemHeart (CardiacAssist, Inc., Pittsburgh, PA) received United States FDA clearance in 2003, as a percutaneous circulatory assist system. The system consists of a 21 French inflow cannula, an extracorporeal centrifugal pump rotating at up to 7,500 rpm, a femoral outflow cannula (15F–17F), and a microprocessor-based pump controller, which can provide an output of up to 4 l/min (Fig. 10). Its inflow cannula draws blood from the left atrium (via femoral vein access and transseptal puncture), and its outflow cannula returns blood to the femoral artery in a retrograde fashion.

Limitations of the device include the need for a large (21 French) cannula size, leading to frequent peripheral vascular compromise, potential for a residual left-to-right shunt due to the transseptal approach, need for atrial cannulation, which has a higher risk of wall suction disruptions (compared to a direct ventricular approach), and limited forward flow through the pump circuit.

In one small, randomized, multicenter trial comparing the IABP to the TandemHeart for cardiogenic shock in a patient population comprised mostly of acute MI patients (of which the majority were failing treatment with an IABP at enrollment), Burkhoff et al. showed significant increases in cardiac index (CI) and mean arterial blood pressure and a significant decrease in pulmonary capillary wedge pressure in those randomized to TandemHeart compared with those randomized to IABP.[55] Overall, 30-day survival and severe adverse events were not significantly different between the two groups, although the study was underpowered to detect a mortality difference. However, the incidence of bleeding and distal leg ischemia was higher in the TandemHeart arm. A single-center study of comparable size reached similar conclusions.[56]

In clinical practice, the complexity of the cannulation, the transseptal technique, and the need for full anticoagulation has limited its use to the most experienced institutions.

IMPELLA

The Impella 2.5 (Abiomed, Inc., Danvers, MA) is a catheter-mounted axial flow miniature pump, capable of delivering up to 2.5 l/min of blood from the left ventricle, across the aortic valve, and into the aortic root. It has only one cannula (functioning as both inflow and outflow) positioned across the aortic valve, and contiguous to the integrated motor that comprises the largest-diameter section of the catheter (12 French) (Fig. 11). Control and power supply to the device are delivered via the Impella console.

An infusion pump controls a purge system designed to keep blood from entering the motor compartment.

Unlike the IABP, the Impella device does not require synchronization with ventricular activity. Since the pump delivers nonpulsatile flow, there is no need for timing of the

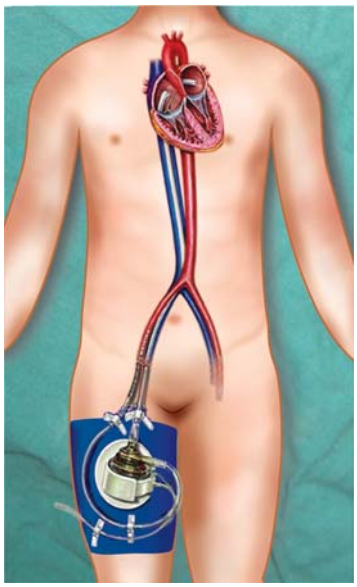


FIGURE 10: The TandemHeart system uses a 21 French intake cannula placed in the left atrium using a transseptal approach, and a 15F–17F femoral arterial return cannula (*Source*: Modified from Kar B, Forrester M, Gemmato C, et al. Use of the TandemHeart percutaneous ventricular assist device to support patients undergoing high-risk percutaneous coronary intervention. J Invasive Cardiol. 2006;18:93-6)

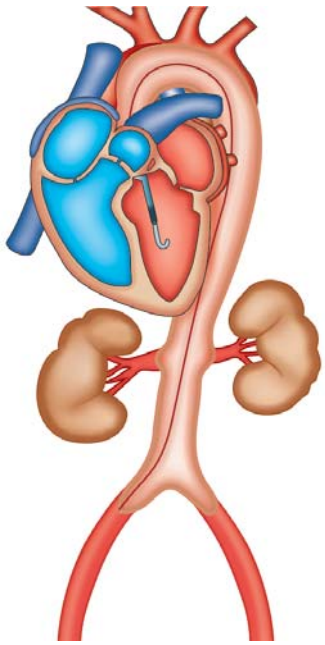


FIGURE 11: The Impella 2.5 device is positioned in the left ventricle in a retrograde fashion across the aortic valve. Blood is removed from the left ventricle and pumped into the ascending aorta (*Source*: http://abiomedtraining.com/QSV/Video1/index.html)

device with the cardiac cycle. Impella 2.5 was approved for use in the United States in June 2008, while the Impella 5 l/min device (Impella 5.0 and Left Direct) was approved for use in the United States in April 2009.

The device is inserted using a modified monorail technique under direct fluoroscopic control. After arterial access is achieved, the 13 French peel-away sheath is positioned. A coronary diagnostic catheter (typically JR4, Multipurpose, or AL1) and, subsequently, a 0.018-inch guidewire are placed across the aortic valve into the left ventricle. Once the guidewire is across the aortic valve, the coronary catheter is removed, and the Impella catheter is advanced to the left ventricle.

Verification of positioning is accomplished by using both a pressure lumen adjacent to the motor as well as motor current monitoring. The device is placed using fluoroscopic guidance to avoid kinking the catheter and compromising the purge lumen. With the device positioned in the left ventricle, the wire is removed, and the device is started at the lowest performance level. Subsequently, once stable positioning and performance have been confirmed, performance characteristics can be adjusted to the desired level.

Implantation time for the Impella device has been reported in a study by Seyfarth et al., and compared to the IABP in a cardiogenic shock patient population.[57] IABP implantation times ranged 6–22 minutes (mean = 14 minutes), while Impella implantation time was 14–31 minutes (mean = 22 minutes; p = 0.40). This ISAR-SHOCK study examined the hemodynamic changes produced by an Impella device compared to an IABP.[57] CI after 30 minutes of support was significantly increased in patients with the Impella 2.5, compared with patients with IABP (Impella: change in CI 0.49 ± 0.46 l/min/m^2; IABP: change in CI 0.11 ± 0.31 l/min/m^2; p = 0.02). Overall 30-day mortality was 46% in both groups, but the study was underpowered for clinical outcomes.

Questions that await clarification from larger randomized trials pertain to the higher incidence of hemolysis (as assessed by measurements of free hemoglobin, which was significantly higher in Impella patients in the first 24 hours), and the higher need for transfusion of packed red blood cells and fresh-frozen plasma in the Impella group (red blood cells: Impella 2.6 ± 2.7 U vs IABP 1.2 ± 1.9 U, p = 0.18; and fresh-frozen plasma: Impella 1.8 ± 2.5 U vs IABP: 1.0 ± 1.7 U, p = 0.39).[58] A major limitation of the trial is the lack of data on major bleeding, which would be expected to be higher in the Impella arm. This could be inferred both from the higher use of blood products (above), as well as the need to use a 13 French sheath for the Impella device (as opposed to 8 French for IABP).

An industry-sponsored clinical trial in the acute MI patient population, RECOVER II, is testing the ability of the device to restore stable hemodynamics, reduce infarct size to improve residual cardiac function, and reduce overall mortality from cardiogenic shock relative to existing treatment modes (IABP).[59] Currently, the trial is still in the recruitment phase (ClinicalTrials.gov identifier: NCT00562016).

REVASCULARIZATION

The question as to whether cardiogenic shock patients would benefit from emergent mechanical coronary revascularization by PCI or CABG (as opposed to aggressive medical therapy) was first answered by the landmark SHOCK trial.[20] In this study, 302 patients were randomly assigned to either initial medical stabilization (150 patients) or emergent revascularization (152 patients). The use of IABP was high (86% in both groups), and a large proportion of patients in the medical stabilization arm received thrombolytics (63%). Although 30-day mortality was not significantly different between the groups, 6-month mortality was lower in the revascularization group than in the medical-therapy group (50.3% vs 63.1%, p = 0.027).

At 1 year, there was a 13% absolute increase in survival for patients assigned to early revascularization, and this benefit was sustained up to 3 years (67% relative improvement in mortality).[12] Although incomplete, another randomized study[60] demonstrated a similar benefit. Numerous registries, including the SHOCK Registry,[30] have strengthened the assertion that early mechanical revascularization is beneficial in cardiogenic shock patients.

Which particular method of mechanical coronary revascularization should be chosen for cardiogenic shock patients: PCI or CABG? PCI has the advantage of wider availability in the community and generally shorter reperfusion times. If successful, timely PCI confers a survival advantage, an important consideration since the SHOCK trial demonstrated a trend toward reduced clinical benefit if reperfusion was delayed. Nonetheless, a reduction in mortality was seen if revascularization was performed even after 48 hours from myocardial infarction and 18 hours after the onset of shock.[61] In this subanalysis of the SHOCK trial, mortality was 38% if TIMI III flow was achieved, but rose to 55% with TIMI II flow, and TIMI I or 0 was always fatal. A retrospective review of 10-year trends in Swiss hospitals showed that more frequent use of PCI in ACS patients without initial cardiogenic shock was associated with a decrease in incidence of cardiogenic shock.[62] Unsuccessful PCI has consistently been shown to be associated with significantly worse outcomes.[63] Adjunctive pharmacological treatment to PCI (GPIIb/IIIa inhibitors) have independently been associated with improved outcomes in patients undergoing PCI in the large ACC-National Cardiovascular Data Registry,[64] and in a small subset of cardiogenic shock patients in a randomized trial using abciximab.[65]

A history of previous myocardial infarction or failed thrombolysis is generally viewed as conferring a worse prognosis. Although some studies cite the presence of multivessel disease as being an adverse predictor, others do not.[62] Nonetheless the prevalence of multivessel disease is very high in cardiogenic shock patients (87% in the SHOCK trial). Therefore the question of performing complete versus culprit vessel revascularization is quite important, yet not entirely clarified. Despite having a high prevalence of multivessel disease, most patients in the SHOCK trial (87%) underwent single-vessel PCI, although the proportion of those undergoing multivessel PCI rose steadily as the study was progressing. One-year survival was only 20% after a single-stage multivessel procedure, compared to 55% after single-vessel PCI. It is not clear if these observations might be due to the low utilization rate of stents (34%), since stenting has been correlated with improved outcomes in multiple registries.[64]

CABG has historically been able to achieve complete revascularization in a larger proportion of patients and was used in 37.5% of patients in the SHOCK trial. Patients having left main and multivessel disease were more likely to undergo CABG. Despite the possibility of selection bias, overall outcomes with PCI and CABG were equivalent for both survival and quality of life. Outside of randomized studies, emergent CABG is much less likely to be used as an initial revascularization method (under 10%).[66]

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Chapter 53

Acute Right Ventricular Infarction

James A Goldstein

Chapter Outline

- Patterns of Coronary Compromise Resulting in RVI
- Right Ventricular Mechanics and Oxygen Supply-Demand
- Effects of Ischemia on RV Systolic and Diastolic Function
- Determinants of RV Performance in Severe RVI
  - Importance of Systolic Ventricular Interactions
  - Compensatory Role of Augmented Right Atrial Contraction
  - Deleterious Impact of Right Atrial Ischemia
- Natural History of Ischemic RV Dysfunction
- Effects of Reperfusion on Ischemic RV Dysfunction
- Rhythm Disorders and Reflexes Associated with RVI
  - Bradyarrhythmias and Hypotension
  - Ventricular Arrhythmias
- Mechanical Complications Associated with RVI
- Clinical Presentations and Evaluation
- Noninvasive and Hemodynamic Evaluation
- Differential Diagnosis of RVI
- Therapy
  - Physiologic Rhythm
  - Optimization of Preload
  - Anti-ischemic Therapies
  - Reperfusion Therapy
  - Inotropic Stimulation
  - Mechanical Assist Devices

INTRODUCTION

Based on early experiments of right ventricular (RV) performance, it was felt for many years that RV contraction was unimportant in the circulation and that, despite loss of RV contraction, pulmonary flow could be generated by a passive gradient from a distended venous system and active right atrial contraction.[1] However, recognition of the profound hemodynamic effects of RV systolic dysfunction became evident during the 1970s with the description of severe RV infarction (RVI), resulting in severe right heart failure, clear lungs and hypotension low output despite intact global left ventricular (LV) systolic function.[2-4] Nearly 50% of patients with acute ST elevation inferior myocardial infarction (IMI) suffer concomitant RVI, which is associated with higher in-hospital morbidity and mortality related to hemodynamic and electrophysiologic complications.[5-7] Although the magnitude of hemodynamic derangements is related to the extent of RVFW contraction abnormalities,[7] some patients tolerate severe RV systolic dysfunction without hemodynamic compromise whereas others develop life-threatening low output, emphasizing that additional factors modulate the clinical expression of RVI. Importantly, the term RV "infarction" is to an extent a misnomer. For in most cases acute RV ischemic dysfunction appears to represent viable myocardium which recovers over time, especially following successful reperfusion and even after prolonged occlusion.[8-10]

This chapter will review the pathophysiology, hemodynamics, natural history and management of patients with IMI complicated by RVI. Importantly, we will highlight five key areas in which advances may impact catheterization and laboratory management of these acutely ill patients, including:

- The relationship between the site of right coronary artery (RCA) occlusion and the presence and magnitude of right heart ischemia and its complications.
- The pathophysiologic mechanisms leading to hemodynamic compromise and their relevance to pharmacologic and mechanical interventions.
- Bradyarrhythmias and tachyarrhythmias complicating management during acute occlusion and reperfusion.
- The concept that RV "infarction" is actually a misnomer, for even severe acute ischemic RV dysfunction is nearly always reversible.
- The compensatory mechanisms maintaining hemodynamic performance under conditions of profound RV pump function.
- The benefits of mechanical reperfusion therapy on hemodynamics and clinical outcome, even after prolonged occlusion and in patients with severe shock.

PATTERNS OF CORONARY COMPROMISE RESULTING IN RVI

Significant RVI nearly always occurs in association with acute transmural inferior-posterior LV myocardial infarction (MI) and the RCA is always the culprit vessel,[11] typically a proximal occlusion compromising flow to one or more of the major RV branches (Figs 1 and 2). In contrast, distal RCA occlusions or circumflex culprits that spare RV branch perfusion rarely

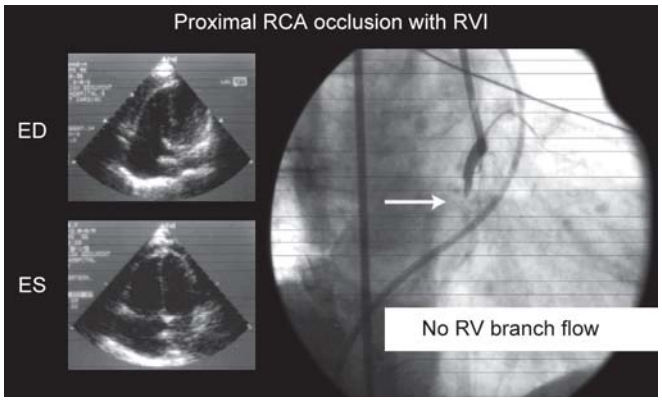


FIGURE 1: Patient with a proximal right coronary artery (right panel, arrow) compromising the right ventricular branches and resulting in severe RVI, indicated on echo as severe RV free wall dysfunction and depressed global RV performance at end systole (ES) and marked RV dilation at end diastole (ED)

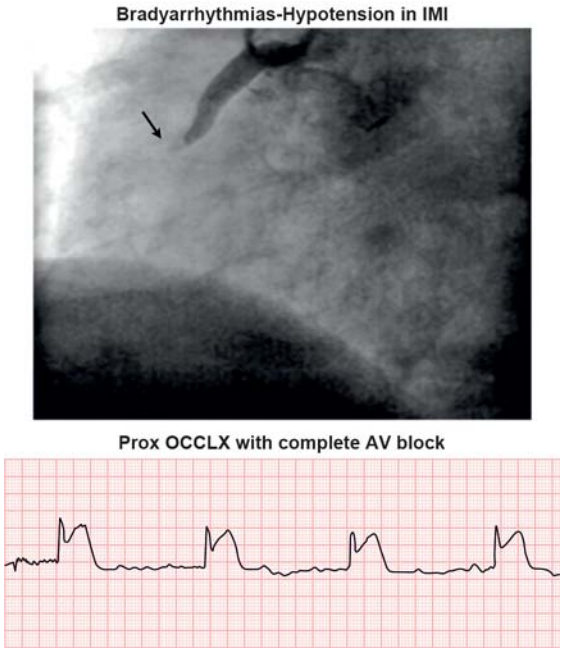


FIGURE 2: Patient with proximal right coronary artery occlusion (arrow) complicated by third-degree AV block. (*Source*: Goldstein JA, et al. Coronary Artery Disease. 2005;16:267, with permission)

compromise RV performance.[9] Occasionally, isolated RVI may develop from occlusion of a nondominant RCA or selective compromise of RV branches during percutaneous interventions.

At necropsy, RVI inscribes a "tripartite" signature consisting of LV inferior-posterior wall, septal and posterior RV free wall (FW) necrosis contiguous with the septum.[12] However, it is important to emphasize that these autopsy patterns do not reflect the vast majority of patients who survive acute RVI, for even in the absence of reperfusion of the infarct-related artery, most patients with severe ischemic RV dysfunction manifest spontaneous early hemodynamic improvement and later recovery of RV function.[7-10] In fact, chronic right heart failure attributable to RVI is rare. Thus, the term RV "infarction" is to an extent a misnomer, as in most cases acute RV ischemic dysfunction appears to represent predominantly viable myocardium. These responses are in marked contrast to the effects of ischemia on the LV.[13-15]

RIGHT VENTRICULAR MECHANICS AND OXYGEN SUPPLY-DEMAND

The right and left ventricles differ markedly in their anatomy, mechanics, loading conditions and metabolism, therefore it should not be surprising that they have strikingly different oxygen supply and demand characteristics,[16-18] and thus manifest disparate responses to ischemic insults. The LV is a thick-walled pressure pump. In contrast, the pyramidal-shaped RV with its thin crescentic free wall is designed as a volume pump, ejecting into the lower resistance pulmonary circulation. RV systolic pressure and flow are generated by RVFW shortening and contraction toward the septum from apex to outflow tract.[7,18] The septum is an integral architectural and mechanical component of the RV chamber and, even under physiologic conditions, LV septal contraction contributes to RV performance. The RV has a more favorable oxygen supply-demand profile than the LV. RV oxygen demand is lower owing to lesser myocardial mass, preload and afterload.[16,17] RV perfusion also is more favorable, due to the dual anatomic supply system from left coronary branches. Also, the RVFW is thinner, develops lower systolic intramyocardial pressure and faces less diastolic intracavitary pressure, and lower coronary resistance favors acute collateral development to the RCA.[19]

EFFECTS OF ISCHEMIA ON RV SYSTOLIC AND DIASTOLIC FUNCTION

Proximal RCA occlusion compromises RVFW perfusion, resulting in RVFW dyskinesis and depressed global RV performance reflected in the RV waveform by a sluggish, depressed and systolic waveform (Figs 3 and 4).[8,11,20-22] RV systolic dysfunction diminishes transpulmonary delivery of LV preload, leading to decreased cardiac output despite intact LV contractility. Biventricular diastolic dysfunction contributes to hemodynamic compromise.[20-24] The ischemic RV is stiff and dilated early in diastole, which impedes inflow leading to rapid diastolic pressure elevation. Acute RV dilatation and elevated diastolic pressure shift the interventricular septum toward the volume-deprived LV, further impairing LV compliance and filling. Abrupt RV dilatation within the noncompliant pericardium elevates intrapericardial pressure, the resultant constraint further impairing RV and LV compliance and filling. These effects contribute to the pattern of equalized diastolic pressures and RV "dip-and-plateau" characteristic of RVI.[20–24]

DETERMINANTS OF RV PERFORMANCE IN SEVERE RVI

IMPORTANCE OF SYSTOLIC VENTRICULAR INTERACTIONS

Despite the absence of RVFW motion, an active albeit depressed RV systolic waveform is generated by systolic interactions mediated by primary septal contraction and through mechanical displacement of the septum into the RV cavity associated with paradoxical septal motion (Fig. 1).[8,22-24] In the LV, acute

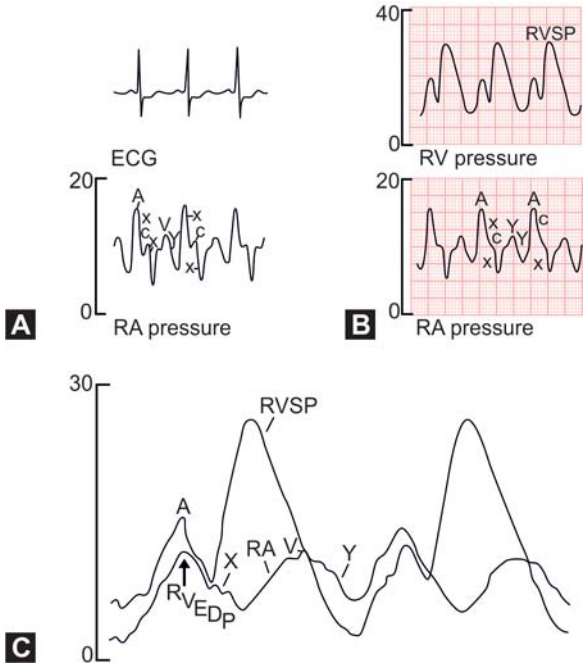
ischemia results in regional dyskinesis; such dyssynergic segments are stretched in early isovolumic systole by neighboring contracting segments through regional intraventricular interactions that dissipate the functional work of these neighboring regions.[25] The ischemic dyskinetic RVFW behaves similarly and must be stretched to the maximal extent of its systolic lengthening through interventricular interactions before providing a stable buttress upon which actively contracting segments can generate effective stroke work, thereby impose a mechanical disadvantage that reduce contributions to cardiac performance.[17,22-24] The compensatory contributions of LV septal contraction are emphasized by the deleterious effects of LV septal dysfunction, which exacerbates hemodynamic compromise associated with RVI.[24] In contrast, inotropic stimulation enhances LV septal contraction and thereby augments RV performance through augmented compensatory systolic interactions.

COMPENSATORY ROLE OF AUGMENTED RIGHT ATRIAL CONTRACTION

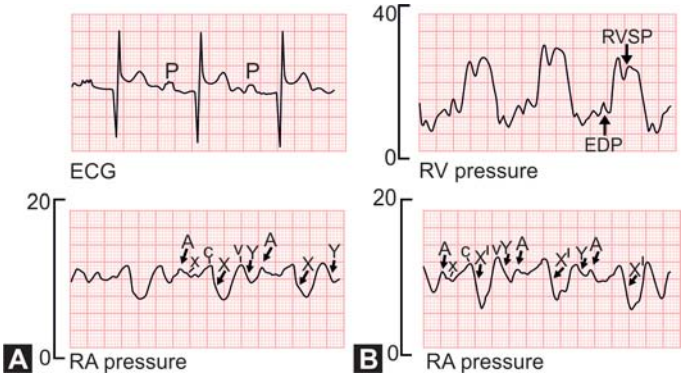
The hemodynamic benefits of augmented atrial contraction to performance of the ischemic LV are well documented.[26] Similarly, augmented RA booster pump transport is an important compensatory mechanism that optimizes RV performance and cardiac output.[21-23] When RVI develops from occlusions compromising RV but sparing RA branches, RV diastolic dysfunction imposes increased preload and afterload on the right atrium, resulting in enhanced RA contractility that augments RV filling and performance. This is reflected in the RA waveform as a "W" pattern characterized by a rapid upstroke and increased peak A wave amplitude, sharp X descent reflecting enhanced atrial relaxation and blunted Y descent owing to pandiastolic RV dysfunction (Figs 3A to C).

DELETERIOUS IMPACT OF RIGHT ATRIAL ISCHEMIA

Conversely, more proximal RCA occlusions compromising atrial, as well as RV branches result in ischemic depression of atrial function, which compromises RV performance and cardiac output.[21-23] RA ischemia manifests hemodynamically as more severely elevated mean RA pressure and inscribes an "M" pattern in the RA waveform characterized by a depressed A wave and X descent, as well as blunted Y descent (Figs 4A and B). Ischemic atrial involvement is not rare, with autopsy studies documenting atrial infarction in up to 20% of cases of ventricular infarction, with RA involvement five times commoner than left.[27,28] Under conditions of acute RV dysfunction, loss of augmented RA transport due to ischemic depression of atrial contractility or AV dyssynchrony precipitates more severe hemodynamic compromise.[21-23] RA dysfunction decreases RV filling, which impairs global RV systolic performance, thereby resulting in further decrements in LV preload and cardiac output. Impaired RA contraction diminishes atrial relaxation; thus RA ischemia impedes venous return and right heart filling owing to loss of atrial suction associated with atrial relaxation during the X descent.



FIGURES 3A TO C: Hemodynamic recordings from a patient with right atrial (RA) pressure W pattern, timed to ECG (A) and RV pressures (B and C). Peaks of W are formed by prominent A waves with an associated sharp "X" systolic descent, followed by a comparatively blunted "Y" descent. Peak RV systolic pressure (RVSP) is depressed, RV relaxation is prolonged, and there is a dip and rapid rise in RV diastolic pressure. (*Source*: Goldstein et al. Circulation. 1990;82:259, with permission)



FIGURES 4A AND B: RA pressure M pattern timed to electrocardiogram (A) and RV pressure (B). M pattern comprises a depressed A wave, X descent before a small C wave, a prominent "X" descent, a small V wave and a blunted Y descent. Peak RVSP is depressed and bifid (arrows) with delayed relaxation and an elevated end-diastolic pressure (EDP) (all pressures are measured in mm Hg). (*Source*: Goldstein et al. Circulation. 1990;82:259)

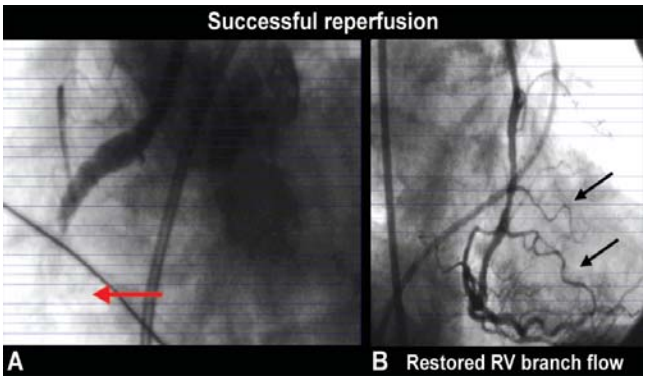
NATURAL HISTORY OF ISCHEMIC RV DYSFUNCTION

Although RVI may result in profound acute hemodynamic effects, arrhythmias and higher in-hospital mortality, many patients spontaneously improve within 3–10 days regardless of the patency status of the infarct-related artery.[9,10] Furthermore, global RV performance typically recovers with normalization within 3–12 months. Moreover, chronic unilateral right heart

failure secondary to RVI is rare. This favorable natural history of RV performance is in marked contrast to the effects of coronary occlusion on segmental and global LV function.[13-15] Observations from experimental animal studies confirm spontaneous recovery of RV function despite chronic RCA occlusion attributable to the more favorable oxygen supply-demand characteristics of the RV in general and the beneficial effects of collaterals in particular.[29] Similarly, in patients with chronic proximal RCA occlusion, RV function is typically maintained at rest and augments appropriately during stress.[10] The relative resistance of the RVFW to infarction is undoubtedly attributable to more favorable oxygen supply-demand characteristics. Preinfarction angina appears to reduce the risk of developing RVI, possibly due to preconditioning.[19]

EFFECTS OF REPERFUSION ON ISCHEMIC RV DYSFUNCTION

Although RV function may recover despite persistent RCA occlusion, acute RV ischemia contributes to early morbidity and mortality.[5-7] Furthermore, spontaneous recovery of RV contractile function and hemodynamics may be slow. The beneficial effects of successful reperfusion in patients with predominant LV infarction are well documented.[43,44] Observations in experimental animals[30] and in humans[8,31-33] now demonstrate the beneficial effects of reperfusion on recovery of RV performance. In patients, successful mechanical reperfusion of the RCA including the major RV branches leads to immediate improvement in and later complete recovery of RVFW function and global RV performance (Figs 5 and 6). Reperfusion-mediated recovery of RV performance is associated with excellent clinical outcome (Fig. 7). In contrast, failure to restore flow to the major RV branches is associated with lack of recovery of RV performance and refractory hemodynamic compromise leading to high in-hospital mortality, even if flow was restored in the main RCA. Findings now also demonstrate that successful mechanical reperfusion leads to superior late survival of patients with shock due to predominant RVI versus those with LV shock.[33]



FIGURES 5A AND B: Angiogram showing successful reperfusion in patient with right ventricular infarction who underwent primary angioplasty. (A) Total occlusion of the right coronary artery proximal to RV branches (arrow) in a patient before angiography, and (B) after angioplasty shows complete reperfusion in the right main coronary artery including the major RV branches (arrows). (*Source*: Bowers et al. N Eng J Med. 1998;338: 933, with permission)

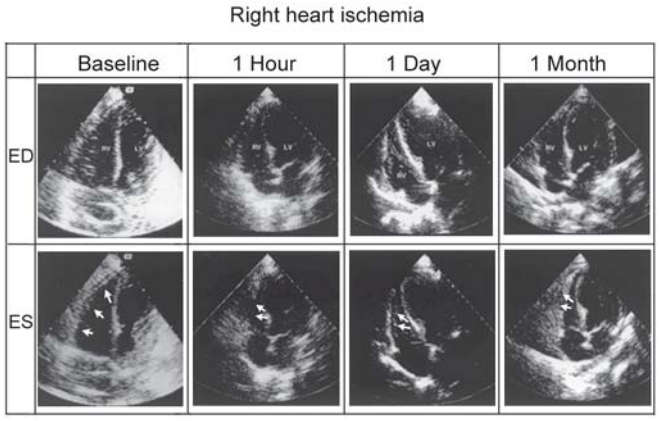


FIGURE 6: Echocardiographic images from a patient with acute IMI and RV ischemia undergoing successful angioplasty. End-diastolic and end-systolic images obtained at baseline show severe RV dilatation with reduced LV diastolic size. At ES, there was RVFW dyskinesis (arrows), intact LV function and compensatory paradoxical septal motion. One hour after angioplasty, there was striking recovery of RVFW contraction (arrows), resulting in marked improvement in global RV performance and markedly increased RV size and LV preload. At one day, there was further improvement in RV function (arrows), which at one month was normal. RV denotes right ventricle while LV denotes left ventricle. (*Source:* Bowers et al. N Eng J Med. 1998;338:933, with permission)

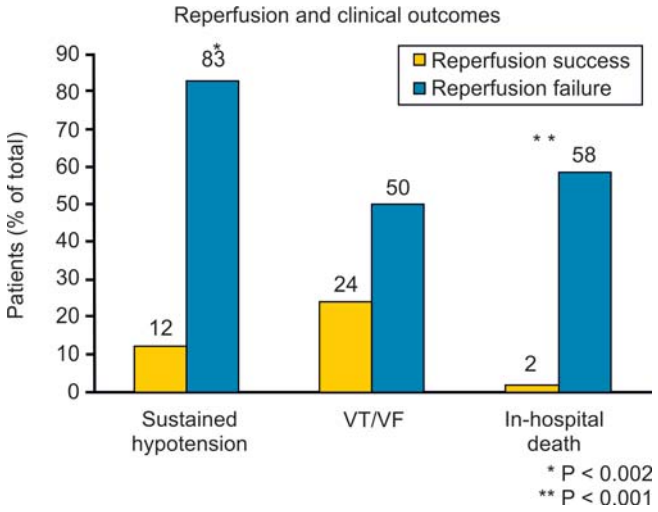


FIGURE 7: Bar graphs demonstrating benefits of successful reperfusion versus reperfusion failure with respect to reduced arrhythmias, sustained hypotension and in-hospital survival. (*Source*: Bowers et al. N Eng J Med. 1998;338:933, with permission)

Although evidence suggests that patients with IMI benefit from timely thrombolytic reperfusion, the specific short-term and long-term responses of those with RVI have not been adequately evaluated. Some thrombolytic studies suggested that RV function improves only in patients in whom RCA patency is achieved,[34-36] whereas others report little benefit.[37,38] More recent prospective reports demonstrate that successful thrombolysis imparts survival benefit in those with RV involvement and that failure to restore infarct-related artery patency is associated with persistent RV dysfunction and increased mortality.[38] Unfortunately, patients with RVI appear to be particularly resistant to fibrinolytic recanalization, owing to proximal RCA occlusion with extensive clot burden which,

together with impaired coronary delivery of fibrinolytic agents is attributable to hypotension.[38] There also appear to be a higher incidence of reocclusion following thrombolysis of the RCA. It is important to consider RVI separately in the elderly. Early reports suggested that elderly patients with RVI suffer 50% in-hospital mortality and that hemodynamic compromise in such cases is irreversible. However, recent studies now document the majority of elderly RVI patients undergoing successful mechanical reperfusion survive, including those with hemodynamic compromise.[32]

RHYTHM DISORDERS AND REFLEXES ASSOCIATED WITH RVI

BRADYARRHYTHMIAS AND HYPOTENSION

High-grade atrioventricular (AV) block and bradycardia-hypotension without AV block commonly complicate IMI and have been attributed predominantly to the effects of AV nodal ischemia and cardioinhibitory (Bezold-Jarisch) reflexes arising from stimulation of vagal afferents in the ischemic LV inferoposterior wall.[39-42] Patients with acute RVI are at increased risk for both high-grade AV block and bradycardia-hypotension without AV block.[5,42] Recent findings now document that during acute coronary occlusion, bradycardia-hypotension and AV block are far more common in patients with proximal RCA lesions (Fig. 2) inducing RV and LV inferior-posterior ischemia, compared to more distal occlusions compromising LV perfusion, but sparing the RV branches.[43] These observations suggest that the ischemic right heart may elicit cardioinhibitory-vasodilator reflexes. In patients with IMI, whose rhythm and blood pressure were stable during occlusion, similar bradycardic-hypotensive reflexes may be elicited during reperfusion[43,44] and also appear to be more common with proximal lesions (Fig. 8).

VENTRICULAR ARRHYTHMIAS

Patients with RVI are prone to ventricular tachyarrhythmias,[5,45] which should not be unexpected given that the ischemic RV is often massively dilated.[45] Autonomic denervation in the peri-infarct area may also play a role.[46] In patients with RVI, VT/VF may develop in a trimodal pattern, either during acute occlusion, abruptly with reperfusion or later.[45] However, successful mechanical reperfusion dramatically reduces the incidence of malignant ventricular arrhythmias,[8,45] presumably through improvement in RV function, which lessens late VT/VF. Occasionally, RVI may be complicated by recurrent malignant arrhythmias and in some cases intractable "electrical storm" (Fig. 9), possibly due to sustained severe RV dilatation.[45]

MECHANICAL COMPLICATIONS ASSOCIATED WITH RVI

Patients with acute RVI may suffer additional mechanical complications of acute infarction that may compound hemodynamic compromise and confound the clinical hemodynamic picture. Ventricular septal rupture is a particularly disastrous complication, adding substantial overload stress to the ischemically dysfunctional RV, precipitating pulmonary edema,

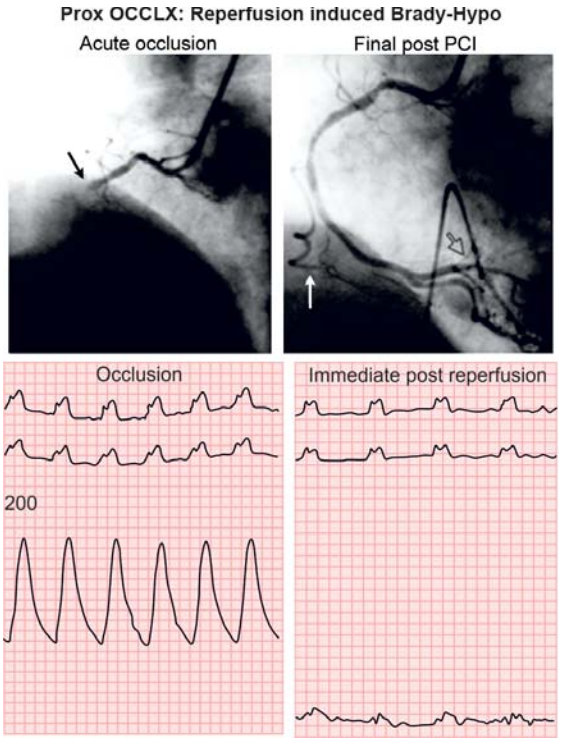


FIGURE 8: Patient with a proximal right coronary artery (left panel, arrow) compromising the RV branches (right panel, solid arrow) as well as the LV and atrioventricular nodal branches (right panel, open arrow), who developed profound repefrusion-induced bradycardia-hypotension. During occlusion there was sinus rhythm with normal blood pressure. Reperfusion by primary percutaneous transluminal coronary angioplasty resulted in abrupt but transient sinus bradycardia with profound hypotension. PCI denotes percutaneous coronary intervention. (*Source*: Goldstein JA et al. Coronary Artery Disease. 2005;16:269, with permission)

elevating pulmonary pressures and resistance and exacerbating low output.[47] Surgical repair is imperative, but may be technically difficult owing to extensive necrosis involving the LV inferior-posterior free wall, septum and apex. Catheter closure of such defects may be possible. Severe right heart dilatation and diastolic pressure elevation associated with RVI may stretch open a patent foramen ovale, precipitating acute right-to-left shunting manifest as systemic hypoxemia or paradoxical emboli.[48] Most PFO complications abate following successful mechanical reperfusions, as right heart pressures diminish with recovery of RV performance; rarely, some may require percutaneous closure.[49] Severe tricuspid regurgitation may also complicate RVI, developing as a result of primary papillary muscle ischemic dysfunction or rupture, as well as secondary functional regurgitation attributable to severe RV and tricuspid valve annular dilatation.[50]

CLINICAL PRESENTATIONS AND EVALUATION

Right ventricular infarction is often silent as only 25% of patients develop clinically evident hemodynamic manifestations.[7] Patients with severe RVI but preserved global LV function may be hemodynamically compensated, manifest by elevated JVP but clear lungs, normal systemic arterial pressure and intact perfusion. When RVI leads to more severe hemodynamic compromise, systemic hypotension and hypoperfusion result. Patients with IMI may initially present without evidence of

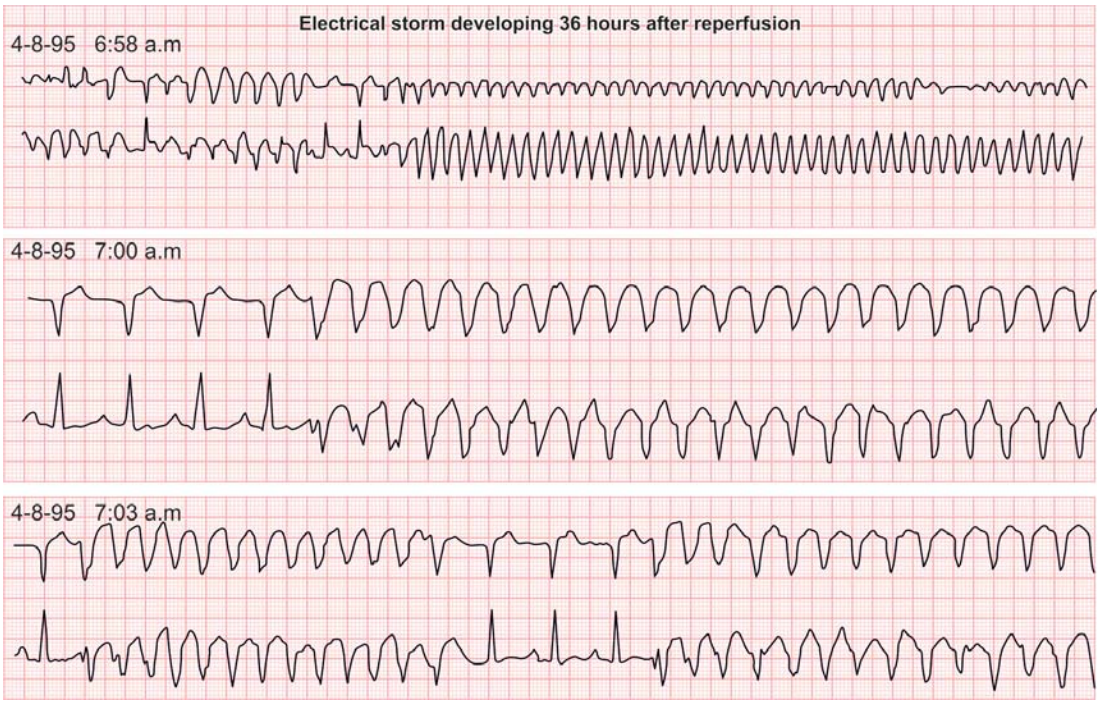


FIGURE 9: Patient with acute RVI who developed intractable ventricular arrhythmias 36 hours following otherwise successful mechanical reperfusion. The patient had sustained marked RV dilatation and dysfunction

hemodynamic compromise, but subsequently develop hypotension precipitated by preload reduction attributable to nitroglycerin[51] or associated with bradyarrhythmias.[43] When RVI develops in the setting of global LV dysfunction, the picture may be dominated by low output and pulmonary congestion, with right heart failure.

NONINVASIVE AND HEMODYNAMIC EVALUATION

Although ST segment elevation and loss of R wave in the right-sided ECG leads (V_{3R} and V_{4R}) are sensitive indicators of the presence of RVI,[52,53] they are not predictive of the magnitude of RV dysfunction nor its hemodynamic impact. Echocardiography is the most effective tool for delineation of the presence and severity of RV dilatation and depression of global RV performance. Echo also delineates the extent of reversed septal curvature that confirms the presence of significant adverse diastolic interactions, the degree of paradoxical septal motion indicative of compensatory systolic interactions, and the presence of severe RA enlargement which may indicate concomitant ischemic RA dysfunction and/or tricuspid regurgitation.

Invasive hemodynamic assessment of the extent and severity of right heart ischemic involvement has been extensively discussed.

DIFFERENTIAL DIAGNOSIS OF RVI

Important clinical entities to consider in patients who present with acute low output hypotension, clear lungs and disproportionate right heart failure include cardiac tamponade, acute pulmonary embolism, severe pulmonary hypertension, right heart mass obstruction and acute severe tricuspid regurgitation; entities including constrictive pericarditis or restrictive cardiomyopathy present a similar picture but are not acute processes (Table 1). The general clinical presentation of chest pain with acute IMI, together with echocardiographic documentation of RV dilatation and dysfunction, effectively excludes tamponade, constriction and restriction. Acute massive pulmonary embolism may also mimic severe RVI and, since the unprepared RV cannot acutely generate elevated RV systolic pressures (> 50–55 mm Hg), severe pulmonary hypertension may be absent. In such cases, absence of inferior LV myocardial infarction by ECG and echo point to embolism, easily confirmed by CT or invasive angiography. Severe pulmonary hypertension with RV decompensation may mimic severe RVI, but delineation of markedly elevated PA systolic pressures by Doppler or invasive hemodynamic monitoring excludes RVI, in which RV pressure generation is depressed. Acute primary tricuspid regurgitation should be evident by echocardiography, typically due to infective endocarditis with obvious vegetations.

TABLE 1

Differential diagnosis of hypotension with disproportionate right heart failure

- RVI
- Cardiac tamponade
- Acute pulmonary embolus
- Acute tricuspid regurgitation
- Pulmonary hypertension with RV failure
- Acute MI with LV failure
- Right heart mass obstruction
- Constriction/Restriction

THERAPY

Therapeutic options for the management of right heart ischemia (Table 2) follow directly from the pathophysiology discussed. Treatment modalities include: (1) restoration of physiologic

TABLE 2

RVI: Therapeutic algorithm

- Optimize oxygen supply-demand
- Establish physiological rhythm
- Optimize preload
- Inotropic stimulation for persistent low output
- Mechanical support devices:
  - IABP for refractory hypotension
  - RVAD
  - Reperfusion by primary PCI

rhythm; (2) optimization of ventricular preload; (3) optimization of oxygen supply and demand; (4) parenteral inotropic support for persistent hemodynamic compromise; (5) reperfusion and (6) mechanical support with intra-aortic balloon counterpulsation and RV assist devices.

PHYSIOLOGIC RHYTHM

Patients with RVI are particularly prone to the adverse effects of bradyarrhythmias. The depressed ischemic RV has a relatively fixed stroke volume, as does the preload-deprived LV. Therefore, biventricular output is exquisitely heart rate dependent, and bradycardia even in the absence of AV dyssynchrony may be deleterious to patients with RVI. For similar reasons, chronotropic competence is critical in patients with RVI. However, not only are such patients notoriously prone to reflex-mediated frank bradycardia, they often manifest a relative inability to increase the sinus rate in response to low output, owing to excess vagal tone, ischemia or pharmacologic agents. Given that the ischemic RV is dependent on atrial transport, the loss of RA contraction due to AV dyssynchrony further exacerbates difficulties with RV filling and contributes to hemodynamic compromise.[7,21,22] Although atropine may restore physiologic rhythm in some patients, temporary pacing is often required. Although ventricular pacing alone may suffice, especially if the bradyarrhythmias are intermittent, some patients require AV sequential pacing.[53] However, transvenous pacing can be difficult due to issues with ventricular sensing, presumably related to diminished generation of endomyocardial potentials in the ischemic RV. Manipulating catheters within the dilated ischemic RV may also induce ventricular arrhythmias.[54] Intravenous aminophylline may restore sinus rhythm in some patients with atropine-resistant AV block, a response likely reflecting reversal of ischemia-induced adenosine elaboration.[55,56]

OPTIMIZATION OF PRELOAD

In patients with RVI, the dilated, noncompliant RV is exquisitely preload dependent, as is the LV, which is stiff but preload deprived. Therefore, any factor that reduces ventricular preload tends to be detrimental. Accordingly, vasodilators and diuretics are contraindicated. Although experimental animal studies of RVI demonstrate hemodynamic benefit from volume loading,[57] clinical studies have reported variable responses to volume challenge.[58-60] These conflicting results may reflect a spectrum of initial volume status in patients with acute RVI, with those patients who are relatively volume-depleted benefiting, and those who are more replete manifesting a flat response to fluid resuscitation. Nevertheless, an initial volume challenge is appropriate for patients manifesting low output without pulmonary congestion, particularly if the estimated central venous pressure is less than 15 mm Hg. For those unresponsive to an initial trail of fluids, determination of filling pressures and subsequent hemodynamically monitored volume challenge may be appropriate. Caution should be exercised to avoid excessive volume administration above and beyond that documented to augment output, since the right heart chambers may operate on a "descending limb" of the Starling curve, resulting in further depression of RV pump performance as well as inducing severe systemic venous congestion. Abnormalities of volume retention and impaired diuresis may be related in part to impaired responses of the atrial natriuretic factor.[61]

ANTI-ISCHEMIC THERAPIES

Treatment of RVI should focus on optimizing oxygen supply and demand to optimize recovery of both LV and RV function and LV function. However, most anti-ischemic agents exert hemodynamic effects, which may be deleterious in patients with RVI. Specially, beta-blockers and some calcium channel blockers may reduce heart rate and depress conduction, thereby increasing the risk of bradyarrhythmias and heart block in these chronotropically dependent patients. The vasodilator properties of nitrates and calcium channel blockers may precipitate hypotension. In general, these drugs should be avoided in patients with RVI.

REPERFUSION THERAPY

The beneficial effects of successful reperfusion on RV function and clinical outcome, as well as the demonstrated efficacy and advantages of primary angioplasty versus thrombolysis in patients with acute right heart ischemic dysfunction have been discussed.

INOTROPIC STIMULATION

Parenteral inotropic support is usually effective in stabilizing hemodynamically compromised patients not fully responsive to volume resuscitation and restoration of physiologic rhythm.[7,23,58] The mechanisms by which inotropic stimulation improve low output and hypotension in patients with acute RVI have not been well studied. However, experimental animal investigations suggest that inotropic stimulation enhances RV performance by increasing LV septal contraction, which thereby augments septal-mediated systolic ventricular interactions.[23] Although an inotropic agent, such as Dobutamine, that has the least deleterious effects on afterload, oxygen consumption and arrhythmias is the preferred initial drug of choice, patients with severe hypotension may require agents with pressor effects (such as Dopamine) for prompt restoration of adequate coronary perfusion pressure. The "inodilator" agents, such as milrinone, have not been studied in patients with RVI, but their vasodilator properties could exacerbate hypotension.

MECHANICAL ASSIST DEVICES

Intra-aortic balloon pumping may be beneficial in patients with RVI and refractory low output and hypotension. Although there

is little research to shed light on the mechanisms by which it exerts salutary effects, balloon assist likely does not directly improve RV performance, but stabilizes blood pressure and thereby improves perfusion pressure throughout the coronary tree in severely hypotensive patients. Since RV myocardial blood flow is dependent on perfusion pressure, balloon pumping may therefore also improve RV perfusion and thereby benefit RV function, particularly if the RCA has been recanalized or if there is collateral supply to an occluded vessel. Intra-aortic balloon pumping may also potentially improve LV performance in those patients with hypotension and depressed LV function. Since performance of the dysfunctional RV is largely dependent on LV septal contraction, RV performance may also benefit. Recent reports suggest that percutaneous RV assist devices can improve hemodynamics in patients with refractory life-threatening low output, thereby providing the reperfused RV a bridge to recovery.[62]

SUMMARY

Acute RCA occlusion proximal to the RV branches results in RVFW dysfunction. The ischemic, dyskinetic RVFW exerts mechanically disadvantageous effects on biventricular performance. Depressed RV systolic function leads to a diminished transpulmonary delivery of LV preload, resulting in reduced cardiac output. The ischemic RV is stiff, dilated and volume dependent, resulting in pandiastolic RV dysfunction and septally mediated alterations in LV compliance, exacerbated by elevated intrapericardial pressure. Under these conditions, RV pressure generation and output are dependent on LV septal contraction and paradoxical septal motion. Culprit lesions distal to the RA branches augment RA contractility and enhance RV filling and performance. Bradyarrhythmias limit the output generated by the rate-dependent ventricles. Ventricular arrhythmias are common, but do not impact short-term outcomes if mechanical reperfusion is prompt. Patients with RVI and hemodynamic instability often respond to volume resuscitation and restoration of physiologic rhythm. Vasodilators and diuretics should generally be avoided. In some patients, parenteral inotropes are required. The RV is relatively resistant to infarction and usually recovers even after prolonged occlusion. However, prompt reperfusion enhances recovery of RV performance and improves the clinical course and survival of patients with ischemic RV dysfunction.

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Chapter 54

Surgical Therapy in Chronic Coronary Artery Disease

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Chapter Outline

- Technique of Surgical Therapy for Chronic Coronary Artery Disease
- Indications for Surgical Coronary Revascularization Advantages of CABG over Medical Treatment
- Comparing CABG to PTCA
- The Changing CABG Population
- When CABG may be Indicated
- When CABG is not Indicated
- Risk Factors for In-hospital Mortality Following CABG
  - Modifiable Risk Factors
  - Nonmodifiable Risk Factors
- Outcomes of Surgery
  - Graft Patency
  - Survival
  - Left Ventricular Function
  - Relief of Anginal Symptoms
  - Quality of Life
- Major Clinical Trials in Chronic Coronary Artery Disease
  - CABG versus Medical Management
  - PCI versus Medical Management
  - CABG vs Multivessel PTCA (Trials Comparing)
  - Trials Comparing Coronary Artery Bypass Grafting versus Percutaneous Coronary Transluminal Angioplasty Using Bare Metal Stent
  - Trials Comparing Coronary Artery Bypass Grafting versus Percutaneous Coronary Transluminal Angioplasty Using DES

TECHNIQUE OF SURGICAL THERAPY FOR CHRONIC CORONARY ARTERY DISEASE

Surgical management of coronary artery disease (CAD) has evolved over the last few decades from patients undergoing revascularization through full sternotomy and cardiopulmonary bypass (CPB) to off-pump revascularization and introduction of robotics for revascularization. The modern performance of aorto-coronary bypass by Favolaro at the Cleveland Clinic and the subsequent payment for coronary artery bypass grafting (CABG) by Medicare led to the impetus for the development of modern hospitals, with intensive care units, cardiac catheterization labs for diagnosis and treatment, and the evolution of heart failure specialization. Surgical revascularization has had far reaching applications and allowed the field of cardiothoracic surgery to evolve from its infancy.

While no two surgeons will perform any CABG in the exact same way, it has largely become routine. The standard coronary revascularization is approached through a median sternotomy. This approach has the advantage of allowing global access to the heart and allows harvesting the internal thoracic artery (left internal mammary artery—LIMA), which is used as a conduit. The standard CPB circuit consists of a venous drainage [either through a right atrial cannula, bicaval (SVC and IVC) cannulation, or femoral venous cannulation depending on the operation] and an arterial inflow cannula after full heparinization. Typically a two stage venous cannula is used in the right atrium for CABG, whereas entry into the cardiac chambers uses bicaval cannulation. Venous blood is collected in a reservoir and circulated through a heat exchanger/oxygenator and returned, circulated though an arterial filter and returned to the patient via an arterial cannula.

Myocardial protection has evolved over the past four decades. Over the years, numerous ways have evolved to allow better myocardial protection. The goal is to allow a bloodless field, minimize myocardial energy demand and decrease the extent of ischemia/reperfusion. The basic mode of cardioplegia requires rapid arrest of the heart with a high potassium substrate, mild hypothermia (32C), appropriate buffering solutions and avoiding depletion of intracellular substrate. Induction of immediate cardiac arrest after aorta has been cross-clamped minimizes depletion of high-energy phosphates by mechanical work. Potassium is the most common agent used and produces rapid arrest. Hypothermia protects ischemic myocardium by decreasing heart rate, slows the rate of high-energy phosphate degradation and decreases oxygen consumption. Buckberg's seminal experiments documented that the warm beating heart uses approximately 20 cc O_2/g myocardial tissue. The warm fibrillating heart consumed 16–20 cc, the cold fibrillating heart approximately 8 cc and the still potassium arrested heart approximately 4 cc. Thus, various strategies have evolved to induce a diastolic arrested cold heart for the perfomance of CABG.

Buffering of cardioplegia is necessary to prevent intracellular acidosis associated with surgically induced myocardial ischemia. Maintaining tissue pH of 6.8 or greater is associated with adequate protection. Hence, frequent infusion of cardioplegia every 10–20 min are necessary to prevent intracellular acidosis. Bicarbonate, phosphate, aminosulfonic acid, tris-

hydroxymethylaminomethane (THAM) and histidine buffers have all been utilized as cardioplegia additives to modulate the pH. To avoid intracellular edema, cardioplegia solution is isotonic in the range of 290–330 mOsm/L or slightly hyperosmolar. Over the years numerous cardioplegia solutions have been utilized ranging from crystalloid to blood to a mixture of the two.

Cardioplegia is infused either antegrade through the aortic root and in normal fashion through the coronary arteries or alternatively in a retrograde fashion through a cannula placed in the coronary sinus. Cardioplegia then flows retrograde through the coronary veins and into the coronary arteries. In a heart with significant CAD, most surgeons will employ a combination of the two techniques. Retrograde cardioplegia has the advantage of being distal to proximal stenoses, but is relatively poor for protection of the right heart. An advantage of retrograde is that it minimizes the interruption of the procedure, since there is no need for a competent aortic valve to administer cardioplegia.

At the University of Iowa, the conduct of a CABG is as follows:

- Median sternotomy.
- Harvesting internal thoracic artery(ies) and saphenous vein.
- After heparinization, cannulating aorta and right atrium.
- Ascending aorta is cross clamped, cardioplegia is infused down the aortic root to induce diastolic arrest. After 5 cc/kg is administered antegrade, an additional 5 cc/kg is administered retrograde. The pericardial well is cooled with iced saline.
- The right coronary vessel is bypassed first, followed by the obtuse marginals and diagonals. Distals are performed first.
- Each bypassed vessel is infused with cardioplegia.
- Cardioplegia is also given antegrade/retrograde every 10–20 min.
- Proximal anastomosis on the aorta is performed followed by the internal thoracic artery to LAD (if LAD needs to be bypassed).
- Potassium is discontinued. Air is evacuated from both the aorta and the ventricles as the heart starts to contract and the clamp is removed from the aorta.
- Hemostasis is confirmed and the patient is weaned from CPB.
- Temporary pacing wires are placed.
- Hemostasis is assured. Drainage tubes are placed and the sternum is closed followed by skin and subcutaneous layers.

INDICATIONS FOR SURGICAL CORONARY REVASCULARIZATION ADVANTAGES OF CABG OVER MEDICAL TREATMENT

The techniques of coronary artery bypass used today were first described in the 1960s. It was not until the 1970s that three major trials were conducted, establishing CABG superiority over medical management in only a select subset of patients. The CASS, VA-CABSCSG and European CSS trials randomized patients with stable angina to either contemporary medical management or CABG. Recent improvements in cardioprotection during CPB and a significant increase in the number of arterial grafts used have lead to an improvement in outcomes. On the other hand, statin therapy, aspirin and beta-blocker use was not standard of care at the time. Despite significant improvements in both medical and surgical management with reductions in mortality the major findings generated by these landmark studies remain in place.

The Coronary Artery Surgery Study (CASS) was designed to assess the effect of coronary artery bypass surgery on mortality and selected nonfatal end points.[1] Around 780 patients with stable ischemic heart disease were randomly assigned to receive surgical or nonsurgical treatment. At 5 years, a significant difference could not be established between the two management strategies. Annual mortality rates in patients with single-, double- and triple-vessel disease who were in the surgical group were 0.7%, 1.0% and 1.5%; the corresponding rates in patients in the medical group were 1.4%, 1.2% and 2.1%. However, the subset of patients with left ventricular ejection fraction (LVEF) less than 50% treated surgically had a statistically significant difference in survival (61% vs 79%) at 10 years. The excellent survival rates observed both in CASS patients assigned to receive medical and those assigned to receive surgical therapy and the similarity of survival rates in the two groups of patients in this randomized trial lead to the conclusion that patients similar to those enrolled in this trial can safely defer bypass surgery until symptoms worsen to the point that surgical palliation is required if they have preserved (ejection fraction > 50%) left ventricular function.[1]

The Veterans Affairs Coronary Artery Bypass Surgery Cooperative Study Group (VA-CABSCSG) randomly assigned 686 patients with stable angina to medical or surgical treatment at 13 hospitals and followed for an average of 11.2 years. Similar to the CASS trial, the VA trial was not able to demonstrate a significant survival advantage in low-risk patients. However, a group of high-risk patients was defined which clearly had a survival advantage when treated surgically. A statistically significant difference in survival suggesting a benefit from surgical treatment was found in patients who were subdivided into high-risk subgroups defined by either angiographic criteria, clinical criteria or by a combination. The angiographically defined high-risk group consisted of patients with three-vessel disease and impaired left ventricular function. At 7 years, this group demonstrated survival of 52% in the medically treated patients versus 76% in surgically treated patients; at 11 years, 38% and 50%, respectively. The clinically defined high-risk group consisted of patients with at least two of the following: resting ST depression, history of myocardial infarction (MI), or history of hypertension. At 7 years, this group demonstrated survival of 52% in the medical group versus 72% in the surgical group; at 11 years, 36% versus 49%, respectively. The third group consisted of patients with combined angiographic and clinical risk factors. This group had a survival rate at 7 years of 36% in the medical group versus 76% in the surgical group; at 11 years, 24% versus 54%, respectively (VA-CABSCSG).

The European Coronary Surgery Study randomized 767 men with good left ventricular function to either early coronary bypass surgery or medical therapy. At the projected 5-year follow-up there was a higher survival rate in the group assigned to surgical treatment than in the group assigned to medical treatment (92.4% vs 83.1%). The survival advantage diminished

during the subsequent 7 years but still favored the surgical treatment group (70.6% vs 66.7%).

In the 1970s and 1980s, studies tested whether CABG would improve the survival in patients with CAD who had acute myocardial infarction (AMI). These trials showed no better and possibly lower survival rates with CABG than with conservative treatment. Operative revascularization is unlikely to occur within 6 hours of the infarct. As a result, emergency CABG for AMI has been replaced by percutaneous revascularization. Randomized studies have been done with patients admitted to the hospital with unstable angina to see if they may live longer with CABG. The VA Study of Unstable Angina found no overall benefit from surgery. However, they discovered a statistically significant difference favoring CABG at 8 years in the high-risk subgroup and a statistically significant advantage favoring medical treatment in the low-risk subgroup.

COMPARING CABG TO PTCA

The modern era of coronary revascularization is marked by the hotly debated role of percutaneous versus surgical revascularization. Comparisons have been difficult due to evolving technologies. Nevertheless, several principals have emerged that currently define the patient which would benefit the most from surgical revascularization. In the 1990s several randomized trials compared angioplasty techniques with CABG. It became clear that although the survival rates were similar revascularization and anginal rates were much higher in the percutaneous groups.

The ERACI,[2] RITA,[3] BARI,[4] GABI,[5] EAST[6] and CABRI[7] trials failed to demonstrate a significant advantage of CABG or PTCA in mortality or in the frequency of MI. However, patients who had bypass surgery were more frequently free of angina and required fewer additional reinterventions than patients who had coronary angioplasty. These finding were held up to 10 years after revascularization in the BARI trial. The BARI trial, although, was able to demonstrate a survival advantage in patients with diabetes undergoing surgical revascularization.

In a similar vein, trials comparing percutaneous bare metal stenting with CABG have not demonstrated a mortality difference despite increased revascularization rates with percutaneous techniques. In the ARTS I trial[8] there was no difference in mortality (8.0% vs 7.6%) or the rate of the combined endpoint of death, MI, or stroke (18.2% vs 14.9%) at five years. However, event-free survival was lower with stenting due to a significant increase in the need for repeat revascularization (21% vs 4% at one year, 27% vs 7% at three years, and 30% vs 9% at five years). Among stented patients in the ARTS I trial, two groups had worse outcomes: those with incomplete revascularization and patients with diabetes. The Stent or Surgery (SoS) trial[9] is unique in establishing a mortality advantage to surgical revascularization in nondiabetic patients. At six years, mortality was significantly higher in the PCI group (10.9% vs 6.8%). It is not clear if this difference was at least in part by chance since there was a larger number of cancer deaths in the stenting group. The ERACI II trial randomized 450 patients to undergo either or CABG.[10] At 5-years follow-up, patients initially treated with PCI had similar survival and freedom from nonfatal AMI than those initially treated with CABG (92.8% vs 88.4% and 97.3% vs 94%, respectively). Freedom from repeat revascularization procedures (PCI/CABG) was significantly lower with PCI compared with CABG (71.5% vs 92.4%). Freedom from major adverse cardiac event was also significantly lower with PCI compared with CABG (65.3% vs 76.4%; p = 0.013). The study concluded that there were no survival benefits from any revascularization procedure; however, patients initially treated with CABG had better freedom from repeat revascularization procedures and from major adverse coronary event.[10]

The effort to reduce the revascularization rate of percutaneous techniques has resulted in the production of drug-eluting stents (DES). Recent trials have compared DES to CABG. The SYNTAX is currently the only head to head comparison of DES to CABG. The SYNTAX trial[11] randomly assigned 1,800 patients with three-vessel or left main CAD to either CABG or PCI with DES. All patients were eligible for either procedure and were treated with the intention of complete revascularization. After 12 months follow-up the composite primary endpoint (death from any cause, stroke, MI or repeat revascularization) was significantly higher in the PCI group (17.8% vs 12.4%). This was the result mostly of more frequent revascularizations with PCI (13.5% vs 5.9%). The secondary endpoint of the rate of death, stroke or MI were similar (7.6% for PCI vs 7.7% for CABG). More complete revascularization was achieved with CABG (63% vs 57%).

Coronary artery bypass surgery is superior to percutaneous techniques in reducing angina and revascularization rates. This has not translated into a survival advantage except in a select subset of patients. Specifically, the BARI[4] and ARTs I trial[8] demonstrated a survival advantage in diabetics. There has also been established a survival advantage in patients with greater than 95% stenosis of left anterior descending artery and at least 2 vessel disease[11,12] [CABG vs PTCA, Heart 95:1061–6, J Am Coll Cardiol. 53:2389–403, Circulation 119:1013–20, Circulation—11-SEP-2007; 116(Suppl. 11):I200–6].

THE CHANGING CABG POPULATION

Analysis of the patient population undergoing CABG over the last decade has revealed a threefold increase in octogenarians. There also has been a concomittant increase in comorbidities including obesity, hypertension reduced ejection fraction. Despite these worsening comorbidities mortality outcomes were unchanged (Table 1). (PMID 20399675)

WHEN CABG MAY BE INDICATED

The goal of coronary revascularization is to delay or prevent the complications of coronary disease and in turn prolong life

TABLE 1

Progression of worsening comorbidities by decade based on Society of Thoracic Surgery Database CABG mortality

Risk factor	*1980*	*1990*	*2000*
LVEF	62%	51%	45%
Female	17%	27%	33%
Reoperative	2%	9%	14%
Urgent/Emergent	4%	27%	38%

Abbreviation: LVEF: Left Ventricular Ejection Fraction

and alleviate symptoms. Patients who have symptoms despite maximal medical management or who have coronary anatomy for which revascularization has been proven to have a survival benefit should be considered for revascularization in the absence of any contraindications such as a nonresectable cancer or severe dementia. The choice of revascularization strategy is based on the patient comorbidities and extent of disease.

Early trials comparing CABG to percutaneous techniques demonstrated lower rates of freedom from restenosis with angioplasty or stenting. Despite the need for subsequent repeat revascularization or CABG after PTCA survival rates were similar. The SYNTAX trial and observations from the ARTS II, ERACI III, the New York State registry and the Beijing registry all demonstrated higher rates of revascularization following PTCA despite the use of a DES.

The findings of these and other trials have lead to the following ACC/AHA guidelines for CABG. Bypass surgery is recommended in the following patients:

- Significant left main coronary artery (LMCA) stenosis (> 50%)
- Greater than 70% stenosis of the proximal left anterior descending and circumflex arteries (left main equivalent)
- Three-vessel disease, especially if EF less than 50%
- Two-vessel disease with significant proximal LAD stenosis, EF less than 50% (proximal to the first septal perforators of the left anterior descending artery)

CABG should be considered in the patients with proximal LAD stenosis with one vessel disease with an extensive area of ischemia despite an EF greater than 50% and in those with one- or two-vessel disease even without proximal LAD disease if there is a moderate to large area of at risk myocardium. Patients with diabetes mellitus, as shown in the BARI and ARTS I trials, likely benefit from CABG over PTCA due to the higher rate of repeat revascularization.

Based on the subgroup analysis of the SYNTAX trial and the smaller Le Mans registry it may be reasonable to offer a patient who is poor surgical candidate with left main disease and well preserved left venticular function either CABG or PCI depending upon anatomic factors.[13]

Other indications for surgical revascularization include ischemia on physiological studies or significant coronary stenosis prior to other major cardiac surgery, congenital anomalies, such as aberrant left coronary artery, that are associated with sudden death. No guidelines may substitute for the collaboration between the patient, cardiologist and cardiac surgeons at each individual institution to ensure informed consent and meet the needs of each individual patient.

The indications for surgical revascularization after MI are similar to that of patients with stable angina. Prolonging the interval between acute MI and CABG reduces the risks of perioperative complications. Patients who have an LVEF of greater than 30% may proceed with CABG at any point after the MI is complete but in general at least a minimum of 48 hours. Patients with an EF less than 30% should be stablized for a period of one week prior to revascularization. The generalized edema surrounding infarcted tissue can technically aggravate an operation, and thus a certain amount of judgment is required in timing an intervention after MI. Data now exists that postponing revascularization 5 days after the contrast load from angiography to lessen kidney injury.

WHEN CABG IS NOT INDICATED

Given the success of rapid percutaneous revascularization emergency CABG does not play a role for AMI. In the 1970s and 1980s, studies tested whether CABG would improve the survival in patients with CAD who had AMIs within a few hours to days. These trials showed no better and possibly lower survival rates with CABG than with conservative treatment, so emergency CABG for AMI was abandoned.

Single vessel disease that is not left main or proximal LAD (proximal defined as proximal to first septal perforator) is often best managed by medical therapy or PTCA in the symptomatic patient. The CASS[1] and VA-CABSCSG trials[14] failed to demonstrate an advantage over medical mangement in patients with single vessel disease. Futhermore, the New York State registry demonstrates a survival disadvantage for single vessel disease when compared to PTCA. On the other hand patients with proximal LAD and an EF less than 50% have a significant survival advantage especially if revascularization is performed using the internal mammary artery. Similarly, two-vessel CAD should not undergo CABG without a diminished EF or proximal LAD disease. Lastly, patient with three-vessel disease who have a good left ventricular function and have mild reversible ischemia can safely be managed medically.

RISK FACTORS FOR IN-HOSPITAL MORTALITY FOLLOWING CABG

The perioperative and in-hospital mortality rate after CABG continues to improve with advancements in perioperative care and prevention. The risks associated with CABG are highly dependent upon patient comorbidities (Table 2), hospital procedure volumes and whether or not concomitant procedures are performed with CABG. Models to predict perioperative risks have been developed. One of the most widely used algorithms was developed by the Society of Thoracic Surgeons (STS).[15] This proprietary algorithm incorporates 26 variables including age, sex and comorbidities as well as the severity and acuity of presentation. Another proposed algorithm, the EuroSCORE, has widely been used in Europe. One analysis compared the performance of the STS Database with the EuroSCORE in predicting the survival of 4,497 patients undergoing isolated CABG between 1996 and 2001.[16] Overall 30 days mortality was 1.9%, and was accurately predicted by both risk scores, although, the EuroSCORE had significantly greater discriminatory power. The STS continues to gather new data to permit progressive algorithm revision. There is general consensus that the Euroscore tends to over estimate risk.[16] Other models include the Cleveland Clinic Model, the New York Model, ACEF (Age, Creatinine, Ejection Fraction). The Mayo Clinic Risk Score (MCRS)[17] is unique in that it may be used to provide a risk prediction for either PCI or CABG. First developed using patients undergoing PCI, the MCRS was shown to correlate with the STS Database for observed in-hospital mortality.[17] However, when compared to the 26 variable STS algorithm, its performance was inferior.

TABLE 2

Logistic regression analysis of early postoperative CABG mortality risk factors

	Patient risk factor	*Logistic*	*Regression*
Coefficient p value OR Age	0.0511	< 0.0001	1.052
Female Gender	0.3548	0.0005	1.426
Hemodynamic instability	1.2128	< 0.0001	3.363
Shock	2.0533	< 0.0001	7.794
Athero – carotid dz	0.04685	< 0.0001	1.598
Aortoiliac dz	0.7428	< 0.0001	2.102
Calcified asc ao	0.4816	0.0008	1.619
Previous MI < 6h	0.6174	0.0174	1.854
Malignant ventricular arrythmia	0.8056	< 0.0001	2.238
CHF same admission	0.9587	< 0.0001	2.608
CHF previously	0.8088	< 0.0001	2.245
Renal Failure (Cr>2)	1.0615	< 0.0001	2.891
Previous open heart	1.2167	< 0.0001	3.376

MODIFIABLE RISK FACTORS

The American College of Cardiology/American Heart Association (ACC/AHA) guidelines on bypass surgery address general recommendations for preventive measures to minimize the risk of both morbidity and mortality after CABG. These include the use of perioperative aspirin, beta-blockers and statin therapy. Further recommendation on reducing surgical site infection included the appropriate use of prophylactic antimicrobials and strict glycemic control. Health care reform in the United States of America and changes in payment strategy have incorporated some of these measure as part of the Surgical Care Improvement Project (SCIP).

Aspirin 325 mg should be administered to all patients without a contraindication perioperatively to reduce in-hospital mortality and to enhance graft patency after CABG. Concerns of excess bleeding in patients undergoing CABG while under aspirin therapy were raised by two randomized trials in the early 1990s.[18,19] Since, there has been an accumulation of overwhelming data supporting the use of perioperative aspirin. The same 1991 Veterans Administration Cooperative Study that found increased bleeding with aspirin showed that although there was no difference in saphenous vein graft occlusion between the two groups at an average of eight days after surgery (7.4% vs 7.8%), there was a trend toward a lower rate of occlusion of internal mammary artery grafts (0% vs 2.4%, p = 0.08) for the group receiving aspirin preoperatively.[18] A systematic review from the Antiplatelet Trialists' Collaboration concluded that antiplatelet therapy, particularly if given early, was associated with improved graft patency at an average of one year after surgery.[20] A large case patient-control patient study of 8,641 consecutive undergoing isolated CABG procedures performed between July 1987 and May 1991 demonstrated that preoperative aspirin use appeared to be associated with a decreased risk of mortality in CABG patients without significant increase in hemorrhage, blood product requirements, or related morbidities.[21] In a retrospective study published in 2005 of 1,636 consecutive patients undergoing CABG surgery; 80% of patients had taken aspirin within the five days before surgery, all patients received postoperative aspirin six hours after surgery and all patients received an internal mammary artery graft. Preoperative aspirin was associated with a significant reduction in postoperative in-hospital mortality 1.7% versus 4.4% without an increased in bleeding rate. Furthermore, a prospective study of 5,065 patients undergoing coronary bypass surgery, of whom 5,022 survived the first 48 hours after surgery demonstrated a reduced risk of death and ischemic complications involving the heart, brain, kidneys and gastrointestinal tract. Among patients who received aspirin (up to 650 mg) within 48 hours after revascularization, subsequent mortality was 1.3%, as compared with 4.0% among those who did not receive aspirin during this period (P < 0.001). Aspirin therapy was associated with a 48% reduction in the incidence of MI (2.8% vs 5.4%, P < 0.001), a 50% reduction in the incidence of stroke (1.3% vs 2.6%, P = 0.01), a 74% reduction in the incidence of renal failure (0.9% vs 3.4%, P < 0.001), and a 62% reduction in the incidence of bowel infarction (0.3% vs 0.8%, P = 0.01).

The perioperative use of statin has been associated with a reduction in mortality following CABG. The Multicenter Study of Perioperative Ischemia (McSPI) Epidemiology II Study[22] was a prospective, longitudinal study of 5,436 patients undergoing coronary artery bypass graft surgery between November 1996 and June 2000 at 70 centers in 17 countries. Following multivariate analysis, this study concluded that preoperative statin therapy was independently associated with a significant reduction in the risk of early cardiac death after primary, elective coronary bypass surgery (0.3% vs 1.4%; P < 0.03).[22] Discontinuation of statin therapy after surgery was independently associated with a significant increase in late all-cause mortality (2.64% vs 0.60%; P < 0.01). Others have associated statin therapy with a reduction in need for RRT following CABG.[23] Investigators at the Texas Heart Institute performed a retrospective cohort study of patients undergoing primary CABG surgery with CPB (n = 1,663) between January 1, 2000 and December 31, 2001. They did not find a risk reduction in in-hospital morbidities including postoperative MI, cardiac arrhythmias, stroke or renal dysfunction. Nevertheless, they found that preoperative statin therapy was independently associated with a significant reduction in the composite endpoint of 30-day all-cause mortality and stroke (7.1% vs 4.6%; P < 0.05).[24]

Perioperative uses of beta-blockers have been associated with a reduction in atrial arrhythmias and reduced short-term mortality. A review of 629,877 patients undergoing isolated CABG between 1996 and 1999 at 497 US and Canadian sites revealed that patients who received beta-blockers had lower 30-day mortality than those who did not 2.8% versus 3.4%. Patients with LVEF of less than 30%, however, had a trend toward higher mortality rate.[25]

Regardless of diabetic status, glycemic control plays a large role in postoperative morbidity and mortality. Postoperative glycemic control is an established standard to reduce sternal wound infection rates and in-hospital mortality. The largest randomized trial of surgical ICU patient randomized to intensive insulin therapy included patients undergoing CABG. Patients undergoing intensive insulin therapy had a reduction in in-hospital mortality (7% vs 11%).[26] Postoperative CABG patients

should be treated with continuous insulin to maintain a glucose between 100 mg/dL and 140 mg/dL.

Intraoperative glycemic control has also been studied. A direct benefit from intraoperative glycemic control has not been elucidated in nondiabetics receiving continuous insulin therapy. In a study of 400 patients randomly assigned to receive continuous insulin infusion to maintain intraoperative glucose levels between 4.4 mmol/l (80 mg/dL) and 5.6 mmol/l (100 mg/dL) or conventional treatment. The intensive therapy group experienced nonstatisically significant increase in deaths and strokes. On the other hand, patients with diabetes who receive a continuous solution of glucose, insulin and potassium (GIK) appear to benefit. Patients were randomly assigned to a GIK or No-GIK group. The GIK group received an infusion through a central line consisting of 500 ml D5W with 80 U of regular insulin and 40 mEq of KCl infused at 30 ml/h. Patients receiving intraoperative GIK had a significantly lower incidence of atrial fibrillation, a shorter length of stay, and at two years less recurrent ischemia (5% vs 19%), fewer wound infections (1% vs 10%), and lower mortality (2% vs 10%).[27] Further research regarding the goals of intraoperative glycemic control is needed.

Carotid duplex ultrasound to identify severe carotid artery stenosis may be warranted in patients at risk for cerbrovascular disease including those with prior history of stroke, transient ischemic attack, carotid bruit or age greater than 65. The management of concomitant carotid stenosis during coronary artery revascularization surgery continues to be controversial. Nevertheless, patients with symptomatic carotid disease should undergo carotid revascularization prior to or during CABG. Patients with asymptomatic carotid stenosis greater than 80% may also benefit from revascularization prior to or concomitantly with CABG.

The in-hospital mortality after CABG has been shown by some groups to be related to the volume of CABG procedures performed at the hospital. In an analysis of over 900,000 CABG procedures in the Medicare database between 1994 and 1999, the adjusted in-hospital or 30-day mortality was inversely related to hospital volume ranging from 6.1% for hospitals performing less than 230 procedures per year to 4.8% when the volume was greater than 849 procedures per year.[28] In a report on over 200,000 procedures from the Society of Thoracic Surgeons (STS) National Cardiac Database between January 2000 and December 2001, the overall operative mortality was 2.7%. The mortality rate ranged from 3.5% for hospitals performing less than or equal to 150 procedures per year to 2.4% for hospitals performing greater than 450 procedures per year.[29]

The use of the LIMA is associated with a higher graft patency rate and a lower perioperative mortality. In 21,873 consecutive, isolated, first-time coronary artery bypass graft procedures from 1992 through 1999, the crude odds ratio for death (LIMA vs no LIMA) was 0.26 (95% confidence intervals, 0.22, 0.31; P: < 0.001). LIMA grafts were protective across all major patient and disease subgroups, and in any age group.[30] In the STS database, non-use of the LIMA in any subgroup is tracked. The data for a free LIMA are almost as compelling as an *in situ* LIMA graft.

In general, patients undergoing elective CABG should continue a beta-blocker, statin and antiplatelet therapy perioperatively. Perioperative morbidity is further reduced by appropriate antiobiotic selection which may require MRSA screening. Glycemic control with postoperative insulin drips may further reduce surgical site infections. The use of the internal mammary as a conduit reduces postoperative mortality. Patients at risk for stroke should undergo preoperative carotid ultrasonography. Hospital volume may affect patient outcomes.

NONMODIFIABLE RISK FACTORS

Age is a predictor of operative mortality. Moreover, CABG is more frequently being performed on the elderly. Fortunately, the operative mortality in the elderly continues to decline. In one study 3,330 consecutive patients age 70 years and older were evaluated. The operative mortality reduced from 7.2% in 1982–1986 to 4.4% in 1987–1991. The prevalence of elderly patients rose from 16.2% to 19.5% during the same time periods.[31] Octogenarians also fare worse than younger patients. Around 725 out of 15,070 patients greater than or equal to 80 years of age underwent CABG between 1996 and 2001 in four Canadian centers were reviewed. Death was higher among the octogenarians (9.2% vs 3.8%; $p < 0.001$), as was the rate of stroke (4.7% vs 1.6%, $p < 0.001$).[32] The difference amongst patients undergoing elective surgery was not statistically significant.

Gender is an independent risk factor for complications after both CABG and PCI. Women experience greater complications and early mortality after revascularization. When adjusted for comorbidities this difference declines but still persists. It is unclear if gender along or concomittent risk factors including decreased coronary size and latter presentation which are responsible for these differences.[33]

After adjustment for comorbidities, redo CABG remains a predictor of operative mortality. 13,436 patients undergoing isolated CABG procedures between June 1, 2001 and May 31, 2008 were analyzed. Operative mortality was 4.8% for redo CABG and 1.8% for first-time CABG ($p < 0.001$). After adjustment, redo status remained a predictor for operative mortality, MI and prolonged ventilation.[34] Patients that undergo urgent or emergent CABG fair worse than there elective counterparts. A meta-analysis of studies stratifying patients undergoing elective versus urgent or emergency CABG demonstrated that the mortality rate was significantly lower in the elective CABG (1.5% vs 1.8%, $p < 0.05$).[35] Left ventricular dysfunction and heart failure is one of the most important independent predictors of operative mortality and other major adverse events after CABG. Outcome data were collected prospectively on 20,614 patients undergoing isolated coronary operations during 1982–1997. The operative mortality varied from less than 2% with an LVEF greater than 40% to 3.5–4% with an LVEF between 20% and 40% to approximately 8% with an LVEF less than 20%. Traditionally LMCA stenosis has been viewed as a risk factor for mortality after CABG. Swedish investigators noted that this was no longer the case after 1995. During 1970–1984, early mortality was 5.8% in patients with LMCA stenosis compared with 1.5% in patients without LMCA stenosis. The corresponding rates during 1995–1999 were 2% versus 2.2%, respectively.[36] The authors attribute this change to perioperative care.

Mortality following CABG rises sharply in proportion to renal dysfunction. Even minor renal impairment (Cr > 1.5) is

associated with a higher mortality. A prospective study of 4,403 consecutive patients undergoing first-time isolated CABG were divided based on preoperative renal function. There were 458 patients with a serum creatinine 130–199 µ/mol/l or 1.47–2.25 mg/dL (mild renal dysfunction group) and 3,945 patients with a serum creatinine less than 130 µ/mol/l (< 1.47 mg/dL). Operative mortality was higher in the mild renal dysfunction group (2.1% vs 6.1%; P < 0.001) Overall there is a 2–3 fold increase in mortality with renal insufficiency. Part of the risk comes from arrhythmias that are difficult to manage from electrolyte imbalances rather than strict fluid management. In fact, patients with known renal failure on dialysis tend to do better than those with worsening renal insufficiency after CABG.

In general, older female patients with left ventricular dysfunction and renal dysfunction undergoing reoperative emergent CABG carry the highest perioperative risk.

OUTCOMES OF SURGERY

GRAFT PATENCY

Short-term graft patency is dependent on technical issues such as graft type, handling of the graft, the quality of the anastomosis, runoff, competitive flow and the size of the target vessel. Long-term patency may be influenced by technical factors but is predominately determined by neointimial hyperplasia and progression of atherosclerotic disease. A short arterial bypass to a large target with good runoff provides for the best patency. A review of CABGs performed on 930 patients revealed that the best conduits were the bilaterally internal mammary arteries. One-year patency rate of the left internal thoracic artery, right internal thoracic artery, radial artery, gastroepiploic artery and saphenous vein graft was 96.1%, 92.0%, 69.5%, 81.4% and 82.6%, respectively.[37] One-year patency rates of *in situ* and free right internal artery graft were not significantly different. One-year patency rate of the radial artery was significantly worse than that of the free right internal thoracic artery graft and saphenous vein graft. The patency rate of saphenous vein grafts may be expect to be 50% at 10 years. Austrialian investigators randomized patients younger that 70 years to either radial artery or free right internal thoracic artery and patients older than 70 years to radial artery or saphenous vein grafts. At 5.5 years the patencies were similar in the two groups.[38] Thus in older patients the saphenous vein graft may be a suitable alternative. The benefit of radial arterial grafts may not be seen until after 10 years when half of saphenous grafts have failed. As conduit for coronary artery bypass the LIMA bypass to the left anterior descending artery has supplanted all others as the gold standard (Fig. 1).

LIMA bypassing to the left anterior descending artery is the most durable form of revascularization. Several studies have demonstrated that 90% of Internal mammary artery conduits are patent after 20 years. The internal thoracic artery has been shown to be equally resistant to atherosclerosis and maintains its patency as a pedicled conduit and as an *in situ* graft from the aorta to the left anterior descending coronary artery. Additionally, multiple studies have demonstrated multiple benefits in addition to prolonged graft patency including decreased incidence of reoperation, increased median interval of reoperation from eight to twelve years, and event-free

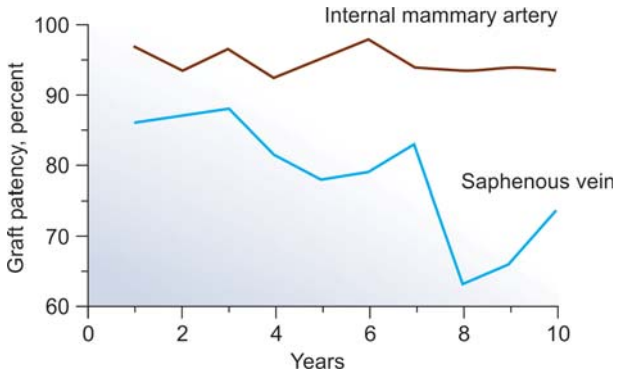


FIGURE 1: Ten-year graft patency for internal mammary artery and saphenous vein grafts[39]

survival. Loop et al. found that patients who had only vein grafts had a 1.61 times greater risk of death throughout the 10 years, as compared with those who received an internal-mammary-artery graft. In addition, patients who received only vein grafts had 1.41 times the risk of late MI, 1.25 times the risk of hospitalization for cardiac events, 2.00 times the risk of cardiac reoperation and 1.27 times the risk of all late cardiac events, as compared with patients who received internal-mammary-artery grafts. They also showed in 2,509 consecutive patients who underwent reoperation for myocardial revascularization at the Cleveland Clinic during a 20-year period (1967–1987).[40] Several factors associated with improved 10-year actuarial survival including age younger than 65 years, mild angina, no major comorbidity, no left main CAD, good left ventricular performance and the use of the internal thoracic artery graft.

As a result of the success of the LIMA as a excellent conduit there has been enusthiasm to use bilateral internal mammary arteries.[41] Unfortunately anatomical constraints limit the usefulness of the right internal thoracic artery as *in situ* graft. Instead it is often used as a free graft. Furthermore, use of bilateral internal mammary arteries may be of no survival benefit, 67% versus 64% at 15 years (Fig. 2). This comes at the cost of slightly increase sternal wound infection presumably due to revascularization especially in diabetics, 4.8% versus 1.2% with only one mammary used.[41]

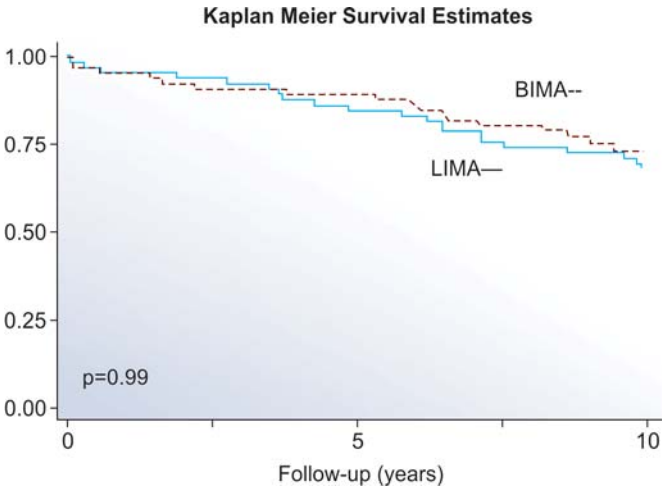


FIGURE 2: Survival of propensity-matched CABG patients who received LIMA or BIMA grafts

The long-term survival of patients undergoing isolated CABG, may be divided into three hazard phases. Following the initial perioperative period there is a rapidly decline in risk of death that plateaus between 6 months and 12 months. After the first year there is a slow gradual rise in the mortality rate which is likely the result of progression of disease and lose of graft patency. The 1-, 5-, 10- and 15-year survival may be expected to be 97%, 92%, 81% and 66%, respectively.[42] The use of the internal thoracic artery to left anterior descending coronary bypass has protective affect increasing 10-year survival up 90%.[39] This is likely the result of increase patency rates. The benefit of CABG is most accentuated in patients with diminished left ventricular function, multivessel disease and diabetes. Nevertheless, these comorbidites continue to affect the survival rate of patients despite CABG. Patients requiring reoperation for CAD do not fair as well with 10-year survival of 65%.

LEFT VENTRICULAR FUNCTION

Increased regional perfusion after CABG results in improved systolic function. It is not unusual to see improvement in wall motion abnormalities of hypokinetic, akinetic and even dyskinetic segment. With improved systolic function, maximal exercise capacity is improved along with functional capacity. Improvement in global function is dependent on complete revascularization. A lack of increase in excercise capacity usually translates into a missed vessel to be bypassed. Late loss of regional wall motions may be the result of graft occlusion or restenosis. Despite improved perfusion and function CABG does not decrease frequency or severity of exercise induced or resting ventricular arrythmias. These are likely due to scar which is uneffected by revascularization. Patients with EF less than 50% and/or large areas of regional malperfusion benefit the most from complete revascularization with CABG. Patient with very low EF less than 30% need to be carefully evaluated with cardiac MRI, PET scan or other imaging modality to determine if there is viable myocardium to revascularize, since risk may outweigh benefit as the EF approaches 20%.

RELIEF OF ANGINAL SYMPTOMS

The Medicine, Angioplasty or Surgery Study-II (MASS-II),[43] compared medical therapy, PCI and CABG. In addition to demonstrating reduction in revascularization in patients undergoing CABG, it demonstrated a 25% incidence of recurrent angina as compared with a 6% in patients undergoing CABG. These effects are reduced by the use of DES as demonstrated by the ARTS II trial. Freedom from recurrent angina is dependent on graft patency and progression of disease. Revascularization using the internal mammary artery is associated with an increase in the symptom-free period from 50% at 10 years w/vein grafts to 70% at 10 years using a LIMA.

QUALITY OF LIFE

Operative procedures have generally been judged based on their effectiveness and safety. Patients nowadays are much better informed and evaluate cardiovascular procedures not only on safety, efficacy and durability but also on the length of hospitalization, pain, postoperative recovery of function and improvement in their quality of life (QOL).[44] Several methods have been used to assess a patient's QOL both before and after operative intervention yet there is no universal agreement as to what QOL means or how it can be measured. Health related QOL is a reflection of the way a patient perceives and reacts to their health status and to nonmedical aspects of their lives (i.e. jobs, family, friends).[45] Major aspects of most QOL surveys include assessment of physical functioning, emotional status, cognitive performance, social functioning, general perception of health and well-being, and disease specific symptoms. One of the main goals of revascularization is to relieve symptoms of angina and improve physical activity. This in turn can affect work, leisure, social and sexual activities, and mood. Most studies have demonstrated improved functional status within 6 months of surgery. Improvements in general health status, 1 year postoperatively, seem to compare favorable with age-matched controls.[45] CABG has been shown to have a better 1-year physical functioning status compared to patients who receive PCI.[46] However, not everyone benefits to same degree from revascularization. Elderly patients and women have limited functional capacity and suffer more comorbidities. Although they benefit from a symptomatic standpoint as much as younger patients, they have less benefit from a QOL standpoint.[47] Women also seem to be at increased risk of subjective cognitive difficulties, increased anxiety and decreased ability to perform tasks of daily living. Patients with multivessel disease have also been shown to have a better QOL 12 months after surgery versus medical management perhaps related to less episodes of angina or heart failure symptoms. There is no significant difference between the conventional CABG and OPCAB in relation to QOL.

MAJOR CLINICAL TRIALS IN CHRONIC CORONARY ARTERY DISEASE

CABG VERSUS MEDICAL MANAGEMENT

CASS (1983)

CASS[1] is a randomized controlled clinical trial with an associated registry. It was designed to assess the effect of coronary artery bypass surgery on mortality and selected nonfatal endpoints. Around 780 patients with stable ischemic heart disease were randomly assigned to receive surgical (n = 390) or nonsurgical treatment (n = 390). At 5 years, the average annual mortality rate in patients assigned to surgical treatment was 1.1%. The annual mortality rate in those receiving medical therapy was 1.6%. Annual mortality rates in patients with single-, double- and triple-vessel disease who were in the surgical group were 0.7%, 1.0% and 1.5%; the corresponding rates in patients in the medical group were 1.4%, 1.2% and 2.1%. The differences were not statistically significant. Of the nearly 75% with an ejection fraction of at least 50%, the annual mortality rates in patients in the surgical group with single-, double- and triple-vessel disease were 0.8%, 0.8% and 1.2% and corresponding rates in the medical group were 1.1%, 0.6% and 1.2%. The annual rate of bypass surgery in patients who

were initially assigned to receive medical treatment was 4.7%. The excellent survival rates observed both in CASS patients assigned to receive medical and those assigned to receive surgical therapy, and the similarity of survival rates in the two groups of patients in this randomized trial leads to the conclusion that patients similar to those enrolled in this trial can safely defer bypass surgery until symptoms worsen to the point that surgical palliation is required if they have preserved left ventricular function.

VA-CABSCSG (1984)

The Veterans Affairs Coronary Artery Bypass Surgery Cooperative Study Group[14] randomly assigned 686 patients with stable angina to medical or surgical treatment at 13 hospitals and followed for an average of 11.2 years. For all patients and for the 595 without left main coronary-artery disease, cumulative survival did not differ significantly at 11 years according to treatment. The 7-year survival rates for all patients were 70% with medical treatment and 77% with surgery (P = 0.043), and the 11-year rates were 57% and 58%, respectively. A statistically significant difference in survival suggesting a benefit from surgical treatment was found in patients without left main coronary-artery disease who were subdivided into high-risk subgroups defined angiographically, clinically or by a combination of angiographic and clinical factors: (1) high angiographic risk (three-vessel disease and impaired left ventricular function)—at 7 years, 52% in medically treated patients versus 76% in surgically treated patients (P = 0.002); at 11 years, 38% and 50%, respectively (P = 0.026); (2) clinically defined high risk (at least two of the following: resting ST depression, history of MI, or history of hypertension)—at 7 years, 52% in the medical group versus 72% in the surgical group (P = 0.003); at 11 years, 36% versus 49%, respectively (P = 0.015) and (3) combined angiographic and clinical high risk—at 7 years, 36% in the medical group versus 76% in the surgical group (P = 0.002); at 11 years, 24% versus 54%, respectively (P = 0.005).[14]

European CSS (1988)

The European Coronary Surgery Study randomized 767 men with good left ventricular function to either early coronary bypass surgery or medical therapy.[48] At the projected 5-year follow-up there was a higher survival rate in the group assigned to surgical treatment than in the group assigned to medical treatment (92.4% vs 83.1%). The survival advantage diminished during the subsequent 7 years but still favored the surgical treatment group (70.6% vs 66.7%).

PCI VERSUS MEDICAL MANAGEMENT

ACME (1992)

A comparison of angioplasty with medical therapy is a prospective randomized control veterans administration study,[49] 212 patients with documented ischemia and a single coronary artery stenosis ranging from 70% to 99% in one epicardial coronary artery and with exercise-induced myocardial ischemia were randomly assigned either to undergo PTCA or to receive medical therapy and were evaluated monthly. After 6 months, they found that there was no mortality difference in either treatment group, but percutaneous intervention provided more complete angina relief with fewer medications and better QOL scores, as well as longer exercise duration on stress testing, than medical therapy. But among the 100 angioplasty patients, 19 underwent repeat PCI, and 7 underwent CABG during the first 6 months, compared with 11 angioplasty procedures and no CABG in the patients randomized to medical therapy. Additionally, it was demonstrated that nearly half of all patients assigned to initial medical therapy were asymptomatic at 6 months. Because this modest symptomatic benefit was achieved at such a large procedural and financial cost, patients who are either asymptomatic or have mild symptoms should have objective evidence of ischemia prior to PCI.

RITA-2

In the Randomized Intervention Treatment of Angina-2 (RITA-2) trial,[50] of 1,018 patients from the United Kingdom and Ireland with stable angina, 514 were randomized to medicine, receiving antianginal medications and optimal medical therapy and 504 to PTCA. One-third of the 1,018 patients had two-vessel disease and 7% had three-vessel disease. At a median follow-up of 2.7 years, the primary endpoints of death or MI had occurred twice as often in the PTCA group (6.3% vs 3.3%, p < 0.02, CI of 0.4–5.7%). Surgical revascularization was required during the follow-up interval in 7.9% of the PTCA group, and repeat angioplasty was required in 11%. In the medical group, 23% of patients required revascularization mostly due to worsening symptoms. Angina improved in both groups, but more in the PTCA group. There was a 16.5% absolute excess of grade 2 or worse angina in the medical group 3 months after randomization (p < 0.001), which attenuated to 7.6% after 2 years. Angina relief and exercise tolerance were improved to a greater degree in the patients undergoing angioplasty but this difference disappeared by three years.

TIMI-IIIB

The Thrombolysis in Myocardial Ischemia (TIMI)-IIIB clinical trial[51] enrolled 1,473 patients who received conventional anti-ischemic medical therapies. It compared the efficacy of t-PA with early invasive versus early conservative strategies in patients with unstable angina and non-Q-wave MI. In this large study of patients with unstable angina and non-Q-wave MI, the incidence of death and nonfatal infarction or reinfarction was low but not trivial after 1 year (4.3% mortality, 8.8% nonfatal infarction). The incidence of death or nonfatal infarction for the t-PA- and placebo-treated groups was similar after 1 year (12.4% vs 10.6%, p = 0.24). The incidence of death or nonfatal infarction was also similar after 1 year for the early invasive and early conservative strategies (10.8% vs 12.2%, p = 0.42). This study found that an early invasive management strategy was associated with slightly more coronary angioplasty procedures but equivalent numbers of bypass surgery procedures than was a more conservative early strategy of catheterization, in which revascularization was performed only when there were signs of recurrent ischemia. No difference was seen in death or nonfatal infarction, or both, after 1 year, according to strategy

assignment, but fewer patients in the early invasive strategy group underwent later repeat hospital admission (26% vs 33%, p = 0.001). According to these results, either strategy appears to be acceptable for treatment of patients with unstable angina and non-Q-wave MI; in this regard, physicians have latitude in individualizing care for such patients. In the patients with unstable angina and non-Q-wave MI, thrombolytic therapy did not reduce mortality or morbidity.[51]

CABG VERSUS MULTIVESSEL PTCA (TRIALS COMPARING)

BARI (1997)

The Bypass Angioplasty Revascularization Investigation (BARI)[4] compared the effectiveness of CABG versus PTCA in 1829 highly symptomatic patients with two or three-vessel coronary disease and an anatomy that was deemed equally suitable for revascularization with either technique. Outcomes have been published at 5-, 7- and 10-year follow-up. There was no significant difference in cumulative survival between CABG and PTCA (89% vs 86%, 84% vs 81% and 73% vs 71%, respectively) or cardiac survival between the two groups. Survival rates in the two treatment arms were similar in most patient subgroups, with the exception of diabetes. Revascularization occurred significantly less often in the CABG group (8% vs 54%, 13% vs 60% and 23% vs 77%, respectively). Angina occurred less frequently in the CABG group in the first year but was equivalent at ten years.

RITA (1993)

The Randomized Intervention Treatment of Angina (RITA) trial[52] randomly assigned 1,011 patients, 45% of whom had single vessel disease, to either PTCA or CABG. After a median follow-up of 6.5 years, the rates of death or nonfatal infarction for PTCA or CABG were the same (17% vs 16%). Angina was consistently higher in the PTCA group, 26% of whom required CABG, and 19% of whom required another PTCA.

ERACI (1993)

The ERACI trial[2] (Argentine Randomized Trial of Percutaneous Transluminal Coronary Angioplasty versus Coronary Artery Bypass Surgery in Multivessel Disease) randomized 127 patients who had multivessel CAD and clinical indications for myocardial revascularization to undergo coronary angioplasty (n = 63) or bypass surgery (n = 64). At 3-year follow-up freedom from combined cardiac events (death, Q-wave MI, angina and repeat revascularization procedures) was significantly greater for the bypass surgery group than the coronary angioplasty group (77% vs 47%; p < 0.001). There were no differences in overall (4.7% vs 9.5%; p = 0.5) and cardiac (4.7% vs 4.7%; p = 1) mortality or in the frequency of MI (7.8% vs 7.8%; p = 0.8) between the two groups. However, patients who had bypass surgery were more frequently free of angina (79% vs 57%; p < 0.001) and required fewer additional reinterventions (6.3% vs 37%; p < 0.001) than patients who had coronary angioplasty. Of note the cumulative cost at 3-year follow-up was greater for the bypass surgery group than for the coronary angioplasty group.

GABI (1994)

The German Angioplasty Bypass Surgery Investigation (GABI)[5] was a multicenter study of patients in whom complete revascularization of at least two major vessels supplying different myocardial regions was deemed clinically necessary and technically feasible. Patients with totally occluded arteries supplying viable myocardium were excluded. At 12 months, no significant differences existed between the two groups with respect to Q-wave MI, severe angina, or freedom from angina. However, the total reintervention rate was lower with surgery (6% vs 44%).

EAST (1994)

In the Emory Angioplasty versus Surgery Trial (EAST)[6,53] nearly 400 patients with multivessel disease (most patients had normal left ventricular function) were randomly assigned to either PTCA or CABG. At 3-year follow-up no significant differences were found with respect to the combined endpoint of mortality, Q-wave MI, or large thallium perfusion defect. However, patients treated with CABG had fewer additional procedures at three years (2% vs 23%). After 8-year follow-up, the combined endpoint was the same in the two groups (79% vs 83% for CABG).[53]

CABRI (1995)

The Europe-based multicenter Coronary Angioplasty versus Bypass Revascularization Investigation (CABRI)[7] compared CABG to PTCA in 1,054 patients. There was a similar mortality rate (2.7% vs 3.9%) in the two groups at one year. However, patients assigned to PTCA required more repeat procedures (34% vs 7%) and had a higher incidence of clinically significant angina (relative risk 1.54). Restenosis after PTCA only partially accounted for this difference; of greater importance was the higher likelihood of residual disease after PTCA compared with CABG.

TRIALS COMPARING CORONARY ARTERY BYPASS GRAFTING VERSUS PERCUTANEOUS CORONARY TRANSLUMINAL ANGIOPLASTY USING BARE METAL STENT

ARTS I (2001)

In the ARTS I trial,[8] 1,205 patients (17% diabetics) with multivessel disease were randomly assigned to undergo BMS implantation or bypass surgery, usually with an arterial graft, when a cardiac surgeon and an interventional cardiologist agreed that the same extent of revascularization could be achieved with either procedure. Complete revascularization was significantly more likely to be achieved with CABG (84% vs 71%). There was no difference in mortality (8.0% vs 7.6%) or the rate of the combined endpoint of death, MI or stroke (18.2% vs 14.9%) at five years. However, event-free survival was lower with stenting due to a significant increase in the need for repeat revascularization (21% vs 4% at one year, 27% vs 7% at three years, and 30% vs 9% at five years). Among stented patients in the ARTS I trial, two groups had worse outcomes: those with incomplete revascularization and patients with diabetes.

SoS (2002)

The SoS trial[9] randomly assigned 988 patients with multivessel coronary disease to CABG or PCI with bare metal stent. At a median follow-up of two years, PCI was associated with a significantly higher rate of repeat revascularization (21% vs 6%) with CABG. At six years, mortality was significantly higher in the PCI group (10.9 vs 6.8; hazard ratio 1.66, 95% CI 1.08–2.55). It is not clear if this difference was at least in part by chance since there was a larger number of cancer deaths in the stenting group.

ERACI II (2001)

The ERACI II trial randomized 450 patients to undergo either PCI (n = 225); or CABG (n = 225). Clinical follow-up during five years was obtained in 92% of the total population after hospital discharge.[10] At 5-year follow-up, patients initially treated with PCI had similar survival and freedom from nonfatal AMI than those initially treated with CABG (92.8% vs 88.4% and 97.3% vs 94%, respectively, p = 0.16). Freedom from repeat revascularization procedures (PCI/CABG) was significantly lower with PCI compared with CABG (71.5% vs 92.4%, p = 0.0002). Freedom from major adverse cardiac event was also significantly lower with PCI compared with CABG (65.3% vs 76.4%; p = 0.013). The study concluded that there were no survival benefits from any revascularization procedure; however, patients initially treated with CABG had better freedom from repeat revascularization procedures and from major adverse coronary event.

TRIALS COMPARING CORONARY ARTERY BYPASS GRAFTING VERSUS PERCUTANEOUS CORONARY TRANSLUMINAL ANGIOPLASTY USING DES

SYNTAX (2009)

The SYNTAX trial[11] randomly assigned 1,800 patients with three-vessel or left main CAD to either CABG or PCI with DES. All patients were eligible for either procedure and were treated with the intention of complete revascularization. After 12 months follow-up the composite primary endpoint (death from any cause, stroke, MI or repeat revascularization) was significantly higher in the PCI group (17.8% vs 12.4%). This was the result mostly of more frequent revascularizations with PCI (13.5% vs 5.9%). The secondary endpoint of the rate of death, stroke or MI were similar (7.6 for PCI vs 7.7 for CABG). More complete revascularization was achieved with CABG (63% vs 57%).

ERACI III Registry (2006)

The ERACI III[54] registry consisted of 225 patients who would have met the ERACI II trial inclusion criteria and underwent drug-eluting stenting. The primary endpoint was 3-year major cardiac or cerebrovascular events. ERACI III-DES patients (n = 225) were compared with the BMS (n = 225) and CABG (n = 225) arms of ERACI II. Patients treated with DES were older, more often smokers, more often high risk by EuroSCORE and less frequently had unstable angina. They also received more stents than the BMS-treated cohort. Major adverse event rates at 3 years were similar in DES and CABG-treated patients (22.7%, P = 1.0). Death or nonfatal MI at 3 years trended higher in the DES (10.2%) than BMS cohort (6.2%, P = 0.08) and lower than in CABG patients (15.1%, P = 0.07).

ARTS II Registry (2008)

The ARTS II registry[55] compared differences in outcomes between sirolimus-eluting stents (SES) in 607 patients with the 1,205 patients from the ARTS I trial. The primary outcome was a composite of all-cause mortality, any MI or cerebrovascular event, or any reintervention. After 3 years freedom from revascularization was 85.5% in patient receiving SES compared to 93.4% with CABG in ARTS I. Conclusions must be tempered since this was not a head-to-head comparison, as the CABG patients were historical controls from the original ARTS I trial.

The New York State Registry (2008)

This registry included 17,400 patients in New York State[12] who underwent CABG or drug-eluting stenting between October 1, 2003 and December 31, 2004. In comparison with treatment with a drug-eluting stent, CABG was associated with lower 18-month rates of death and of death or MI both for patients with three-vessel disease and for patients with two-vessel disease (92.7% vs 94.0% and 94.6% vs 96.0%, respectively). Unfortunately, the design for this registry allows for significant selection bias with the inclusion of unstable patients in the stenting arm.[12]

The Beijing Registry (2009)

A report from Beijing evaluated 3,720 consecutive patients with multivessel disease who underwent isolated CABG surgery or received DES between April 1, 2004 and December 31, 2005. Patients who underwent CABG (n = 1,886) were older and had more comorbidities than patients who received DES (n = 1,834). Patients receiving DES had considerably higher 3-year rates of target-vessel revascularization. DES were also associated with higher rates of death (adjusted hazard ratio, 1.62; 95% confidence interval, 1.07–2.47) and MI (adjusted hazard ratio, 1.65; 95% confidence interval, 1.15–2.44).

SUMMARY

The goal of medical therapy or revascularization is to prevent the complications of CAD, by decreasing the mortality and morbidity associated with cardiac disease and alleviating symptoms. Both CABG and PCI may diminish anginal symtoms, and reduce major adverse cardiac events. In general, patients managed with CABG and PCI have similar combined outcomes of death, MI and stroke. Revascularization rates, although, are higher with PCI. Major clinical trials comparing PCI to CABG have helped stratify patients. The decision to proceed with a specific revascularization strategy is dependent on the coronary anatomy, myocardial function, patient risk factors, patient preference and local expertise. Most patients with single- or two-vessel disease and normal ejection fraction are best managed with PCI unless the proximal left anterior descending artery is involved with a high-grade stenosis. Patients with multivessel disease or left main disease associated with impaired

left venticular systolic function benefit most from CABG. Patients with diabetes mellitus, as shown in the BARI and ARTS I trials, benefit from CABG over stenting, especially if they have left ventricular dysfunction. Patient with unprotected left main CAD who are reasonable surgical candidates should be treated with CABG. The use of DES in three-vessel or left main CAD is associated with similar 1 year death, stroke or MI rates at the cost of less complete and more frequent revascularization. Modern day management of chronic CAD requires a frank and integrated discussion between the patient, cardiologist and cardiac surgeon.

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Index

Entries from figures/flow charts and tables are represented by locators with *italics* suffix "*f*" and "*t*", respectively.

A

α_1-Adrenergic receptors
  and hypertrophy, 26–27
β-Adrenergic receptor antagonists, 78
  in hypertension, 1135*t*
β-Adrenergic signaling
  and calcium regulation, 24
  receptor mediated, 23
β-Arrestin. *See* G-protein receptor kinase-2 (GRK-2)
5 As
  cigarette cessation, 833, 1879–1880
AAA/AHA guidelines, for ambulatory electrocardiographic monitoring, 784–786
$ABCD_2$ score, in TIA and stroke prediction, 1909*t*
Abciximab, 133, 882
  in dialysis patients, 1701
  in high-risk angioplasty, 548
Abdominal aortic aneurysm (AAA)
  and 9p21, 1942
  modular Z-stent-based stent grafts, 1177
  polymer filled stent grafts, 1177–1178
  ringed stent grafts, 1177
  and tobacco smoking, 1873
  unibody stent grafts, 1177
  uni-iliac stent grafts, 1177
Abdominojugular reflux. *See* Hepatojugular reflux
ACC/AHA guidelines, 908
  preoperative diagnostic testing, 1790*t*
  preoperative management, 1793*t*
  risk mitigation
    other management, 1792*t*
    pharmacological management, 1791*t*
ACC/AHA/ACP-ASIM guidelines, for management of stable angina, 935
Accelerated digoxin administration, 99
Accelerated idioventricular rhythm, in electrocardiograph, 199*f*
Accidental Death and Disability: the Neglected Disease of Modern Society, 790
Accreditation Council for Graduate Medical Education (ACGME), in safe workforce creation, 1973
Acetazolamide, 54, 57, 58*t*
  and loop diuretics, 1242
Acetylsalicylic acid (ASA). *See* Aspirin
"Acoustic shadowing", in IVUS imaging, 353*f*
Acquired immunodeficiency syndrome (AIDS), 845, 852, 1622, 1629, 1636. *See also* Human immunodeficiency virus (HIV) infection
Acquired long QT syndrome, 693, 1812, 1825*t*
Acromegaly, 1718
  cardiac hypertrophy in, 1719
  valvular heart disease in, 1719
Acute ischemic stroke
  definition, 1909
  treatment of, 1920–1922
Action in diabetes and vascular disease (ADVANCE) trial, 1716
Action potential
  for automaticity and contraction, 572–573
  in ion channel and cellular properties, 570–572
  ion channel opening and inactivation, 569–570
  by surface electrocardiogram, 573–574
Action to control cardiovascular risk in diabetes (ACCORD) trail, 111, 114, 1608, 1716
  fenofibrate and statin therapy, 1801
Activated clotting time (ACT), 119
Activated factor X (Xa), 1761
Activated partial thromboplastin time (aPTT), 116, 1761
ACTIVE (A Clinical Trial in IPF to Improve Ventilation and Exercise) trial, 1523
ACTIVE A trials (Atrial Fibrillation Clopidogrel with Irbesartan for Prevention of Vascular Events), 1944
Active ischemia, 694
Active smoking, and cardiovascular disease, 1874–1875
ACUITY trial, heparin versus bilvarudin, 1837
Acupressure-based massage, 2032
Acute and Chronic Therapeutic Impact of a Vasopressin Antagonist in Congestive Heart Failure (ACTIV in CHF), 1277
Acute aortic dissection (AAD), 316, 865, 1166, 1172
  and chest pain, 145
  type A dissection outcome, 1172
  type B dissection outcome, 1172–1173
Acute aortic regurgitation, 162*t*, 476, 1047, 1056, 1741
Acute cardiopulmonary response, to exercise, 215
Acute chest pain syndromes, imaging in, 392
Acute coronary artery thrombosis, due to cocaine usage, 1616
Acute coronary syndrome (ACS), 119, 123, 508–509, 871–887, 927, 1692, 1956
  clinical features, 873–875
    creatinine kinase (CK), 874–875
    electrocardiogram (ECG), 874
    physical examination, 874
    troponins, 875
  definite ACS, 875
  early invasive strategy, 884–885
  early medical therapy, 877–884
    antiplatelet agents, 879–883
    antithrombotic agents, 883–884
    beta blockers, 878–879
    calcium channel blockers, 879
    general measures, 878
    morphine, 878
    nitrates, 878
  initial conservative strategy, 884–885
  noncardiac chest pain, 875
  pathophysiology, 871–873
    etiology, 871–872
    platelets and coagulation system, 872–873
    systemic factors (vulnerable patient), 872
    vulnerable plaque, 872
  and physical examination, 151
  possible ACS, 875
  revascularization, 885–887
  risk stratification, 875–877
    biomarkers, 876–877
    electrocardiogram (ECG), 876
    history, 876
  stable angina, 875
  STEMI. *See* ST segment elevation myocardial infarction (STEMI)
Acute coronary syndromes, cardiogenic shock in *See* Cardiogenic shock, in acute coronary syndromes
Acute decompensated heart failure (ADHF), 1281
Acute Decompensated Heart Failure National Registry (ADHERE)
  risk classification system, 1283i
Acute decompensation, therapy for
  for cor pulmonale, 1764
Acute DVT treatment , 123
Acute heart failure syndromes (AHFS), 1298
  classification, 1299–1300
  clinical trial, 1306–1307
    T1 translation phase, 1307
  definition, 1298
  epidemiology, 1298
  pathophysiology, 1300
    cardiac metabolism, 1301
    congestion, 1300
    myocardial injury, 133
    renal impairment 1301
    untoward drug effects, 1301
    vascular failure, 1301
    viability, 1301
  patient's characteristics, 1298–1299
    preserved versus reduced systolic function, 1299*t*

Acute heart failure syndromes management, 1301–1302
phases of, 1302*t*
reconstruction phase, 1306
vulnerable phase, 1306
stabilization phase, 1302
diagnosis, 1302
disposition, 1303
goals of, 1303
precipitants, 1302
treatment, as per clinical profile, 1302
transition to evidence-based phase, 1303–1305
goals of, 1305–1306
quality measures, 1306
Acute hemorrhagic stroke
treatment of, 1922–1923
Acute limb ischemia (ALI), 1149
treatment of, 1155
Acute myocardial infarction (AMI)
hemodynamic subsets in, 508*t*
left ventricular thrombus in, 310
and renal function monitoring, 1281
and tobacco smoking, 1873
Acute myocardial ischemia
characteristic of, 873
myocardial response to, 1811*t*
and sodium channels, 1617, 1618
Acute pericarditis
presentation and etiology, 1489–1490
diagnosis, 1490
and management of, 1492*f*
examination, 1490
treatment, 1490–1491
Acute pulmonary embolism (acute PE), 145, 1750
Acute rejection
in transplant patients, 1341
types of, 1343*t*
Acute renal failure (ARF), 62, 1283
and ARBs, 77
renin-angiotensin-aldosterone inhibitors, 1158
Acute stroke, 1919–1920
emergency management, 1920*t*
Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF) trial, 1294, 1306
Acute type B dissection, 1182–1183
Acyanotic heart disease, 1551
atrial septal defects, 1559–1562
coarctation of aorta, 1554–1557
congenital valvar aortic stenosis, 1551–1554
patent ductus arteriosus, 1566–1568
right ventricular outflow tract obstruction, 1557
subvalvar aortic stenosis, 1554
subvalvar pulmonic stenosis, 1559
supravalvar aortic stenosis, 1554
supravalvar pulmonic stenosis, 1559
valvar pulmonic stenosis, 1557–1559
ventricular septal defects, 1562–1566
Acyanotic lesions
Ebstein's anomaly, 1568–1570
Adeno-associated virus (AAV), 2004–2005
Adenosine dinucleotide phosphate (ADP), 880
Adenosine, 594, 678, 679, 668, 859–860
Adenoviruses, 2004
cardiotropic virus, 488
in myocarditis, 1426
ADHERE registry
systolic and diastolic heart failures, demographic differences between, 1211*t*
Adhesion molecules, in molecular imaging, 456
Adipose tissue derived stem cells (ASCs), 1989, 1993
Adjunctive coronary interventional devices
directional coronary atherectomy, 552
rotational coronary atherectomy, 552
thrombectomy, 551–552
Adrenal disorders
adrenal insufficiency, 1722
Cushing's syndrome, 1721–1722
paraganglioma, 1720
pheochromocytoma, 1720
primary aldosteronism, 1720–1721
Adrenergic inhibitors, 1140–1141
in hypertension, 1135*t*
Adrenergic-blocker therapy, neurogenic cardiac injury, 1692
Adria cells, doxorubicin cardiotoxicity, 1481
Adult AIDS Clinical Trials Group (AACTG), HAART-related hyperlipidemia management, 1640
Adult congenital heart disease (ACHD), 266*t*, 426, 1557*f*. *See also* Congenital heart disease (CHD)
Adult respiratory distress syndrome (ARDS)
balloon flotation catheter, 509
and septic shock, 506
Adult stem cells, 1987
ADVANCE trial, 1608
Advanced cardiac therapies, identifying candidates for
heart transplantation
donor selection and perioperative period, 1339–1343
indications and contraindications, 1338–1339
survival with, 1343
mechanical circulatory support, 1343–1345
future directions, 1350
indications and contraindications, 1345–1347
myocardial recovery with device explanation, 1349–1350
postoperative patient and device management, 1348–1349
recipient care, 1348
survival with mechanical circulatory support, 1349
VAD, design and postimplant physiology, 1347–1348
VAD, patient selection, 1345
recognition of poor prognosis, 1335
evaluation of patient referred for, 1336–1338
functional assessment, 1336
optimal medical management, 1336
preoperative assessment of, 1338
prognostic determinants and risk scores, 1335–1336
prognostic scores, 1336
Advanced life support (ALS), 791, 795–799
advanced airway management, 795
defibrillation, 797–799
pharmaceutical interventions, 795–796
success rate, 795
Aerobic exercise, 1890
in pressure lowering, 1134
Aerosolized Randomized Iloprost Study (AIR trial), 1539
African-American Heart Failure Trial (A-HeFT), 73, 1241
Afterload reduction
in HF, immediate postoperative management, 1340
with nitroprusside, 1940–1941
Afterload, LV ejection impedance, 71
Age
as heart failure risk factor, 1900
cellular aging, 1830–1832
Aggrastat. *See* Tirofiban
AgomiRs, 28
Airway management, 793
Ajmaline, 693
AL cardiomyopathy (AL-CMP), 1458
symptoms of, 1459
Alagille syndrome, treatment of, 1036
Alanine transaminase (ALT), 110
Alcohol and arrhythmia
alcohol consumption
atrial flutter, 1596–1597
chronic atrial fibrillation, 1596–1597
sudden cardiac death, 1597–1598
binge drinking, 1596
ethanol exposure effects, 1595
ethanol ingestion, 1595–1596
guidelines, 1598
Alcohol, 1631
and CHD, 838
Aldosterone
role of, 79*f*
and systolic heart failure, 78–80
Aldosterone antagonists, 46
for heart failure, 1607
Aldosterone receptor antagonists, 78
Aldosterone Receptor Blockade in Diastolic Heart Failure (ALDO-DHF), 1260
Allgrove syndrome, 1195
Allosensitization prevention, transplant list patients, 1338
Alpha agonists, 796
Alpha-2 adrenergic receptor agonists, in perioperative period, 1782
Alteplase, 902
Alveolar hypoventilation, diseases of, 1763
Alzheimer's disease, 1831
Ambrisentan (Letairis®), for PAH, 1539
Ambulatory ECG monitoring, variant angina diagnosis, 941

Ambulatory electrocardiographic (AECG) monitoring
AAA/AHA guidelines for, 784–786
characteristics of, 778*t*
event recorder, 780–782
Holter monitoring, 777–780
implantable loop recorders (ILRs), 783
mobile cardiac outpatient telemetry, 782
modality selection, considerations for, 779*t*, 783–784
Ambulatory heart failure, renal impairment in, 1282*t*
American College of Cardiology (ACC)
exercise suggestion, 1891
exercise testing, physicians guidelines, 209
heart failure, concept of, 1899
American College of Cardiology Foundation (ACCF), 3994
American College of Physicians (ACP)
exercise testing, physicians guidelines, 209
American College of Sports Medicine (ACSM)
exercise suggestion, 1891
American Diabetes Association (ADA), 129
American Heart Association (AHA), 788
air pollution, statement on, 1884
exercise testing, physicians guidelines, 209
heart failure, concept of, 1899
American Heart Association and American College of Cardiology (AHA/ACC)
sports eligibility criteria, 1824–1825
American Society of Echocardiography (ASE), 310, 324
LV mass, 266
on LVEF, 229
American Society of Nuclear Cardiology (ASNC), 394
workup algorithm, for women, 1804*f*
American trypanosomiasis. *See* Chagas disease
American-Australian-African Trial with Dronedarone in AF or Flutter Patients for the Maintenance of Sinus Rhythm (ADONIS), 591
Amiloride, 54, 55, 58*t*, 62, 64, 66
in CHF and renal dysfunction, 1289
in hypertension, 1138
Amino-terminal pro-B-type natriuretic peptide (NT-proBNP), 1903
in heart failure, 1221–1222
Amiodarone, 588–590, 655, 667, 680, 681, 688, 690, 691
for cardiac arrest, 821–822
for CPR, 796
Amiodarone-induced thyroid disease, due to cardiac complications, 1717–1718
Amlodipine, 74, 1242
arteriolar dilating drug, 72
for stable angina and CAD, 931
AMP-activated protein kinase (AMPK)
in Cushing syndrome, 1721
Amyloid, history of, 1454–1455
Amyloid A (AA) amyloidosis, 1457
Amyloid cardiomyopathy, treatment of
device therapies, 1465
heart failure medical management, 1464–1465
heart transplantation, 1466–1467
underlying amyloid disease, 1465–1466
Amyloid fibril proteins, classification of, 1457*t*
Amyloid heart disease
amyloid cardiomyopathy, treatment of
device therapies, 1465
heart failure medical management, 1464–1465
heart transplantation, 1466–1467
underlying amyloid disease, 1465–1466
amyloid, history of, 1454–1455
amyloidogenesis, 1455–1456
amyloidosis, classification of, 1456
cardiac amyloidosis, 1456–1457
clinical features of, 1459–1464
overview of, 1456
familial (hereditary) systemic amyloidosis, 1458–1459
isolated atrial natriuretic factor, 1459
light chain (AL) amyloidosis, 1457–1458
secondary amyloidosis, 1459
senile systemic amyloidosis. 1458
Amyloid light (AL). *See* Light chain (AL) amyloidosis
Amyloid transthyretin (ATTR),
Amyloidosis, 492, 493–494, 1455–1456
restrictive cardiomyopathy, 1452
Anabolic steroids, 1627–1628
Anaconda stent graft, 1177
Anaerobic threshold (AT). *See* Ventilatory threshold (VT)
Analgesics, for cocaine abuse treatment, 1619
Ancure, stent graft design, 1176
Andersen disease, 495
Androgenic anabolic steroid
on myocardial function, in athletes 1824*t*
Anemia
due to CKD, 1699–1700
coronary blood flow during, 42
Anemia, in HF patients
erythropoietin stimulating proteins (ESPs) in, 1266
safety concerns on, 1266–1268
HF treatment, 1265–1266
using ESPs, 1266–1267
iron deficiency and iron replacement in, 1268–1270
mechanism of, 1264–1265
overview, 1264
prevalence, 1264
prognostic significance of, 1265
AneuRx, stent graft design, 1176
Aneurysm, 464
clinical aneurysm inflammation imaging, 465
preclinical aneurysm imaging investigations, 466
Angina
aortic stenosis, symptoms, 987–988
coronary circulation during, 42–43
Angina pectoris, 143, 144, 219, 544. *See also* Ischemia
Anginal chest pain, 873
Anginal equivalents, 145
Anginal pain, in HF, 1358
Angiogenesis, 2007, 2008*f*
inflammation, in atherosclerosis, 1850
Angiogenesis, basic concepts of
angiogenic growth factors and response to hypoxia, 2010–2011
blood vessel growth, 2007–2009
cellular involvement in, 2009–2010
Angiogenic gene therapy
in animal models, 2011–2012
for chronic heart failure, 2014
clinical trials in heart, 2010–2014
Angiogenic growth factors
and hypoxia, response to, 2010–2011
Angiogenic protein therapy, 2011
Angiographic versus IVUS Optimization (AVIO) study, 361
Angiography versus IVUS-directed stent placement (AVID) trial, 360
Angioplasty, and cardiac rehabilitation, 1895
Angioplasty Compared to Medical Therapy Evaluation (ACME) trial, 553, 977
Angiopoietin, 1525, 2011
Angiotensin converting enzyme (ACE) inhibitors, 72, 74–77, 78, 1140
arteriolar dilator drug, 72
chemotherapy-induced cardiomyopathy, 1485
congenital valvar aortic stenosis, 1553
in diastolic heart failure, 1257, 1258
in heart failure prevention, 1901
for heart failure, 1289, 1607
in hyponatremia, 1272
in LVEF, 267
in LVH regression, 1698
in PPCM, 1475
stroke prevention, 1917
for stable angina and CAD, 930
Angiotensin converting enzyme (ACE), 61
Angiotensin II
in atherosclerotic lesions, 1850
neurohormone, 74
Angiotensin II receptor-1 (AT-1), 38
Angiotensin inhibitors, in HF treatment, 1238*t*
Angiotensin receptor blocker (ARB), 61, 72, 77, 78, 1140
for diastolic heart failure, 1257, 1258
for heart failure, 1607, 1901
in LVH regression, 1698
in PPCM, 1475
stroke prevention, 1917
trials and inference, 77
Angiotensinogen, 75
Angle of Louis, 154
Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), 1904
Ankle-brachial index (ABI), 840, 1145
as PAD diagnosis, 1150
and PAD prevalence, 1146*t*
Ankylosing spondylitis, 152, 1651
Annulus, in tricuspid valve anatomy, 1019
Anomalous coronary artery from the opposite sinus (ACAOS), 530
"Anomalous left coronary artery from the pulmonary artery" (ALCAPA), in hibernating myocardium, 1325

Anomalous origin of the LCA from the pulmonary artery (ALCAPA), 529
Anorexia, 1628
as HF symptom, 1214, 1359
AntagomiRs, 28
Anthracycline-induced cardiomyopathy
pathophysiology
cardiac changes, 1480
histopathologic changes, 1481
prevention of, 1484*t*
Antiadrenergic therapy, 1606
Antianginal drug therapy
invasive vs. optimal, 933
pharmacologic actions of, 928*t*
precautions, 928*t*
vs. revascularization, 931–932, 933–934, 934*f*
side effects and contraindications of, 928*t*
for stable angina, 928–930
Antiarrhythmic drugs (AADs), 578–579, 655–656
antiarrhythmic efficacy, 1963
arrhythmia mechanisms and, 579
in atrial fibrillation, 595
calcium channel blockers, 1962–1963
classification scheme, 579
clinical implications, 1963
on defibrillation and pacing thresholds, 597*t*
digoxin, 1962–1963
drug-device interactions, 597
emerging drugs, 595
and implantable cardioverter defibrillators, 596–597
indications for, 579
major drug interactions of, 583*t*
out-patient versus in-hospital initiation for, 595–596
perioperative arrhythmia prevention, 1782
in pregnancy and lactation, 596
procainamide, 1963
propafenone, 1963
toxicity, 1963
Antiarrhythmic Trial with Dronedarone in Moderate to Severe Congestive Heart Failure Evaluating Morbidity Decrease (ANDROMEDA), 592
Anticoagulation, 908–909
risk of bleeding, 1099*t*
Antidiuretic hormone, and dieresis, 1286
Antihypertensive and Lipid-Lowering to prevent Heart Attack Trial (ALLHAT), 63
Antihypertensive therapy
antihypertensive agents, 1135*t*
lifestyle management, 1133
alcohol restriction, 1134
cigarette smoking, 1134–1135
exercise, 1134
non-antihypertensive drugs, 1135
obesity, 1134
salt, 1134
pharmacological therapy, 1135
Antilipid agents, 104
add-on to statin therapy, 110–111
appropriate uses, 104
bile acid sequestrants, 111
efficacy, 111
safety, 111
drug development, 114
ezetimibe, 111
efficacy, 111
safety, 111–112
fibrates, 105, 113
efficacy, 113
safety, 113–114
lipid lowering options, 110*t*
lipid treatment goals and strategies, 105
lipid-modifying drug mechanisms, 106*f*
niacin, 112
efficacy, 112
flushing, 112
safety, 112–113
omega-3 fatty acids, 114
efficacy, 114
safety, 114
residual risk, 111
statins, 104, 105
drug interactions, 106–108, 109*t*
efficacy, 105
lipid level change , 107*t*
liver safety, 110
muscle safety, 105–106
pharmacokinetics, 109*t*
renal excretion, 108
symptom management, 108*f*, 110
triglyceride-lowering therapy, 113
Antioxidant defense, in dyslipidemia, 1863
Antiphospholipid antibody syndrome (APLAS), 121, 1656
Antiphospholipid syndrome (APS). *See* Antiphospholipid antibody syndrome
Antiplatelet agents, cardiovascular pharmacogenomics, 1943–1945
Antiplatelet agents, 127, 128*f*, 879–883, 908
adenosine dinucleotide phosphate (ADP), 880
aspirin, 879–880
glycoprotein IIb/IIIa inhibitors, 882–883
clopidogrel, 880–881
resistance to, 881
platelet activation inhibitors
ADP/P2Y12 signaling inhibitors, 129–130
phosphodiesterase inhibitors, 131–132
prasugrel, 130–131
thrombin receptor antagonists, 132–133
TXA2 pathway inhibitors, 128–129
platelet adhesion inhibitors, 127–128
platelet aggregation inhibitors, 133
prasugrel, 881–882
therapeutics, 116
ticagrelor, 882
in VAD implantation, 1349
Antischkow myocyte, 1928
Anti-streptolysin O (ASO), 1931
Antithrombotic agents, 883–884
direct thrombin inhibitors, 884
fondaparinux, 120, 884
heparin, 883
and indirect Xa inhibitors, 119
idrabiotaparinux, 120–121
low-molecular weight heparins (LMWH), 119, 883–884
warfarin, 884
therapeutics, 116
Anxiety
and physical examination, 151
Aorfix stent graft, 1177
Aorta, inflammation of, 453
in molecular imaging, 453
Aortic atherosclerotic plaques, and hypertension, 310
Aortic balloon valvotomy, in adolescents or young adults, 1119
Aortic dissection
anatomical classification, 1168
clinical manifestations
physical findings, 1169–1170
symptoms, 1169
Debakey classification, 1168
diagnosis
chest X-ray, 1170
D-dimer, 1170
electrocardiography, 1170
imaging, 1170–1171
new classification, 1168–1169
predisposing factors
atherosclerosis, 1166–1167
inherited disease, 1167–1168
Stanford classification, 1168
treatment
acute aortic dissection outcome, 1172–1173
endovascular repair, 1172
initial treatment, 1171–1172
Aortic impedance components, 72*t*
Aortic insufficiency, plain film imaging, 185
Aortic regurgitation (AR), 1119, 1741
aortic valve replacement, 1110
cardiac catheterization, 1110
coronary blood flow during, 41
diagnosis and valuation, 1109
cardiac catheterization, 995
chest X-ray, 994
echocardiography, 994–995
electrocardiograph, 994
exercise testing, 995
imaging modalities, 995
etiology of, 992
aortopathy, 992–993
leaflet abnormalities, 993
medical therapy, 1109
natural history of, 993–994
pathophysiology of, 993
in perioperative setting, 1777
physical examination, 994
symptoms, role of, 993–994
treatment of
acute severe AR, 995–996
AVR, surgery and timing of, 995
medical therapy, 995
Aortic regurgitation severity, classification of, 279*t*
Aortic root motion, amplitude of, 232
Aortic stenosis (AS)
aortic balloon valvotomy, 1108–1109
aortic valve replacement, 1108

in asymptomatic adolescents or young adults, 1118–1119
cardiac catheterization, 1107
catheter-based therapies for, 1045
percutaneous aortic balloon valvuloplasty, 1045–1047
percutaneous aortic valve implantation, 1047–1048
coronary blood flow in, 41
diagnosis of
calcium scoring, 989
cardiac catheterization, 989
chest X-ray, 989
echocardiography, 989
electrocardiograph, 989
natriuretic peptides, 989
echocardiography for, 1107
in elderly patients, 991
etiology of
calcific aortic stenosis, 985–986
rheumatic disease, 986
left ventricular hypertrophy
growth, 987
physiologic and pathologic, comparison of, 987
low ejection fraction, 990–991
low gradient, 990–991
natural history of, 987
normal ejection fraction, 991
pathophysiology of, induced left ventricular pressure overload, 986–987
in perioperative setting, 1776–1777
physical examination, 988
plain film imaging, 183–185
symptoms, 987
angina, of, 987–988
heart failure, of, 988
syncope, of, 988
treatment of
asymptomatic, AVR in, 990
medical therapy, 990
symptomatic, AVR for, 990
Aortic stenosis progression observation: measuring effects of rosuvastatin (ASTRONOMER) study, 1605
Aortic stenosis severity, classification of, 277*t*
Aortic valve disease
description of, 985
regurgitation of *See* Aortic regurgitation
stenosis. *See* Aortic stenosis (AS)
Aortic valve replacement (AVR)
in asymptomatic AS, 990
during coronary artery bypass surgery, 1126
during coronary artery disease treatment, 1126
surgery and timing of, 995
for symptomatic AS, 990
Aortic valve, 3, 15–16
major criteria for, selection, 1122
valvular disorders, assessment of, 334
Aortography, of aortic dissection, 1171
Aortopathy, etiology of, 992–993
AP films, 174
vs PA films, 175*f*
pulmonary vascular congestion, 180*f*
Apical hypertrophic cardiomyopathy (ApHCM), 1408
Apixaban, 123–124
Apolipoprotein C (apo C), 106
Apolipoprotein E (*ApoE*) locus, 1953–1954
Apoliporotein B (Apo B), and CHD, 839
APOLLO trial, for ASCs benefits, 1993
Apoptosis, in molecular imaging, 460
Apoptosis inducing factor (AIF), 28
Apoptosome, 28
"Apple-green" birefringence, of amyloid, under polarized light, 1455, 1456, 1460
Aquaporin-2 (AQP-2), water transport, 1275
Argatroban, 125–126, 1762
Arginine vasopressin (AVP), 76
and dieresis, 1286
hyponatremia in HF, pathophysiology of, 1274, 1275
neurohormone, 74
Argyria, 152
Arm sign, 144*f*
Aroylhydrazone, in cardiotoxicity, 1485
Arrhythmia initiation
action potentials
for automaticity and contraction, 572–573
in ion channel and cellular properties, 570–572
ion channel opening and inactivation, 569–570
by surface electrocardiogram, 573–574
molecular and cellular mechanisms, 565–569
proarrhythmic substrates, 575
Arrhythmias, 1702–1703, 1777
atrial fibrillation
4q25 SNPs, 1942–1943
4q25 variant carriers, 1943
and conduction abnormalities, 1785–1786
QT interval and sudden cardiac death, 1943
variant angina, treatment of, 943–944
Arrhythmogenic right ventricular cardiomyopathy (ARVC), 444–445, 806
EMB in, 492
Arrhythmogenic right ventricular dysplasia and cardiomyopathy (AVRD/C)
clinical diagnosis, 709
arrhythmias, 712
depolarization abnormalities, 711–712
ECG criteria, 711
endomyocardial biopsy, 711
family history, 712–713
global and/or regional dysfunction and structural alterations, 709–711
repolarization abnormalities, 712
clinical presentation, 708–709
differential diagnosis, 713–714
epidemiology, 708
molecular and genetic background
autosomal dominant disease, 707–708
autosomal recessive disease, 707
desmosomal dysfunction and pathophysiology, 706–707
desmosome structure and function, 706
non-desmosomal genes, 708
molecular genetic analysis, 714
non-classical subtypes
Carvajal syndrome, 713
left dominant type, 713
Naxos disease, 713
prognosis and therapy, 714–715
Arrhythmogenic substrate, due to percutaneous alcohol septal ablation, 1408–1411
Arterial dissection, 1909*t*
Arterial pulse, monitoring of, 157–159
Arterial stiffness, and tobacco smoking, 1878
Arteriogenesis, 2008, 2009*f*
Arteriovenous oxygen difference
exercise testing, peripheral factor for, 216–217
arterial oxygen content, 217
venous arterial content, 217
Arthropathy, in hemochromatosis, 1450
Artichoke leaf extract, for dyslipidemia, 2034–2035
ARTS I trial, 978
ARTS II registry, 979
Aschoff's bodies, and ARF, 1928
Ashman's phenomenon, 677
Aspirin, 128, 908, 909
and bleeding, 1837
for cardiovascular disease, 1958
for carditis, 1932
for chest pain syndrome, 1808
and clopidogrel, 881, 1808, 1919, 1943
for cocaine abuse treatment, 1619–1620
in LV dysfunction, 1695
for MI, 879–880
in noncardiac perioperative setting, 1783
for PCI, 545
in pericardial injury, 1734
for stroke, 1918
TxA2 pathway inhibitor, 128*f*
versus warfarin, 884, 1982
ASSERT trial (Aortic Stentless vs Stented valve assessed by Echocardiography Randomized Trial), 1078
Asymmetric septal hypertrophy (ASH), 238, 1380
Asymptomatic left ventricular systolic dysfunction, 1902–1903
Atenolol, 722
for stable angina and CAD, 929
ATHENA trial, 591
Atherosclerosis
due to diabetes mellitus, 1714*f*
endothelial activation in, 1848–1850
inflammation
angiogenesis, 1850
plaque rupture and thrombosis, 1850–1852
inflammation role in, 1848*t*
innate immunity, toll-like receptors, 1850
macrophage heterogeneity in, 1850
predilection sites for, 1847–1848
and tobacco smoking, 1876–1877
triggers of inflammation in, 1850
Atherosclerosis Risk in Communities (ARIC) cohort study, anemic rate in, 1264
Atherosclerosis, molecular imaging of, 453
apoptosis, 460
calcification, 460–461

inflammation
additional promising preclinical molecular imaging strategies. 456
adhesion molecules, 456
cell tracking, 456–458
coronary arteries, 456
large arteries, 453–456
macrophages, 456
molecular CT imaging, 456
NIRF imaging, 456
proteases, 456
neovascularization, 459–460
oxidative stress, 458–459
Atherosclerosis, surrogate measures of
brachial artery flow-mediated dilation, 1641
carotid artery intima-media thickness, 1641
coronary artery calcium scoring, 1641
Atherosclerotic lesions, 872
Atherosclerotic plaques, 1851*f*
in IVUS imaging, 354*f*
Atherosclerotic renal artery stenosis (ARAS), 1157
epidemiology and natural history of, 1158
Atherosclerotic risk factors, management of, 1151
Atherothrombosis. *See* Atherosclerosis
Athlete's heart
and exercise physiology, 1818–1819
exercise-induced cardiac remodeling
aorta, 1820
left atrium, 1820–1821
left ventricle, 1819–1820
right ventricle, 1820
historical perspective, 1818
issues relevant to cardiovascular care,
arrhythmia, 1821–1823
clinical approach to, 1821
left ventricular hypertrophy, etiology of, 1821
steroids and sport performance supplements, 1824
sudden death and preparticipation disease screening, 1824–1825
syncope, 1923–1824
Athletes
with cardiovascular disease
medical-legal framework for, 1406*t*
with hypertrophic cardiomyopathy, 1405
ATI-5923, 122
Atorvastatin, for stable angina and CAD, 930, 931
Atorvastatin therapy: effects on reduction of macrophage activity (ATHEROMA) trial, 453–454
ATP-binding cassette, sub-family B (MDR/TAP), member 1 (ABCB1) gene, 1953
Atrial activity, identification of,
electrocardiogram, 194–201
Atrial Arrhythmia Conversion Trials (ACT), 594
Atrial effective refractory period (AERP), 1812
Atrial fibrillation (AF), 313, 647, 768, 799
arousal from sleep, 2022
in athletes, 1823
and cardiac rehabilitation, 1895
in constrictive pericarditis, 1499
cost-effectiveness, 1982
definition and classification, 647
diagnosis
diagnostic testing, 653
electrocardiogram, 652–653
physical examination, 652
presentation, 652
epidemiology
incidence and prevalence, 647–648
natural history, 648–649
etiology and pathogenesis, 649–650
electrophysiological abnormalities, 650
lone atrial fibrillation, 651
non-cardiac causes, 651
structural heart disease, 650
guidelines, 659–660
in HCM, 1412–1413
left atrial thrombus in, 310
management
new-onset atrial fibrillation, 653
rate control strategies, 657–658
recurrent AF, rate control versus rhythm control in, 653–654
sinus rhythm maintenance, 655–657
sinus rhythm restoration, 654–655
thromboembolism prevention, 658
and OSA, 2025
Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study, 1812
Atrial flutter, 667–668
ablation of CTI dependent, 734–735
ablation of non-CTI dependent, 735
catheter ablation clinical implications and indication, 734
in electrocardiograph, 195*f*
end-point of CTI ablation, 735
history of nonpharmacologic treatment in patients, 734
left atrial flutter circuits, 735–736
right atrial flutter circuits, 735
Atrial pressure, measurement of, 153–154
Atrial septal aneurysms, 312
Atrial septal defects (ASDs), 335, 1738–1739
associated anomalies, 1560
classification of, 1559–1560
clinical findings, 1560–1561
diagnostic studies, 1562
endocarditis prophylaxis, 1562
general considerations, 1559–1560
genetic inheritance, 1560
guidelines, 1562
pathophysiology, 1560
pregnancy, 1562
treatment and prognosis, 1562
tricuspid regurgitation in, 169
Atrial switch operations (ASOs)
for d-TGA, 1579–1580
Atrial tachycardia, 668
and pulmonary venous activity, 650
Atrial-based AV nodal independent SVT, 666
atrial flutter, 667–668
atrial tachycardia, 668
focal atrial tachycardia, 668
intra-atrial reentrant tachycardia, 668–669
multifocal atrial tachycardia, 669–670
sinoatrial re-entry tachycardia, 669
sinus tachycardia, 666–667
Atrioventricular (AV) nodal dependent SVT, 680
atrioventricular nodal reentrant tachycardia, 670–672
atrioventricular re-entry tachycardia, 672–673
junctional ectopic tachycardia, 674
permanent junctional reciprocating tachycardia, 674
pre-excitation syndromes, 673–674
and regular SVT, 678–680
Atrioventricular (AV) node, 189
Atrioventricular nodal re-entrant tachycardia, 729
catheter ablation, 730
electrophysiology, 729–730
Atrioventricular node tumors, 1675
Atrio-ventricular reentratachycardia
in electrocardiograph, 197*f*
Atrioventricular valve
and arterial valve, relationship of, 8*f*
Atropine, 678, 701
Atropine, for CPR, 796
ATS valve, 1075
Attenuated plaques
in IVUS imaging, 355*f*
Augmented right atrial contraction
compensatory role of, 962
"Augmented unipolar leads", 191
Auscultation, 160–163
of heart murmurs, 166
ejection systolic murmurs, 166–167
innocent murmurs, 167
pulmonary outflow obstruction, 167–168
S_3 and S_4 heart sounds, 163–167
Austin Flint" murmur, 170, 172
Autologous iPS cells, 1996. *See also* Induced pluripotent stem cells (iPSCs)
Automatic external defibrillators, 794
Automatic implantable cardioverter defibrillator (AICD), 794
Autonomic dysfunction, in HCM, 1387
Autonomic nervous system (ANS), 1187
and cigarette smoking, 1879
components of, 1187–1188
in heart metabolic demands, 1689
Autonomic testing, 1190
baroreflex sensitivity, 1191
cardiac sympathetic imaging, 1193
catecholamine blood measurement, 1192–1193
heart rate recovery, 1192
heart rate variability, 1191–1192
orthostatics, 1190
resting heart rate, 1191
valsalva maneuver, 1190–1191
Autoregulatory vascular resistance, 35–36
Autosomal dominant disease, 707–708
Autosomal recessive disease, 707
AVE5206, 121
Average peak velocity (APV), 38
aVF lead, 191

aVL lead, 191
aVR lead, 191
AVRO (A Phase III Superiority Study of Vernakalant versus Amiodarone in Subjects With Recent Onset Atrial Fibrillation) trial, 594
Axial scanning, 409
Azimilide Cardioversion Maintenance Trial (ACOMET II) study, 593
Azimilide dihydrochloride, 593
AzimiLide post-Infarct surVival Evaluation (ALIVE) trial, 593
Azimilide Supraventricular Tachyarrhythmia Reduction (A-STAR) trial, 593

B

B cell alloantigens, and ARF, 1928
Bachmann's bundle, 16
Bacterial endocarditis, 152, 153, 1414
  tricuspid regurgitation in, 169
Balloon valvotomy
  valvar pulmonic stenosis, treatment of, 1033–1034
Baltimore Longitudinal Study on Aging (BLSA), 1833
Bare metal stents (BMS), 553
  versus DES, 553–555
BARI-2D study, revascularization benefits, 1809
Barlow's disease, degenerative mitral valve disease, pathology of, 1011
Barth syndrome, 1379
Basic fibroblast growth factor (bFGF), 40
Basic life support (BLS), 791, 792–795
  automatic external defibrillators, 794
  cardiopulmonary resuscitation
    complications of, 794–795
    compression only type, 793
    dispatcher assisted, 793
    mechanical devices for, 793–794
  chest compressions or airway management, 793
  emergency medical services (EMS) activation, 792–793
  pacemaker or automatic implantable cardioverter defibrillator, 794
  bystanders, role of, 792
"Batista" procedure, left ventricular volume reduction surgery, 1245
BEAUTIFUL (morBidity mortality EvAlUaTion of the If inhibitor ivabradine in patients with coronary disease and left ventricULar dysfunction) trial, 595, 1244
Becker and Duchenne muscular dystrophy, dystrophin in, 495
Beijing registry, 979
Bendroflumethiazide, 54, 56, 58*t*, 60, 62, 63, 64, 65
BENEFIT trial, in Chagas disease, 1517
Benzathine penicillin, for RF, 1933*t*
Benzodiazepine
  for cocaine abuse treatment, 1619
  for dyspnea, in HF, 1358
  in TEE, 310
Beta blockers, 219, 878–879, 909, 1938. *See also* Beta-adrenergic receptor blockers
  mechanism of action, 1138
Beta-adrenergic blockade, preoperative pharmacologic intervention, 1780–1781
Beta-adrenergic blocking agents
  chemotherapy-induced cardiomyopathy, 1485
Beta-adrenergic pathways and signaling
  in VAD, 1348
Beta-adrenergic receptor blockers. *See also* Beta-blockers (BBs)
  in hypertension, 1138
Beta-blocker evaluation survival trial (BEST), 1239
Beta-blockers (BBs), 1960–1961
  adverse events, 1962
  clinical benefit, in cardiovascular disease
    ADBR1, 1962
    ADBR2, 1962
    GRK1, 1962
  clinical implications, 1962
  congenital valvar aortic stenosis, 1553
  for HCM, 1405
  for heart failure, 1607
    cardiovascular pharmacogenomics, 1945–1946
  heart rate and blood pressure reduction
    ADBR1, 1961
    ADBR2, 1961
    CYP2D6, 1961
    GRK1, 1962
  in hyponatremia, 1272
  in LVEF, 267
  for stable angina and CAD, 928–929
  ventricular function improvement, in systolic heart failure, 1962
Beta-glucan
  for dyslipidemia, 2034
Bevacizumab (Avastin)
  in left ventricular dysfunction, 1480*t*
Bezafibrate Infarction Prevention (BIP) study on β-blockers, 1698
Bezold-Jarisch reflex, 1197
Bicarbonate, for cocaine abuse treatment, 1620
Bicuspid aortic valve related aortic disease, 1168
Bicuspid aortic valve with dilated ascending aorta, 1110–1111
Bicuspid aortic valves (BAVs), 1551, 1552
  NOTCH1 gene mutation, 1552, 1555
  systolic murmur, 1556
Bicycle ergometer, 212
BiDil®, 72
Bidirectional tachycardia, 691
Bile acid sequestrants, 111
Bile-acid sequestering agents (BAS), 106
Bioprosthetic valves, 1101
Biphasic defibrillators, 797–798
Biplane imaging, 321
Birmingham Treatment of Atrial Fibrillation in the Aged Study (BAFTA), 1838
Bivaliridin, 124–125, 884, 909, 1762
Bjork-Shiley valve, 1073
Blood alcohol concentration (BAC), and normal cardiac conduction system, 1595–1596
Blood pool imaging, 398
Blood pressure (BP)
  chemoreflex influence on, 1189
  classification of, 1130*t*
  during exercise, 218
  measurement, 1129–1130
    in cardiac rehabilitation, 920
  regulation of, 1188–1189
Blood urea nitrogen (BUN), 77
  in hyponatremia, 1272
  survival predictor, 1282
"Blooming", in IVUS imaging, 351*t*
Blunt cardiac injury (BCI), 1734–1735. *See also* Myocardial contusion
Blunt injury, 1730–1731. *See also* Myocardial contusion; Non-penetrating injury
Body mass index (BMI), 231, 920, 1798, 1894
  anthracycline cardiotoxicity, 1480
  as HF risk factor, 1901
  obesity classification by, 836
  in LV function assessments, 231
Body surface area (BSA), 1019, 1820
  in LV function assessments, 231
  nomogram for, 231*f*
Bone marrow cells, 1994
Bone marrow derived stem cells, 1987–1989
Bone marrow mononuclear cells (BMMNCs), 1991–1993
Bone morphogenetic protein receptor type 2 (BMPR2), mutations in
  in PAH, 1524
BOOST Trial, using BMC post-MI, 1991, 1992*t*
Bortezomib (Velcade), in left ventricular dysfunction, 1480*t*
Bosentan (Tracleer®), for PAH, 1538–1539
Bosentan Use in Interstitial Lung Disease (BUILD-1) trial, 1524
Botanical medicines
  with adverse cardiovascular effects, 2047–2048
  for dyslipidemia, 2033–2037
  for hypertension, 2038–2040
  and heart failure, 2045–2047
  for hypertension, 2038–2040
Both ventricles endomyocardial fibrosis (BVEMF), 1442
Brachial artery flow-mediated dilation, 1641
"Brady heart". *See* Hypertrophic cardiomyopathy (HCM)
Bradyarrhythmias, 2021
  in athletes, 1821, 1823
Bradycardia and heart block, 698
  AV node disease
    first-degree AV block, 701
    paroxysmal AV block, 701
    pathology, 700–701
    second-degree AV block, 701
    third-degree AV block, 701
  bradycardia syndromes and diseases, cardiac transplantation, 699–700
    familial, 699
    iatrogenic and noncardiac causes, 698–699
    vagal tone, 699
  bundle branch block
    LBB block, 702

RBB block, 702
clinical presentation, 700
conduction system anatomy and development, 698
hemiblock, 701–702
measurement/diagnosis, 700
sinus node disease
sick sinus syndrome, 700
treatment, 702–703
Brain attack. *See* Acute ischemic stroke
Brain natriuretic peptide (BNP), 1780
cardiac marker, for myocardial wall stress, 1780
in heart failure, 1221–1222
as mortality predictor, 1355
"Braking" phenomenon, 56
Branched stent grafts, 1180
Brazilian Ministry of Health Trial
clinical trial, in post-MI patients, 1993
Breast cancer, radiation-induced cardiotoxicity, 1505
Brugada syndrome, 693–694, 724, 805, 2022
in athletes, 1823
clinical manifestations, 724
in cocaine use, 1618
diagnosis, 724–725
genetics, 724
pathogenesis, 724
prognosis, risk stratification and therapy, 725
B-type natriuretic peptide (BNP), 147, 877
in diastolic heart failure, 1254
in euvolemic CKD patients, 1703
myocyte stress, 1286
in PPCM, 1475
in SAH, 1691
Budget-impact analysis, 1983
Bulemia, 1628
Bumetanide, 54, 58*t*, 59, 65*t*
for CRS, 1288
to relieve congestive symptoms, 1242
Bundle branch block
LBB block, 702
RBB block, 702
Bundle of His, 189, 190
Bundles of Kent, 17
Bupropion, 918
anti-depressant drug, 834
in nicotine replacement therapy, 918
sustained release (SR)
tobacco dependency, first-line treatment for, 1151*t*, 1880, 1881, 1882*t*
"Burned-out phase"
end-stage LVH, 1380
Bypass Angioplasty Revascularization Investigation (BARI), 978

C

C statistic, 832–833
Ca^{2+}-induced Ca^{2+} release (CICR), 573
Cachexia
in HF, 1359
CAD, and 9p21, 1942
CAD diagnosis, prognostic variables in
combined clinical variables, 300
exercise variables, 300
imaging variables, 300
Cadiovascular trauma, 1729–1730
classification and physics of, 1730
non-penetrating injury, 1730–1731
penetrating injury, 1730
intracardiac injuries, 1737–1738
aortic and arterial trauma, 1742–1744
coronary artery laceration, 1742
iatrogenic cardiovascular injuries, 1745–1746
intracardiac fistulas, 1741–1742
retained foreign bodies, 1744–1745
septal defects, 1738–1739
thrombosis, 1742
valvular injuries, 1739–1741
pathology of, 1731
thoracoabdominal injury, management of, 1731–1732
cardiac laceration, 1734
cardiac tamponade, 1732–1733
cardiovascular injuries, 1732
myocardial contusion, 1734–1737
penetrating cardiac injury, 1733*t*
pericardial injury, 1733–1734
CADUCEUS, for cardiosphere-derived stem cells, 1993–1994
Caffeine, in athletes, 1823
Calcific aortic stenosis, 985–986
Calcific coronary sclerosis, 530
Calcification, inflammatory lesions, 460–461
Calcified valvular disease, 1100
Calcium, in pressure lowering, 1134
Calcium antagonists, 1139–1140
in hypertension, 1135*t*
variant angina, treatment of, 944–946
Calcium channel blockers (CCBs), 879, 1962–1963
for HCM, 1405
in HTN due to CKD, 1698–1699
in LV dysfunction, 1695
in perioperative risk reduction, 1781–1782
for stable angina and CAD, 929
stroke prevention, 1917
Calcium chloride, for CPR, 796
Calcium regulation, 24
and β-adrenergic signaling, 24
receptor mediated, 23
Calcium scoring, diagnosis of, 989
Calcium sensitizers, 97
levosimendan, 97–98
Calcium/calmodulin kinase II (CamKII), 24
"Calcium-binding HCM", 1378
Calmodulin-dependent protein kinase II (CaMKII), 573
Camellia sinensis, 2036. *See also* Green tea extract, for dyslipidemia
Can routine ultrasound improve stent expansion (CRUISE) trial, 360
Canadian Amiodarone Myocardial Infarction Arrhythmia Trial (CAMIAT), 589
Canadian Cardiovascular Society (CCS), 145
functional classification, 146*t*
specific activity scale, 146*t*
Canadian Registry of Atrial Fibrillation (CARAF) database, 1812
Canadian Trial of AF (CTAF), 589
Candesartan in heart failure assessment of reduction in mortality and morbidity (CHARM) trial, 1238
Candesartan in Heart Failure-Assessment of Reduction in Mortality and Morbidity-Preserved (CHARM-Preserved) trial, 1252
Cangrelor, 131
CarboMedics valve, 1074–1075
Carbonic anhydrase inhibitors, 57
Carcinoid heart disease
primary tricuspid valve regurgitation, surgical treatment of, 1026
tricuspid regurgitation in, 169
Carcinoid syndrome, 1723
Cardiac innervations, 3, 21–22
Cardiac "abnormalities", in athletes, 1818
Cardiac "syndrome X", 43
coronary blood flow during, 42, 43*t*
Cardiac action potentials, 570. *See also* Myocardial action potentials
Cardiac aging, 30–31
Cardiac amyloidosis, clinical features
cardiac catheterization hemodynamics, 1463–1464
cardiac magnetic resonance imaging, 1463
diagnostic tests, 1460
electrocardiography, 1460–1461
findings, 1461–1462
history and physical examination, 1459–1460
laboratory findings, 1462–1463
prognosis, 1464
radiologic findings, 1460
serum amyloid P component scintigraphy, 1465
tissue diagnosis, 1460
Cardiac apical impulse, in HCM, 1388
Cardiac arrest, 789–790
advanced life support (ALS), 791, 795–799
advanced airway management, 795
defibrillation, 797–799
pharmaceutical interventions, 795–796
success rate, 795
basic life support (BLS), 791, 792–795
automatic external defibrillators, 794
bystanders, role of, 792
cardiopulmonary resuscitation, complications of, 794–795
cardiopulmonary resuscitation, compression only, 793
cardiopulmonary resuscitation, dispatcher assisted, 793
cardiopulmonary resuscitation, mechanical devices for, 793–794
chest compressions or airway management, 793
emergency medical services (EMS) activation, 792–793
pacemaker or automatic implantable cardioverter defibrillator, 794
cardiac resuscitation, drug therapy in, 821–822

cardiac resuscitation centers, 822–823
myocardial ischemia causing cardiac arrest, 823
therapeutic mild hypothermia, 822–823
etiology and pathophysiology of, 812–821
bystander resuscitation efforts, 818
cardiocerebral resuscitation, prehospital component, 819–821
coronary perfusion pressures, during resuscitation efforts, 813–814
primary cardiac arrest, ability to identify 818
primary cardiac arrest, assisted ventilation in, 814–815
primary cardiac arrest, in children and adolescents, 812
primary cardiac arrest, not following guidelines for, 815–816
primary cardiac arrest, pathophysiology of, 812–813
public mindset, 817–818
ventricular fibrillation (VF), phases of, 818–819
post-resuscitative care, 800
cardiac interventions, 800
cardiopulmonary support, 800
therapeutic hypothermia, 800
termination of resuscitation, 799–800, 823
Cardiac arrhythmias
by afterdepolarizations, 575
autonomic perturbations associated with, 1200
due to cocaine usage, 1617
and sex, 1812–1813
Cardiac arrhythmias surgical and catheter ablation, 728
atrial flutter, 734–736
atrioventricular nodal re-entrant tachycardia, 729–730
atrioventricular re-entrant tachycardia, 730–731
focal atrial tachycardia, 731–734
idiopathic ventricular tachycardia, 744–751
supraventricular tachycardia, 728–729
ventricular tachycardia ablation, in patients with structural cardiac disease, 736–744
Wolff-Parkinson-White syndrome, 730–731
Cardiac assist devices, in PPCM, 1475
Cardiac biopsy
analysis of EMB tissue, 487–488
cardiotropic virus detection, 488
light microscopy and stains, 488
cardiac transplantation, 497–498
disease states
EMB in cardiomyopathy, 491–492
EMB in special cardiac disease states, 492–497
guidelines, 499
history and devices, 485
indications, 488–491
safety and complications, 487
techniques, 485–487
Cardiac cachexia, end stage heart failure, 1215
Cardiac catheterization
aortic regurgitation, diagnosis of, 995
aortic stenosis, diagnosis of, 989
basic, 470–471
complications and risks for, 537*t*
contraindications to, 519*t*
and coronary angiography, risks of, 471*t*
isolated infundibular stenosis, 1034
mitral regurgitation, 1014
right heart catheterization, 472
supravalvar stenosis, 1036
valvar pulmonic stenosis, 1032
Cardiac chambers, normal dimensions, 232*t*
Cardiac chest pain, 143*t*
Cardiac complications, substance abuse, 1613–1614
alcohol and tobacco, 1631
body image drugs
anabolic steroids, 1627–1628
anorexia and bulemia, 1628
diet drugs, 1628
club drugs, 1625
gammahydroxybutyrate, 1626
ketamine, 1626–1627
methylenedioxymethamphetamine, 1625–1626
Rohypnol, 1627
cocaine, 1615–1622
hallucinogenic drugs, 1627
lysergic acid diethylamide, 1627
hashish, 1624–1625
inhalants, 1628
magnitude of the problem, 1614
adolescents, 1614
college and medical students, 1614
iatrogenic issues, 1614–1615
trauma associations, 1614
unemployed adults, 1614
marijuana, 1624–1625
methamphetamine, 1622–1624
narcotics
heroin, 1629–1630
methadone, 1630
over the counter drugs, 1630–1631
phencyclidine, 1624
phenylpropanolamine, 1624
tetrahydrocannabinol, 1624–1625
Cardiac computed tomography (Cardiac CT)
incidental findings, 423
technical aspects
basic principles, 408–411
contrasting, 413–414
image analysis, 411–413
image quality and artifacts, 413
radiation, 411
future, 423
guidelines, 424–426
Cardiac contractility, 89
Cardiac cycle pressure waveforms
atrial pressures, 473
ventricular pressures, 473–474
Cardiac dyspnea, and physical examination, 151
Cardiac electrophysiology studies, 601–604
ablative therapy guidance
three-dimensional mapping systems, 624–625
cardiac access and catheterization, 604–605
complications, 625
for drug therapy evaluation, 623–624
fundamentals, 605
conventions, 605
normal propagation patterns, 605–607
sinus rhythm and normal atrioventricular conduction parameters, 607–609
programmed electrical stimulation and associated, 609–610
atrial stimulation, 613, 615
atrioventricular conduction disease evaluation, 615–616
baseline observations, 613
continuous pacing, 610
intermittent and interrupted pacing with extrastimuli, 610
short-long-short pacing cycles, 610–611
sudden cardiac arrest survivors, 621–623
unexplained syncope evaluation, role in, 621
ventricular stimulation assessment, 616–621
ventriculoatrial conduction assessment, 616–621
signals and filtering, 605
Cardiac energy metabolism, 1603*f*. *See also* Myocardial energy metabolism
Cardiac evaluation and care algorithm, 1774*f*
Cardiac fibroma, 1673
histopathology, 1674
imaging, 1673–1674
Cardiac function
calcium regulation, 24
cardiac muscle hypertrophy, 26
cardioprotection, 28–30
energy production, 23
ischemia/reperfusion injury, 28
mitochondria and, 24–26
β-adrenoceptors, 23
Cardiac glycosides, 1228
Cardiac hemodynamics, and coronary physiology
cardiac catheterization, 470–472
cardiac cycle pressure waveforms, 473–474
cardiomyopathy, 479–481
catheterization computations, 472–473
coronary hemodynamics, 482–484
in pericardial disease, 481–482
in valvular heart disease, 474–479
Cardiac hypertrophy, due to acromegaly, 1719
Cardiac infections, EMB in, 496
Cardiac Insufficiency Bisoprolol Study (CIBIS), 84
Cardiac Insufficiency Bisoprolol Survival (CIBIS II) trial, 1239
Cardiac laceration, 1734
Cardiac lymphatics, 3, 21
Cardiac magnetic resonance imaging (CMRI), 326, 331
ischemic versus nonischemic LV dilatation, 1425
Cardiac masses, 445
Cardiac muscle hypertrophy, 26
α_1-adrenergic receptors and, 26–27
Cardiac myxoma, 1667–1668
microscopic diagnosis, 1669–1670

imaging techniques, 1668–1669
pathology, 1669
treatment, 1669
Cardiac neoplastic disease, 1663
benign cardiac neoplasms, 1667
atrioventricular node tumors, 1675
cardiac fibroma, 1673–1674
cardiac myxoma, 1667–1670
cardiac paraganglioma, 1675
hemangioma, 1674
lipomas, 1674
lipomatous hypertrophy, 1674
papillary fibroelastoma, 1670–1672
rhabdomyoma, 1672–1673
clinical symptoms, 1663–1665
common neoplasms, locations of, 1664*t*
imaging techniques, 1665–1667
malignant tumors, 1675
angiosarcoma, 1679
leiomyosarcoma, 1681
malignant fibrous histiocytoma, 1679
osteosarcoma, 1679–1681
primary cardiac sarcomas, 1675–1679
rhabdomyosarcoma, 1681
synovial sarcoma, 1681
undifferentiated sarcomas, 1681
metastatic tumors, 1684–1686
pericardial mesothelioma, 1683–1684
primary cardiac lymphoma, 1681–1683
Cardiac nervous system dysfunction, 650
Cardiac output, catheterization computation, 472
Cardiac pain, 143
Cardiac papillary fibroelastoma (CPF), 1670–1671
histology, 1672
imaging techniques, 1671
pathology, 1671–1672
Cardiac paragangliomas, 1675
Cardiac rehabilitation, 919–921, 1890
advantages of, 921
clinical population considerations, 1895
core components, 1893
exercise training, 1894
medical assessment, 1893
medication assessment and management, 1894
nutrition, 1894
psychosocial assessment and management, 1893–1894
risk factor management, 1894
definitions and goals, 1892
phases of
early outpatient (phase II), 1893
inpatient (phase I), 1892–1893
long-term outpatient (phase III), 1893
referral, 1895
reimbursement issues, 1895–1896
in United States, 921
Cardiac resuscitation, drug therapy in, 821–822
Cardiac resynchronization therapy (CRT), 85, 289, 327, 758
for acute decompensated heart failure, 770
benefit summary, 761–762
complications, 767–768
phrenic nerve simulation, 767
dyssynchrony imaging role, 764, 777
magnetic resonance imaging, 765–766
multidetector computed tomography, 766–767
nuclear imaging, 766
PROSPECT trial, 765
real-time three dimensional echocardiography, 766
septal to posterior wall motion delay, 764
speckled tracking, 765
strain rate imaging, 765
tissue Doppler imaging, 764
tissue synchronization imaging, 764–765
emerging indications
atrial fibrillation, 768
minimally symptomatic heart failure, 769–770
narrow QRS, 768
pacemaker dependant patients, 768–769
guidelines, 770–773
in HF, 1360
in women, 1810
loss, 767
LV lead placement, 767
in practice, 759
CARE-HF trial, 759, 761
COMPANION study, 759
MIRACLE study, 759
prediction of response to therapy, 762
BIV capture, 762–763
device optimization, 763–764
rational for use, 758–759
and ventricular arrhythmias, 767–768
Cardiac resynchronization-heart failure (CARE-HF), 1426
Cardiac retransplantation, 1343
Cardiac rhabdomyomas, 1672
imaging, 1672–1673
pathology, 1673
Cardiac rupture, cardiogenic shock in acute coronary syndromes, cardiac causes of, 953, 954*f*
Cardiac sarcomere, 1378*f*
Cardiac stem cells (CSCs), 1989
Cardiac surface anatomy, 3, 6–8
Cardiac tamponade, 506, 1172, 1732–1733
in cardiac catheterization, 1495
diagnostic testing in, 1494*t*
TTE in, 273
Cardiac temponade
Cardiac thrombi, 445
Cardiac transplantation. *See also* Heart transplantation
cardiopulmonary stress testing, 1338*t*
contraindications in, 1338*t*
EMB in, 497–498
in PPCM, 1475
post-transplant infections, 1342*t*
survival with, 1343
Cardiac troponin I (cTnI)
in AL amyloidosis, 1463
cardiac marker, for myocardial injury, 1780
Cardiac troponin T (cTnT)
in asymptomatic ESRD patients, 1703
in asymptomatic multiple vessel coronary artery stenoses, 1703
in AL amyloidosis, 1463
cardiac marker, for myocardial injury, 1780
Cardiac tumors, 1663. *See also* Cardiac neoplastic disease
primary tumors, 1667*t*
surgical series, 1664*t*
types and symptoms, 1665*t*
Cardiac veins, 419–420
Cardiac venous system, 34
Cardioactive agents, 622–623
Cardiocerebral resuscitation, prehospital component, 819–821
Cardioembolic stroke, neurologic abnormalities, 151
Cardiogenic shock, 506
mental status evaluation, 151
Cardiogenic shock, in acute coronary syndromes
cardiac causes, 951–954
cardiac rupture, 953
mitral regurgitation, 953–954
right ventricular infarction, 951–952
ventricular septal rupture, 952
description of, 949
diagnosis of, 954
incidence of, 949
mechanical support, 954–957
Impella, 956–957
intra-aortic balloon pump, 955
left ventricular assist devices, 955–956
TandemHeart, 956
medical management for, 954
mortality, 949–950
pathology of, 951
pathophysiology of, 950–951
predictors of, 950
revascularization, 957–958
Cardiologists, in tobacco control, 1884
Cardiomegaly, 1718
Cardiomyopathy
due to cocaine usage, 1621
definition, 1424–1425
classification, 1424*f*
Cardiomyopathy, and insulin resistance, 1600*f*
diastolic heart failure, 1601–1602
dyslipidemia, 1604
epidemiology, 1600–1601
lipotoxicity, 1604
metabolic effects of, 1603–1604
@3detection of, 1604–1605
myocardial energy metabolism, 1602–1603
pathophysiology, 1602
structural effects of, 1605
antiadrenergic therapy, 1606
diastolic dysfunction, 1605–1606
insulin sensitization, 1608–1609
insulin therapy, 1607–1608
metabolic modulators, 1609
systolic dysfunction, 1606
Cardiomyopathy, hemodynamics in, 479
hypertrophic obstructive cardiomyopathy, 479
restrictive cardiomyopathy, 479–481
Cardioplegia additives, 969–970
Cardioprotection, mechanism of,–30

Cardiopulmonary bypass (CPB), 119
Cardiopulmonary exercise (CPX) testing, 1314
  conducting test, 1316
  dyspnea, 1317–1318
  exercise measurement, 1315
    oxygen pulse, 1315–1316
    oxygen uptake, 1315
    respiratory exchange ratio, 1316
    ventilation, 1316
    ventilatory efficiency, 1316
    ventilatory threshold, 1315
  heart failure, indications for, 1316–1317
    deconditioning and deriving exercise prescription, 1318
    peak VO_2 and prognosis, 1317
Cardiopulmonary resuscitation (CPR), 790
  complications of, 794–795
  compression only, 793
  dispatcher assisted, 793
  emergency medical services (EMS), 790–792
  evolution of, 788–789
  forward blood flow during, 788
  mechanical devices for, 793–794
  pump model, 789, 789*f*
  termination of resuscitation, 799–800
Cardiorenal syndrome (CRS), in congestive heart failure, 1281, 1284*t*
  definition of, 1283–1284, 1301
  development of, 1286*f*
  evidence-based therapies
    ACE-I AND ARB, 1289–1290
    diuretics, 1288–1289
    inotropes, 1290–1292
  pathophysiology of, 1286
  ultrafiltration on diuretic resistance, 1292
  treatment of, 1292–1296
    dialysis, 1295
    vasodilators, 1294
Cardiorenal syndrome. *See* Chronic kidney disease (CKD)
Cardiosphere-derived stem cells, 1993–1994
Cardiothoracic ratio (CTR), 174
Cardiotoxin, exposure to
  as heart failure risk factor, 1902
  chemotherapeutic agents for, 1902*t*
Cardiovascular aging, 1829–1830
  age-related changes, 1830, 1832*f*
    attenuating age-related changes, 1833–1834
    cellular aging, 1830–1832
    electrophysiologic changes, 1833
    exercise-related changes, 1833
    myocardial changes, 1833
    vascular changes, 1832–1833
  clinical syndromes, 1834
    conduction disease, 1837–1838
    heart failure, 1834–1835
    ischemic heart disease, 1836–1837
    isolated systolic hypertension, 1835–1836
    valvular disease, 1838–1839
  special issues,
    end-of-life care, 1839–1840
    prevention, 1839
Cardiovascular care
  arrhythmia, 1821–1822
  for athletes, clinical approach, 1821
  cost of, 1976
    CV contribution to, 1977
  left ventricular hypertrophy, etiology, 1821
Cardiovascular complications, cocaine usage, 1616
Cardiovascular conditions, autonomic perturbations associated with
  baroreflex failure, neurogenic hypertension, 1198
  cardiac arrhythmias, 1200
  heart failure and ischemic heart disease, 1198–1199
  obstructive sleep apnea, 1199
  pheochromocytoma, 1199–1200
Cardiovascular disease (CVD), 129, 829, 844
  global response for, 850–852
  in high income countries, 844–845
  prevention levels in, 830*t*
  in low income countries, 845–849
  in middle income countries, 845–849
  risk factors for, 829*t*, 849–850
  risk prediction scores for, 830–832, 831*t*
Cardiovascular disease, and gender
  heart failure in women, 1809–1812
  IHD in women
    acute ischemic syndromes, 1806–1808
    diagnostic approaches, 1803–1806
    prevalence in, 1798–1799
    risk factors, identification and management of, 1799–1802
  myocardial ischemia
    symptom assessment, 1802–1803
  sex and cardiac arrhythmias, 1813–1814
  sex-specific research, 1814
  stable CAD, 1808
    coronary angiography and revascularization, 1809
    medical therapy and risk factor management, 1808–1809
    treatment strategies, 1808
Cardiovascular disease, genomics of
  arrhythmias
    atrial fibrillation, 1942–1943
    QT interval and sudden cardiac death, 1943
  cardiovascular pharmacogenomics, 1943
    antiplatelet agents, 1943–1945
    beta-blockers, in heart failure, 1946
    statins, 1945–1946
    warfarin, 1945
  coronary artery disease
    9p21, 1942
    lipoprotein (a), 1941–1942
  future directions, 1947
  genomic primer, 1937–1940
  intermediate phenotypes
    hypertension, 1940–1941
    lipid traits, 1940
  SNP profiling studies, 1946–1947
Cardiovascular injuries, 1732
Cardiovascular magnetic resonance (CMR)
  in hemochromatosis, 1450
  information, 431–432
  normal values for, 431*t*
Cardiovascular magnetic resonance coronary angiography, 433
Cardiovascular magnetic resonance imaging
  mitral regurgitation, 1014
Cardiovascular magnetic resonance-guided therapy, 440
Cardiovascular medicine, economics of
  basic concepts, 1978–1979
  cost of, 1976
  cost-effectiveness
    of atrial fibrillation, 1982
    benchmarks for, 1979
    of coronary artery disease, 1981–1982
    of heart failure, 1981
    of quality improvement interventions, 1982–1983
  efficiency, 1980
  evaluating uncertainty, 1979–1980
  future estimates, 1983
  government's use of cost-effectiveness
    Britain's NICE, 1980–1981
    in United States, 1980
  health expenditures
    US vs non-US, 1976–1977,
  perspective, 1980
  resource
    scarcity and value, 1977–1978
    usage, variations in, 1977
  rising cost, CV contribution to, 1977
Cardiovascular medicine, preventing errors, 1969
  communication and culture, 1971–1972
  diagnostic error prevention, 1973
  learning from mistakes, 1972
  patient safety
    computerization, 1970–1971
    modern approach to, 1969–1970
    standardization and forcing functions, 1970
  patients role, 1973
  policy context, 1973–1974
  safe workforce creation, 1973
Cardiovascular nuclear medicine
  blood pool imaging, 398
  equilibrium gated imaging, ERNA, 399–401
  first pass curve analysis
    left-to-right shunt analysis, 399
    ventricular function, 398–399
  functional imaging, value of, 401
  general and specific patient populations, risk assessment of
    CAD in women, of 393
    diabetics, 393
    elderly, myocardial perfusion imaging in, 393
    general principles, 393
    heart failure, 394
    noncardiac surgery, preoperative evaluation for, 393
    perfusion imaging, 394
    postrevascularization, 393–394
  imaging myocardial sympathetic innervations, 401–402
  imaging myocardial viability
    nonscintigraphic imaging options, 396
    principles, 395–396

scintigraphic imaging options, metabolism based, 396
scintigraphic imaging options, perfusion related, 396
imaging perfusion
nitrogen (^{13}N) ammonia, 397
rubidium (^{82}Rb) chloride, 397
myocardial perfusion imaging
ACS evaluation strategy, 393
CAD-related risk, nonperfusion indicators of, 391–392
dense cavitary photopenia, 392
diagnostic accuracy and cost effectiveness, 390–391
gated-myocardial perfusion imaging, 385–389
image acquisition protocols, 385
image display, 385
interpretation, 389–390
multivessel coronary artery disease and related risk, indicators of, 391
myocardial perfusion imaging, clinical applications of, 392
transient ischemic dilation, 392
unstable angina/non-ST elevation myocardial infarction, 392
pathophysiologic considerations
ischemic cascade, 383
lesion severity, 382
stress testing, 383–385
stress testing deficiencies, 383
phase analysis, 401
positron emission tomography perfusion and metabolism
PET and SPECT technology, 394–395
radiation concerns, 402–405
regional coronary flow and flow reserve, quantitation of, 397–398
Cardiovascular pharmacogenetics
antiarrhythmic drugs
antiarrhythmic efficacy, 1963
calcium channel blockers, 1962–1963
clinical implications, 1963
digoxin, 1962–1963
procainamide, 1963
propafenone, 1963
toxicity, 1963
antiplatelet agents, 1943–1945
aspirin, 1958
beta-blockers, 1960–1961
adverse events, 1962
blood pressure reduction, 1961–1962
clinical benefit, in cardiovascular disease, 1962
clinical implications, 1962
heart rate reduction, 1961–1962
ventricular function improvement, in systolic heart failure, 1962
beta-blockers, in heart failure, 1946
diuretics
blood pressure lowering response, 1960
clinical outcomes, 1960
future directions, 1963
HMG-CoA reductase inhibitors
cardiovascular events, reduction in, 1954–1955
clinical implications, 1955–1956
compliance with statin therapy, 1955
low-density cholesterol lowering, 1953–1954
statin induced musculoskeletal side effects, 1955
principles of, 1951–1953
variation sources, 1952*t*
recent breakthroughs, 1944*t*
statins, 1945–1946
thienopyridines, 1956
clinical implications, 1958
clinical response to, 1957–1958
laboratory response to, 1956–1957
warfarin, 1945
clinical response, 1960
dose requirements, 1958–1960
tailored therapy, 1960
Cardiovascular phenotypes, gene variants, 1938*t*
Cardiovascular prognosis, influencing factors, 1811*t*
Cardiovascular radionuclide studies, radiation dosage of, 405*t*
Cardiovascular system, autonomic regulation of, 1187–1188
blood pressure, regulation of, 1188–1189
chemoreflex influence on heart rate and blood pressure, 1189
heart rate control, 1189
orthostatic hypotension, 1189–1190
Cardiovasular disease
and SHS exposures, 1875–1876
and tobacco smoke, pathophysiology, 1876
arterial stiffness, 1878
atherosclerosis, 1876–1877
autonomic effects and heart rate variability, 1879
dyslipidemia, 1878
endothelial dysfunction, 1877
impaired oxygen transport, 1879
inflammation, 1878–1879
oxidative stress, 1879
platelet activation and thrombosis, 1878
Cardioversion usage, DC, 681
Carditis, echo, role of, 1930
CARE-HF trial, 759, 761
Carey-Coombs murmur, 172
Carnitine deficiency, 495
Carotid artery disease
diagnosis, 1156
management, 1156–1157
natural history and risk stratification, 1155
pathophysiology, 1155
screening, 1155–1156
Carotid artery intima-media thickness, 1641
Carotid artery, inflammation of, 453
in molecular imaging, 453
Carotid endarterectomy (CEA)
in ipsilateral infarction, 1919
Carotid IMT
in HIV patients, major studies in, 1642*t*
See also Carotid artery intima-media thickness
Carotid pulse
in HCM, 1388
Carotid Revascularization Endarterectomy versus Stenting Trial (CREST), 1157
Carotid sinus massage, 679
Carvajal syndrome, 713
Carvedilol
arteriolar dilator drug, 72
and dobutamine, 94
in LV dysfunction, 1695
relative risk reduction, 1904, 1905*f*
Carvedilol or Metoprolol European trial (COMET), 1239
Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS), 84, 1239
Catecholamine polymorphic VT, 805
Catecholaminergic PVT, 695
Catecholamines
and action potential, 572
sources of, 1193*f*
Catheter ablation, 656, 681–682
Catheter designs
historical perspective and evolution of, 503
Catheter-based biopsy system, 485
Catheter-based imaging devices, characteristics of, 376*t*
Catheterization computations, 472
cardiac output, 472
Fick method, 472
indicator dilution method, 472–473
intracardiac shunt ratio, 473
vascular resistance, 473
CAuSMIC trial
catheter based study, after myoblast transplantation, 1994
Caves-Schultz-Stanford bioptome, 485, 486*f*
C-E Perimount valve, 1076
Cell therapy, randomized clinical trials
for acute myocardial infarction, 1992*t*
for CAD, 1995*t*
Cell tracking
in molecular imaging, 456–457
Center for Medicare and Medicaid Services (CMS), 1979, 2032
Centers for Disease Control (CDC)
exercise suggestion, 1891
Central nervous system (CNS)
in myocardial activity, 1689
Central sleep apnea, 2028
heart failure, 2028
treatment of central sleep apnea, 202
Central venous catheterization (CVC) guided therapy, 510
Central venous pressure (CVP)
assessment, in thoracoabdominal injury, 1732
Centrally-acting postsympathetic alpha-adrenergic agonists, 1141
Cerebral autosomal dominant arteriopathy with subcortical leukoencephalopathy (CADASIL), 1911

Cerebral edema, as neurologic symptom, of hyponatremia, 1276
Cerebral hemorrhage, 1571
in chronic cyanosis, 1571
Cerebrovascular disease
in HIV infection, 1643
CHADS2 score, stroke risk in AF, , 1911*t*
Chagas disease
cardiac magnetic resonance imaging, 1516
clinical manifestations, 1513–1515
echocardiography, 1516
epidemiology, 1513
left ventricular apical aneurysm, 1515*t*
life cycle, 1513
natural history of, 1516
prevention, 1517
Romaña's sign, 1515*f*
transmission, 1513
treatment, 1516–1517
mortality predictors, 1517
in United States, 1517
Channelopathies
due to cocaine usage, 1617
potassium channels, 1618
sodium channel, 1617–1618
Charcot-Bouchard aneurysm, 1910
CHARM-Preserved trial
candesartan, 1835
Chemotherapy-induced cardiac dysfunction
alkylating agents, 1482
anthracyclines, 1482
antimetabolites, 1482
antimicrotubule agents
monoclonal antibody-based tyrosine kinase inhibitors, 1482–1483
proteasome inhibitors, 1483
small molecule tyrosine kinase inhibitors, 1483–1484
Chemotherapy-induced cardiotoxicity
classification of, 1479
diagnosis, 1483–1484
management
dose limitation, 1485
preventive strategies, 1484–1486
monitoring, 1484
risk factors, 1480
treatment
adrenergic inhibition therapy, 1485–1486
angiotensin inhibition therapy, 1485
Chest compressions management, 793
Chest discomfort. *See also* Chest pain
cardiac causes of, 144*f*
hypertension, with cardiac involvement, 1129
Chest film technique, 174
inspiratory vs expiratory, 175*f*
Chest pain, 143, 854–868. *See also* Canadian Cardiovascular Society (CCS); Dyspnea; Syncope
acute aortic dissection, 145, 146*t*
in acute coronary syndromes, 145*t*
acute pericarditis, 146*t*
acute pulmonary embolism, 145, 146*t*
angina, 855–856
anginal equivalents, 145
cardiac pain, 143*t*
due to cocaine usage, 1619
diagnostic testing, 859–863
invasive coronary angiography, 863
MPI and stress ECHO, comparison of, 862
noninvasive computed tomographic angiography, 863
positron emission tomographic (PET) perfusion imaging, 861
stress myocardial perfusion imaging, 860–861
stress testing with echocardiogram imaging, 861–862
stress testing with myocardial imaging, 860
treadmill exercise stress testing (ETT), 860
differential diagnosis, 854–855
by system, 855*t*
edema, 149
Framingham risk score, 857*f*
functional classification, 146*t*
as HF symptom, 1213
history, 854
investigations
chest X-ray, 858
electrocardiogram (ECG), 858
laboratory investigations, 858
noncardiac pain, 144*t*
past medical history, 856
patient's description, 855
alleviating and aggravating factors, 855
associated symptoms, 855
pain, 855
patient's gestures during, 144*f*
physical examination, 856–858
risk estimation, 859
scope, 854
specific activity scale, 146*t*
stable angina, 145*f*, 145*t*
vasospastic angina, 145
Chest radiographs
aortic regurgitation, diagnosis of, 994
aortic stenosis, diagnosis of, 989
cardiac anatomy on, 176–177
isolated infundibular stenosis, 1034
supravalvar stenosis, 1035
tricuspid valve disease, 1021
valvar pulmonic stenosis, 1031
Chest roentgenogram. *See* Chest radiographs
Chest X-ray. *See* Chest radiographs
Cheyne-Stokes respiration, 147
and physical examination, 151
Chiari network, 10
Chlorothiazide, 54, 56, 58*t*, 60
Cholesterol 7α hydroxylase deficiency, 1860
Cholesteryl ester transfer protein (CETP), 1857
Chordate tendineae, 10
tricuspid valve anatomy, 1019
Chorea, 1930
management of, 1933
signs of, 1930
Chronic aortic regurgitation, 476
Chronic atrial fibrillation
in HCM, 1413
Chronic coronary artery disease
coronary artery bypass grafting *See* Coronary artery bypass grafting (CABG)
major clinical trials in, 976–979
surgery, outcomes of
anginal symptoms, relief of, 976
graft patency, 975
left ventricular function, 976
quality of life, 976
survival, 976
technique of surgical therapy for, 969
Chronic heart failure
definition of, 1228
drugs used, 78*t*
hemodynamic subsets in, 510
"Chronic ischemia", 396. *See also* Hibernation
Chronic kidney disease (CKD)
and cardiovascular disease, treatment of, 1704
cardiovascular risk factors in
abnormal divalent ion metabolism and vascular calcifications, 1700
anemia, 1699–1700
arteriosclerosis, 1700
arteriovenous fistulae, 1700
diabetes mellitus, 1699
hyperhomocysteinemia, 1700
hyperlipidemia, 1699
hypertension, 1698–1699
hypoalbuminemia, 1700
increased extracellular volume, 1700
left ventricular hypertrophy, 1699
oxidative stress and inflammation, 1700
prothrombotic factors, 1700
smoking, 1699
diagnostic tests
cardiac markers, 1703
computerized tomography scans, 1704
coronary angiography, 1704
echocardiography, 1703
electrocardiography, 1703
stress tests, 1703–1704
epidemiology, 1697
kidney transplant recipients, 1704–1705
in patients with heart failure
epidemiology of, 1281–1282
pathophysiology, 1698
spectrum of cardiovascular disease in, arrhythmias, 1702–1703
congestive heart failure, 1702
infective endocarditis, 1702
ischemic heart disease, 1700–1702
pericardial disease, 1702
valvular heart disease, 1702
Chronic mesenteric ischemia (CMI), 1160
Chronic obstructive pulmonary disease (COPD), 1763
in constrictive pericarditis, 1499
Chronic orthostatic intolerance
orthostatic hypotension, treatment of, 1196–1197
postural orthostatic tachycardia syndrome. 1195–1196
Chronic relapsing pericarditis
diagnosis, 1493

presentation and etiology, 1491–1493
Chronic resynchronization treatment with or without ICD
for refractory systolic heart failure, 1244
Chronic stable angina, 145*f*
Chronic thromboembolic pulmonary hypertension, WHO Group 4 PH, 1524
Chronic type B dissection, 1183–1184
Chronic venous insufficiency, 149
Churg-Strauss vasculitis, 1657–1658
Chylomicrons, 1856–1857
Chymase inhibitors, in myocardial fibrosis, 1261
Cilostazol (Pletal), 132, 1151
in stroke prevention, 1918
Circulating angiogenic cells (CACs), 1988, 1993
Cirrhosis, 66
and cardiovascular dysfunction, 1429
in hemochromatosis, 1450
secondary hyperaldosteronism in, 66
CKD-CVD interaction, 1697
CV risk factors, 1698
and diabetes mellitus, 1699
Class effect theory, 64
Classic angina. *See* Heberden's angina
Classification and regression tree (CART) analysis, 1282
Claudication, and cardiac rehabilitation, 1895
Cleft tricuspid valve, 1026
Clinical arrhythmias, and sex, 1812*t*
Clinical congestion
versus hemodynamic congestion, 1300*t*
Clofarabine (Clolar)
in left ventricular dysfunction, 1480*t*
Clonidine
tobacco dependency, second-line treatment for, 1883
Clopidogrel resistance, 881
Clopidogrel, 128, 545, 880–881, 908. *See also* Thienopyridines
clinical response to
CYP2C19, 1957–1958
laboratory response to
ABCB1, 1957
CYP2C19, 1956–1957
in LV dysfunction, 1695
in stroke prevention, 1918–1919
Clotting, 116–119, 117*f*
fibrin production, 117*f*
platelet activation, 118*f*
Club drugs, 1625–1626
in college students, 1614
gammahydroxybutyrate, 1626
ketamine, 1626–1627
methylenedioxymethamphetamine, 1625–1626
rohypnol, 1627
Clubbing, 153
Coarctation of aorta
associated anomalies, 1555
and BAVs, 1552
clinical findings, 1555–1556
diagnostic studies, 1556
general considerations, 1554–1555
genetic inheritance, 1555
guidelines, 1557
pathophysiology, 1555
pregnancy, 1557
prognosis and treatment, 1556–1557
Coat-hanger headache", 1190
"Cocaine washout", 1622
Cocaine, 1615
acute coronary artery thrombosis, 1616
cardiac arrhythmias, 1617
cardiovascular complications, 1616
channelopathies, 1617
potassium channels, 1618
sodium channel, 1617–1618
channelopathies, 1617–1618
chest pain, 1619
coronary artery atherosclerosis, 1617
coronary artery vasoconstriction, 1616
direct myocardial damage, 1616–1617
ECG changes, 1618
epidemiology, 1615
myocardial ischemia and infarction, 1618
pharmacology, 1615–1616
subacute and chronic problems, 1620–1622
treatment, 1619–1620
Cockcroft-Gault formula, 587*t*, 588, 1283*f*
Cockroft-Gault equation, 1282, 1831*t*
Cocoa (*Theobroma cacao*), for dyslipidemia, 2035–2036
Coenzyme Q10 (CoQ10)
in cellular ATP production, 1382
for dyslipidemia, 2036–2037
for hypertension, 2038–2039
Colchicine, 914
for acute pericarditis, 1490–1491
Combination therapy
for stable angina and CAD, 930
Communication, with end-stage patients
steps in, 1361*t*
COMPANION study, 759
Complementary and alternative medicine (CAM)
categories of, 2031–2032
Complete blood count (CBC), in hypertension measurement, 1132
Complex polygenic traits, 1937
Compression only cardiopulmonary resuscitation, 793
Compressive vascular resistance, 35
Computed tomographic angiography (CTA), 863
Computed tomography, mitral regurgitation, 1014
Computer assisted tomography (CAT), 409
Concomitant valvular lesions, 1348
in MCS, 1348
Conduction system disease, 650, 1509
Conduction system, 3, 16–18
Congenital absence of pericardium
plain film imaging, 188
Congenital autonomic failure
Congenital central hypoventilation syndrome, 1195
Congenital heart disease (CHD), 641, 806–807, 1777
Congenital long QT interval syndrome, 692–693
Congenital pulmonic stenosis
description of, 1028
isolated infundibular stenosis. *See* Isolated infundibular stenosis
supravalvar stenosis. *See* Supravalvar stenosis
valvar pulmonic stenosis. *See* Valvar pulmonic stenosis
Congenital valvar aortic stenosis
associated anomalies, 1552
clinical findings, 1552–1553
diagnostic studies, 1553
general considerations, 1551–1552
genetic inheritance, 1552
pregnancy, 1554
prognosis, 1554
treatment, 1553–1554
Congenitally corrected transposition of the great arteries (CCTGA)
general considerations, 1582
recommendations for
CCTGA, 1582–1583
surgical intervention, 1583
Congestion
assessment of, 1300*t*
Congestive heart failure (CHF), 23, 27–28, 1702
beta blocker therapy studies, 84*f*
catecholamine level, 23
diuretics in, 66
due to diabetes mellitus, 1601*f*, 1715
Framingham study criteria for, 1213*t*
gender differences, 1210*t*
glucose disposal rate, 1601*f*
racial differences, 1210*t*
radiographic manifestations of, 179–182
cephalad redistribution, 180*f*
interstitial edema, 181*f*
Kerley lines, 181
pulmonary edema, 181*f*
pulmonary vascular congestion, 180*f*
vascular pedicle, 182*f*
and renal dysfunction, 1282
Congestive Heart Failure Survival Trial of Antiarrhythmic Therapy (CHFSTAT), 589
Conivaptan, for euvolemic and hypervolemic hyponatremia, 1279
Connective tissue disease (CTD), inflammatory changes in
in PAH, 1524
Constrictive pericarditis
diagnosis, 1497–1502
Doppler echocardiographic features, 1500*f*
and management of, 1503*f*
examination, 1497
presentation and etiology, 1496–1497
physical findings, 157*t*
from restrictive cardiomyopathy, differentiation, 277*t*
TTE in, 273, 274
treatment, 1502–1503
Continuous chest compression (CCC) [CCO CPR], 814, 815, 816–817
Continuous positive airway pressure (CPAP), 2025
in HCM, 1413
Contrast-enhanced echocardiography, 236–237
Contrast-induced nephropathy (CIN), 536

Control of Ventricular Rate during AF (ERATO) study, 591
Convulsive disorders, 149
Cool-down period
in exercise training, 1894
Cooperative north candinavian enalapril survival study (CONSENSUS), 1237
Cor pulmonale
echocardiography, 1764
pulmonary function testing, 1763
signs and symptoms, 1763
studies, 1763
therapy, 1764
CoreValve ReValving System, 1839
Cori disease, 495
Coronary allograft vasculopathy (CAV)
in transplant patients, 1341
Coronary and/or graft cannulation, general principles for, 531
coronary bypass graft cannulation, 532
gastroepiploic artery (GEA), 534
internal mammary artery grafts, 533–534
left main coronary artery cannulation, 531–532
right coronary artery cannulation, 532
saphenous vein grafts (SVGs), 532–533
standardized projection acquisition, 534–535
Coronary aneurysms, 416
Coronary angiogram, potential errors in interpretation, 543
catheter-induced spasm, 543
coronary anomalies, 543–544
eccentric stenoses, 544
inadequate vessel opacification, 543
incomplete study, 543
microchannel recanalization, 544
superimposition of vessels, 544
total occlusion of coronary artery, 544
Coronary angiography, 517, 863, 911–912, 1806
in AAD diagnosis, 1171
access site hemostasis, 536–537
angiographic projections, 524
arterial nomenclature and extent of disease, 523–254
cardiac catheterization, complications of, 537–538
access site complications, 538
other complications, 538–539
catheters for bypass grafts, 522
transradial specific catheters, 522–523
catheters for coronary angiography, 520–522
Amplatz-type catheters, 522
Judkins-type coronary catheters, 521–522
multipurpose catheter, 522
clinical outcomes, 553
DES versus BMS, 553–555
contraindications for, 518
contrast media
characteristics of, 535–536
reactions, 535
contrast-induced renal failure, 536
coronary and/or graft cannulation, general principles for, 531–535
coronary angiogram, potential errors in interpretation of, 543–544
coronary circulation, congenital anomalies of, 528–531
degenerated saphenous vein grafts, 540
fluoroscopic imaging system, 535
indications for, 517–518
lesion calcification, 540
coronary perfusion, 541
thrombus, 540
total occlusion, 540
lesion quantification
angulated lesions, 540
bifurcation lesions, 540
lesion complexity, 539–540
lesion length, 540
ostial lesions, 540
quantitative angiography, 539
non-atherosclerotic coronary artery disease and transplant vasculopathy
coronary artery spasm, 542
spontaneous coronary artery dissection, 542
transplant vasculopathy, 542–543
vasculitis, 542
normal coronary anatomy, 524–528
patient preparation, 518–519
percutaneous coronary intervention, 544–545
antiplatelet therapy
pharmacotherapy for, 545–548
physiologic assessment of angiographically indeterminate coronary lesions
fractional flow reserve (FFR), 541
relative contraindications to, 471*t*
translesional physiologic measurements, clinical use of, 541–542
vascular access, sites and techniques of, 519–520
Coronary Angioplasty versus Bypass Revascularization Investigation (CABRI), 978
Coronary arteries, 3, 18–19, 1656
in molecular imaging, 456
Coronary arteriography
variant angina, diagnosis of, 942
Coronary artery atherosclerosis
due to cocaine usage, 1617
Coronary artery bypass grafting (CABG), 880, 885, 887, 902, 911, 912
aortic valve replacement in, 1126
contraindications, 972
in-hospital mortality, 972
modifiable risk factors, 973–974
nonmodifiable risk factors, 974–975
indications, 971–972
and medical management, comparison of, 976–977
and multivessel PTCA (trials comparing), 978
and OPCAB, 1329
vs PCI, 957, 1976, 1977*f*
and percutaneous coronary transluminal angioplasty using bare metal stent, 978–979
population undergoing, 971
and PTCA, comparison, 971
for stable angina and CAD, 932–933
surgical coronary revascularization advantages over medical treatment, 970–971
Coronary artery calcium (CAC) score, 839–840, 1641
Coronary artery disease (CAD), 291, 381, 414, 807–808
9*p*21, 1942
anomalous coronary arteries, 416
botanical medicines and supplements
arginine, 2042
B vitamins, 2043
beta-carotene, 2043
calcium, 2043
carnitine, 2043
fish oil, 2042
folate, 2043
garlic, 2042
ribose, 2043
vitamin E, 2043
chelation, 2043–2044
contrast CT and coronary angiography, 414–415
appropriate indication, 415
coronary bypass grafts, 415–416
coronary stent, 415
due to diabetes mellitus
endothelial changes in, 1713–1714
gout, 1715
homeostatic mechanisms, 1714
lipid abnormalities, 1714
platelets changes, 1714–1715
diagnosis of, 1125
diet, 2040
enhanced external counterpulsation, 2042
exercise, 2040–2041
lipoprotein (a), 1941–1942
mental health, 2041
mind-body medicine therapies, 2041–2042
noncontrast CT and coronary calcifications, 414
pretest probability, 210*t*
risk factors, 146
sleep, 2041. *See also under* Hypertension
and stable angina. *See* Stable angina
and sudden cardiac death, 2025
survival curves, 45*f*
as systolic heart failure risk factor, 1229
treatment
during aortic valve replacement, 1126
cost-effectiveness of, 1981–1982
weight loss, 2041
Coronary artery disease (CAD), in women. *See* Ischemic heart disease (IHD), in women
Coronary artery disease, and SE
and exercise stress echo
ESE in ischemia, 300–302
ESE in special population, 302
prognostic variables in, 299–300
prognosis assessment, 299

Coronary artery risk development in young adults (CARDIA) study, 1425
Coronary artery spasm
pathophysiology, questions of, 939
Coronary artery stenosis (CAS), 432
Coronary artery surgery study (CASS) registry, 1328
angina, definition, 292
Coronary Artery Surgery Study (CASS), 523, 970, 976–977
Coronary artery vasoconstriction, due to cocaine usage, 1616
Coronary blood flow (CBF), 40
adenosine effect on, 36
alpha-adrenergic blocking agent on, 47*f*
angiotensin converting enzyme inhibitor on, 39*f*, 47*f*
antianginal drugs on, 43*t*
B-type natriuretic peptide, 40
coronary collateral circulation, 39
determinants of, 35
during hypertension, 40–41
flow mediated regulation, 36
hormonal modulation, 38-39
in hypertrophic cardiomyopathy, 42
in ischemic heart disease, 42–44
metabolic factors, 36
myocardial oxygen demand effect on, 43*f*
nesiritide on, 47*f*, 48*f*
neurohormonal abnormalities on, 45*t*
neurohormonal regulation, 40
reserve, 45
in systolic heart failure, 44–48
in valvular heart disease, 41–42
Coronary circulation
coronary blood flow, modulation of, 36
flow mediated regulation, 36
hormonal modulation, 38–39
metabolic factors, 36
neurogenic modulation, 37–38
coronary blood flow regulation, 34
myocardial oxygen demand, 34–35
myocardial oxygen supply, 35
coronary circulation in
hypertension, 40–41
hypertrophic cardiomyopathy, 42
ischemic heart disease, 42–44
metabolic disorders, 42
systolic heart failure, 44–48
valvular heart disease, 41–42
coronary collateral circulation, 39–40
coronary vascular anatomy, 34
coronary vascular resistance, 35
autoregulatory resistance, 35–36
compressive resistance, 35
myogenic resistance, 36
viscous resistance, 35
Coronary circulation, congenital anomalies of, 528–529
anomalous coronary artery, from opposite sinus, 529–530
congenital coronary stenosis or atresia, 530–531
coronary arteries, anomalous pulmonary origin, 529
coronary artery fistulae, 530
myocardial bridging, 531
Coronary collateral vessels, 39
Coronary computed tomographic angiography (CCTA), 1806
Coronary fistulas, 417
Coronary heart disease (CHD)
risk categories, 832*t*
risk factors for, 829–840
alcohol, 838
apolipoprotein B (Apo B), 839
clustering and multiplicative effects, 830
diabetes, 838
emerging risk factors, 838–839
European Risk Scores, 832
fibrinogen and other hemostatic factors, 839
Framingham Risk Score (FRS), 830–832
Framingham Risk Score for General Cardiovascular Disease, 831*t*
high-sensitivity C-reactive protein (hs-CRP), 838–839
hyperhomocysteinemia, 839
hyperlipidemia, 837–838
hypertension, 837
lifestyle risk factors, 833–837
lipoprotein (A) [LP(A)], 839
lipoprotein-associated phospholipase A2 (LP-PLA2), 839
modifiable risk factors, 833–838
non-modifiable risk factors, 833
QRISK, 831*t*, 832
Reynolds Risk Score, 831*t*, 832
risk estimation, 830–832, 831*t*
risk prediction models, measures to evaluate, 832–833
SCORE, 831*t*, 832
sub-clinical atherosclerosis, 839–840
Third Report of NCEP Adult Treatment Panel, 831*t*
traditional risk factors, 833
translating risk factor screening into event reduction, 840
screening and prevention, 830, 830*t*
and tobacco smoking, 1873
Coronary heart disease (CHD), in women. *See* Ischemic heart disease (IHD), in women
Coronary hemodynamics
coronary flow reserve, 483–484
fractional flow reserve, 482–483
microcirculatory resistance, index of, 484
Coronary intervention
procedural success and complications related to, 555
Coronary interventions, equipment for, 549
balloons
general use balloons, 550
guide catheters, 549
guidewire, 549–550
specialized intracoronary balloons
cutting balloons, 550
perfusion balloon catheter, 550
Coronary lesions, characteristics of, 539*t*
Coronary perfusion pressures (CPP), during resuscitation efforts, 813–814
Coronary plaque
lysophosphatidylcholine in, 373*f*
Coronary revascularization
MI prevention, during surgery, 1783
Coronary sinus defects, 1559
"Coronary steal" mechanism, 383
Coronary stents, 550–551
Coronary vascular system, 34. *See* Coronary blood flow (CBF)
acetylcholine effects, 37
angiotensin receptor blocking agent's effect, 38*f*
coronary arterial system, 37
coronary blood flow determinants of, 35
coronary vascular tone, 38
myocardial oxygen demand, 34–35
myocardial oxygen supply, 35
nitric oxide, 38
NO-synthase inhibitors, 39*f*
vascular resistance, 35–36
Coronary vascular tone, 38
Coronary vasodilators, 915
Coronary veins, 3, 19–21
Coronary heart disease (CHD), as heart failure risk factor, 1901
Correction of Hemoglobin and Outcomes in Renal Insufficiency Trial (CHOIR), 1266
Cost-benefit analysis, 1983
Cost-effectiveness analysis, 1983
Cost-minimization analysis, 1984
Costs-direct, 1984
Costs-indirect, 1984
Cost-utility analysis, 1984
Cough, paroxysms of, 149
Coumadin. *See* Warfarin
COURAGE study, revascularization benefits, 1809
Coxsackievirus, in myocarditis, 1426
CPR guidelines, 788
"Crack". *See* Cocaine
C-reactive protein (CRP), 876–877
inflammatory marker, 1780
valve disease and heart failure, discrimination, 1223
in variant angina syndrome, 540
Creatine kinase (CK), 858, 874–875
in cardiac injury, 1736
Crescendo systolic ejection murmur, in HCM, 1388
CREST syndrome (calcinosis, Raynaud phenomenon, esophageal motility disorder, sclerodactyly and telangiectasia)
and PAH, 1527
and scleroderma, 152
Cribier-Edwards valve model, 1839. *See also* Edwards SAPIEN valve model, 1839
Crista supraventricularis, 11
Critical limb ischemia, 1148–1149
Cross-sectional area (CSA), 38
CT angiogram (CTA), in AAD diagnosis, 1170
CT protocol terms, 409*t*
"dose modulation" protocol, 410

"prospective" "axial-sequential" protocol, 411
"retrospective" protocol, 410
Culture-negative endocarditis
medical therapy of, 1063–1066
microbiology of, 1059
CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events), 1944
Current thoracic aortic stent graft designs, 1181
Cushing's syndrome, 1721–1722
Cutaneous systemic sclerosis (SSc), and PAH, 1527
Cyanosis, reduced hemoglobin, 151–152
Cyanotic congenital heart disease, 1570–1571
classifications of, 1571*f*
double-inlet left ventricle, 1587–1588
double-outlet right ventricle, 1584–1586
Eisenmenger's syndrome, 1589–1590
endocarditis, 1572
great arteries
congenitally corrected transposition of, 1582–1583
d-transposition of, 1578–1582
hypoplastic left heart, 1588–1589
palliative shunts, 1571–1572
pregnancy and contraception, 1572
tetralogy of Fallot, 1572–1577
total anomalous pulmonary venous return, 1583–1584
tricuspid atresia/univentricular heart, 1586–1587
truncus arteriosus, 1577–1578
Cyclic adenosine monophosphate (cAMP), 23, 26, 81, 131
and positive inotropy, 89
Cyclic guanosine monophosphate phosphodiesterase (cGMP-PDE), 132
Cyclooxygenase (COX), 128
Cyclophosphamide (Cytoxan)
in inducing cardiotoxicity, 1482
in left ventricular dysfunction, 1480*t*
Cystatin C
for renal dysfunction, 1223
Cystic medial degeneration, 1166
Cytochrome P450 enzyme (CYP), 106
drug metabolizing enzyme, 1955
Cytomegalovirus (CMV)
cardiotropic virus, 488
in myocarditis, 1427
Cytoskeletal proteins, 567

D

2,3-Diphosphoglycerate (2,3-DPG)
in systolic heart failure, 45–46
3,4-Dihydroxy-L-phenylalanine (dopa), 1192
Dabigatran, 126–127
thrombin inhibitor, in stroke prevention, 1918
DAD study, for HIV infection, 1636
Dalteparin (Fragmin®), 1761
Danish Investigators of Arrhythmia and Mortality on Dofetilide trial (DIAMOND), 587
Darbepoetin alfa, safety concerns, 1266
Dasatinib (Sprycel)
in inducing heart failure, 1483
in left ventricular dysfunction, 1480*t*
DASH diet (from the Dietary Approaches to Stop Hypertension trial), 2037
Daunorubicin, cardiotoxic effects in, 495
Davie's disease. *See* Tropical endomyocardial fibrosis
Debakey classification, of aortic dissection, 1168
Decreased cardiac output, in CRS, role of, 1286–1287
Decrescendo systolic ejection murmur, in HCM, 1388
Deep venous thrombosis (DVT), 914, 1750. *See also* Venous thromboembolism (VTE)
Deferiprone, in cardiotoxicity, 1485
Defibrillation, 797–799
"critical mass" theory, 797
"extension of refractoriness" theory, 797
risk
to environment, 798
to patient, 798
to rescuer, 798–799
types, 797–798
"upper limit of vulnerability" theory, 797
Degenerative mitral valve disease
clinical diagnosis
physical signs, 1011
symptoms, 1011
complications, 1011
natural history of, 1011
pathology of, 1010–1011
pathophysiology of, 1011
Degenerative valvular disease, 1100
Delayed afterdepolarizations (DADs), 574
in life-threatening arrhythmias, 574
Delayed hyperenhancement magnetic resonance imaging (DHE-MRI)
in HCM finding, 1396
"Delayed orthostatic hypotension", 1190
Demeclocycline, for congestion in HF, 1276
Dense cavitary photopenia, 392
Depression, in HF, 1359
Desferrioxamine, in cardiotoxicity, 1485
Desmosomal dysfunction, and ARVD/C pathophysiology, 706–707
Desmosome, structure and function, 706
"Destination therapy", 1335
Detection of Ischemia in Asymptomatic Diabetics (DIAD) study, 223
Dexfenfluramine, 836
diet drug, 1628
Dexrazoxane, in cardiotoxicity, 1485
Diabetes Control and Complications Trial (DCCT), 1716
Diabetes management, in cardiac rehabilitation, 920
Diabetes mellitus
and cardiac rehabilitation, 1895
and CHD, 838
and CKD and CVD interaction, 1699
coronary blood flow in, 42
as heart failure risk factor, 1901
in hemochromatosis, 1450
with hypertension, 1132
necrobiosis diabeticorum, 152
as systolic heart failure risk factor, 1229
Diamorphine, on exercise tolerance, in HF, 1358
Diastolic dysfunction, in HCM, Doppler inflections, 1395
Diastolic dysfunction, 1605–1606
detection of, 1606
Diastolic function, 242, 259, 270–272
Doppler indices in, age-related changes, 272*t*
formulae, 249–250
left ventricular filling pressures, evaluation of, 248–249
measurement of, 259
cardiac computed tomography, 256–257
cardiac magnetic resonance imaging, 259–260
echocardiography, 259
nuclear scintigraphy, 259
RV, ischemia on, 961
technical aspects of, 242–248
early diastolic flow, propagation velocity of, 243–245
left atrial volume and function, 247–248
mitral annular motion in diastole, Doppler tissue imaging of, 246–247
pulmonary venous flow, 245–246
transmitral flow, 242–243
types of, 248
left ventricle, impaired relaxation of, 248
pseudonormal filling, 248
restrictive filling, 248
Diastolic heart failure, 1207, 1251, 1253*t*. *See also* Heart failure with preserved ejection fraction (HFPEF)
clinical presentation, 1255–1256
CMRI in, 1256
definition, 1251
diagnosis, 1256
epidemiology, 1251–1252
future directions, 1261
management strategies, 1261*t*
MMPs/TIMPs ratio, 1253
myocardial structure and function in, 1253*t*
pathophysiology
functional derangements, 1254–1255
hemodynamic consequences, 1255
neurohormonal changes, 1253–1254
ventricular remodeling, 1252–1253
prognosis, 1256–1258
treatment strategies, 1258–1261
versus systolic heart failure, 1252*t*, 1252–1253
morbidity and mortality in, 1258*t*
symptoms and signs of, 1256*t*
Diastolic murmur
"Austin flint" murmur, 172
Carey-Coombs murmur, 172
continuous murmur, 172
early diastolic murmur, 169
aortic regurgitation, 169–171
pulmonic regurgitation, 171
mid-diastolic murmurs, 171
mitral stenosis, 171
tricuspid stenosis, 171–172
Diastolic pressure time index (DPTI), and the systolic pressure time index (SPTI), 41
Diet drugs, 1628

Dietary lipids, and CHD, 834
Diffuse intravascular coagulation (DIC), 124
Diffusing lung capacity for carbon monoxide (DLCO), 1753
Diflunisal, for SCA, 1835
DiGeorge syndrome, with TOF, 1573
Digital imaging and communications in medicine (DICOM) Standard 3.0, for IVUS imaging, 349
Digitalis Investigation Group (DIG) trial, 98–99
Digitalis purpura, 1228
Digitalis. *See* Digoxin
Digitalization". *See* Accelerated digoxin administration
Digoxin, 98, 668, 680, 723, 1962–1963
  agents affecting serum concentrations, 100
  indications and application, 99
Digoxin-toxic dysrhythmias, 100
Dihydroxyphenylacetic acid (DOPAC), 1192
Dihydroxyphenylglycol (DHPG), 1192
Dilatation, 207
Dilated aortic roots
  at risk, during pregnancy, 1572
Dilated cardiomyopathy (DCM), 238, 434, 1379, 1425
  EMB in, 491
  epidemiology, 1425
  etiology, 434
    cirrhosis, 1429
    coronary artery stenoses, 434
    familial dilated cardiomyopathy, 1427–1428
    HCM, dilated hypokinetic evolution of, 1429
    hemodialysis and end-stage renal failure, 1429
    ischemic versus nonischemic etiology, 1425–1426
    myocarditis, 434–435, 1426–1427
    nutritional deficiency, 1429–1430
    stress-induced cardiomyopathy, 1429
    tachycardia-induced cardiomyopathy, 1428–1429
  mortality, predictors of, 1430–1431
  PA chest radiograph, 187*f*
  pathology, 1425
  prognosis, 1430
    ischemic dilated cardiomyopathy, 435–436
Diltiazam, 293, 679, 680, 879. *See also* Calcium channel blockers (CCBs)
  in variant angina, 944
  for HCM, 1405
DIONYSOS trial, 591
Dipyridamole perfusion scintigraphy (DPS), 1778
Dipyridamole stress echocardiography (DiSE), 296
  and CAD, prognosis in, 304
Dipyridamole stress protocol, 296–297
Dipyridamole, 859–860
  and adenosine, in SE, 292
  in myocardial ischemia, 1385
  in stroke prevention, 1918
Direct factor XA inhibitors, 122
  apixaban, 123–124
  rivaroxaban, 122–123
Direct myocardial damage
  due to cocaine usage, 1616–1617
Direct pulmonary vasodilator therapy
  for cor pulmonale, 1764
Direct thrombin inhibitors, 118, 124, 884, 1761–1762
  argatroban, 125–126
  bivalirudin, 124–125
  dabigatran, 126–127
  hiurdin, 124
  ximelagatran, 126
Direct-acting vasodilators
  in hypertension, 1135*t*
Discount rate, 1984
Disease burden, 844–853
Disopyramide, 586, 723
Dispatcher assisted cardiopulmonary resuscitation, 793
Diuretic optimization strategies evaluation (DOSE), 1289
Diuretic resistance, 67
Diuretic-induced hyponatremia, 1277
Diuretics, 53, 54
  action sites, 54, 55*t*
  adaptations to administration, 56–57
  adverse effects, 67–68
  blood pressure lowering response, 1960
  class effect theory, 64
  classes
    carbonic anhydrase inhibitors, 57
    loop diuretics,58–59
    osmotic diuretic, 62
    potassium-sparing diuretics,61–62
    thiazide diuretics, 60–61
  classification, 54–55*t*
  clinical outcomes, 1960
  clinical pharmacology,
  clinical use, 62
    in edematous disorders, 64–67
    in hypertension, 63–64
  complications, 68
  distal convoluted tubule diuretics, 1288–1289
  dose and response, 56*f*
  glomerular filtration rate, 62
  history, 53–54
  in hypertension, 1135*t*, 1136
  in hyponatremia, 1272
  in morbidity and mortality, 1289–1290
  loop diuretics, 1288
  pharmacokinetic parameters, 58*t*
  pharmacology of, 55–56
  potassium sparing diuretics, 1289
  renal solute handling, 53
  uses, 55*t*, 62
Diuretics, individual classes
  carbonic anhydrase inhibitors, 57
    acetazolamide, 57
  loop diuretics,58–59
  osmotic diuretic, 62
  potassium-sparing diuretics,61–62
  thiazide diuretics, 60–61
Dizziness
  as HF symptom, 1213
Dobutamine, 91, 859–860, 1243. *See also* Inotropes
  administration and dosing, 93–94
  clinical indications and applications, 92*t*, 93
  in CO and renal function, 1290–1291
  dose and hemodynamic effects, 94*f*
  in heart failure, 93*f*
  ischemic stress agent, 384
  undesirable effects, 95
Dobutamine echocardiography
  for hibernation myocardial diagnosis, 1425
Dobutamine stress echocardiographic (DSE) study, 296, 1778
  and CAD, prognosis in, 302–303
    prognostic variables in, 303
  and ischemia, prognosis in, 303
  and special settings, prognosis in, 303–304
Dobutamine stress protocol, 296
Docetaxel (Taxotere)
  in left ventricular dysfunction, 1480*t*
Dock's murmur, 171
Docohexanoic acid (DHA), 114
Docosahexaenoic acid (DHA), 834, 2033. *See also* Fish oil
Documented orthodeoxia-platypnea, 1562
Dofetilide, 587, 656
Door to balloon (D2B), 894, 902, 906
Dopamine, 95, 1243. *See also* Inotropes
  for cardiac arrest, 822
  in CO and renal function, 1290–1292
  hazard ratio, 96*f*
  for renal perfusion, 1171
Doppler peak tricuspid regurgitant velocity (TRV), 1532
Dore" procedure
  left ventricular volume reduction surgery, 1245
Double inversion-recovery ("black blood") techniques, 440
Double product (HR times BP), 856
"Double-chambered right ventricle", 1563
Double-inlet left ventricle, 1587
  clinical findings, 1587
  diagnostic studies, 1587–1588
  Fontan operation, 1587
  Fontan repair, guidelines for, 1588
  recommendations for
    Fontan repair, 1588
    prior Fontan repair, 1588
  treatment and prognosis, 1588
Double-outlet right ventricle (DORV)
  associated anomalies, 1584
  general considerations, 1584
  treatment and prognosis, 1584–1586
Down syndrome, 152
Doxorubicin (Adriamycin)
  cardiotoxic effects in, 495
  in left ventricular dysfunction, 1480*t*
Doxorubicin cardiomyopathy, 1479*t*. *See also* Doxorubicin cardiotoxicity
  prevention of, 1484*t*
Doxorubicin cardiotoxicity, 1481*t*
  electron microscopic findings, 1482*t*
  hemodynamic grading, 1484*t*
  histopathologic ounsel in, 1481

Dressler's syndrome, 914
Dronedarone, 590–593, 656, 688
Drug eluting stents (DES), 129, 361, 548, 1784–1785
  versus BMS, 553–555
Drug-induced and toxin-induced PAH, 1526
d-Transposition of the great arteries (d-TGA)
  associated anomalies, 1579
  clinical findings, 1579
  diagnostic studies
    atrial switch, 1579–1580
    Rastelli procedure, 1580
  general considerations, 1578–1579
  guidelines, 1580–1582
  pregnancy, 1580
  prognosis, 1579–1580
  treatment, 1579
Dual-chamber pacemaker, for HCM, 1411–1412
Duchenne muscular dystrophy (DMD), gene repair strategy, 2004
Duke activity status index (DASI), 292, 294*t*
Duke treadmill score, 221*t*
Dutch Echocardiographic Risk Evaluation Applying Stress Echocardiography (DECREASE-III) study, 1781
Dutch randomized endovascular aneurysm management (DREAM) study, 1176
"Dye dilution" analysis, 399
Dynamic exercise testing, 383
Dynamic exercise, 212
Dysbetalipoproteinemia, 1862
Dyslipidemia
  botanical medicines and supplements
    artichoke leaf extract, 2034–2035
    beta-glucan, 2034
    cocoa, 2035–2036
    coenzyme Q10, 2036–2037
    fish oil, 2033
    garlic, 2035
    green tea extract, 2036
    guggul (*Commiphora mukul*), 2036
    niacin, 2036
    plant stanols and sterols, 2034
    policosanol, 2036
    psyllium, 2034
    red rice yeast, 2033–2034
  diagnosis of
    laboratory analysis, 1859
  diet, 2032–2033. *See also under* Coronary artery disease (CAD)
  exercise, 2033
  as heart failure risk factor, 1901
  hyperlipoproteinemia, 1859
    pattern 1: elevated cholesterol, normal triglycerides, 1859–1860
    pattern 2: increased triglycerides and moderate cholesterol, 1860–1862
    pattern 3: increased cholesterol and triglycerides increased, 1862
  hypoalphalipoproteinemia, 1863
  in insulin-resistance, 1604
  lipid transport, 1856–1858
  lipoprotein
    metabolism, 1856–1858
    treatment goals, 1859
  management considerations, 1863
  NCEP evidence statements, 1865–1872
  and tobacco smoking, 1878
  weight loss, 2033
Dyspnea, 146–148
  cardiac causes of, 146*t*, 148*t*
  etiology of, 147–148
  exertional dyspnea, 147
  in HCM, 1387
  as HF symptom, 1213, 1357–1358
  idiopathic restrictive cardiomyopathy, 1451
  orthopnea, 147
  paroxysmal nocturnal dyspnea, 147
  pulmonary causes of, 146*t*
  pulmonary edema, 147*f*
  pulmonary embolism, 147
  sleep-disordered breathing, 147
  tachyarrhythmias, 147
  wheezing, 147
Dysrhythmias, and STEMI, 913–914
Dyssynchrony imaging role and CRT, 764, 777
  magnetic resonance imaging, 765–766
  multidetector computed tomography, 766–767
  nuclear imaging, 766
  PROSPECT trial, 765
  real-time three dimensional echocardiography, 766
  septal to posterior wall motion delay, 764
  speckled tracking, 765
  strain rate imaging, 765
  tissue Doppler imaging, 764
  tissue synchronization imaging, 764–765

E

Early afterdepolarizations (EADs), 574
  in life-threatening arrhythmias, 574
Early invasive strategy, 884–885
Early repolarization, on ECG, 805
EARLY study, on PAH, 1539
Ebstein's anomaly
  associated anomalies, 1568–1569
  clinical findings, 1569
  diagnostic studies, 1569
  general considerations, 1568
  genetic inheritance, 1569
  guidelines, 1570
  pathophysiology, 1569
  pregnancy, 1570
  primary tricuspid valve regurgitation, surgical treatment of, 1025
  treatment and prognosis, 1569–1570
  tricuspid regurgitation in, 169
Ecarin clotting time (ECT), 124
ECG exercise testing, 209
  after the test
    ECG interpretation, 220
    exercise induced arrhythmias, 220–221
    prognostic utilization of, 221
    silent ischemia, 220
  before the test
    with acute coronary syndromes, 210
    after myocardial infarction, 211
    contraindications to, 211
    for diagnosis, 209–210
    with heart failure, 210–211
    indications for, 209
    for prognosis, 210
  during the test
    autonomic control, 217
    autonomic modulation, 217
    clinical correlations, 218–220
    physiology review, 213–217
  guidelines, 224–225
  methodology of, 211
    modalities, 212
    pretest preparations, 212
    safety precautions and equipment, 211–212
  rules of, 223–224
  screening, 221–222
  termination of, indications, 212*t*
ECG studies
  variant angina, diagnosis of, 940
Echo right heart catheterization, 273*f*
Echocardiography, 631
  aortic regurgitation, diagnosis of, 994–995
  aortic stenosis, diagnosis of, 989
  infective endocarditis, 1061–1062
  isolated infundibular stenosis, 1034
  mitral regurgitation, 1013–1014
  mitral stenosis, 1003–1004
  supravalvar stenosis, 1035–1036
  tricuspid valve disease, 1021–1023
    detection of, 1022
    morphology, 1021–1022
    quantitation of, 1023
  valvar pulmonic stenosis, 1031
Ecstasy, 1614, 1625. *See also* Methylenedioxymethamphetamine (MDMA)
Ectopic adrenocorticotropic hormone syndrome, 1721
Edema, 149
  in HF, 1358–1359
Edwards SAPIEN valve model, 1839
EFFECT model, in hyponatremia, 1274
Effective blood flow (EBF)
  catherization computation, 473
Effective orifice area (EOA), 1074, 1075
  and PPM, 1081
  normal reference values
    for aortic prostheses, 1082*t*
    for mitral prostheses, 1082*t*
Efficacy of Vasopressin Antagonism in hEart failuRE Outcome Study with Tolvaptan (EVEREST) trial, 1278, 1280
Efficiency, 1984
Effient. *See* Prasugrel
Ehler-Danlos syndrome, 152, 1168
Eicosapentaenoic acid (EPA), 114, 834, 2033. *See also* Fish oil
Einthoven's triangle, 192, 193
Eisenmenger's physiology, due to PDA. *See* Patent ductus arteriosus (PDA)
Eisenmenger's syndrome
  at risk, during pregnancy, 1572
  pulmonary arterial hypertension, 1589

recommendations for
medical therapy of Eisenmenger's physiology, 1589–1590
pulmonary arterial hypertension, 1589
for reproduction, 1590
Ejection fraction, 990, 992*f*, 1283*t*. *See also* Left ventricular ejection fraction (LVEF)
in AHFS therapy, as prognostic indicator, 1305*t*
AR stages, 993*f*
cardiac resynchronization therapy, study design, 760*t*
cardiovascular prognosis, influencing factor, 1811*t*
after coronary angiography, 538
in structural heat disease, 639*f*
systolic vs diastolic heart failure, 1252*t*, 1258*t*, 1282*t*
in workup algorithm, in women, 1804*f*
Ejection systolic murmurs, 166–167
"Eject-obstruct-leak" mechanism, and MR, 1385
Elderly patients
aortic stenosis in, 991
and cardiac rehabilitation, 1895
Elective coronary angiography, 906
Electrical and mechanical data
pump management, in MCS, 1349
Electricity for cardioversion and defibrillation, 789
Electrocardiogram (ECG), 189, 631
for ACS, 874
aortic regurgitation, diagnosis of, 994
aortic stenosis, diagnosis of, 989
atrial activity, identification of, 194–201
basics of, 189–190
component parts of, 191
electrode misplacements, 192–193
left arm, 193
right leg electrode, 193–194
exercise testing
and SE, 291
interpretation of, 194
isolated infundibular stenosis, 1034
lead systems in, 191–192
mitral regurgitation, 1012
mitral stenosis, 1003
monitoring, continuous
external devices, 632
implantable loop recorders, 632, 634
P wave characteristics, 677
QRS complex, characterization of, 201–206
QT interval, 207
abnormalities, 207
signal averaged, 634
for STEMI, 895–901
ST-T wave abnormalities, 206
supravalvar stenosis, 1035
tricuspid valve disease, 1021
"U" wave, 206–207
valvar pulmonic stenosis, 1031
wide QRS tachycardia, 677–678
Electrocardiogram (EKG).
See Electrocardiogram (ECG)
Electromagnetic interference (EMI), during surgery, 1787–1788
Electron beam computed tomography (EBCT), 408, 863. *See also* Ultrafast CT
for coronary artery calcium, 1220–1221
Electron transport chain (ETC), 24
Electrophysiologic Study Versus Electrocardiographic Monitoring (ESVEM) trial, 587
Electrophysiology studies, 678
Elevated central venous pressure, in renal perfusion, 1287
Embolic protection devices (EPDs), 1156
Embolism, sources of, 310
Embryonic stem cells, 1986–1987
Emergency medical services (EMS), 790–792
activation, 792–793
components of, 790–791, 791*t*
emergency medical technician-basic (EMT-B), 791, 792
emergency medical technician-intermediate (EMT-I), 791, 792
first responder, 791, 792
paramedics, 791, 792
systems, 791
Emory Angioplasty versus Surgery Trial (EAST), 978
Empty heart syndrome", 1197
EMS Systems Act, 790
Enalapril
effects on congestive heart failure, 75*f*
in long-term survival, 1905*f*
End diastolic volume (EDV), 228
End diastolic volume index, normal values for, 236*t*
End of life care in heart failure, palliative medicine. *See also* Heart failure
communication and patient's understanding, 1355–1356, 1357*t*
prognostication, issues of, 1355
suffering in, 1357
End systolic volume (ESV), left ventricular, 228, 232–233
and clinical outcome, 234–235
EF component, 232–233
physiologic basis of, 233–234
End systolic volume index, normal values for, 234*t*
Endarterectomy versus Angioplasty in Patients with Severe Symptomatic Carotid Stenosis (EVA-3S), 1157
Endocarditis prophylaxis, 1093–1095
Endocarditis, 313, 1572. *See also* Infective endocarditis
Endocrine disorders
in hemochromatosis, 1450
Endocrine heart disease
adrenal disorders
adrenal insufficiency, 1722
Cushing's syndrome, 1721–1722
paraganglioma, 1720
pheochromocytoma, 1720
primary aldosteronism, 1720–1721
carcinoid syndrome, 1723
diabetes mellitus, 1713
congestive heart failure, 1715
coronary artery disease, 1713–1715
metabolic syndrome, 1715
sudden death, 1715–1716
parathyroid disorders
hypoparathyroidism, 1722–1723
primary hyperparathyroidism, 1722
pituitary disorders
growth hormone excess, 1718–1719
hypopituitarism, 1719–1720
thyroid disease, 1716
amiodarone-induced thyroid disease, 1717–1718
hyperthyroidism, 1716–1717
hypothyroidism, 1717
End-of-life considerations, 1373–1374
Endoleak, 1179
Endomyocardial biopsy (EMB). *See also* Cardiac biopsy
clinical scenarios, role of, 489*t*
for myocardial fibrosis, 1224, 1225*f*
in cardiomyopathy
arrhythmogenic right ventricular cardiomyopathy, 492
dilated cardiomyopathy, 491
hypertrophic cardiomyopathy, 491
restrictive cardiomyopathy, 491–492
in special cardiac disease states
amyloidosis, 493–494
cardiac infections, 496–497
drug toxicity, 495–496
hemochromatosis, 494–495
sarcoidosis, 492–493
storage diseases and myopathy, 495
tissue, analysis of, 487–488
Endomyocardial biopsy, 711
Endomyocardial fibrosis (EMF), 1440, 1442–1443
endocardial calcification, 1443
Endomyocardial fibrosis, 492
Endothelial dysfunction, and tobacco smoking, 1877
Endothelial progenitor cells (EPCs), 2009–2010
Endothelial substances, in vascular wall health, 1982
Endothelins, 38
neurohormone, 74
Endothelium-derived hyperpolarizing factors (EDHF), 36
Endovascular aortic repair (EVAR), 1175, 1176
adjunctive devices and techniques, 1178
angulated neck, 1178
iliac aneurysm, 1179
narrow iliac arteries, 1178
short neck, 1178
anatomic substrate for, 1175, 1177
devices of, 1176
follow-up imaging, 1180
history of, 1176
late-occurring complications of. 1179
endotension, 1179
migration, 1179
neck dilatation, 1179–1180
thoracic aortic aneurysms, 1181
End-stage heart disease
and physical examination, 151

End-stage hypertrophic cardiomyopathy (ESHCM), 1413–1414
End-systolic volume
exercise testing, central factor for, 216
Endurance exercise, 1819. *See also* Isotonic exercise
Endurant stent graft, 1177
Energy metabolism
insulin resistance, metabolic effects of, 1603–1604
Enhanced CCD array cameras, 375
Enhanced external counterpulsation (EECP), for CAD, 2042
Enoxaparin (Lovenox®), 1761
Enoxaparin, 883
Enterococcal endocarditis, 1063
Enteroviruses, cardiotropic virus, 488
Eosinophilic heart disease, 1440
Ephedrine, 1197
Epicardial anatomy
acute margin, 7*f*
inferior surface, of heart, 8*f*
transverse sinus, 4, 5*f*
Epicardial coronary arteries, 34
Epicardial coronary artery stenosis, diagnosis of, 432
Epicedial coronary arterial heart disease
hypertension, with cardiac involvement, 1129
Epidemiological transition theory, 845, 845*t*
Epinephrine, 96
for cardiac arrest, 821
for CPR, 796
Epirubicin (Ellence), in left ventricular dysfunction, 1480*t*
Episodic autonomic failure, syndromes associated with
carotid sinus hypersensitivity, 1197–1198
hemorrhage, 1197
inferior wall myocardial ischemia/infarction, 1197
neurocardiogenic syncope, 1197
Eplerenone in patients with systolic heart failure and mild symptoms (EMPHASIS–HF) trial, 1240
Eplerenone, 61–62. *See also* Potassium-sparing agents
in CHF and renal dysfunction, 1289
in hyperkalemia, 1137–1138
in left ventricular remodeling, 1240
Epoetin alfa, safety concerns, 1266
E-point to septal separation (EPSS), 232
Epoprostenol (Flolan® and Veletri®), for PAH, 1538
Epoxyeicosatrienoic acids (EETs), 36
Epstein-Barr virus
cardiotropic virus, 488
in myocarditis, 1427
Eptifibatide, 133, 882
Equilibrium radionuclide angiography (ERNA), 398
ERACI trial, 978, 979
Ermenonville classification, 372
Erythropoietin stimulating proteins (ESPs), 1264
in treating anemia, 1266
safety concern on, 1266
ESCAPE trial, 1294
ESC-derived cardiomyocytes (ESCCM), 1986
Esmolol, 680, 1171
Estimated glomerular filtration rate (eGFR), 1697
Estudio Piloto Argentino de Muerte Sfibita y Amiodarone (EPAMSA), 589
Ethacrynic acid, 58*t*, 59
for CRS, 1288
to relieve congestive symptoms, 1242
Ethanol exposure, on heart cells and tissues, 1595
Ethanol ingestion, and normal cardiac conduction system, 1595–1596
Etomoxir, FFA, beta-oxidation, 1609
European Coronary Surgery Study, 970, 977
European Myocardial Infarction Amiodarone Trial (EMIAT), 589
European Risk Scores, 832
European Society of Cardiology (ESC)
classification of AHFS, 1299*f*
exercise suggestion, 1891
sports eligibility criteria, 1824–1825
European Trial in AF or Flutter Patients Receiving Dronedarone for the Maintenance of Sinus Rhythm (EURIDIS), 591
EuroQual 5D, quality of life assessment, 1269
EuroSCORE model, 1072
Eustachian valve, 10. *See also* Chiari network
Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial, 1287
Event recorder, in ambulatory electrocardiographic monitoring, 780–782
loop recorders, 780–781
non-loop (postevent) recorders, 781–782
EVEREST clinical status trials, on tolvaptan, 1306
Ex vivo gene therapy with retrovirus, 2006
Excitation-contraction coupling, of myocardial cells, 569*f*
Excitation-excitation coupling, 572
Excluder, stent graft design, 1176
Exercise
for CAD, 2040–2041
for dyslipidemia, 2033
and heart failure, 2044
for hypertension, 2037
measurements by CPX, 1315–1316
normal response to, 1312–1313
response in heart failure, 1313–1314
technical aspects, 1315
Exercise capacity, 218, 1890–1891
Exercise prescription recommendation, 1320
Exercise protocol, selection of, 293–295
Exercise stress echo (ESE), and CAD diagnosis
assessment prior to, 292
conducting of, 295
interpretation of, 295–296
protocol selection of, 293–295
Exercise stress echo (ESE), in ischemic disease
after PCI, prognosis, 302
atypical chest pain, 301–302
early studies and prognosis, 301
with suspected CAD, 302
Exercise test modalities, 212
adds-on to, 213
bicycle ergometer versus treadmill, 212
exercise protocols, 212–213
Exercise testing, 362
aortic regurgitation, diagnosis of, 995
in cardiac rehabilitation, 920
in heart failure, 1246*t*
Exercise testing, clinical correlations, 218
diagnostic scores, 219–220
exercise capacity, 218–219
heart rate, 218
hemodynamics, 218
recovery after exercise, 219
women, 219
Exercise testing, physiology review, 213
acute cardiopulmonary response to, 215–216
central factors, 216
metabolic equivalents term, 215
oxygen consumption 213–215
peripheral factors, 216–217
Exercise tests, in heart failure, 1223–1224
Exercise training, in heart failure
bed rest, deleterious effects of, 1318
benefits of, 1319
guideline recommendation, 1319–1320
history of, 1318–1319
mortality and morbidity, 1319
safety, 1319
Exercise, 1890
benefits of, 1891
clinical population considerations, 1895
definitions, 1890–1891
and inflammation and endothelial function, 1891–1892
performing capacity, 1891
recommendations, 1891
recovery from, 219
referral, 1895
reimbursement issues, 1895–1896
response to, 1891
safety considerations, 1892
Exercise-induced arrhythmias, 220–221
Exercise-induced cardiac remodeling (EICR), 1818–1819
aorta, 1820
left atrium, 1820–1821
left ventricle, 1819–1820
right ventricle, 1820
Exercise-induced ischemia, 215
Exertional dyspnea, 147
Exertional fatigue, as HF symptom, 1213
Exertional hypotension, and exercise, 219
Expansion of extracellular fluid volume (ECFV), in GFR, 1286
Extended-release dipyridamole (ERDP), 132
Extracorporeal Membrane Oxygenation (ECMO), for MCS, in HF, 1341
"Eye-balling" method, 324
Ezetimibe (EZE), 106, 111–112

F

^{18}FDG-PET imaging
for aneurysm, 451*t*, 465, 466*f*
for atherosclerosis detection, 451*t*, 453

for cardiac regeneration, 451*t*
for hibernation myocardial diagnosis, 1425
in metabolic syndrome, 455*f*
^{18}F-Fluorodeoxyglucose
in molecular imaging
coronary arteries, 456
for large arteries, 454–456
Fabry's disease, 495
Facilitated percutaneous coronary intervention (PCI), 902–906
elective angiography and PCI after successful thrombolysis, 905–906
full dose thrombolytic agent, 903
Familial (hereditary) systemic amyloidosis (ATTR and others), 1458–1459
Familial combined hyperlipidemia (FCH), 1860
Familial dilated cardiomyopathy (FDC), 1427–1428
Familial dysautonomia, 1195
Familial hypercholesterolemia (FH), 1860
Familial hypoalphalipoproteinemia, 1863
Familial ligand-defective apo B-100, 1860
Family history, as heart failure risk factor, 1900
Fasting, before TEE, 310
Fatigue, in HF, 1359
Fenestrated stent grafts, 1180
Fenfluramine, 836
diet drug, 1628
Fenofibrate intervention and event lowering in diabetes trial (FIELD trial), 114
Ferinject Assessment in Patients with IRon Deficiency and Chronic Heart Failure Trial (FAIR-HF), 1269
safety endpoints, 1269*t*
Fetal and umbilical cord blood cells, 1989–1991
Fibrates, 113–114
Fibrin production,117*f*
Fibrinogen and other hemostatic factors and CHD, 839
Fibrinolysis in STEMI, contraindications and cautions for, 904*t*
Fibrin-rich thrombi, clinical imaging of, 462–464
Fibroblast growth factor (FGF), 2010–2011
Fibroelastic deficiency (dysplasia), degenerative mitral valve disease, pathology of, 1011
Fibrous pericardium, 1489
Fick equation, 1818
Fick equation, for oxygen consumption rate, 1833
Fick method, catherization computation, 472
First pass curve analysis
left-to-right shunt analysis, 399
ventricular function, 398–399
First pass radionuclide angiography (FPRNA), 398
First-degree AV block, in athletes, 1821
Fish oil
for CAD, 2042
for dyslipidemia, 2033
and heart failure, 2046
for hypertension, 2038
Flail mitral valve, assessment using TEE, 313
Flamm formula, 473
Flavin adenine dinucleotide (FAD), 25
Flavin mononucleotide (FMN), 25
Flecainide, 585, 667, 681
Flow characteristics, pump management, in MCS, 1349
"Flow drag" phenomenon, in LVOT obstruction, 1382
Flow-mediated vasodilatation (FMD), 36
Fludrocortisones, for POTS, 1196
Flufenamic acid, for SCA, 1835
Flunitrazepam. *See* Rohypnol
Fluorescence spectroscopy, 374
Focal atrial tachycardia, 668, 731–732
catheter ablation
efficacy, 733–734
indications, 732
techniques, 732–733
differentiation of the mechanisms, 732
mechanisms and classification, 732
Focal ectopic atrial tachycardia, in electrocardiograph, 196*f*
Focused Assessment by Sonography in Trauma (FAST) examination, 1732, 1733
Fondaparinux, 120, 884, 1761
Forkhead box (Fox), 26
Fourth (S4) heart sounds, 163–164
artificial valve sounds, 166–167
early diastolic high-frequency sounds, 165–166
ejection sounds, 164–165
midsystolic click, 165
Fractional flow reserve (FFR), coronary hemodynamics, 482–483
Fractional shortening, 232
Framework Convention on Tobacco Control (FCTC), 1883
Framingham Heart Study
on heart failure, 1899
BMI on, 1901
Framingham Risk Score for General Cardiovascular Disease, 831*t*
Framingham risk score, 857*f*
Frank-Starling mechanism, 1189, 1440
Free (unesterified) fatty acids (FFA), 1856
Free cholesterol (FC), 106
Free fatty acids (FFA), 106
Free radicals in disease, 1863
Freestyle aortic root bioprosthesis, 1078
French maritime pine tree (*Pinus pinaster*), 2039. *See also* Pycnogenol
Friedreich's ataxia, 530
Furosemide, 54, 56, 57, 58*t*, 59, 65*t*, 67
for CRS, 1288
in hyperuricemia, 1137
to relieve congestive symptoms, 1242

G

Gabapentin, for pain, in HF, 1358
Gäisbock syndrome, with hypertension, 1132
Gallavardin sign, 166
Gammahydroxybutyrate (GHB), 1626
Ganglion blockers, 1141
Gantry, of CT scanner, 409
Ganz, William, 504
Garlic
for CAD, 2042
for dyslipidemia, 2035
for hypertension, 2038
Gastrointestinal bleeding (GIB), 129
Gastrointestine (GI), 127
GEMINI study, for insulin-resistance, 1607
Gene therapy
ex vivo gene therapy with retrovirus, 2006
gene replacement, gene correction and gene overexpression, 2003–2004
gene transfer to myocardium, 2006–2007
plasmid DNA delivery versus viral transduction
adeno-associated virus (AAV), 2004–2005
adenovirus, 2004
lentivirus, 2005–2006
Gene transfer to myocardium, 2006
Genetic arrhythmia syndromes
due to ion channel protein mutation, 574*t*
Genetic linkage and recombination on disease risk, 1939*f*
Genome-Wide Association Studies (GWAS), 1937
Gerbode defect, 1019
German Angioplasty Bypass Surgery Investigation (GABI), 978
Gallop sounds
and HF, 1214
Giant cell arteritis, 1658. *See also* Giant cell arteritis
Giant cell myocarditis (GCM), 489*f*
in DCM, 1427
EMB for, 488
Giant T wave inversions, 1218*t*
GISSI-HF trial, 1240–1241
Glomerular filtration rate (GFR), 57, 62–63
renal disease, indicator, 1281
Glossopharyngeal syncope, 149
Glucose management, 917–918
Glucose transporters (GLUT), in energy metabolism, 1603
Glycoprotein IIb/IIIa inhibitor (GPI), 125, 908
platelet aggregation inhibition, 133
Glycoprotein IIb/IIIa inhibitors (GPI), 882–883
Glycosylated hemoglobin (HbA1c)
in DM, with hypertension, 1132
Good bag-valve-mask (BVM), 795
Gorlin equation, 475
G-protein coupled receptors
in angiotensin II binding, 1275
rhodopsin-like receptors, in AVP binding, 1275
G-protein receptor kinase-2 (GRK-2), 23
GRACE risk score, 877
Graft related sequelae, 1341–1343
management of, 1341–1342
Granulomatosis with polyangiitis (GPA), 1658
See also Wegener's granulomatosis
Green tea extract, for dyslipidemia, 2036
Griffonia simplicifolia
biotinylated isolectin
for endothelial cell detection, 2012
Group A beta hemolytic streptococci (GABHS) infection, in RF, 1927

Grupo de Estudio de la Sobrevida en la Insuficiencia Cardiaca en Argentina (GESICA), 589
Guggul (*Commiphora mukul*), for dyslipidemia, 2036
Guillain-Barre syndrome, 1194
GUSTO-1 study, 950

H

3-Hydroxy-3-methylglutarul coenzyme A reductase (HMG CoA reductase), 1953
  inhibition
    by guggulsterones, 2036
    by luteolin, 2034
    by statins, 105, 837, 917, 1402, 1699
Hakki formula, 475
Hallucinogenic drugs, 1627
Haloperidol, for chorea, 1933
Hashish, 1624–1625
HCM proband, diagnostic pathway, 1401*f*
HCM with restrictive features, 492
HCM, clinical presentation
    symptoms, , 1387–1388
    physical examination, 1388–1390
  diagnosis
    electrocardiogram, 1390
    Holter monitoring, 1390
    chest X-ray, 1390
    echocardiography, 1391–1394
    Doppler inflections, 1394–1395
    cardiac magnetic resonance imaging,
    cardiac catheterization, 1396–1399
    stress test, 1400
HCM, dilated hypokinetic evolution of, 1429
Health economics
  measuring cost, 1978–1979
  measuring outcome, 1979
  quality of life, incorporation, 1979
  trials versus modeling, 1978
  in US vs non-US, 1976–1977
Healthcare-associated endocarditis, 1053–1054
Heart
  autonomic nerve supply, 21*f*
  fibrous skeleton, 3, 8
  internal structure, 3, 8
  and pericardium, 3–6
Heart failure (HF), 650, 912–913
  aortic stenosis, symptoms, 988
  botanical medicines and supplements
    arginine, 2046
    carnitine, 2046
    CoQ10, 2045–2046. *See also under* Hypertension
    creatine, 2046–2047
    fish oil, 2046
    hawthorn (*Crataegus monogyna*), 2045
    magnesium, 2047
    ribose, 2046
    taurine, 2046
    thiamine, 2047
  comprehensive HF program, 1362–1362*t*
  cost-effectiveness of individual treatments and strategies, 1981
  diet, 2044
  drugs used, 78*t*
  economic impact of, 1352–1353
  enhanced external counterpulsation, 2045
  epidemiology of, 1207, 1352
    in USA, 1207*t*
  exercise, 2044
  in hemochromatosis, 1450
  incidence, 1209
    gender differences, 1210
    geographic differences, 1210
    racial differences, 1209–1210
  and ischemic heart disease, 1198–1199
  mental health, 2044
  mind-body therapies, 2044-2045
  optimization of, 1339
  palliative care, feasibility of, 1354–1355
  perioperative complications, 1776
  prevalence, 1207–1209
  risk factors for, 1209*t*
    risk factors, comparison of, 1337*t*
  secular trends, 1211
  sleep, 2044
  spironolactone and eplerenone, 80–81
  and STEMI, 912–913
  symptom management in, 1357
    anorexia/cachexia, 1359
    depression, 1359
    dyspnea, 1357–1358
    edema, 1358–1359
    fatigue, 1359
    pain, 1358
  thermal vasodilation, 2045
  and tobacco smoking, 1873
Heart failure guidelines, 1366
  practice guidelines, implementation, 1374
  recommendations for
    initial clinical assessment, 1366–1367
    @3serial clinical assessment, 1367
Heart failure management
  in VAD implantation, 1349
Heart failure survival score (HFSS), 1336
  in hyponatremia, 1274
  as mortality predictor, 1355
Heart failure with concomitant disorders
  recommendations, 1373
Heart failure with normal ejection fraction (HFNEF), 1439
Heart failure with preserved ejection fraction (HFPEF), 1207, 1323, 1833, 1834
  etiology
    SCA, 1835
  See also Diastolic heart failure
Heart failure with preserved ejection fraction (HfpEF)
  renin-angiotensin-aldosterone system, 1810
Heart failure with reduced ejection fraction (HFREF), 1323. *See also* Systolic heart failure
  definition of, 1207
Heart failure, diagnosis
  biomarkers, 1221–1223
  cardiac magnetic resonance, 1220
  cardiac tomography, 1220–1221
  chest radiograph
    cardiomegaly, 1218*f*
    pulmonary edema, 1218*f*
  coronary arteriography, 1224
  echocardiography, 1218–1219
  electrocardiogram, 1215–1218
    anterolateral myocardial infarction, 1216*f*
    apical hypertrophic cardiomyopathy, 1217*f*
    concentric left ventricular hypertrophy, 1216*f*
    eccentric left ventricular hypertrophy, 1217*f*
  endomyocardial biopsy, 1224, 1225*f*
  exercise tests, 1223–1224
  genetics studies, 1225
  myocardial ischemia, 1224
  physical examination, 1214–1215
  radionuclide ventriculography, 1219–1220
  routine laboratory tests, 1221
  six-minute walk test, 1224
  symptoms, 1213–1214
    new classification, 1215*t*
Heart failure, exercise response
  central factors, 1313–1314
  peripheral changes, 1314
  skeletal muscle changes in, 1314*t*
Heart failure, in women, 1809–1812
Heart failure, prevention of
  future perspective, 1905
  risk factors of, 1900*t*
  Stage A heart failure, 1900–1902
  Stage B heart failure, 1902–1905
  stages, classification of, 1899*t*
Heart rate
  chemoreflex influence on, 1189
  control of, 1189
  exercise testing
    central factor for, 216
    clinical correlation, 218
  myocardial oxygen requirement, 34
  non-dihydropyridine, 43
  recovery, 1192
  resting rate, 1191
  variability, 1191–1192
Heart rate variability (HRV), and tobacco smoking, 1879
Heart Rhythm Society (HRS), 1361
Heart transplantation
  of advanced heart failure, 1334
  donor selection and perioperative period, 1339
    donor heart transplantation, 1340
    donor management, 1339–1340
    hemodynamic stabilization, 1340–1341
    immediate postoperative management, 1340
    immunosuppressive and antimicrobial management, 1341
    long-term management, 1341
    organ explanation and prevention, 1340
  during amyloid cardiomyopathy, 1466–1467
  indications and contraindications for, 1338–1339

long-term problems associated with, 1344*t*
survival with, 1343
waiting list patient, management, 1339
HeartMate XVE trial, 1344–1345
Heberden's angina, 144–145
coronary blood flow during, 42, 43*t*
Heberden's nodes, 153
Helical (or spiral) scanning, 409
Hemangiomas, 1674
Hematopoietic stem cells (HSCs), 1988
Hemiblock, 701–702
Hemochromatosis, 492, 494–495, 1450
Hemodialysis 1429
and end-stage renal failure, 1429
Hemodynamic congestion, versus clinical congestion, 1300*t*
Hemodynamic derangement
in aortic stenosis, with aortic valve thickness, 183
heart failure, 1198
in left ventricular hypertrophy, 1553
myocardial ischemia, 1198
pulmonary regurgitation, after repair, 1576
in RV pacing, 768
Hemodynamic monitoring
in noncardiac surgery, 1787
Hemodynamic optimization
in noncardiac surgery, 1786
Hemodynamic stabilization
in aortic dissection treatment, 1171
in BiVAD patients, 1348
in immediate postoperative management, 1340, 1348
in LVAD, 1348
Hemodynamic subsets
in acute myocardial infarction, 508*t*
in prognosis assessment, 511
Hemodynamics, 1446. *See also* Cardiac hemodynamics, and coronary physiology
apex cardiogram, 160
cardiac catheterization, 1463–1464
exercise testing, clinical correlation, 218
in cardiomyopathy, 479–481
in mitral stenosis, 1001–1002
in pericardial disease, 481–482
and pulmonary embolism, 1752
of valvular disease, 304–305, 474–479
Hemolysis, 957, 1057, 1095
methyldopa-induced, 1132
in nitric oxide deficient state, 1528
Hemoptysis, 149, 1170, 1757*t*,
in Eisenmenger's syndrome, 1564
in PA perforation, 512
in PE patients, 1754
in pulmonary venous congestion, 1002
Hemorrhagic stroke, 1909*t*
differential diagnosis of, 1914*t*
See also Ischemic stroke
Heparins, 119, 883, 909, 1760–1761
for cocaine abuse treatment, 1619–1620
Heparin-induced thrombocytopenia (HIT), 119, 121
Hepatitis C virus (HCV)
cardiotropic virus, 488
in myocarditis, 1426
Hepatocyte growth factor (HGF), 2011
Hepatojugular reflux, 157
Heritable PAH (HPAH), 1525–1526
Heroin, 1629–1630
Herpes simplex virus, cardiotropic virus, 488
HF-ACTION, 1319
Hiatal hernia, 423
Hibiscus (*Hibiscus sabdariffa*), for hypertension, 2039
High density lipoprotein (HDL)
in atherosclerotic disease, 1856
and cigarette smoking, 833
as CV risk factors, 1698
and endogenous estrogen, 1800
and exercise, 920
after menopause, 1799
in metabolic syndrome, 237, 1604, 1628
High volume systemic to pulmonary shunts in PAH, 1524
High-ceiling diuretics. *See* Loop diuretics
High-dose digoxin administration. *See* Accelerated digoxin administration
High-dose melphalan (HDM)/SCT, in AL amyloidosis, 1464, 1465
Highly active antiretroviral therapy (HAART) for HIV infection, 1636, 1639–1640
High-sensitivity C-reactive protein (hs-CRP)
in HIV patients, 1638
and CHD, 838–839
Hirschsprung disease, 1195
His-Purkinje system, 689
Histone deacetylases (HDACs), 26
History and physical examination, 143
general approach, 143
symptoms analysis
chest pain, 143–146
cough, 149
dyspnea, 146–148
edema, 149
hemoptysis, 149
palpitation, 148
syncope, 148–149
Hirudin, 124
HIV infection, CHD in
clinical characteristics, 1638–1639
cardiovascular risk factors, 1639
epidemiology, 1636–1638
hyperlipidemia, 1640
risk factors, modification of, 1640–1641
observational studies in, 1637*t*
pathogenesis, 1639
treatment, 1639
highly-active antiretroviral therapy, 1639–1640
HIV Medicine Association (HIVMA), in HAART initiation, 1640
HIV-associated pulmonary arterial hypertension, 1641–1643
HIV-related left ventricular dysfunction, 1643
HLA association, and acute RF, 1927–1928
HMG-CoA (3-hydroxy-3-methylglutaryl-coenzyme A) reductase inhibitors
low-density cholesterol lowering, 1953
ABCB1, 1953
APOE, 1953–1954
HMGCR, 1953
PCSK9, 1954
Hodgkin's lymphoma, radiation for
radiation-induced cardiotoxicity, 1505
extensive myocardial fibrosis, 1507
Holiday heart, 1596, 1598
Holo-uptake receptor (HUR), 106
Holter ambulatory monitoring, 777–780
Holt-Oram syndrome, 152
Homocysteine, and CHD, 839
Homocystinuria, 530
Hong Kong Diastolic Heart Failure Study, 1258
Hormonal studies, hypertension, 1131*t*
Hospitalized patients, recommendations, 1371–1372
Human herpes 6 (HHV-6)
cardiotropic virus, 488
in myocarditis, 1426
Human immunodeficiency virus (HIV) infection, 1636
cardiotropic virus, 488
in myocarditis, 1426
Human leukocyte antigen-DR (HLA-DR), in atherosclerotic lesions, 1849
"Hump-like" convex ST segment elevation, acute pericarditis, 1490
Hurler syndrome, 530
Hydralazine, 72–73, 100
arteriolar dilating drug, 72
positive inotropic properties, 100
Hydrochlorothiazide, 58*t*
"Hyparterial" bronchus, 13
Hypereosinophilic syndromes (HESs), 492, 1449–1450
Hyperhomocysteinemia, and CHD, 839
Hyperlipidemia
and CHD, 837–838
in CKD, 1699
HAART related, 1640
in HIV infection, treatment, 1640*f*
Hyperlipoproteinemia, 1859
pattern 1: elevated cholesterol, normal triglycerides
genetic disorders, 1860
secondary causes, 1859–1860
pattern 2:increased triglycerides and moderate cholesterol, 1860–1861
genetic disorders, 1861–1862
secondary causes, 1861
pattern 3: increased cholesterol and triglycerides increased
genetic disorders, 1862
secondary causes, 1862
Hypertension (HTN)
botanical medicines and supplements
coenzyme Q10, 2038–2039
fish oil, 2038
garlic, 2038
hibiscus, 2039
L-arginine, 2040
pomegranate, 2039

potassium, 2039
Pycnogenol, 2039
stevia, 2040
and cardiac rehabilitation, 1895
coronary blood flow during, 40–41
diet, 2037
due to cocaine usage, 1616
eplerenone, 61–62
exercise, 2037
and CHD, 837
in CKD, 1698–1699
as heart failure risk factor, 1900–1901
mental health, 2037
mind-body medicine, 2037
biofeedback, 2037–2038
meditation, 2038
perioperative complications, 1776
and SDB, 2024–2025
sleep, 2037
sodium reabsorption, 53
as systolic heart failure risk factor, 1229
spironolactone, 61
weight loss, 2037
whole medical systems, 2040
in women, 1798, 1800
Hypertension, evaluation of
antihypertensive therapy, 1133–1135
chest roentgenogram, 1133
clinical manifestations, 1129
clinical pharmacologic concepts, 1136
diuretics, 1136
mechanisms of action, 1136–1137
metabolic effects, 1137–1142
thiazides and congeners, 1136
electrocardiography, 1133
hemodynamic concepts, 1135–1136
laboratory studies, 1130–1132
blood chemistries, 1132
complete blood count, 1132
urinary studies, 1133
physical findings
BP measurement, 1129–1130
cardiac examination, 1130
optic fundi, 1130
peripheral pulses, 1130
treatment algorithms
hypertensive emergencies, 1142–1143
individualized stepped-care approach, 1142
stepped care approach, 1142
Hypertensive heart disease
classification of, 1130*t*
Hypertensive hemorrhages, 1910
Hyperthyroidism
due to cardiac complications, 1716–1717
Hypertriglyceridemia (HTG), 1940
Hypertrophic cardiomyopathy (HCM), 42, 437, 640, 650, 806
2D echocardiographic views of, 1383*f*
atrial fibrillation, 1412–1413
CMR images, 1380*f*
coronary blood flow in, 42
correlative findings, 438–439
definition, 1377
diagnosis, 437
cardiac catheterization, 1396–1399
cardiac magnetic resonance imaging, 1395–1396
chest X-ray, 1390
Doppler inflections, 1394–1395
echocardiography, 1391–1394
electrocardiogram, 1390
Holter monitoring, 1390
stress test, 1400
EMB in, 491
end-stage hypertrophic cardiomyopathy, 1413
epidemiology and genetic considerations, 1377–1379
infective endocarditis, 1414
management, 1402
of sudden death, 1403–1405
hypertrophic cardiomyopathy, in athletes, 1405
dual-chamber pacemaker, 1411–1412
genetical and family screening, 1402–1403
medical therapy, 1405–1407
percutaneous alcohol septal ablation, 1408–1411
septal myectomy, 1407–1408
natural history, 1400–1402
and obstructive sleep apnea, 1413
and OSA, 2025–2026
pathology, 1379–1381
pathophysiology, 1381–1382
arrythmogenic substrate and sudden death, 1386
autonomic dysfunction, 1387
diastolic dysfunction, 1384–1385
left ventricular outflow tract obstruction, 1382–1384
mitral regurgitation and mitral valve abnormalities, 1385–1386
myocardial fibrosis, 1386–1387
myocardial ischemia, 1385
systolic dysfunction, 1385
phenocopies, 1379*t*
physical examination, 1388–1390
and pregnancy, 1413–1414
primary HCM, 238
echocardiographic features, 238–239
prognosis, 437–438
secondary HCM, 239
echocardiographic features, 239
susceptibility genes, 1378*t*
symptoms, 1387–1388
Hypertrophic obstructive cardiomyopathy (HOCM), 479
Hypertrophic osteodystrophy, in chronic cyanosis, 1571
Hypertrophy, 207
Hyperuricemia, in hypertension, 1137
Hyperuricemia, in chronic cyanosis, 1571
Hypoalbuminemia, due to dialysis, 1700
Hypoalphalipoproteinemia, 1863
Hypodiastolic failure", 1251
Hypokalemia
as thiazide side effect, 1137
factors responsible for, 1131*t*
Hyponatremia, and congestive heart failure, 1272–1274
causal mechanism
arginine vasopressin, 1275–1276
renin-angiotensin-aldosterone system, 1275
sympathetic nervous system, 1274
conivaptan, 1279
diuretic therapy in, 68, 1276–1277
EFFECT model, 1274
lixivaptan, 1278–1279
as mortality predictor, 1273, 1274
tolvaptan, 1277–1278
treatment of, 1276
vasopressin receptor antagonists in, 1277
Hypoparathyroidism, 1722
Hypopituitarism, due to vascular disease, 1719–1720
Hypoplastic left heart syndrome (HLHS), 1588–1589
Hypothyroidism
due to cardiac complications, 1717
and heart failure, 100
Hypovolemic shock, 506
HYVET trial, 1939
indapamide, with perindopril, 1836

I

^{123}I-Metaiodobenzylguanidine (^{123}I-MIBG), 1193
for cardiac sympathetic imaging, 1194, 1433
for coronary spasm, 942
for extra adrenal tumors, 1199
^{123}I-β-Methyl-*p*-iodophenyl pentadecanoic acid (BMIPP), 1326*t*
for abnormal fatty acid metabolism, 1483–1484
for coronary spasm, 942
with SPECT imaging, 1327–1328
Iatrogenic VT, 691–692
Ibutilide, 579, 588, 654
Ibutilide repeat dose study, 588
ICOPER study, 1760
Idarubicin (Idamycin PFS), in left ventricular dysfunction, 1480*t*
Idiopathic dilated cardiomyopathy (IDC), 435–436, 1425
prognosis in, 436–437
Idiopathic left ventricle VT, 691
Idiopathic pulmonary arterial hypertension (IPAH), 1522*t*, 1525
Idiopathic restrictive cardiomyopathy, 491, 1440, 1451–1452
Idiopathic ventricular tachycardia, 744
catheter ablation, 748, 750, 751
cusp VT, 746
ECG recognition, 748, 750
epicardial VT, 746–747
ILVT and fascicular VT, 748
LVOT VT, 746
management, 747–748
mitral annular VT, 750
outflow tract-ventricular tachycardia, 744
RVOT VT, 744–745
tricuspid annular VT, 751

VT arising from the pulmonary artery, 746
Idiopathic ventricular fibrillation, 695
Idrabiotaparinux, 120–121. *See also* Fondaparinux
Ifosfamide (Ifex)
in inducing cardiotoxicity, 1482
in left ventricular dysfunction, 1480*t*
Iliofemoral artery, inflammation of, 453
in molecular imaging, 453
Illicit drug use, endocarditis in, 1053
Iloprost (Ventavis®), for PAH, 1538
Images, technetium-99 m labeled agents, for hibernation myocardial diagnosis, 1425
Imaging, common modes, 323*t*
Imatinib mesylate (Gleevec)
in inducing cardiotoxicity, 1483
in left ventricular dysfunction, 1480*t*
Immunosuppressants
and side effects, in heart transplantation, 1341*t*
Immunosuppression related organ dysfunction, 1342
Impaired oxygen transport, and tobacco smoking, 1879
Impella, cardiogenic shock, mechanical support in, 956–957
Implantable cardiac defibrillator (ICD), 637
cost of, and QALYs, 1979
for heart failure, in women, 1810
management of, 1360–1361
in PPCM, 1475
for SD prevention, 1386
Implantable loop recorders (ILRs), 783
IN-CHF, hyponatremia in HF, 1274
Incomplete right bundle branch block (RBBB)
in atrial septal defects, 1560
Incraft stent graft, 1177
Increased myocardial demand, due to cocaine usage, 1616
Indapamide, 54, 58*t*, 60, 64
Indicator dilution method, catherization computation, 472–473
Indinavir, and AZT, in HIV infection, 1643
Induced pluripotent stem cells (iPSCs), 1991
Inducible nitric oxide synthase (iNOS), 951
in hibernating myocardium, 1325
Infection prevention
in transplant list patients, 1338
in VAD implantation, 1349
Infectious Disease Society of America (IDSA), HAART-related hyperlipidemia management, 1640
Infectitious endocarditis, 1414. *See also* Bacterial endocarditis
Infective endocarditis (IE), 1093, 1702
description of, 1052
epidemiology of, 1052
adults, 1052–1054
children, 1054
management, 1062, 1116
anticoagulation, 1067
definitive medical therapy, 1063–1066
empiric medical therapy, 1063
endocarditis, prevention of, 1067–1068
persistent fever, 1067
surgical therapy, 1066–1067
timing of surgery, 1066–1067
manifestations of, 1055
embolization, 1056
immunologic manifestations, 1057
metastatic foci of infection, 1056–1057
periannular extension, 1056
valvular destruction, 1055–1056
microbiology of, 1057
culture-negative endocarditis, 1059
native valve, 1057–1058
prosthetic valve, 1058–1059
pathogenesis of, 1054
abnormal pressure-flow dynamics, 1054
host response, 1055
manifestations of infection, 1055
microbial factors, 1055
non-bacterial thrombotic endocarditis, 1055
patient presentation and diagnosis, 1059
blood culture, 1060–1061
clinical presentation, 1060
echocardiography, use of, 1061–1062
mimickers of infectious endocarditis, 1062
other diagnostic studies, 1062
primary tricuspid valve regurgitation, surgical treatment of, 1026
transesophageal echocardiography, 1116–1117
transthoracic echocardiography, 285, 1116
Inferior myocardial infarction (IMI), concomitant RVI, 960
Inflammation, 1878–1879
in atherosclerosis, 1832
to diagnose myocarditis, 490
and tobacco smoking, 1878–1879
Inflow cannula, position of, in MCS, 1348
Influenza virus, cardiotropic virus, 488
In-hospital ECG recording, variant angina, diagnosis of, 941–942
Initial conservative strategy, 884–885
Innocent murmurs, 167
Inodilators. *See* Phosphodiesterase inhibitors
Inotropes, 1290–1291, 1339
Inotropic support, 966, 1294, 1347
in CO and renal function, 1290–1291
by dobutamine, 91
in HF, immediate postoperative management, 1340
Insufficient physical activity, 1890
Insulin sensitization, 1608–1609
Insulin therapy, 1607–1608
Integrated Backscatter (IB) IVUS, 355
Integrative cardiology, 2032
Integrative medicine, 2031–2032
for cardiovascular conditions, 2032
Integrilin. *See* Eptifibatide
Intention-to-treat (ITT) analysis, 932
Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS), 1335
advanced heart failure patients, classification of, 1346*t*
heart transplantation need for, 1338
Intercellular adhesion molecule-1 (ICAM-1), 1848
in HIV patients, 1638
Interleukin-1 (IL-1), in LDL binding, 1849
Interleukin-6 (IL-6)
in rheumatoid arthritis, 1650
in variant angina syndrome, 540
Intermediate density lipoprotein (IDL), 1856
Intermediate density lipoprotein cholesterol (IDL-C), 106
International AIDS Society USA Panel guidelines in early HAART initiation, 1639
International Cooperative Pulmonary Embolism Registry (ICOPER) study, 1750
International Registry of Aortic Dissection (IRAD), 1166
International Society of Heart and Lung Transplantation (ISHLT) guidelines, 1338
Interstitial fibrosis, in HCM, 1386–1387
Interstitial lung disease, 1763
Interventricular septum (IVS), 1380. *See also* Asymmetric septal hypertrophy (ASH)
Intestinal angina, 1160. *See also* Chronic mesenteric ischemia (CMI)
Intestinal bile acid transporter (IBAT), 106
Intra-aortic balloon pump (IABP) support, 912–913
cardiogenic shock, mechanical support in, 955
for MCS, in HF, 1341
Intra-atrial reentrant tachycardia, 668–669
Intra-atrial septum, lipomatous hypertrophy of, 423
Intracardiac echocardiography (ICE), 335
Intracardiac fistulas, 1741–1742
Intracardiac injuries, 1737–1738
aortic and arterial trauma, 1742–1744
coronary artery laceration, 1742
iatrogenic cardiovascular injuries, 1745–1746
intracardiac fistulas, 1741–1742
retained foreign bodies, 1744–1745
septal defects, 1738–1739
thrombosis, 1742
valvular injuries, 1739
aortic regurgitation, 1741
mitral regurgitation, 1740–1741
pulmonic valvular regurgitation, 1741
tricuspid regurgitation, 1739
Intracardiac masses, TTE in, 285–286
Intracardiac shunt ratio, catherization computation, 473
Intracardiac shunt, 443
Intracellular Ca^{2+}, in arrhythmia initiation, 565
Intracerebral hemorrhage (ICH), 1908, 1910
clinical features of, 1913*t*
Intracoronary angioscopy, 370
clinical experience, 372
future directions, 374
image interpretation, 371–372
imaging systems and procedures. 371
safety and limitations, 373–374
vulnerable plaque, detection of, 372–373
Intracranial aneurysm, and 9p21, 1942
Intracranial hemorrhage (ICH), 121
Intramural hematoma, 1186
Intramural vessels, 3, 19

Intraoperative TEE, 316–317. *See also* Procedural adjunct TEE
Intravascular coronary ultrasound. *See* Intravascular ultrasound (IVUS)
Intravascular ultrasound (IVUS)
balloon angioplasty, 358–359
procedural guidance, 359
bare metal stent implantation, 359
long-term outcomes, 360–361
procedural guidance, 359–360
basics of and procedures, 349
drug-eluting stent implantation, 361
long-term outcomes, 361–362
procedural guidance, 361
future directions, 363–364
interventional applications, 356–357
measurements, 352
normal vessel morphology, 349–352
plaque formation and distribution, 356
preinterventional imaging, 357–358
safety, 362–363
tissue characterization, 352–356
Intravenous catecholamines, in refractory heart failure, 1243
Intravenous urography, hypertension, 1131*t*
Intraventricular hemorrhage (IVH), 1908, 1910
Invasive coronary angiography, 863
Invasive evaluation, mitral stenosis, 1004
Iodinated contrast agents, in cardiac angiography, 536*t*
"Iodine mapping", 411
Ion channel protein mutation, and genetic arrhythmia syndromes, 574*t*
Ion channels, 569
I-PRESERVE trial, irbesartan, 1835
IRB irbesartan versus placebo, 1835
Irbesartan in patients with heart failure and preserved ejection fraction (I-PRESERVE) trial, 1252
Iron chelators, in cardiotoxicity, 1485
Iron deficiency and iron replacement, in heart failure, 1269–1270
ISAR-SHOCK study, 957
Ischemia
in coronary anomalies, 529*t*
during postoperative setting, 1788
Ischemia/reperfusion injury, 28
reperfusion injury salvage kinase, 29
"Ischemic burden", 382
Ischemic cardiomyopathy, 1425
and exercise, 219
Ischemic cascade, 383
Ischemic heart disease (IHD), 650, 927
coronary blood flow in, 42–44
noncardiac surgery for, 1776
CHD in CKD, 1700–1701
interventional therapy, 1701–1702
medical therapy, 1701
and tobacco smoking, 1873
Ischemic heart disease (IHD), in women
diagnostic approaches, 1803–1804
cardiovascular MR assessment, 1805–1806
coronary angiography, 1806
coronary computed tomographic angiography, 1806
exercise ECG, 1804
stress-induced perfusion abnormality assessment, 1804–1805
stress-induced wall motion abnormality assessment, 1805
management of
acute ischemic syndromes, 1806–1808
prevalence of, 1798–1799
risk factors, and management of
aspirin, 1801
dietary modifications, 1800
lipid lowering therapy, 1801
risk factors, identification
diabetes, 1800
HTN, 1800
postmenopause, 1800
premenopause, 1799
tobacco use, 1800
with RA, 1799
Ischemic RV dysfunction
natural history of, 962–963
reperfusion effects on, 963–964
Ischemic stroke, 1908, 1909*t*. *See also* Stroke
clinical features, 1913*t*
differential diagnosis of, 1914*t*
prevention of, 1915*t*
Isolated atrial natriuretic factor, 1459
Isolated infundibular stenosis
clinical findings, 1034
differential diagnosis, 1035
laboratory investigations
cardiac catheterization, 1034
chest roentgenogram, 1034
echocardiography, 1034
electrocardiogram, 1034
natural history, 1034
pathological anatomy, 1034
pathophysiology, 1034
treatment of, 1035
Isometric exercise, 212, 1819
Isometric exercise. *See* Aerobic exercise
Isoproterenol, 95–96, 622–623, 678, 691, 693
Isosorbide dinitrate/hydralazine effect, 73*f*
Isotonic exercises, 1819
and hypertension, 1134
Isotope renography, hypertension, 1131*t*
IV immune globulin (IVIG), in PPCM, 1475
Ivabradine, 595, 1244
for stable angina and CAD, 930

J

Jaccoud's arthritis, 1929
Janus kinases (JAKs), 26
Japan, incidence of heart failure in, 1210
Jugular venous pressure (JVP), 154–157
in HCM, 1388
and HF, 1214
Jugular venous pulsations, 155–158
prominent "a" wave, 156
prominent "v" wave, 156
Junctional bradycardia, in athletes, 1821
Junctional ectopic tachycardia, 674
JUPITER (Justification for the Use of Statin in Prevention: an Intervention Trial Evaluating Rosuvastatin) trial
genetic data, on CRP, 1939
statin use, 1801
J-wave syndromes, 695

K

Kansas City Cardiomyopathy Questionnaire (KCCQ), quality of life measure, 1266, 1268
Kaplan-Meier survival curves, 910*f*
Kawasaki disease (KD), 542, 1657
CMR coronary angiography, 433
Ketamine, 1626–1627
Kidney/disease outcomes quality initiative (K/DOQI) guidelines, 1698
Koch's triangle, 17, 190*f*
Konno-Sakakibara bioptome, 485
Krebs cycle, 25
Kruppel-like factor 2 (KLF2), 1847
Kussmaul's sign, 157

L

12-Lead surface electrocardiogram, 762
for acute coronary syndrome, 874
during angina, 940*f*
for AVRD/C, diagnosis of, 711
of Brugada syndrome, 694*f*
hypertrophic cardiomyopathy, 1381*f*, 1390*f*
12-Lead resting electrocardiography, 866, 1778, 1790*t*, 1893
LA pressure, in constrictive pericarditis, 1499
Labetalol
for cocaine abuse treatment, 1620
for heart rate maintenance, 1171
Lactate dehydrogenase (LDH), in cardiac injury, 1736
Lapatinib (Tykerb)
in left ventricular dysfunction, 1480*t*
in symptomatic left ventricular dysfunction, 1483
Lardaceous disease, 1454–1455
L-Arginine, for hypertension, 2040
Late gadolinium enhancement (LGE), 434, 436, 439
Leads orientation
in electrocardiogram, 194*f*
and vector forces, in electrocardiogram, 192*f*
Leaflets
in aortic regurgitation, etiology of, 993
tricuspid valve anatomy, 1019
Left atria, assessment of, 330–331
Left anterior hemiblock (LAH), 702
Left atrial appendage (LAA), 331
Left atrial enlargement, 178–179, 207
Left atrial thrombus, 310
Left atrium, 3, 13
Left bundle branch block (LBBB), 702, 759
Left dominant ARVD/C (LDAC), 713
Left fibrous trigone, 8
Left heart, normal dimensions, 232*t*
Left ventricle (LV), 3, 14–15, 228

cardiac dysfunction, etiology of, 237–238
contrast-enhanced echocardiography, 236–237
diastolic function, 242
formulae, 249–250
left ventricular filling pressures, evaluation of, 248–249
technical aspects of, 242–248
types of, 248
dilated cardiomyopathy, 238
echocardiographic findings, 238
ischemic cardiomyopathy, 238
distinct anatomical features, 15
fiber orientation, 15
intramural vessels, 19
hypertrophic cardiomyopathy
primary hypertrophic cardiomyopathy, 238–239
secondary hypertrophic cardiomyopathy, 239
left ventricular noncompaction, 240
restrictive cardiomyopathy, 239
amyloid infiltrative cardiomyopathy, 239–240
diabetes mellitus, 239
endomyocardial fibrosis, 240
strain-derived indices, 237
systolic dysfunction, visual qualitative indicators of, 240
left ventricular mass, 240–242
systolic function, 228
components of ejection fraction, 232–236
echo-derived indices of, 237
left ventricular ejection fraction, 229–232
Left ventricle trabeculations and noncompaction, 445
Left ventricular apical ballooning (LVAB) cardiomyopathy, 940
Left ventricular assist devices (LVADs), 27. *See also* Ventricular assist devices (VADs)
of advanced heart failure, 1334
anticoagulation, 1348
cardiogenic shock, mechanical support in, 955–956
hemodynamic stabilization, 1348
pump management, 1348–1349
Left ventricular biopsy, 487
Left ventricular dysfunction, chemotherapy associated, 1480*t*
Left ventricular ejection fraction (LVEF), 1820
assessment of, 909–910
CHARM-Preserved trial, 1835
during aging, 1933, 1834
mortality, 267
pulsus alternans, 158
tachycardia-induced cardiomyopathy, 1429
Left ventricular ejection fraction (LVEF), components of, 228
end diastolic volume, 236
end systolic volume, 232–233
physiologic basis of, 233–234
and clinical outcome, 234–236
Left ventricular end-diastolic pressure (LVEDP), in PAH, 1522
Left ventricular endomyocardial fibrosis (LVEMF), 1442, 1446–1447
angiographic diagnosis of, 1447–1448
etiology, 1449
pathology, 1448–1449
treatment, 1449
cardiac catheterization, hemodynamics, 1447
Left ventricular enlargement, 177–178
Left ventricular function, at inotropic stress and rest, assessment of, 432–433
Left ventricular hypertrophy (LVH), 1379
due to CKD, 1699
growth, 987
hypertension, with cardiac involvement, 1129
physiologic and pathologic, comparison of, 987
and thick ventricle, in HCM, 1391–1393
Left ventricular mass, determination of, 330
Left ventricular noncompaction (LVNC), 1379
Left ventricular outflow tract (LVOT) disease, 71, 231, 1554
Left ventricular performance, determinants of, 252
afterload, 253
contractile element, velocity of, 254–255
contractile state, 253
maximum rate of pressure development, 253–254
preload, 252–253
ventricular-arterial coupling, 253
Left ventricular posterior wall flattening, in constrictive pericarditis, 1499*f*
Left ventricular pump function
ejection fraction, 256
assessment of
cardiac computed tomography, 256–257
cardiac magnetic resonance imaging, 257
contrast ventriculography, 257
echocardiography, 256
nuclear scintigraphy, 257
pressure-volume relations, 257–258
ventricular function curve, 255–256
Lentivirus, 2005–2006
LEOPARD syndrome, 152
Lepirudin, 1762
Levine sign, 144*f*
Levitronix Centrimag device, for MCS, in HF, 1341
Levosimendan Infusion Versus Dobutamine (LIDO) Study, 1291
Levosimendan, 97–98. *See also* Inotropes
in CO and renal function, 1290–1291
Lewy body disorders, 1193
Libman-Sachs endocarditis, 152
Lidocaine, 586–587
for CPR, 796
Lifestyle Heart Trial, 2032
Light chain (AL) amyloidosis, 1457–1458
Lightheadedness, 630, 639
as HF symptom, 1213
in nicotine withdrawal, 1880
with POTS, 1195
RV outflow VT, 691
in syncope, 1823
with stroke, 1913
third-degree AV block, 701
Limbus of the fossa ovalis, 9
Linked angina, 43
coronary blood flow during, 42, 43*t*
Lipid abnormalities, in HIV patients, 1639
Lipid lowering options, 110*t*
Lipid lowering therapy, for stable angina and CAD, 930–931
Lipid management, 917
in cardiac rehabilitation, 920
Lipid treatment goals and strategies, 105*t*
Lipid-modifying drug mechanisms, 106*f*
Lipodystrophy, HIV associated, 1639
Lipomas, 1674
Lipomatous hypertrophy, 1674
Lipoprotein
composition, 1856*t*
metabolism, 1856–1858
treatment goals, 1859
Lipoprotein (A) [LP(A)], 1856
and CHD, 839
Lipoprotein lipase (LPL), 106
in VLDL metabolism, 1857
Lipoprotein lipase deficiency, 1861–1862
Lipoprotein-associated phospholipase A2 (LP-PLA2), and CHD, 839
Lipotoxicity, in diabetes, 1604*f*
Liver X receptor/retinoid X receptor heterodimer (LXR), 106
Livedo reticularis, 152
Lixivaptan, 1278–1279
Loeffler's endocarditis, 1449–1450
Loeys-Dietz syndrome, 1167
Loffler's endocarditis, 491–492
Long QT syndromes (LQTS), 571, 718, 805
clinical manifestations, 718
diagnosis, 721
genetic testing, 721–722
genotype-phenotype correlation studies and risk, 720–721
genotype-specific therapy, 722
ICD therapy, 722
left cardiac sympathetic denervation, 722
molecular genetics, 719–720
pathogenesis, 718–719
therapy, 722
Loop diuretics, 58
in hyperuricemia, 1137
in sodium retention, 1277
therapeutic regimens, 65
Losartan heart failure survival study (ELITE II), 1238
Low cardiac output, signs of, 1215
Low density lipoprotein (LDL), 1231, 1507, 1971
in atherosclerotic disease, 1856, 1876
in cardiovascular complications, 1628
in premenopausal women, 1800
Low density lipoprotein cholesterol (LDL-C), 104, 1132, 1834
aerobic exercise, 2033
dietary lipids, 834
and diuretics, 68
and exercise, 917
Low molecular weight heparins (LMWH), 116, 119–120, 883–884

Low-tar cigarettes, 1876
Lp(a) hyperlipoproteinemia, 1860
Lung/heart ratio (LHR), 391
  CAD related risk, 391–392
Lunulae, 12
LV dysfunction and afterload stress, 71*f*
LV function assessments, linear dimensions, 231–232
LV internal dimensions at end-diastole (LVIDd), for TTE, 265
LV internal dimensions at end-systole (LVIDs), for TTE, 265
LV noncompaction, 694
LV systolic dyssynchrony index (LVSDI), 327
LVOT obstruction, at risk, during pregnancy, 1572
Lyme disease, 1194
  annular skin rash, 152
Lymphocytic myocarditis, 489*f*
  EMB for, 488
Lyposomal anthracyclines, in cardiotoxicity, 1485–1486
Lysergic acid diethylamide, 1627. *See also* Hallucinogenic drugs
Lysophosphatidylcholine, 373*f*, 374

M

6 minute walking test (6MWT), 760*t*, 1048
  AHFS management
    phases of, 1302*t*
    prognosis of, 1305*t*
  quality of life measure, 759, 769, 1269, 2044
Macroglossia, in systemic amyloidosis, 1460
Macrophage colony stimulating factor (M-CSF), in LDL binding, 1849
Macrophages, in molecular imaging, 456
MADIT II, ICD primary prevention trial, 1839
MAGIC (Myoblast Autologous Grafting in Ischemic Cardiomyopathy), clinical trial, 1994
Magnesium, in pressure lowering, 1134
Magnesium sulfate, for CPR, 796
Magnetic resonance imaging (MRI), 765–766, 865, 1756
  in AAD diagnosis, 1171
  of cardiac tumors, 422
  with endocarditis, 1056
  with TOF, 1573
Mahaim fiber, 674, 675*f*
MAIN-COMPARE registry, 361
Major histocompatability complexes (MHC), 126
Malaysia, incidence of heart failure in, 1210
Malignant tumors, 1675
  angiosarcoma, 1679
  leiomyosarcoma, 1681
  malignant fibrous histiocytoma, 1679
  osteosarcoma, 1679–1681
  primary cardiac sarcomas, 1675–1679
  rhabdomyosarcoma, 1681
  synovial sarcoma, 1681
  undifferentiated sarcomas, 1681
Manganese superoxide dismutase (MnSOD), 26
Mannitol, 54, 55, 58*t*, 62
Marfan syndrome, 152, 806, 1167, 1553
  Ghent nosology for, 1197*t*
Marijuana, 1624–1625
Masses, 422
  malignant cardiac neoplasm, 422
  noncancerous masses, 422–423
Masters series valves, 1074
Matrix metalloproteinases (MMPs), 27, 1253
Maximal oxygen uptake, 1891
Maximum heart rate (MHR), during exercise, 1833
Maximum intensity projection (MIP), 412
Mean circulatory filling pressure, 812
Mean pulmonary artery pressure (MPAP), 504
Mechanical circulatory support (MCS), 1334, 1343–1345
  VAD patient selection, 1345
  indications and contraindications for, 1345–1347
  patient care
    intraoperative management, 1348
    preoperative management, 1348
  survival with, 1349
Mechanical circulatory support, 1339*t*
  in HF, immediate postoperative management, 1341
Mechanical prosthetic valves, anticoagulation regimen in pregnancy, 1118
Mechanical valves, 1100–1101
  binding therapy, 1124
Mechanically rotating single-transducer system, and solid-state dynamic aperture system, 350*t*
Mediastinal radiation
  anthracycline cardiotoxicity, risk factor, 1480*t*
  cardiovascular complications of, 1505*t*
"Medication reconciliation", 1971
Mediterranean diet, for CAD, 2040
Medtronic-Hall valve, 1073–1074
Membranous septum, atrioventricular portion of, 15
Membranous VSDs, 1563
Men, heart failure risk factor in, 1900
"Mendelian randomization" principles, 1939
Mercurial diuretics, 58
Mesenchymal stem cells (MSCs), 1988, 1993, 1994
Mesenteric ischemia, 1160
Metabolic equivalents term (MET), 215, 1891
Metabolic modulators, and glucose utilization, 1609
Metabolic syndrome, 1861
  due to diabetes mellitus, 1715
  as heart failure risk factor, 1901
  HIV associated, 1639
  and physical examination, 151
Metaiodobenzylguanidine (MIBG), 401. *See also* ^{123}I-metaiodobenzylguanidine (^{123}I-MIBG)
  cardiac adrenergic denervation, 1483
  imaging of congestive heart failure, 404*f*
  in X syndrome, 43
Metastatic secondary tumors, EMB in, 496
Metastatic tumors, 1684–1686
Methadone, 1630
Methamphetamine, 1622
  cardiovascular complications, 1623–1624
  epidemiology, 1623
  in energy metabolism, 1603
  noncardiac complications, 1624
  pharmacology, 1623
Methylenedioxymethamphetamine (MDMA), 1625–1626
Methylphenidate, use in athletes, 1824
Metolazone, 54, 58*t*, 60, 64, 66
  diuretic agent in HF, 1288
Metoprolol, 46*t*, 680, 1239
Metoprolol CR/XL randomized intervention trial in congestive heart failure (MERIT-HF), 84, 1239, 1982
Metoprolol in Dilated Cardiomyopathy (MDC), trial, 84, 1238
Mexiletine, 584, 693, 723
Micro-RNAs (miRs), 28
Microvascular angina, 43
Microvascular structure and function, in VAD, 1348
Micturition syncope, 149
Mid-diastolic murmurs, 171
Midodrine, for POTS, 1197
Migraine headache, in variant angina syndrome, 540
Milrinone, 96–97. *See also* Inotropes
  in CO and renal function, 1290–1291
Mind-body medicine, 2032
Mineralocorticoid (aldosterone) receptor blockers
  aldosterone and systolic heart failure, 78–80
  eplerenone, in chronic heart failure, 80–81
  spironolactone, in chronic heart failure, 80–81
Minimum intensity projection (MinIP), 412
Minnesota Living with Heart Failure Questionnaire, quality of life measure, 1266–1267
MIRACLE study, 759
Mitochondria, in cardiac myocytes, 24–26
Mitochondrial encephalopathy with lactic acidosis and stroke like episodes (MELAS), 1911
Mitochondrial myopathies, 495
Mitral annular calcifications, 183
Mitral balloon valvuloplasty, 316
Mitral cusp VT, aortic sinus of, 691
Mitral regurgitation (MR), 1120, 1740–1741
  acute mitral regurgitation, 1011–1012
  cardiac catheterization, 1114–1115
  cardiogenic shock in acute coronary syndromes, cardiac causes of, 953–954
  clinical diagnosis
    physical signs, 1009–1010
    symptoms, 1009
  complications, 1010
  degenerative mitral valve disease. *See* Degenerative mitral valve disease
  etiology of, 1008–1009
  in HCM, Doppler inflections, 1395
  hemodynamics of, 1007–1008
  and mitral valve abnormalities, 1385
  infective endocarditis, caused by, 1011
  investigations
    cardiac catheterization, 1014

cardiovascular magnetic resonance imaging, 1014
computed tomography, 1014
echocardiography, 1013–1014
electrocardiogram, 1012
radiological evaluation, 1012–1013
management
medical treatment, 1014
secondary mitral regurgitation, treatment of, 1016–1017
surgical treatment, 1015–1016
natural history of, 1010
pathophysiology of, 1007–1008
percutaneous therapies for, 1043
perioperative events, 1777
plain film imaging, 186
rheumatic heart disease, 1009
secondary mitral regurgitation, 1012
severity, classification of, 282*t*
in systolic heart failure, 1214
transesophageal echocardiography, 1114
transthoracic echocardiography for, 1114
Mitral stenosis (MS), 1120
asymptomatic patients, 1113
clinical diagnosis
physical signs, 1002–1003
symptoms, 1002
echocardiography for, 1111
etiology of, 1001
hemodynamic of, 1001–1002
invasive hemodynamic evaluation, 1112
investigations
echocardiography, 1003–1004
electrocardiogram, 1003
invasive evaluation, 1004
radiological evaluation, 1003
stress testing, 1004
management
mechanical relief of obstruction, 1005–1007
medical treatment, 1004–1005
medical therapy, for systemic embolization, 1111
natural history of, 1004
pathology of, 1001
pathophysiology of, 1001–1002
percutaneous mitral balloon valvotomy, 1112–1113
in perioperative setting, 1777
plain film imaging, 185–186
severity, classification of, 281*t*
special populations, 1004
surgery for, 1112
symptomatic patients, 1113–1114
Mitral valve disease
assessment of, 331–334
catheter-based treatment of
mitral regurgitation, percutaneous therapies for, 1043
percutaneous balloon mitral valvuloplasty, 1040–1043
percutaneous mitral annuloplasty, 1043
percutaneous mitral leaflet repair, 1043–1044
pregnancy, mitral valvuloplasty in, 1043
management, 1115
mitral valve operation, 1115–1116
normal mitral valve morphology and function, 1000
regurgitation of *See* Mitral regurgitation
rheumatic heart disease, global burden of, 1000–1001
stenosis of *See* Mitral stenosis
Mitral valve prolapsed, 1100
assessment using TEE, 313
Mitral valve prosthesis, selection of, 1122–1123
Mitral valve, 3, 13–14
chordate, groups of, 14
Mixed angina, 43
coronary blood flow during, 42, 43*t*
Mixed connective tissue disease (MCTD), 1654
and PAH, 1527
M-mode echocardiograms, LVOT obstruction, 1389*f*
Mobile cardiac outpatient telemetry (MCOT), 782
Mobitz type I AV block, in athletes, 1821
Moderator band courses, 12
Modular Z-stent-based stent grafts, 1177
Molecular imaging, of vascular diseases, 450
animal imaging modalities, comparison of, 452*t*
of coronary arteries, 456
fundamentals, 450–452
imaging agents, 451*t*
modalities, 452–453
of plaque inflammation, 458*f*
of vascular disease processes, 453
aneurysm, 464–466
atherosclerosis, 453–461
outlook, 467
thrombosis, 461–464
vascular injury, 466
Monacolins, 2033
Monascus purpureus, red rice yeast, 2033, 2034
Monitored anesthesia care (MAC), 1787
Monocyte-derived macrophages, in atherosclerosis, 1849
Monocytes, in variant angina syndrome, 540
Monomorphic ventricular tachycardia
in association with structurally normal heart, 691–692
myocardial VT in association with structural heart disease, 687–690
Monophasic defibrillators, 797–798
Mood, and CHD, 2041
Mood-altering substances, 1613
MOOD-HF trial, on escitalopram, 1359
"Morganroth hypothesis", 1820
Morphine, 878, 907–908
on breathlessness, in HF, 1358
for CPR, 796
Morrow procedure. *See* Septal myectomy
Motion-based mode (m-mode), 265
Moxonidine in heart failure (MOXCON) trial, 1239
Moyamoya syndrome, 1911
MPI and stress ECHO, comparison of, 862
Mucocutaneous lymph node syndrome". *See* Kawasaki disease
MUerte Subita en Insuficiencia Cardiaca (MUSIC) score, 1336
Multicenter Automatic Defibrillator Implantation Trial I (MADIT I), for HCM, 1404
Multicenter InSync randomized clinical evaluation (MIRACLE), 1426
Multicenter Study of Perioperative Ischemia (McSPI) Epidemiology II Study, 973
Multicenter Ultrasound-guided Stent Implantation in Coronaries (MUSIC) trial, 360
Multi-cycle reconstruction, 409
Multidetector computed tomography (MDCT), 766–767, 863
coronary artery disease, 1221
Multifocal atrial tachycardia, 669–670
Multifunctional Ca^{2+}, 573
Multiple system atrophy, 1194
Multi-segment reconstruction, 409
Mural thrombosis, in atherosclerotic lesions, 1849
Muscle of Lancisi, 11*f*
Muscular VSDs, 1563
Musculoskeletal abnormalities, 152
of cardiovascular disorders, 153*f*
Musculoskeletal side effects
statin induced, 1955
clinical implications, 1955–1956
CYP450 drug metabolizing enzymes, 1955
SLCO1B1, 1955
statin therapy, compliance with, 1955
Myeloperoxidase, in heart failure, 1223
Myocardial action potentials, 570
Myocardial bridging, 416
Myocardial contrast imaging
and quantification of perfusion, 330
Myocardial contusion, 1734
clinical picture of, 1735
diagnosis of, 1735
imaging techniques, 1735
incidence of, 1734
laboratory data
cardiac enzymes, 1736–1737
echocardiography, 1736
electrocardiogram, 1736
magnetic resonance imaging, 1736
multidetector computed tomography, 1736
late complications, prognosis and development of, 1737
management of, 1737
Myocardial energy metabolism, 1602–1603
Myocardial fibrosis. *See also* Interstitial fibrosis
in HCM, 1386–1387
in idiopathic DCM, 436–437
Myocardial hibernation
and stunning, 1325
definition, 1323–1324
detection of, 1325
rationale, 1325
techniques, 1325–1328
historical perspective, 1323
pathophysiology, 1324–1325
revascularization of
changes in prognosis, 1328–1331
changes in ventricular function, 1328
Myocardial hypertrophy, 694

Myocardial infarction(MI), 116, 432, 912–913
and rheumatoid arthritis, 1650
as systolic heart failure risk factor, 1229
Myocardial infarction heart failure efficacy and survival study (EPHESUS), 79, 80*f*, 81
Myocardial interstitial fibrosis, 1718–1719
doxorubicin cardiotoxicity, 1481
Myocardial ischemia
coronary artery occlusion, 39
in coronary artery disease, 1224
in women, symptom assessment, 1802–1803
Myocardial ischemia and infarction, due to cocaine usage, 1618
Myocardial ischemia causing cardiac arrest, 823
Myocardial oxygen consumption, 213*t*, 213–214
Myocardial oxygen demand, 34–35
Myocardial oxygen supply, 35
Myocardial perfusion imaging, 433
Myocardial revascularization
vs. antianginal drug therapy, 931–932, 933–934, 934*f*
for stable angina and CAD, 931–932
in rheumatoid arthritis, 1650
Myocardial structure, in VAD, 1348
Myocardial stunning, 1323
Myocardial ventricular tachycardia, in association with structural heart disease
fibrosis and scar, 687–689
monomorphic VT
with arrhythmogenic right ventricular dysplasia, 690
due to bundle branch reentry, 689–690
post surgery for congenital heart disease, 690
Myocardial viability, and stress echo, 304
Myocarditis
clinical scenarios, diagnosis of, 490*t*
causes of, 1426*t*
in HIV infection, 1643
in MCTD, 1654
Myocardium
and chambers, 417–418
contractility, 34
Myocyte hypercontraction
in EMB tissue, 487
Myocyte necrosis
to diagnose myocarditis, 490
Myofilament HCM, 1379*t*
Myogenic resistance, 36
Myxomatous mitral valve, 1122

N

^{13}N-Ammonia positron emission tomography (^{13}N PET)
myocardial blood flow quantification, 42, 942
Nadolol, 692, 722, 1139, 1405, 1938*t*
National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) guidelines, 104, 1640
National Hospice and Palliative Care Organization (NHPCO), 1353, 1354
National Institute for Health and Clinical Excellence (NICE)
for cost-effectiveness, in Britain, 1981
National Institutes of Health (NIH), 2031
National Research Council's Committee on the Biological Effects of Ionizing Radiation (BIER), 403
Native valve endocarditis
epidemiology of, 1052–1053
microbiology of, 1057
drug users, 1058
non-drug users, 1057–1058
surgery for, 1117
Native valve endocarditis
Native valvular heart disease, 1100
anticoagulation INR range for, 1099*t*
Natriuretic peptides
aortic stenosis, diagnosis of, 989
in heart failure, 1221
Naxos disease, 713
palmer and planter keratoses, 152
Near-infrared (NIR) spectroscopy, 374
Necrotizing eosinophilic myocarditis
EMB for, 488
Nellix stent graft, 1176, 1178
Neovascularization, in molecular imaging, 459–460
Nephrogenic systemic fibrosis, 1150
Nephron, 53, 54*f*
"braking" phenomenon, 56
Nephrotic syndrome, 67
Nernst equation, 565
for K^+, 566
Nesiritide,83
BNP, 1243
in CRS, 1294
safe vasodilator, 95
Neural control mechanisms
for cardiovascular response, 217
Neuraxial anesthesia care (MAC), 1787
Neurocardiogenic syncope, 148, 1197
Neurogenic cardiomyopathy, 1689
clinical features, 1689
arrhythmias, 1689–1690
cardiac biomarkers, 1690–1691
ECG abnormalities, 1689
left ventricular dysfunction, 1691
diagnosis, 1692
pathophysiology, 1691–1692
prognosis, 1693
treatment, 1692–1693
Neurogenic hypertension, 1198
Neurohormonal milieu, in VAD, 1348
Neurohormones, in heart failure, 76*f*
Neutrophil gelatinase-associated lipocalin (NGAL), in heart failure, 1223
New Approaches to Coronary Intervention (NACI) Registry
percutaneous revascularization, women versus men, 1807
New classification, of aortic dissection, 1168–1169
New York Heart Association (NYHA) classification, functional class assessment, 1215
New York Model, 1072
New York State registry, 979
Niacin, 112–113, 917, 2036
Nicotine delivery formulations (NRT), tobacco dependency, first-line treatment for, 1880
Nicotine replacement therapy, 918, 1881
Nicotine withdrawal, 1880
Niemann-Pick C1-Like 1 transporter (NPC1L1 transporter), 106
Nifedipine, 879
congenital valvar aortic stenosis, 1553
for stable angina and CAD, 929
in variant angina, 944
vasospasm, prevention of, 1692
Nimodipine, 1139, 1692, 1693, 1923
NIRF imaging
of atherosclerosis inflammation, 458*f*
of coronary arteries, 456
Nitrates, 878, 906–907, 1228
arteriolar dilator drug, 72
in LV dysfunction, 1695
safe vasodilator, 95
for stable angina and CAD, 928
Nitric oxide (NO), 81
Nitrogen (^{13}N) ammonia
imaging perfusion, 397
Nitroglycerin (NTG), 73, 907
for cocaine abuse treatment, 1619
intravenous, 82
limitations of, 82–83
pulmonary capillary wedge pressure, effect on, 83*f*
and isosorbide dinitrate, 73
for stable angina and CAD, 928
in vasodilatation, 1782
venodilator, 1243
Nitroprusside (NP), 82, 97*f*
in CRS, 1294
metabolism and toxicity of, 82
and severe heart failure, 82
Nitroprusside sodium, for heart rate maintenance, 1171
Nocturnal cough, as HF symptom, 1213–1214
Nocturnal stress, in HCM, 1413
Nodes of Ranvier, 572
Nomogram
for body surface area, 231*f*
in exercise stress testing, 300
Non-acute coronary syndromes, 509–510
Nonalcoholic fatty liver disease, 1861
Non-anginal pain, in HF, 1358
Non-atrial septal defect, 1741–1742
Non-bacterial thrombotic endocarditis (NBTE), 1055
Noncardiac chest pain, 144*t*, 875
Noncardiac surgery, in cardiac patients, 1773
implanted electronic devices, management of, 1787–1788
intraoperative management, 1786
anesthesia, choice of, 1786–1787
hemodynamic monitoring, 1787
postoperative management, 1788
ischemia, surveillance for, 1788
pain management, 1789
postoperative arrhythmias, 1788–1789
pulmonary artery catheters, 1788

preoperative diagnostic testing, 1778
12-lead resting electrocardiography, 1778
ambulatory electrocardiography, 1778
cardiac biomarkers, 1780
coronary angiography, 1779–1780
heart rate variability, 1778
left ventricular function, assessment, 1778
myocardial ischemia, noninvasive studies for, 1778–1779
preoperative risk assessment, 1773–1774
arrhythmias, 1777
congenital heart disease, 1777
general risk stratification, 1774–1776
heart failure, 1776
hypertension, 1776
ischemic heart disease, 1776
valvular heart disease, 1776–1777
preoperative risk mitigation strategies
nonpharmacologic and other interventions, 1783–1786
pharmacologic interventions, 1780–1783
Noncompaction, of LV, 806
Non-conventional therapies, and cardiology, 2031
Non-desmosomal genes, 708
Nonesterified fatty acid (NEFA), in energy metabolism, 1603
"Non-HDL cholesterol", 1859
Non-highdensity lipoprotein cholesterol (non-HDL-C), 104
Non-Hispanic blacks, heart failure risk factor in, 1900
Noninvasive computed tomographic angiography, 863
Non-ischemic cardiomyopathy (NICM), 640–641, 807
Non-penetrating injury, 1730
Non-pitting lymphedema, 149
Non-rapid eye movement (NREM) sleep, on cardiac physiology, 2021
Non-restrictive VSDs, 1563
Non-ST elevation myocardial infarction (NSTEMI), 517
stress testing in, 210
Nonsteroidal anti-inflammatory agents (NSAIDs), 112
drug interaction, 1290
Non-syndromic familial thoracic aortic aneurysms and dissections, 1167–1168
Nonuniform rotational distortion (NURD), 351*f*
Non-ventricular septal defect, 1741–1742
Norepinephrine, 96, 1192
neurohormone, 74
in hypotensive patients, 1244
hazard ratio, 96*f*
Normal coronary anatomy
co-dominant or balanced coronary circulation, 527
coronary collateral circulation, 527–528
left anterior descending artery (LAD), 525–526
left circumflex artery (LCX), 526
left dominant coronary circulation, 527
left main coronary artery (LMCA), 524–525
right coronary artery (RCA), 526–527
right dominant coronary circulation, 527
North Glasgow MONICA Risk Factor Survey
BNP role in, 1904
Nortriptyline, 1359
tobacco dependency, second-line treatment for, 1883
N-terminal pro-brain natriuretic peptide (NT pro-BNP), 147, 1780
in AL amyloidosis, 1463
cardiac marker, for myocardial wall stress, 1780
LV systolic dysfunction, 1703
NTG tolerance, 73*f*, 74*f*
Nuclear cardiology. *See* Cardiovascular nuclear medicine
Nuclear factor of activated T cells (NFAT), 26
Nuclear imaging, 766
Nucleus tractus solitarii (NTS), 1188, 1189
Nutrition, and CHD, 834
Nutritional counseling, in cardiac rehabilitation, 920
Nutritional deficiency, in HF,1429–1430
calcium, 1429–1430
L-carnitine, 1430
selenium, 1429
vitamin B, 1430
vitamin D, 1429

O

O'Brien valve, 1078
Obesity
and CHD, 834–836
classification, by body mass index, 836*t*
effects on organs, 836*t*
ethnic specific values for abnormal waist circumference, 836*t*
as heart failure risk factor, 1901
and hypertension, 1134
as systolic heart failure risk factor, 1229
Obliterative cardiomyopathy. *See* Endomyocardial fibrosis (EMF)
Obstructive sleep apnea (OSA)
autonomic perturbations associated with, 1199
cardiac physiology, effects on
atrial fibrillation, 2025
coronary artery disease and sudden cardiac death, 2025
hypertension, 2024–2025
hypertrophic cardiomyopathy, 2025–2026
stroke, 2026
in HCM, 1413
treatment of
continuous positive airway pressure, 2027–2028
obesity and treatment position, 2027
oral appliances and surgery, 2028
OCT for DES SAfety (ODESSA), 368
Off-pump coronary artery bypass surgery (OPCAB)
and CABG, 1329
Older-adults. *See also* Aging; Cardiovasular aging
beta-blockers, use in, 1835
calorific restriction, 1834
cellular aging, cardiovascular mechanisms in, 1831*t*
common comorbidities in, 1831*t*
conduction disease, 1837
epidemiology, 1837
management, 1837–1838
pathogenesis, 1837
CVD in, 1829
demographics, 1830*f*
end-of-life care, 1839–1840
exercise, 1833
heart failure
epidemiology, 1834
pathogenesis, 1834–1835
therapy, 1835
ischemic heart disease
epidemiology, 1836
management, 1837
pathogenesis, 1836
valvular disease, 1838
epidemiology, 1838
management, 1838–1839
pathogenesis, 1838
Omega 3 fatty acids, 114, 917
in left ventricular ejection fraction, 1240
"Ondine's curse". *See* Congenital central hypoventilation syndrome
On-X LTI valves, 1075
Open heart surgery, 4
for constrictive pericarditis, 1502
versus endovascular repair (OVER) study, 1176
Opioids, for dyspnea, in HF, 1358
Optical coherence tomography (OCT)
clinical experience, 366–368
detection of vulnerable plaque, 368–370
future directions, 370
image interpretation, 365–366
imaging systems and procedures, 364–365
safety and limitations, 370
Optimal medical therapy (OMT). *See also* Antianginal drug therapy
for stable angina and CAD, 933
Optimal Pharmacologic Therapy in Cardioverter Defibrillator Patients (OPTIC) trial casts, 597
Oral hydralazine therapy, for chronic heart failure, 1228
Oral nitrates, 74
for variant angina, 943
Oral penicillin, for RF, 1933*t*
Oral β-adrenergic blocking drugs, 83–85
Orally administered positive inotropic agents, 98
digoxin, 98–100
Organisation for Economic Cooperation and Development (OECD) countries
CV contribution status, 1977
health expenditure, trends in, 1976
Orlistat, 836
Ornish diet, for CAD, 2040
Orthopnea, 147
Orthostatic hypotension, 149, 151, 629, 1189–1190, 1836

treatment of, 1196
non-pharmacologic therapy, 1196
pharmacologic therapy, 1196–1197
Orthotopic heart transplantation (OHT), 1336
Orthotopic heart transplantation (OHT)/SCT
in AL amyloidosis, 1464
Ortner's syndrome, 149
Osler maneuver, 154
Osler-Weber-Rendu syndrome, 152
Osmotic diuretic, 62
Ostium primum, 9, 1559
Ostium secundum, 1559
Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbation of Chronic Heart Failure (OPTIME-CHF) study, 1272, 1426
Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbation of Heart Failure (OPTIME-HF) study, 1272
Out-of hospital cardiac arrest (OHCA), 811–812
Ovation stent graft, 1176, 1178
Over the counter drugs, 1630–1631
Over weight. *See also* Obesity
and hypertension, 1134
Oxidative stress
in molecular imaging, 458
and tobacco smoking, 1879
Oxygen
for cocaine abuse treatment, 1619–1620
for CPR, 796, 800
Oxygen consumption (MVO2), 34
Oxygen therapy
for cor pulmonale, 1764
Oxyhemoglobin, for CPR, 800

P

β-PRESERVE, metoprolol versus placebo, in HFPEF, 1835
P wave characteristics, 677
P waves, 191
P2Y1 receptor, 873
P2Y12 activation
inhibition, 128*f*
P2Y12 receptor, 873, 880
PA films, 174
absence of pericardium, 188*f*
aortic stenosis, 186*f*
vs AP films, 175*f*
dilated cardiomyopathy, 187*f*
interstitial edema, 181*f*
left atrial enlargement, 179*f*
left ventricular aneurysm, 184*f*
left ventricular enlargement, 178*fi*
mitral annular calcification, 184*f*
mitral valve insufficiency, 187*f*
normal arterial-bronchial relationship, 176*f*
normal films, 176*f*, 177*f*
pericardial cyst, 188*f*
pericardial effusion, 187*f*
pulmonary valve stenosis, 187*f*
right atrial enlargement, 179*f*
right ventricular enlargement, 178*f*
PA occlusion pressure. *See also* Pulmonary capillary wedge pressure (PCWP)
pulmonary venous and left atrial pressure, indirect assessment of, 504
Pacemaker dependant patients, 768–769
Pacemaker, 794
PAD Awareness, Risk and Treatment: New Resources for Survival (PARTNERS) trial, 1147
PAH, disease specific therapies
endothelin receptor antagonists, 1539–1540
phosphodiesterase type 5 inhibitors, 1540–1541
prostacyclin analogs, 1538–1539
PAH, surgical options
atrial septostomy, 1541
lung transplantation, 1541
PAH, survival
associated with
connective tissue disease, 1536
portal hypertension, 1536
schistosomiasis, 1536
in congenital heart disease, 1536
in HIV, 1536
and prognostic factors of, 1535–1536
PAH, therapeutic options, 1536–1537
anticoagulation, 1537
calcium channel blockers, 1537–1538
digitalis, 1537
oxygen,1537
PAH, treatment algorithm, 1541–1542
Pain control
in perioperative setting, 1789
Pakistan
incidence of heart failure in, 1210
Palliative care
history of, 1353–1354
multidisciplinary approach to, 1354*f*
Palliative shunts, 1571–1572
Palm sign, 144*f*
Palpitations, 148
as HF symptom, 1213
symptom of mild hypertension, 1129
Papillary muscles
tricuspid valve anatomy, 1019
Parachute mitral valve
and BAVs, 1552
Paradoxic embolization, 311–312
Paradoxical embolism, 1562
Paraganglioma, 1720
Paraneoplastic process, 1194–1195
Parasympathetic nervous system (PNS)
in cardiac functioning, 1691
Paravalvular regurgitation, 1095
Parenteral anticoagulant therapy, 548
bivalirudin, 549
enoxaparin, 549
heparin, 548–549
Parkinson's disease, 1193
Paroxysmal atrial fibrillation (PAF)
in HCM, 1413
Paroxysmal atrioventricular block, 701
Paroxysmal nocturnal dyspnea, 147
Paroxysmal orthostatic tachycardia syndrome (POTS) syncope, 148
Paroxysmal supraventricular tachycardia, 196
Particulate air pollution
mechanism of, 1883–1884
Parvovirus B19
cardiotropic virus, 488
in myocarditis, 1426
"PAT with block". *See* Digoxin-toxic dysrhythmias
Patent ductus arteriosus (PDA)
and BAVs, 1552
associated anomalies, 1567
clinical findings, 1567
diagnostic studies, 1567–1568
general considerations, 1566
guidelines, 1568
pathophysiology, 1566–1567
pregnancy, 1568
treatment and prognosis, 1568
PCI
for cocaine abuse treatment, 1619–1620
indications for, 546*t*
PCI, complications specific to, 555
acute thrombotic closure, 556
no-reflow, 556
perforation, 556
threatened or acute closure, 555–556
PCI, pharmacotherapy for, 545
antiplatelet therapy
aspirin, 545
IIb/IIIa platelet receptor inhibitors, 548
thienopyridine, 545–548
"Peak and dome" configuration
Peak VO2 consumption, as mortality predictor, 1355
Penetrating aortic ulcer, 1186
Penetrating injuries, 1730
Penetrating thoracic trauma, 1733*t*
Pentoxifylline (Trental), 1151–1152
PEP-CHF study, perindopril, 1835
Percutaneous alcohol septal ablation
for HCM, 1408–1411
arrhythmogenic substrate, 1409
limitations of, 1410–1411
major complications, 1408
morphologic heterogeneity, 1409–1410
patient selection in, 1408
and septal myectomy, 1412*t*
Percutaneous coronary intervention (PCI), 125, 349, 800, 880, 882–883, 884, 885, 886, 894, 902, 906, 911
vs CABG, 957, 1976, 1977*f*
creatinine signals, 1285
and medical management, comparison of, 977–978
Percutaneous lead, position of
in MCS, 1348
Percutaneous transluminal coronary angioplasty (PTCA), 125, 358, 550, 1762
and CABG, comparison, 971
for stable angina and CAD, 933
for variant angina, 946
Perhexiline, FFA, beta-oxidation, 1609
Pericardial calcifications, 183
Pericardial cysts, plain film imaging, 188
Pericardial disease, 445, 1702
acute pericarditis, 1489–1491
chronic relapsing pericarditis, 1491–1493

constrictive pericarditis, 1496–1503
hemodynamics in, 481
cardiac tamponade, 482
constrictive pericarditis, 481–482
pericardial effusion and pericardial tamponade, 1493–1496
TTE in, 273–274
Pericardial effusion
and pericardial tamponade
diagnosis, 1494–1496
examination, 1493–1494
presentation and etiology, 1493
treatment, 1496
plain film imaging, 187–188
TTE in, 273
Pericardial injury, 1733–1734
Pericardial mesothelioma, 1683–1684
Pericardial reflections, 5*f*
clinical importance of, 4
Pericarditis, 421, 914
and heart in mediastinum, 3–6
Perimount Magna aortic valve, 1076
Perindopril. *See also* Angiotensin-converting enzyme inhibitors
in diastolic heart failure, 1259
for stable angina and CAD, 930
Periorbital purpura, in systemic amyloidosis, 1460
Peripartum cadiomyopathy (PPCM)
clinical presentation
biomarkers, 1473–1474
laboratory evaluation, 1474
definition, 1473
etiology, 1473
incidence, 1473, 1474*t*
labor and delivery, 1475–1477
prognosis, 1474–1475, 1476*t*
treatment, 1475
in women, 1473
Peripheral arterial disease (PAD), 130
and cardiac rehabilitation, 1895
causes of, 1145
clinical presentation and natural history, 1146–1147
asymptomatic and symptomatic, 1147–1148
critical limb ischemia, 1148–1149
@3acute limb ischemia, 1149
diagnosis
ankle-brachial index, 1150
noninvasive vascular modalities, 1150
epidemiology, 1145–1146
management, 1151–155
risk factors for, 1146
screening for, 1150
and tobacco smoking, 1873
vascular history and physical examination, 1146
Peripheral nervous system, 1187
Peripheral vascular disease (PVD)
Perivascular landmarks
in IVUS imaging, 352*f*
Permanent junctional reciprocating tachycardia, 674
Persantine, 132, 679*t*
Personality factors, and CAD, 2041
Pharmacologic stress echo
assessment prior to, 296
complications of
dipyridamole, 297
dobutamine, 297
conducting of, 297
interpretation of, 297–298
protocols of, 296–297
dipyridamole stress protocol, 296–297
dobutamine stress protocol, 296
Pharmacologic stress testing, 383–385
Pharmacotherapy, in molecular imaging, 453–454
Phencyclidine, 1624
Phenobarbital, for chorea, 1933
Phenoxybenzamine, for coronary spasm, 943
Phenteramine, diet drug, 1628
Phentolamine, 96
for coronary spasm, 943
in hypotensive patients, 1244
neurogenic cardiac injury, 1692
Phenylpropanolamine, 1197, 1624
Pheochromocytoma, 1720
autonomic perturbations associated with, 1199–1200
PHIRST (PAH and Response to Tadalafil) trial, 1540
Phosphodiesterase 5 (PDE 5), 81
Phosphodiesterase III (PDE III), 96
antagonism of, 1291
Phosphodiesterase inhibitors, 96
milrinone, 96–97*f*
Phospholamban, 24
in hibernating myocardium, 1324
Phrenic nerve simulation, 767
Physical activity, 1890
and CHD, 834
Physical examination, 151
for ACS, 874
general appearance, 151
jugular venous pulse, 154
of musculoskeletal system, 152–153
of skin, 151–152
Physical inactivity, 1890
Pituitary apoplexy, 1909*t*
Pituitary disorders
growth hormone excess, 1718–1719
hypopituitarism, 1719–1720
Placement of balloon flotation catheters, placement of, 503–504
Plain film imaging, of adult cardiovascular disease
acquired valvular heart disease
aortic insufficiency, 185
aortic stenosis, 183–185
mitral regurgitation, 186
mitral stenosis, 185–186
pulmonary valve insufficiency, 186
pulmonary valve stenosis, 186
tricuspid insufficiency, 187
cardiac anatomy on, 176–177
cardiac calcifications, 182–183
cardiac chamber enlargement
left atrial enlargement, 178–179
left ventricular enlargement, 177–178
right atrial enlargement, 179
right ventricular enlargement, 178
cardiomediastinal anatomy, overview of, 175–176
chest film technique, 174
congestive heart failure, 179–182
pericardial disorders
congenital absence of pericardium, 188
pericardial cysts, 188
pericardial effusion, 187–188
Plant fox gloves, 1228
Plant stanols and sterols, for dyslipidemia, 2034
Plaque neovascularization, cardiovascular molecular imaging, 459*f*
Plasma B-type natriuretic peptide (BNP), 1903
Plasma homocysteine, in atherosclerosis, 1850
Plasma renin activity, hypertension, specialized studies, 1131*t*
Plasma volume, hypertension, 1131*t*
Plasmid DNA delivery
versus viral transduction, 2004
adeno-associated virus (AAV), 2004–2005
adenovirus, 2004
lentivirus, 2005–2006
Platelet activation and thrombosis, and tobacco smoking, 1877
Platelet activation inhibitors, 128
ADP/P2Y12 signaling inhibitors, 129–130
PDE inhibitors, 131–132
prasugrel, 130–131
thrombin receptor antagonists, 132–133
TXA2 pathway inhibitors, 128–129
Platelet activation, mechanism of, 118*f*
Platelet adhesion, in atherosclerotic lesions, 1849
Platelet adhesion inhibitors, 127–128
Platelet aggregation inhibitors, 133
Platelet factor 4 (PF4), 119
Platelet Inhibition and Patient Outcomes (PLATO) trial, 1944
Platelet-derived growth factor (PDGF), 2011
Platelets, 872–873, 873*f*
Pleiotrophin, 2011
Plexiform lesion, in PAH, 1525
Pluripotent stem cells
human tissue differentiation, 1987*f*
Pointing sign, 144*f*
Policosanol, for dyslipidemia, 2036
Poly (ADP-ribose) (PAR), 28
Poly (ADP-ribose) polymerase 1 (PARP-1), 28
Polyarteritis nodosa, 1656–1657
"Polycythemia", of hypertension, 1132
Polymer filled stent grafts, 1177–1178
Polymorphic ventricular tachycardia
with long QT interval, 692–693
with normal QT prolongation, 693–695
with short QT syndrome, 695–696
Polymyositis-dermatomyositis, 1653
clinical features, 1653
treatment, 1653–1654
Polymyositis-dermatomyositis, 1653–1654
Polysubstance abuse, 1622
Polytetrafluoroethylene (PTFE) fabric, in stent grafts, 1178, 1181
Pomegranate (*Punica granatum*), for hypertension, 2039

Pompe disease, 495
Positive inotropes. *See* Positive inotropic drugs
Positive inotropic drugs, 89
adrenergic receptor agonists, 89–90
calcium sensitizers, 97–98
digoxin, 98–100
dobutamine, 91–93
adverse effects, 95
applications, 93
dosing, 93–94
dopamine, 95
epinephrine, 96
hemodynamic profiles, 90*t*
isoproterenol, 95–96
levosimendan, 97–98
milrinone, 96–97
norepinephrine, 96
phenylethylamine molecule, 91*f*
phenylephrine, 96
spectrum of net vascular properties of, 91*t*
thyroxine, 98
Positive inotropic interventions, intravenously administered, 97
thyroxine, 98
Positive inotropic therapy
DIG trial, 98–99
hydralazine, 100
intravenously administered interventions, 97
intravenously administered, short term, 89
adrenergic receptor agonists, 89–90
calcium sensitizers, 97
dobutamine, 91–95
dopamine, 95
epinephrine, 96
isoproterenol, 95–96
levosimendan, 97–98
norepinephrine, 96
phenylephrine, 96
mechanism, 90*f*
orally administered drugs
digoxin, 98–100
istaroxime, 98
phosphodiesterase inhibitors, 96
milrinone, 96–97
thyroid hormone replacement, 100
Positron emission tomographic (PET) perfusion imaging, 861
Positron emission tomography (PET), 381
Post infectious auto immune neurological diseases (PANDA), 1930
Post MI exercise testing, benefits of, 211*t*
Post myocardial infarction care, 909–912
Post strep reactive arthritis (PSRA), 1929
Postganglionic neuronal depletors, 1141
Post-myocardial infarction (post-MI), therapeutic strategy, limitation, 1986
Postoperative arrhythmias, 1788–1789
Post-resuscitative care, 800
Postsurgical cardiac rehabilitation, 1895
Postsynaptic (peripheral) alpha-receptor antagonists, 1141–1142
Postural orthostatic tachycardia syndrome (POTS), 666, 1195–1196
Potassium, in pressure lowering, 1134
Potassium-sparing agents, in hyperkalemia, 1137–1138
Potassium-sparing diuretics, 61
Powerlink stent graft, 1177
Prasugrel, 545, 881–882, 908
in stroke prevention, 1918
versus clopidogrel, 1837
Prealbumin, 1831, 1835 *See also* Transthyretin-related (TTR) amyloid molecules
transthyretin, 1458
PRECISE, dose escalation trial, refactory angina, 1995
Precordial honk, 164
Precordial pulsation, examination of, 159–160
Predictors and outcomes of stent thrombosis (POST) registry, 360
Pregnancy
and contraception
and CHD, 1572
and HCM, 1413–1414
and lactation
drug safety during, 1477*t*
and valvular heart disease, 1102
Preinfarction angina", 1328
Preload reduction
in HF, immediate postoperative management, 1340
with nitroprusside, 1940–1941
Preoperative diagnostic testing, 1778
12-lead resting electrocardiography, 1778
ambulatory electrocardiography, 1778
cardiac biomarkers, 1780
coronary angiography, 1779–1780
heart rate variability, 1778
left ventricular function, assessment, 1778
myocardial ischemia, noninvasive studies for, 1778–1779
Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial, 1810
Pre-shock or shock syndromes
hemodynamic features of, 506*t*
Prima porcine prosthesis, 1078
Primary aldosteronism, 1720–1721
Primary amyloidosis. *See* Light chain (AL) amyloidosis
Primary cardiac arrest
assisted ventilation in, 814–815
bystander resuscitation efforts, 818
cardiocerebral resuscitation, prehospital component, 819–821
in children and adolescents, 812
coronary perfusion pressures, during resuscitation efforts, 813–814
not following guidelines for, 815–816
pathophysiology of, 812–813
prompt identification, 818
public mindset, 817–818
ventricular fibrillation (VF), phases of, 818–819
Primary cardiac lymphoma, 1681–1683
Primary chronic autonomic failure, 1193
multiple system atrophy, 1194
pure autonomic failure, 1193–1194
Primary hyperparathyroidism, 1722
Primary tricuspid valve regurgitation
surgical treatment of
carcinoid heart disease, 1026
cleft tricuspid valve, 1026
Ebstein's anomaly, 1025–1026
infective endocarditis, 1026
rheumatic valve disease, 1025
traumatic tricuspid regurgitation, 1026
Proarrhythmia, 579
Proarrhythmic substrates, 575
and triggers, in failing hearts, 575–576
Probucol, in dyslipidemia, 1863
Procainamide, 583, 623, 680, 693, 796, 1963
Procedural adjunct TEE, 316–317
Progeria, 530
Programmed cell death. *See* Apoptosis
Progressive CKD. *See* Type 2 CRS (chronic CRS)
Propafenone, 1963, 585–586, 655, 667, 681
Propranolol, 692. *See also* Beta-blockers
for cocaine abuse treatment, 1620
for HCM, 1405
neurogenic cardiac injury, 1692
Proprotein convertase subtilisin/kexin type 9 serine protease (*PCSK9*) gene, 1954
PROSPECT trial, 765
Prospective cardiovascular Münster (PROCAM), 831*t*
Prospective investigation of pulmonary embolism diagnosis (PIOPED) II, 1754
Prospective randomized amlodipine survival evaluation (PRAISE) study, 74, 1242
Prospective Randomized Study of Ventricular Failure and the Efficacy of Digoxin (PROVED), 98
PROSPER study
pravastatin, 1839
Prosthesis-patient mismatch (PPM), 1081–1084
Prosthetic aortic valve regurgitation
Doppler parameters of, 1089*t*
severity of, 1086*t*
Prosthetic heart valves
follow-up visits, 1125
long-term complications
hemolysis, 1095
paravalvular regurgitation, 1095
structural valve deterioration, 1092–1095
thromboembolic and bleeding complications, 1090–1092
long-term management
antithrombotic therapy, 1084–1085
echocardiography follow-up, 1085–1090
management of
antibiotic prophylaxis, 1123
antithrombotic therapy, 1123–1124
optimal prosthesis selection, 1079–1081
prosthesis-patient mismatch, 1081–1084
prosthetic valves, types of, 1073
bioprosthetic valves, 1075–1078
homograft, 1078–1079
mechanical valves, 1073–1075
pulmonic valve autotransplantation, 1079
thrombosis of, 1124–1125
valve replacement risks, 1072–1073

Prosthetic mitral valve regurgitation
Doppler parameters of, 1089*t*
severity of, 1089*t*
Prosthetic valve endocarditis
epidemiology of, 1053
microbiology of, 1058
early prosthetic valve endocarditis, 1059
late prosthetic valve endocarditis, 1059
surgery for, 1117–1118
Prosthetic valve thrombosis, 1090–1091
Prosthetic valves, 1073
anticoagulation INR range for, 1101*t*
in perioperative setting, 1777
mechanical valves, 1100–1101
thrombogenicity of, 1099*t*
valvular disorders, assessment of, 334–335
Protease, in molecular imaging, 456
Protease inhibitors (PI), 123
PROTECT-CAD trial, refactory angina, 1995
Protein kinase A (PKA), 24
Protein kinase G, in myocardial distensibility, 1261
Proteinuria, in chronic cyanosis, 1571
Prothrombin time (PT), 116
Proton pump inhibitors (PPIs), 127
Provocative testings, variant angina, diagnosis of, 942
Pseudoaneurysms, 182
Pseudoephedrine, 1197
Psychosocial factors, and CHD, 836–837
Psychosocial intervention, in cardiac rehabilitation, 920–921
Psyllium (*Plantago ovate*), 2034
for dyslipidemia, 2034
Pulmonary arterial hypertension (PAH), 272–273, 443, 1521, 1562
associated with
chronic hemolytic anemias, 1528
congenital heart disease, 1527
connective tissue diseases, 1526–1527
HIV infection, 1527
schistosomiasis, 1527–1528
clinical classification, 1522
WHO Group 1 PH, 1522–1523
WHO Group 2 PH, 1523
WHO Group 3 PH, 1523–1524
WHO Group 4 PH, 1524
WHO Group 5 PH, 1524
clinical presentation, 1529–1531
diagnostic evaluation, 1528–1529
chronic thromboembolic pulmonary hypertension, 1534
clinical presentation and physical examination, 1529–1531
echocardiography, 1531–1532
laboratory studies, 1533
nocturnal polysomnography, 1534
pulmonary function testing, 1533
right heart catheterization, 1534
vasoreactivity testing, 1534–1535
echocardiography, 1531
hemodynamic classification, 1521–1522
pathophysiology and epidemiology of, 1524–1525
drug-induced and toxin-induced PAH, 1526
heritable PAH, 1525–1526
idiopathic PAH, 1525
portopulmonary hypertension, 1527
pulmonary capillary hemangiomatosis, 1528
pulmonary veno-occlusive disease, 1528
therapy of decompensated right heart failure in, 1542–1544
Pulmonary arterial hypertension,
Pulmonary arterial systolic pressures (PASP), in HIV patients, 1641
Pulmonary arterial wedge pressure (PAWP), in PAH, 1522
Pulmonary arteries, 3, 13
Pulmonary artery catheterization (PAC), 503, 510
in postoperative management, 1788
Pulmonary artery catheters, 1788
Pulmonary artery disease. *See* Pulmonary arterial hypertension (PAH)
Pulmonary artery systolic pressure (PASP), 1532
Pulmonary capillary hemangiomatosis (PCH), 1528
as PAH, 1522
Pulmonary capillary wedge pressure (PCWP), 73
in constrictive pericarditis, 1499
pulmonary venous and left atrial pressure, indirect assessment of, 504
Pulmonary crackles, in pulmonary venous congestion, 1214
Pulmonary edema, 147*f*
Pulmonary embolism, 147, 914
Pulmonary endarterectomy (PEA), 1524
"Pulmonary heart disease", 1763. *See also* Cor pulmonale
Pulmonary hypertension
during stem cell clinical trial, 1996
in MCTD, 1654
Pulmonary infarction, 1753
Pulmonary outflow obstruction, 167–168
regurgitant murmurs, 168
mitral regurgitation, 168–169
tricuspid regurgitation, 169
Pulmonary stenosis, definition, 1558
Pulmonary system, and cardiovascular system, 1314
Pulmonary valve disease
catheter-based treatment of
percutaneous pulmonic balloon valvuloplasty, 1044
percutaneous pulmonary valve implantation, 1044–1045
Pulmonary valve insufficiency
plain film imaging, 186
Pulmonary valve stenosis
PA film, 187*f*
plain film imaging, 186
Pulmonary vascular resistance (PVR), 505, 1521, 1562, 1762
Pulmonary veins, 418–419
Pulmonary veno-occlusive disease (PVOD), 1528
as PAH, 1522
Pulmonary venous hypertension, WHO Group 2 PH, 1523
Pulmonic cusp VT, aortic sinus of, 691
Pulmonic stenosis
in adolescents and young adults, 1121
balloon valvotomy in, 1121–1122
Pulmonic valve autotransplantation, 1079
Pulmonic valve, 3, 12–13
Pulmonic valvular regurgitation, 1741
Pump optimization
pump management, in MCS, 1349
Pure autonomic failure, 1193–1194
Purkinje fibers, 16
PURSUIT risk score, 877
PURSUT study, eptifibatide, 1837
Pycnogenol, for hypertension, 2039

Q

Q wave, 191
in myocardial loss, 1325
Qigong, 2032. *See also* Mind-body medicine
QRISK, 831*t*, 832
QRS complex, characterization of, 201–206
left bundle branch block,201, 202*f*
left ventricular hypertrophy, 205*f*
myocardial infarction, 203*f*
right bundle branch block, 202*f*
right ventricular hypertrophy, 204*f*
Quality adjusted life-years (QALYs), 1978, 1979, 1984
and ICD therapy cost, 1979
Quality improvement (QI) interventions
cost-effectiveness, 1982–1983
Quinidine, 581–583, 693, 723

R

5 Rs
cigarette cessation, 1880
^{82}Rb positron emission tomography (^{82}Rb PET), 386*f*, 405*t*
for blood flow quantification, 1805
for CAD, 397
R waves, 191
in myocardial loss, 1325
RA pressure waveforms, 504
RAAS system modulators, 656
Race, as heart failure risk factor, 1900
Radiation-induced heart disease (RIHD)
carotid and other vascular disease, 1509
conduction system disease. 1509
prevention, 1509
risk factors, 1510*t*
strategies, 1510*t*
radiation-induced
coronary artery disease, 1507–1508
myocardial disease, 1506–1507
pericardial disease, 1505–1506
valvular heart disease, 1508–1509
Radionucleotide scintigraphy
variant angina, diagnosis of, 942
Radionuclide ventriculography, 910

RADT (Rapid antigen tests), 1931
Raman scattering, 374
Raman spectroscopy, 374, 375
Ramipril, for stable angina and CAD, 930
Randomized Aldactone Evaluation Study (RALES) trial, 79, 80*f*, 811, 239
Randomized Assessment of the effect of Digoxin in Inhibitors of the Angiotensin-Converting Enzyme (RADIANCE), 98
Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial, 1353
Randomized Intervention Treatment of Angina (RITA) trial, 978
Randomized Intervention Treatment of Angina-2 (RITA-2) trial, 977
Ranolazine, 595
  for stable angina and CAD, 929–930
Rapid eye movement (REM) sleep
  on cardiac physiology, 2021–2022
Rasmussen Score, 831*t*
Rastelli operation, for d-TGA, 1580
Rate Control versus Electrical Cardioversion (RACE) study, 1812
Rauwolfia slkaloids, 1141
Raynaud's phenomenon
  in MCTD, 1654
  in scleroderma, 1651–1652
  in variant angina syndrome, 540
Reactive arthritis, 1651
Reactive oxygen species (ROS), 25
  in arrhythmia initiation, 565
Real time 2DTEE, 335
Real-time three-dimensional echocardiography (RT3DE), 256, 319–320, 766
  clinical applications
    left and right atria, assessment of, 330–331
    left ventricular mass, determination of, 330
    left ventricular volumes and function, determination of, 323–327
    miscellaneous conditions, 335
    myocardial contrast imaging and quantification of perfusion, 330
    percutaneous procedures, guidance of, 335–339
    regional wall motion and dyssynchrony, determination of, 327–328
    right ventricular volumes and function, assessment of, 330
    stress imaging, applications to, 328–329
    valvular disorders, assessment of, 331–335
  future directions, 339–342
  limitations, 342–345
  technique, 320–324
    commonly used pathways, 321*f*
    diagnostic value, factors, 321–323
Receiver operating characteristic (ROC), 832–833
Recurrent chest discomfort, and STEMI, 914
Red rice yeast
  for dyslipidemia, 2033–2034
Red wine (Pinot noir), 1596
RED-HF, 1267
Refractory angina, 1996
REGEN-AMI
  clinical trial, in post-MI patients, 1993
Regurgitant orifice area (ROA), 324
Rehabilitation
  post stroke survivors, 1924
Reiter's syndrome. *See* Reactive arthritis
RELAX trial
  sildenafil, 1835
Relief for acutely fluid-overload patients with decompensated congestive heart failure (RAPID-CHF) trial, 1243
REMATCH trial, 1344, 1360
Renal arterography
  hypertension, specialized studies, 1131*t*
Renal artery stenosis (RAS)
  fibromuscular dysplasia, 1158
  and hypertension, 1158
  medical management, 1158
  revascularization, 1158–1159
  screening and diagnostic tests, 1158
Renal function
  as mortality predictor, 1355
Renal impairment
  in ambulatory heart failure, 1282*t*
  in community setting, 1282*t*
  in heart failure hospitalizations, 1283*t*
Renal insufficiency, 65–66
Renal scans
  hypertension, specialized studies, 1131*t*
Renal solute handling, 53
Renin, neurohormone, 74
Renin angiotensin aldosterone system (RAAS) and GFR level, 1288
Renin inhibitors, 1140
Renin-angiotensin system inhibitors, in hypertension, 1135*t*
Renin-angiotensin-aldosterone, for left ventricular hypertrophy regression, 1905
Renin-angiotensin-aldosterone axis inhibition, 916–917
Renin-angiotensin-aldosterone system (RAAS), 75
  hyponatremia in HF, pathophysiology of, 1274, 1275
Renin-angiotensin-aldosterone system blockers (RAAS blockers), ACE inhibitors, 74
REPAIR-MI, clinical trial, using BMC post-MI, 1991, 1992*t*
Reperfusion injury salvage kinase (RISK) pathway, 29
Reperfusion, for STEMI, 902–906
  facilitated percutaneous coronary intervention (PCI), 902–906
  primary coronary intervention, 906
  thrombolysis, 902
Reperfusion, for STEMI, 902–906
Repetitive stunning hypothesis, 1324
Rescue breaths, 815
Resistance training, 1890
Respiratory syncytial virus
  cardiotropic virus, 488
Restrictive cardiac disorders, 1440*t*
Restrictive cardiomyopathy (RCM), 239, 439–440, 479–480, 1440–1442
  amyloid infiltrative cardiomyopathy, 239–240
  diabetes mellitus, 239
  diagnosis, 440
  Doppler features of, 1440
  EMB in, 491–492
  endomyocardial fibrosis, 240
  etiology, 440
  physical findings, 157*t*
"Restrictive filling pattern", in advanced HF, 1219
Restrictive VSDs, 1563
Reteplase, 902
Retrovirus
  replication, 2005*f*
  ex vivo gene therapy with, 2006
Revascularization, 885–887, 911–912. *See also* Myocardial revascularization
  for PAD, 1152
    infrainguinal revascularization, 1152–1155
    infrapopliteal occlusive disease, 1155
    suprainguinal (aortoiliac) revascularization, 1152
  mortality and morbidity in patients, 1330*t*
REVEAL Registry, 1528
Revised Cardiac Risk Index (RCRI), 1774
Reynolds Risk Score, 831*t*, 832
Rheumatoid arthritis (RA)
  and conducting system, 1650
  coronary artery disease, 1650
  endocardial and valvular involvement, 1649–1650
  myocardial involvement, 1649
  pericardial involvement, 1648–1649
Rheumatic fever (RF), 1927
  chorea, management of, 1933
  clinical features
    age and gender, 1929
    arthritis, 1929
    carditis, 1929–1930
    chorea, 1930
    erythema marginatum, 1930
    preceding Group A strep infection, 1930–1931
    subcutaneous nodules, 1930
    tests for, 1931
  diagnosis of, 1928–1929
    recurrence of, 1929
  epidemiology, 1928
  pathogenesis
    Aschoff's body, 1928
    GABHS infection, 1927
    host factors, susceptibility to, 1927–1928
    immune response, 1928
  primary prevention of, 1106*t*
  residual heart disease, 1933
  secondary prevention, 1107*t*
  treatment
    anti-inflammatory drugs, 1932
    drugs and recurrence rates, 1933

prevention, 1933
recommended bed rest, 1932
secondary prevention, 1932
secondary prophylaxis, duration of, 1932
streptococci eradication, 1931–1932
treatment algorithm, 1933
Rheumatic heart disease
aortic stenosis, cause of, 986
global burden of, 1000–1001
mitral regurgitation, 1009
Rheumatic mitral stenosis, left atrial thrombus in, 310
Rheumatic valve disease, surgical treatment of, 1025
Rheumatic valvular heart disease, 1100
Rheumatoid arthritis, 152
Rhythm disorders and reflexes associated with
bradyarrhythmias, 964
hypotension, 964
ventricular arrhythmias, 964
Rhythm management, immediate postoperative management, 1341
Right atria, assessment of, 330–331
Right atrial enlargement, 179, 207
Right atrial ischemia, deleterious impact of, 962
Right atrium (RA), 3, 8–10
pectinate muscle, 10
Right bundle branch block (RBBB), 702
due to percutaneous alcohol septal ablation
Right fibrous trigone, 8
Right heart catheterization, 472
Right heart failure
in constrictive pericarditis, 1497–1498
hypotension with, 965*t*
Right ventricle, 3, 11–12
distinct anatomical features, 12
Right ventricular endomyocardial fibrosis (RCEMF), 1444–1446
hemodynamics, 1446
Right ventricular endomyocardial fibrosis (RVEMF), 1442
Right ventricular enlargement, 178. *See also* Right ventricular hypertrophy (RVH)
Right ventricular hypertrophy (RVH)
Right ventricular hypertrophy (RVH)
in valvar pulmonic stenosis, 1558
Right ventricular infarction (RVI)
augmented right atrial contraction, compensatory role of, 962
cardiogenic shock in acute coronary syndromes, cardiac causes of, 951–952
clinical presentations, 964–965
coronary compromise, patterns of, 960–961
description of, 960
diastolic function, effects of ischemia on, 961
differential diagnosis, 965
evaluation, 964–965
hemodynamic evaluation, 965
ischemic RV dysfunction
natural history of, 962–963
reperfusion effects on, 963–964
mechanical complications associated with, 964
mechanics of, 961
noninvasive evaluation, 965
oxygen supply-demand, 961
rhythm disorders and reflexes associated with
bradyarrhythmias, 964
hypotension, 964
ventricular arrhythmias, 964
right atrial ischemia, deleterious impact of, 962
RV performance in severe RVI, determinants of
augmented right atrial contraction, compensatory role of, 962
right atrial ischemia, deleterious impact of, 962
systolic ventricular interactions, importance of, 961–962
systolic function, effects of ischemia on, 961
systolic ventricular interactions, importance of, 961–962
therapy, 965
anti-ischemic therapies, 966
inotropic stimulation, 966
mechanical assist devices, 966–967
physiologic rhythm, 966
preload, optimization of, 966
reperfusion therapy, 966
Right ventricular infarction, and STEMI, 912
Right ventricular myocardial infarction
tricuspid regurgitation in, 169
Right ventricular outflow tract, VT from, 691
Right ventricular outflow tract (RVOT) obstruction, 1557
Right ventricular predominance, diseases with, 442–443
arrhythmogenic right ventricular cardiomyopathy, 444–445
intracardiac shunt, 443
pulmonary artery hypertension, 443
Right ventricular systolic pressure (RVSP), in pulmonary stenosis, 1558
Rimonabant, 836
Ringed stent grafts, 1177
Risk, Injury, and Failure; Loss; and End-stage kidney disease (RIFLE) consensus, 1285
Ritonavir, drug interaction, in HIV patients, 1643
Rivaroxaban, 122–123
Rohypnol, 1627
Ross procedure. *See* Pulmonic valve autotransplantation
Rubella syndrome, 530
Rubidium (^{82}Rb) chloride
imaging perfusion, 397
Rumbles". *See* Mid-diastolic murmurs
RV infarct, diagnosis, 952
RV myocardial performance index, for PAH, 1531
Rytand's murmur. *See* Carey-Coombs murmur

S

2D speckle tracking echocardiography (2DSTE) in multidirectional myocardial strain, 328
S waves, 191
SADHART-HF trial, on sertraline, 1359
SAFE-T trial, 590
Salt. *See* Sodium
Saquinavir, drug interaction, in HIV patients, 1643
Sarcoidosis, 492–493
restrictive cardiomyopathy, 1452
"Sarcomeric HCM", 1378
Sarcoplasmic reticulum (SR), 24
Sarcoplasmic-calcium ATPase (SERCA2a) in hibernating myocardium, 1324
Saturated fatty acids, and CHD, 834
Saver" procedure, left ventricular volume reduction surgery, 1245
SCD-HeFT, ICD primary prevention trial, 1839
Scleroderma, 1651–1652
abnormal coronary perfusion, 1652–1653
conduction disturbance, 1653
myocardial disease, 1652
pericarditis, 1652
pulmonary hypertension, 1653
restrictive cardiomyopathy, 1452
SCORE, 831*t*, 832
Seattle heart failure model (SHFM), 1336
Seattle Heart Failure Score (SHFS), as mortality predictor, 1355
Second heart sound
clinical conditions of, 163*t*
Secondary amyloidosis, 1459. *See also* Amyloid A (AA) amyloidosis
Secondary autonomic failure, 1194–1195
Second-hand smoke (SHS) exposures, cardiovascular disease, 1874, 1875–1876
Selective angiography, tricuspid valve disease, 1023
SELECT-MI randomized trial, for epicardial coronary circulation, 1993
Self-initiated transtelephonic ECG monitoring, variant angina, diagnosis of, 941
Senile systemic amyloidosis (SSA), 1458
"Senile" cardiac amyloidosis (SCA), 1831
SENIORS trial, 1239
nebivolol, 1835
Sensitivity analysis, 1984
Septal bounce, in constrictive pericarditis, 1499*f*
Septal myectomy
for HCM, 1407–1408, 1409*f*
and percutaneous alcohol septal ablation, 1412*t*
Septic shock, 504
Serotonin receptor inhibitors (SSRIs)
for depression, in HF patients, 1359
Serous pericardium, 1489
Serum brain-type natriuretic peptide (BNP)
in AL amyloidosis, 1463
Serum glutamic oxaloacetic transaminase (SGOT), in cardiac injury, 1736
Serum uric acid, in hypertension, 1132
Severe pulmonary hypertension, during pregnancy, 1572
SHock Inhibition Evaluation with azimiLiDe (SHIELD) trial, 593
SHOCK trial, 950, 951, 957, 958
mechanical reperfusion therapies, 1807
Shone's syndrome, 1552
Short QT syndrome, 805
Shy-Drager syndrome, and physical examination, 151

Sicilian Gambit" scheme, 579, 581*f*
Sildenafil (Revatio), 81
in diastolic heart failure, 1260*t*
drug interaction, in HIV patients, 1643
for PAH, 1540
Sildenafil citrate (Revatio®), 81
Sildenafil Trial of Exercise Performance in Idiopathic Pulmonary Fibrosis (STEP-IPF) trial, 1523
Silent ischemia, after exercise testing, 220
Simple 'monogenic' disorders, 1937
Simvastatin, for stable angina and CAD, 931
Simvastatin therapy, atherosclerotic plaque inflammation, 457*f*
Singapore, incidence of heart failure in, 1210
Single nucleotide polymorphisms (SNPs), 1939*f*
Single photon emission computed tomography (SPECT), 256, 326, 381, 860–861
for coronary spasm, 942
Sinoatrial (SA) node, 16
histology of, 16*f*
Sinoatrial conduction time (SACT), 615
Sinoatrial node (SAN) action potentials, 572
Sinoatrial re-entry tachycardia, 669
Sinus bradycardia
in athletes, 1821
with junctional escape rhythm
in electrocardiograph, 198*f*
Sinus node recovery time (SNRT), 615, 636
Sinus rhythm
maintenance
invasive approaches, 656–657
pharmacological approaches, 655–656
restoration, 654–655
Sinus tachycardia, 666–667
due to cocaine usage, 1617
Sinus venarum cavarum, 10
Sinus venosus defect, 1559
Sirolimus-eluting stents, 361
Six-minute walk test, 1224
Skeletal myoblast cells, 1994–1996
Skin abnormalities. *See also* Skin discoloration
of cardiovascular disorders, 153*f*
Skin discoloration
argyria, 152
carcinoid heart disease, 152
cyanosis, 151–152
hemochromatosis, 152
jaundice, 152
Skin pigmentation, in hemochromatosis, 1450
Sleep and heart
arousal, 2021
arrhythmias and sleep
atrial fibrillation, 2022
bradyarrhythmias, 2021
Brugada syndrome, 2022
heart rate variability, 2021
nocturnal QT interval changes, 2021–2022
sudden infant death syndrome, 2022
unexplained nocturnal death syndrome, 2022
ventricular arrhythmias, 2022
cardiovascular physiology, effects of
non-rapid eye movement sleep, 2020
obstructive sleep apnea
rapid eye movement sleep, 2021
central sleep apnea, 2028
heart failure, 2028
treatment of central sleep apnea, 2028
diagnosis of sleep apnea, 2026
overnight oximetry, 2026
polysomnography, 2026–2027
screening questionnaires, 2026
physiologic sleep, 2020
sleep disordered breathing, 2022
obstructive sleep apnea, 2022–2026
treatment of obstructive sleep apnea
continuous positive airway pressure, 2027–2028
obesity and sleeping position, 2027
oral appliances and surgery, 2028
Sleep disordered breathing (SDB), 147, 1763, 2022
in HCM, 1413
obstructive sleep apnea, 2022–2024
effects on cardiovascular physiology, 2024–2026
"Smart heart hypothesis", 1324
Smoking
and CHD, 833
and CKD, 1699
Smoking and air pollution
active smoking and cardiovascular disease, 1874–1875
cardiologists role, 1884
epidemiology of, 1874
low-tar cigarettes, 1876
particulate air pollution, 1883–1884
pathophysiology of, 1876
arterial stiffness, 1878
atherosclerosis, 1876–1877
autonomic effects and heart rate variability, 1879
dyslipidemia, 1878
endothelial dysfunction, 1877
impaired oxygen transport, 1879
inflammation, 1878–1879
oxidative stress, 1879
platelet activation and thrombosis, 1878
second-hand smoke and cardiovascular disease, 1875–1876
smoke-free environments, 1883
smoking cessation, 918–919, 1879–1880
benefits of, 1873–1874
nicotine withdrawal, 1880
pharmacotherapy, 1880–1883
Smooth muscle vasodilators, 1142
Snti-digoxin Fab-fragment immunotherapy, 100
Social factors, and CAD, 2041
Society for the Recovery of Drowned Persons, 788
Society of Thoracic Surgeons (STS) Database, 1072
Sodium
and CHD, 834
and hypertension, 1134
reabsorption, 53
retention, in CRS, 1286
Sodium-calcium exchanger
in hibernating myocardium, 1324
Solid-state dynamic aperture system, and mechanically rotating single-transducer system, 350*t*
Solute carrier organic anion transporter family, member *1B1* gene (*SLCO1B1*), 1955
Sondergaard's groove, 8
in mitral valve assessment, 7
Sorin group stentless valves, 1078
Sotalol, 586–587, 655, 656, 681, 688, 690, 691
Southeast Asians, incidence of heart failure in, 1210
Special population treatment, recommendations, 1372–1373
Speckled tracking, 765
SPECTroscopic Assessment of Coronary Lipid (SPECTACL) study, 376
Spectroscopy, for coronary applications, 374–375
clinical experience, 376
experimental data, 375
future directions, 376
imaging systems and procedures, 375
safety and limitations, 376
Sphingosine 1-phosphate (S1P), 29
Spike and dome arterial pulse
Spironolactone, 54, 55, 58*t*, 61, 62, 64, 66, 67. *See also* Potassium-sparing agents
in CHF and renal dysfunction, 1289
in hyperkalemia, 1137–1138
in left ventricular remodeling, 1240
survival curves for, 80*f*
Spondyloarthropathies, 1651
ankylosing spondylitis, 1651
reactive arthritis, 1651
scleroderma, 1651–1653
Sprituality, and CHD, 2041
SQT syndrome, 722–723
clinical manifestations, 723
diagnosis, 723
molecular genetics, 723
pathogenesis, 723
therapy, 723–724
SR calcium ATPase (SERCA-2), 24
ST segment elevation, during angina, 940*f*
ST segment elevation myocardial infarction (STEMI), 85, 145, 517
St. Vitus dance. *See* Chorea
Stable angina, 145*t*, 875
and CAD, patients with, 927–935
antianginal drug therapy, 928–930, 931–932
combination therapy, 930
current therapeutic approaches for, 927–928
myocardial revascularization for, 931–932
percutaneous revascularization vs medical therapy, 933–934, 934*f*
clinical features of, 145*f*
Stable coronary artery disease, 1808
coronary angiography and revascularization, 1809
medical therapy and risk factor management, 1808–1809

beta-blockers, 1809
calcium antagonists, 1809
lipid-lowering drugs, 1808
nitrates, 1809
treatment strategies, 1808
Stage A heart failure, 1900
age, 1900
cardiotoxin, exposure to, 1902
coronary artery disease, 1901
diabetes mellitus, 1901
dyslipidemia, 1901
family history, 1900
gender, 1900
hypertension, 1900–1901
metabolic syndrome, 1901
obesity, 1901
race, 1900
treatment for, 1902
Stage A high risk patients
recommendations, 1367–1368
Stage B cardiac structural abnormality patients
no HF symptoms, 1368
Stage B heart failure, 1902
asymptomatic left ventricular systolic dysfunction, 1902–1903
cardiac imaging for screening, 1904
cost-effect screening for, 1904
electrocardiogram and biomarker evaluation, 1903–1904
treatment for, 1904–1905
Stage C patients
with HF symptoms, 1368–1371
STAMINA-HeFT, 1267
Stanford classification
of aortic dissection, 1168
Staphylococcal endocarditis, 1063
Statin therapy, 840. *See also* Lipid lowering therapy
in heart failure prevention, 1905*f*
in perioperative cardiac events, 1781
Statins, 104, 105. *See also* HMG-CoA (3-hydroxy-3-methylglutaryl-coenzyme A) reductase inhibitors
add-on to statin therapy, 110–111
cardiovascular pharmacogenomics, 1945–1946
drug interactions, 106–108, 109*t*
efficacy, 105
lipid level change, 107*t*
liver safety, 110
muscle safety, 105–106
muscle symptom management, 108*f*, 110
musculoskeletal side effects, 1955
clinical implications, 1955–1956
CYP450 drug metabolizing enzymes, 1955
SLCO1B1, 1955
pharmacokinetics, 109*t*
renal excretion, 108
therapy, compliance with, 1955
ST-elevation myocardial Infarction (STEMI), 892
Stellate ganglion, 21
Stem cell clinical trials, 1991
Stem cell therapy and cardiology
adipose tissue derived stem cells, 1989
cardiac stem cells, 1989
fetal and umbilical cord blood cells, 1989–1991
induced pluripotent stem cells, 1991
skeletal myoblast, 1989
stem cell clinical trials
acute myocardial infarction, 1991–1994
chronic coronary artery disease and chronic heart failure, 1994–1996
pulmonary hypertension, 1996
refractory angina, 1996
routes and methods of cell delivery, 1996–1997
stem cells, 1986
adult stem cells, 1987
bone marrow derived stem cells, 1987–1989
embryonic stem cells, 1986–1987
Stem cell transplantation (SCT)
in AL amyloidosis, 1464
STEMI. *See also* Acute coronary syndrome (ACS)
clinical presentation, 894–902
emergency room evaluation, 894–902
prehospital assessment, 894
with cocaine use, 915
complication
dysrhythmias, 913–914
heart failure, 912–913
recurrent chest discomfort, 914
right ventricular infarction, 912
continued medical therapy for patients with a myocardial infarction, 916–919
glucose management, 917–918
lipid management, 917
renin-angiotensin-aldosterone axis inhibition, 916–917
smoking cessation, 918–919
in diabetic population, 914–915
discharge, 919–922
MI, rehabilitation and prevention, 919–921
nitrates, 919
predischarge education, 921–922
early medical therapy, 906–909
anticoagulation, 908–909
antiplatelet agents, 908
beta blockers, 909
general measures, 906
morphine, 907–908
nitrates, 906–907
in elderly, 916
pathophysiology of, 893–894
cocaine-associated, 893–894
methamphetamine-associated, 893–894
stent thrombosis, 893
post myocardial infarction care, 909–912
coronary angiography, 911–912
left ventricular ejection fraction assessment, 909–910
revascularization, 911–912
stress testing prior to discharge, 910–911
post myocardial infarction depression, 915–916
reperfusion, 902–906
facilitated percutaneous coronary intervention (PCI), 902–906
primary coronary intervention, 906
thrombolysis, 902
survivors of out of hospital cardiac arrest, 916
in women, 916
Stent deployment techniques on clinical outcomes of patients treated with the cypher stent (STLLR) trial, 361
Stent deployment, 551
Stent graft design, 1176–1177
for abdominal aortic aneurysm, 1177
Stent or Surgery (SoS) trial, 979
Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial, 1156
Stent-Protected Angioplasty versus Carotid Endarterectomy (SPACE), 1157
Stents, types of, 551
Steroids
and sport performance supplement, 1824
Stevia (*Stevia rebaudiana*), for hypertension, 2040
STICH trial, 1329
Still's disease, 1648. *See also* Systemic juvenile inflammatory arthritis
Stokes-Adams-Morgagni syndrome, 148
"Stop-action" heart imaging, 408
Storage diseases, and myopathy, 495
Strain rate imaging, 765
Strategies for management of antiretroviral therapy (SMART) study, 1636
Strength training, 1819. *See also* Isometric exercise
Streptococcal endocarditis, 1063
Streptokinase, 902
Streptozyme test, 1931
Stress, and CAD, 2041
Stress cardiomyopathy, 1693–1694
clinical features, 1694
arrhythmias, 1694
cardiac biomarkers, 1694
ECG abnormalities, 1694
left ventricular dysfunction, 1694
diagnosis, 1695
due to dobutamine, 95
pathophysiology, 1694–1695
prognosis, 1695
treatment, 1695
Stress echocardiography (SE electrocardiogram, 291
and coronary artery disease
diagnosis of, 292–299
estimating risk or prognosis in, 299–304
endpoints for, 295*t*
future of, 305
and hemodynamics of valvular disease, assessment of, 304–305
and myocardial viability, 304
pathophysiology involved in, 291–292
Stress imaging, applications to, 328–329
Stress myocardial perfusion imaging, 860–861
Stress testing
CAD, detection of, 293*t*

contraindications to, 293*t*
with echocardiogram imaging, 861–862
in HCM, 1400
mechanism of, 383*t*
mitral stenosis, 1004
with myocardial imaging, 860
prior to discharge, 910–911
Stress-induced cardiomyopathy, 1429
Stroke
and SDB, 2026
and tobacco smoking, 1873
Stroke, prevention and treatment
definitions, 1908–1909
general acute treatment, 1919–1920
general in-hospital care, 1924–1925
prevention, 1916–1919
rehabilitation, 1925
as symptom 1909–1911
clinical presentations, 1912–1913
diagnostic evaluation, 1914–1916
differential diagnosis, 1913–1914
epidemiology and highest risk groups, 1911–1912
subtypes and causes, 1909*t*
treatment
acute ischemic stroke, 1920–1922
of acute hemorrhagic stroke, 1922–1923
Stroke Prevention using an Oral Thrombin Inhibitor (SPORTIF) trial, 1812
Stroke volume
exercise testing, central factor for, 216
Stromal cell-derived factor-1 (SDF-1), 2011
Structural valve assessment, 313–316
Structural valve deterioration, 1092–1095
ST-segment analysis, after exercise testing, 220
ST-segment elevation, during exercise, 218
ST-segment elevation myocardial infarction (STEMI), and cardiogenic shock, 949
ST-T wave abnormalities, 206
Studies of Left Ventricular Dysfunction (SOLVD), 1209, 1289
on neuroendocrine activation, 1275
Subaortic stenosis, and BAVs, 1552
Subarachnoid hemorrhage (SAH), 1908, 1909–1910
differential diagnosis of, 1913*t*
meningeal irritation, 1913
Subclavian artery stenosis (SAS), 1159–1160
Sub-clinical atherosclerosis, and CHD, 839–840
Subendocardial plexus, 34
Subvalvar aortic stenosis, 1554
Subvalvar pulmonic stenosis, 1559
Sudden cardiac death (SCD), 432, 804–808
arrhythmogenic right ventricular cardiomyopathy (ARVC), 806
Brugada syndrome, 805
catecholamine polymorphic VT, 805
congenital heart disease (CHD), 806–807
coronary artery disease (CAD), 807–808
definition, 804
early repolarization, 805
hypertrophic cardiomyopathy (HCM), 806
in healthy athletes, 804–805
long QT interval syndrome, 805
Marfan syndrome, 806
noncompaction, 806
non-ischemic cardiomyopathy (NICM), 807
short QT syndrome, 805
and tobacco smoking, 1873
Wolff-Parkinson-White (WPW) syndrome, 805–806
Sudden Cardiac Death Heart Failure Trial (SCD-HeFT), 597
Sudden death (SD)
arrythmogenic substrate and, 1386
due to diabetes mellitus, 1715–1716
during exercise, 219
due to HCM, prevention, 1403–1404
ICD therapy, 1404
preparticipation screening, 1824
cardiovascular conditions, 1825*t*
Sudden infant death syndrome (SIDS), 2022
Sulfadiazine, for RF, 1933*t*
Sunitinib (Sutent)
in inducing cardiotoxicity, 1483
in left ventricular dysfunction, 1480*t*
SUPER-1 trial (Sildenafil Use in Pulmonary Arterial Hypertension), 1540
Supplemental oxygen, 906
Supravalvar aortic stenosis, 1554
Supravalvar pulmonic stenosis, 1559
Supravalvar stenosis
clinical course, 1035
clinical findings
history, 1035
physical examination, 1035
laboratory investigations
cardiac catheterization, 1036
chest roentgenogram, 1035
echocardiography, 1035–1036
electrocardiogram, 1035
natural history, 1035
pathological anatomy, 1035
pathophysiology, 1035
treatment of
Alagille syndrome, 1036
Williams-Beuren syndrome, 1036
Supravalvular aortic stenosis, 530
Supraventricular tachycardia (SVT), 650, 665, 799
cardiac-surgical ablation, 729
catheter ablation, 729
classification, 665–666
atrial-based AV nodal independent SVT, 666–670
AV nodal dependent SVT, 670–674
clinical electrophysiologic studies history, 729
diagnosis, 674, 677
electrocardiograpahic recordings, 677–678
electrophysiology studies, 678
treatments
acute care, 678–681
long-term management, 681–682
Surgical Care Improvement Project (SCIP), 973
Surgical treatment for ischemic heart failure (STICH) study, 434
Survival With Oral d-Sotalol (SWORD) trial, 587
Survivor activating factor enhancement (SAFE) pathway, 29
Suspected heart failure syndromes1303*f*
Swan, H.J.C., 504
Swan-Ganz catheters
abnormal pressures and waveforms, 506–507
clinical applications
acute coronary syndromes, 508–509
cardiac catheterization laboratory, 507–508
chronic heart failure, 510
non-acute coronary syndromes, 509–510
pulmonary hypertension, 510–512
complications, 512
guidelines, 513–514
indications for use of, 512*t*
normal pressures and waveforms, 504–506
pulmonary artery catheterization, indications for, 512
Swedish Doppler-echocardiographic study (SWEDIC), 1259
Swiss cheese model, for systems thinking, 1970
Sydenham's chorea. *See* Chorea
Sympathetic nervous system (SNS), 76
hyponatremia in HF, pathophysiology of, 1274
Symptomatic systolic heart failure
non-pharmacologic treatments, 1244–1245
pharmacologic treatments, 1237–1244
Syncope, 148–149, 627
aortic stenosis, symptoms, 988
in athletes, 1823–1824
diagnostic tests, 629
blood tests, 630
cardiac catheterization, 638
continuous ECG monitoring, 632, 634
echocardiography, 631
electrocardiogram, 631
electrophysiology study, 636–638
exercise testing, 632
history and physical examination, 629–630
neurologic tests, 638
signal averaged ECG, 634
upright tilt table testing, 634–636
and driving, 642
epidemiology
causes and classification, 628–629
economic burden, 628
incidence and prevalence, 628
evaluation approach, 638–639
guidelines, 642–644
specific patient groups, 639
congenital heart disease, 641
elderly patients, 641
hypertropic cardiomyopathy, 640
nonischemic cardiomyopathy, 640–641
vasovagal (neurocardiogenic) syncope, 639–640
SYNTAX trial, 979
Systemic amyloidosis (SSA), 1455
Systemic and pulmonary venous congestion in diastolic heart failure, 1258
Systemic autoimmune diseases
antiphospholipid antibody syndrome, 1656
Churg-Strauss vasculitis, 1657–1658

coronary arteritis, 1656
giant cell arteritis, 1658
Kawasaki disease, 1657
mixed connective tissue disease, 1654
polyarteritis nodosa, 1656–1657
polymyositis-dermatomyositis, 1653
clinical features, 1653
treatment, 1653–1654
rheumatoid arthritis, 1648
coronary artery disease, 1650
disease of the conducting system, 1650
endocardial and valvular involvement, 1649–1650
myocardial involvement, 1649
pericardial involvement, 1648–1649
spondyloarthropathies, 1651
ankylosing spondylitis, 1651
reactive arthritis, 1651
scleroderma, 1651–1653
systemic lupus erythematosus, 1654
coronary artery disease, 1655–1656
electrophysiological disturbance, 1655
endocarditis, 1655
myocarditis, 1655
pericarditis, 1654–1655
Takayasu's arteritis, 1658
Wegener's granulomatosis, 1658
Systemic inflammatory response syndrome (SIRS)
in acute coronary syndromes, 949
Systemic juvenile inflammatory arthritis, 1648
Systemic lupus erythematosus (SLE), 1654
coronary artery disease, 1655–1656
electrophysiological disturbance, 1655
endocarditis, 1655
myocarditis, 1655
pericarditis, 1654–1655
with PAH (SLE-PAH), 1527
Systemic sclerosis, 1651–1653. *See also* Scleroderma
Raynaud's phenomenon, 1651–1652
Systemic vascular resistance (SVR)
calculation, 71
Systolic "whoop", 164
Systolic anterior motion (SAM)
in LVOT obstruction, 1382
of mitral valve
in HCM, 1393–1394
Systolic blood pressure
in hyponatremia, 1272
Systolic dysfunction
detection of, 1606
visual qualitative indicators of, 240
left ventricular mass, 240–242
Systolic function
ejection fraction, components of
end systolic volume, 232–233
LVESV physiologic basis of, 233–234
left ventricular ejection fraction, 229–231
linear measurements in the assessment, 231–232
RV, ischemia on, 961
Systolic heart failure (SHF), 44, 1207, 1228. *See also* Heart failure with reduced ejection fraction (HFREF)
converting enzyme inhibitor, 46
coronary circulation in, 44
follow-up evaluation, 1245–1246
functional derangements and hemodynamic consequences, 1235
historical perspective, 1228
definitions, 1229
risk factors, 1229
initial treatment of, 1235–1237
myocardial metabolic function, 45
myocardial oxygen consumption, 46*f*
myocardial oxygen demand, 45
myocardial structure and function in, 1253*t*
symptomatic failure, 1237–1245
therapies, 46*t*
ventricular remodeling, 1229–1235
versus diastolic heart failure, 1252*t*, 1252–1253
morbidity and mortality in, 1258*t*
prognosis in, 1257*t*
symptoms and signs of, 1256*t*
Systolic Hypertension in the Elderly Program (SHEP), 1836
Systolic time ratio (STR), 174
Systolic ventricular interactions, importance of, 961–962

T

T cell activation, in HIV patients, 1638
T wave, 191
T2-star" (T2*) technique, in hemochromatosis, 1450
Tachyarrhythmias, 147
in athletes, 1823
Tachycardia-induced cardiomyopathy, 1428–1429
Tachycardias, 799
classification of, 799*t*
due to cocaine usage, 1616
and mild hypertension, 1129
Tadalafil (Adcirca®), 81
for PAH, 1540
Tai-chi, 2037*f*
Takayasu's arteritis, 1658
Takotsubo cardiomyopathy. *See* Stress cardiomyopathy
TandemHeart
cardiogenic shock, mechanical support in, 956
for MCS, in HF, 1341
Tansient ischemic attack (TIA), 1908–1909
clinical features of, 1913*t*
differential diagnosis of, 1914*t*
Tedisamil, 594
Tei index. *See* RV myocardial performance index, for PAH
Telemedicine interventional monitoring in heart failure (TIM-HF) trial, 1245
Temporal arteritis, 1658
Temporal resolution, 409
Tenecteplase (TNK-tPA), 902
Tetrahydriocannabinol, 1624–1625
Tetralogy of Fallot (TOF)
associated anomalies, 1572–1573
clinical findings, 1573
diagnostic studies, 1573–1575
general considerations, 1572
guidelines, 1576–1577
pathophysiology, 1572
pregnancy, 1576
prognosis, 1575–1576
treatment, 1575
Thallium-201 myocardial perfusion imaging, for hibernation myocardial diagnosis, 1425
Thebesian veins, 19
Therapeutic mild hypothermia, 822–823
Thiazide diuretics, 54, 55*t*, 57, 58*t*, 60
diuretic agent in HF, 1288
hemodynamic responses to, 61*f*
in hyponatremia, 1276–1277
Thiazide-like diuretics, 54, 55*t*,
Thiazides, in hyperuricemia, 1137
Thienopyridines, 908, 909, 1956
clinical implications, 1958
laboratory response to
ABCB1, 1957
CYP2C19, 1956–1957
clinical response to
CYP2C19, 1957
P2RY12, 1957
ABCB1, 1958
Thin-cap fibroatheroma (TCFA), 356
Third (S3) heart sounds, 163–164
artificial valve sounds, 166–167
early diastolic high-frequency sounds, 165–166
ejection sounds, 164–165
midsystolic click, 165
pericardial knock, 164
Third Report of NCEP Adult Treatment Panel, 831*t*
Thoracic aortic aneurysms and dissections (TAAD), 1167
Thoracic aortic dissection, 1181–1182
Thoracic endovascular aortic repair (TEVAR)
complications of, 1184
endoleak, 1184
failed insertion, 1184–1185
neurological complications, 1184
Thoracic valves, types of, 1073
bioprosthetic valves, 1075
stented porcine valves, 1075–1076
stented bovine pericardial, 1076
stentless, 1076–1078
homograft, 1078–1079
mechanical valves, 1073
bileaflet tilting-disk design, 1074–1075
single tilting-disk design, 1073–1074
Starr-Edwards caged-ball valve, 1073
pulmonic valve autotransplantation, 1079
Thoracic veins, 6*f*
Thoracoabdominal injury, 1731–1732
Thoratec HeartMate II trial, 1344
ventricular assist device, 1810
Three-dimensional echocardiography (3DE), 319
common artifacts, 323*f*
protocol of, 324*t*
Three-dimensional wall motion tracking (3DWMT), 326*f*

Thrombin, 873
Thrombin receptor antagonists (TRA), 132
Thrombin time (TT), 127
Thrombolysis in Myocardial Infarction (TIMI) risk score, 877
Thrombolysis in Myocardial Infarction (TIMI) study group, 541
Thrombolysis in Myocardial Ischemia (TIMI)-IIIB clinical trial, 977–978
Thrombolysis, 902, 904–905
  alteplase, 902, 903*t*
  reteplase, 902, 903*t*
  streptokinase, 902, 903*t*
  tenecteplase (TNK-tPA), 902, 903*t*
Thrombolytics
  for cocaine abuse treatment, 1619–1620
Thrombopoietin, 2011
Thrombosis management
  in VAD implantation, 1349
Thrombosis, 461–462
  fibrin-rich thrombi, clinical imaging of, 462–464
  preclinical thrombus imaging strategies, 464
Thrombotic valve complications
  diagnosis of, 1101–1102
Thromboxane A2 (TXA2), 119, 1753
Thrombus formation, propensity for, 312–313
Thyroid disease, 1716
  amiodarone-induced thyroid disease, 1717–1718
  hyperthyroidism, 1716–1717
  hypothyroidism, 1717
Thyroid hormone replacement
  in myocardial contractility, 100
Ticagrelor, 545, 882
  in stroke prevention, 1918
Ticlopidine, 545, 1957
  $P2Y_{12}$ inhibitor, 130
  in stroke prevention, 1918
Time in therapeutic range (TTR), 121, 127
Tinzaparin (Innohep®), 1761
Tirofiban, 133, 882
  in dialysis patients, 1701
Tissue Doppler imaging (TDI), 328, 764
Tissue factor (TF), 116
Tissue inhibitors of metalloproteinases (TIMPs), 27, 1253
Tissue synchronization imaging, 764–765
Titin, in diastolic heart failure, 1253
Tobacco cessation, in cardiac rehabilitation, 920
Tobacco dependence, 5As for intervention, 833*t*
Tobacco smoking. *See* smoking
Tobacco, 1631
Tocopherols, in dyslipidemia, 1863
Toll-like receptors (TLRs), and atherosclerosis, 1850
Tolvaptan, to treat euvolemic hyponatremia, 1277
TOPCAT trial, spironolactone, 1835
Toronto Stentless Porcine valve, 1077
Torsades de pointes, in electrocardiograph, 199*f*
Torsemide, 54, 58*t*, 59, 65, 67
  for CRS, 1288
  to relieve congestive symptoms, 1242
Total anomalous pulmonary venous return (TAPVR), 1583–1584
Total artificial hearts, in HF, 1360
Trabeculae carneae, 11
Transcendental meditation (TM), 2038
Transcutaneous energy transfer system (TETS), 1350
Transduction, 2004. *See also* Viral transduction
Transesophageal echocardiography (TEE)
  in AAD diagnosis, 1170
  acute aortic dissection, 316
  atrial fibrillation, 313
  in coarctation, localization, 1556
  endocarditis, 313
  guidelines, 309
  history, 309
  major clinical applications
    embolism, sources of, 310
    masses, 310–311
    paradoxic embolization, passageways for, 311–312
    thrombus formation, propensity for, 312–313
  performance, 309–310
  procedural adjunct or intraoperative TEE, 316–317
  safety, 310
  in septal myectomy, 1408
  structural valve assessment, 313–316
  tricuspid valve disease, 1023
  views, 310
Transesophageal three-dimensional echocardiography (3D TEE), 319
Trans-fatty acids, 834
Transforming growth factor-beta (TGF-beta)
  in myocardial fibrosis, 1261
Transient ischemic dilation (TID), 391, 392
Transplant vasculopathy, pathogenesis of, 1342*f*
Transthoracic echocardiography (TTE), 265, 309
  in AAD diagnosis, 1170
  appropriate indications for, 266*t*
  cardiac resynchronization therapy, 289
  chamber quantitation, 265–269
  contrast echocardiography, 286–288
  diastolic function, 270–272
  Doppler echo, 269–270
  infective endocarditis, 285
  intracardiac masses, 285–286
  pericardial disease, 273–274
  pulmonary hypertension, 272–273
  valvular heart disease
    aortic regurgitation, 279
    aortic stenosis, 274–279
    mitral regurgitation, 281–282
    mitral stenosis, 279–281
    pulmonic regurgitation, 285
    pulmonic stenosis, 284–285
    tricuspid regurgitation, 284
    tricuspid stenosis, 283
Transthyretin (TTR), 1458
Transthyretin-related (TTR) amyloid molecules SCA, 1831–1832
  in HFPEF, 1835
Trastuzumab (Herceptin), in left ventricular dysfunction, 1480*t*
Traumatic ruptured chordate, tricuspid regurgitation in, 169
Traumatic tricuspid regurgitation, 1026
Treadmill exercise, 212
Treadmill exercise stress testing (ETT), 860
Treadmill exercise testing, in variant angina diagnosis, 942
Treat Angina with aggrastat and determine Cost of Therapy with an Invasive or Conservative Strategy—Thrombolysis In Myocardial Infarction (TACTICS-TIMI), 210
Treatment of Hyponatremia Based on Lixivaptan in NYHA Class III/IV Cardiac Patient Evaluation (BALANCE) trial, 1279
  in phase 3 clinical trials, 1278–1279
Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT), 1260
Treprostinil (Remodulin®), for PAH, 1539
Treprostinil (Tyvaso™), for PAH, 1538
Triamterene, 54, 55, 58*t*, 62, 64
  in CHF and renal dysfunction, 1289
  in hypertension, 1138
Tricuspid annular plane systolic excursion (TAPSE), 1531
  for PAH, 1531
Tricuspid atresia/univentricular heart, 1586
  bilateral Glenn, 1586–1587
  classification, 1586
Tricuspid insufficiency, plain film imaging, 187
Tricuspid regurgitation (TR), 1739
  in heart failure, 1214–1215
  interventions in, 1121
  intraoperative assessment, 1123
  in pulmonary stenosis, 1558
  severity, classification, 284*t*
  tricuspid valve surgery, 1123
Tricuspid valve, 3, 10–11
Tricuspid valve disease
  in adolescents or young adults, 1120
  anatomy of, 1019
    annulus, 1019
    chordae tendineae, 1019
    leaflets, 1019
    papillary muscles, 1019
  assessment of, 334
  clinical presentation
    physical signs, 1021
    symptoms, 1021
  description, 1018
  dysfunction, 1019
  embryology, 1018
  etiology of
    primary tricuspid valve disease, 1019–1020
    secondary or functional tricuspid valve disease, 1020
  laboratory diagnosis
    cardiac catheterization, 1023
    chest radiograph, 1021
    echocardiography, 1021–1023
    electrocardiogram, 1021
    selective angiography, 1023
    transesophageal echocardiography, 1023
  normal tricuspid valve function, 1019

percutaneous tricuspid balloon valvuloplasty, 1045
regurgitation of, 1024–1025
replacement, 1025
stenosis of, 1024
treatment of, 1023
appropriate timing, 1023–1024
management strategies, 1024–1025
medical treatment, 1024
for primary tricuspid valve regurgitation, 1025–1026
surgical treatment, 1024–1025
Tricuspid valve regurgitation, 1024–1025
primary tricuspid valve regurgitation, surgical treatment of
carcinoid heart disease, 1026
cleft tricuspid valve, 1026
Ebstein's anomaly, 1025–1026
infective endocarditis, 1026
rheumatic valve disease, 1025
traumatic tricuspid regurgitation, 1026
Tricuspid valve stenosis, 1024
Tricyclic antidepressants (TCAs)
for pain, in HF, 1358
Triggered arrhythmias
and afterdepolarizations, 574–575
Triglyceride-lowering therapy, 113
Trimetazidine, 1244
FFA, beta-oxidation, 1609
"Tripartite" signature, of RVI, 961
Triple-H therapy" (HHH—hypertension, hypervolemia and hemodilution), 1692
TRITON TIMI-38, 1944
TRIUMPH-1 trial (*TReprostinil* sodium inhalation Used in the Management of Pulmonary Hypertension-1), 1539
Tropical endomyocardial fibrosis, 1442
clinical features, 1444
definition, 1442–1443
epidemiology, 1443
natural history, 1443–1444
Troponin I (TnI), 858. *See also* Cardiac troponin I
in chronic heart failure, 1222, 1223
Troponin T (TnT), 858. *See also* Cardiac troponin I
in chronic heart failure, 1222, 1223
Troponin, 875, 876–877
myocardial ischemia, 1286
Truncus arteriosus (TA)
classification, 1577–1578
clinical findings, 1578
diagnostic studies, 1578
general considerations, 1577
genetic inheritance, 1578
pregnancy, 1578
treatment and prognosis, 1578
Trypanosoma cruzi
Chagas disease, 1513
life cycle of, 1514*f*
Tui Na, 2032. *See also* Acupressure-based massage
Tumor necrosis factor alpha (TNF-α)
in hibernating myocardium, 1324
in LDL binding, 1849
in rheumatoid arthritis, 1650
Turner's syndrome, 152
Two-dimensional echocardiography (2DE), 319
TxA2 pathway, aspirin as inhibitor, 128*f*
Type 1 CRS (acute CRS), 1285
Type 2 CRS (chronic CRS), 1285
Type 2 diabetes, 1831
Type 3 CRS (acute renocardiac syndrome), 1285–1286
Type 4 CRS (chronic renocardiac syndrome), 1286
Type 5 CRS (secondary CRS), 1286
Type A acute aortic dissection, 1172
Type B acute aortic dissection, 1172

U

U wave, 191, 206–207
acute pericarditis, 207*f*
Ubiquinone, 2039
Uhl's syndrome, tricuspid regurgitation in, 169
UK-HEART, hyponatremia in HF, 1274
Ultrafast CT, 408
Ultrasmall superparamagnetic iron oxide (USPIO) nanoparticle enhanced MRI for atherosclerosis detection, 453
Ultrasmall superparamagnetic iron oxide (USPIO), 453
Ultrasound contrast agents, reuse, warning, 295
Unfractionated heparin (UFH), 119, 883, 1760–1761. *See also* Antithrombotic agents; Heparins
Unibody stent grafts, 1177
Unifit stent graft, 1177
Uni-iliac stent grafts, 1177
United Kingdom, incidence of heart failure in, 1210
United Network of Organ Sharing (UNOS), 1335
United States of America
Chagas disease in, 1517
heart failure
epidemiology of, 1207*t*
prevalence of, 1207*t*
Medical Coverage Advisory Commission (MCAC), 1980
University of Iowa, CABG, 970
UNLOAD study, 1243
Unrecognized myocardial infarction, 433–434
Unstable angina (UA) and non-ST-elevation myocardial infarction (NSTEMI), 871, 872, 874, 876, 877, 879, 880, 884, 892–893
Upright tilt table testing, 634–636
Urine toxicology screen, for STEMI, 901
Utility, 1984

V

VA treadmill score, 221*t*
Vagally mediated atrial fibrillation". *See* Atrial fibrillation
Valproate, for chorea, 1933
Valsalva aneurysm, 3
Valsalva cusp VT, aortic sinus of, 691
Valsartan heart failure trial (Val-Heft), 1238
Value, 1984
Valvar pulmonic stenosis
anatomy of, 1028–1029
associated anomalies, 1558
clinical course, 1029–1030
clinical findings, 1558
history, 1030
physical examination, 1030–1031
diagnostic studies, 1558–1559
differential diagnosis, 1032
endocarditis prophylaxis, 1559
exercise, effects of, 1029
general considerations, 1557
genetic inheritance, 1558
guidelines, 1559
laboratory investigations
cardiac catheterization, 1032
chest roentgenogram, 1031
echocardiography, 1031
electrocardiogram, 1031
natural history of, 1029–1030
pathology of, 1028–1029
pathophysiology of, 1029, 1557–1558
pregnancy, 1559
treatment and prognosis, 1032, 1559
balloon valvotomy, 1033–1034
surgery, 1033
Valve replacement
risks of, 1072–1073
operative mortality, 1073
perioperative stroke, 1072
Valve thrombosis, 1102
Valvular disease, 420–421
hemodynamics, and stress echo, 304–305
Valvular disorders, assessment of
aortic valve, 334
mitral valve, 331–334
prosthetic valves, 334–335
tricuspid valve, 334
Valvular heart disease, 152, 440–441, 650, 1098, 1702
due to acromegaly, 1719
aortic regurgitation, 279
aortic stenosis, 274–279
butterfly rash, 152
general considerations, 1098–1099
risk of thromboembolism, 1099*t*
hemodynamics in
aortic regurgitation, 475–476
aortic stenosis, 474–475
mitral regurgitation, 477–478
mitral stenosis, 476–477
pulmonic regurgitation, 478
pulmonic stenosis, 478
tricuspid regurgitation, 478–479
tricuspid stenosis, 478
management issues
elective surgery, 1102
endocarditis, 1102–1103
pregnancy, 1102
thrombotic valve complications, 1101–1102
valve thrombosis, 1102

mitral regurgitation, 281–282
mitral stenosis, 279–281
in perioperative setting, 1776–1777
prophylactic antithrombic therapy, 1099
pulmonic regurgitation, 285
pulmonic stenosis, 284–285
tricuspid regurgitation, 284
tricuspid stenosis, 283
valve stenosis, 441
valvular regurgitation, 441–442
valvuloplasty and valve repair, 1101
Valvular heart diseases guidelines
cardiac murmurs, 1104
classification, 1104
echocardiography, 1105
interventions, 1104
endocarditis prophylaxis, 1105–1106
for dental procedures, 1106
Valvular lesions
during surgery, 1785
Vanguard, stent graft design, 1176
Varenicline, 918
tobacco dependency, first-line treatment for, 1880, 1881, 1882*t*
Variant angina
arrhythmias, treatment of, 943–944
calcium antagonists, 944–946
clinical presentation of, 939–940
description of, 938
diagnosis of
ambulatory ECG monitoring, 941
coronary arteriography, 942
ECG studies, 940
history, 940
in-hospital ECG recording, 941–942
laboratory findings, 940
noninvasive studies, 940–942
physical examination, 940
provocative testings, 942
radionucleotide scintigraphy, 942
self-initiated transtelephonic ECG monitoring, 941
treadmill exercise testing, 942
differential diagnosis, 942–943
incidence of, 938
management
arrhythmias, treatment of, 943–944
calcium antagonists, 944–946
medical therapy, 943–946
surgical and percutaneous intervention, 946
natural history, 946–947
pathophysiology of, 939
predisposing risk factors, 938
prognosis, 946–947
Vascular access, sites and techniques of, 519
brachial artery approach, 520
femoral artery approach, 519–520
transradial approach, 520
Vascular cell adhesion molecule 1 (VCAM-1), 1848
in HIV patients, 1638
Vascular closure devices, advantages and disadvantages of, 537*t*
Vascular endothelial growth factor (VEGF), 40, 2009
members of, 2010
Vascular injury, 467
Vascular permeability factor (VPF), 2010
Vascular resistance
autoregulatory, 35–36
catheterization computation, 473
compressive, 35
myogenic resistance, 36
neurogenic modulation, 37
and normal pressures, 475*t*
viscous, 35
Vasculogenesis, 40, 2007
Vasoconstrictors, 38
Vasodilation in the management of acute congestive heart failure (CHF) (VMAC) study, 1243
nesiritide, 83
Vasodilators
aldosterone receptor blockers
aldosterone and systolic heart failure, 78–80
spironolactone and eplerenone in chronic heart failure, 80–81
and low blood pressure, 72
aortic impedance components, 72*t*
arterial versus venous effects of,
in systolic heart failure, 72
arteriolar vasodilators
amlodipine, 74
hydralazine, 72–73
oral nitrates, 74
enalapril effects, 75*f*
intravenous vasodilators
intravenous nitroglycerin limitations in heart failure, 82–83
intravenous nitroglycerin, 82
nesiritide, 83
nitroprusside, 82
isosorbide dinitrate/hydralazine effect, 73*f*
LV dysfunction and afterload stress, 71*f*
NTG tolerance, 73*f*, 74*f*
oral β-adrenergic blocking drugs, 83–85
phosphodiesterase type 5 inhibitors
sildenafil and tadalafil, 81–82
RAAS blockers
ACE inhibitors, 74–77
angiotensin receptor blockers, 77
Vaso-occlusive disease, 1847
Vasopressin receptors
on AVP, 1276*t*
Vasopressin, 38, 45
for cardiac arrest, 821
for CPR, 796
Vasopressor support, immediate postoperative management, 1340
Vasopressors, in refractory heart failure, 1243
Vasospastic angina, 145
coronary blood flow during, 42, 43*t*
Vasovagal syncope, 639–640. *See also* Neurocardiogenic syncope
Vaughan-Williams classification, 580*t*
beta-adrenoceptor blockers, Class II, 586
calcium channel antagonists, Class IV, 593–594
drugs that prolong repolarization, Class III, 586–593
sodium channel blockers, Class I, 579–581
Class IA, 581–583
Class IB, 583–584
Class IC, 584–586
Vegetative lesions, of infective endocarditis, 310
VEGF-C. *See also* VEGF-2
in lymphangiogenesis. 2013
Vein of Marshal, 21
Velocity time integral (VTI), 324
Venoluminal channels, 19
Venous bypass graft PCI, embolic protection devices for, 552
distal embolic filters, 552
distal occlusion devices, 552–553
proximal occlusion devices, 553
Venous thromboembolism (VTE), 121
acute management, 1759
anticoagulation therapy, 1760
inferior vena cava filters, 1762–1763
new anticoagulants, 1763
parenteral anticoagulants, 1760–1762
clinical manifestations, 1754
diagnostic approach, 1757
high probability clinical assessment, 1758
low probability clinical assessment, 1757–1758
moderate probability clinical assessment, 1758
diagnostic testing, 1755–1757
epidemiology, 1750–1751
etiology, 1751–1752
high-risk death patients, management of, 1759–1760
intermediate risk populations, 1760
low risk populations, 1760
mortality risk assessment, 1759
optional pathways, 1758–1759
outcomes, 1753–1754
pathophysiology, 1752–1753
risk factors for, 1751*t*
signs, 1754–1755
surgical and catheter-based thrombectomy, 1760
symptoms, 1754
thrombolysis, 1760
Venous thrombosis, 1909*t*
Ventilatory oxygen consumption, 213*t*
Ventilatory threshold (VT)
in exercise measurement, 1315
Ventral septal defect, 1738–1739
Ventricular arrhythmias, 2022
and CRT, 767–768
Ventricular assist devices (VADs)
Center for Medicare services approved indications for, 1346*t*
contraindications to, 1346*t*
design of, 1347
in HF, 1360
long-term complications in, 1350*t*
monitoring of, 1348

patient selection, 1345
physiology of, 1347
structural and molecular effects of mechanical unloading, 1347–1348
Ventricular fibrillation (VF), 789, 798–799
phases of, 818–819
Ventricular function, assessment and clinical application, 252
determinants of left ventricular performance, 252–255
diastolic function, 259
heart rate, 258–259
left ventricular functional assessment during stress, 259–260
left ventricular pump function, 255–258
right ventricular function, 260–262
Ventricular septal defects (VSDs), 335
associated anomalies, 1563–1564
and BAVs, 1552
classification of, 1563*f*
clinical findings, 1564
diagnostic studies, 1564–1565
general considerations, 1562–1563
guidelines, 1566
pathophysiology, 1563
pregnancy, 1566
treatment and prognosis, 1565–1566
Ventricular septal myectomy, 1408. *See also* Septal myectomy
Ventricular septal rupture, cardiac causes of, 952
Ventricular tachycardia (VT), 686–687, 789, 798–799, 1777
monomorphic
myocardial VT in association with structural heart disease, 687–690
with structurally normal heart, 691–692
nonsustained, 1777
polymorphic
with long QT interval, 692–693
with normal QT prolongation, 693–695
with short QT syndrome, 695–696
sustained, 1777
Ventricular tachycardia ablation, in structural cardiac disease, 736–737
12-lead localization, 738
ablation, approach to, 738
activation mapping (focal tachycardias), 738
anatomic substrate, 737
electroanatomic three-dimensional mapping, 740
entrainment mapping, 739–740
epicardial VT, 743–744
pace mapping, 741–742
patient selection, 737–738
prior to ablation, 738
re-entrant tachycardia, 738–739
safety, 742–743
substrate-based ablation, 742
voltage mapping, 740–741
Ventricular thrombus, 423
Venturi effect, in LVOT obstruction, 1382
Verapamil ordiltiazem, 1171
Verapamil, 293, 679, 680, 691, 879. *See also* Calcium channel blockers (CCBs)
for HCM, 1405
in variant angina, 945
Vernakalant, 594–595
Vertebrobasilar artery stenosis (VAS), 1160
Very low density lipoprotein (VLDL), 1856–1858
fish oils, 2033
metabolism, 1857*f*
Very low density lipoprotein cholesterol (VLDL-C), 106, 111
Very small embryonic-like stem cells (VSELs), 1988
Veteran Administration Diabetes Trial (VADT) trail, 1716
Veterans Affairs Coronary Artery Bypass Surgery Cooperative Study Group (VA-CABSCSG), 970, 977
Veterans Affairs HDL Intervention Trial (VAHIT) study, 1716
VF lead, 191
Viral transduction, 2004
and plasmid DNA delivery, 2004
adeno-associated virus (AAV), 2004–2005
adenovirus, 2004
lentivirus, 2005–2006
Virtual Histology™ (VH) IVUS, 355
Viscous vascular resistance, 35
Vitamin C, in dyslipidemia, 1863
Vitamin D, in dyslipidemia, 1863
Vitamin K antagonists (VKAs), 121–122, 1762
warfarin, 121–122
Vitamin K epoxide reductase (VKOR), 121
subunit 1 (*VKORC1*) gene, 1959
VL lead, 191
Volatile agents versus opiates, as anesthetic choice, 1786–1787
Voltage-gated ion channels, 567
Volume adjustment, for cocaine abuse treatment, 1619
von Willebrand Factor (vWF), 118, 127
Vorapaxar, 132
VR lead, 191

W

Waldenström's macroglobulinemia, in AL amyloidosis, 1457
Wall motion abnormality, 291
Wall stress, 252
Warfarin, 121–122, 884, 1958–1959
cardiovascular pharmacogenomics, 1945
clinical response to, 1960
dose requirements
CYP2C9, 1959
CYP4F2, 1959
VKORC1, 1959
side effects, 1969
tailored therapy, 1960
Warm-up period, in exercise training, 1894
Weber classification, functional impairment, 1315*t*
Wegener's granulomatosis, 1658
Weight management, in cardiac rehabilitation, 920
Wellen's syndrome, 874
Wheezing, 147
White blood cells (WBC)
in variant angina syndrome, 540
White coat hypertension, 153
Wide QRS tachycardia, 677–678
Williams-Beuren syndrome, supravalvar stenosis, treatment of, 1036
Wilson's central terminal, 192
Wolff-Parkinson-White (WPW) syndrome, 673, 680, 805–806
in AF patients, 588
cardiac-surgical contribution, 730
catheter ablation complications, 731
catheter ablation development, 731
catheter ablation efficacy and challenges for accessory pathways, 731
classification and localization of accessory pathways, 731
historical evolution of ventricular pre-excitation, 730
WPW syndrome clinical implications and AVRT, 731
Women
evaluation of CAD in, 393
exercise testing in, 219
Women's Health Initiative (WHI) study, 1945
Worsening renal function (WRF), 1281
during heart failure hospitalization, 1284*t*
prognosis of, 1282

X

Ximelagatran, 126, 1762
X-SOLVD study
in enalapril benefits, 1904

Z

"Z-disc HCM", 1378
Zenith Low Profile stent graft, 1177
Zenith stent graft, 1177
Zidovudine
in HIV infection, 1643
Zoom mode, 321

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VOLUME 2

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Foreword



It is a privilege to write this foreword for this comprehensive *Cardiology—An Illustrated Textbook*. Because of the excessive morbidity and mortality from cardiovascular disease, the subject is extensively discussed in the world's literature and existing textbooks. A fair question from the reader is: why do we need another textbook of cardiology? That question can be answered in different ways.

First of all, our knowledge of and ability to treat all kinds of cardiovascular diseases have expanded exponentially in the past few decades. I recall when I was a cardiology fellow at the Peter Bent Brigham Hospital, Boston (USA), and watched my first Vineberg procedure as an attempt to revascularize the heart. It was a brutal punishing treatment for the myocardium, and was a great disincentive to the cardiologist to refer such patients to the cardiac surgeon. Now, when we approach coronary artery disease, we have so many options available to us; including angioplasty, stents, "keyhole" surgery and potent pharmacologic ways to alter the lipid profile. Rapid advances in noninvasive imaging and electrophysiology remind us how quickly our knowledge base is changing.

Second, it is always useful to know and compare the different approaches to cardiovascular disease at world-class institutions. The Contributors and Editors of this textbook are primarily based at the University of Iowa and the University of California, San Francisco, USA, two well-known centers for research and treatment of cardiovascular disease. Many other institutions are also represented. This unique blending of knowledge and expertise also reflects the fact that the principal editor, Dr Kanu Chatterjee, has spent most of his career at University of California, San Francisco (UCSF) and the University of Iowa, USA. It was my privilege to be associated with him as a colleague at UCSF, and to appreciate his broad knowledge of cardiology. His receipt of "best teacher" awards from the Department of Medicine attest to his ability to transmit that knowledge to students, housestaff, fellows and faculties.

Third, we are part of the fast- food generation. We are bombarded by so much information that we frequently are more attentive to our electronic devices than we are to the real people around us. We love photographs and graphs which can tell a whole story at a glance. I think that the reader will be pleased with the quality of the illustrations in the textbook, and find it easy-to-learn from them. I suppose that a few people (perhaps cardiology fellows and those studying for the cardiovascular boards) will sit down and read the textbook from cover to cover. More likely, however, it will serve as a reference text, wherein the reader can go to a specific chapter, and benefit from a concise and informative discussion of the particular problem at hand.

Fourth, every textbook of Cardiology has its strengths and weaknesses, and its distinctive sections. I believe that the reader will be pleased to review the Section on Evolving Concepts. Subjects such as the genomics of cardiovascular disease, gene therapy and angiogenesis, and stem cell therapy, to mention but a few chapters, will be of interest to all those concerned with cardiovascular disease.

Overall, the comprehensive textbook will continue the tradition of excellent textbooks of cardiology. It will be of great interest not only to the cardiologist but also to all those interested in cardiovascular disease including internists and other specialists. I am pleased to recommend the book most highly.

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Preface

Cardiology—An Illustrated Textbook is a revived but really a new textbook in cardiology. "Cardiology" was initially published as a loose-leaf referenced textbook. In 1993, it was published as a hard copy illustrated and referenced textbook. Since its publication, almost two decades ago, there have been enormous advances in every aspect of cardiology. Substantial progress has occurred in the understanding of coronary circulation, the molecular mechanisms of myocyte function and in the assessment of regional and global ventricular functions in physiologic and pathologic conditions. In this textbook, these advances have been emphasized.

The advances in cardiovascular pharmacology have also been considerable. The advantages and disadvantages of diuretic therapy, vasodilators, neurohormone modulators, positive inotropic agents, antilipid, antithrombotic and antiplatelet agents have been discussed. The clinical pharmacology of these agents in the management of various cardiovascular disorders has been emphasized. In the textbook, these advances are the subject of entirely new chapters.

We have witnessed the development of newer diagnostic techniques and the refinement of older diagnostic methods for detection of cardiovascular pathology. Molecular imaging and three-dimensional echocardiography and intravascular ultrasound imaging have been introduced. Advances have occurred in nuclear, cardiovascular computerized tomographic and magnetic resonance imaging. In the textbook, the advances in these diagnostic techniques and their clinical applications in the practice of cardiology have been extensively discussed. The role of rest and stress and electrocardiography and echocardiography has been emphasized.

During last two decades, we have witnessed enormous advances in the understanding of the genesis of atrial and ventricular arrhythmias, in the techniques of electrophysiologic and the pharmacologic and nonpharmacologic treatment of arrhythmias. The function and dysfunction of ion channels and the diagnosis and management of supraventricular and ventricular arrhythmias have been presented in details.

There have been revolutionary changes in the understanding of the pathophysiologic mechanisms and management of acute coronary syndromes. The new therapeutic modalities for the management of chronic coronary artery diseases have been discovered and devoted to discuss.

The diagnosis and management of valvular heart disease and heart failure are discussed in detail as well as chemotherapy and radiation-induced cardiovascular disorders. The progress in vascular biology, in genetics and pharmacogenomics in cardiology has also been considerable. In recent years, awareness of the cost of health care, errors in the practice of cardiology and gender and geographic differences in the incidence, diagnosis and management of cardiovascular disorders has risen. In the textbook, we have addressed these important and controversial topics.

We have also added modified guidelines for the management of angina, arrhythmias, heart failure, valvular heart diseases and perioperative cardiac evaluations.

All the chapters in the textbook have been written by the nationally and internationally recognized experts in their respective fields. The editors are very appreciative of and grateful to the contributors.

We sincerely thank Mr Joseph Gallo for his generous support enabling publication of the textbook of cardiology. We also acknowledge the help of all our administrative assistants and colleagues.

We also sincerely thank Shri Jitendar P Vij (Chairman and Managing Director), Mr Tarun Duneja (Director-Publishing), Ms Samina Khan (PA to Director-Publishing), Dr Richa Saxena and the expert team of M/s Jaypee Brothers Medical Publishers (P) Ltd, New Delhi, India. Without their hard work, the textbook could not have been published.

Kanu Chatterjee
Mark Anderson
Donald Heistad
Richard E Kerber

Volume 1

Section 1
BASIC CARDIOLOGY

1. Cardiac Anatomy 3
Melvin D Cheitlin, Philip C Ursell

Pericardium and Heart in the Mediastinum 3
Cardiac Surface Anatomy 6
Internal Structure of the Heart 8
Right Atrium 8
Tricuspid Valve 10
Right Ventricle 11
Pulmonic Valve 12
Pulmonary Arteries 13
Left Atrium 13
Mitral Valve 13
Left Ventricle 14
Aortic Valve 15
Conduction System 16
Coronary Arteries 18
Intramural Vessels 19
Coronary Veins 19
Cardiac Lymphatics 21
Cardiac Innervation 21

2. Cardiac Function in Physiology and Pathology 23
Joel S Karliner, Jeffrey Zimmet

Beta-adrenergic Receptor-mediated Signaling 23
Calcium Regulation 24
Links Between B-adrenergic Signaling and Calcium Regulation 24
Mitochondria 24
Cardiac Hypertrophy 26
α_1-adrenergic Receptors and Hypertrophy 26
Congestive Heart Failure 27
Micro-RNAs 28
Ischemia/Reperfusion Injury 28
Mechanisms of Cardioprotection 28
Aging 30

3. Coronary Circulation in Physiology and Pathology 34
Kanu Chatterjee

Coronary Vascular Anatomy 34
Regulation of Coronary Blood Flow 34
Coronary Vascular Resistance 35
Modulation of Coronary Blood Flow 36
Coronary Collateral Circulation 39
Coronary Circulation in Pathologic States 40

Section 2
CARDIOVASCULAR PHARMACOLOGY

4. Diuretics 53
Michael E Ernst

Normal Renal Solute Handling 53
History and Classification of the Diuretic Compounds 53
Clinical Pharmacology of the Diuretic Compounds 55
Adaptive Responses to Diuretic Administration 56
Individual Diuretic Classes 57
Clinical Use of Diuretics in Cardiovascular Diseases 62
Adverse Effects of Diuretics 67

5. Vasodilators and Neurohormone Modulators 71
Gary S Francis, Suma Konety

Vasodilator Drugs and Low Blood Pressure 72
Arteriolar Vasodilators 72
Renin-angiotensin-aldosterone System (RAAS) Blockers 74
Mineralocorticoid (Aldosterone) Receptor Blockers 78
Phosphodiesterase Type 5 Inhibitors 81
Intravenous Vasodilators 82
Oral B-adrenergic Blocking Drugs 83

6. Positive Inotropic Drugs 89
Carl V Leier, Garrie J Haas, Philip F Binkley

Intravenously Administered, Short-term Positive Inotropic Therapy 89

7. Antilipid Agents 104
Jennifer G Robinson

Appropriate Uses 104
Statins 105
Add-on to Statin Therapy 110
Bile Acid Sequestrants 111
Ezetimibe 111
Niacin 112
Triglyceride-lowering Therapy 113
Fibrates 113
Omega-3 Fatty Acids 114
Drugs in Development 114

8. Antithrombotic and Antiplatelet Agents 116
Louis P Kohl, Ethan Weiss

Clotting—A Primer 116
Antithrombotic Agents 119
Ave-5206 121
Vitamin K Antagonists (VKA) 121
Ati-5923 122
Direct Factor Xa Inhibitors 122
Direct Thrombin Inhibitors 124
Antiplatelet Agents 127

Section 3
DIAGNOSIS

9. History 143
Kanu Chatterjee

The History 143

10. Physical Examination 151
Kanu Chatterjee

General Appearance 151
Measurement of Arterial Pressure 153
Auscultation 160

11. Plain Film Imaging of Adult Cardiovascular Disease 174
Brad H Thompson, Edwin JR van Beek

Chest Film Technique 174
Overview of Cardiomediastinal Anatomy 175
Cardiac Anatomy on Chest Radiographs 176
Cardiac Chamber Enlargement 177
Radiographic Manifestations of Congestive Heart Failure 179

Cardiac Calcifications 182
Acquired Valvular Heart Disease 183
Pericardial Disorders 187

12. Electrocardiogram 189
Donald Brown

Basis of Electrocardiography 189
Component Parts of the Electrocardiogram 191
Lead Systems Used to Record the Electrocardiogram 191
Common Electrode Misplacements 192
Other Lead Systems 194
Identification of Atrial Activity 194
Characterization of QRS Complex 201
ST-T Wave Abnormalities 206
The "U" Wave 206
The QT Interval 207

13. ECG Exercise Testing 209
Abhimanyu (Manu) Uberoi, Victor F Froelicher

Before the Test 209
Methodology of Exercise Testing 211
During the Test 213
After the Test 220
Screening 221

14. The Left Ventricle 228
Rakesh K Mishra, Nelson B Schiller

Systolic Function 228
Contrast-enhanced Echocardiography 236
Other Echo-derived Indices of LV Systolic Function 237
Strain-derived Indices 237
Recognizing the Etiology of Cardiac Dysfunction 237
Dilated Cardiomyopathy 238
Hypertrophic Cardiomyopathy 238
Restrictive Cardiomyopathy 239
Left Ventricular Noncompaction 240
Visual Qualitative Indicators of Systolic Dysfunction 240
Diastolic Function 242

15. Ventricular Function—Assessment and Clinical Application 252
Kanu Chatterjee, Wassef Karrowni, William Parmley

Determinants of Left Ventricular Performance 252
Left Ventricular Pump Function 255
Heart Rate 258
Diastolic Function 259
Right Ventricular Function 260

16. Transthoracic Echocardiography 265
Byron F Vandenberg, Richard E Kerber

Chamber Quantitation 265
Doppler ECHO 269
Diastolic Function 270
Pulmonary Hypertension 272
Pericardial Disease 273
Valvular Heart Disease 274
Infective Endocarditis 285
Intracardiac Masses 285
Contrast Echocardiography 286
Cardiac Resynchronization Therapy 289

17. Stress Echocardiography 291
Ellen El Gordon, Richard E Kerber

Using Stress Echocardiography in Clinical Decisions 291
The Future of Stress Echo 305

18. Transesophageal Echocardiography 309
Seyed M Hashemi, Paul Lindower, Richard E Kerber

History 309
Guidelines 309
Performance 309
Safety 310
Views 310
Major Clinical Applications 310
Structural Valve Assessment 313
Acute Aortic Dissection 316
Procedural Adjunct or Intraoperative TEE 316

19. Real Time Three-dimensional Echocardiography 319
Manjula V Burri, Richard E Kerber

Technique 320
Clinical Applications 324
Future Directions 339
Limitations 342

20. Intravascular Coronary Ultrasound and Beyond 349
Teruyoshi Kume, Yasuhiro Honda, Peter J Fitzgerald

Intravascular Ultrasound 349
Optical Coherence Tomography 364
Angioscopy 370
Spectroscopy 374

21. Cardiovascular Nuclear Medicine—Nuclear Cardiology 381
Elias H Botvinick

Pathophysiologic Considerations 382
Myocardial Perfusion Imaging 385
Risk Assessment of General and Specific Patient Populations 393
Positron Emission Tomography Perfusion and Metabolism 394
Imaging Myocardial Viability 395
Imaging Perfusion 397
Quantitation of Regional Coronary Flow and Flow Reserve 397
Blood Pool Imaging—Equilibrium Radionuclide Angiography and First Pass Radionuclide Angiography 398
First Pass Curve Analysis 398
Equilibrium Gated Imaging—ERNA 399
The Value of Functional Imaging 401
Phase Analysis 401
Imaging Myocardial Sympathetic Innervation 401
Radiation Concerns 402

22. Cardiac Computed Tomography 408
Isidore C Okere, Gardar Sigurdsson

Technical Aspects 408
Coronary Artery Disease 414
Myocardium and Chambers 417

Pulmonary Veins 418
Cardiac Veins 419
Valvular Disease 420
Pericardium 421
Masses 422
Incidental Findings 423
Future 423

23. Cardiovascular Magnetic Resonance 431
Robert M Weiss

Diagnosis of Epicardial Coronary Artery Stenosis 432
Assessment of Global and Regional Left Ventricular Function at Rest and during Inotropic Stress 432
Myocardial Perfusion Imaging 433
Cardiovascular Magnetic Resonance Coronary Angiography 433
Unrecognized Myocardial Infarction 433
Dilated Cardiomyopathy 434
Hypertrophic Cardiomyopathy 437
Restrictive Cardiomyopathy 439
Cardiovascular Magnetic Resonance-guided Therapy 440
Valvular Heart Disease 440
Diseases with Right Ventricular Predominance 442
Miscellaneous Conditions 445

24. Molecular Imaging of Vascular Disease 450
Eric A Osborn, Jagat Narula, Farouc A Jaffer

Molecular Imaging Fundamentals 450
Molecular Imaging Modalities 452
Molecular Imaging of Vascular Disease Processes 453

25. Cardiac Hemodynamics and Coronary Physiology 470
Amardeep K Singh, Andrew Boyle, Yerem Yeghiazarians

Cardiac Catheterization—The Basics 470
Catheterization Computations 472
Cardiac Cycle Pressure Waveforms 473
Hemodynamics in Valvular Heart Disease 474
Hemodynamics in Cardiomyopathy 479
Hemodynamics in Pericardial Disease 481
Coronary Hemodynamics 482

26. Cardiac Biopsy 485
Vijay U Rao, Teresa De Marco

History and Devices 485
Techniques 485
Safety and Complications 487
Analysis of EMB Tissue 487
Indications 488
Disease States 491
Cardiac Transplantation 497

27. Swan-Ganz Catheters: Clinical Applications 503
Dipti Gupta, Wassef Karrowni, Kanu Chatterjee

Historical Perspective and Evolution of Catheter Designs 503
Placement of Balloon Flotation Catheters 503
Normal Pressures and Waveforms 504
Abnormal Pressures and Waveforms 506
Clinical Applications 507
Indications for Pulmonary Artery Catheterization 512
Complications 512

28. Coronary Angiography and Catheter-based Coronary Intervention 517
Elaine M Demetroulis, Mohan Brar

Indications for Coronary Angiography 517
Contraindications for Coronary Angiography 518
Patient Preparation 518
Sites and Techniques of Vascular Access 519
Catheters for Coronary Angiography 520
Catheters for Bypass Grafts 522
Arterial Nomenclature and Extent of Disease 523
Angiographic Projections 524
Normal Coronary Anatomy 524
Congenital Anomalies of the Coronary Circulation 528
General Principles for Coronary and/or Graft Cannulation 531
The Fluoroscopic Imaging System 535
Characteristics of Contrast Media 535
Contrast-induced Renal Failure 536
Access Site Hemostasis 536
Complications of Cardiac Catheterization 537
Lesion Quantification 539
Degenerated Saphenous Vein Grafts 540
Lesion Calcification 540
Physiologic Assessment of Angiographically Indeterminate Coronary Lesions 541
Clinical Use of Translesional Physiologic Measurements 541
Non-atherosclerotic Coronary Artery Disease and Transplant Vasculopathy 542
Potential Errors on Interpretation of the Coronary Angiogram 543
Percutaneous Coronary Intervention 544
Pharmacotherapy for PCI 545
Parenteral Anticoagulant Therapy 548
Equipment for Coronary Interventions 549
Percutaneous Transluminal Coronary Angioplasty 550
Coronary Stents 550
Types of Stents 551
Stent Deployment 551
Adjunctive Coronary Interventional Devices 551
Embolic Protection Devices for Venous Bypass Graft PCI 552
Clinical Outcomes 553
Procedural Success and Complications Related to Coronary Intervention 555
Complications Specific to PCI 555

Section 4
ELECTROPHYSIOLOGY

29. Arrhythmia Mechanisms 565
Mark Anderson

Arrhythmia Initiation 565

30. Antiarrhythmic Drugs 578
Rakesh Gopinathannair, Brian Olshansky

Arrhythmia Mechanisms and Antiarrhythmic Drugs 579
Indications for Antiarrhythmic Drug Therapy 579
Proarrhythmia 579
Classification Scheme 579
Vaughan-Williams Classification 579
Miscellaneous Drugs 594
Newer Drugs 594
Emerging Antiarrhythmic Drugs 595

Antiarrhythmic Drug Selection in Atrial Fibrillation 595
Out-patient versus in-hospital Initiation for Antiarrhythmic Drug Therapy 595
Antiarrhythmic Drugs in Pregnancy and Lactation 596
Comparing Antiarrhythmic Drugs to Implantable Cardioverter Defibrillators in Patients at Risk of Arrhythmic Death 596
Antiarrhythmic Drug-device Interactions 597

31. Electrophysiology Studies 601
Indrajit Choudhuri, Masood Akhtar
Cardiac Electrophysiology Study: Philosophy, Requirements and Basic Techniques 601
Fundamentals of the Cardiac Electrophysiology Study 605
Programmed Electrical Stimulation and Associated Electrophysiology 609
Cardiac Electrophysiology Study for Evaluation of Drug Therapy 624
Electrophysiology Study to Guide Ablative Therapy 624
Complications 625

32. Syncope 627
Vijay Ramu, Fred Kusumoto, Nora Goldschlager
Epidemiology 628
Diagnostic Tests 629
Approach to the Evaluation of Syncope 638
Specific Patient Groups 639
Syncope and Driving 642

33. Atrial Fibrillation 647
Vasanth Vedantham, Jeffrey E Olgin
Definition and Classification 647
Epidemiology 647
Etiology and Pathogenesis 649
Diagnosis 652
Management 653

34. Supraventricular Tachycardia 665
Renee M Sullivan, Wei Wei Li, Brian Olshansky
Classification 665
Diagnosis 674
Treatments 678

35. Clinical Spectrum of Ventricular Tachycardia 686
Masood Akhtar
Monomorphic Ventricular Tachycardia 687
Polymorphic Ventricular Tachycardia 692

36. Bradycardia and Heart Block 698
Arthur C Kendig, James B Martins
Conduction System Anatomy and Development 698
Bradycardia Syndromes/Diseases 698
Clinical Presentation 700
Measurement/Diagnosis 700
Sinus Node Disease 700
AV Node Disease 700
Hemiblock 701
Bundle Branch Block 702
Treatment 702

37. Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy 705
Richard NW Hauer, Frank I Marcus, Moniek GJP Cox
Molecular and Genetic Background 706
Epidemiology 708
Clinical Presentation 708
Clinical Diagnosis 709
Non-classical ARVD/C Subtypes 713
Differential Diagnosis 713
Molecular Genetic Analysis 714
Prognosis and Therapy 714

38. Long QT, Short QT and Brugada Syndromes 718
Seyed M Hashemi, Peter J Mohler
LQT Syndrome 718
SQT Syndrome 722
Brugada Syndrome 724

39. Surgical and Catheter Ablation of Cardiac Arrhythmias 728
Yanfei Yang, David Singh, Nitish Badhwar, Melvin Scheinman
Supraventricular Tachycardia 728
Atrioventricular Nodal Re-entrant Tachycardia 729
Wolff-Parkinson-White Syndrome and Atrioventricular Re-entrant Tachycardia 730
Focal Atrial Tachycardia 731
Atrial Flutter 734
Ablation of Ventricular Tachycardia in Patients with Structural Cardiac Disease 736
Idiopathic Ventricular Tachycardia 744

40. Cardiac Resynchronization Therapy 758
David Singh, Nitish Badhwar
CRT: Rational for Use 758
CRT in Practice 759
Summary of CRT Benefit 761
Prediction of Response to CRT Therapy 762
Role of Dyssynchrony Imaging 764
Dyssynchrony Summary 767
LV Lead Placement 767
CRT Complications 767
Emerging CRT Indications 768

41. Ambulatory Electrocardiographic Monitoring 777
Renee M Sullivan, Brian Olshansky, James B Martins, Alexander Mazur
Holter Monitoring 777
Event Recorders 780
Mobile Cardiac Outpatient Telemetry 782
Implantable Loop Recorders 783
Key Considerations in Selecting A Monitoring Modality 783

42. Cardiac Arrest and Resuscitation 788
Christine Miyake, Richard E Kerber
Overview or Background 788
Basic Life Support 792
Advanced Cardiac Life Support 795
Cessation of Resuscitation 799
Post-resuscitation Care 800

43. Risk Stratification for Sudden Cardiac Death 804
Dwayne N Campbell, James B Martins
Healthy Athletes 804
Brugada Syndrome 805
Long QT Interval Syndrome 805
Early Repolarization 805
Short QT Syndrome 805

Catecholamine Polymorphic Ventricular Tachycardia 805
Wolff-Parkinson-White Syndrome 805
Arrhythmogenic Right Ventricular Cardiomyopathy 806
Hypertrophic Cardiomyopathy 806
Marfan Syndrome 806
Noncompaction 806
Congenital Heart Disease 806
Non-ischemic Cardiomyopathy 807
Coronary Artery Disease 807

44. Cardiocerebral Resuscitation for Primary Cardiac Arrest 811
Jooby John, Gordon A Ewy

Etiology and Pathophysiology of Cardiac Arrest 812
Drug Therapy in Cardiac Resuscitation 821
Cardiac Resuscitation Centers 822
Ending Resuscitative Efforts 823

Section 5
CORONARY HEART DISEASES

45. Coronary Heart Disease: Risk Factors 829
Bilal Aijaz, Vera Bittner

CHD Screening and Prevention 830
Clustering and Multiplicative Effects of Risk Factors 830
CHD Risk Estimation 830
Measures to Evaluate Risk Prediction Models 832
Traditional CHD Risk Factors 833
Emerging Risk Factors 838
Sub-clinical Atherosclerosis 839
Translating Risk Factor Screening into Event Reduction 840

46. Changing Focus in Global Burden of Cardiovascular Diseases 844
Rajeev Gupta, Prakash C Deedwania

CVD in High Income Countries 844
Low and Middle Income Countries 845
Risk Factors 849
Global Response for Combating CVD 850

47. Evaluation of Chest Pain 854
Kirsten E Fleischmann, Raveen Pal

Scope 854
History 854
Differential Diagnosis 854
Patient's Description 855
Angina 855
Past Medical History 856
Physical Examination 856
Investigations 858
Estimation of Risk 859
Diagnostic Testing 859

48. Acute Coronary Syndrome I (Unstable Angina and Non-ST-Segment Elevation Myocardial Infarction): Diagnosis and Early Treatment 871
Saket Girotra, Theresa M Brennan

Pathophysiology 871
Clinical Features 873
Risk Stratification—Putting it All Together to Determine the Optimal Treatment Strategy 875
Early Medical Therapy 877
Early Invasive or Initial Conservative Strategy 884
Revascularization 885

49. Acute Coronary Syndrome II (ST-Elevation Myocardial Infarction and Post Myocardial Infarction): Complications and Care 892
Theresa M Brennan, Patricia Lounsbury, Saket Girotra

Pathophysiology 893
Clinical Presentation 894
Reperfusion 902
Early Medical Therapy 906
Post Myocardial Infarction Care 909
Complications 912
Special Considerations 914
Continued Medical Therapy for Patients with A Myocardial Infarction 916
Discharge 919

50. Management of Patients with Chronic Coronary Artery Disease and Stable Angina 927
Prakash C Deedwania, Enrique V Carbajal

Current Therapeutic Approaches for Stable Angina 927
Antianginal Drug Therapy 928
Newer Antianginal Drugs 929
Combination Therapy 930
Other Drugs in Patients with Stable Angina and Chronic CAD 930
Role of Myocardial Revascularization 931
Comparison of Revascularization with Pharmacological Antianginal Therapy 931
Medical Therapy versus Percutaneous Revascularization or Strategies Comparing Invasive versus Optimal Medical Therapy 933

51. Variant Angina 938
Reza Ardehali, John Speer Schroeder

Incidence and Predisposing Risk Factors 938
Pathophysiology 939
Clinical Presentation 939
Diagnosis 940
Differential Diagnosis 942
Management 943
Natural History and Prognosis 946

52. Cardiogenic Shock in Acute Coronary Syndromes 949
Sanjay K Shah, Eugen Ivan, Andrew D Michaels

Incidence 949
Mortality 949
Predictors of Cardiogenic Shock 950
Pathophysiology 950
Pathology 951
Other Cardiac Causes of Cardiogenic Shock 951
Diagnostic Evaluation 954
Medical Management 954
Mechanical Support 954
Revascularization 957

53. Acute Right Ventricular Infarction 960
James A Goldstein

Patterns of Coronary Compromise Resulting in RVI 960

Right Ventricular Mechanics and Oxygen Supply-demand 961
Effects of Ischemia on RV Systolic and Diastolic Function 961
Determinants of RV Performance in Severe RVI 961
Natural History of Ischemic RV Dysfunction 962
Effects of Reperfusion on Ischemic RV Dysfunction 963
Rhythm Disorders and Reflexes Associated with RVI 964
Mechanical Complications Associated with RVI 964
Clinical Presentations and Evaluation 964
Noninvasive and Hemodynamic Evaluation 965
Differential Diagnosis of RVI 965
Therapy 965

54. Surgical Therapy in Chronic Coronary Artery Disease 969
Joss Fernandez, Samad Hashimi, Karam Karam, Jose Torres, Robert Saeid Farivar
Technique of Surgical Therapy for Chronic Coronary Artery Disease 969
Indications for Surgical Coronary Revascularization Advantages of CABG Over Medical Treatment 970
Comparing CABG to PTCA 971
The Changing CABG Population 971
When CABG may be Indicated 971
When CABG is not Indicated 972
Risk Factors for in-hospital Mortality Following CABG 972
Outcomes of Surgery 975
Major Clinical Trials in Chronic Coronary Artery Disease 976

Volume 2

Section 6
VALVULAR HEART DISEASES

55. Aortic Valve Disease 985
Blase A Carabello
Aortic Stenosis 985
Aortic Regurgitation 992

56. Mitral Valve Disease 1000
Satyavan Sharma, Bharat V Dalvi
Normal Mitral Valve Morphology and Function 1000
Global Burden of Rheumatic Heart Disease 1000
Mitral Stenosis 1001
Mitral Regurgitation 1007

57. Tricuspid Valve Disease: Evaluation and Management 1018
Pravin M Shah
Embryology 1018
Valve Anatomy 1019
Normal Tricuspid Valve Function 1019
Tricuspid Valve Dysfunction 1019
Clinical Presentation 1021
Laboratory Diagnosis 1021
Treatment 1023

58. Congenital Pulmonic Stenosis 1028
Jullien Hoffman
Valvar Pulmonic Stenosis 1028
Isolated Infundibular Stenosis 1034
Supravalvar Stenosis 1035

59. Catheter-based Treatment of Valvular Heart Disease 1040
Hjalti Gudmundsson, Philip A Horwitz
Catheter-based Treatment of Mitral Valve Disease 1040
Catheter-based Treatment of Pulmonary Valve Disease 1044
Percutaneous Tricuspid Balloon Valvuloplasty 1045
Catheter-based Therapies for Aortic Stenosis 1045
Summary/Future Directions 1048

60. Infective Endocarditis 1052
Ehrin J Armstrong, Ann Bolger, Henry F Chambers
Epidemiology 1052
Pathogenesis 1054
Microbiology 1057
Patient Presentation and Diagnosis 1059
Management 1062

61. Prosthetic Heart Valves 1072
Byron F Vandenberg
Risk of Valve Replacement 1072
Types of Prosthetic Valves 1073
Selecting the Optimal Prosthesis 1079
Prosthesis-patient Mismatch 1081
Long-term Management 1084
Long-term Complications 1090

62. Antithrombotic Therapy in Valvular Heart Disease 1098
Michael H Crawford
General Considerations 1098
Prophylactic Antithrombic Therapy 1099
Native Valvular Heart Disease 1100
Rheumatic Valvular Heart Disease 1100
Mitral Valve Prolapse 1100
Calcified or Degenerative Valvular Disease 1100
Prosthetic Valves 1100
Bioprosthetic Valves 1101
Valvuloplasty and Valve Repair 1101
Management Issues 1101

Guidelines for Valvular Heart Diseases 1104

Section 7
VASCULAR DISEASES

63. Evaluation and Management of the Patient with Essential Hypertension **1129**
Edward D Frohlich

Evaluation of the Patient with Hypertension 1129
Antihypertensive Therapy 1133
Hemodynamic Concepts 1135
Clinical Pharmacologic Concepts 1136
Treatment Algorithms Advocated Over the Years 1142

64. Peripheral Vascular and Cerebrovascular Disease **1145**
Babak Haddadian, Suhail Allaqaband, Tanvir Bajwa

Peripheral Arterial Disease 1145
Carotid Artery Disease 1155
Renal Artery Stenosis 1157
Subclavian Artery Stenosis 1159
Vertebrobasilar Artery Stenosis 1160
Mesenteric Ischemia 1160

65. Aortic Dissection **1166**
Ariane Neyou

Predisposing Factors 1166
Classification 1168
Clinical Manifestations 1169
Diagnosis 1170
Treatment 1171

66. Endovascular Treatment of Aortic Aneurysm and Dissection **1175**
AM Timothy, DM Chuter

History of Endovascular Aortic Repair 1176
Stent Graft Design: The Lessons of Experience 1176
Anatomic Substrate for Endovascular Aneurysm Repair 1177
Current Stent Graft Designs for Abdominal Aortic Aneurysm (AAA) 1177
Adjunctive Devices and Techniques 1178
Endoleak 1179
Late-occurring Complications of Endovascular Aneurysm Repair 1179
Follow-up Imaging 1180
Branched and Fenestrated Stent Grafts 1180
Current Thoracic Aortic Stent Graft Designs 1181
Endovascular Repair of Thoracic Aortic Aneurysms 1181
Thoracic Aortic Dissection 1181
Acute Type B Dissection 1182
Chronic Type B Dissection 1183
Complications of Thoracic Endovascular Aortic Repair 1184
Intramural Hematoma 1185
Penetrating Aortic Ulcer 1185

67. Autonomic Dysfunction and the Cardiovascular System **1187**
Milena A Gebska, Christopher J Benson

Autonomic Regulation of the Cardiovascular System 1187
Autonomic Testing 1190
Primary Chronic Autonomic Failure 1193
Secondary and Congenital Autonomic Failure 1194
Chronic Orthostatic Intolerance 1195
Syndromes Associated with Episodic Autonomic Failure 1197
Autonomic Perturbations Associated with Cardiovascular Conditions 1198

Section 8
HEART FAILURE

68. Heart Failure: Epidemiology **1207**
Kanu Chatterjee

Epidemiology 1207
Prevalence 1207
Incidence 1209
Secular Trends 1211

69. Heart Failure: Diagnosis **1213**
Kanu Chatterjee

Analysis of Symptoms 1213
Physical Examination 1214
Electrocardiogram 1215
Chest Radiograph 1218
Echocardiography 1218
Radionuclide Ventriculography 1219
Cardiac Magnetic Resonance 1220
Cardiac Tomography 1220
Routine Laboratory Tests 1221
Biomarkers 1221
Exercise Tests 1223
Six-minute Walk Test 1224
Coronary Arteriography 1224
Myocardial Ischemia 1224
Endomyocardial Biopsy 1224
Genetics Studies 1225

70. Systolic Heart Failure (Heart Failure with Reduced Ejection Fraction) **1228**
Kanu Chatterjee

Historical Perspective 1228
Ventricular Remodeling 1229
Functional Derangements and Hemodynamic Consequences 1235
Initial Treatment of Systolic Heart Failure 1235
Symptomatic Systolic Heart Failure 1237
Follow-up Evaluation 1245

71. Diastolic Heart Failure (Heart Failure with Preserved Ejection Fraction) **1251**
Kanu Chatterjee

Definition 1251
Epidemiology 1251
Pathophysiology 1252
Clinical Presentation 1255
Diagnosis 1256
Prognosis 1256
Treatment Strategies 1258
Future Directions 1261

72. Anemia in Patient with Chronic Heart Failure (Prevalence, Mechanism, Significance and Treatment) **1264**
James Prempeh, Barry M Massie

Overview of the Problem 1264

Prevalence of Anemia in Heart Failure Patients 1264
Mechanisms Underlying Anemia in Heart Failure Patients 1264
Prognostic Significance of Anemia in Heart Failure Patients 1265
Should Anemia be Treated in Heart Failure Patients? 1265
Safety Concerns Related to ESPS in A Variety of Anemic Patients 1266
Treatment of Anemia in Heart Failure Patients 1266

73. Hyponatremia and Congestive Heart Failure 1272
Anne Mani, David J Whellan

Mechanisms Causing Hyponatremia and Heart Failure 1274
Treatment of Hyponatremia 1276
Role of Diuretic Therapy in Hyponatremia 1276
Role of Vasopressin Receptor Antagonists in Hyponatremia 1277
Tolvaptan 1277
Lixivaptan 1278
Conivaptan 1279

74. Cardiorenal Syndrome: The Interplay between Cardiac and Renal Function in Patients with Congestive Heart Failure 1281
Nestor Mercado, J Thomas Heywood

Epidemiology of Chronic Kidney Disease in Patients with Heart Failure 1281
Prognosis of Worsening Renal Function 1282
Definition of the Cardiorenal Syndrome 1283
Pathophysiology of the Cardiorenal Syndrome 1286
Role of Decreased Cardiac Output 1286
Role of Elevated Central Venous Pressure 1287
Role of Evidence-based Therapies in Patients with Heart Failure and the Cardiorenal Syndrome 1288
Role of Ultrafiltration on Diuretic Resistance and the Cardiorenal Syndrome 1292
Treatment of the Cardiorenal Syndrome: An Approach to the Individual Patient 1292

75. Acute Heart Failure Syndromes 1298
Peter S Pang, Michel Komajda, Mihai Gheorghiade

Definition 1298
Epidemiology 1298
Patient's Characteristics 1298
Classification 1299
Pathophysiology 1300
Acute Heart Failure Syndromes Management 1301
Clinical Trials in Acute Heart Failure Syndromes 1306

76. Cardiopulmonary Exercise Testing and Training in Heart Failure 1312
Ileana L Piña

Normal Response to Exercise 1312
Exercise Response in Heart Failure 1313
Cardiopulmonary Exercise Testing 1314
Indications for CPX Testing in Heart Failure 1316
Exercise Training in Heart Failure 1318

77. Hibernating Myocardium 1323
Kanu Chatterjee

Historical Perspective 1323
Definition 1323
Pathophysiology 1324
Hibernation and Stunning: Clinical Prevalence 1325
Detection of Hibernating Myocardium 1325
Revascularization of Hibernating Myocardium and Changes in Ventricular Function 1328
Revascularization of Hibernating Myocardium and Changes in Prognosis 1328

78. Advanced Cardiac Therapies for End Stage Heart Failure: Cardiac Transplantation and Mechanical Circulatory Support 1334
Ashrith Guha, Frances Johnson

Identifying Candidates for Advanced Cardiac Therapies 1335
Heart Transplantation 1338
Mechanical Circulatory Support 1343

79. Palliative Medicine and End of Life Care in Heart Failure 1352
KellyAnn Light-McGroary

Epidemiology of Heart Failure 1352
Economic Impact of Heart Failure 1352
History of Palliative Care/Definitions 1353
Feasibility of the Use of Palliative Care in Heart Failure 1354
Issues of Prognostication 1355
Communication and Patient's Understanding of their Disease 1355
Suffering in End Stage Heart Failure 1357
Symptom Management in Heart Failure 1357
Management of Implantable Cardiac Devices 1360

Guidelines for Heart Failure 1366

Section 9
MYOCARDIAL AND PERICARDIAL DISEASES

80. Hypertrophic Cardiomyopathy 1377
M Fuad Jan, A Jamil Tajik

Definition 1377
Epidemiology and Genetic Considerations 1377
Pathology 1379
Pathophysiology 1381
Clinical Presentation 1387
Diagnosis 1390
Natural History 1400
Management 1402
Additional Points of Interest 1412

81. Dilated Cardiomyopathy 1424
Jalal K Ghali

Definition 1424
Epidemiology 1425
Pathology 1425
Etiology 1425
Prognosis 1430
Predictors of Mortality 1430

82. Restrictive and Obliterative Cardiomyopathies 1439
G Vijayaraghavan, S Sivasankaran

Restrictive Cardiomyopathies 1440

Tropical Endomyocardial Fibrosis (Davie's Disease) 1442
Right Ventricular Endomyocardial Fibrosis 1444
Left Ventricular Endomyocardial Fibrosis 1446
Loeffler's Endocarditis 1449
Hemochromatosis 1450
Idiopathic Restrictive Cardiomyopathy 1451
Other Forms of Cardiomyopathies 1452

83. Amyloid Heart Disease 1454
Eveline Oestreicher Stock, Dana McGlothlin

History of Amyloid 1454
Amyloidogenesis 1455
Overview of Cardiac Amyloidosis 1456
Classification of Amyloidosis 1456
Cardiac Amyloidosis 1456
Clinical Features of Cardiac Amyloidosis 1459
Treatment of Amyloid Cardiomyopathy 1464

84. Peripartum Cardiomyopathy 1473
Uri Elkayam, Nudrat Khatri, Mohamad Barakat

Definition 1473
Incidence 1473
Etiology 1473
Risk Factors 1473
Clinical Presentation 1473
Prognosis 1474
Treatment 1475
Labor and Delivery 1475

85. Chemotherapy-induced Cardiomyopathy 1479
Wassef Karrowni, Kanu Chatterjee

Classification of Chemotherapy-induced Cardiotoxicity 1479
Risk Factors 1480
Pathophysiology of Anthracycline-induced Cardiomyopathy 1480
Mechanism of Chemotherapy-induced Cardiac Dysfunction 1482
Diagnosis 1483
Monitoring 1484
Management 1484
Treatment 1486

86. Pericardial Diseases 1489
Masud H Khandaker, Rick A Nishimura

Acute Pericarditis 1489
Chronic Relapsing Pericarditis 1491
Pericardial Effusion and Pericardial Tamponade 1493
Constrictive Pericarditis 1496

87. Radiation-induced Heart Disease 1505
Wassef Karrowni, Kanu Chatterjee

Radiation-induced Pericardial Disease 1505
Radiation-induced Myocardial Disease 1506
Radiation-induced Coronary Artery Disease 1507
Radiation-induced Valvular Heart Disease 1508
Conduction System Disease 1509
Carotid and Other Vascular Disease 1509
Prevention 1509

88. Chagas Disease 1513
Diane C Kraft, Richard E Kerber

Life Cycle 1513
Transmission 1513
Epidemiology 1513
Clinical Manifestations 1513
Echocardiography 1516
Cardiac Magnetic Resonance Imaging 1516
Treatment 1516
Prevention 1517
Chagas Disease in the United States 1517

Section 10
PULMONARY VASCULAR DISEASE AND ADULT CONGENITAL HEART DISEASE

89. Pulmonary Arterial Hypertension 1521
Dana McGlothlin, David MaJure

Definitions and Classifications 1521
Pathophysiology and Epidemiology of Pulmonary Arterial Hypertension 1524
Diagnostic Evaluation 1528
Survival and Prognostic Factors of Pulmonary Arterial Hypertension 1535
Therapeutic Options for the Treatment of Pulmonary Arterial Hypertension 1536
Treatment Algorithm and Evaluating Response to Therapy 1541
Therapy of Decompensated Right Heart Failure in Pulmonary Arterial Hypertension 1542

90. Congenital Heart Disease in the Adult Patient 1550
Deepa Upadhyaya, Elyse Foster

Acyanotic Heart Disease 1551
Congenital Valvar Aortic Stenosis 1551
Supravalvar Aortic Stenosis and Subvalvar Aortic Stenosis 1554
Coarctation of the Aorta 1554
Right Ventricular Outflow Tract Obstruction 1557
Valvar Pulmonic Stenosis 1557
Subvalvar and Supravalvar Pulmonic Stenosis 1559
Atrial Septal Defects 1559
Ventricular Septal Defects 1562
Patent Ductus Arteriosus 1566
Other Acyanotic Lesions 1568
Ebstein's Anomaly 1568
Cyanotic Congenital Heart Disease 1570
Palliative Shunts 1571
Endocarditis 1572
Pregnancy and Contraception 1572
Tetralogy of Fallot 1572
Truncus Arteriosus 1577
D-transposition of the Great Arteries 1578
Congenitally Corrected Transposition of the Great Arteries 1582
Total Anomalous Pulmonary Venous Return 1583
Double-outlet Right Ventricle 1584
Tricuspid Atresia/Univentricular Heart 1586
Double-inlet Left Ventricle 1587
Hypoplastic Left Heart 1588
Eisenmenger's Syndrome 1589

Section 11
SECONDARY DISORDERS OF THE HEART

91. Alcohol and Arrhythmia 1595
Mary Gray

Direct Effects of Ethanol Exposure on Heart Cells and Tissues 1595

Ethanol Ingestion and the Normal Cardiac Conduction System 1595
Binge Drinking and Transient Clinical Arrhythmias—Holiday Heart 1596
Alcohol Consumption, Chronic Atrial Fibrillation and Atrial Flutter 1596
Alcohol Consumption and Sudden Cardiac Death 1597
Summary and Clinical Guidelines 1598

92. Insulin-resistance and Cardiomyopathy 1600
Dipanjan Banerjee, Ronald Witteles, Michael B Fowler
Epidemiology 1600
Diastolic Heart Failure and Insulin-resistance 1601
Pathophysiology 1602
Myocardial Energy Metabolism 1602
Metabolic Effects of Insulin Resistance—Energy Metabolism 1603
Other Metabolic Effects of Insulin-resistance 1604
Detection of Metabolic Effects of Insulin-resistance 1604
Structural Effects of Insulin-resistance 1605

93. Cardiac Complications of Substance Abuse 1613
Hugh H West
Magnitude of the Problem 1614
Substances of Abuse 1615
Marijuana, Tetrahydriocannabinol, Hashish 1624
Club Drugs: MDMA, GHB, Ketamine, Rohypnol 1625
Hallucinogenic Drugs 1627
Body Image Drugs 1627
Inhalants 1628
Narcotics 1629
Prescription and Over the Counter Drugs 1630
Alcohol and Tobacco 1631

94. HIV/AIDS and Cardiovascular Disease 1636
Jennifer E Ho, Priscilla Y Hsue
HIV and Coronary Heart Disease 1636
Surrogate Measures of Atherosclerosis 1641
Other Cardiovascular Conditions 1641

95. Systemic Autoimmune Diseases and the Heart 1648
Tamara Nelson, Jonathan L Halperin, Scott A Vogelgesang
Rheumatoid Arthritis 1648
Spondyloarthropathies 1651
Polymyositis-dermatomyositis 1653
Mixed Connective Tissue Disease 1654
Systemic Lupus Erythematosus 1654
Antiphospholipid Antibody Syndrome 1656
Coronary Arteritis 1656
Polyarteritis Nodosa 1656
Kawasaki Disease 1657
Churg-Strauss Vasculitis 1657
Wegener's Granulomatosis 1658
Giant Cell Arteritis 1658
Takayasu's Arteritis 1658

96. Cardiac Neoplastic Disease 1663
Elena Ladich, Naima Carter-Monroe, Renu Virmani
Clinical Symptoms 1663
Imaging Techniques 1665
Benign Cardiac Neoplasms 1667
Malignant Tumors 1675
Other Sarcomas 1681

97. Neurogenic and Stress Cardiomyopathy 1689
Hoang Nguyen, Ahsan Chaudhary, Kunal Mehtani, Stefanie Kaiser, Jonathan Zaroff
Neurogenic Cardiomyopathy 1689
Stress Cardiomyopathy 1693

98. Kidney and the Heart 1697
Mony Fraer
Definition 1697
Epidemiology 1697
Pathophysiology 1698
Cardiovascular Risk Factors in Chronic Kidney Disease 1698
Spectrum of Cardiovascular Disease in Chronic Kidney Disease 1700
Diagnostic Tests 1703
Principles of Treatment of Cardiovascular Disease 1704
Kidney Transplant Recipients 1704

99. Endocrine Heart Disease 1713
Aarthi Arasu, Umesh Masharani
Diabetes Mellitus 1713
Thyroid Disease 1716
Pituitary Disorders 1718
Adrenal Disorders 1720
Parathyroid Disorders 1722
Carcinoid Syndrome 1723

100. Cardiovascular Trauma as Seen by the Cardiologist 1729
Arthur Hill, Melvin D Cheitlin
History 1729
Classification and Physics of Traumatic Injury to the Cardiovascular System 1730
Classifying the Pathology of Cardiac Trauma 1731
Management of the Acutely Injured Patient with Thoracoabdominal Injury 1731
Intracardiac Injuries From Both Penetrating Wounds and Blunt Cardiac Injury 1737

101. Venous Thromboembolism and Cor Pulmonale 1750
Jorge Velazco, Christopher Spradley, Bernardo Menajovsky, Alejandro C Arroliga
Venous Thromboembolism 1750
Cor Pulmonale 1763

Section 12
RELEVANT ISSUES IN CLINICAL CARDIOLOGY

102. Noncardiac Surgery in Cardiac Patients 1773
Gabriel Gregoratos, Ameya Kulkarni
Preoperative Cardiac Risk Assessment 1773
Preoperative Diagnostic Testing 1778
Preoperative Risk Mitigation Strategies 1780
Intraoperative Management 1786
Management of Patients with Implanted Electronic Devices 1787

Postoperative Management 1788
Appendix 1789

103. Gender and Cardiovascular Disease **1798**
Susan Zhao, Rita Redberg

Prevalence of IHD in Women 1798
Identification and Management of IHD Risk Factors in Women 1799
Assessment of Symptoms and Myocardial Ischemia in Women 1802
Management of IHD in Women 1806
Heart Failure in Women 1809
Sex and Cardiac Arrhythmias 1812
Call for More Sex-specific Research 1813

104. Overview of the Athlete's Heart **1818**
Aaron L Baggish, Paul D Thompson

Historical Perspective 1818
Exercise Physiology and the Athlete's Heart: Overview 1818
Exercise-induced Cardiac Remodeling 1819
Issues Relevant to the Cardiovascular Care of Athletes 1821

105. Cardiovascular Aging **1829**
John A Dodson, Mathew S Maurer

Age-related Changes 1830
Clinical Syndromes 1834
Special Issues 1839

Section 13
PREVENTIVE STRATEGIES FOR CORONARY ARTERY DISEASES

106. Pathophysiology of Atherothrombosis **1847**
PK Shah

Sites of Predilection for Atherosclerosis 1847

107. Dyslipidemia **1856**
Mary Malloy, John Kane

Lipid Transport and Lipoprotein Metabolism 1856
Diagnosis of the Dyslipidemias 1859
Hyperlipoproteinemia 1859
Hypoalphalipoproteinemia 1863
Other Management Considerations 1863

108. Smoking and Air Pollution **1873**
Joaquin Barnoya, Ernesto Viteri, Stanton A Glantz

Epidemiology of Smoking and Exposure to Second-hand Smoke 1874
Active Smoking and Cardiovascular Disease 1874
Second-hand Smoke and Cardiovascular Disease 1875
Low-tar ("Light") Cigarettes 1876
Pathophysiology of Tobacco Smoke and Cardiovascular Disease 1876
Smoking Cessation 1879
Smoke-free Environments and Their Effect on Heart Attack Admissions 1883
Similar Effects and Mechanisms of Particulate Air Pollution 1883
Cardiologists as Tobacco Control Advocates 1884

109. Exercise and Rehabilitation **1890**
Lisa Bauer, Patrick McBride

Exercise: Definitions 1890
Exercise: Recommendations 1891
Responses to Exercise 1891
Benefits of Exercise 1891
Exercise Capacity 1891
Inflammation and Endothelial Function 1891
Safety Considerations 1892
Cardiac Rehabilitation Definition and Goals 1892
Cardiac Rehabilitation Phases 1892
Cardiac Rehabilitation Core Components 1893
Clinical Population Considerations 1895
Referral 1895
Reimbursement Issues 1895

Section 14
PREVENTIVE STRATEGIES FOR OTHER CARDIOVASCULAR DISEASES

110. Prevention of Heart Failure **1899**
Clay A Cauthen, WH Wilson Tang

Introduction 1899
Staging of Heart Failure 1899
Future Perspectives 1905

111. Stroke: Prevention and Treatment **1908**
Harold P Adams

Introduction 1908
Definitions 1908
Stroke as a Symptom 1909
Prevention 1916
General Acute Treatment 1919
Treatment of Acute Ischemic Stroke 1920
Treatment of Acute Hemorrhagic Stroke 1922
General in-hospital Care 1923
Rehabilitation 1924

112. Rheumatic Fever **1927**
V Jacob Jose

Pathogenesis 1927
Epidemiology 1928
Diagnosis of Rheumatic Fever 1928
Clinical Features 1929
Treatment 1931
Residual Heart Disease 1933
Management of Chorea 1933

Section 15
EVOLVING CONCEPTS

113. The Genomics of Cardiovascular Disease **1937**
Samir B Damani, Eric J Topol

A Genomic Primer 1937
Intermediate Phenotypes 1940
Coronary Artery Disease 1941
Arrhythmias 1942
Cardiovascular Pharmacogenomics 1943

SNP Profiling Studies 1946
Future Directions 1947

114. Cardiovascular Pharmacogenetics 1951
Deepak Voora, Victor J Dzau, Geoffrey S Ginsburg

Principles of Pharmacogenetics 1951
hMG-CoA Reductase Inhibitors 1953
Thienopyridines 1956
Aspirin 1958
Warfarin 1958
Diuretics 1960
Beta-blockers 1960
Antiarrhythmic Drugs 1962
Future Directions 1963

115. Preventing Errors in Cardiovascular Medicine 1969
Robert M Wachter

Modern Approach to Patient Safety 1969
How to Improve Patient Safety? 1970
Communication and Culture 1971
Learning from Mistakes 1972
Creating a Safe Workforce 1973
Preventing Diagnostic Errors 1973
What Can Patients do to Keep Themselves Safe? 1973
Changing Policy Context for Patient Safety 1973

116. Economics in Cardiovascular Medicine 1976
Paul A Heidenreich

Cost of Cardiovascular Care 1976
Trends in Health Expenditures (US versus Non-US) 1976
CV Contribution to the Rising Cost of Care 1977
Variation in Resource Use 1977
Resource Scarcity and Value 1977
Basic Concepts of Health Economics 1978
Benchmarks for Cost-effectiveness 1979
Evaluating Uncertainty 1979
Perspective 1980
Efficiency 1980
Government's Use of Cost-effectiveness 1980
Cost-effectiveness of Individual Treatments and Strategies 1981
Cost-effectiveness of Quality Improvement Interventions 1982
Future Estimates of the Cost of Heart Disease 1983

117. Stem Cell Therapy in Cardiology 1986
Franca S Angeli, Yerem Yeghiazarians

Stem Cell 1986
Skeletal Myoblast 1989
Adipose Tissue Derived Stem Cells 1989
Cardiac Stem Cells 1989
Fetal and Umbilical Cord Blood Cells 1989
Induced Pluripotent Stem Cells 1991
Stem Cell Clinical Trials 1991
Conclusion and Future Directions 1997

118. Gene Therapy and Angiogenesis 2003
Matthew L Springer

Gene Therapy Overview 2003
Basic Concepts of Angiogenesis 2007
Angiogenic Protein Therapy 2011
Angiogenic Gene Therapy 2011
Gene Therapy for Chronic Heart Failure 2014

119. Sleep and the Heart 2020
Tomas Konecny, Virend Somers

Physiologic Sleep 2020
Effects of Non-rapid Eye Movement Sleep on Cardiovascular Physiology 2020
Effects of Rapid Eye Movement Sleep on Cardiovascular Physiology 2020
Arousal 2021
Arrhythmias and Sleep 2021
Sleep Disordered Breathing 2022
Diagnosis of Sleep Apnea 2026
Treatment of Obstructive Sleep Apnea 2027
Central Sleep Apnea 2028

120. Integrative Cardiology: The Use of Complementary Therapies and Beyond 2031
Kevin Barrows

Non-conventional Therapies and Cardiology 2031
What Is Integrative Medicine? 2031
What Is Integrative Cardiology? 2032
Lifestyle Heart Trial 2032
What Other Integrative Medicine Therapies are Effective for Cardiovascular Conditions? 2032
Dyslipidemia 2032
Hypertension 2037
Coronary Artery Disease 2040
Heart Failure 2044
Botanical Medicines with Adverse Cardiovascular Effects 2047

Section 6

VALVULAR HEART DISEASES

Chapter 55

Aortic Valve Disease

Blase A Carabello

Chapter Outline

- Aortic Stenosis
  - Etiology
  - Pathophysiology of Aortic Stenosis Induced Left Ventricular Pressure Overload
  - Natural History and the Role of Symptoms
  - Physical Examination
  - Diagnosis
  - Treatment
  - Special Cases
  - Summary
- Aortic Regurgitation
  - Etiology
  - Pathophysiology
  - Natural History and the Role of Symptoms
  - Physical Examination
  - Diagnosis
  - Treatment

INTRODUCTION

Aortic valve disease is prevalent throughout the world and affects about 5,000,000 Americans. Typically progressive, aortic valve disease eventually leads to symptoms, morbidity and death if severe and left untreated. Fortunately, proper timing of corrective valve replacement (or repair) may add decades of quality life to affected patients and understanding of the natural history, and warning symptoms and signs of severe aortic valve disease help time corrective surgery and are crucial for proper patient management. This chapter reviews the etiology, pathophysiology and clinical presentation of aortic valve disease, integrating those data into best modern diagnosis and therapy.

AORTIC STENOSIS

ETIOLOGY

Calcific Aortic Stenosis

Though calcific aortic stenosis (AS) was once considered a degenerative disease caused by wear and tear on the valve, our understanding of the pathways leading to valve calcification and stenosis have matured considerably in the past 15 years. Otto et al. noted that the histology of the early lesion of AS resembled that of the plaque of atherosclerosis, a disease that also leads to lesion calcification (Fig. 1).[1] Subsequent investigations found similarity between the risk factors for developing AS and the risk factors for coronary artery disease (CAD) including hypertension, diabetes, hyperlipidemia, the metabolic syndrome and smoking.[2-6] These observations about the atherosclerotic properties of AS led to the hypothesis that statin drugs, so effective in reducing mortality from CAD, might also retard the progression of AS. While initial observational studies were encouraging, randomized trials examining potent doses of different statins in severe, moderate and mild to moderate disease failed to show benefit from statin administration in slowing the rate of progression of AS.[7-9] These results are not so surprising considering the differences between AS and CAD. CAD kills from plaque rupture leading to sudden vessel occlusion and myocardial infarction while AS causes stiffening and immobility of the valve. More importantly, despite the failure of statins to retard the disease, the recognition of AS as an active disease fostered exciting research into its causes, potentially leading to new therapeutic targets at preventing AS or slowing its progress.

Hemodynamic shear stress likely plays a role in initiating AS since calcium deposition is greatest on the aortic side of the valve where shear stress is the highest.[1] Additionally, it is rare for all three aortic leaflets to be identical in size, and size difference likely causes inhomogeneity of stress across the valve, lending further credence to shear as one factor involved in the pathogenesis of AS.[10,11] It is clear that inflammation also plays a major role in valvular calcium deposition. Toutouzas, Yacoub et al.[12] found substantial thermal heterogeneity in AS lesions. That some areas of stenotic valves at the time of surgery were "hot" indicated that an active inflammatory process was ongoing in the diseased valve. Increased lesion temperature correlated with lymphocyte infiltration, calcium deposition and the presence of cytokines TNFα and IL-6, lending additional support to the concept that AS is at least in part, an inflammatory disease. Elevated superoxide in experimental AS added further evidence for active inflammation as part of the process,[13] possibly due in part to endothelial dysfunction and dysregulation of nitric oxide synthesis and release.[14,15] Other contributors to the inflammatory cascade include activation of the renin-angiotensin system (RAS),[16] release of transforming growth factor-beta (TGF-β) from myofibroblasts and stimulation of

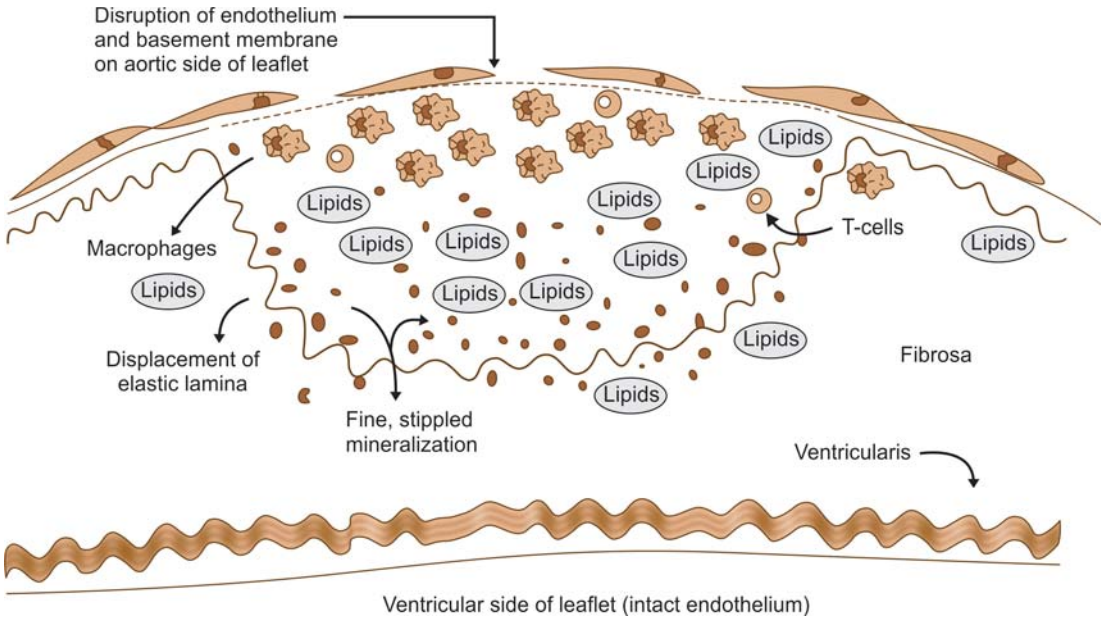
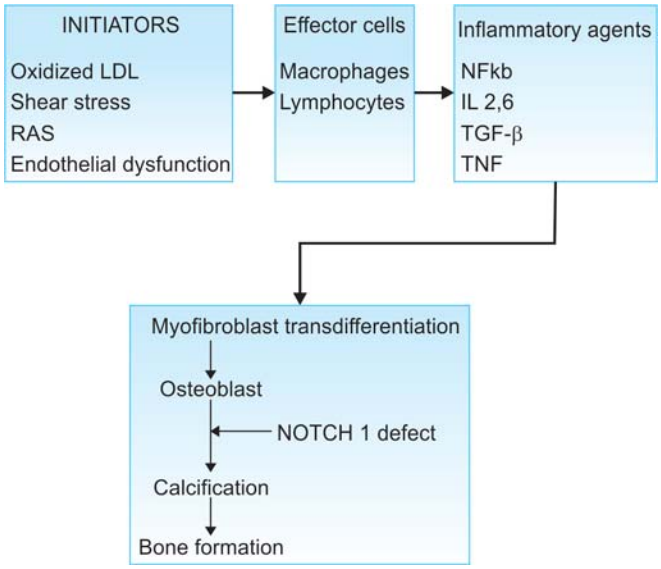


FIGURE 1: A diagram of the early lesion in AS is shown. Infiltration with lipids and inflammatory cells similar to the plaque of coronary disease is a prominent feature. (*Source:* Otto CM, Kuusisto J, Reichenbach DD, et al. Characterization of the early lesion of 'degenerative' valvular aortic stenosis: histological and immunohistochemical studies. Circulation. 1994;90:844-53, with permission)

nuclearfactor-kappa B (NF-κB).[17-20] Once the inflammatory cascade is initiated myofibroblasts transdifferentiate in osteoblasts leading to calcium deposition and bone formation.[21] Indeed lamellar bone, not just calcification is found in many stenotic aortic valves. Calcification is further facilitated by abnormalities of NOTCH1, a gene that represses calcification.[22] The NOTCH1 abnormality may also responsible for causing congenital bicuspid aortic valve, a condition leading to calcification of the valve 10–20 years before it is usually seen in patients born with a normal tricuspid aortic valve. Exactly how all of these abnormalities work in concert to cause valvular calcification and bone formation is unclear. One possible schema is shown in Flow chart 1.

FLOW CHART 1: A schema a potential cascade of events leading to aortic valve calcification is shown



Rheumatic Disease

Rheumatic fever has become rare in the developed world and thus rheumatic heart disease has become a rare cause of AS. However, worldwide, rheumatic heart disease is a leading cause of aortic valvular inflammation leading to AS. Since rheumatic heart disease virtually always affects the mitral valve, the diagnosis of rheumatic AS should not be made in the presence of an anatomically normal mitral valve.

Other Causes

Congenital aortic cusp fusion resulting in AS is almost always diagnosed during childhood but occasionally the diagnosis is first made in the adult patient. Other rare causes of AS include chest irradiation and ochronosis.

PATHOPHYSIOLOGY OF AORTIC STENOSIS INDUCED LEFT VENTRICULAR PRESSURE OVERLOAD

Aortic stenosis is the quintessential example of pressure overload. As the aortic orifice narrows, the left ventricle (LV) must generate increased force to drive blood past the narrowing, generating a pressure gradient between LV and aorta. This gradient is small until the aortic orifice becomes less than one half its normal 3 cm^2 orifice area. However, further narrowing causes a progressive and geometric increase in the transaortic valve gradient (Table 1). The gradient that develops between LV and aorta represents the pressure overload required for the LV to perform its task as a pump.

Decades ago Grossman et al. postulated that pressure overload in some way informed the myocardium to generate sarcomeres laid down in parallel thereby increasing myocyte thickness in turn increasing left ventricular wall thickness [concentric hypertrophy, left ventricular hypertrophy (LVH)].[23] By the law of Laplace where stress (σ) = P x r/2th, and P = LV

TABLE 1

The relationship of gradient to AVA at a cardiac output of 6 l/min

AVA cm^2	*Mean gradient (mm Hg)*
3.0	4
2.0	9
1.5	16
1.0	36
0.8	56
0.6	100

pressure, r = LV radius and th = LV thickness, increased pressure in the numerator can be offset by increased wall thickness in the denominator, thereby maintaining normal systolic wall stress (afterload). Since ejection performance declines as afterload increases, concentric LVH has been considered a compensatory mechanism, allowing maintenance of normal afterload and ejection fraction. While there is no doubt that LVH develops in response to a pressure overload, the compensatory nature of LVH has been debated for decades.

Growth and Physiologic versus Pathologic LVH

Although some myocyte replication occurs after birth, most myocytes are terminally differentiated so that heart growth occurs primarily through hypertrophy. Considering that man's body weight increases 20 fold from infancy to adulthood and the heart has approximately a similar increase in weight, LVH is in fact necessary for life. Similarly athletes' hearts may develop substantial LVH, yet there is no evidence of a deleterious effect of what is apparently physiologic LVH.[24-27] But these are natural states. The question remains whether LVH that develops in response to pathologic conditions (such as AS) is compensatory or deleterious. Clearly, some properties of LVH are disadvantageous. It is well established that subendocardial coronary blood flow is reduced in LVH as is coronary flow reserve.[28-30] Additionally, LVH due to pressure overload is almost invariably associated with diastolic dysfunction in part due to decreased distensibility of a thickened LV wall and in part due to increased collagen content.[31-32] Thus, LVH may lead to myocardial ischemia and heart failure, obviously producing negative outcomes.[33] On the other hand, LVH or at least increased wall thickness may in some cases be truly beneficial. The clearest case for benefit is in patients who develop concentric remodeling without LVH in response to AS.[34] Such patients have an increase in wall thickness at the same time left ventricular radius decreases so that an actual increased LV weight does not occur. For such remodeling to occur the basic process of increasing myocyte sarcomeres in parallel is almost surely present, but apparently the negative aspects of LVH are muted or absent. Thus, concentric remodeling allows for normalization of afterload, a beneficial effect. Further in some animal models of pressure overload where LVH is prevented from occurring by genetic manipulation, mortality is increased compared to controls in which LVH does develop.[35] In a large animal model of progressive AS, it was only when LVH was adequate to normalize wall stress that contractility at the sarcomere level was normal.[36] However, in other cases, LVH is clearly detrimental. In the presence of coronary disease, a frequent comorbidity of AS, LVH increases mortality several fold.[33] In some reports the presence of LVH reduces LV ejection fraction even though it compensates for the pressure overload[34] and although proposed as a mechanism to maintain normal afterload, in fact, afterload is excessive in most patients with AS and advanced disease.[37] In still other cases, the amount of LVH present seems in excess of that needed to compensate for the pressure overload present.[38] Patients with this degree of hypertrophy may still suffer many of the negative consequences of LVH even though the afterload is subnormal.

It is often assumed that there is a transition from compensatory LVH to LVH with heart failure, but the mechanism for such a transition has never been fully elucidated. There is in fact progressive fibrosis and myocyte loss as cardiac function diminishes supporting the concept of a transition to failure.[39-41] However, there is no unanimity on this subject. Others have proposed densification of intra-myocyte microtubules producing an internal stent impeding sarcomere shortening.[42] Abnormalities that develop in calcium handling are other potential mechanisms leading to LV dysfunction,[43] while still another mechanism is repeated bouts of subendocardial ischemia potentiated by reduced coronary blood flow as noted above.[44] A recent observation that there are differences in gene expression early in the development of LVH between subjects who do versus those that do not go on to develop failure suggest that perhaps there are two different LVH pathways, one that leads to contractile dysfunction and another one that does not, rather than a transition from one to the other.[45]

In summary, the pressure overload of AS causes the development of LVH. The LVH may be beneficial by normalizing LV afterload, permitting normal LV ejection performance. However, in many cases LV is not adequate to normalize systolic wall stress, afterload increases and ejection fraction falls. Whether LVH does or does not normalize afterload, LVH often has deleterious consequences. These include myocardial ischemia, diastolic dysfunction and decreased LV contractility, all potentiating the morbidity and mortality of AS.

NATURAL HISTORY AND THE ROLE OF SYMPTOMS

Calcific AS is an invariably progressive disease, but on the other hand the rate of progression from patient to patient is extraordinarily variable. Progression in the decrease in valve area may be less than 0.1 cm^2 to as much as 0.3 cm^2 per year, while gradient may increase from less than 5 mm Hg to as much as 20 mm Hg per year.[46] As shown in Figures 2A and B, the survival is nearly normal as long as the patient is truly asymptomatic.[47,48] However, once the classic symptoms of angina, syncope or the symptoms of heart failure develop the mortality rate soars to as much as 2% per month so that 3 years after the onset of symptoms, 75% of patients with AS will have died unless the aortic valve is replaced.

Angina

While many patients with AS also have CAD, angina occurs frequently in AS patients without obstructive CAD and about 35% of AS patients have angina as their presenting complaint.[49] The mechanism of angina in such patients is not entirely clear.

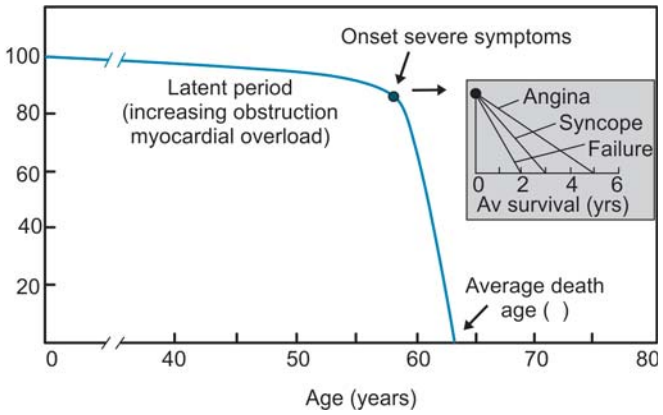


FIGURE 2A: The natural history of AS, as compiled primarily from autopsy studies performed in the sixties shows that survival is nearly normal until the classic symptoms of AS develop at which time mortality increases sharply. (*Source:* Ross J Jr, Braunwald E. Aortic stenosis. Circulation. 1968;38(suppl. 1):61-7, with permission)

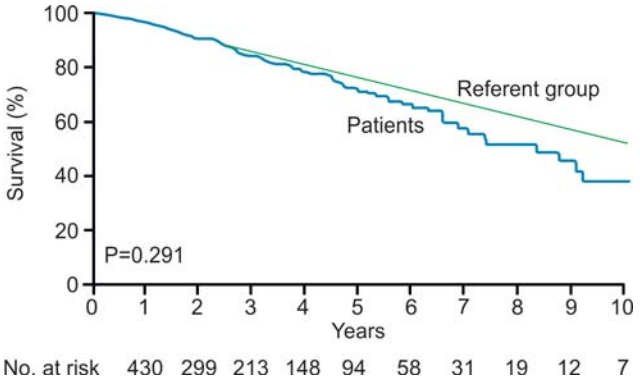


FIGURE 2B: The relative benignity of asymptomatic AS is confirmed 40 years later from follow-up of 622 patients with echo-proven severe AS. Survival is slightly but not significantly worse than an age-matched well population. (*Source:* Ross J Jr, Braunwald E. Aortic stenosis. Circulation. 1968;38(suppl. 1):61-7, with permission)

The LVH reduces coronary blood flow reserve[29,30] and wall stress, a key determinant of myocardial oxygen consumption, is increased in many cases as noted above and both factors would contribute to causing angina. However, these changes occur in most patients with AS including the many who do not have angina and no specific valve area or degree of LVH predicts the onset of angina. In fact, the best predictor of whether or not an AS patient will have angina (in the absence of CAD) is the ratio of the systolic ejection period (ischemic debt) to diastolic filling period (debt repayment).[50]

Syncope

Approximately, 15% of AS patients present with syncope. The exact mechanism of syncope in AS is uncertain. Ohms Law as it pertains to the cardiovascular system is BP = CO x TPR, where BP = blood pressure, CO = cardiac output and TPR = total peripheral resistance. The classic explanation is that an obligate fall in total peripheral resistance during exercise cannot be met by the normal increase in cardiac output, forcing a fall in blood pressure, impairing cerebral perfusion, resulting in syncope. Indeed when syncope in AS occurs, it is almost always during exercise and exercise-induced falls in blood pressure have been noted in patients with AS.[51,52] Another proposed mechanism is that high LV pressure generated during exercise leads to a vasodepressor response and thus to syncope. Still another possible cause is that exercise-induced arrhythmia triggers a fall in blood pressure.[53]

Heart Failure

Dyspnea and other symptoms of heart failure are the most common presenting complaints from AS patients, occurring in about 50% of patients. As noted above, AS may cause both systolic and diastolic dysfunction. Systolic dysfunction stems both from afterload excess (when remodeling fails to compensate the pressure overload) and from contractile dysfunction. Diastolic dysfunction accrues from increased chamber stiffness due to increased wall thickness and also due to increased myocardial stiffness from increased collagen content and crosslinking that develops as LVH becomes severe. The LV dysfunction in turn leads to the typical symptoms of heart failure, i.e. dyspnea on exertion, orthopnea and paroxysmal nocturnal dyspnea. As the syndrome progresses, pulmonary hypertension may ensue leading to edema and ascites.

PHYSICAL EXAMINATION

Palpation of the carotid arteries finds their upstroke delayed in timing and reduced in volume (parvus et tardus Fig. 3).[54] Palpation of the apical beat usually finds it in its normal position but increased in duration, width and forcefulness. Palpation of a powerful apical beat simultaneously with palpation of a weakened carotid pulse gives an important clue that obstruction (AS) lies between the LV and the carotid arteries.

Auscultation finds an S_1 that is usually normal in intensity. An S_2 is often soft and single as the diseased aortic valve, neither opens nor closes, well leaving only the soft P_2 component of S_2. In cases of severe AS with LV dysfunction (or when left bundle branch block accompanies LVH), S_2 may be paradoxically split. An S_4 indicative of reduced LV compliance from LVH is usually present. The murmur of AS is often the physical finding that alerts the practitioners for the presence of the disease. It is a harsh systolic ejection murmur heard best in the aortic area, radiating to the neck. In mild to moderate disease, it typically peaks in mid-systole and is often accompanied by a thrill. As the disease becomes more severe, the murmur may lessen in intensity (as aortic flow diminishes) and the murmur reaches its peak intensity progressively later in systole.[49]

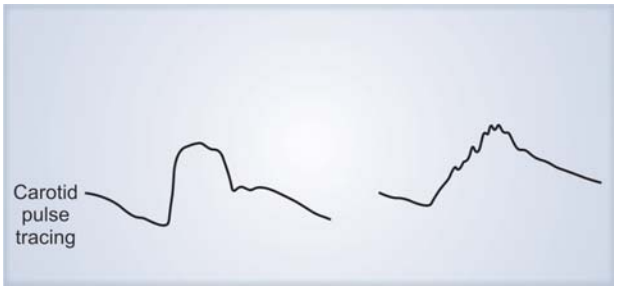


FIGURE 3: The normal carotid upstroke (left) is compared to the classic delayed and reduced (parvus et tardus) carotid upstroke of severe AS (right). [*Source:* Modified from reference 54)

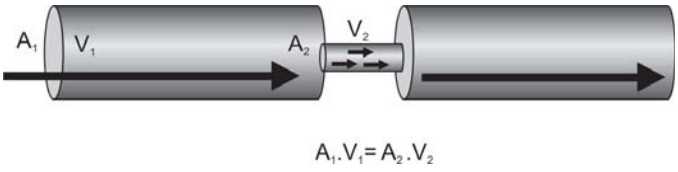


FIGURE 4: A schematic explaining the continuity equation is shown. As the area at the aortic valve decreases from stenosis, velocity must increase to maintain equal (continuous) flow on both sides of the valve. [*Source:* Modified from Carabello (Reference 54)]

DIAGNOSIS

Electrocardiograph and Chest X-Ray

The electrocardiograph usually demonstrates the voltage criteria for the presence of LVH but the absence of this finding does not rule out the diagnosis of severe AS. The chest X-ray may show a boot shaped cardiac silhouette indicative of LVH. In extreme cases of aortic valve calcification, calcium may be seen deposited in the valve in the lateral view.

Echocardiography

The echocardiogram is the modality of choice in diagnosing AS and in assessing its severity. The echocardiogram can evaluate the amount of LVH present, the effect of AS on LV systolic and diastolic function, estimate left atrial size and pulmonary artery pressure, and image the reduced movement of the aortic valve. Echocardiography can also estimate the amount of valvular calcification which can in turn be used as a prognostic factor in the progression of the disease.[55]

Importantly, echocardiography can also fairly precisely estimate the transvalvular gradient and the aortic valve area (Fig. 4),[54] criteria for basing disease severity as categorized in Table 2.[56] By using the modified Bernoulli formula,[57] the velocity (v) of the blood stream as it accelerates through the narrowed aortic valve can be used to calculate the transvalvular gradient (G) as $G = 4v^2$. The continuity equation that assumes that blood flow must be equal (continuous) on both sides of the valve can be used to calculate the valve area where F = A x V, and F = flow, A = area and V = velocity. $A_1 \times V_1 = A_2 \times V_2$ where, A_1 is the area of the aortic outflow tract, V_1 = the outflow tract velocity, A_2 = aortic valve area and V_2 = aortic valve velocity. A_2 (aortic valve area) = $A_1 \times V_1/V_2$. In some cases, the aortic orifice can be visualized en fosse and aortic valve area can be directly planimetered using echocardiography, multislice CT scanning or magnetic resonance imaging.[58-60] However, Doppler interrogation at echocardiography remains the noninvasive gold standard for assessing AS severity.

Calcium Scoring

Non-rheumatic AS is an inflammatory disease that leads to progressive calcification and stiffening of the valve leaflets. Not surprisingly the amount of calcium deposited in the valve gives a clue to AS severity. Both Cardiac CT and electron-beam imaging have been used successfully to help quantify the amount of calcium in the valve, which in turn can be helpful in predicting the rapidity of disease progression.[61,62] However, aortic valve calcium scoring is not universally accepted as a surrogate for other imaging studies in assessing AS severity.[63]

Natriuretic Peptides

Natriuretic peptides, such as brain natriuretic peptide (BNP) and proBNP, are increased with LVH as the LV resorts to preload reserve to overcome afterload excess. There are significant correlations between natriuretic peptides and AS severity and symptoms.[64-67] Further, asymptomatic patients with higher BNP levels become symptomatic sooner than similar patients with lower BNP levels.[68] In addition, BNP levels have been found predictive of outcome in asymptomatic AS patients.[69] Unfortunately no level of BNP elevation is universally agreed upon as a danger level indicating an impending bad outcome.[70] Thus natriuretic peptides are likely to become useful in monitoring the patient with AS, but only after prospective studies arrive at specific levels indicating when the patient is approaching the need for valve replacement.

Cardiac Catheterization

In most cases, echocardiography can accurately diagnose both the presence and severity of AS making or obtaining invasive hemodynamic data unnecessary. However, in some cases, doubt about the diagnosis may remain after noninvasive testing, either due to difficult patient imaging or because the assessment of AS severity from various echo data and from the physical examination are discordant. In such cases, simultaneous recording of LV pressure, aortic pressure and cardiac output can be related through the Gorlin formula to calculate the aortic valve area.[71] In invasive evaluation the directly measured transvalvular gradient is converted into flow velocity to calculate valve area. As with the echocardiographic calculation F = A x V and A = F/V. Using the Gorlin formula, AVA = CO/44.3 $\sqrt{-P_1 - P_2}$. Where, CO = cardiac output, P_1-P_2 = equals the mean transvalvular gradient. Since hemodynamic evaluation is employed only when there is doubt about the diagnosis, it is imperative in such cases that special attention be paid to accurate pressure and cardiac output measurements.[72,73]

TABLE 2

Classification of the severity of aortic stenosis in adults

	Aortic stenosis		
Indicator	*Mild*	*Moderate*	*Severe*
Jet velocity (m per second)	Less than 3.0	3.0–4.0	Greater than 4.0
Mean gradient (mm Hg)	Less than 25	25–40	Greater than 40
Valve area (cm^2)	Greater than 1.5	1.0–1.5	Less than 1.0
Valve area index (cm^2 per m^2)			Less than 0.6

Medical Therapy

There is no effective chronic medical therapy for AS. No therapies have been successful in retarding progression of the disease in asymptomatic patients and for symptomatic patients. Aortic valve replacement (AVR) is life saving and is the only long-term therapy that affects outcome. Diuretics can be used cautiously to treat heart failure acutely. Nitrates can be used to treat angina episodically.

AVR for Symptomatic AS

Figure 5 demonstrates the dramatic difference in survival for symptomatic patients undergoing AVR versus those who refused surgery.[74] Nonetheless it is estimated that only about one half of patients with severe AS ever undergo AVR.[75] The reasons for this lack of treatment include the absence of symptoms, judgment that the patient is too high surgical risk, refusal by the patient to undergo the procedure or lack of surgical referral by non-surgeon health care providers.

The advent of percutaneously and/or transapically placed stented aortic valves [transcutaneous aortic valve implantation (TAVI)] represents a sea change in the therapy for patients deemed too high risk for standard AVR.[76] In this procedure a stented valve is delivered into the aortic annulus percutaneously or transapically after the calcified native valve is pushed aside by prior balloon dilatation. As shown in Figures 6A to D, the survival benefit is striking.[77] The eventual scope of this less invasive method for AVR will depend upon the durability of the valves and technical advances in valve delivery, but it almost certainly will have a substantial impact.

AVR in Asymptomatic AS

As shown in Figure 2, asymptomatic patients with AS have an excellent prognosis until symptoms develop. Still there is small but definite risk of sudden death in such patients of about 0.5% per year.[56] In addition, some patients progress from the asymptomatic phase to developing symptoms to sudden death in a matter of a few months.[78] This small but definite risk raises the issue of performing AVR in asymptomatic patients where the risk of surgical mortality is also low, approximately 1% or less[79] in expert hands. Thus, there is a small but definite risk of waiting for symptoms and a small but definite risk of proceeding to AVR, a situation with no clear cut proper course of action. A reasonable solution to this conundrum is to identify a high risk group of asymptomatic AS patients for whom AVR is preferable to waiting for symptoms to develop. Several data lend themselves to implementing this strategy. First, when transvalvular jet velocity exceeds 4.0 m/sec, there is a 70% likelihood that symptoms will develop in 2 years;[80] if jet velocity exceeds 5.5 m/sec, there is a 70% chance that symptoms will develop in 1 year (Fig. 7).[81] Thus, jet velocity helps to identify a group at high risk for developing symptoms thus needing AVR. Once AS severity reaches the benchmarks noted above, increased patient surveillance is advisable and it is arguable that there is little point in waiting for the nearly inevitable onset of symptoms to perform AVR.

Figure 2 also demonstrates that the onset of symptoms is a crucial demarcation in the natural history of the disease and in some cases the advent of symptoms is obvious. However, in other cases patients may deny symptoms or fail to recognize their onset. In this regard, formal exercise testing of asymptomatic patients with severe AS may help to uncover latent symptoms or detect a failure of blood pressure to rise normally with exercise. While symptomatic patients with AS should never undergo exercise testing, asymptomatic patients will exercise in the course of their daily activities, and therefore an observed episode of exercise may be very helpful in assessing true symptomatic status and to help gauge what level of activity is safe for the AS patient to engage in. Patients who fail to achieve their age-predicted exercise level or fail to show a normal rise in blood pressure have a high likelihood of requiring AVR in the next calendar year.[82-84] Thus very high jet velocity, declining LV function, heavy valve calcification, a rapid increase in gradient, severe LVH and a rising BNP level are associated with a high risk of symptom development and might be indication for early AVR. All of the foregoing must be tempered by patient preference and the existence of comorbidities that alter the risk and benefit of AVR.

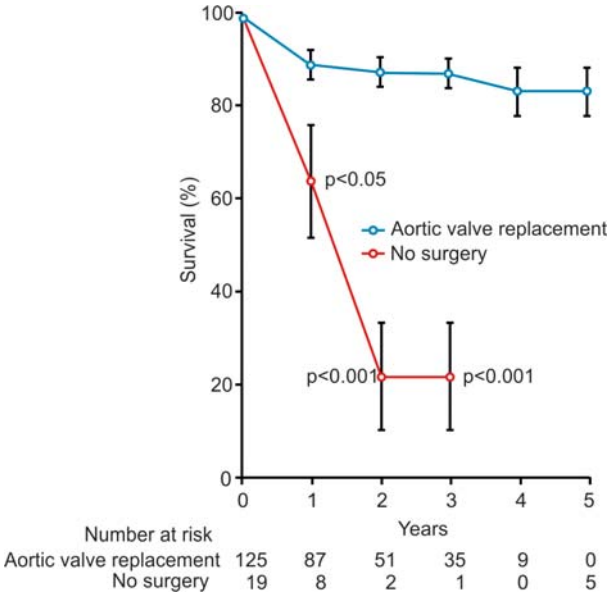
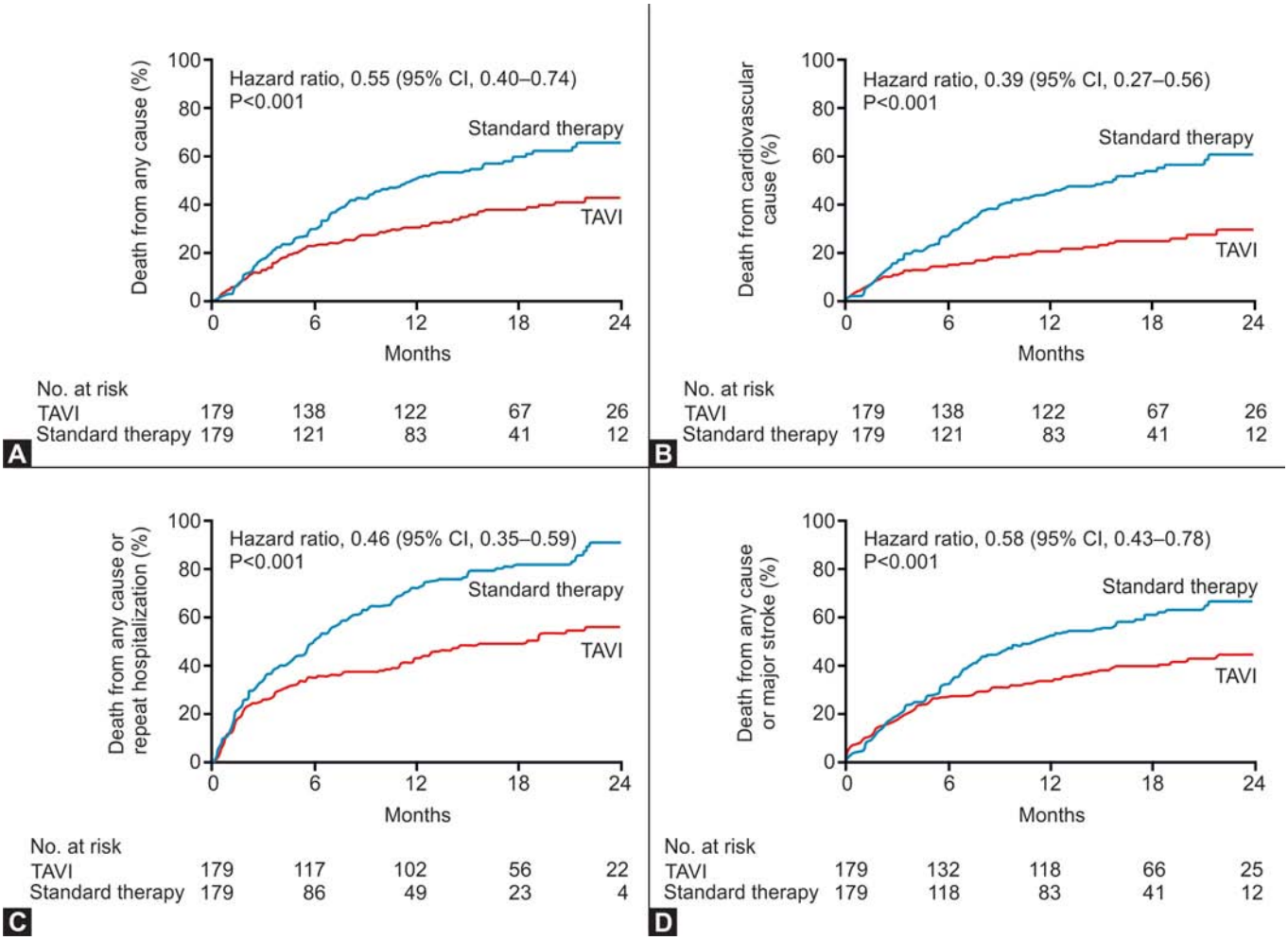


FIGURE 5: The large survival benefit is shown for patients with severe symptomatic AS who underwent AVR versus those who refused surgery. (*Source:* Schwarz F, Baumann P, Manthey J, et al. The effect of aortic valve replacement on survival. Circulation. 1982;66(5):1105-10, with permission)

SPECIAL CASES

Low Gradient, Low Ejection Fraction AS

Ejection fraction (EF) is dependent upon preload, afterload and contractility. Although LVH may normalize afterload, helping to maintaining a normal EF, in many cases of AS afterload is increased, reducing EF. When afterload excess is responsible for reduced EF, EF returns to or toward normal following AVR[85,86] and the risk of AVR is relatively low. However, as shown in Figure 8, in some cases EF is reduced below that which would be expected from afterload alone; in such cases there is profound muscle damage and reduced contractility. Reduced contractility in turn reduces LV stroke volume producing a low transvalvular gradient. Thus, the syndrome of low EF, low



FIGURES 6A TO D: Four different analyzes of survival are shown for very high risk AS patients who underwent transcutaneous aortic valve implantation (TAVI) versus medical therapy in a randomized trial. The benefit from TAVI is striking. [*Source:* Modified from Leon et al. (Reference 77)]

gradient AS, defined as an EF of less than 0.30 and a mean transvalvular gradient less than 30 mm Hg, is one of severe myocardial dysfunction. Concordant with LV dysfunction is the poor prognosis that attends the syndrome.[85,87,88] Whereas the average operative risk for symptomatic patients with AS is about 2.5%, the operative risk for low EF, low gradient AS ranges 10–40%. Prognosis is better for patients with inotropic reserve (> 20% increase in stroke volume with dobutamine infusion) and for patients with a mean gradient greater than 20 mm Hg where operative risk ranges 10–15%.[89-91] Conversely, prognosis is especially poor for patients lacking inotropic reserve and for patients with a mean gradient less than 20 mm Hg (Figs 9 and 10).[89,91] However, even in this group EF may improve for patients who survive AVR.[92] Currently, it is not clear how to identify patients who will benefit from AVR despite very low gradient and the absence of inotropic reserve.

Low Gradient Normal Ejection Fraction

Recently, attention has been called to a group of patients who have severe AS, low gradient and normal EF.[93,94] Patients with this combination of hemodynamics have LVs that have undergone concentric remodeling without an increase in LV radius.[34] As such, increased wall thickness diminishes LV cavity volume. Thus, an LV that ejects normally but from a small end diastolic volume generates a small stroke volume and hence a small transvalvular gradient. A small transvalvular gradient may in turn mislead the practitioner to believe that the AS is less than severe because traditionally the mean gradient associated with severe AS and normal EF has been greater than 40 (or 50) mm Hg (Table 2).[56] However, patients with severe symptomatic AS and this syndrome have a poor outcome without surgery, just as does any patient with severe symptomatic AS.[93]

AS in the Elderly Patients

As noted above, AS is a disease of aging, which is obviously increasing its incidence in older patients. While the risk of cardiac surgery increases with age, it is not age itself that increases risk so much as do the comorbidities that are also associated with aging. Thus advanced age alone, in the absence of other cardiac and systemic abnormalities, is not a reason to deny surgery to older patients with symptomatic AS.

SUMMARY

AS in developed areas of the world is usually due to valve calcification from a process similar to that of atherosclerosis. Once severe disease causes the symptoms of angina, syncope

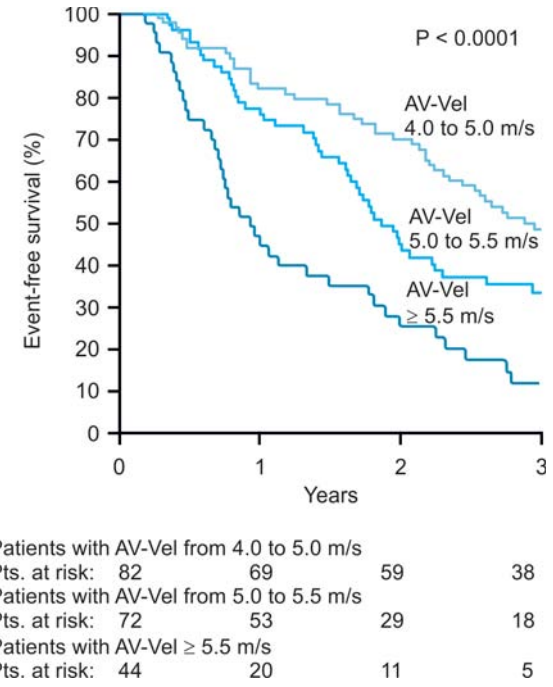


FIGURE 7: Event free survival for asymptomatic AS patients is segregated by transaortic jet velocity. (*Source:* Rosenhek R, Zilberszac R, Schemper M, et al. Natural history of very aortic stenosis. Circulation. 2010;121:(1):151-6, with permission)

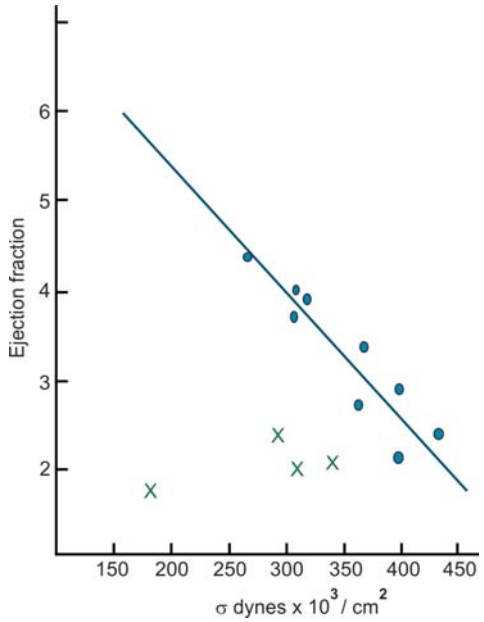


FIGURE 8: Ejection fraction (EF) is plotted against systolic wall stress for patients with severe AS. Patients with a good outcome (circles) had EF reduced in proportion to the increase in stress (afterload). Patients with a poor outcome (Xs) had EF reduced below that which could be accounted for by afterload excess indicating myocardial dysfunction. (*Source:* Carabello BA, Green LH, Grossman W, et al. Hemodynamic determinants of prognosis of aortic vale replacement in critical aortic stenosis and advanced congestive heart failure. Circulation. 1980;62(1):42-8, with permission)

or heart failure, prognosis is poor unless AVR is performed. At one end of the spectrum of severe disease, AVR may be justified in some asymptomatic patients exhibiting high risk features yet at the other end of the spectrum when disease is far-advanced,

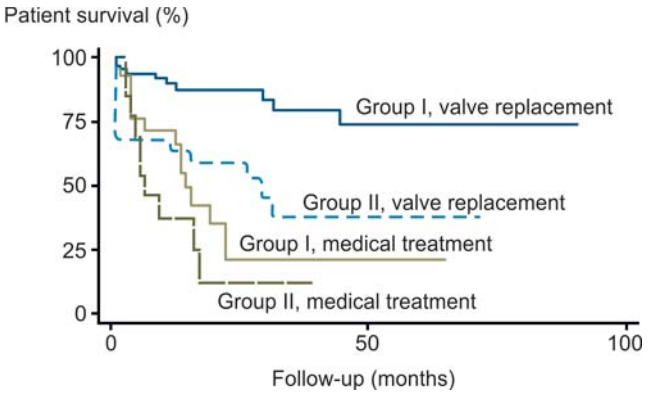


FIGURE 9: Survival for AS patients with low ejection fraction, low gradient is shown according to inotropic reserve. Group I patients who had reserve fared much better with surgery than Group II patients without reserve and also better than patients treated without surgery. (*Source:* Monin JL, Quere JP, Monchi M, et al. Low-gradient aortic stenosis: operative risk stratification and predictors for long-term outcome: a multicenter study using dobutamine stress hemodynamics. Circulation. 2003;108(3):319-24, with permission)

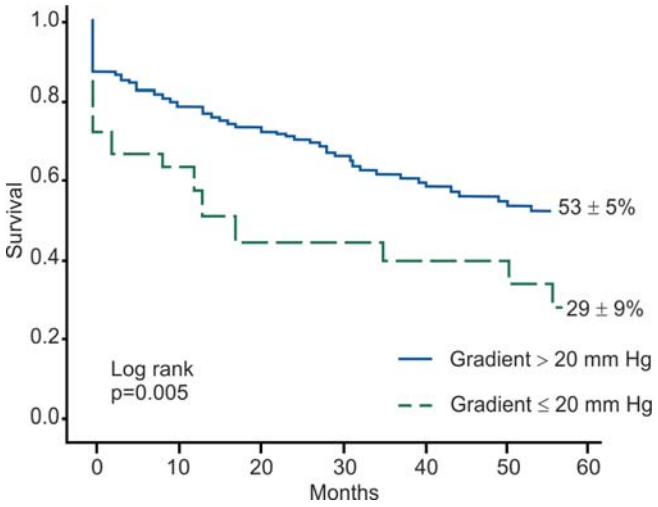


FIGURE 10: Survival of AS patients with low gradient, low EF is shown. Patients with especially low gradients, less than 20 mm Hg have very poor postoperative survival. [*Source:* Modified from Levy et al. (Ref. 91)]

it is rarely too late to perform AVR. The advent of relatively less invasive ways of performing AVR is likely to transform therapy for this disease in the coming years.

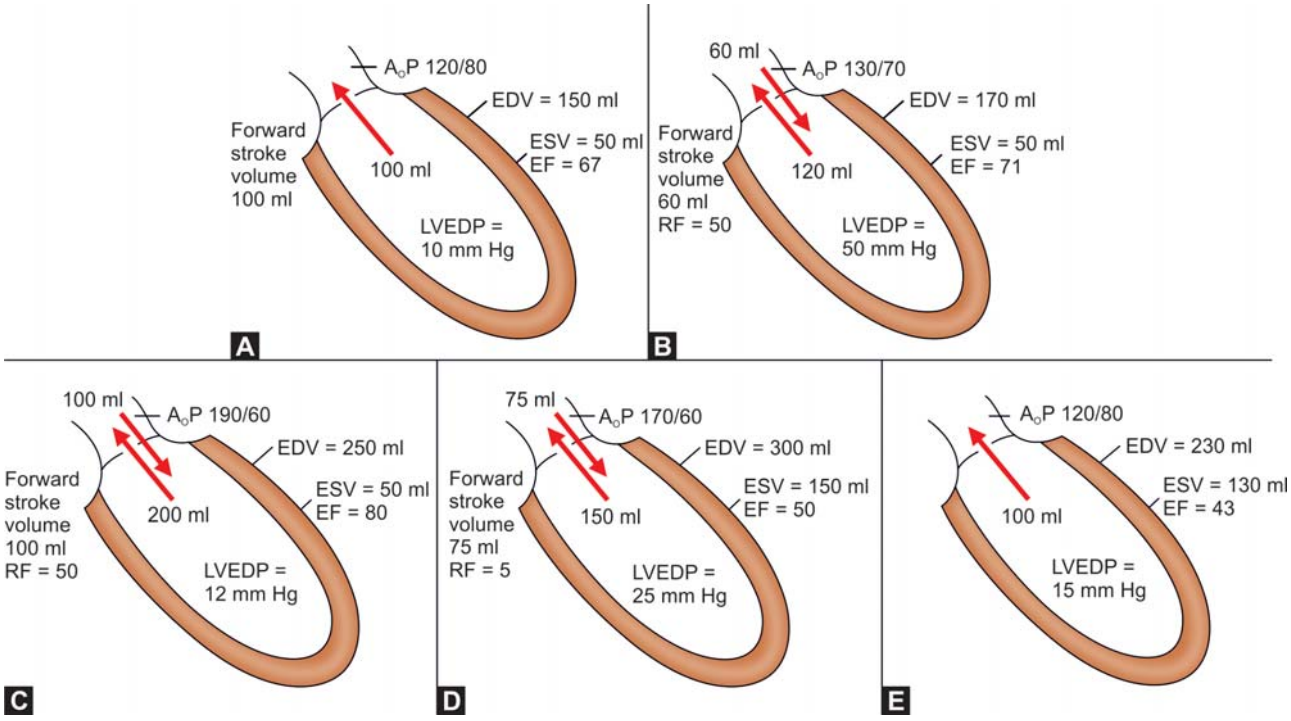
AORTIC REGURGITATION

ETIOLOGY

Aortic regurgitation (AR) may arise from disease either of the aortic root in which root dilatation pulls the leaflets away from their coaptation points or from disease of the valve leaflets.[95]

Aortopathy

Bicuspid aortic valve noted above to cause AS, may also be the cause of AR. While sometimes involving leaflet pathology, bicuspid valve is also frequently associated with a dilated aortic root. Such dilatation is now recognized to be due to inherent



FIGURES 11A TO E: The pathophysiologic stages or AR are depicted here. (A) Shows a normal LV. (B) Depicts acute AR. Increased sarcomere stretch (preload) increases end diastolic volume slightly so that total stroke volume increases slightly. However regurgitation of 50% of the total stroke volume decreases forward stroke volume from 100 cc to 60 cc. The LV volume overload greatly increases LV end diastolic pressure. (C) Shows chronic compensated AR. LV dilatation has permitted an increase in both total and forward stroke volume while allowing LV filling pressure to return toward normal. (D) LV contractile dysfunction has ensued. End systolic volume has increased greatly as the weakened myocardium in concert with increased afterload curtail LV emptying. In turn stroke volume has fallen and LV filling pressure has increased. (E) Depicts the beneficial effects of AVR (Abbreviations: EDV: End diastolic volume; EF: Ejection fraction; ESV: End systolic volume; LVEDP: Left ventricular end diastolic pressure). [*Source:* Modified from Carabello (Reference 97)]

structural abnormalities of the aorta in many cases rather than caused by the hemodynamic abnormalities stemming from AR.[96] Extreme dilatation of the aorta may lead to aortic dissection, and thus this pathology must be viewed as a duel problem that includes the consequences of valvular AR as well as the potential of aortic dissection. Other diseases of the aortic root leading to AR include Ehlers-Danlos syndrome, Marfan's syndrome, ankylosing spondylitis, hypertension and syphilis.

Leaflet Abnormalities

The most common leaflet abnormality leading to severe AR in developed nations is leaflet destruction from infective endocarditis. In other parts of the world rheumatic heart disease causing leaflet scarring and retraction is still a leading cause of AR.

PATHOPHYSIOLOGY

Aortic regurgitation produces a combined volume and pressure overload on the LV. The blood volume regurgitated into the LV during diastole is lost to forward flow. This loss is compensated by eccentric LVH whereby new sarcomeres are laid down in series, increasing myocyte length and LV chamber volume. Normal ejection of an increased end diastolic volume enables total stroke volume to increase (Figs 11A to E).[97] Increased total stroke volume in turn allows for an increase in forward stroke volume, compensating for the volume lost to regurgitation. Increased total stroke volume increases pulse pressure tending to increase systolic blood pressure. While not all patients with AR are frankly hypertensive, systolic pressure is higher than in the other typical LV volume overload, mitral regurgitation, and higher LV pressure together with a large LV radius increases systolic stress.[98] While this is partially compensated by increased LV wall thickness, systolic wall stress (afterload) is often elevated in AR and may be as high as that seen in AS. Thus, afterload excess is a major contributor to LV dysfunction in advanced disease.[99] Prolonged severe AR also results in contractile dysfunction, further impeding LV ejection. Contractile dysfunction results in part as proliferation of the extracellular matrix leads to myocyte loss.[100]

NATURAL HISTORY AND THE ROLE OF SYMPTOMS

Severe aortic regurgitation is relatively well tolerated, especially when compared to the other major regurgitant lesion, mitral regurgitation (MR). From the time of diagnosis of severe AR, progression to the need for surgery (see below) occurs at a rate of about 4% per year (Fig. 12), roughly half the rate of MR progression.[101-103] As with AS, the onset of symptoms represents a demarcation in the natural history of AR and prognosis worsens when symptoms arise unless the patient is treated with AVR; however, the risk of mortality per year for symptomatic AR is not as high as it is for AS.[104] The symptoms for AR are similar to those of AS but the frequency distribution is different in that syncope and angina are relatively rare in AR and heart

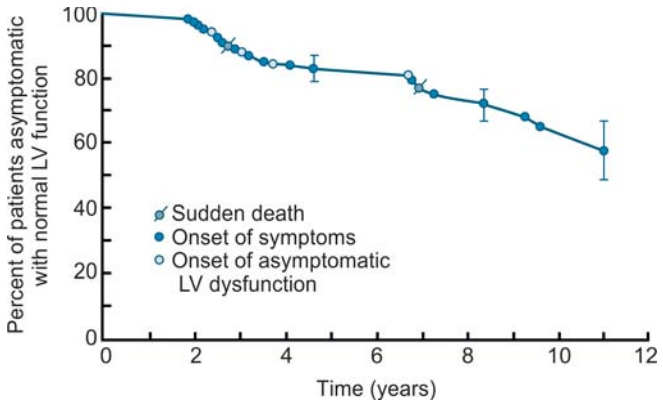


FIGURE 12: The natural history of AR is shown. After 10 years only 60% of patients develop a need for AVR due to symptoms (dark circles), asymptomatic LV dysfunction (open circles), or sudden death (slashed circles). (*Source:* Bonow RO, Lakatos E, Maron BJ, et al. Serial long-term assessment of the natural history of asymptomatic patients with chronic aortic regurgitation and normal left ventricular systolic function. Circulation. 1991;84(4):1625-35, with permission)

failure is much more common. Heart failure develops from both diastolic and systolic LV dysfunction.[105] Angina and syncope are probably due to reduced diastolic blood pressure leading to reduced myocardial and cerebral perfusion respectively. In addition, LVH present in AR reduces coronary flow reserve similar to that seen in AS patients.[106] Patients with AR may also complain of annoying neck pulsations and even carotid pain from the high pulse pressure produced by the high total LV stroke volume.

PHYSICAL EXAMINATION

The physical examination of the patient with severe chronic AR is one of the most dynamic in cardiology, predicated in large part upon the large total stroke volume requirements of the AR left ventricle. The apical beat is forceful and displaced downward and to the left of the mid-clavicular line. The typical murmur is diastolic, has a blowing quality and is heard best at the left lower sternal border with the patient sitting up and leaning forward. The murmur may be heard only in early diastole (when the pressure gradient between LV and aorta is greatest) in mild disease, becoming pandiastolic as AR worsens, and then shortening again as LV diastolic pressure increases (reducing the driving gradient) if heart failure supervenes. This AR murmur may be associated with a diastolic mitral rumble (Austin Flint) caused by impingement of the AR jet upon the mitral valve, partially closing the mitral valve while causing it to vibrate. This murmur is a sign that the AR is severe.

The AR causes a large total stroke volume to be ejected into the aorta, in turn causing a widened pulse pressure. These act in concert to cause a myriad of physical signs. The carotid pulse is brisk in upstroke and collapses rapidly (Corrigan's Pulse). The pulse may cause the head to bob with each cardiac cycle (De Musset's sign). The stethoscope placed over the femoral artery may detect a sound similar to a pistol shot, or when the bell is pressed into the femoral artery, a to and fro murmur (Duroziez's sign) may be heard. Traction on the nail bed may cause systolic plethora and diastolic blanching of the bed (Quincke's pulse). Systolic blood pressure in the leg may be augmented by greater than 40 mm Hg compared to brachial pressure (Hill's sign). It should be noted that the exact definition of Hill's sign is controversial since the original description was one of a "marked" increase in leg versus arm blood pressure.

DIAGNOSIS

Electrocardiograph and Chest X-Ray

The electrocardiograph and chest X-ray in AR are non-diagnostic, but do form part of the patient's database. The electrocardiogram usually shows LVH. The chest X-ray demonstrates an enlarged heart. The absence of this finding suggests that the heart has not dilated indicating that the disease is either mild or acute. The aorta may also be enlarged. If heart failure has intervened, there may be congestion in the lung fields.

Echocardiography

As is true for other valvular heart diseases, the echocardiogram forms the mainstay of diagnosis. Left ventricular size and function can be quantified. Valve and root anatomy are assessed to yield the etiology of the patient's AR. The AR jet is visualized and used to determine disease severity (Table 3).[56] Regurgitant flow can be calculated in two ways. First forward flow can be

TABLE 3
Classification of the severity of aortic regurgitation in adults

	Aortic regurgitation		
	Mild	*Moderate*	*Severe*
Qualitative			
Angiographic grade	1+	2+	3–4+
Color Doppler jet width	Central jet, width less than 25% of LVOT	Greater than mild but no signs of severe AR	Central jet, width greater than 65% LVOT
Doppler vena contracta width (cm)	Less than 0.3	0.3–0.6	Greater than 0.6
Quantitative (cath or echo)			
Regurgitant volume (ml per beat)	Less than 30	30–59	Greater than or equal to 60
Regurgitation fraction (%)	Less than 30	30–49	Greater than or equal to 50
Regurgitant orifice area (cm^2)	Less tha 0.10	0.10–0.29	Greater than or equal to 0.30
Additional essential criteria			
Left ventricular size			Increased

quantified from the time-velocity integral from a non-regurgitant valve, often the mitral valve. Then the time-velocity integral from the aortic valve is calculated to give total aortic flow. Regurgitant flow is then calculated as total flow per minute or the proximal isovelocity surface area (PISA) of the aortic jet can also be used to calculate regurgitant flow[107] and effective regurgitant orifice area (ERO). As the regurgitant flow approaches the aortic valve it often converges to form a hemisphere. The area of a hemisphere is calculated as $2\pi r^2$ where r is the distance from the valve plane to the jet aliasing border. Jet velocity is known from the echocardiography machine settings for jet aliasing. Flow is then calculated as isovelocity surface area × jet velocity, and ERO as flow/velocity. Echocardiography is also useful in assessing the degree of aortic root dilatation when aortopathy is the cause of AR.

Other Imaging Modalities

Accurate assessment of AR severity, of LV volumes and mass and of aortic root dimensions can be accomplished using cardiac magnetic resonance imaging (CMR).[108] However, CMR is less able to image valve pathology than echocardiography, which is also more portable and less expensive.

Exercise Testing

In general, exercise testing in asymptomatic patients is advisable to gain insight into the patient's exercise tolerance and as an objective method for assessing symptomatic status because the presence or absence of symptoms represents a key determinant of the natural history of the disease. Whether imaging of LV performance during exercise aids in determining the timing of surgery remains controversial [102]

Cardiac Catheterization

If the degree of AR severity is still unclear following noninvasive testing, right and left cardiac catheterization may yield important diagnostic information. Elevated LV filling pressures at rest and/or during static or dynamic exercise help to support that a patient's complaint of dyspnea has a cardiac cause. Aortography adds another imaging modality during which blood flow from aorta to LV, diastole can be visualized, and assessed to determine AR severity semiquantitatively.

TREATMENT

Medical Therapy

Asymptomatic patient with normal LV function: Aortic regurgitation is often a disease of excess afterload. Thus, therapy to reduce aortic impedance is logical both to reduce afterload and to increase forward flow while decreasing regurgitant flow. Several observational studies have suggested benefit to this approach in patients with severe asymptomatic disease while relatively small randomized trials have generated disparate results. One study randomized such patients to hydralazine versus placebo. After 2 years, the patients taking hydralazine had significantly smaller LV volumes than the patients receiving placebo.[109] In a second study, asymptomatic patients with normal LV function were randomized to receive digoxin (as a pseudo placebo) versus nifedipine.[110] Nifedipine forestalled the need for AVR as triggered by the onset of LV dysfunction or of symptoms by about 2 years. However a third study randomized patients to receive a true placebo in one arm of the trial, nifedipine in a second arm and enalapril in a third arm.[111] There was no benefit to either drug versus placebo. It should be noted that in the first nifedipine trial[110] the patients tended to be hypertensive while in the second trial systolic blood pressure was significantly lower.[111] Perhaps the differences in outcome were based more upon the differences in blood pressure rather than the effect of the drugs on AR. Obviously the disparate results of these trials make it impossible to make any firm recommendation regarding medical therapy for patients with AR.

Symptomatic AR patients or those with LV dysfunction: The only accepted therapy for symptomatic patients with severe AR is AVR or valve repair. AR patients with heart failure should presumably be treated with standard therapies for heart failure including ACE inhibitors and beta-blockers. However some have questioned the safety of ACE inhibitor therapy in AR patients.[112] Beta-blocker use is also of concern because theoretically by slowing heart rate, there would be greater diastolic regurgitant time, potentially worsening AR. However a recent report indicates benefit to beta-blocker use in AR patients with heart failure.[113]

Surgery and the Timing of AVR

The definitive therapy for severe AR is correction of the lesion. Occasionally the aortic valve can be repaired but usually therapy requires AVR. Currently there is no indication for correcting less than severe disease, as defined in Table 3 above, because there is no evidence that mild to moderate AR is harmful unless it worsens. Prognosis for patients with severe AR is excellent until either symptoms or asymptomatic LV dysfunction develops, and prognosis remains excellent as long as AVR is performed promptly when these triggers for surgery arise. Six to twelve month clinical and echocardiographic follow-up is indicated to surveil for the onset of symptoms and to assess changes in LV size and function. If EF is falling toward 50–55% or end systolic dimension is increasing toward 50–55 mm, AVR is indicated.[56,104,114] Since AVR reduces LV afterload, LV EF may return to or toward normal following surgery if it was depressed preoperatively. This is especially true if LV dysfunction when present has been so for less than 15 months.[115] If EF has fallen to very low levels prognosis is reduced but even then AVR is preferable to continued medical therapy in most cases.[116]

Acute Severe AR: A Dangerous Masquerader

In many respects, acute severe AR as might occur from leaflet perforation due to infective endocarditis is almost a different disease from severe chronic AR.[117] In acute AR there has been no time for LV enlargement to occur and thus total stroke volume and pulse pressure are not increased. Therefore, most of the signs leading to the dramatic physical examination of the patient with chronic AR are absent, and physical exam is often misleadingly bland. The apical impulse is not displaced. A rapid rise in LV diastolic pressure as the LV fills both from the left

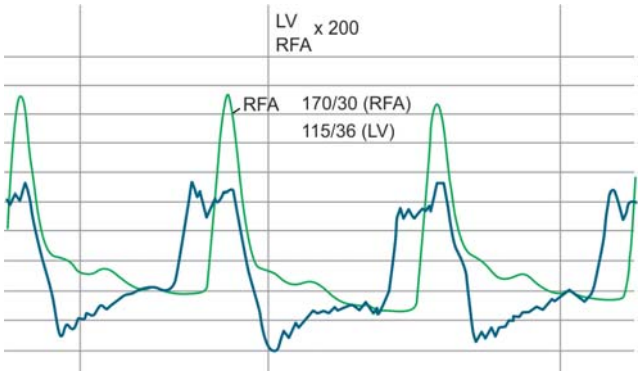


FIGURE 13: The hemodynamics of acute AR are shown. There is increased right femoral artery systolic pressure (RFA) over that of the LV (Hill's sign). The rapid LV filling and diastasis of LV and femoral artery pressures reduce the gradient driving AR, causing the murmur to be brief and unimpressive. [*Source:* Modified from Carabello (Ref. 118)]

atrium and the aorta may close the mitral valve in diastole (mitral pre-closure) making S_1 soft. This rapid rise in LV filling pressure together with a decrease in the aortic diastolic pressure (Fig. 13)[118] diminishes the gradient for backward flow, such that the diastolic AR murmur may become soft and short. This is the same gradient that generates coronary blood flow potentially making the LV susceptible to ischemia. Perhaps this is why severe acute AR that causes mitral valve pre-closure has a very high mortality when treated medically.[119-121] In severe acute AR any sign of heart failure or mitral valve pre-closure is an indication for urgent AVR. While there is often concern of reinfection of the prosthetic valve used to correct acute AR, this in fact only occurs rarely.[121] Further there is no proven effective medical therapy for acute severe AR other than appropriate antibiotic coverage.

SUMMARY

Like AS, AR is a mechanical problem that requires a mechanical solution in the form of AVR (or occasionally aortic valve repair). While severe chronic disease is relatively well tolerated, patients should be followed carefully for the onset of symptoms or for objective proof of LV dysfunction. If either occurs, prompt AVR is indicated. Acute severe AR is a dangerous condition requiring urgent surgical therapy.

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Chapter 56

Mitral Valve Disease

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Chapter Outline

- Normal Mitral Valve Morphology and Function
- Global Burden of Rheumatic Heart Disease
- Mitral Stenosis
  - Etiology and Pathology
  - Pathophysiology and Hemodynamics
  - Clinical Diagnosis
  - Investigations
  - Natural History
  - Special Populations
  - Management
- Mitral Regurgitation
  - Pathophysiology and Hemodynamics
  - Etiology
  - Rheumatic Mitral Regurgitation
  - Clinical Diagnosis
  - Degenerative Mitral Valve Regurgitation
  - Mitral Regurgitation Caused by Infective Endocarditis
  - Acute Mitral Regurgitation
  - Secondary Mitral Regurgitation
  - Investigations
  - Management

NORMAL MITRAL VALVE MORPHOLOGY AND FUNCTION

Normal mitral valve (MV) function depends on the structural integrity and coordinated action of the anatomic components of the mitral apparatus (Fig. 1). The MV is a complex structure formed by four elements. The annulus is asymmetrical, with a fixed portion (corresponding to the anterior leaflet) shared with the aortic annulus and a dynamic portion (corresponding to the posterior leaflet) that represents most of the circumference of the annulus. The two leaflets are asymmetrical, the anterior leaflet has the greater length of tissue but occupies a smaller portion of the circumference of the annulus than the posterior.

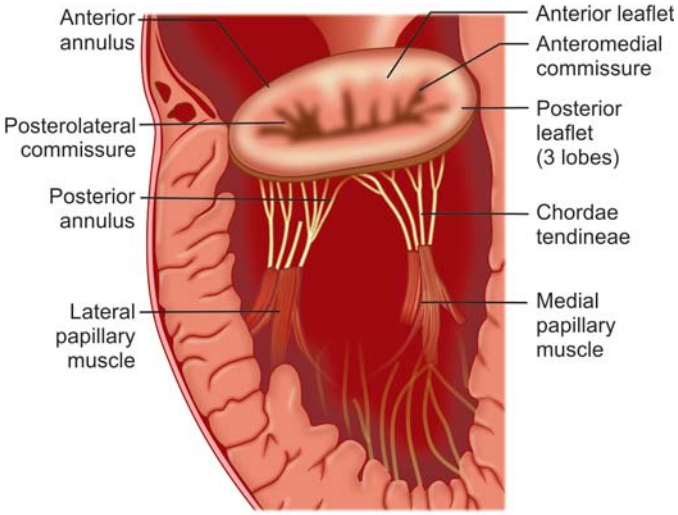


FIGURE 1: Mitral valve apparatus. [*Source:* Modified from Otto CM (Reference 23)]

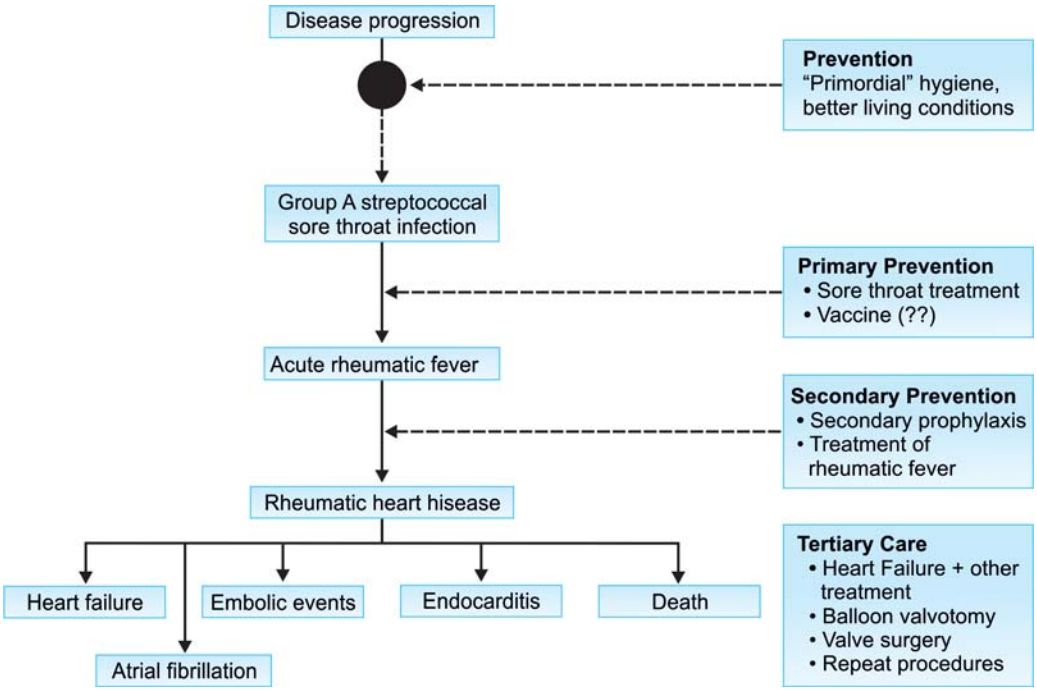
The commissures are a distinct area where the anterior and posterior mitral leaflets come together. The chordae join each papillary muscle (PM) to the corresponding commissure and the adjoining halves of both leaflets, so as to allow the two leaflets to coapt during systole. The anterolateral and posteromedial PMs and the adjacent wall attach the mitral apparatus to the left ventricle (LV). Normal valvular mechanics require a sophisticated interaction of its components, along with the adjacent LV and atrial myocardium. Abnormality in anyone of the components can result in valvular dysfunction.

GLOBAL BURDEN OF RHEUMATIC HEART DISEASE

There is an undeniable relationship between the incidence of rheumatic fever (RF)[1,2,7] and living standards. The RF is a disease of poverty. In the developed countries of the world, the incidence of RF has fallen markedly during the last century. This decrease in incidence preceded the introduction of antibiotics and is a reflection of improved socioeconomic standards, less overcrowded housing and improved access to medical care.

The current prevalence of rheumatic heart disease (RHD)[3-7] in the USA and Japan stands at 0.6–0.7 per 1,000 population, which contrasts sharply with that in the developing countries of Africa and Asia,[4] where rates as high as 30 per 1,000 have been reported. According to recent World Health Organization (WHO) estimate, 15.6 million people are affected by RHD with 470,000 new cases of RF have been reported. Annual mortality attributable to RF or RHD is estimated to 233,000. Australia is a wealthy country with living standards amongst best in the world. However, even in Australia, there

FLOW CHART 1: Preventive and therapeutic strategies in rheumatic fever and rheumatic heart disease



are some populations who live in poverty. Amongst aboriginal people of northern Australia, the incidence of acute RF is 0.2–0.5% of school age children. The prevalence of RHD is 2% amongst all ages. Systematic screening with echocardiography as compared with clinical screening revealed a much higher prevalence (2–3%) of RHD in school going children in Cambodia (Asia) and Mozambique (Africa). A recent study (Heart of Soweto Study) revealed a high incidence of newly diagnosed RHD in adult urban African community.[5] In India, the incidence of RF has declined to 0.08 per 1,000 per year in some states; however, the disease continues to have high incidence in regions with poor health care infrastructure.[6] These data outline the fact that RF and RHD are of sufficient importance to warrant an attention of international public health and research communities.[7] As shown in Flow chart 1, the sequelae of RF and chronic RHD are devastating and contribute to a large financial burden on the individual, family and the society.

MITRAL STENOSIS

ETIOLOGY AND PATHOLOGY

In clinical practice, the predominant cause of mitral stenosis[8] (MS) is RF. Congenital MS is rare and is typically diagnosed in infancy or early childhood. In the elderly, extensive mitral annular calcification may result in restriction of the size of the conduit for left ventricular diastolic filling with functional MS. In some cases, calcification extends into the base of mitral leaflets but rarely results in severe valve obstruction. Other conditions causing and mimicking MS are very rare (Table 1).

Rheumatic MS results from the affection of commissures, cusps, chordae and the PMs (Figs 2A and B). Fibrotic process tends to involve all the structures resulting in a funnel shaped mitral orifice. In severe forms of MS, fibrosis is so intense that the leaflets, chordae and the PMs become a single mass, hence making it difficult to differentiate at what level one component of the MV ends and the other component begins. Secondary pathological changes include left atrial (LA) hypertrophy and dilatation, LA thrombi and changes of venous, and arterial hypertension in the pulmonary vasculature with secondary right ventricular (RV) hypertrophy.

PATHOPHYSIOLOGY AND HEMODYNAMICS

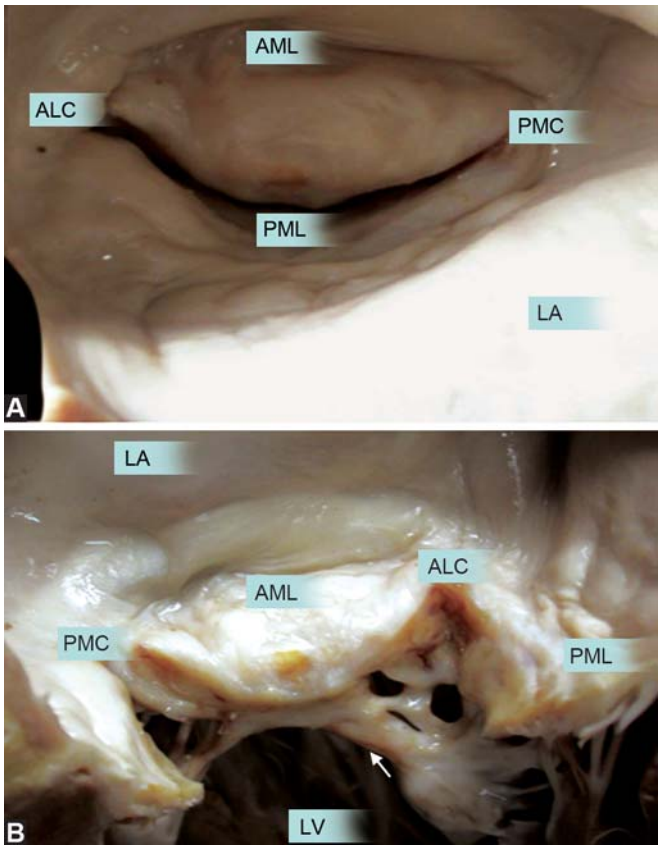
The cross sectional area of the normal MV is 4–6 cm^2. The hemodynamic severity of MS is based on a variety of parameters. The stenosis is considered mild when MV area is greater than 1.5 cm^2, mean gradient less than 5 mm and pulmonary artery systolic pressure (PASP) is less than 30 mm. Severe stenosis is defined as valve area less than 1 cm^2, mean gradient greater than 10 mm and PASP is 30–50 mm. Moderate MS is diagnosed when valve area is 1.0–1.5 cm^2, mean gradient 5–10 mm and PASP 30–50 mm. Transmitral gradients, which

TABLE 1

Causes of mitral stenosis

• Rheumatic fever
• Degenerative mitral annular calcification
• Congenital (parachute valve, DOMV, as a part of HLHS)
• Rare causes: malignant carcinoid disease, systemic lupus erythematosus, rheumatoid arthritis, mucopolysaccharidoses of Hunter-Hurler phenotype, Fabry disease, Whipple disease
• Conditions mimicking MS: left atrial tumors, cor triatriatum, ball valve thrombus, infective endocarditis with large vegetation

(Abbreviations: DOMV: Double orifice mitral valve; HLHS: Hypoplastic left heart syndrome; MS: Mitral stenosis)



FIGURES 2A AND B: Pathology of mitral stenosis. (A) Mitral valve viewed from left atrial (LA) aspect shows crescentic appearance of the valve orifice. (B) The opened out valve highlights the commissural and chordal fusion (arrow) and leaflet thickening. (Abbreviations: AML: Anterior mitral leaflet; PML: Posterior mitral leaflet; ALC: Antero-lateral commissure; PMC: Posteromedial commissure; LV: Left ventricle)

form the basis of symptomatology are determined by MV area, cardiac output and duration of diastole. Tachycardia by shortening the diastolic interval increases the transmitral gradient for a given MV area and cardiac output.

The LA and pulmonary arterial (PA) pressures are determined by the severity of MS, heart rate and most importantly by the LA compliance. More compliant the LA, lesser is the elevation of LA and the PA pressure. In India, there can be an accelerated progression of rheumatic fibrosis leading to MS at young age. These patients have a small, non-compliant LA resulting in very high LA and PA pressures but a low incidence of atrial fibrillation (AF).

High PA pressure is a result of passive transmission of backward pressure from the LA and pulmonary arteriolar constriction, which is considered as a protective reflex to prevent pulmonary edema. Long standing pulmonary hypertension (PH) can result into morphological changes in the pulmonary vasculature comprising of endothelial proliferation and medial hypertrophy. Once these changes set in, at least a part of PH becomes irreversible despite adequate relief of MS. Tricuspid regurgitation (TR) and rarely pulmonary regurgitation (PR) develop secondary to RV failure and dilatation. The enlarged atria predispose to AF which causes further hemodynamic embarrassment.

The contractility of LV is usually normal. In some patients, LV ejection performance is reduced secondary to reduced preload from the impairment of LV filling and from increased LV afterload secondary to reflex systemic vasoconstriction and decreased cardiac output. Ejection performance may return to normal shortly after MS is relieved. Rarely, the LV contractility is reduced due to severe subvalvar affection resulting in regional wall motion abnormalities affecting in the postero-basal segment of the LV. Tachycardiomyopathy resulting from uncontrolled ventricular rate in AF, which can also impair the LV contractile function.

CLINICAL DIAGNOSIS

Symptoms

The interval between the initial episode of RF and MV obstruction is variable. Unlike in the west, where the presentation is in the fifth or the sixth decade, patients tend to present much early in the developing world. In India, patients may present in the first or early second decade, and this group is described as "juvenile MS". Female gender is predominantly affected. Patients frequently adapt to their level of functional capacity and deny symptoms despite objective effort limitation. Anemia, fever, infection, pregnancy, undue exertion or onset of AF often precipitates pulmonary edema.

The symptoms result from increased LA pressure and reduced cardiac output, primarily caused by mechanical obstruction to filling of the LV. The first symptom usually is dyspnea on effort. Increased venous return and transmitral blood flow in the supine position causes orthopnea and paroxysmal nocturnal dyspnea. Acute pulmonary edema can occur when pulmonary capillary pressure exceeds 25 mm Hg. Hemoptysis, nocturnal or paroxysmal cough are other manifestations of pulmonary venous congestion. The hemodynamic basis and mechanism of symptoms are summarized in Table 2.

Physical Signs

Clinical findings are influenced by severity of MS, presence and severity of PH, rhythm, morphology of the valve and associated valve lesions. The physical findings seen in MS are shown in Table 3.

The precordial palpation reveals a tapping apex (counterpart of accentuated S1). Left parasternal heave, palpable P2 and cardiomegaly usually indicate PH with secondary RV hypertrophy. A loud S1 due to closure of MV with rapid apposition of leaflets which are well separated at end-diastole is an important auscultatory sign. This finding usually indicates a pliable and non-calcific valve which is suitable for balloon mitral valvotomy (BMV).[9] A low intensity S1 suggests valve calcification or associated dominant mitral regurgitation (MR). The S2 is usually split with accentuated P2 reflecting PH. Opening snap (OS) is a sharp and snappy sound which occurs 30–100 m seconds after the S2, reflects elevated LA pressure which forced open the MV during diastole.

As the MS increases in severity, and the LA pressure rises, the MV opens earlier and the A2-OS interval narrows. The OS is absent in a calcified or severely fibrotic valve. The diagnostic hallmark on auscultation is the classical low frequency, low pitched diastolic rumble of varying duration best heard at the apex with the bell of the stethoscope in the lateral position. The

TABLE 2

Symptoms in mitral stenosis

Hemodynamic/other mechanism	*Symptoms*
Elevated PWP	Dyspnea, orthopnea, PND, pulmonary edema
↑ PAP, RVF, low cardiac output	Fatigue, chest pain, dyspnea, pain abdomen, pleural effusion, edema feet, ascites
Atrial fibrillation	Palpitations, precipitation of heart failure, systemic emboli, tachycardiomyopathy (rare)
Dislodgement of LA thrombi	Systemic emboli (stroke, limb ischemia, saddle emboli, etc.)
Multi-factorial	Hemoptysis
Compression of recurrent laryngeal nerve by LA or PA	Hoarseness of voice (Ortner's syndrome)

(Abbreviations: PWP: Pulmonary wedge pressure; PND: Paroxysmal nocturnal hyspnea; PAP: Pulmonary artery pressure; RVF: Right ventricular failure; LA: Left atrial (atrium); PA: Pulmonary artery)

TABLE 3

Physical examination in mitral stenosis

Pulse	Normal, low volume, AF
JVP	Normal, "a" wave (if PH), signs of TR
Palpation	Tapping apex, parasternal heave, palpable P2
Auscultation	Loud S1, OS, diastolic murmur with presystolic crescendo component, loud P2, RV S3, TR, PR (rare)
Assessment of severity	A2-OS interval, length of murmur, signs of PH
Assessment of valve morphology	Intensity of S1, and OS
Associated valve lesions	Murmurs of AR, MR, AS, organic tricuspid valve disease

(Abbreviations: JVP: Jugular venous pulse; PH: Pulmonary hypertension; TR: Tricuspid regurgitation; P2: Pulmonic component of second heart Sound; S1: First heart sound; RV-S3: Right ventricular gallop; PR: Pulmonary regurgitation; AR: Aortic regurgitation; MR: Mitral regurgitation; AS: Aortic stenosis; OS: Opening snap)

duration of the murmur (rather than its loudness) is a useful sign of the severity of stenosis. In severe MS (MV area $< 1\ cm^2$) the murmur is characteristically long, loud, and present through out the diastole with presystolic crescendo component marching in to loud S1. The presystolic crescendo murmur is present in sinus rhythm or during AF with short diastolic periods. It is absent in those with calcific valve or in low cardiac output. Occasionally, in patients with critical MS and low output, the mitral diastolic murmur may also be absent and the physical findings are dominated by severe PH and TR. The mitral diastolic murmur tends to become apparent only after decongestive therapy. MS is often associated with involvement of other cardiac valves and several other murmurs can be observed (Table 3).

INVESTIGATIONS

Electrocardiogram

The electrocardiogram can be completely normal especially in those with mild MS. Patients in sinus rhythm usually show evidence of LA enlargement. Right axis deviation, RV hypertrophy and right atrial enlargement are seen in patients with PH. AF is common with increasing age.

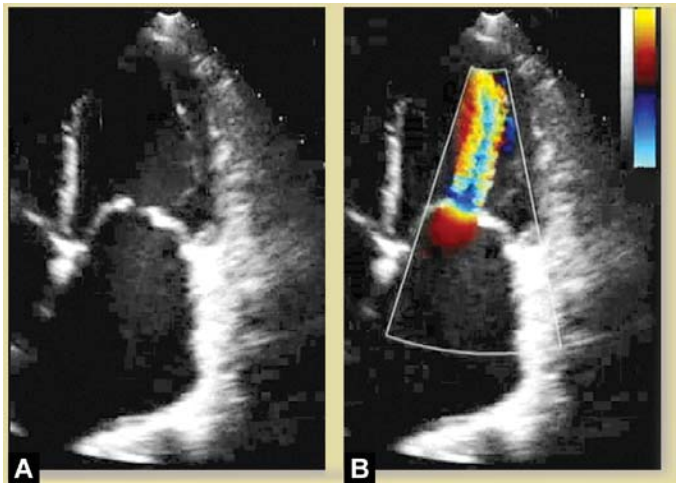
Radiological Evaluation

The chest X-ray can be normal but usually reflects the hemodynamic changes of pulmonary venous hypertension. LA enlargement occurs early and the signs include: straightening of the left heart border (due to LA appendage enlargement), double cardiac density and elevation of left main bronchus. Giant left atria are usually seen in mixed MV disease and occupy large part of the cardiac silhouette.

Evidence of pulmonary venous hypertension includes redistribution of blood flow in upper lobe veins, Kerley B lines, hilar haze and features of interstitial and alveolar pulmonary edema. PH causes prominence of main pulmonary trunk and right, and left pulmonary arteries. The RV hypertrophy contributes to cardiomegaly, and right atrium enlarges only when there is significant TR. Calcification of MV is uncommon in young patients. Calcification of the LA wall, LA appendage and atrial thrombus are rarely seen these days.

Echocardiography

Two dimensional (2D) transthoracic echocardiography (TTE) with Doppler assessment helps in confirming the diagnosis, evaluating the valve area, transvalvar gradient, valve morphology, estimates of PH and LV function. Presence of LA thrombus or rare occurrence of vegetation on the MV can also be diagnosed by TTE. However, sensitivity of transesophageal echocardiogram (TEE) is much more as compared to TTE in diagnosing LA thrombi or MV vegetations. TEE provides superior quality images of the MV as compared to TTE and is, therefore, useful in those with poor TTE window. Obese individuals, patients with associated chronic obstructive



FIGURES 3A AND B: 2D echocardiography and color Doppler in mitral stenosis. 2D echocardiography with color flow mapping during diastole in a patient with mitral stenosis showing thickened, but pliable leaflets and severe flow acceleration across the stenosed valve. The valve morphology is ideally suited for a balloon mitral valvotomy

pulmonary disease as well as those who have undergone previous surgeries on the MV are some of the examples where TEE is more useful in defining the MV morphology. Simple echocardiogram scoring system designed by Wilkins et al. based on the amount of thickening, degree of pliability, severity of subvalvar affection and presence and extent of calcification helps in deciding whether or not the valve is suitable for BMV (Figs 3A and B). TTE also helps in assessing the aortic and tricuspid valves which are not uncommonly affected by the rheumatic process. In most patients, therapeutic strategy can be evolved based on echo-Doppler data without the need for cardiac catheterization.

Stress Testing

Treadmill stress testing or bicycle ergometry may provide a useful objective assessment of functional capacity in patients whose symptoms are equivocal or discordant with the severity of MS. Exercise echocardiography can also be used to assess the evolution of mitral gradient and PASP in patients with doubtful symptoms.

Invasive Evaluation

The accuracy of echocardiography has virtually eliminated the use of invasive hemodynamic assessment for diagnosis of MS or associated valve disease. Coronary angiography is required for exclusion of atherosclerotic coronary artery disease (CAD) either prior to surgery or during BMV.

NATURAL HISTORY

The studies on natural history are old and uncontrolled. In India and several other developing countries, severe MS is often observed in adults and adolescents, whereas in industrialized nations symptoms are usually delayed until the fifth decade of life. The rate of progression is variable ranging 0.1–0.3 cm^2/year. Rapid progression is observed in patients with persistent rheumatic activity, severe anatomic deformity and high transmitral gradients. In asymptomatic patients, survival is 84% at 10 years, and among patients with minimal symptoms, survival is 42% at 10 years with 60% incidence of heart failure. Symptomatic patients had a poor prognosis with a 5-year survival of only 44%. AF can occur in asymptomatic patients as well with incidence tending to increase with age and the LA size. The incidence of thromboembolism is also higher in older population with AF having large LA, small valve area and the presence of LA spontaneous echo contrast.

SPECIAL POPULATIONS

Mitral stenosis in pregnancy often affects young women who are in their child bearing years. The increased intravascular volume, increased cardiac output, and tachycardia associated with pregnancy impose additional hemodynamic burden and there is often symptomatic deterioration. Percutaneous BMV can be performed safely in the second trimester with excellent clinical and hemodynamic results.

Mitral restenosis following BMV or previous surgical commissurotomy is common and can be treated by a repeat balloon procedure, if valve morphology is favorable and the predominant mechanism of restenosis is commissural fusion. If characteristics are not favorable, then surgical treatment is required.

MANAGEMENT

Medical Treatment

There is a limited role for medical therapies especially for those who are in sinus rhythm. Treatment of precipitating factors, like anemia, infection, AF and electrolyte imbalance, can help in relieving the symptoms. In general, all patients should receive the recommended rheumatic prophylaxis such as injection of benzathine penicillin or other suitable agent. All patients should receive appropriate antibiotic prophylaxis for those procedures known to cause bacteremia. Diuretics are often recommended for relieving the congestive symptoms. The role of digoxin in patients with sinus rhythm remains controversial. With its modest inotropic effect, digoxin seems to be of some value in patients with PH and RV failure.

Atrial ectopic per se do not need any treatment although they usually precede AF. The contributors to AF in RHD are LA size, pressure, fibrosis and persistent rheumatic activity. Acute AF is often associated with a rapid ventricular response. The arrhythmia causes reduction in diastolic filling leading to impairment of LV filling, abrupt LA hypertension and reduced cardiac output. Immediate rate control is necessary and can be achieved by administration of digoxin, beta-blockers or rate reducing calcium channel blockers like verapamil or diltiazem. Cordarone is effective in rhythm control but in the presence of unrelieved MS, maintaining sinus rhythm is difficult. Moreover, cordarone action is not immediate and may take days before conversion can actually occur. If patient is hemodynamically unstable, immediate direct current cardioversion is indicated. Generally, low molecular weight heparin or unfractionated heparin is administered initially to be followed by oral anticoagulation.

Chronic AF increases the risk of embolic stroke between the rates of 7% and 15% per year. The rate of stroke has been highly variable in the reported series. After the first embolic event, the recurrence rate is increased ≈ 2 fold without anticoagulation. The embolic complications are usually thought to be caused by stasis, secondary to lack of effective LA contraction. Accordingly, all such patients require oral anticoagulation with a target international normalized ratio of 2.5–3.5. Chronic rate control for these patients is achieved with the use of digoxin, a beta-blocker, a calcium channel blocker or a combination of these agents. It is important to monitor the adequacy of rate control at rest as well as during activity. In some patients, tachycardia occurs even with mild activity. Such patients are at a risk for developing tachycardia induced cardiomyopathy.

Mechanical Relief of Obstruction

Mitral stenosis results in a mechanical obstruction to forward flow and available therapies are aimed at relieving this obstruction. Four procedures are effective in providing the desired palliation. These are percutaneous BMV, closed surgical commissurotomy, open surgical commissurotomy and MV replacement.

The timing of intervention is guided by the observational data. Figure 4 shows that the survival benefits with mechanical relief of obstruction (surgical commissurotomy in this series) compared with medical therapy are greater in patients with advanced symptoms. It seems reasonable to provide mechanical relief once more than mild symptoms are present. PH increases the risk of surgery, and it is advisable to relieve the mechanical obstruction prior to development of significant PH.

Closed surgical commissurotomy has largely been abandoned in most regions of the world. However, this procedure should not be considered as obsolete. It provides an effective short- and long-term palliation from symptoms of MS.

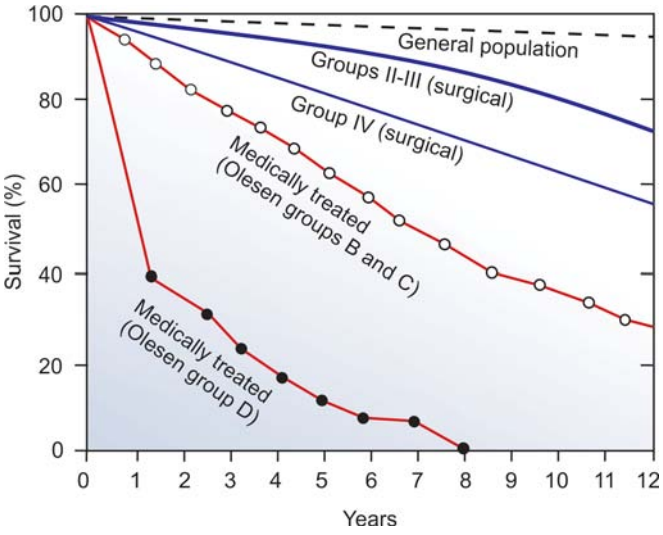


FIGURE 4: Survival according to therapy and symptomatic status for patients with MS. Groups II, III and IV equivalent to NYHA classifications II, III and IV are approximately similar to the groups B, C and D respectively. Class IV patients had improved survival when treated surgically. [*Source:* Modified from Roy and Gopinath (Reference 8)]

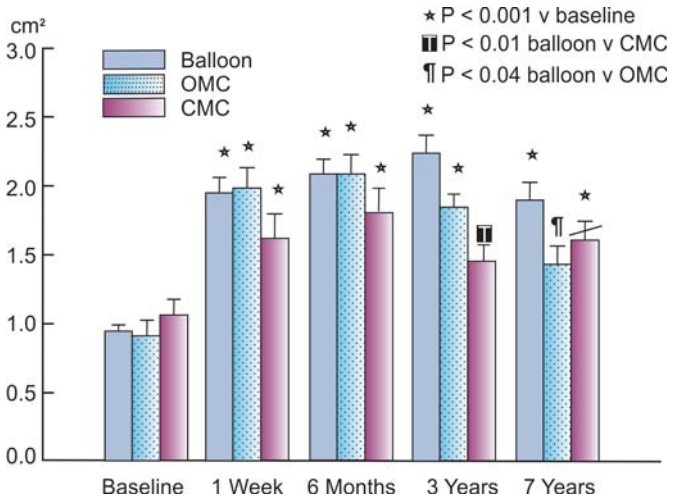
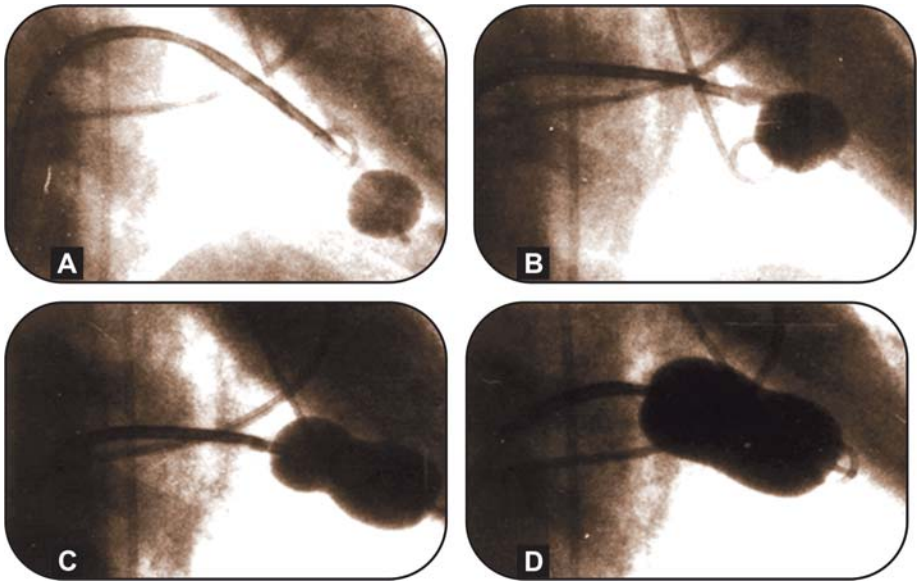


FIGURE 5: Mitral valve area following balloon, open mitral commissurotomy (OMC) and closed mitral commissurotomy (CMC). Mitral valve area at base line, 1 week, 6 months, 3 and 7 years after balloon dilation, CMC or OMC, in prospective randomized trials conducted in Hyderabad, India. [*Source:* Modified from Turi ZG (Ref. 10) and Reyes PP (Reference 11)]

This technique can be used in those areas of the world where percutaneous BMV facilities are not available, and in regions where it is less expensive to perform closed commissurotomy than BMV.[10,11]

Percutaneous BMV is currently the technique of choice. Percutaneous BMV has been found to be equal or superior in safety and efficacy to closed or open surgical commissurotomy, acutely as well as in long term. Figure 5 shows MV area at base line and during the study period with the three techniques in prospective randomized trials conducted in India. The technique and device developed by Inoue (Figs 6A to E) remains the preferred approach all over the world. The predominant mechanism of benefit following BMV as demonstrated by 2D or three dimensional (3D) echocardiography is commissural splitting (Fig. 7). The other possible mechanisms for relief of obstruction are stretching of the valve orifice and cracking of valvular calcifications. The procedure typically results in a doubling of the MV area (on average from 1.0 cm^2 to 2.0 cm^2) with a 50% reduction in gradients. The success rate is 80–95% and is defined as the MV area increasing to greater than 1.5 cm^2 and LA pressure decreasing to less than 18 mm Hg without major complications.[12]

Suitability for BMV is determined by valve morphology and the degree of MR. Wilkins score is a useful guide to the suitability of the valve's morphology for BMV. In general, patients with a score of ≤ 8 and with not more than mild MR have the best outcomes, although many patients have benefited from BMV despite higher valve scores. In most patients with high scores (Fig. 8A) a surgical approach is advisable, however, in patients with serious comorbidities, BMV may still provide limited benefit. Clot in the LA resting against the interatrial septum in the region of fossa-ovalis as well as a free floating thrombus remain an absolute contraindication (Fig. 8B). Experienced operators have performed successful and uncomplicated BMV in patients with a thrombus limited to the LA appendage. In experienced centers, the complications and mortality are very low. The complications include tamponade



FIGURES 6A TO D: The BMV using Inoue balloon technique. Steps in BMV using Inoue balloon: (A) Balloon inserted in left ventricle (LV) through left atrium (LA) after trans-septal puncture; (B) Balloon positioned at mitral valve; (C) Waist in partially inflated balloon across the narrowed valve and (D) Fully inflated balloon with disappearance of waist-indicating relief of obstruction

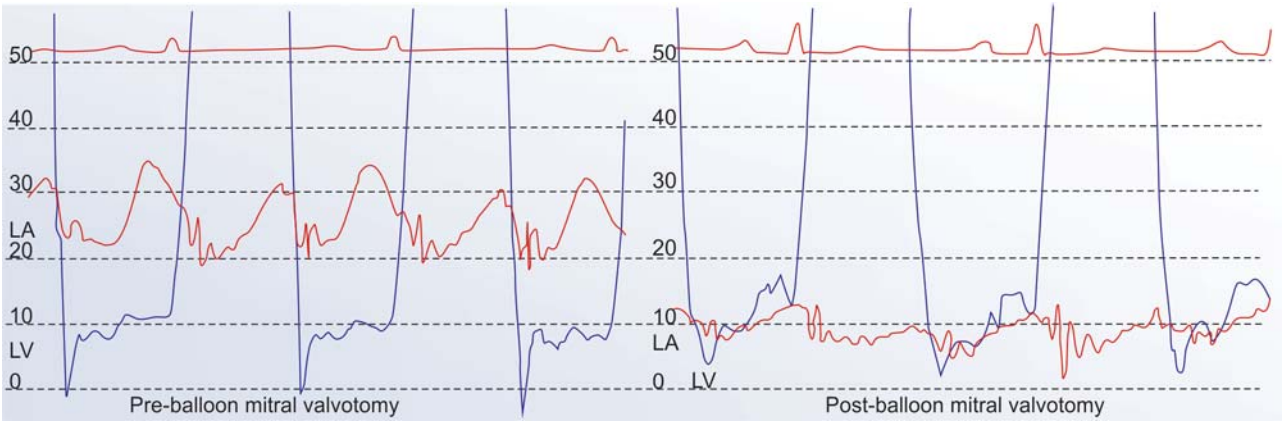


FIGURE 6E: Hemodynamic traces during BMV using Inoue balloon technique. Simultaneously recorded LV, LA pressures show remarkable reduction in gradient after BMV

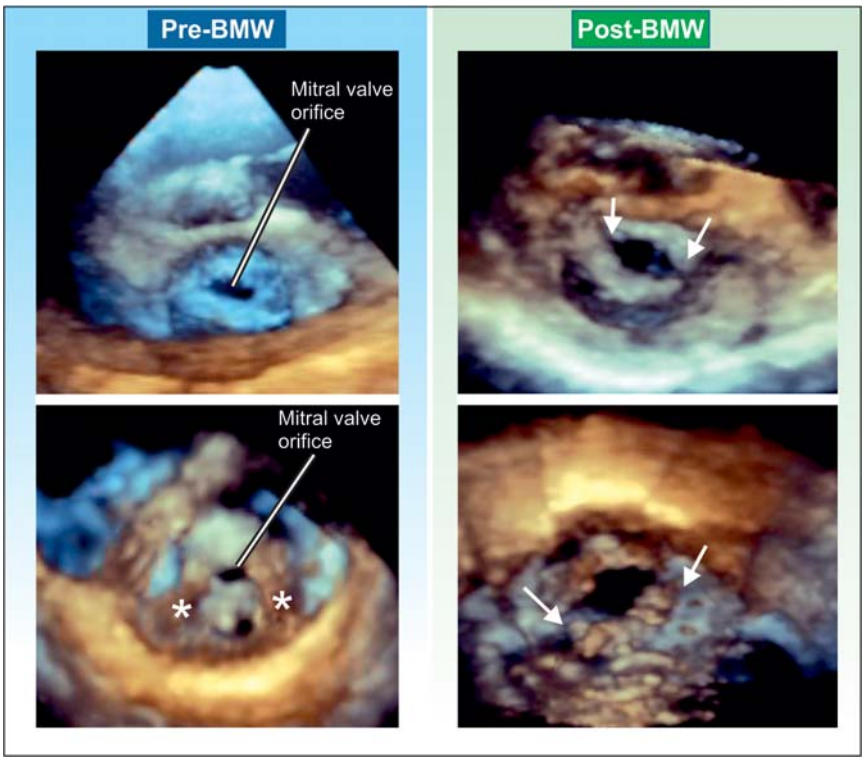


FIGURE 7: Three dimensional echocardiography pre-balloon mitral valvotomy and post-balloon mitral valvotomy. Three dimensional (3D) echocardiographic images recorded in diastole from atrial (upper panel) and ventricular aspect (lower panel) before (left panel) and after (right panel) Inoue balloon mitral valvotomy (BMV) in mitral stenosis. These images demonstrate commissural splitting (short white arrows) as the mechanism of benefit after BMV. The restricted leaflet motion due to fibrosis in chordo-papillary apparatus (stars) remains unchanged

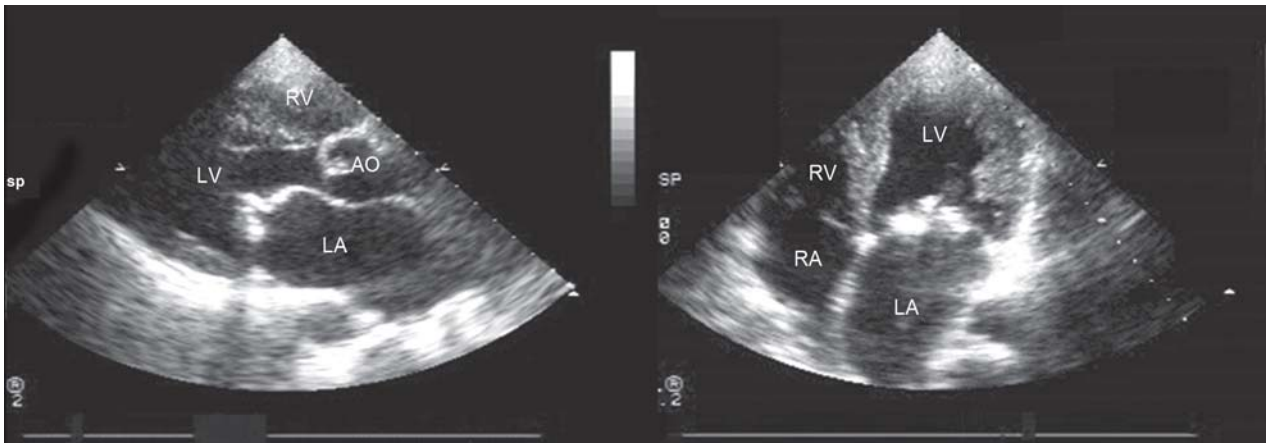


FIGURE 8A: Two dimensional echocardiography in mitral stenosis. Two dimensional echocardiography images in parasternal long axis view (left panel) and four chamber view (right panel) demonstrate a high score valve showing marked thickening, calcification, immobility and subvalvar affection. (Abbreviations: RV: Right ventricle; AO: Aorta; LV: Left ventricle; LA: Left atrium; RA: Right atrium)

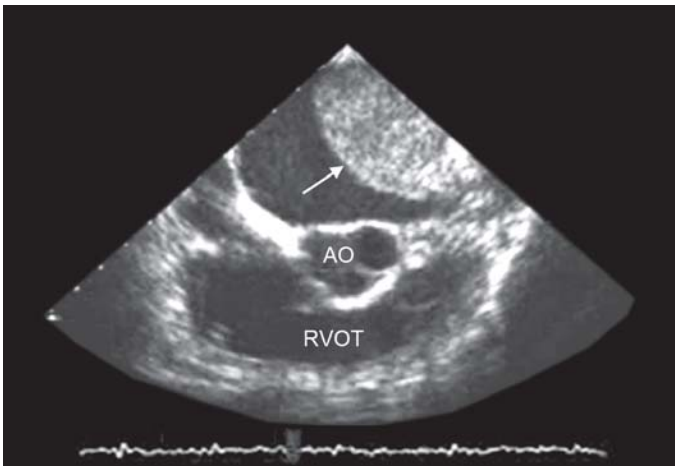


FIGURE 8B: Transesophageal echocardiography in mitral stenosis. A large clot (arrow) is seen in left atrium which is an absolute contraindication for balloon mitral valvotomy. (Abbreviations: AO: Aorta; RVOT: Right ventricular outflow tract)

from transseptal catheterization, severe MR, systemic thromboembolism and residual atrial septal defect.

Open mitral valvotomy is reserved for patients judged to be unsuitable for percutaneous procedures because of calcification, thrombus or associated regurgitation. The operation consists of dealing with cusps, commissures and subvalvar apparatus by use of fairly standardized techniques. Open surgical commissurotomy is currently indicated in patients with LA thrombus, poor valve morphology and for technical failures with BMV.

Mitral valve replacement (MVR) is needed in patients where valve morphology precludes valve conservation and in those with combined MS and MR. Emergency valve replacement is needed, if severe acute MR occurs during BMV. Valve replacement has higher post procedural event rates, including mortality, but superior freedom from repeat MV intervention. TR secondary to PH frequently accompanies MS. As such, mild to moderate TR usually improves after correction of MS. However, if severe TR exists or if there is anatomic deformity of the tricuspid valve, surgical intervention in form of ring annuloplasty is needed. A variety of surgical techniques (Maze, Cox, cryoablation and radiofrequency ablation) are available for treatment of chronic AF and are used in selected cases.

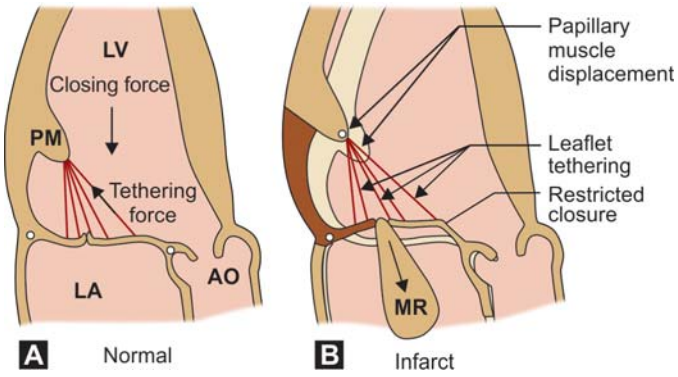
MITRAL REGURGITATION

PATHOPHYSIOLOGY AND HEMODYNAMICS

The MR consists of backflow of blood from the LV to the LA. The abnormal coaptation of the mitral leaflets creates a regurgitant orifice during systole. The severity of MR is determined by the regurgitant orifice area and the left ventricle-left atrium pressure difference which in turn is determined by the preload, the afterload and the state of LV contractility. Severe MR corresponds to greater than 50% of total LV stroke volume (the regurgitant fraction) ejected into LA through the regurgitant orifice. Moderate and mild degrees of MR correspond to regurgitant fractions of 30–50% and less than 30% respectively. To maintain a normal forward stroke volume in presence of regurgitant flow, the LV volume increases and the LV ejection fraction (EF) is usually normal to high. However, progressive LV remodeling may result in reduced LV function.[13]

The compliance of the LA (and pulmonary venous bed) is an important determinant of clinical picture and hemodynamic in patients with severe MR. In patients with normal or reduced compliance, the LA pressure and size is usually normal and sinus rhythm is maintained. However, there is marked elevation of LA (particularly V-wave), pulmonary wedge and PA pressures. This usually happens in acute MR as seen with chordal rupture and patients present with prominent congestive symptoms including florid pulmonary edema. Most of the patients with chronic MR have markedly or moderately increased LA compliance with variable enlargement. The LA pressure is normal at rest and on exertion in the majority of the patients. The incidence of AF increases in those with large LA.

In clinical practice, assessment of LV function is commonly done on echocardiography using parameters such as fractional shortening, EF and velocity of circumferential fiber shortening. All these ejection phase indices are inversely related to afterload. Since the afterload is reduced in patients with MR, these indices continue to remain normal despite impairment of myocardial contractility. A normal EF for a patient with MR is 65–75%. Once the EF drops below 60%, long-term mortality is higher. Therefore, even mild abnormality of these indices is an indicator of severe abnormality of myocardial function. This need to be



FIGURES 9A AND B: Mechanism of secondary mitral regurgitation. Balance of forces acting on mitral leaflets in systole (A) and effect of papillary muscle (PM) displacement (B). Dark shading indicates myocardial infarction; light shading indicates normal baseline (Abbreviations: AO: Aorta; LA: Left atrium; LV: Left ventricle; MR: Mitral regurgitation). [*Source:* Modified from Di Salvo (Ref. 32)]

kept in mind during follow-up of these patients especially when they are asymptomatic or mildly symptomatic.

ETIOLOGY

The MR is classified in several ways, i.e. depending on the presentation, mechanism (primary or secondary), etiology and the component of MV apparatus it involves.

A distinction is made between primary (organic) and secondary (functional) MR. In primary MR, there is derangement of one or more components of the valve apparatus, permitting back flow, causing LV volume overload. If this overload is severe and prolonged, it results in LV remodeling, dysfunction, PH, heart failure and eventually death. Correction of primary MR in a timely fashion reverses these consequences, thus, there is an unchallenged cause and effect relationship between the primary MR and its effect on the LV. It is the abnormal valve that makes the heart sick. In secondary MR, the valve itself is usually normal. However, LV previously damaged by infarction develops PMs displacement and annular dilatation, causing the MV to leak (Figs 9A and B). It is the damaged LV that causes the valve's malfunction. Because this is primarily a ventricular problem, it is less obvious that correcting the MR by itself will be curative or even beneficial. Thus, although the treatment for primary MR is relatively straight forward, the therapy for secondary MR remains controversial.

The MR can result from involvement of any of its components, e.g. valve leaflets, chordae tendineae, PMs and annulus (Table 4), and the presentation can be acute or chronic. Valve leaflets are commonly involved in RHD, degenerative valve disease and infective endocarditis (IE). In RHD, shortening of the leaflets with restricted mobility can result in incomplete coaptation of the leaflets during systole resulting in MR. The IE can actually result in perforation of the leaflets. The MV leaflets can also be affected due to trauma and as a result of congenital malformations such as double orifice mitral valve (DOMV), MV arcade, isolated cleft of the MV or cleft of the MV as a part of atrioventricular septal defect.

Chordal involvement in the form of a rupture may be seen in degenerative valve disease, RHD, IE and trauma. Chordae supporting the posterior mitral leaflet are commonly involved in degenerative mitral valve prolapse (MVP) whereas those supporting the anterior mitral leaflet are usually affected by rheumatic process. The severity of MR is dependent on the number of chordae ruptured, which in turn determines the loss of support to the leaflet and the resultant prolapse. If the loss of support is significant, it may actually result in the leaflet becoming "flail" with severe MR. Abnormality of the chordal insertion (without rupture) is known to occur in parachute MV, DOMV and MV arcade resulting in MR.

The PM involvement is most commonly seen with ischemic heart disease (IHD) resulting in acute as well as chronic MR. The posterior PM is more susceptible to ischemic injury since it has a single source of blood supply coming from the posterior descending branch of the right coronary artery. The anterior PM has a dual blood supply coming from the diagonal branches of the left anterior descending artery and the obtuse marginal branches arising from the left circumflex artery. Acute ischemia can result in transient MR due to PM dysfunction. This could revert to normal once the blood supply is reestablished. Chronic ischemia can result in shortening of the PM causing chronic MR. Although atherosclerotic CAD remains the most common cause of ischemia producing PM dysfunction, Kawasaki disease and anomalous origin of coronary artery from pulmonary artery can also result into ischemic PM dysfunction with secondary MR. Rupture of the PM is a rare complication of acute ischemia, if it is severe and long standing, and is also seen in traumatic injuries of the heart. Rupture may also occur secondary to trauma. The PM fibrosis is seen in RHD as well as in endomyocardial fibrosis, a form of restrictive cardiomyopathy. Parachute MV and MV arcade are associated with PM

TABLE 4

Causes of mitral regurgitation according to involvement of valve structures

Structure	*Etiology*
Valve leaflets	Rheumatic, degenerative, IE, trauma (surgery, BMV, others), congenital (cleft, arcade, DOMV), SLE, tumors
Chordae tendineae (rupture/abnormal insertion)	Degenerative, IE, trauma,RHD, congenital anomalies, Marfan's, Ehlers-Danlos syndrome
Annulus disorders	Degenerative, calcification, IE (abscess), trauma (surgery)
Annular dilatation	Degenerative, dilated cardiomyopathy, submitral aneurysm, other causes of LV dilatation
Papillary muscle	CAD, cardiomyopathy, trauma, infiltrative disease, Kawasaki's disease, congenital

(Abbreviations: IE: Infective endocaritis; BMV: Balloon mitral valvotomy; DOMV: Double orifice mitral valve; SLE: Systemic lupus erythematosus; RHD: Rheumatic heart disease; LV: Left ventricular; CAD: Coronary artery disease)

TABLE 5

Etiology of mitral regurgitation

Inflammatory	RHD, SLE, nonspecific aortoarteritis, Kawasaki's disease, scleroderma
Degenerative	Degenerative (MVP, flail, Barlow's disease) Marfan's, Ehlers-Danlos syndrome, pseudoxanthoma elasticum, calcification of MV annulus
Infective	IE affecting normal or abnormal valve
Congenital	MV cleft, parachute MV, MR in association with atrioventricular septal defect, CTGA, anomalous origin of coronary artery from left pulmonary artery
Traumatic	Surgery, balloon valvotomy, chest trauma

(Abbreviations: RHD: Rheumatic heart disease; SLE: Systemic lupus erythematosus; MVP: Mitral valve prolapse; MV: Mitral valve; IE: Infective endocarditis; MR: Mitral regurgitation; CTGA: Corrected transposition of great arteries)

anomalies. Infiltration of the PM is seen in restrictive cardiomyopathies secondary to sarcoidosis or amyloidosis.

Mitral annular constriction during ventricular systole is an important aspect of normal MV closure. Any condition causing dilatation of the LV causes mitral annular dilatation, thus resulting in MR. Dilated cardiomyopathy, aortic regurgitation, ischemic LV dysfunction, post tricuspid left to right shunts, such as ventricular septal defect or patent ductus arteriosus, are some of the common causes of LV dilatation resulting in mitral annular dilatation which producing MR. The MR itself can cause LV volume overload producing mitral annular dilatation thereby perpetuating MR. That is the basis of "MR begetting MR". Distortion of the MV annulus causing MR is also seen in submitral and subaortic aneurysms. Mitral annular calcification is an important cause of MR in the elderly. It is usually idiopathic and is accelerated in those with diabetes, hypertension and chronic renal failure. Annular calcification impinges on the basal portions of the MV leaflets resulting in abnormal opening as well as closing of the valve.

The etiology of MR is changing the world over. The RHD still remains a leading cause of MR in the developing countries, whereas degenerative MR is the most common etiology in the Europe and the USA. An etiological classification of MR is shown in Table 5.

RHEUMATIC MITRAL REGURGITATION

The RHD is a common cause of chronic MR. The MR often occurs in association with MS or as pure MR. The MV disease often coexists with aortic valve disease, usually aortic regurgitation. The pathology in MR includes marked fibrosis, thickening and often shortening of both leaflets and chordae tendineae, with or without calcification. These changes result in incomplete coaptation of the leaflets during systole. Secondary pathological changes consist of LA enlargement, LV dilatation and hypertrophy. The LA enlargement seen in MR is usually greater than that seen in MS.

CLINICAL DIAGNOSIS

Symptoms: Patients with chronic MR remain asymptomatic for several years due to the ease with which the LA and LV accommodate the volume overload. The regurgitation volume is initially less than the forward stroke volume. However, as the regurgitant volume exceeds the forward stroke volume, the effective forward cardiac output falls and symptoms appear. Palpitations at rest or on exertion are a common symptom and result from volume overload and forcefully contracting LV. The AF and ventricular premature beats can also cause palpitations. Fatigue is of insidious onset and is a prominent symptom when the effective forward cardiac output is compromised. Dyspnea on effort is a late event reflecting the advent of PH and LV dysfunction. Hoarseness of voice due to recurrent laryngeal nerve compression is a rare symptom. The RV failure is unusual as the PH is generally not severe. In patients with mixed MV disease, severe PH and RV failure are not uncommon. In a small percentage of patients with juvenile MR, severe PH can occur. The onset of AF usually indicates deterioration in disease status. The hemodynamic basis of symptoms in chronic and acute MR is shown in Table 6.

Signs: The arterial pulse has a brisk upstroke which becomes less pronounced with the onset of LV failure. Features of systemic venous congestion are seen in those with significant PH and subsequent RV failure. The apical impulse is normal in mild MR, slightly displaced leftward and downward in moderate MR. In severe MR, there is cardiomegaly and the apex is hyperdynamic. An apical systolic thrill is appreciated in some cases of moderate or severe MR. A diastolic thrill at the apex, due to increased transmitral gradient in diastole, may be rarely felt in severe MR even in absence of MS. A palpable left

TABLE 6

Symptoms in chronic and acute mitral regurgitation

Hemodynamics/other mechanism	*Symptoms*
Chronic MR	
LVVO, AF, VPB	Palpitations
LV dysfunction	Dyspnea, PND, orthopnea
PH, RVF	Fatigue, dyspnea, edema, pain abdomen
Compression of recurrent laryngeal nerve by LA	Hoarseness of voice
Acute MR	
Elevation of LA, PA pressure	Acute onset dyspnea, PND, orthopnea, pulmonary edema

(Abbreviations: LVVO: Left ventricular volume overload; AF: Atrial fibrillation; VPB: Ventricular premature beat; LV: Left ventricle; PND: Paroxysmal nocturnal dyspnea; PH: Pulmonary hypertension; RVF: Right ventricular failure; LA: Left atrium; PA: Pulmonary artery)

parasternal impulse in mid and late systole may be noted when a grossly dilated LA pushes the heart anteriorly against the sternum. Such a systolic impulse is late in onset, ill-sustained and less forceful as compared to the RV heave.

The auscultatory findings are influenced by severity of MR, valve morphology, rhythm and presence or absence of PH. The S1 is loud, normal or reduced in intensity whereas S2 is usually wide split in severe MR. Widening of A2P2 is due to premature closure of the aortic valve. The P2 becomes loud with the advent of PH and the split narrows when LV failure ensues. An S3 appears with severe MR and reflects rapid filling of the volume overloaded but not failing ventricle. The typical murmur of MR is usually blowing, high pitched, pansystolic but can be holosystolic with mid-systole or late-systole peak. A short mid-diastolic flow rumble may be heard at the apex indicating a large volume of transmitral diastolic flow. Additional, murmur of aortic regurgitation and stenosis may be present, if aortic valve disease coexists.

The murmur of MR at bedside needs to be differentiated from TR, ventricular septal defect and aortic stenosis. The murmur of TR is usually loudest at the lower left sternal border and increases on inspiration, in contrast to the murmur of MR which is located at the apex with radiation to back and increases on expiration. Patients with TR also show prominent "V" waves in the jugular venous pulse and pulsatile hepatomegaly. The murmur of ventricular septal defect is usually located at the left sternal border, is of higher frequency and may be associated with a systolic thrill. Aortic stenosis murmur is an ejection systolic murmur, best heard in left second intercostal space and usually radiates to the neck. The etiological differentiation of rheumatic MR from other causes like degenerative disease or functional MR is made on the basis of the typical clinical features of each entity (Table 7).

Natural History and Complications

The natural history of chronic MR is usually of slow progression from the compensated and asymptomatic state to symptomatic heart failure. The prognosis of compensated MR is usually good, with 5 and 10 years survival of 80% and 60% respectively. However, survival does not exceed 4–5 years after the onset of heart failure. Patients with combined MS and MR have a poorer prognosis, with only 70% surviving 5 years and 30% surviving 10 years after the diagnosis. Rheumatic MR may be complicated by IE and AF. The LA thrombus formation and systemic embolisation are less common than with MS, as the regurgitation stream does not permit stasis and clot formation, but the incidence of IE is distinctly higher.

DEGENERATIVE MITRAL VALVE REGURGITATION

Degenerative disease is the most common form of organic MV disease in the United States (with an estimated incidence of 2–3%), Europe and other developed countries. In developing countries, like India, MR secondary to degenerative disease is frequently encountered. The MV prolapse due to degenerative disease is defined by a spectrum of lesions, varying from simple chordal rupture involving prolapse of an isolated segment (most commonly the middle scallop of the posterior leaflet) in an otherwise normally shaped valve, to multi-segment prolapse involving one or both leaflets in a valve with significant excess tissue and large annular size. Two common forms of MV disease have been described. In the more common classic form, there are thickened and redundant myxomatous mitral leaflets resulting from abnormal connective tissue. In the non-classic form, the prolapsing mitral leaflets are normal in thickness.[14,15]

Pathology

The pathological characteristics of degenerative MV disease are variable. There is a spectrum from Barlow's disease to fibroelastic deficiency (dysplasia) (Fig. 10).

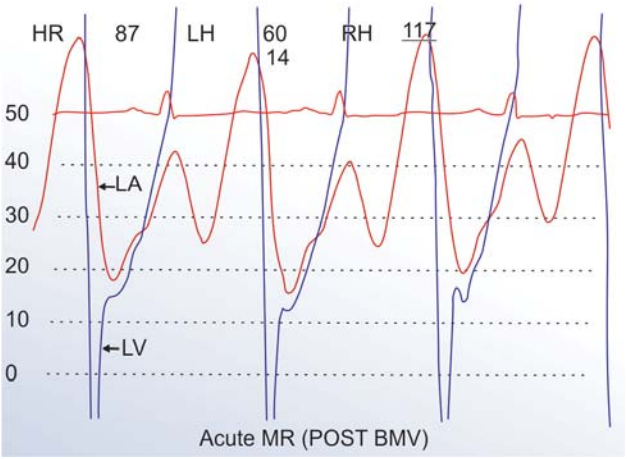


FIGURE 10: Hemodynamics in acute mitral regurgitation. Simultaneous left ventricular (LV) and left atrial (LA) pressure trace showing large V-wave in a patient who developed acute mitral regurgitation (MR) following balloon mitral valvotomy (BMV)

TABLE 7

Physical signs in mitral regurgitation

Category	*Findings*
Chronic severe MR	Cardiomegaly, LV apex, LA pulsations, apical grade 3–4/6, holosystolic murmur, MDM, S3, signs of PH, AF
Acute MR	Normal heart size, apical low pitched soft systolic murmur, S4, PH-TR
Specific signs for rheumatic MR	Findings of associated MS, aortic valve involvement
Specific signs for degenerative MR	Mid systolic click, late systolic murmur, findings of flail leaflet
Specific signs for secondary MR	Cardiomegaly, S3, early systolic murmur

(Abbreviations: LV: Left ventricle; LA: Left atrium; MDM: Mid diastolic murmur; PH: Pulmonary hypertension; AF: Atrial fibrillation; TR: Tricuspid regurgitation)

TABLE 8

Differentiation amongst common forms of degenerative mitral valve disease

	Barlow's disease	*Fibroelastic deficiency*
Pathology	Diffuse, generalized thickening of leaflets	Localized changes
Age of surgical referral (years)	Below 60	Above 60
History	Long duration of murmur	Usually short
Annulus size (mm)	≥ 36	28–32
Echocardiography	Mid-systolic and complex MR, multiple jets	• Isolated segmental prolapse (chordal rupture) • Only MVP, mild to moderate MR, late systolic prolapse

(Abbreviations: MR: Mitral regurgitation; MVP: Mitral valve prolapse)

Barlow's disease: Patients with Barlow's disease have diffuse, generalized thickening and billowing of the leaflets. The disease is characterized by diffuse excess tissue. Annulus size is generally quite large, and multiple segments are usually affected with myxomatous pathological changes, resulting in "floppy leaflets" that are thickened and distended. Diffuse chordal elongation in addition to chordal rupture is common. Severe annular dilatation, annular calcification, subvalvular fibrosis and calcification of the PMs may occur.

Fibroelastic deficiency (dysplasia): Carpentier described a condition associated with a fibrillin deficiency in which the disease is localized to isolated regions of the valve and often leads to rupture of middle scallop of the posterior leaflet. The valve segments may appear completely normal with the isolated finding of thinned chordae or the myxomatous changes in the prolapsing segment. The differences between the two variants of degenerative valve disease are shown in Table 8.

Pathophysiology

The pathophysiology of MR due to degenerative disease depends on the severity of MR and whether it is chronic or acute. Volume overload due to MR leads to LA and LV dilatation. When the severity of MR acutely increases, the pressure in the small "normal" LA abruptly increases, resulting in increase in pulmonary wedge pressure and PA pressure with resultant pulmonary edema. In contrast, when MR progresses gradually, the LA enlarges with resultant AF and the pathophysiology is nearly similar to that observed in chronic rheumatic MR.

Clinical Diagnosis

Symptoms: Those with mild or moderate MR may remain completely asymptomatic for many years. The symptoms of shortness of breath, palpitations and increased fatigability usually occur gradually and are secondary to LV dysfunction in those with severe but chronic MR. The AF worsens the existing symptoms or can present manifestation. Patients with chordal rupture present with features of acute MR like abrupt onset of dyspnea and orthopnea (Table 6).

Signs: In the majority of cases, MVP is suspected on the basis of typical auscultatory findings. A late systolic murmur is more frequent than a midsystolic click. The murmur becomes holosystolic and musical when there is flail leaflet secondary to chordal rupture. The radiation of the murmur is in the direction of the regurgitant jet. With a flail posterior leaflet, the murmur radiates anteriorly and may mimic aortic stenosis, whereas a murmur associated with a flail anterior leaflet radiates to the back (Table 7). Findings in patients with chronic severe MR resemble those seen in rheumatic MR and include a displaced apical impulse, an S3 and an accentuated P2, due to PH.

Natural History and Complications

Rupture of chordae, resulting in flail leaflet tip is the most common cause of severe MR, occurring in up to 12% patients over an average follow-up period of 1.5 years. The risk of AF, heart failure and death increases with increasing severity of MR and size of LA (≥ 50 mm). Patients with AF are at increased risk of adverse outcomes including stroke. IE is relatively uncommon in patients with MVP (life time incidence, approximately 100 cases per 100,000 patients). However, the rate is higher among those with flail leaflets (approximately 1.5% per year). Patients with flail leaflets are also at increased risk for sudden death (incidence, 1.8% per year).

MITRAL REGURGITATION CAUSED BY INFECTIVE ENDOCARDITIS

The IE can occur in normal MV but the infective process usually involves the valves affected by rheumatic, degenerative or other pathology. Endocarditis of the MV is the most common form of native valve endocarditis and carries a high morbidity and mortality in the acute phase. The most common organisms are *Streptococcus viridans*, *Staphylococcus aureus* and *Enterococcus*. The disease results in varying degrees of damage to leaflets, chordae and annular tissue, and can cause abscesses involving the surrounding myocardium. The clinical presentation is characterized by infective illness, appearance of a new murmur and heart failure. Acute MR can be the presenting manifestation if there is leaflet perforation or chordal rupture. Diagnosis of IE is confirmed by blood cultures and echocardiography.

ACUTE MITRAL REGURGITATION

Acute MR usually results from chordal rupture, PM dysfunction or rupture, leaflet tear or perforation and often presents as an emergency. The causes of acute MR are diverse and represent

TABLE 9

Causes of acute mitral regurgitation

- Infective endocarditis (leaflet perforation, chordal rupture, abscess formation)
- Chordal rupture (degenerative disease, spontaneous, Marfan's, RHD, IE)
- Papillary muscle dysfunction/rupture
- Leaflet tear during balloon mitral valvotomy, surgery
- Trauma (Blunt chest trauma, penetrating injuries, surgical technical problems)

(Abbreviations: IE: Infective endocarditis; RHD: Rheumatic heart disease)

acute manifestations of disease processes that may under other circumstances, cause chronic MR (Table 9).

Acute severe MR causes a marked reduction of forward stroke volume, a marginal reduction in end systolic volume and an increase in end-diastolic LV volume. A major difference between acute and chronic MR derives from the variation in LA compliance. Patients who develop acute severe MR usually have a normal sized LA with normal or reduced LA compliance. The LA pressure (particularly the V-wave) (Fig. 11) rises abruptly and there is marked elevation of pulmonary vascular resistance. Almost all patients are symptomatic and symptoms include dyspnea, orthopnea, exercise intolerance, fatigue, right sided heart failure, pulmonary edema or shock. The murmur of acute MR is lower pitched, softer and decrescendo rather than holosystolic. A left sided S4 is frequent, P2 is often accentuated and TR can occur due to PH (Tables 6 and 7). Majority of the patients require early valve repair or replacement surgery.

SECONDARY MITRAL REGURGITATION

In secondary MR, the valve's malfunction is secondary to the damaged LV. In these patients, the mitral leaflets are structurally normal but leaflets fail to coapt due to an imbalance between the forces tending to close the valve and those trying to tether it. Impaired LV contractility, global LV dyssynchrony and reduced mitral annulus systolic contraction lead to a significant reduction in valve closing forces. In turn, valve tethering forces are increased due to mitral annulus dilatation, LV remodeling and PM displacement. Furthermore, MR per se induces additional adverse ventricular remodeling through volume overload and plays an important role in the progression of the cardiomyopathy.

Functional MR is common in the setting of ischemic or nonischemic LV dysfunction. Ischemic MR is increasingly prevalent with significant MR occurring in 30% of the patients with myocardial infarction (MI). The presence and severity of MR, as well as its progression, are independently associated with increased mortality. The clinical picture is dominated by chronic heart failure and at times the presentation is with angina, AF or ventricular arrhythmias. Chronic MR can lead to acute pulmonary edema even in absence of acute myocardial ischemia. Usually, there is cardiomegaly, displaced apical impulse, S3 and low intensity apical systolic murmur which peaks in early systole.

INVESTIGATIONS

Electrocardiogram

Electrocardiogram is frequently normal in patients with mild or moderate chronic MR. The LA and LV enlargement occurs with increasing severity and duration of MR. The AF is frequent and the incidence varies with the etiology, age and severity of MR.

In secondary MR, electrocardiography shows Q waves, most frequently in the inferior and/or lateral leads and a left bundle branch block.

Radiological Evaluation

Roentgenogram of the chest is usually normal in patients with mild MR. Cardiomegaly is often seen in patients with chronic severe MR and is contributed by enlargement of LV and LA (Fig. 12). The LA size is determined by the compliance of the LA. In chronic severe MR, giant LA is seen occupying the entire cardiac silhouette. Signs of pulmonary venous hypertension are seen late and usually indicate LV dysfunction. In severe acute MR, despite marked elevation of PASP, the cardiac size is

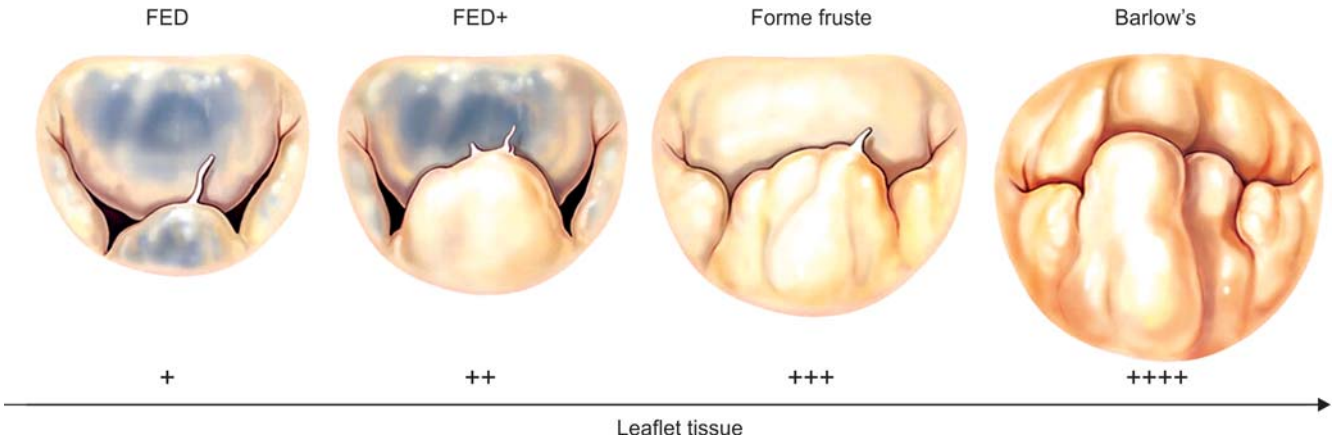


FIGURE 11: Spectrum of degenerative mitral valve disease. In isolated fibroelastic dysplasia (FED) there is deficiency of collagen and a ruptured thin chordae. In long-standing prolapse, myxomatous changes occur with leaflet thickening (FED+). Forme fruste has excessive tissue, myxomatous changes in one or more leaflets, but does not involve a large valve size. In Barlow's the hallmarks are large valve size, with diffuse myxomatous changes and excess leaflet tissue, with thickened, elongated and often ruptured chordae

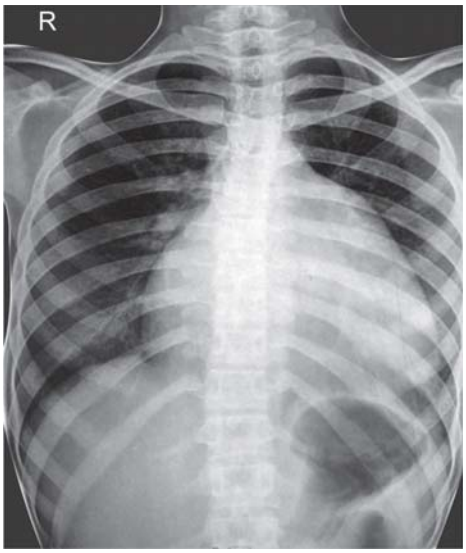


FIGURE 12: Roentgenogram of chest posteroanterior view. X-ray in a patient with chronic severe mitral regurgitation shows prominent left atrial appendage and cardiomegaly

usually normal and only mild enlargement of LA is seen. Signs of pulmonary venous congestion are often prominent.

Echocardiography

Apart from confirming the diagnosis of MR, the technique provides information regarding etiology and severity thereby helping and deciding the time and type of intervention (e.g. valve repair or replacement). A systematic approach to echocardiography is recommended. The 2D or 3D TTE and TEE, Doppler interrogation and color flow mapping give comprehensive information. The TEE is superior to TTE for defining the anatomy of the MV, for detection of vegetation especially if the valve is calcific and to interrogate the LA appendage. It is extremely useful in those with suboptimal TTE window. The 3D echocardiography provides superior imaging of the MV components and is currently utilized intraoperatively. Stress echocardiography is emerging as a useful modality. This technique estimates the LV functional reserve in patients with chronic MR. Exaggerated rise in PA pressure (i.e. > 60 mm Hg with exercise), is suggestive of reduced LV functional reserve and can be considered as an indication for surgery.

It can help distinguish among rheumatic MR (thickened leaflets with restricted motion, calcification, and chordal shortening) (Fig. 13), degenerative disease[16-18] (characterized by thickened and redundant leaflets with excessive motion and prolapse) (Figs 14A and B) and congenital heart disease (cleft valve) and rule out secondary MR due to ischemic or non-ischemic LV dysfunction. In fibroelastic deficiency, echocardiographic findings include an isolated segment prolapse due to chordal rupture leading to holosystolic MR. In Barlow's disease, echocardiography shows midsystolic and often complex regurgitation with multiple jets consistent with diffuse myxomatous involvement. Billowing of one or both leaflets is often seen. The posterior leaflet is displaced toward the LA free wall away from the ventricular hinge, resulting in a cul-de-sac along the posterior portion of the annulus, which may be a precipitating factor for annular fissures and calcification. Echocardiography (TTE or TEE) demonstrates vegetations, delineates valve morphology, hemodynamics and dictates the timing of surgery in IE. Involvement of other valves, e.g.

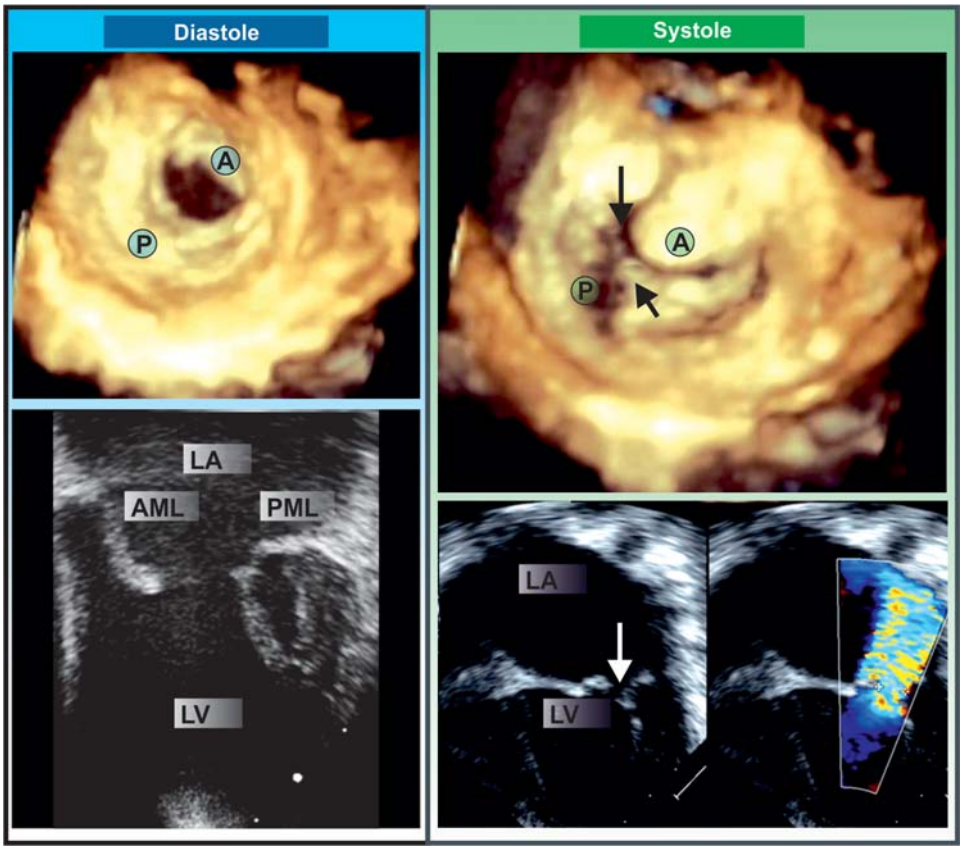
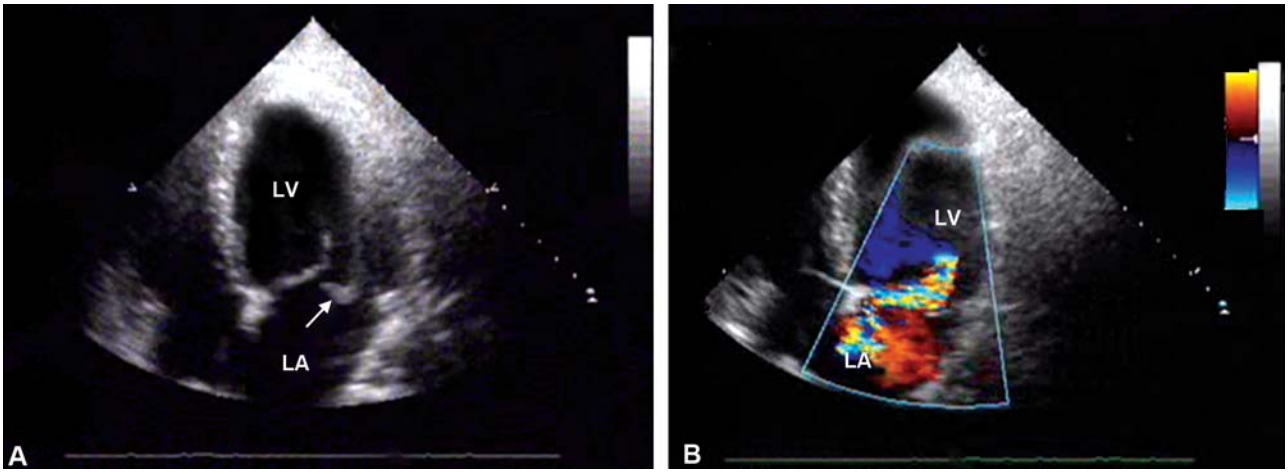


FIGURE 13: Three dimensional (3D) echocardiography, two dimensional (2D) echocardiography and color Doppler in mitral regurgitation (MR). The 3D echocardiography and 2D echocardiography images of the mitral valve (MV) in diastole and systole reveal in a 10-year-old boy with rheumatic MR. The 3D diastolic frame reveals adequate mitral valve orifice from the left atrial (LA) aspect. The 2D image in diastole reveals restricted posterior mitral leaflet (PML) motion, thickened subvalvar structures which are hallmarks of rheumatic affection. The 2D systolic frame shows incomplete coaptation of the MV leaflets with posteriorly directed mitral regurgitation jet. The true crescentic regurgitant orifice is obvious only on 3D systolic frame



FIGURES 14A AND B: Echocardiography in degenerative mitral valve disease. (A) Two dimensional echocardiography images in apical four chamber view showing prolapse of the posterior mitral leaflet (arrow). (B) Color flow showing images severe mitral regurgitation. (Abbreviations: LV: Left ventricle; LA: Left atrium)

associated aortic and tricuspid valve involvement in RHD or degenerative tricuspid valve disease can also be assessed.

Echocardiography guides the timing of surgical intervention[19] especially in those patients with chronic MR who are asymptomatic by estimating the severity of regurgitation, LV function and size, LA size, PA pressure, LA volume, LV end systolic and end diastolic volumes, stroke volume, EF and regurgitant fraction. There are number of techniques which use color flow mapping and spectral Doppler for semiquantitative and quantitative assessment of MR. Specific signs for the presence of severe MR include a vena contracta with greater than or equal to 0.7 cm with a large central regurgitant jet (area > 40% of LA), wall impinging jet of any size, a large flow convergence, systolic flow reversal in pulmonary veins or a prominent flail mitral leaflet or ruptured chordal apparatus. The supportive signs include a dense triangular continuous wave (CW) Doppler MR jet, E-wave dominant mitral inflow (E > 1.2 m/s) or enlarged LV and LA. The quantitative parameters include an effective regurgitant orifice area greater than or equal to 40 cm^2, a regurgitant volume greater than or equal to 60 ml and a regurgitant fraction greater than or equal to 50%. Since estimation of all these parameters have limitations, it is important to look at multiple echocardiographic variables and assess them in the background of the clinical presentation in order to make a decision regarding the nature and timing of intervention.

Echocardiographic findings that are predictive of cardiovascular complications or death from cardiovascular causes among patients with degenerative MV disease include a flail mitral leaflet, severe regurgitation (i.e. regurgitation with an effective regurgitant orifice area > 0.4 cm^2), a left ventricular ejection fraction (LVEF) of less than 60%, an LV end systolic dimension of 40 mm or greater, and an LA dimension of 50 mm or greater.

In acute MR, echocardiography shows little increase in internal diameter of either the LA or LV. Characteristic features of Doppler echocardiography are the wide jet of MR and elevation of the PASP. It demonstrates structural abnormality like chordal rupture, flail leaflet or PM rupture depending on the etiology and dictates the need of early surgery.

In secondary MR, 2D echocardiography, 3D echocardiography, tissue Doppler imaging and dobutamine echocardiography provide key information regarding the LV function, LV volumes, morphology of MV, severity of MR and regional dyssynergy and viability.

Cardiac Catheterization

Cardiac catheterization is rarely indicated for the diagnosis of MR. Coronary angiography is required in patients who have known or suspected CAD, risk factors for CAD or in ischemic MR.

Computed Tomography

Recently, 64-slice multislice computed tomography[20] (MSCT) has been utilized to provide anatomic and geometric information about the MV apparatus. The technique may be of value to guide surgical treatment of MR.

Cardiovascular Magnetic Resonance Imaging

Cardiovascular magnetic resonance imaging[21] has recently been used to identify MVP and show regurgitant jets. It can match the diagnostic sensitivity and specificity of TTE. This technique, in addition, can measure LV volumes, identify myocardial scar and detect fibrosis involving the PMs.

MANAGEMENT

Medical Treatment

There is no proven medical therapy[22] for the treatment of chronic MR. In MR, secondary to RHD, rheumatic prophylaxis using benzathine penicillin or other suitable agent is recommended. The IE prophylaxis is often warranted. The vasodilators are useful in stabilizing patient with acute MR by reducing regurgitant fraction. Role of vasodilator in chronic, asymptomatic MR with preserved LV function is debatable. However, angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) are certainly recommended for the treatment of heart failure. Diuretics are useful in patients with congestive symptoms.

Surgical Treatment

The MR is a mechanical problem that can only be corrected with a mechanical solution, that is, restoration of valve competence, thus removing the volume overload and its deleterious consequences. The definitive treatment of hemodynamically significant MR is the surgical correction of MR. Three different MV operations are currently used for correction of MR: (1) Repair; (2) MVR with preservation of part or all of the mitral apparatus and (3) MVR with removal of the valve apparatus. Each procedure has its advantages and disadvantages and, therefore, the indications for each vary according to the etiology and the surgical expertise.

According to American College of Cardiology/American Heart Associating guidelines (2006), surgery is recommended for the management[10,23,24] of chronic severe MR in symptomatic patients and asymptomatic patients with evidence of LV dysfunction, defined as an LVEF of 30–60% and LV end systolic dimension of 40 mm or greater. The guidelines mention that patients with a severely reduced LVEF (< 30%) may not benefit from surgery. Other reasonable indications for surgery[25] in asymptomatic patients include elevation of PA pressure and new onset AF. The management of asymptomatic patients with normal LVEF remains controversial. The debate regarding surgery in these patients stems from reports suggesting reduced long-term survival in patients managed conservatively. In this group, surgery is recommended if chances of a successful repair are greater than 90%. Recent reports[26] from the Europe and the USA indicate that despite guidelines many patients are not referred for surgery due to reluctance on the part of patients and physicians as well as due to advanced age, comorbidities or impaired LV function.

The MVR in which MV apparatus is resected is often performed in RHD where the valve apparatus is severely distorted by the disease process. The advantages of MVR with preservation of the chordal apparatus is that this operation preserves LV function, enhances postoperative survival compared with MVR, in which the apparatus is disrupted. This procedure is performed in selected patients with RHD or end stage Barlow's degenerative disease. The use of prosthetic valve has inherent disadvantages, the risk of deterioration in tissue valves or the need of anticoagulation in mechanical valves. The choice of mechanical or tissue valve is guided by the age, presence or absence of AF, feasibility of anticoagulation and cost considerations.

The MV repair[27-30] has a clear advantage over replacement, as it preserves LV systolic function, obviates the need for oral anticoagulation and improves survival. Figure 15 shows lower operative mortality and better survival rates at 10 years by valve repair compared with MVR. It is currently the operation of choice for MR secondary to degenerative valve disease. Valve repair with artificial chordal reconstruction is occasionally feasible in rheumatic MR.

Repair is associated with low rates of operative mortality (1–3%). In a recent meta-analysis of 29 observational studies, the early and longer term mortality were significantly lower after repair than with replacement. The valve morphology and surgical expertise are of crucial importance for the success of the procedure. In experienced high volume centers, the likelihood that repair (rather than valve replacement) can be performed is 80–90%. The valve repair procedure restores a good surface of leaflet coaptation and corrects the annular dilatation. In terms of valve repair techniques, Carpentier's techniques which involve resection of abnormal or pathologic tissue with precise reconstruction toward essentially "normal valve anatomy" remain the most commonly performed worldwide, and are associated with excellent long-term outcomes. Another technique, which has become popular, is based on the use of polytetrafluoroethylene (PTFE) neochordae to reconstruct support of the free edge of the prolapsing segments. This technique is preferred in many centers due to its simplicity and encouraging early results. Calcification of the MV apparatus may occur in the setting of degenerative valve disease and debridement of calcified tissue is required to ensure a good mobility of leaflet tissue and to ensure an adequate surface of coaptation. Prosthetic ring or band annuloplasty restores the normal circumference and shape of the MV annulus and is a mainstay of all repair procedures regardless of the technique employed (Figs 16A to D).

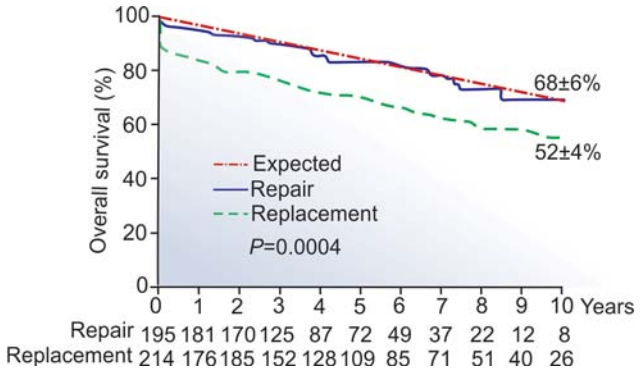
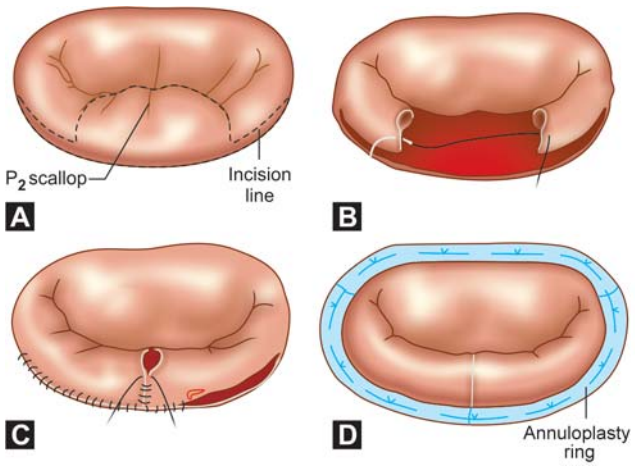


FIGURE 15: Postoperative survival. Following mitral valve repair, postoperative survival is compared to that mitral valve replacement. [*Source:* Modified from Carabello BA (Ref. 25)]



FIGURES 16A TO D: Steps for surgery for mitral valve prolapse. (A) Shows the surgeon's view, from the atrium of a valve with a flail P2 scallop. Dashed line shows the planned incision of ruptured and elongated chordae. (B) View after resection of the diseased portion. (C) Re-apposition of the leaflet edges. (D) Reconstructed valve with a annuloplasty ring



FIGURE 17: MitraClip device. This device is covered with polyester fabric to facilitate tissue ingrowth. The distal gripping element helps with leaflet fixation. The clip delivery system exits through a guide catheter. (*Source:* Feldman T, Kar S, Rinaldi M, et al. Percutaneous mitral repair with the MitraClip system: safety and midterm durability in the initial EVEREST (Endovascular Valve Edge-to-Edge REpair Study) cohort. J Am Coll Cardiol. 2009;54(8):686-94, with permission)

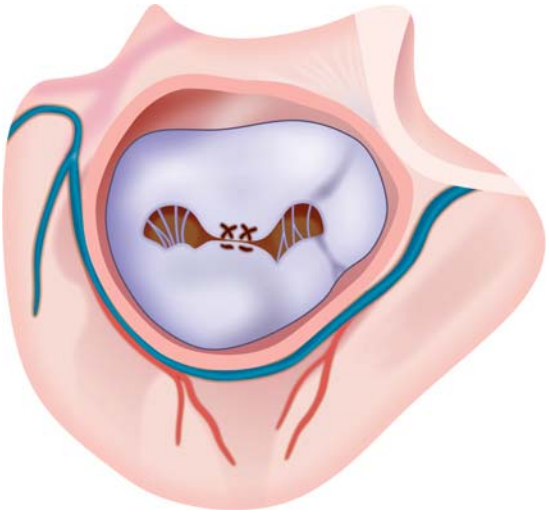


FIGURE 18: Double orifice mitral valve (MV) surgical repair. The MV is viewed from the left atrial side. The middle scallops of the anterior and posterior leaflets have been sutured together, which creates a double orifice, edge-to-edge, or bow-tie repair. [*Source:* Modified from Feldman T (Reference 29)]

Unfortunately, surgical repair is not always feasible, and at many centers, the required surgical expertise is not available which results in patients ending up with MVR.

Minimally invasive valve surgery[31] refers to a constellation of surgical techniques/technologies that minimize surgical trauma through smaller incisions compared with a conventional sternotomy. The most common minimally invasive approach for MV repair, MVR includes a right thoracotomy, a robotically assisted right thoracic approach, and a partial sternotomy. In highly experienced centers, minimally invasive surgery is safe, efficient treatment option providing greater patient satisfaction and fewer complications.

Percutaneous MV repair is a new technique which has been investigated for treatment of MR due to degenerative valve disease and secondary MR using a clip (Evalve MitraClip) (Fig. 17) made of a cobalt-chromium alloy and Dacron. The edge to edge technique (Fig. 18) mimics the surgical procedure introduced by O Alfieri, which creates a double mitral orifice by means of a few stitches securing the two leaflets together at their mid part. The current experience in more than 500 patients suggests that the technique although demanding, is feasible and safe in experienced hands. The immediate outcomes are favorable with 30 day mortality in 0–2% and functional improvement in 66–90% of patients at 30 days. Two-thirds of patients can be discharged with a clip in place and less than or equal to two-fourth with MR . Mid-term (3 years) results show that two-thirds of patients remain alive without severe MR or need of repeat surgery. In future, this technique may play a role in the treatment of patients with MR who are denied surgery due to high surgical risk.

Surgery in IE is indicated for those with acute MR secondary to chordal rupture or leaflet perforation, uncontrolled heart failure,[32] large and mobile vegetation and when intensive specific antibiotic therapy fails to control infection. The MVR has been the standard surgical therapy but recent reports suggest that repair is feasible depending on the degree of tissue destruction. The principles of MV repair in endocarditis are to remove all the infected tissue and to avoid implantation of foreign material. Early repair could avoid excessive damage to the valve and gives excellent long-term result. Repair techniques include excision of infected tissue followed by direct reconstruction, use of autologous or xenogenic pericardium to repair leaflets, or use of artificial chordae. The results of repair appear to be superior to those of replacement, in terms of both survival and incidence of complications or recurrence of infection.

Treatment of Secondary Mitral Regurgitation

The therapeutic options in functional MR include medical therapy, devices and surgery. The ACE inhibitors and beta-blockers which reduce MR by progressive reverse remodeling are indicated. Digoxin, diuretics, nitrates and spironolactone are also useful. Cardiac resynchronization therapy[33] (CRT) is beneficial in selected patients and has been shown to reduce functional MR. The benefits are attributed to several mechanisms. The reduction in LV dyssynchrony and the improvement in LV contraction immediately after CRT can significantly increase valve closing forces. Chronically (≥ 6 months), LV reverse remodeling and changes in mitral apparatus geometry can further reduce MR by reducing mitral leaflet tethering. More than half of the responders to CRT sustain decrease of at least one grade in MR for at least 6 months. Significant MR recurs if effective CRT is interrupted or discontinued.

The failing ventricle usually benefits from relief of severe MR. Several procedures like coronary artery bypass grafting (CABG), MVR with chordal sparing, MV repair (surgical or percutaneous) and ventricular remodeling are available. There are several unanswered questions regarding appropriate patient selection, acceptable perioperative mortality, long-term survival benefit and the choice of the operation. Percutaneous MV repair

using MitraClip[34] has recently been shown to be feasible and safe in patients with functional MR secondary to severe LV dysfunction. The precise indications and long-term follow-up remain uncertain. The role of percutaneous ring annuloplasty to reduce annular dilatation is also being investigated.

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Chapter 57

Tricuspid Valve Disease: Evaluation and Management

Pravin M Shah

Chapter Outline

- Introduction
  - Tricuspid Valve—Forgotten No More
- Embryology
- Valve Anatomy
  - Annulus
  - Leaflets
  - Chordae Tendineae
  - Papillary Muscles
- Normal Tricuspid Valve Function
- Tricuspid Valve Dysfunction
  - Etiology of Tricuspid Valve Disease
- Clinical Presentation
  - Symptoms
  - Physical Signs
- Laboratory Diagnosis
  - Electrocardiogram
  - Chest Radiograph
  - Echocardiography
  - Transesophageal Echocardiography
  - Cardiac Catheterization and Selective Angiography
- Treatment
  - Appropriate Timing
  - Management Strategies
  - Surgical Treatment of Primary Tricuspid Valve Regurgitation

INTRODUCTION

TRICUSPID VALVE—FORGOTTEN NO MORE

Tricuspid valve (TV) is often described as the forgotten valve deserving of more respect. The background for de-emphasis of TV function relates to clinical observations in congenital and acquired heart disorders.[1-4] For instance, a surgical anastomosis of vena cava to pulmonary artery (Glenn procedure) is capable of sustaining life when pulmonary artery pressure is normal or low. Secondly, total resection of the TV in recurrent infective endocarditis among intravenous drug users has resulted in successful outcome at least in the intermediate term. Thirdly, surgical mitral commissurotomy resulted in reduction in pulmonary hypertension, even when advanced, and progressive improvement in tricuspid regurgitation (TR). These observations led to a clinical paradigm of ignoring functional TR during mitral and/or aortic valve surgery and more recently coronary bypass surgery with expectation that the TR would regress and not pose a long-term hazard. Recent reports have contradicted this paradigm based on observational studies. A new paradigm has emerged for diagnosis and management of functional TR. This has been discussed in this chapter.

EMBRYOLOGY

The septation of atria and ventricles in the fetal circulation is followed by formation of endocardial cushions at the crux of the heart. The atrioventricular (AV) valves develop subsequently. Prior to septation, the right atrium communicates directly into the cavity of the left ventricle. The ventricular septation communicates right atrium to the right ventricle and subsequently the TV leaflets and their tension apparatus develops. The septal leaflet is formed from the muscular ventricular septum together with posteroinferior endocardial cushions. This may provide an explanation for the septal leaflet participating in spontaneous closure of a small perimembranous ventricular septal defect (VSD) in childhood. The architecture of the two AV valves is intimately tied to the corresponding ventricles. This relationship demonstrates that the mitral valve is connected to the anatomic left ventricle, and the TV is connected to the anatomic right ventricle. This relationship is emphasized in the congenitally corrected transposition of great arteries with functionally intact circulation, such that the anatomic right ventricle becomes the systemic ventricle and anatomic left ventricle becomes the pulmonary ventricle. The corresponding AV valves are transposed along with the ventricles. Thus, the TV becomes a left sided valve between the left atrium and anatomic right ventricle, which is the systemic ventricle connected to the aorta. Similarly, the mitral valve is transposed with anatomic left ventricle, which is the pulmonary ventricle connected to the pulmonary artery and low resistance pulmonary circulation. Congenitally corrected transposition, in absence of other malfunctions, is compatible with life into sixth and seventh decades. This speaks the adaptation of the anatomic right ventricle and TV to high pressure, high resistance systemic circulation.

Since the formation of AV cushions at the crux of the heart are central to distinctive anatomy of the two AV valves, the

congenital absence of AV cushions, partial or complete, result in striking abnormalities of the two AV valves. The attachment of septal leaflet of TV is normally more apical as that the mitral valve, a small defect is capable of providing shunting of blood from the left ventricle with the right atrium. This defect, when isolated, is anatomically small and is known as Gerbode defect. Another anatomic consideration is that the septal leaflet of the TV is attached to membranous interventricular septum. Thus, perimembranous VSDs distort this portion of the TV, which can grow over the defect resulting in spontaneous closure of small perimembranous VSD in childhood.

VALVE ANATOMY

The TV is most caudally located and has the largest orifice among the four intracardiac valves. It functions as a unidirectional valve permitting systemic venous blood flow from right atrium, and hence from the two vena cava and the coronary sinus to the right ventricle during diastole and prevents backflow or regurgitation during systole. The TV apparatus is composed of the annulus, the leaflets, the chordae and papillary muscles. Its coordinated function is also influenced by the geometric alterations of the right ventricle and the right atrium.

ANNULUS

The tricuspid annulus is oval in shape, but assumes a more circular shape on dilatation. It has been shown to have a more complex nonplanar shape with posteroseptal commissure being the highest. The annular shape, besides becoming more circular flattens out and becomes more planar in presence of severe "functional" regurgitation. The annular diameter, circumference and area are all larger than the mitral valve by about 20%. Although values of major tricuspid annular diameter of 30–35 mm are described for normal adults body surface area (BSA) (1.5–1.7 m^2), the orifice size is influenced by overall body size as reflected in BSA. Thus, while a measured diameter of 40 mm in an average size normal adult represents dilated annulus, this may be normal for a person with BSA in excess of 2.0 m^2. Thus, size of an individual patient must be considered in assigning the given measure as normal or abnormal. The average normal annular diameter is 21 ± 2 mm/m^2. A hemodynamic consequence of the normal larger tricuspid annulus orifice is lower transvalve flow velocities and lower pressure drops during diastolic inflow than in the normal mitral valve. The annulus exhibits a dynamic behavior similar to the mitral annulus with expansion of the orifice in diastole and reduction in systole.[5] The maximum to minimum area reduction is nearly 30%. This dynamic behavior promotes forward flow while maintaining low right atrial and systemic venous pressures.

LEAFLETS

The TV has three leaflets; anterior, septal and posterior, the anterior being the largest and septal being the smallest. The septal leaflet attachment is from posterior ventricular wall across the interventricular septum, its insertion being more apical relative to the anterior leaflet. The anterior leaflet is attached to the right AV junction. The posterior leaflet has mural attachment. Some anatomists have described the TV as being truly bicuspid; however, there is little support of this observation. Occasionally, four distinct cusps are observed.

CHORDAE TENDINEAE

The tendinous chords are attached to the ventricular surface of the leaflets or the free edges of the leaflets to the papillary muscle supporting the leaflet. There may be accessory chords that attach from the septal leaflet to the moderator band or the right ventricular (RV) free wall.

PAPILLARY MUSCLES

There are three sets of papillary muscles, each set being composed of up to three muscles. The chordae arising from each set are inserted into two adjacent leaflets. Thus, the anterior set chordae insert into half of anterior and half of posterior leaflets, the medial set provides chordae to anterior and septal leaflets. The third posterior set is more rudimentary and is attached to the diaphragmatic wall of the right ventricle.[6]

NORMAL TRICUSPID VALVE FUNCTION

The diastolic opening of the valve along with corresponding expansion of the annulus provides a tricuspid orifice area of 7–9 cm^2. This large orifice provides unimpeded flow both at rest and with physical activity without elevations in central venous pressures. The systolic narrowing of the orifice provides an effective seal for valve closure. However, a measure of TR detected by Doppler echocardiography is observed in 80–90% of normal subjects. The majority of patients with physiologic TR are in the mild category, but a small number of otherwise healthy individuals may have moderate regurgitation. A failure to appreciate this may result in identifying as abnormal what is a normal variant.

TRICUSPID VALVE DYSFUNCTION

The TV disease is generally classified as primary or intrinsic valve pathology or secondary or functional valve dysfunction.[7,8] The primary valve disease results from structural abnormality of the valve apparatus. The secondary or functional TV disease results from the factors that generally lead to tricuspid annular dilatation commonly from left heart disease and resulting RV hypertension, dilatation and dysfunction[9] (Flow chart 1).

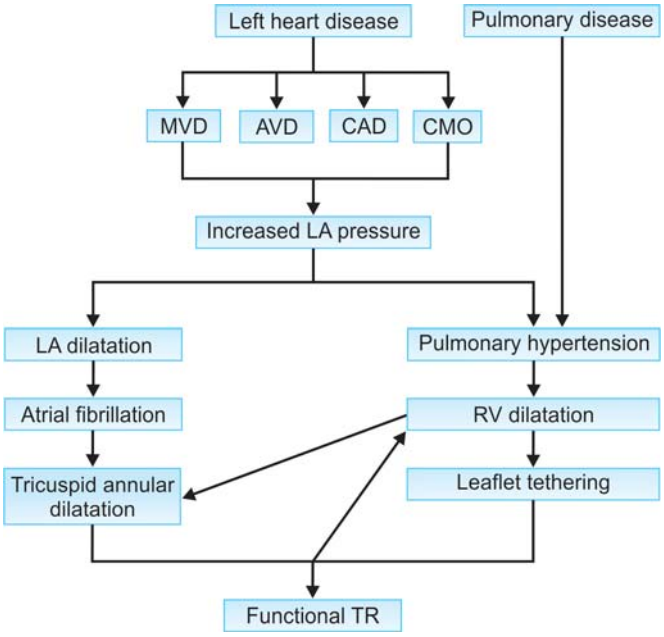
ETIOLOGY OF TRICUSPID VALVE DISEASE

Primary Tricuspid Valve Disease

These are characterized by intrinsic pathology of the valve apparatus:

- Congenital
  - — Ebstein's anomaly
  - — Congenital cleft valve
  - — Congenital tricuspid stenosis
  - — Tricuspid atresia
- Acquired
  - — Rheumatic
  - — Infective endocarditis
  - — Degenerative: tricuspid valve prolapse

FLOW CHART 1: Functional TR—Pathogenesis

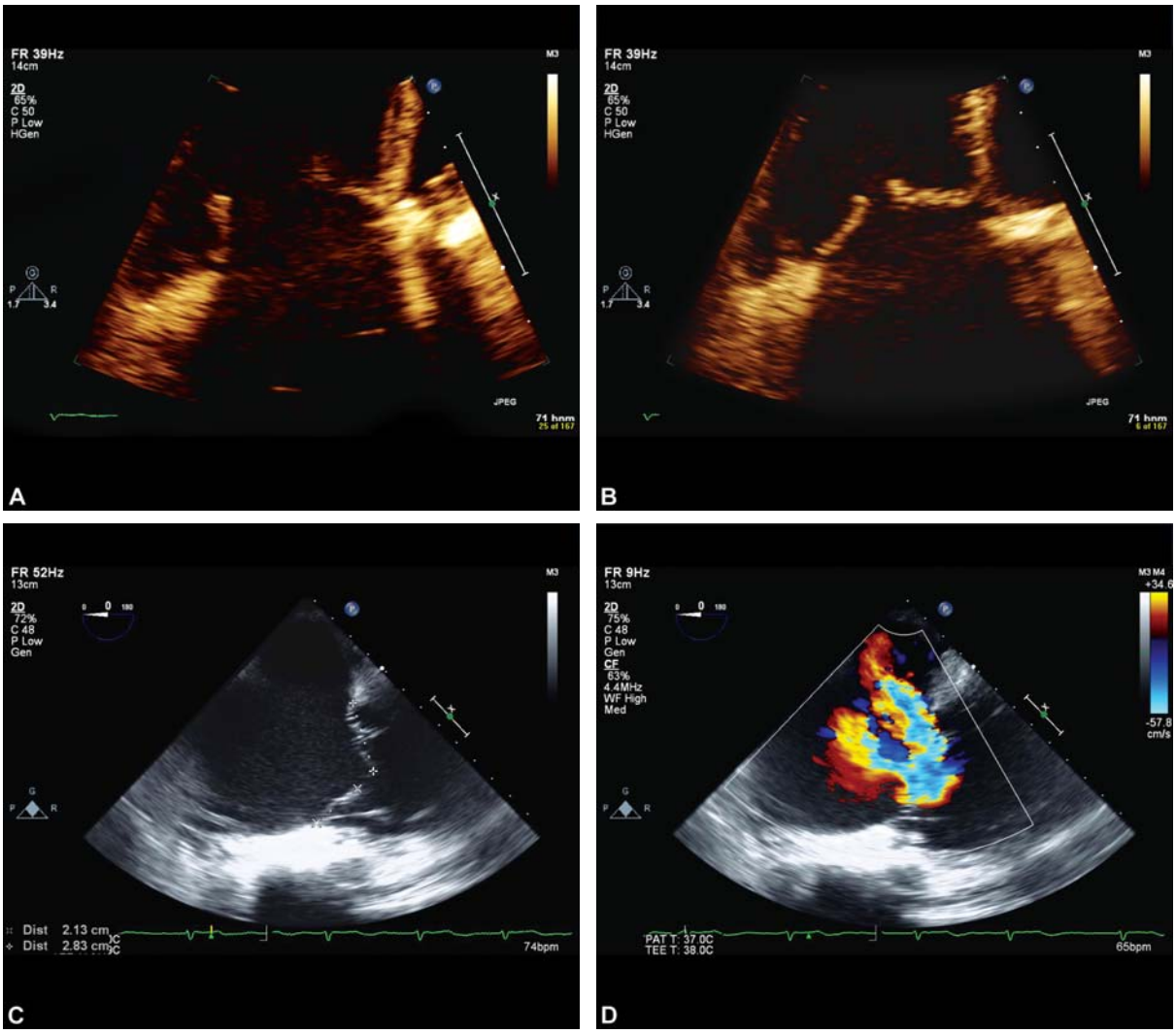


— Carcinoid heart disease
— Toxic [e.g. phen-fen or methysergide valvulopathy (?)]
— Tumors (e.g. fibroelastoma, myxoma)
— Trauma (e.g. pacemaker lead trauma, or use of biopsy instrument)
— Radiation injury.

Secondary or Functional Tricuspid Valve Disease

These are characterized by normal valve apparatus aside from abnormal annular dilatation and tethering of leaflets in systole (Figs 1A to D):

- RV dilatation (e.g. atrial septal defect, pulmonary regurgitation)
- RV hypertension (e.g. pulmonary hypertension, pulmonary stenosis)
- RV dysfunction (e.g. cardiomyopathy, myocarditis)
- Segmental RV dysfunction (e.g. ischemia or infarction, endomyocardial fibrosis, arrhythmogenic RV dysplasia) Asymmetric tethering with segmental pathology may lead to an eccentric jet
- Chronic atrial fibrillation (with right atrial and annular dilatation).



FIGURES 1A TO D: Functional tricuspid regurgitation. (A) Tricuspid valve in diastole in fully open position. (B) Tricuspid valve in systole exhibits incomplete closure with central orifice of regurgitation. (C) Transesophageal echocardiography cross-section exhibits dilated annulus (4.9 cm), and systolic tethering distance of 1.6 cm with incomplete valve closure. (D) Transesophageal echocardiography cross-section with prominent central jet of tricuspid regurgitation

CLINICAL PRESENTATION

The abnormal valve function may be in the form of: (1) pure or predominant tricuspid stenosis; (2) pure or predominant TR or (3) mixed.

SYMPTOMS

Since the TV disease is rarely observed in isolating the symptoms of left heart disease predominate. The symptoms specific to advanced TV disease are related to: (1) decreased cardiac output, for example, fatigue; (2) right atrial hypertension, for example, liver congestion resulting in right upper quadrant discomfort, or gut congestion with symptoms of dyspepsia, indigestion, or fluid retention with leg edema and ascites. It may be emphasized that significant TV disease may not be associated with any symptoms until a late stage of the disease involving progressive RV dysfunction. Symptoms caused by underlying etiology, such as flushing, diarrhea, abdominal pain, etc. associated with carcinoid heart disease point to the etiology.

PHYSICAL SIGNS

These include signs related to TV disease and those secondary to chronic venous congestion, that is, leg edema and ascites.

Tricuspid stenosis results in characteristic changes in the jugular venous pulse in the form of a slow "V" to "Y" descent and prominent "A" waves. The liver is enlarged with a firm edge, and pulsatile in presystole. Auscultation reveals a low-to-medium-pitched diastolic rumble with inspiratory accentuation. This is usually localized to the lower sternal border.[10]

The TR results in the jugular venous pulse exhibiting prominent "C-V" wave or systolic wave. The prominent systolic (C-V) wave is observed in the absence of severe right atrial dilatation, which may render it more compliant. The C-V wave indicates severe regurgitation. It may be confused with high central venous pressure and rapid Y descent seen in constrictive pericarditis. The latter is also associated with rapid X descent. Observing the venous pulsations simultaneously with cardiac auscultation provides striking differences between severe TR and constrictive pericarditis, both conditions associated with jugular venous distension. There is often a parasternal lift from RV enlargement. The liver is pulsatile in systole and is best appreciated by observing the examiner's hand pulsate during held respiration. The cardiac auscultation reveals a soft early or holosystolic murmur which is augmented with inspiratory effort (Carvallo's sign). A systolic honk may be present with TV prolapse.[11] Substantial TR may exist without the classic auscultatory findings. Thus, neither presence nor quantitation of TR can be reliably judged by auscultation. The pulsatile liver and prominent C-V waves in jugular veins are signs of severe regurgitation. These should be carefully assessed at the bedside (Table 1).

TABLE 1

Clinical signs of severe tricuspid regurgitation

- Venous pulse: Prominent systolic (C-V) wave
- Holosystolic murmur increasing in intensity with inspiration (Carvallo's sign)
- Hepatomegaly with systolic pulsation
- Parasternal lift especially with right ventricular hypertension

Note:

- The classic systolic V wave is present in less than 75% of patients
- The murmur is heard in less than 20% of patients
- Hepatomegaly is noted in 90%, but systolic pulsation is inconsistent
- Parasternal lift also occurs with severe mitral regurgitation, being late systolic

LABORATORY DIAGNOSIS

ELECTROCARDIOGRAM

There are no specific markers of TV disease, although the following clues may be present: (1) RV hypertrophy and "strain" with right QRS axis and (2) right atrial enlargement with prominent P waves. Specific electrocardiograph signs of primary etiology may be noted such as left axis deviation and complete right bundle branch block in AV canal defect associated with cleft valve, and Ebstein's anomaly may exhibit wide QRS.

CHEST RADIOGRAPH

Cardiomegaly associated with prominent right heart borders may be noted. There are no specific findings to suggest a diagnosis of TV disease.

ECHOCARDIOGRAPHY

Two-dimensional echocardiogram combined with spectral and color flow Doppler evaluation provides the most accurate laboratory test in detection and quantitation of TV disease. In addition, the TV morphology provides clues of underlying etiology and pathophysiology of valve dysfunction.[12]

Tricuspid Valve Morphology

Ebstein's anomaly is characterized by apical displacement of the septal tricuspid leaflet into the right ventricle by more than 8 mm/m² from the insertion point of the anterior mitral leaflet at the crux. The right atrium is enlarged; composed of anatomic right atrium proper and atrialized proximal inflow right ventricle. The residual right ventricle is reduced in size.

AV cushion defect with associated cleft valve abnormality is best seen in apical four chamber view. The mitral and TVs are seen as a common valve straddling the defect. The cleft may be visualized with confirmation by color flow image showing the regurgitation jet going across the valve abnormality.

Carcinoid heart disease is characterized by thickened immobile valve leaflets held in half open position resulting in appearance of stenosis as well as free flowing regurgitation with color flow Doppler.[13]

Rheumatic TV disease is nearly always associated with rheumatic mitral and/or aortic valve disease. The valve leaflets are thickened and exhibit some doming in diastole.

The TV prolapse is seen in nearly 30% of patients with mitral valve prolapse (Fig. 2). The characteristic appearance includes dilated annulus, billowing prolapse, less commonly chordae rupture with flail leaflet.[13] Apart from the general syndrome of degenerative valve disease, TV prolapse has been described in congenital heart disease associated with systemic right ventricles.

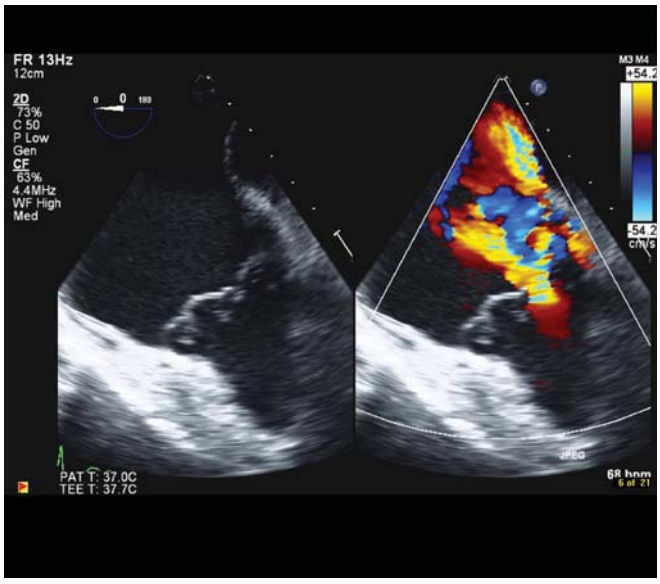


FIGURE 2: Transesophageal echocardiography image of tricuspid valve in systole exhibits billowing valve prolapse and multiple jets of regurgitation

Infective endocarditis is generally apparent with demonstration of mobile vegetation with transthoracic echocardiography (TTE). In some cases, the transesophageal approach (TEA) may be used for confirmation. Differentiation of vegetation from a tumor requires clinical correlation.[13]

Valvulopathy associated with Phen-Fen and methysergide consists of thickened fibrotic less mobile tricuspid leaflets. These appearances are nonspecific and require historical confirmation of drug use.

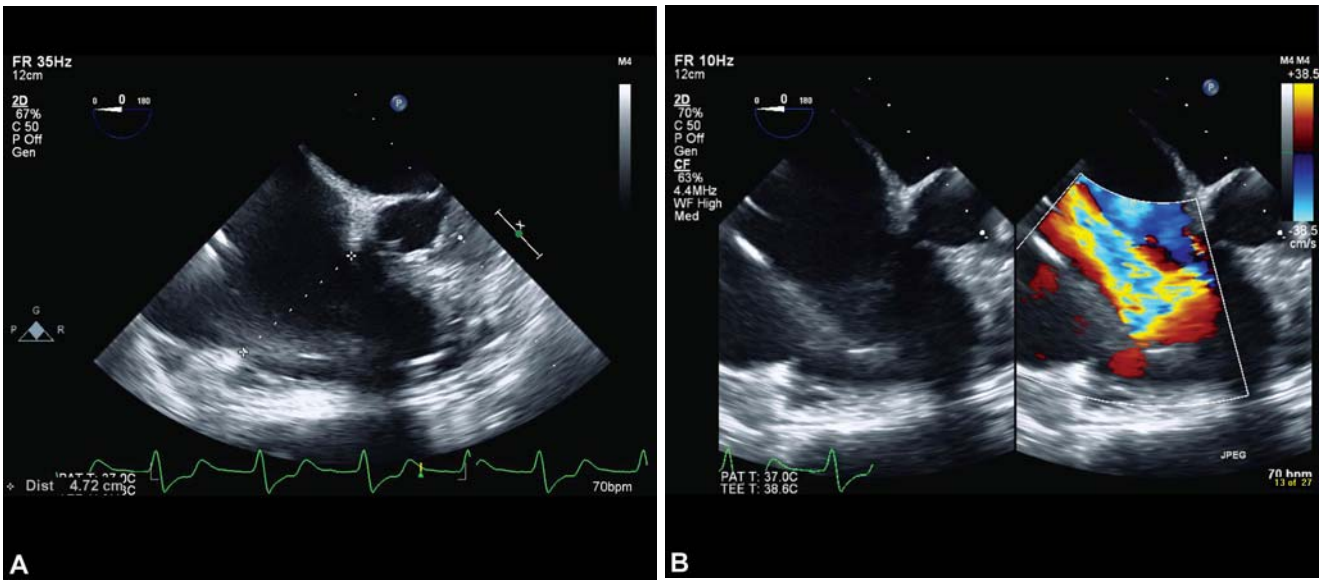
Pacemaker lead related trauma exhibits leaflet entrapment by a pacemaker lead (Figs 3A and B). The color flow jet of TR may be localized at the pacemaker contact site along the tricuspid leaflet. Less commonly, leaflet perforation may be noted.

Secondary or functional TR is characterized by annular dilatation, generally the annular diameter greater than 40 mm or greater than 25 mm/m², and tethering of leaflets with tenting distance in excess of 6 mm. In extreme cases, the leaflets fail to coapt with wide open regurgitation. Severe RV hypertension is associated with shift of the interventricular septum toward the left ventricle resulting in asymmetric tethering. In addition, characteristic appearances of RV infarction, arrhythmogenic RV dysplasia, or myocarditis and cardiomyopathy may be observed.

Detection and Quantitation of Tricuspid Valve Disease

Color flow Doppler and spectral Doppler are sensitive for detection of valve regurgitation and generally accurate for semiquantitative assessment of tricuspid stenosis and regurgitation.[14] Tricuspid stenosis is detected with color flow imaging by demonstrating a central core of high velocity jet. The continuous wave Doppler permits measurements of mean and end diastolic gradients. The normal mean gradient is less than 3 mm Hg, and the end diastolic gradient is nearly zero. Severe stenosis is associated with mean gradient of 5 mm Hg and pressure half-time measured in end inspiratory beat is greater than 190 millisecond. It has been proposed, but not well validated, that TV area may be determined by 190 divided by pressure half-time.

The TR using color flow imaging is readily recognized from parasternal tricuspid inflow view, short axis view, and apical or subcostal four chamber cross sections. Regurgitant jet area correlates roughly with severity of regurgitation, being less than 5 cm² in mild, 6–10 cm² in moderate and greater than 10 cm² in severe cases. In clinical practice, a visual estimate rather than actual planimetry is utilized. A more accurate estimate may be obtained by utilizing flow acceleration and proximal isovelocity surface area (PISA) measurements from which regurgitant orifice area may be calculated. The measured PISA radius is by



FIGURES 3A AND B: Transesophageal echocardiography cross sections of tricuspid valve restricted by pacemaker lead resulting in severe regurgitation and secondary annular dilatation. (A) Tricuspid annulus measures at 4.7 cm. (B) Pacemaker lead restricting the leaflet with severe regurgitation

TABLE 2

Echocardiography: diagnosis of severe tricuspid regurgitation

- Regurgitant jet area greater than 10 cm² (least utilized)
- PISA: radius greater than 9 mm with aliased scale adjusted to peak TR velocity
- Continuous wave Doppler velocity profile with early peak and rapid deceleration indicative of high right atrial LV wave
- Hepatic vein flow: systolic flow reversal in both respiratory phases

(Abbreviations: PISA: Proximal isovelocity surface area; TR: Tricuspid regurgitation; LV: Left ventricular)

itself a good guide to severity of regurgitation. The technique is important. The color flow baseline should be shifted in direction of regurgitation to get appropriate aliased velocity in relation to TR velocity. The aliased velocity scale should be set at 25–30 cms/sec for TR velocity less than 3.0 meters/sec corresponding to RV systolic pressure of less than 45 mm Hg. The scale should be 30–40 cms/sec for the regurgitation velocity 3.0–3.9 meters/sec corresponding to RV systolic pressures between 46 mm Hg and 70 mm Hg. The aliased scale may be placed at 40–50 cms/sec for regurgitation velocities in excess of 4.0 meters/sec, i.e. RV systolic pressure in excess of 70 mm Hg. When the aliased scale is appropriately set, the hemispherical radius of PISA provides an accurate and quantitative assessment of regurgitation severity. It is feasible to calculate regurgitant orifice area based on continuity principle of flow. In routine clinical practice the PISA radius provides quantitation of mild, moderate or severe regurgitation. The radius of hemispherical PISA of greater than 9 mm indicates severe regurgitation, 5–9 mm moderate regurgitation and less than 5 mm mild regurgitation. The spectral Doppler image of TR represents pressure gradient between right ventricle and right atrium through systole. The shape of TR velocity profile using continuous wave Doppler provides a clue to this relationship. The regurgitation profile is generally parabolic except in severe cases, where high right atrial "C-V" waves result in rapid equalization with RV pressure giving a profile with rapid deceleration, also described as "V" wave cut-off sign.[13] Additional indirect clues of regurgitation severity are density of continuous wave Doppler profile, size of right ventricle and atrium, paradoxical interventricular septal motion and systolic bulge of interatrial septum toward left atrium. The hepatic vein flow exhibits systolic reversal of flow in severe cases (Table 2).

A calculation of RV systolic pressure (i.e. pulmonary artery systolic pressure in absence of outflow obstruction) using peak TR velocity is extremely useful in clinical practice. The formula used is; RV Systolic Pressure = 4 × TR velocity + right atrial pressure.[15] The latter may be assumed to be 7–10 mm, or more accurately determined from size of inferior vena cava and its collapse with sniff test. It is important to emphasize that height of TR velocity is not indicative of severity of regurgitation, but rather the degree of RV systolic pressure or pulmonary hypertension in absence of RV outflow obstruction.

TRANSESOPHAGEAL ECHOCARDIOGRAPHY

The TTE is often of diagnostic quality because the TV and the right ventricle are closer to the anterior chest wall and several parasternal, apical and subcostal views are used to image these structures. However, TTE is indicated for better anatomic definitions of the valve lesions or precise measurement of the tricuspid annulus. The assessment of severity of tricuspid stenosis or TR is generally more accurate with TTE. In the intraoperative setting, severity of TR may be underestimated as a result of lowered pulmonary vascular resistance from the anesthetic agents. It is therefore erroneous to use the severity of TR in the operating room to decide if a surgical procedure be performed on the TV.

In the intraoperative setting, TEE is especially used for measuring the tricuspid annulus diameter. This is done in the mid-esophageal four-chamber view and a plane perpendicular (90°) to it. When the annulus is significantly dilated, these diameters are nearly equal indicating a circular geometry.

CARDIAC CATHETERIZATION AND SELECTIVE ANGIOGRAPHY

Prior to the advent of diagnostic echocardiography, cardiac catheterization was used to confirm the presence and severity of tricuspid stenosis. It was recognized that simultaneous recordings of right atrial and RV diastolic pressures was needed for accurate assessment because the pressure gradients are small and there is considerable respiratory variation in the pressure waveforms. The diagnosis of TR posed a greater challenge, as selective angiography into the right ventricle would often distort the TV. The pressure waveform in the right atrium shows the characteristic prominent systolic V wave with rapid descent only in the most severe cases. Diagnostic cardiac catheterization should rarely, if ever, be undertaken for the diagnosis or quantitation of TV disease.

TREATMENT

The treatment of TV disease must entertain two important considerations, namely the appropriate timing and the appropriate management strategy.

APPROPRIATE TIMING

The decision to treat TV disease is based largely on hemodynamic and functional consequences of the diseases as well as coexistence of other associated valvular or congenital lesions. As an isolated lesion, mild or moderate TV disease does not need to be treated. Mild or even moderate TR may be observed using current echo-Doppler techniques in normal subjects. In the absence of structural changes, such as annular dilatation or leaflet disruption, such lesions are not known to progress. On the other hand, severe TV disease results in enlargement of right atrium and right ventricle and increase in right atrial and systemic venous pressures. If untreated, RV dysfunction with reduction in cardiac output develops first with exercise and subsequently at rest. This is accentuated by development of atrial fibrillation. In addition, chronic hepatic congestion results in fibrosis and development of cardiac cirrhosis. The liver function tests become increasingly abnormal. Progressive dilatation of right heart chambers bring about progressive annular dilatation, worsening severity of regurgitation. Thus, chronic severe regurgitation often begets more regurgitation. For isolated severe TV disease, intervention should be considered as earliest signs of RV and/or hepatic dysfunction develop.

The rules governing management are different when moderate TV dysfunction is associated with other valvular or myocardial disorders. The timing of intervention is generally dictated by considerations relating to accompanying left heart disease. Approximately 40% of patients exhibit regression of TR following mitral valve surgery with reduction in pulmonary hypertension. There is no reliable criterion to predict as to which patients are likely to regress. Since it fails to regress in nearly 60% of patients and reoperations tend to carry higher morbidity and mortality, it is a recommended practice to treat tricuspid lesion more aggressively during the mitral valve surgery.[16]

MANAGEMENT STRATEGIES

Primary or intrinsic TV disease with severe dysfunction nearly always requires surgery with possible exception of rheumatic tricuspid stenosis which may be approached by percutaneous balloon valvuloplasty. Secondary or functional TR offers a wider array of options as discussed in the following sections.

Medical Treatment

The TR secondary to pulmonary hypertension may be treated by medical management of underlying etiology, when feasible. Thus, appropriate treatment of myocarditis or depressed left ventricular function may result in amelioration of functional TR. Similarly, improvement in lung function in chronic obstructive lung disease or appropriate control of sleep apnea may improve the associated TR. It is worth emphasizing that functional TR may be dynamic, being load dependent. Intensive medical treatment of heart failure may substantially improve the severity of TR. This is especially relevant when a patient is undergoing surgery of left heart disease (such as mitral or aortic valve disease) following intensive medical treatment of heart failure such that the most recent echocardiogram may fail to show significant TR. In this setting, even if the TR is mild to moderate, it will require surgical treatment.

Surgical Treatment

Tricuspid stenosis: Rheumatic tricuspid stenosis is nearly always associated with rheumatic mitral valve disease. Successful mitral and tricuspid repair may be carried out; however, long-term results are poor. Mitral valve replacement with TV replacement may be considered in patients unwilling to entertain a risk of reoperation. These patients will require mechanical prosthesis being in younger age group.

Tricuspid regurgitation: Since the most commonly observed TR undergoing surgery is functional or secondary to mitral, aortic or ischemic heart disease; the surgical approaches will be considered in some detail. Significant TR is often a marker of adverse outcome.[17,18] A variety of techniques for valve repair have been used over the years. These fall broadly into two categories: (1) suture techniques and (2) annuloplasty techniques (Table 3).

1. Suture techniques
   a. DeVega purse string repair: Since its inception in 1972, this technique has extensively been used with early success.[19] However, late follow-up studies reveal a significantly higher recurrence rate as compared to repair using annuloplasty ring or band.[20] The early results (up to 6 months) are good, such that one would recommend its use in cases where a rapid and sustained fall in pulmonary artery pressure is likely to result following mitral valve surgery and TV and annulur geometry are not markedly abnormal. It is a more practical and economical to use DeVega approach in developing countries with high incidence of rheumatic mitral disease being operated on at early age.[20]
   b. Suture plication of posterior leaflet: This approach has been used in some cases with extreme annular dilatation, but generally in combination with annuloplasty.
2. Annuloplasty techniques: There is growing body of evidence to support improved outcome and durability of TV repair using annuloplasty ring. Tant et al. reported freedom from recurrent TR in those receiving rings was 82 ± 5% at 15 years as compared to 39 ± 11% (p = 0.0003) in repairs without use of a ring. They also observed improved long-term survival as well as event free survival for those with TV repair with ring. McCarthy et al. also reported a higher rate of failed TV repair without use of rings. They observed 30% of patients with DeVega procedure had severe regurgitation at 8 years as compared to none with ring annuloplasty.[20] A variety of annuloplasty rings and bands have been used:
   - Peri-Guard annuloplasty consists of customized semi-circular annuloplasty using bovine pericardium. A high rate of early and late recurrence of TR has been reported. This approach is not favored at the present time.
   - Carpentier ring devised for the TV introduced more than 30 years ago has been extensively used. This semi-rigid ring has had excellent early and late outcome. Special care has to be taken to avoid injury to the AV node.
   - Duran flexible ring has been proposed in order to preserve the normal annular function of dilatation in diastole and reduction in systole. Good early and late outcome has been reported using the flexible ring.
   - Annuloplasty bands or incomplete rings are used to avoid risk of AV node injury. A partial ring specially devised with knowledge of three dimensional geometry of the TV (MC3 ring) has been introduced with promising early and midterm results.

TABLE 3

Surgical approaches for secondary or functional

- Suture techniques
  - DeVega purse string suture repair
  - Suture plication of posterior leaflet
  - Edge-to-edge suture technique
- Annuloplasty techniques
  - Carpentier ring annuloplasty
  - Duran flexible ring annuloplasty
  - MC3 partial ring devised to replicate tricuspid geometry
  - Peri-Guard annuloplasty
  - Other rings and bands
- Valve replacement
  - Bioprosthesis
  - Mechanical valve

TABLE 4

Tricuspid valve repair versus replacement: midterm outcomes

Study design		Retrospective analysis; a single center experience
Patient groups		178 with TV repair; 72 with TV replacement (54 bioprosthesis, 18 mechanical)
Type of follow-up		Clinical and echocardiographic
Duration of follow-up		5.2 ± 4.1 years
In hospital deaths		Repair, 4%; Replacement, 22%
Survival	5 years	Repair, 90 ± 3%; Replacement, 63 ± 6%
	10 years	Repair, 76 ± 5%; Replacement, 55 ± 6%

Source: Modified from Singh et al.[4]

- Edge-to-edge annuloplasty technique comprising of stitching together free edges of the tricuspid leaflets producing a clover shaped valve has been described.[21,22]

Tricuspid Valve Replacement

Although most studies have reported a better early and long-term outcome with valve repair, there are some cases with marked distortion of the annulus and severe tethering of the leaflets where valve replacement may be necessary. Generally bioprosthetic valves are preferred, since valve thrombosis and infection following mechanical valve replacement are distinct risks.[4] Some studies have shown no significant difference in long-term outcome between tissue and mechanical valves.[23-25] Residual regurgitation following TV replacement is lower than after valve repair; however, the perioperative midterm survival and event free survival is better with valve repair[4] (Table 4).

The 2006 American College of Cardiology/American Heart Association (ACC/AHA) Guidelines for management of patients with valvular heart disease pertaining to TV are summarized in Table 5.[26]

The current approaches to surgical treatment of TV disease at time of mitral and/or aortic valve surgery are summarized in Table 6.

SURGICAL TREATMENT OF PRIMARY TRICUSPID VALVE REGURGITATION

Rheumatic Valve Disease

The surgical options include valve repair techniques similar to those employed for rheumatic mitral valve disease. In rare cases with extreme fibrotic distortion of the valve, TV replacement may need to be considered. In a study of 328 patients followed over a mean 8.7 years, in hospital mortality was 7.6% and late mortality was 52.1%. Valve repair had a more favorable outcome.[27]

Ebstein's Anomaly

The TV repair may be feasible in milder cases, the majority requires valve replacement. Good long-term outcomes and survival are reported. A study examined outcome of 40 consecutive patients at one center. The valve was repaired in

TABLE 5

The 2006 American College of Cardiology/American Heart Association (ACC/AHA) guidelines for management of patients with valvular heart disease (Bonow RO et al.[26])

Class	*Management*
Class I	• TV repair is beneficial for severe TR in patients with MV disease requiring MV surgery (level of evidence: B)
Class IIa	• TV replacement or annuloplasty is reasonable for severe primary TR when symptomatic (level of evidence: C)
	• TV replacement is reasonable for severe TR secondary to diseased/abnormal TV leaflets not amenable to annuloplasty or repair (level of evidence: C)
Class IIb	• Tricuspid annuloplasty may be considered for less-than-severe TR in patients undergoing MV surgery when there is pulmonary hypertension or tricuspid annular dilatation (level of evidence: C)
Class III	• TV replacement or annuloplasty is not indicated in asymptomatic patients with TR whose pulmonary artery systolic pressure is less than 60 mm Hg in the presence of a normal MV (level of evidence: C)
	• TV replacement or annuloplasty is not indicated in patients with mild primary TR (level of evidence: C)[29]

(Abbreviations: MV: Mitral valve; TR: Tricuspid regurgitation; TV: Tricuspid valve)

TABLE 6

Indication for TV surgery during mitral and/or aortic valve surgery

Intraoperative transesophageal echocardiography			
Severe TR			TV Repair
Mild to moderate TR	Prior known severe TR		TV Repair
	No prior severe TR	Annulus diameter ≥ 40 mm	TV Repair
		Annulus diameter 35–39 mm PASP > 50 mm Hg	TV Repair
		Annulus diameter < 35 mm	No need for repair

(Abbreviations: PASP: Pulmonary artery systolic pressure; TR: Tricuspid regurgitation; TV: Tricuspid valve)

18 patients, and in 12 patients in association with cavopulmonary shunt. Twenty-two underwent replacement, 11 with cavopulmonary shunt. There were two postoperative deaths and five late deaths during follow-up for 6.7 ± 4.8 years. Arrhythmias were the most common late complication.[28] The experience reported from the Mayo Clinic on 539 patients showed survival at 5, 10, 15 and 20 years of 94%, 90%, 86% and 76% respectively. Thirty-six percent experienced atrial fibrillation or flutter and 27% had endocarditis.[29]

Carcinoid Heart Disease

Symptomatic patients with severe TV dysfunction despite treatment with somatostatin analogues generally require TV replacement. Surgical intervention, aside from relief of symptoms, is also credited with improved survival in this lethal disease. Balloon valvuloplasty has been used in rare cases with predominant tricuspid stenosis. This represents a high-risk surgical group.[30]

Infective Endocarditis

Infection of the tricuspid is commonly related to intravenous drug abuse and poses a significant challenge in management. Early cases may undergo successful valve repair with resection of vegetation, focal leaflet resection and annuloplasty. However, the large majority have significant valve destruction and are candidates for valve replacement. The chances of reinfection in drug addicts are considerable and medical follow-up is likely to be sporadic. Hence, tricuspid valvectomy has been utilized with good early results, since resulting TR in absence of pulmonary hypertension is hemodynamically well tolerated. However, the long-term results are discouraging. Replacement with bioprosthesis may be preferred despite young age of the patient owing to lack of reliance on oral anticoagulation therapy in this group of patients.[31]

Cleft Tricuspid Valve

Most adult patients presenting with cleft TV have milder pathology and are successfully repaired. Younger patients with extremely malformed valves may require valve replacement.

Traumatic Tricuspid Regurgitation

The TR associated with pacemaker trauma is generally amenable to valve repair. It is often necessary to explant the offending pacemaker lead and place epicardial pacing wires. Rare cases with secondary fibrotic changes may require valve replacement. The timings of surgery for isolated TV disease are summarized in Table 7.

TABLE 7

Indications for isolated TV surgery

- Refractory congestive heart failure
- Hepatic dysfunction due to chronic venous congestion (hepatic cirrhosis)
- Right ventricular dilatation and dysfunction

Note:
For optimal long-term outcome, surgical intervention should be entertained before irreversible right ventricular dysfunction develops

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Chapter 58

Congenital Pulmonic Stenosis

Jullien Hoffman

Chapter Outline

- Valvar Pulmonic Stenosis
  - Anatomy and Pathology
  - Pathophysiology
  - The Effects of Exercise
  - Natural History and Clinical Course
  - Clinical Findings
  - Laboratory Investigations
  - Differential Diagnosis
  - Treatment
- Isolated Infundibular Stenosis
  - Pathological Anatomy
  - Pathophysiology
  - Natural History
  - Clinical Findings
  - Laboratory Investigations
  - Differential Diagnosis
  - Treatment
- Supravalvar Stenosis
  - Pathological Anatomy
  - Pathophysiology
  - Natural History and Course
  - Clinical Findings
  - Laboratory Investigations
  - Treatment

INTRODUCTION

Congenital pulmonic stenosis is a congenital obstruction above, at, or below the pulmonary valve, and does not include extrinsic obstruction to the right ventricular outflow tract from mediastinal masses or internal obstruction from tumors. In 90% of patients the pulmonary valve is stenotic. The anomaly is common, with an incidence per million live births of 532 (median) to 836 (75th percentile).[1] It constitutes about 7% of all congenital heart diseases.

Because normal people have, between the right ventricle and the main pulmonary artery, a tiny systolic pressure gradient that causes the innocent pulmonary flow murmur, it may be difficult to diagnose trivial pulmonic stenosis. Early catheterization studies used for diagnosis a minimal gradient[2,3] or a peak right ventricular systolic pressure[4] greater than 25 mm Hg, and almost certainly missed many with trivial pathological pulmonic stenosis. More recent studies included subjects with a systolic gradient over 5.6 mm Hg[5,6] or 7 mm Hg.[7] There may be more subjects with this anomaly than are reported in incidence studies.

VALVAR PULMONIC STENOSIS

The stenosis is usually isolated, but can occur with almost any other form of congenital heart disease; a secundum atrial septal defect or a patent foramen ovale is a common association. The stenosis may occur in siblings or successive generations. It is seen occasionally in patients with Noonan or Williams-Beuren syndromes, or neurofibromatosis. Chromosome *22q11* deletion (CATCH 22 syndrome, DiGeorge syndrome) is an occasional association. Pulmonic stenosis may occur in the carcinoid syndrome[8,9] where the obstruction may come from carcinoid plaques on the valve cusps and in the sinuses.

ANATOMY AND PATHOLOGY

The stenotic pulmonary valve is thickened but usually flexible, with commissural fusion. Around 80–90% of the valves are tricuspid, 10–20% are bicuspid, quadricuspid valves are rare, and a few severely deformed valves are monocuspid, with merely a thick fibrous plate at valve level and a small eccentric orifice. Some children, especially those with Noonan or other syndromes, have thickened myxomatous valves without fusion.[10,11] Calcification is rare and seldom seen until after 40 years of age.[12-14] There is a semilunar attachment of each leaflet to the arterial wall above and the outflow tract muscle below, without a discrete fibrous annulus.[15,16] Rarely, there is an hourglass deformity[17] with narrowing of the sinotubular junction and no or little commissural fusion.

The main and sometimes the left pulmonary arteries show poststenotic dilatation due to loss of elastic fibers. Dilatation is often absent with a dysplastic valve. Except for some neonates with critical stenosis and right ventricular hypoplasia, the right ventricle is hypertrophied but of normal volume, and the tricuspid valve is normal. Almost all patients with significant stenosis have some hypertrophy of the infundibular muscle,[18-21] but patients with severe generalized right

ventricular hypertrophy may also develop severe localized infundibular hypertrophy. If right ventricular systolic pressure is greater than 100 mm Hg at rest, there may be diffuse fibrosis in the right ventricular muscle, especially in older patients.[18,20,22-24] Myocardial fibrosis may be due to myocardial ischemia.[25] The left sided structures are usually normal.

PATHOPHYSIOLOGY

Neither the stenotic pulmonary valve nor the tricuspid valve has significant regurgitation. The narrowed orifice causes right ventricular systolic pressure to rise so as to maintain cardiac output, and increased pressure work causes right ventricular hypertrophy. If hypertrophy is severe, it reduces right ventricular distensibility and may increase right ventricular end-diastolic and right atrial pressure, leading to an exaggerated "a" wave in the jugular vein.

Classifying severity is often based on the value of the right ventricular systolic pressure or the pressure gradient across the stenotic valve with the subject at rest. Paul Wood[26] classified pulmonic stenosis as: mild-right ventricular systolic pressure less than 50 mm Hg, moderate-right ventricular systolic pressure 50–100 mm Hg and severe-right ventricular systolic pressure greater than 100 mm Hg. Engle et al.[27] had higher limits that were respectively 70, 70–130, and greater than 130 mm Hg, and the natural history collaborative study[28] classification was: trivial (< 25 mm Hg), mild (25–49 mm Hg), moderate (50–79 mm Hg) and severe (≥ 80 mm Hg). Since systolic pressure in the main pulmonary artery remains normal, subtracting 10–15 mm Hg from the above systolic pressure gives the approximate gradients across the valve. One classification using gradients[29] defined gradients as mild if less than 30 mm Hg, moderate if 31–55 mm Hg and severe if more than 55 mm Hg.

An alternative classification is based on calculated valve orifice area: valve area (cm^2/m^2) greater than 1.0 mild, 0.5–1.0 moderate, less than 0.5 severe in one institution[30,31] and greater than 1.0, 0.66–0.99, 0.33–0.65 and less than 0.33 in another.[32]

About 75% of the patients seen in childhood have either trivial or mild stenosis.

If right atrial pressure increases, there can be a right-to-left shunt through an atrial septal defect or a patent foramen ovale, one of which occurs in about 75% of patients with pulmonic stenosis. Right to left shunting happens only with more severe stenosis, and produces cyanosis. When Sir Russell Brock first introduced surgical relief of the stenosis, cyanosis was common due to the large reservoir of patients with severe stenosis. In Brock's survey of 12 years of treatment of pulmonic stenosis,[20] he observed cyanosis in 70% of the first 50 patients, 52% of the first 100 patients, but only 16% of the last 50 patients. Today it is rare to see an untreated older patient with severe stenosis and cyanosis.

THE EFFECTS OF EXERCISE

From the Gorlin formula for valve area,[33] the area of the stenotic pulmonary valve orifice (A) is:

$$A = \frac{\text{Flow / systolic second}}{44.5\sqrt{\overline{DP}}}$$

Where, $\overline{DP}$ is the mean pressure gradient across the valve in systole. Flow is calculated per systolic second because cardiac output is intermittent. This formula can be rearranged to show the factors that affect the mean pressure difference:

$$\overline{DP} = \frac{(\text{Flow/systolic second})^2}{1980\,A^2} = \frac{(SV/SET)^2}{1980\,A^2}$$

Where, SV = stroke volume and SET = systolic ejection time.

With exercise there is little change in the size of the inelastic orifice, so that changes in mean pressure gradient reflect changes in the numerator. The SET tends to be longer than normal at rest, but decreases with exercise.[32,34] In one study[35] stroke volume increased about 50% in most patients, but decreased in a few with severe stenosis. Therefore, the ratio $(SV/SET)^2$ usually increases, as does the mean pressure gradient across the valve. Increase of systolic pressure with exercise ranges from 10 mm Hg to greater than 100 mm Hg, with greater increase in those with more severe stenosis.[30,32,34,35] In one early series, most subjects with severe stenosis had smaller increases in right ventricular systolic pressure, but they also had very small increases in stroke volume.[36]

The effect of stenosis on exercise capacity depends on the severity of the stenosis and how it affects the responses of oxygen uptake, heart rate, cardiac output, stroke volume and systolic ejection time. In general, those with trivial or mild stenosis have entirely normal exercise responses, whereas those with moderate or severe stenosis usually have abnormal responses, even in the absence of cyanosis. It is these latter groups that have a reduced maximal exercise duration or working capacity.[29,32,37,38] They can increase cardiac output, but often not in proportion to maximal oxygen uptake so that the arteriovenous oxygen difference widens.[32,34-36] In these patients too, the ratio of minute ventilation to oxygen uptake increases, indicating hyperventilation. The right ventricular end-diastolic pressure increases in those with moderate or severe stenosis, but may decrease normally in milder forms.[32,39]

Results are similar in adults, adolescents[32,35,36,38] and children.[29,37,39] In one study,[30] adults had poorer function than children for comparable severity of stenosis.

NATURAL HISTORY AND CLINICAL COURSE

Excluding infants with critical pulmonic stenosis, several autopsy studies showed 50% survival at about 30 years of age.[40] These studies were all reported prior to the general use of cardiac catheterization or surgical treatment, and represent outcomes from severe stenosis; the vast reservoir of trivial or mild pulmonic stenosis was not represented. A better reflection of survival comes from the population study in Bohemia who found a 15-year survival from birth of 95.55%, and 3.8% of that 4.45% decrease was due to infants with critical stenosis who died within 6 months.[41] Although the follow-up is short, the equivalent survival at 15 years of age in autopsy studies is about 65%, attesting to the bias in the autopsy data.

Return to the rearranged Gorlin formula given above and consider what happens to a child with a pulmonic stenosis who grows normally, as most of them do. With growth, stroke volume increases a little faster than body surface area, and as systolic ejection time does not increase to the same extent, the numerator

increases. Therefore, the mean pressure gradient across the stenotic valve will increase rapidly unless the area of the stenotic valve orifice increases proportionately. When an infant is first seen, the growth potential of the valve is unknown. In some patients the orifice does not enlarge, or does not enlarge rapidly enough, so that right ventricular systolic pressure increases, sometimes very rapidly. We have seen a 3-month-old infant with a right ventricular systolic pressure of 30 mm Hg that had risen to 130 mm Hg by one year of age.

How often does this increase in severity occur? In a large clinical study, Rowland et al.[42] found increased pressure gradients across the valve in 29% of patients seen before 1 month of age, 7% of patients seen first between 1 month and 1 year of age and 11% of patients seen first over 1 year of age. Drossner and Mahle[43] followed 146 children, 87 of whom were seen first under 6 months of age, whose initial peak systolic gradients were 10–40 mm Hg. Only 3 patients in all and none over 6 months of age developed an increased gradient. As a rule of thumb, if the patient is over 2 years old and has a right ventricular systolic pressure under 50 mm Hg, the gradient is unlikely to increase with age.[44]

Hayes et al.[45] followed 300 patients from an average age of 10 years for 25 years. The percentage requiring valvotomy (which could have been for a number of reasons) was 5% for those with initial peak systolic gradients less than 25 mm Hg, 28% with gradients 25–49 mm Hg and 70% with gradients 50–79 mm Hg.

Spontaneous decrease in severity of the stenosis is extremely rare.[40] Most patients with mild or moderate stenosis are asymptomatic at rest and with exercise. We have no information about what happens to them after 50 or 60 years, although the lack of reports of late deaths due to pulmonic stenosis is encouraging. Those with severe stenosis fall into two groups: (1) young infants with severe stenosis and often a hypoplastic right ventricle, who are cyanotic from left to right atrial shunting, and frequently in congestive heart failure and (2) older patients with severe stenosis. Some of these have fatigue or dyspnea on exertion,[26,27,46,47] or chest pain or syncope,[26,44,45] a few die suddenly, probably from an arrhythmia,[26] and others develop congestive heart failure, usually after the fourth decade.[46,48]

Infective endocarditis is uncommon but may be more frequent in those with severe stenosis.[27,46,49,50] It is very rare postoperatively.[51]

CLINICAL FINDINGS

History

Most patients are asymptomatic at rest and on exercise except for neonates with critical stenosis or the older adult with severe obstruction and myocardial damage. Even those with severe stenosis can be asymptomatic, but some, however, have fatigue, cyanosis, congestive heart failure, or even classical angina pectoris on exertion.

Physical Examination

Body habitus and growth are usually normal. Some patients have a pentagonal or moon shaped face.[26,52] Patients with severe stenosis may show cyanosis and clubbing. If right ventricular end-diastolic pressure is raised, the jugular vein has a prominent "a" wave, but mean venous pressure is usually normal. There may be a prominent right ventricular heave at the lower left sternal border, and a systolic thrill can often be felt at the upper left sternal border.

The mainstay of clinical diagnosis is auscultation. To understand how auscultation helps to assess severity, consider the pressure tracings shown in Figure 1.

Normally, there are small pressure gradients in early systole (cross-hatched) between left ventricle and aorta, and between right ventricle and main pulmonary artery. Corresponding to these pressure differences are crescendo-decrescendo (diamond shaped) systolic murmurs that end by mid-systole (white areas). In pulmonic stenosis (right panel), however, the pressure gradient between right ventricle and main pulmonary artery is prolonged, with a triangular right ventricular pressure wave, and the associated systolic murmur, also diamond shaped, is longer and ends close to the second heart sound.

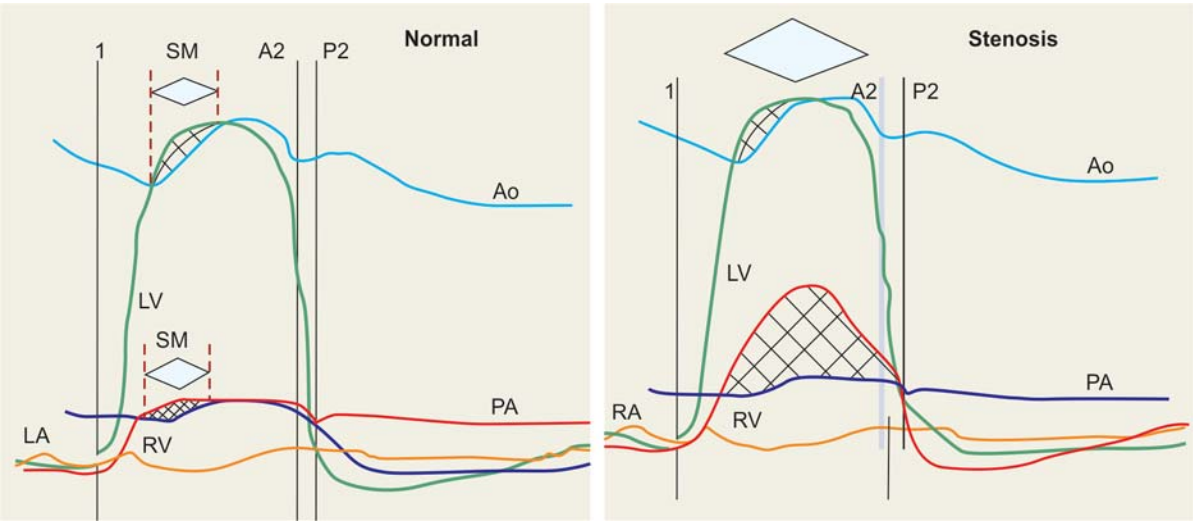


FIGURE 1: Pressure tracings in normal subjects and subjects with aortic or pulmonic stenosis. (Abbreviations: SM: Systolic murmur; LV: Left ventricle; RV: Right ventricle; LA: Left atrium; RA: Right atrium; PA: Main pulmonary artery; Ao: Aorta; A1: Aortic first heart sound; A2: Aortic second heart sound; P2: Pulmonic second heart sound)

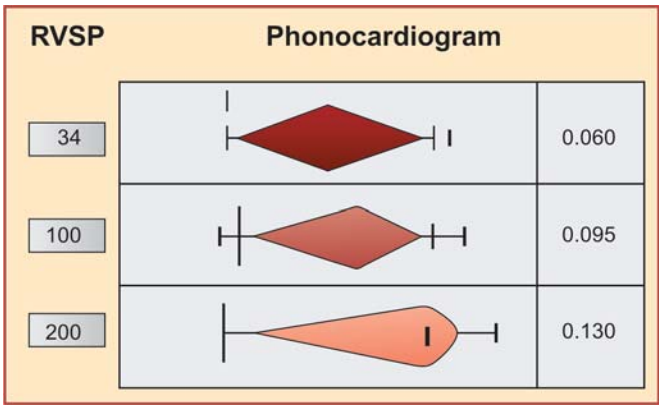


FIGURE 2: Selected phonocardiograms based on a series published by Gamboa et al.[53] The three phonocardiograms represent mild, moderately severe and very severe stenosis. (Abbreviation: RVSP: Right ventricular systolic pressure)

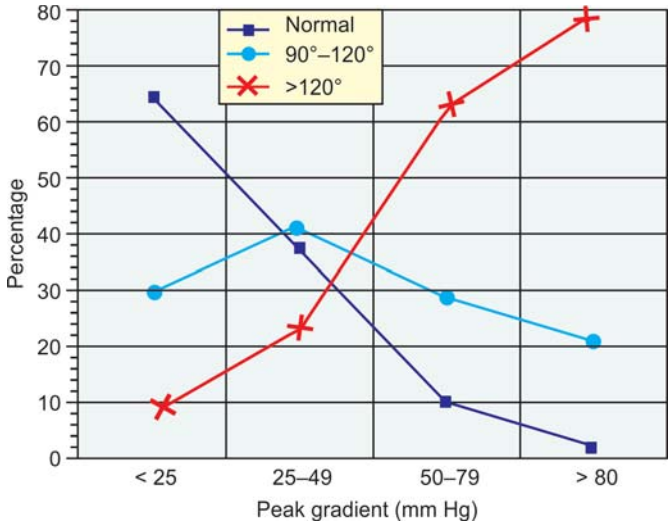


FIGURE 3: Relationship between peak gradient and severity of stenosis. The percentage in each severity group is shown for normal (QRS axis < 90°, mild right axis deviation of 90–120°, and marked right axis deviation > 120°)

With more severe stenosis, right ventricular pressure increases, and ejection lengthens. The murmur is therefore prolonged and its peak intensity occurs beyond mid-systole, and the murmur may even end after the aortic component of the second heart sound (Fig. 2). The murmur is usually quite loud, grade 3/6 or more.

The degree of splitting of the second heart sound increases as stenosis severity increases (Fig. 2), with the measured splitting (taken during held expiration) given to the right of each phonocardiogram in milliseconds. The degree of splitting varies normally with respiration. The more severe the stenosis, the softer the pulmonic second heart sound is due to limited mobility of the thick valve. A third finding is inferred from the phonocardiogram. With a small stenotic orifice, as long as stroke volume is maintained, the velocity of ejection must increase. Therefore, the frequency of the murmur increases, as indicated by loss of space between the thin vertical lines (Fig. 2). Therefore, auscultation can assess severity by the length of the systolic murmur and the position of its maximal intensity, the width of splitting of the second sound, and the frequency of the murmur. Another prominent auscultatory feature, shown well in the middle panel of Figure 2, is the early systolic ejection click. This click is louder during expiration and is more marked in mild or moderate than severe stenosis. It is probably due to sudden limitation of expansion of the main pulmonary artery at the onset of systole due to the lack of elastic fibers in the arterial wall, but could also be due to movement of the valve itself. Sometimes the click is so close to the first heart sound that it is mistaken for an unusually loud first heart sound.

All these findings are unreliable if output is low because the patient has a large right to left shunt or is in cardiac failure, but then these findings by themselves indicate a severe stenosis.

LABORATORY INVESTIGATIONS

Chest Roentgenogram

This is typical beyond the neonatal period. Even mild stenosis produces poststenotic dilatation of the main pulmonary artery. If the right ventricle is hypertrophied, then the heart has a more rounded right heart border, but is not enlarged except in some patients with severe stenosis or congestive heart failure.[32,54] Right ventricular enlargement is best shown in lateral view when more than the lower one-third of the sternum is in contact with the right ventricle.

The pulmonary vascular markings are usually normal except with a right to left shunt, when the lungs fields appear oligemic.

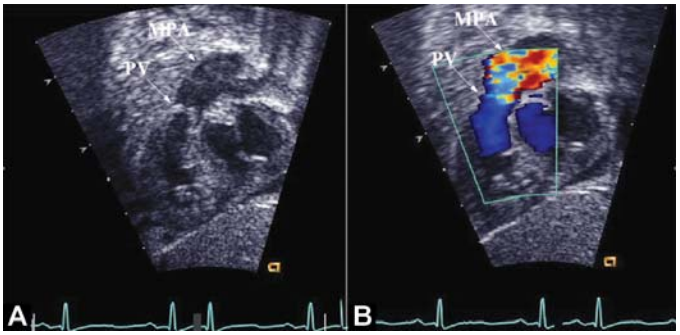
Electrocardiogram

Right ventricular hypertrophy produces increased anterior and rightward forces. Figure 3 shows the relationship between peak pressure gradient and mean frontal axis deviation, adapted from Ellison et al.[54]

Right ventricular hypertrophy enlarges R wave in lead V_1 and the S wave in leads V_5 and V_6. There is a very rough correlation between the height of the R wave in lead V_1 and the right ventricular systolic pressure.[4,54,55] Most patients have an rsR' pattern in lead V_1 and reference to standards is necessary for the diagnosis, but in very severe stenosis lead V_1 may show either a pure R wave or a qR wave—absolute signs of right ventricular hypertrophy. The T wave in lead V_1 is inverted, but this sign is less useful in patients over 10 years of age. Occasionally evidence of right ventricular hypertrophy is observed only in V leads to the right of the sternum. Severe stenosis may show tall peaked P waves of right atrial hypertrophy.

Echocardiography

M-mode and 2-D echocardiograms show the thickened pulmonary valve, changes in wall thickness and volume of the right ventricle. Dysplastic myxomatous valve leaflets are well shown.[56] Additional infundibular stenosis may be detected. If the maximal velocity of the jet through the orifice can be ascertained by Doppler interrogation, then the gradient can be approximated by the Bernoulli equation:[5] peak gradient = 4 × peak velocity^2 (Figs 4A and B).



FIGURES 4A AND B: 2-D echocardiogram to show doming pulmonary valve with tiny central orifice, and marked poststenotic dilatation (A). Doppler study shows turbulence beyond the valve, and hints at the narrow orifice (B). (Abbreviations: PV: Pulmonary valve; MPA: Main pulmonary artery). (*Source:* Echocardiograms by Dr Paul Stanger)

Cardiac Catheterization

This has been replaced almost entirely by echocardiography. Pressures are measured in the right ventricle and right atrium, and with a slow careful pullback from the pulmonary artery the site of obstruction is identified. If right ventricular systolic pressure is very high, no attempt should be made to enter the pulmonary artery lest the orifice be completely obstructed. Angiography demonstrates the site(s) of obstruction, and the doming valve with a jet passing through the narrowed orifice (Figs 5A to C).

This is a good measure of the pressure gradient across the stenotic valve[57,58] with certain caveats. Since the peak pressures in the right ventricle and the main pulmonary artery are not simultaneous, the peak-to-peak pressure gradient measured by catheter is sometimes as much as 20–30 mm Hg less than the instantaneous maximal gradient measured by Doppler interrogation.[59,60] Some investigators recommend using mean Doppler estimated pressure gradients which are much closer to mean measured pressure gradients.[60] Since respiration affects venous return, the gradient is slightly higher in inspiration than expiration but the differences are small and clinically unimportant. A very high velocity may exceed the ability of the system to measure it accurately with pulsed Doppler[61] and pressure gradients above 100 mm Hg may not be estimated accurately. Continuous wave Doppler assesses high velocities more accurately, but may be misinterpreted if there is stenosis below as well as at the valve level.

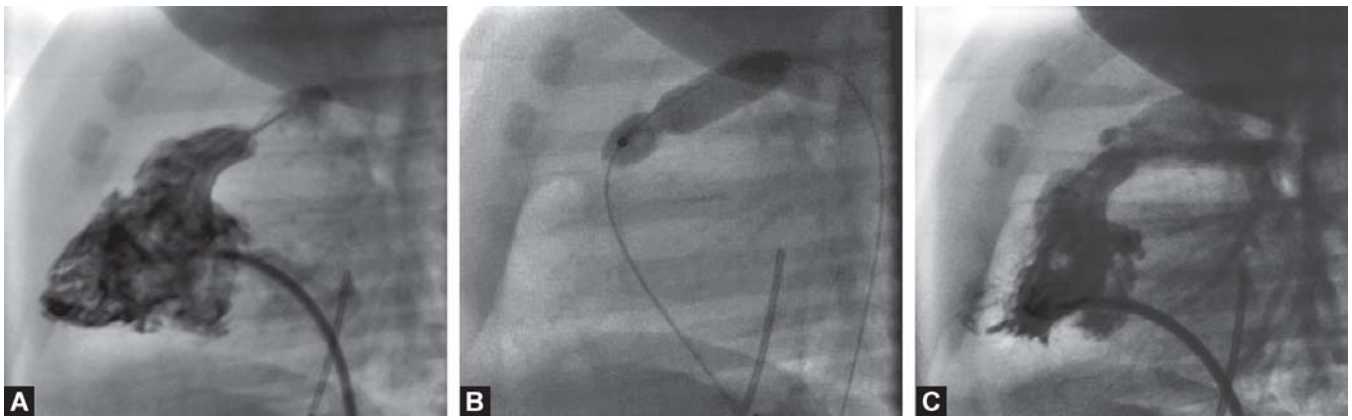
DIFFERENTIAL DIAGNOSIS

In addition to congenital pulmonic stenosis, an ejection murmur at the base is often due to an innocent pulmonary flow murmur, an atrial septal defect, aortic stenosis or idiopathic dilatation of the main pulmonary artery. The innocent murmur is seldom more than grade 2/6 in intensity, and ends by mid-systole. The murmur in patients with a moderate or large atrial septal defect is due to the turbulence of increased flow across the pulmonary valve but can be distinguished from pulmonic stenosis because an atrial septal defect has palpable hyperactivity of the right ventricle and wide fixed splitting of the second heart sound, and often a mid-diastolic rumble over the tricuspid area. In aortic stenosis the murmur is often lower, and the narrow splitting of the second heart sound is incompatible with a loud ejection murmur of pulmonic stenosis. Finally, massive dilatation of the main pulmonary artery associated with no or minimal stenosis at the pulmonic valve may be deceptive. Pulmonic stenosis can coexist with an atrial septal defect or aortic stenosis, but the latter patients seldom present as adults.

Occasionally tumors obstruct the right ventricular outflow tract and can be diagnosed only with imaging techniques.

TREATMENT

Any patient with symptoms or severe stenosis (right ventricular systolic pressure > 100 mm Hg), with or without symptoms, requires valvotomy. We assume that patients with right ventricular systolic pressure less than 50 mm Hg do not need treatment, although if untreated they should evaluated periodically for changes in pressure or ventricular function. For those with intermediate pressures, the decision to treat is made easier by the introduction of balloon valvotomy.



FIGURES 5A TO C: Angiograms (lateral view) in an infant with severe valvar pulmonic stenosis. (A) Angiogram shows doming valve and narrow jet through tiny orifice; (B) Angiogram shows dilating balloon in valve, with almost no waist, indicating enlargement of orifice; (C) Angiogram shows wider outflow orifice after balloon valvotomy, as well as well-marked poststenotic dilatation of the main pulmonary artery. *(Source:* Dr David Teitel. Same patient as shown in Figure 4)

Surgery

Sir Russell Brock first opened the stenotic valve by passing a dilator through the right ventricular wall and then blindly dilating the stenotic pulmonic valve.[62] This was followed by opening the valve under direct vision during brief hypothermic circulatory arrest,[63] and later with cardiopulmonary bypass. However, blind valvotomy has still been used successfully in neonates to avoid complications of cardiopulmonary bypass.[64,65]

The surgeon incises the fused commissures to allow the valves a full range of motion. If the valve is heavily calcified, however, it may need to be replaced by a prosthetic valve.[12,66] Occasionally, especially in neonates, the annulus is too narrow and must be widened with a patch via a right ventriculotomy. Since many patients with severe stenosis, especially if long-standing, have infundibular stenosis as well, there was initially concern about residual obstruction at this level. In fact, removal of the distal obstruction at the valve level removes systolic pressure that was distending the infundibulum, and allows the hypertrophied infundibular muscle to contract excessively so that right ventricular systolic pressure does not decrease after valvotomy. On rare occasions the pressure has even increased and caused death, a phenomenon referred to as "right ventricular suicide". To avoid these problems many surgeons excised the infundibular muscle. However, we now know that the hypertrophied infundibular muscle almost always regresses.[67,68] If there is concern about immediate postoperative infundibular obstruction, β-adrenergic blockers, such as propranolol or esmolol, can be given.[69,70]

Surgical valvotomy has an in-hospital mortality of 10–40% in neonates, but only 0–6% beyond that period. The pressure gradient across the valve and right ventricular systolic pressure decrease, even in neonates, although there are usually residual gradients of 10–30 mm Hg.[71]

Cyanosis and symptoms decrease, right ventricular hypertrophy regresses and exercise tolerance, if reduced preoperatively, improved but in some remained subnormal, especially in older patients who probably had myocardial fibrosis.[31] Indices of right ventricular relaxation (diastolic filling) improve, often to normal.[72]

Long-term postoperative survival up to 40 years after operation is excellent (~95%), except for neonates and older adults, and is close to that for the normal population.[40,73,74] Neonates with critical stenosis have a 4-year survival of about 80%.[71] Older patients aged 21–68 years at the time of operation had a 25-year survival of 70%.[75] This poorer response was probably due to myocardial damage related to long-term myocardial stress because the degree of stenosis was similar in older and younger patients, and is an argument for earlier rather than later relief of the obstruction.

Some patients need reoperation, occasionally to repair an associated lesion such as an atrial or ventricular septal defect, or a tricuspid valve lesion, but most often for marked pulmonic regurgitation or for residual or recurrent pulmonic stenosis.

Pulmonic regurgitation is usually absent or trivial preoperatively, but O'Connor et al.[76] found pulmonic regurgitation postoperatively in 90%, and it was moderate in over 50%. None needed repair, but follow-up was only for an average of 11 years. Earing et al.[73] followed 53 patients operated on between 1951 and 1982 at ages of 5 days to 50 years (mean age 10 years). All 10 patients who had had a closed valvotomy needed reoperation for restenosis or pulmonary regurgitation. In all, 28 patients needed reoperation, most often for pulmonary regurgitation, and deterioration leading to reoperation was more frequent after 25 years' follow-up, in keeping with the long latent period before pulmonary regurgitation causes right ventricular dysfunction.[40] There was a tendency for reoperation to occur more frequently in the 25% who had had infundibular resection. The other long-term follow-up was reported by Roos-Hesselink et al.[74] who followed 64 patients operated on between 1968 and 1980, all being less than 15 years of age and with a median age of 5 years. Forty-seven of them were operated on under inflow occlusion. Ten patients (15%) required reoperation, six for marked pulmonary regurgitation, 16–24 years after the initial surgery. We do not know if marked pulmonary regurgitation is inevitable after surgical valvotomy, or if it was a function of less refined surgical techniques used in earlier days. Regurgitation was more likely if an annular patch had been inserted.[73,74]

Pulmonic regurgitation is treated by repair or replacement of the valve. For some years now in Europe pulmonary valves have been inserted by catheter,[77] and these devices are undergoing clinical trials in the United States.

Restenosis required reoperation in 3 out of 53 patients,[73] all of whom had been operated on by inflow occlusion, and 4 out of 90 patients.[74] Roos-Hesselink et al. considered that at times the surgeon had to choose between too limited an operation that risked restenosis or too extensive an operation that risked pulmonary regurgitation. It is not clear if this is always true.

Arrhythmias on follow-up are usually not a major problem. In the large natural history study[78] after an average follow-up of 35 years, there were several patients with supraventricular or ventricular premature beats, the latter often multiform, but only 12.5% had ventricular tachycardia. Earing et al.[73] observed 38% and 6% with atrial and ventricular arrhythmias respectively, and commented that the only factor associated with arrhythmias was the length of follow-up. Roos-Hesselink et al.[74] observed no atrial arrhythmias, and 2% had episodes of ventricular tachycardia detected by 24 hour ambulatory monitoring, none of which had more than 3–10 complexes.

The quality of life was excellent or good in the majority of patients.[49,74]

Balloon Valvotomy

This was introduced by Kan et al.[79] and is now the preferred form of treatment unless there are other intracardiac lesions that need correction at the same time. The procedure is performed at cardiac catheterization under anesthesia or deep sedation. The diameter of the main pulmonary artery is determined by angiography, and then a balloon is inserted over a guide wire so that the mid-point of the balloon is at the valve level.[80] The balloon, chosen to be 10–20% wider than the pulmonary trunk, is rapidly inflated at high pressure and rapidly deflated. This process may be repeated two to three times. The goal is to eliminate the narrowed waist that the stenotic orifice produces on the balloon (Fig. 5B). If the annulus is very wide, a double balloon technique can be used. In experienced hands the procedure is safe and effective.

Failure to dilate the valve occurred in less than 10% of patients, many of whom had dysplastic valves. Balloon dilatation has been successful in adults (including one octogenarian), even with calcified valves.[14,81-87] Deaths from the procedure are rare, with rates of 0.15% and 0.2% in two large collaborative studies.[88,89] Since these reports included some of the early procedures, the rate is probably lower today. Rarely, complications such as perforation, pulmonary artery tears, hemorrhage, complete heart block, cerebrovascular accidents, and tricuspid valve rupture occur, but in the registry study amounted in all to 0.35% of procedures.[89] Less severe complications include femoral vein thrombosis that is more likely to occur in small infants, and vascular hemorrhage that is less frequent as better catheters and techniques are used.

The results in general are good. Gudausky and Beekman[90] summarized the results of 5 large studies. Eighty percent (688 out of 860) had long-term relief of obstruction, with peak systolic gradients being reduced from about 70–80 mm Hg to about 10–35 mm Hg within 1 day of the dilatation.[80,89] Frequently, there is residual infundibular stenosis,[91] sometimes very severe,[92] but this usually regresses.[80,91,93,94] Marked infundibular stenosis tends to regress less in those with dysplastic valves, greater preprocedural gradients, and older age.[91] As a result of this regression, gradients fall more in the year after the procedure.

About 7% of the patients (64 out of 860) needed intervention for restenosis.[90] Reintervention was most likely to occur in small patients, those with a relatively small annulus, inadequate relief of the obstruction, or valve dysplasia. Adult patients seldom needed reintervention for residual stenosis, probably because they usually had an adequately sized annulus.[83,85,95]

Pulmonic regurgitation was seen in most patients after balloon valvotomy. It was severe in only 1% (9 out of 903) of patients surveyed by Gudausky and Beekman[90] but moderate regurgitation occurred in 22%,[96] 7%,[97] and 6%.[98] Because regurgitation tends to become worse, these figures may increase with time.[80,99]

Dysplastic stenotic valves respond less well to balloon valvotomy in most institutions[89,95,100] but not in all.[101-103] Whether these differences are due to valvotomy technique or the underlying pathology is unknown.

Critical stenosis of neonates and infants has also been treated successfully by balloon valvotomy. The early mortality is higher in younger children than in older children due to the severity of the illness and the associated lesions, but survivors do fairly well. Immediately after the valvotomy the hypoplastic right ventricular cavity becomes smaller because the high pressure keeping it dilated has been removed,[104] but subsequently it grows to reach a low normal volume, and the tricuspid and pulmonary valve annuli also attain normal size. Late follow-up data are not yet available.

ISOLATED INFUNDIBULAR STENOSIS

Infundibular stenosis not secondary to pulmonic valve stenosis is usually associated with a ventricular septal defect or tetralogy of Fallot. In fact, some of the patients who present with isolated infundibular stenosis are known to have had a ventricular septal defect that closed spontaneously.[105,106] Nevertheless, some do not have this association. Isolated infundibular stenosis is rare. It was seen in 17 out of 215 (7.9%) patients operated on for pulmonic stenosis,[20] and less in other series: 1.3%[107] and 2.7%.[108] In one report two such patients also had a right aortic arch.[109] The largest reported series was that of Shyu et al.[110] who over 27 years, operated on 15 such patients out of 3222 patients (0.47%) who were operated on for congenital heart disease.

PATHOLOGICAL ANATOMY

The obstruction is due to a fibromuscular narrowing of the os infundibuli. This must be distinguished from double-chambered right ventricle in which an anomalous muscle bundle divides the body of the right ventricle into two portions, both of which are trabeculated, and with the portion distal to the obstruction including the right ventricular apex. In isolated infundibular stenosis, however, the obstruction is due to hypertrophied septomarginal and parietal muscle (crista supraventricularis), and the small chamber distal to the obstruction and below the normal pulmonary valve is smooth walled and does not include the apex.

PATHOPHYSIOLOGY

This is the same as for valvar pulmonic stenosis.

NATURAL HISTORY

This is unknown. Patients present at ages between 2 and 63 years, and about half are children. A few children have had evidence of increasing obstruction.[105,109]

CLINICAL FINDINGS

History and physical examination are the same as for valvar pulmonic stenosis except that there is no early systolic ejection click, and the pulmonic component of the second heart sound is not softened.

LABORATORY INVESTIGATIONS

Chest Roentgenogram

It differs from that in valvar stenosis in that there is no poststenotic dilatation of the main pulmonary artery.

Electrocardiogram

It is same as described for valvar pulmonic stenosis.

Echocardiogram

It is diagnostic in showing an obstruction of the infundibulum and a normal pulmonary valve.

Cardiac Catheterization

If the procedure is performed carefully with a very slow pull back from the main pulmonary artery to the right ventricle, it shows the level and degree of obstruction.

DIFFERENTIAL DIAGNOSIS

There are not many entities to consider. One is double-chambered right ventricle, discussed above. Bulging of the thickened septum in hypertrophic cardiomyopathy or even the localized right ventricular variant of this must be considered, as must the occasional tumor,[111] especially rhabdomyomas.[112] An unruptured aneurysm of the sinus of Valsalva can project into the outflow tract,[113-115] as can a pseudoaneurysm associated with spontaneous closure of a perimembranous ventricular septal defect.[116-118] Occasionally the enlarged remnant of the valve of the fetal sinus venosus (Eustachian valve) can project through the tricuspid valve and obstruct the right ventricular outflow tract (spinnaker syndrome).[119,120]

TREATMENT

As the pulmonary valve is normal, the surgeon can excise the fibromuscular obstruction widely to reduce the risk of recurrence while not running the risk of pulmonary regurgitation. Short-term results have been excellent, and should parallel those for valvar stenosis of equivalent degree and age.

SUPRAVALVAR STENOSIS

Stenosis above the valve may occur in the main pulmonary artery, at the bifurcation with extension into the right and left pulmonary arteries, in multiple peripheral pulmonary arteries, or combinations of these sites.[121,122] Most supravalvar stenosis is associated with tetralogy of Fallot and pulmonary atresia, or after various operations on the main pulmonary artery, including aorto-pulmonary shunts and arterial switch procedures. Peripheral pulmonary artery stenosis due to rubella embryopathy is rare today.

Supravalvar stenoses occur as part of the Williams-Beuren syndrome due to a contiguous gene deletion at *7q11.23* that affects elastin formation, or the Alagille syndrome (arterio-hepatic dysplasia) due to a heterozygous mutation of the *JAG1* gene on chromosome 22. The Williams-Beuren syndrome consists of an elfin facies, usually some mental retardation but a very pleasing personality, abnormal dentition, hyperacusis, and almost always involvement of multiple parts of the cardiovascular system. The predominant lesion is supravalvar aortic stenosis; pulmonary artery stenosis occurs in 30–80%, (usually in several peripheral arteries but sometimes in the main pulmonary artery), and there may be coarctation of the aorta, aortic or pulmonic valve stenosis, systemic hypertension and enlargement of coronary arteries.[123] In Alagille syndrome, there is a characteristic square shaped head, skeletal and ocular abnormalities, xanthomas, peripheral pulmonary arterial stenosis, and sometimes tetralogy of Fallot and cholestasis due to paucity of intrahepatic bile ducts.

PATHOLOGICAL ANATOMY

Stenosis may be localized or else a long diffuse tunnel-like narrowing. The arteries beyond the obstruction may be hypoplastic.

PATHOPHYSIOLOGY

Stenosis confined to pulmonary arteries of one lung has no effect on the right ventricle, but the distal pulmonary arteries on that side become hypoplastic, and most of the right ventricular output ventricle perfuses the other lung. Excess perfusion of the one lung could possibly cause pulmonary vascular disease in the other, as can occur with unilateral absence of one pulmonary artery.[124]

If the main or both main branches are obstructed, then blood is ejected from the right ventricle into a small relatively stiff chamber, so that systolic pressure in the main pulmonary artery is high, but falls rapidly to a low level in diastole. The right ventricle also has the same high systolic pressure, and hypertrophies if stenosis is marked.

NATURAL HISTORY AND COURSE

In the Williams-Beuren syndrome these supravalvar stenoses have an unusual tendency to grow in proportion to body size or even to regress, so that systolic pressure in the main pulmonary artery and right ventricle either stays the same or decreases.[125-129] One study observed an inverse relationship between age and right ventricular systolic pressure.[123]

Stenoses from other causes do not regress, and pressures tend to rise as stroke volume increases with growth, and presumably exercise. In Alagille syndrome, a few patients present with congestive heart failure due to pulmonary stenosis, but most die from liver failure.[130]

CLINICAL FINDINGS

History

Other family members may be affected in both syndromes. Symptoms depend upon the severity of the stenosis and whether other organ systems are involved.

Physical Examination

The stenotic murmur may be heard better in the axillae if the stenosis is in a peripheral pulmonary artery, but otherwise cannot be differentiated from murmurs at other sites of obstruction. There is no early systolic ejection click. As diastolic pressure in the pulmonary artery is low, the pulmonic second heart sound is not accentuated.

LABORATORY INVESTIGATIONS

Chest Roentgenogram

It may show right ventricular hypertrophy, but there is never poststenotic dilatation of the main pulmonary artery. If stenosis predominantly affects one lung, there may be reduced vascular markings on that side.

Electrocardiogram

It shows typical features of right ventricular hypertrophy.

Echocardiogram

It may show stenosis in the main pulmonary artery or near the bifurcation but is unhelpful with intraparenchymal stenoses. It

is useful, however, in excluding stenosis at or below the pulmonary valve and in evaluating right ventricular function. Other imaging methods, such as magnetic resonance imaging or angiography, are used to examine intrapulmonary arterial stenosis.

Cardiac Catheterization

It allows assessment of pressures and sites of obstruction and with associated angiography can evaluate the peripheral arteries.

TREATMENT

Williams-Beuren Syndrome

Surgery is preferred if the stenosis is severe and in the main pulmonary artery or at the bifurcation, and also if other cardiac lesions are to be repaired at the same time. The stenotic segments are excised with an end-to-end anastomosis if short, but more often are incised longitudinally and a patch is inserted. Residual or recurrent stenosis is common in those severely affected.[123] If the stenosis is in the intrapulmonary arteries, the only option is to dilate the narrowed region with a balloon, or sometimes with a cutting balloon, and maintain the dilatation with a stent.

Stamm et al.[123] observed about 80% survival at 20 years. The reoperation rate over 20 years was about 15% for those with right ventricular systolic pressure below aortic pressure, almost all within the first 2 years, but about 85% for those whose initial right ventricular systolic pressures were suprasystemic.

Alagille Syndrome

The mainstay of treatment is liver transplantation, and if necessary correction of associated cardiac or pulmonary arterial lesions. In one study, 20-year survival after liver transplantation was 80% without and 40% with associated cardiovascular disease are usually complex.[130]

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Chapter 59

Catheter-based Treatment of Valvular Heart Disease

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Chapter Outline

- Catheter-based Treatment of Mitral Valve Disease
  - Percutaneous Balloon Mitral Valvuloplasty
  - Mitral Valvuloplasty in Pregnancy
  - Percutaneous Therapies for Mitral Regurgitation
  - Percutaneous Mitral Annuloplasty
  - Percutaneous Mitral Leaflet Repair
- Catheter-based Treatment of Pulmonary Valve Disease
  - Percutaneous Pulmonic Balloon Valvuloplasty
  - Percutaneous Pulmonary Valve Implantation
- Percutaneous Tricuspid Balloon Valvuloplasty
- Catheter-Based Therapies for Aortic Stenosis
  - Percutaneous Aortic Balloon Valvuloplasty
  - Percutaneous Aortic Valve Implantation
- Summary/Future Directions
- Guidelines

INTRODUCTION

Over the last three decades, the utilization of the cardiac catheterization laboratory has changed from solely obtaining hemodynamic and angiographic data for diagnostic purposes to offer a wide array of interventional procedures. This includes peripheral and coronary interventions, a range of pediatric and adult congenital interventions such as closure of defects in the atrial and ventricular septa, treatment of aortic coarctation, patent ductus arteriosus and balloon dilatation of all four cardiac valves for both acquired and congenital disorders. Most recently, major advances in percutaneous repair and replacement of cardiac valves have the potential to revolutionize the field of interventional cardiology.

Valvular heart disease is an important cause of mortality and morbidity and has been successfully treated with cardiac surgery. However, a large proportion of patients with valvular disease do not undergo surgical treatment due to advanced age, multiple comorbidities and excessive operative risk. Percutaneous valve dilatation is an accepted alternative to surgery in selected patients, particularly in symptomatic rheumatic mitral stenosis. Balloon valvuloplasty of aortic stenosis has been shown to provide only fair short-term results and is at a best palliative or bridge treatment reserved for non-operative patients. Aortic stenosis and mitral regurgitation account for a large proportion of native valve disease in adults. The rising age of the population coupled with patients that have multiple and more severe comorbidities has triggered a great enthusiasm in the field to develop new, minimally invasive techniques to treat valvular heart disease with acceptable complication rates. While a number of these techniques show promise, we emphasize that in many cases, surgery still remains the gold standard of care.

In this chapter, we have discussed current catheter-based treatments and techniques for valvular heart diseases and reviewed new techniques for percutaneous valve repairs and replacements.

CATHETER-BASED TREATMENT OF MITRAL VALVE DISEASE

PERCUTANEOUS BALLOON MITRAL VALVULOPLASTY

Percutaneous balloon mitral valvuloplasty (PMV) is an alternative to surgical mitral valve commissurotomy in patients with symptomatic mitral stenosis.[1,2] The goal of the procedure is to produce a controlled tear of the fused valve commissures toward the mitral annulus, resulting in commissural widening, thereby relieving the signs and symptoms of mitral stenosis. Since the introduction of the procedure described by Inoue et al. PMV has became a widely accepted alternative to surgical commissurotomy in patients with symptomatic rheumatic mitral stenosis.[3-6] The procedure provides excellent early hemodynamic effects and a low rate of residual stenosis and restenosis in appropriate candidates. Long-standing hemodynamic and clinical outcomes have been reported to be comparable to surgical commissurotomy.[1,7] This is a widely used, safe procedure with a low complication rate and is currently the preferred therapy for selected patients with mitral stenosis.[2]

Appropriate patient selection is fundamental in predicting the results of percutaneous mitral valvuloplasty. Pre-procedure is important to know and understand the anatomic details of the mitral valve apparatus. This is a complex anatomic structure whose functional integrity relies on its individual components. Transthoracic and transesophageal echocardiography is the most widely used method to assess the mitral valve apparatus.[8-11] Several echocardiographic scores have been generated to predict the success of a balloon valvuloplasty. The Wilkins score is an anatomic classification of the mitral valve based leaflet mobility,

TABLE 1

Determinants of the echocardiographic mitral valve score (Wilkins score)

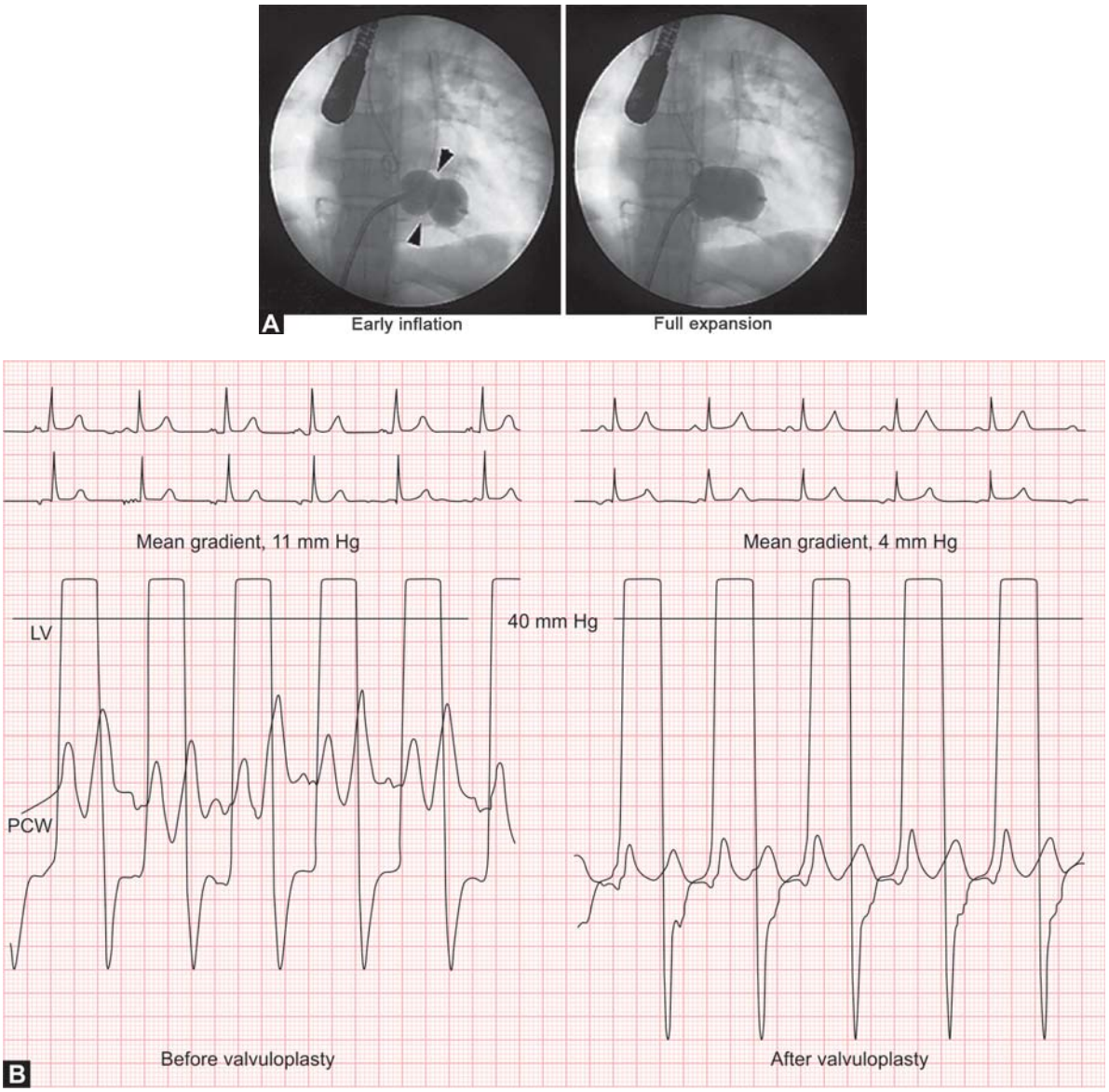
Grade	*Mobility*	*Subvalvular thickening*	*Thickening*	*Calcification*
1	Highly mobile valve with only leaflet tips restricted	Minimal thickening just below the mitral leaflets	Leaflets near normal in thickness (4–5 mm)	A single area of increased echo brightness
2	Leaflet mid and base portions have normal mobility	Thickening of chordal structures extending up to one-third of the chordal length	Mid-leaflets normal, considerable thickening of margins (5–8 mm)	Scattered areas of brightness confined to leaflet margins
3	Valves continues to move forward in diastole, mainly from the base	Thickening extending to the distal third of the chords	Thickening extending through the entire leaflet (5–8 mm)	Brightness extending into the mid-portion of the leaflets
4	No or minimal forward movement of the leaflets in diastole	Extensive thickening and shortening of all chordal structures extending down to the papillary muscles	Considerable thickening of all leaflet tissue (> 8–10 mm)	Extensive brightness throughout much of the leaflet tissue

valvular and subvalvular thickening and valvular calcification (Table 1).[10] A number of observational studies have shown that a Wilkins valve score of less than or equal to 8 (maximum of 16) is predictive of low success with percutaneous valvuloplasty.[12-14] A predictive model has also been introduced that not only takes morphologic features of the valve into account but also clinical factors (such as age, New York Heart Association class, pre-PMV mitral valve area, pre-mitral regurgitation grade and gender) to further predict long-term PMV success.[15] In the Western world, there has been a gradual decrease in rheumatic disease, and patients with mitral stenosis are often older, with calcified, thickened and immobile valves and thus, theoretically, less suitable for PMV.[16] There are several contraindications for percutaneous mitral valvuloplasty including the presence of left atrial thrombus, massive or bicommissural calcification, greater than 2+ mitral regurgitation, severe aortic valve or tricuspid valve disease and severe concomitant coronary artery disease requiring bypass surgery.[17-19]

Procedure

Invasive hemodynamic assessment is routinely performed including left and right heart pressure measurements, as well as cardiac output prior and immediately after the procedure. The Gorlin formula is used to calculate the mitral valve area and, typically, the severity of mitral regurgitation is assessed with a left ventriculography before and after the procedure.[20] Most of the described techniques of percutaneous mitral balloon valvuloplasty use the antegrade transseptal approach.[3,4,8,21,22] A retrograde approach has also been described.[23,24] The antegrade transseptal method can be accomplished by using a single-balloon (Inoue technique) or double-balloon technique via the femoral vein and a transseptal puncture. The Inoue balloon is advanced across the stenotic valve; this balloon is a self-positioning, hourglass shaped device that centers itself in the stenotic orifice of the mitral valve (Fig. 1A). The balloon is then inflated in a stepwise manner with repeat hemodynamic measurements repeated after each inflation to minimize the risk of damaging the mitral leaflets leading to mitral regurgitation. In the retrograde approach, the balloon catheter is advanced over a guidewire that has been inserted through the femoral arteries and snared in the descending aorta with catheters that have been advanced from the femoral vein to the right atrium and transseptally to the left atrium and left ventricle.[23] When using the two-balloon system the cylindrical balloons are inflated simultaneously. There is no significant difference of long-term follow-up results between the two techniques. The increase in the mitral valve area is directly related to balloon size.[25] In addition to these techniques, a nontransseptal retrograde technique has also been decribed.[24,26] Cribier and his colleagues, more recently, introduced a metallic valvulotome device that produces results similar to the balloon devices.[27] The valvulotome can be resterilized and reused, thereby decreasing procedural cost, which is particularly important in developing countries where rheumatic heart disease is most prevalent.[27]

In Figure 1B, an example of hemodynamic tracings pre-PMV and post-PMV has been shown. An immediate reduction in the left atrial mean pressure and reduction of the transmitral gradient should appear. In most reported series, PMV increases the mitral valve area from less than 1.0 cm^2 to approximately 2.0 cm^2 resulting in significant decrease in the mitral valve gradient, left atrial pressure, mean pulmonary artery pressure and an increase in cardiac output.[22,28,29] A large single center observational study including 1,492 PMV procedures reported a reduction of mean pulmonary artery pressure from 35 ± 13 mm Hg to 26 ± 10 mm Hg, a mean left atrial pressure from 22 ± 7 mm Hg to 13 ± 5 mm Hg, mean transmitral gradient from 10.8 ± 4.8 mm Hg to 4.8 ± 2.1 mm Hg and valve area increase from 1.04 ± 0.23 cm^2 to 1.92 ± 0.31 cm^2.[18] Late outcome data is scarce and mainly comes from studies from the 1980s when the dilatation techniques were still primitive and operators inexperienced. However, Palacios and his colleagues reported 15-year follow-up of 879 patients showing the rate of major adverse events to be low in the first 5 years, but progressively increasing after this period.[12] The in-hospital death rate was 1.9% and, of those, 0.6% were procedure-related deaths. Severe mitral regurgitation occurred in 9.4% patients. Emergent surgical mitral valve replacement (MVR) was required in 1.4% and pericardial tamponade occurred in 1.0% of the patients.[12] Clinical follow-up information was available for 96% of the patients. There were 110 (12.5%) deaths, 234 (26.6%) MVRs and 54 (6.1%) redo PMVs, accounting for a total of 398 (45.3%) patients with combined events (death, MVR, or redo PMV) after a mean follow-up 4.2 ± 3.7 years.[12] This is in agreement with a previous report by Hernandez et al. who also showed that the



FIGURES 1A AND B: Percutaneous balloon valvotomy (PMV) for mitral stenosis with the Inoue technique. (A) Fluoroscopic images showing the balloon across the mitral valve during early inflation and the full expansion. (B) Hemodynamic tracings prior and post PMV. Successful PMV results in significant reduction in diastolic pressure gradient between the left ventricle (LV) and the pulmonary capillary wedge pressure (PCW). The tracings show the mean pressure gradient measured dropped from 11 mm Hg to 4 mm Hg. [*Source:* Modified from Delabay A, Goy JJ. Images in clinical medicine: percutaneous mitral valvuloplasty. N Engl J Med. 2001;345:e4]

only independent predictors of good late results long term are the final procedure results (final mitral valve area and degree of mitral regurgitation following PMV).[30]

Failure rates of PMV are variable and highly dependent on the operator's experience and center volume.[31-33] Success rates range from greater than 95% in ideal patients to less than 50–60% in patients with suboptimal anatomy.[33] Overall mortality is low and is reported to be from 0% to 3% and the incidence of major complications has been reported up to 12%.[12,22,30,31] Three well-described major complications have been associated with mitral valvuloplasty: (1) hemopericardium resulting in pericardial tamponade, (2) embolic events and (3) severe mitral regurgitation. Pericardial tamponade is usually linked to the transseptal puncture and occurs in up to 4.0% of cases.[31] When pericardial tamponade occurs during a procedure, an insertion of a pericardial drain may allow the procedure to be successfully completed. Severe mitral regurgitation can result from damage to valve leaflets, valve annulus or chordae during balloon inflations, particularly in patients with high Wilkins scores, and may necessitate emergent surgery. The single-balloon technique may result in lower incidence of mitral regurgitation, but provides less relief of mitral stenosis in comparison to the double-balloon method.[34] Risk of systemic emboli can be reduced by screening for left atrial thrombus on transesophageal echocardiography prior to the procedure and by administering heparin, once the atrial septum has been crossed.[35] The incidence of systemic emboli has been reported in up to 3% of cases.[36] Minor complications may include vasovagal reactions, prolonged hypotensive episodes, arrhythmias requiring treatment, significant atrial septal defect and, rarely, conduction

abnormalities including complete heart block.[31,37] Criteria that have been suggested for terminating the procedure include mitral valve area greater than 1.0 cm^2 per square meter of body surface area, complete opening of at least one commissure or the appearance of increase in mitral regurgitation.

MITRAL VALVULOPLASTY IN PREGNANCY

Pregnant women with severe symptomatic mitral stenosis represent a highly select patient subgroup. The narrowed mitral valve orifice causes a limitation in cardiac output and an increase in left atrial pressure, which can result in pulmonary edema. Hemodynamic changes associated with pregnancy such as increase in circulating blood volume and cardiac output may lead pregnant women to develop decompensated symptoms. The PMV is a safe and effective therapy, and appears to be preferable for the fetus, compared with open mitral valve surgery during pregnancy in patients that do not respond to conservative management.[38] The success rate of this procedure is very high, although there are concerns about the effects of the radiation exposure to the fetus during the procedure.

Summary

In summary, percutaneous mitral valvuloplasty results in acute and long-term results similar to surgical interventions and, in many instances, has become the procedure of choice for patients with favorable valve anatomy and no other compelling indications for cardiac surgery. Several small-randomized trials have shown no significant differences between the two strategies.[1,7,39] Appropriate patient selection is essential for satisfactory valvuloplasty outcomes and requires careful evaluation of mitral morphology prior to the procedure.

PERCUTANEOUS THERAPIES FOR MITRAL REGURGITATION

Mitral regurgitation is a common clinical entity and may cause progressive ventricular and annular dilatation leading to worsening signs and symptoms of congestive heart failure.[40-42] Mitral insufficiency results from primary valvular disease or, more commonly, dilatation of the left ventricle causing functional mitral regurgitation. Mitral regurgitation severity is an independent predictor of prognosis in patients with ischemic heart disease.[43-45] Left ventricular dysfunction or remodeling can result in annular dilatation or papillary muscle displacement with incomplete mitral leaflet apposition or restricted leaflet motion despite normal mitral valve leaflets.[46] Unlike mitral stenosis, this condition, until recently, has been only manageable with surgical interventions. The preferred surgical approach is mitral repair combined with mitral valve annuloplasty or MVR with a prosthetic valve.

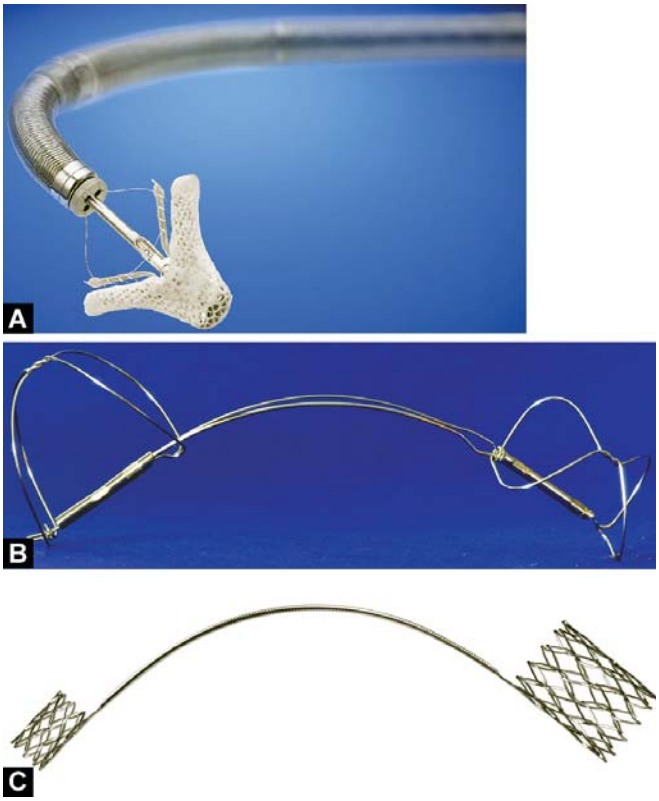
The mainstay of surgical therapy for mitral regurgitation has been ring reduction annuloplasty, either as a stand-alone treatment for mitral regurgitation or in conjunction with mitral leaflet repair. The surgical annuloplasty results in septal-lateral annular shortening and the decrease in mitral regurgitation severity is well established.[47,48] However, according to the European Heart Survey, up to one half of patients with severe symptomatic mitral regurgitation did not undergo surgery largely due to advanced age, presence of comorbidities or impaired left ventricular function.[49,50] These data highlight the need for less invasive alternatives to open heart surgery. Transcatheter techniques of mitral leaflet repair and annuloplasty have evolved over the last few years although all remain under investigation.

PERCUTANEOUS MITRAL ANNULOPLASTY

A simplified interventional approach to simulate surgical annuloplasty has been to utilize devices to, geometrically, deform the antero-posterior or septal-lateral dimension of the mitral annulus. Devices are in development to perform percutaneous annuloplasty either from within the coronary sinus (indirect annuloplasty) or direct approaches to the mitral annulus (direct annuloplasty) via the cavity surface.[51] The coronary sinus lies outside the lateral and posterior mitral annulus and any conformational change of this structure may be used to reduce annular dimension and, thus, decrease mitral regurgitation severity devices are being developed to correct mitral regurgitation through this approach (Figs 2A to C). These techniques are in the early stages of clinical trials.

PERCUTANEOUS MITRAL LEAFLET REPAIR

Direct mitral leaflet repair has been accomplished using a surgical approach pioneered by Alfieri in the early 1990s.



FIGURES 2A TO C: Examples of devices for percutaneous mitral valve repair and annuloplasty. (A) The MitraClip mitral valve repair system. (*Source:* Modified from Abbott Vascular, Abbott Park, Il). (B) The Edwards MONARC device. (*Source:* Modified from Edwards Lifesciences, Irvine, CA). (C) The Carillon device. (*Source:* Modified from Cardiac Dimensions, Inc., Kirkland, WA)

Suturing of the free leaflet edges of the mid-part of the line of coaptation results in a double-orifice mitral valve.[52] The MitraClip valve repair system (Abbott Vascular, Santa Clara, CA) utilizes a technique that is designed to treat degenerative and functional mitral regurgitation, is analogous to the Alfieri surgical procedure[53] and does not involve the coronary sinus. A small clip is delivered with a transaxial steerable delivery system during transseptal catheterization (Fig. 2A). The anterior and posterior leaflets are then, securely attached together (edge-to edge), which creates a double orifice inlet valve that improves leaflet coaptation and thus, decreases mitral regurgitation. This device has now been shown to be feasible and safe in the Endovascular Valve Edge-to-Edge Repair Study (EVEREST) and is approved for use in Europe.[54] The EVEREST II study was a randomized prospective trial designed to evaluate the performance of endovascular mitral repair in comparison to open mitral valve surgery in patients with significant mitral regurgitation.[55] Preliminary results from this trial have demonstrated reasonable safety and efficacy in a population of patients with severe mitral regurgitation randomized between percutaneous and surgical repair.

In summary, surgical mitral repair or replacement remains the "gold standard" treatment for patients with severe mitral regurgitation. However, there are number of potential percutaneous therapies for mitral regurgitation in various stages of clinical development, and some already approved outside the United States.

CATHETER-BASED TREATMENT OF PULMONARY VALVE DISEASE

PERCUTANEOUS PULMONIC BALLOON VALVULOPLASTY

Pulmonic valve stenosis accounts for 7–9% of all congenital heart disease and can be found as an isolated valvular obstruction or in association with more complicated congenital heart syndromes.[56] Most cases are diagnosed and treated in the pediatric population, and these patients are now surviving into adulthood requiring ongoing cardiovascular care. Severity of pulmonic valve stenosis can be graded by the peak systolic gradient across the valve and the degree of elevation of right ventricular systolic pressure (Table 2). Most patients with a peak systolic gradient greater than 50 mm Hg, will ultimately require an intervention.[57]

In the past, surgical valvotomy was the treatment of choice; however, balloon valvuloplasty has now gained acceptance as first line treatment strategy for pulmonary stenosis. The first percutaneous pulmonic valvuloplasty (PPV) procedure was performed in 1982 in a pediatric patient and this technique was quickly adapted to the adult population for relief of pulmonary valve stenosis.[58,59] Chen et al. reported short-term and long-term results of the procedure in 53 adolescents and adults with pulmonic valve stenosis. All patients had a significant reduction in the peak systolic gradient across the pulmonic valve, from 91 ± 46 mm Hg to 38 ± 32 mm Hg. The diameter of the valvular orifice was 8.3 ± 1.4 mm before valvuloplasty and 17.2 ± 2.0 mm immediately, post-procedure as measured by right ventriculogram.[60] These results persisted after nearly 10 years of clinical follow-up.

Percutaneous balloon pulmonic valvuloplasty is highly effective and the pulmonic valve gradient, typically, is reduced by greater than 50%.[61] Major complications of PPV are rare and more frequent in the younger pediatric population. The complications are similar to those of a right heart catheterization in addition to mild pulmonary valve insufficiency without significant hemodynamic consequences. Right ventricular outflow tract (RVOT) perforation and vessel trauma have been reported in the neonatal population. Restenosis following PPV is uncommon and less likely to occur, if the final gradient after PPV is less than 30 mm Hg.[62]

In summary, percutaneous balloon pulmonary valvuloplasty is considered as the treatment of choice for patients with isolated pulmonic valvular stenosis. Patients with isolated, symptomatic pulmonic stenosis or those with a transvalvular gradient greater than 40–50 mm Hg are considered candidates for this procedure.[63]

TABLE 2

Grading system for pulmonic valvular stenosis

Degree of obstruction	*Peak systolic transvalvular gradient (mm Hg)*	*Right ventricular systolic pressure (mm Hg)*
Trivial	< 25	< 50
Mild	25–49	50–74
Moderate	50–79	75–100
Severe/Critical	> 80	> 100

PERCUTANEOUS PULMONARY VALVE IMPLANTATION

Most native pulmonary valve stenosis, whether congenital or acquired, can be managed with balloon valvuloplasty. However, both regurgitant and stenotic disease can occur after surgery for congenital heart defects such as tetralogy of Fallot, RVOT reconstruction and pulmonary atresia. In these patients, surgical repair or replacement is standard therapy for severe pulmonary valvular disease. Recently, transcatheter options have become available for replacement of the pulmonic valve. These treatments may become attractive options for patients at increased risk of operative repair.

The first percutaneous pulmonary valve implantation (PPVI) was performed by Bonhoeffer in 2000, using a bovine jugular vein valve sutured to a balloon expandable stent.[64] This group reported use of this system to treat 59 children with pulmonary valvular disease mostly due to tetralogy of Fallot, transposition of the great arteries and ventricular septal defect with pulmonic stenosis. Procedure success rate was high (98%) and treated patients showed improvements in valve gradients, measures of right ventricular function and exercise capacity.[65]

The bovine jugular Melody valve (Medtronic, Inc. Minneapolis, MN) is the first transcatheter heart valve approved in the United States. It is approved for placement in dysfunctional RVOT conduits (Fig. 3). In the US Melody Valve Trial, this valve was successfully implanted in 124 of 136 (91%) adults and children with pulmonary regurgitation (PR) or conduit stenosis of dysfunctional RVOTs. In stenotic subjects, mean valve gradients were decreased from 37 mm Hg to 12 mm Hg



FIGURE 3: The Melody valve for pulmonic valve implantation. (*Source:* Modified from Medtronic, Inc., Minneapolis, MN)

after valve implantation. In 92 subjects with moderate or severe PR, no implanted patient had more than mild PR at one year follow-up.[66,67]

The PPVI has shown promising early results in managing dysfunctional right ventricle-to-pulmonary artery conduits in patients with congenital heart disease. This device has been approved as an alternative to surgery in pediatric and adult patients with RVOT conduits from previous congenital heart disease surgery and either moderate to severe PR or an RVOT stenosis with a mean gradient of greater than or equal to 35 mm Hg.

PERCUTANEOUS TRICUSPID BALLOON VALVULOPLASTY

Tricuspid stenosis is a rare valvular heart disease and most commonly results as a sequela of rheumatic fever. When due to rheumatic disease, tricuspid stenosis, typically, occurs in conjunction with stenotic disease of the aortic or mitral valve. Only a few reports have been published describing successful treatment of rheumatic tricuspid stenosis with percutaneous tricuspid balloon valvuloplasty.[68-70] Patients with moderate to severe tricuspid regurgitation are not considered candidates for this procedure. Outcomes from this procedure have been similar to the results reported from surgery, showing dramatic clinical improvement, significant reduction of the transvalvular gradient and increase in the cardiac output. Complications of the procedure including tricuspid regurgitation are minimal and restenosis of the valve at follow-up are rare in the available literature.

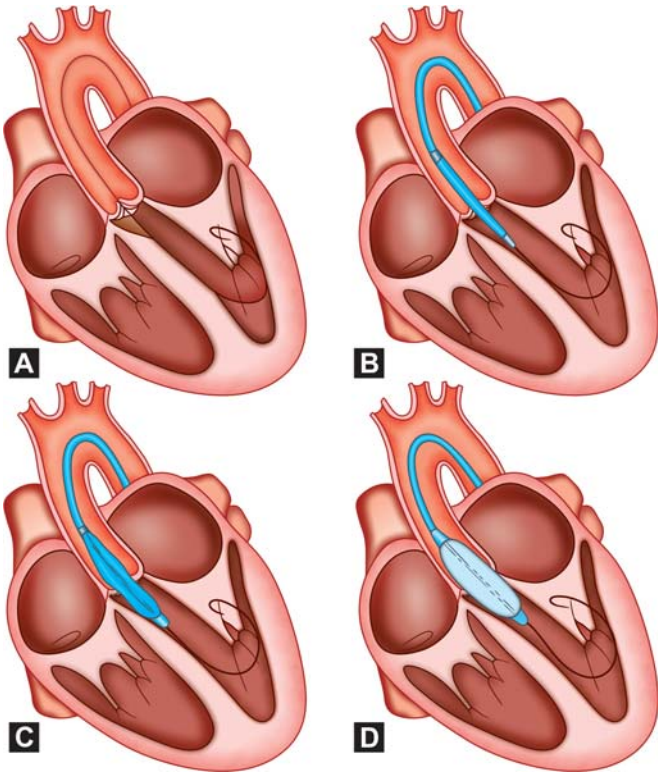
CATHETER-BASED THERAPIES FOR AORTIC STENOSIS

With increasing life expectancy, the prevalence of aortic stenosis has also risen and approaches 5% in patients over 75 years of age.[42] Calcified aortic stenosis is the most common cause of acquired valvular heart disease in Western countries.[71] The majority of acquired aortic stenosis results from senile calcification, in contrast to rheumatic aortic stenosis and congenital aortic stenosis, where the pathology is commissural fusion. No medical therapy has been shown to improve survival in patients with aortic stenosis.[72] Surgical aortic valve replacement for critical aortic stenosis has excellent outcomes and is the treatment of choice for the vast majority of symptomatic, severe aortic stenosis patients.[73] However, perioperative complication rates and associated mortality increase with patient related factors such as advanced age and age-related increase in comorbities. In many cases, the risk is deemed to be so high that surgeons classify patients to be non-operable. Several studies have now shown that up to 30% of patients with symptomatic aortic stenosis are denied surgery for reasons including advanced age, significant left ventricular dysfunction, previous chest surgery or radiation.[74-76] A large portion of elderly patients undergoing aortic valve replacement will need concomitant surgical procedures including coronary artery bypass or mitral valve repair or replacement.[77] Perioperative mortality for octogenarians undergoing elective aortic valve replacement and coronary artery bypass has been reported up to 24%.[77]

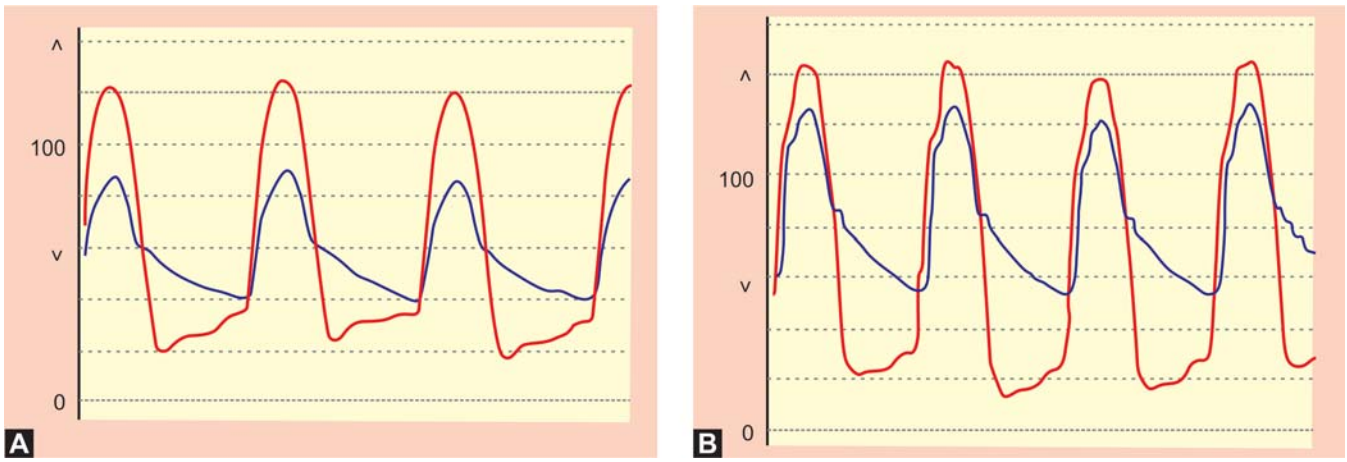
PERCUTANEOUS AORTIC BALLOON VALVULOPLASTY

Balloon aortic valvuloplasty gained popularity, as a therapeutic alternative for patients for critical aortic stenosis in the 1980s. Initial work done by Cribier, Isner and McKay reported safety and immediate efficacy of the procedure.[8,78-81] Advancements in procedural techniques may have improved outcomes in more modern practice beyond the early reported experience.

The modern procedure is most commonly performed with a retrograde approach to the valve via transfemoral arterial access (Figs 4A to D), although some operators prefer



FIGURES 4A TO D: Retrograde technique of balloon aortic valvuloplasty



FIGURES 5A AND B: Hemodynamic tracings of an aortic balloon valvuloplasty. (A) Pressure measurements in the left ventricle (red) and aorta (blue) before and (B) after valvuloplasty

transvenous antegrade, transseptal approach.[82] A pulmonary artery catheter is placed for hemodynamic measurements including measurement of cardiac output before and after completion of the procedure. When the retrograde technique is used, the left ventricular cavity is entered by advancing a catheter through the stenotic aortic valve over a guide wire. With the antegrade technique, the left atrium is entered using transseptal catheterization and a sheath. A guide wire is then manipulated across the stenosed valve to provide support for the balloon catheter. An appropriately sized dilating balloon catheter is then advanced over the guide wire and rapidly inflated to open fused commissures followed by rapid deflation to limit adverse hemodynamic effects of valve obstruction. Balloon inflations are performed with or without rapid ventricular pacing. Rapid pacing via a transvenous pacing catheter can effectively, limit stroke volume and help stabilize balloon position during inflation. As the balloon obstructs flow through the valve, a significant fall in blood pressure occurs and the procedure requires rapid inflation and deflation to prevent hemodynamic collapse. After the valvuloplasty, the resultant valve area is calculated using the Gorlin equation (Figs 5A and B).[83] Left ventricular ejection fraction and degree of any resultant aortic insufficiency is assessed by contrast ventriculography or echocardiography. Further inflations with larger diameter balloons can be performed, if the result is unsatisfactory and aortic insufficiency has not, significantly, worsened.

Over the last 25 years, there have been procedural improvements including reduced vascular access site size requirements, additional options for managing these access sites, improved balloon design and the use of rapid pacing during balloon inflation that may have improved outcomes beyond the early reported experience. Although balloon aortic valvuloplasty results in immediate reduction in the transvalvular gradient, a high incidence of restenosis that leads to recurrent clinical symptoms has caused the procedure to fall out of favor.[72,84]

Two large landmark observational studies for aortic balloon valvuloplasty outcomes have been reported. The National Heart, Lung, and Blood Institute (NHLBI) registry enrolled 674 patients with severe aortic stenosis and The Mansfield Scientific Aortic Valvuloplasty Registry (MSVR) included 492 severe aortic stenosis patients with high surgical risk.[80,85] The immediate results from the two studies were similar. The NHLBI registry reported an increase of the aortic valve area from 0.5 ± 0.2 cm^2 to 0.8 ± 0.3 cm^2 following valvuloplasty accompanied by a fall in mean and peak aortic valve gradients from 55 ± 21 mm Hg and 65 ± 28 mm Hg to 29 ± 13 mm Hg and 31 ±18 mm Hg, respectively.[80,85] Although these hemodynamic results are significant, a postvalvuloplasty valve area of 0.8 cm^2 is still considered to be severe aortic stenosis and may leave patients with ongoing symptoms. Otto et al. reported three year outcomes after balloon aortic valvuloplasty from the NHBLI registry.[72] One year survival rate was 55% and three year survival only 23% which are similar to survival rates in untreated, symptomatic aortic stenosis, although no randomized studies have been conducted comparing balloon aortic valvuloplasty to medical treatment.[86] Major complications were reported to occur in 25% of patients that underwent aortic balloon valvuloplasty enrolled in the NHLBI Balloon Registry.[85] Death occurred in 3%, arrhythmia requiring treatment in 10%, prolonged hypotension in 8%, cardiac tamponade in 1%, aortic insufficiency in 1% and a systemic embolic event in 2%.[72,85]

Aortic Valvuloplasty in Special Circumstances

Cardiogenic shock: The prognosis for a patient in cardiogenic shock secondary to critical aortic stenosis is poor and surgical aortic valve replacement can be life-saving. However, evidence of multiorgan failure and hemodynamic instability may preclude these patients from an immediate operation. Moreno et al. showed that emergency percutaneous aortic balloon valvuloplasty could be performed successfully, as a bridge to ultimate surgical therapy or as a palliative treatment in critically ill patients, although morbidity and mortality remains high, despite a successful procedure.[87]

Aortic valvuloplasty in pregnancy: Severe symptomatic aortic stenosis in the pregnant woman is poorly tolerated, if left unrelieved. Altered hemodynamics during pregnancy combined with a relatively fixed cardiac output caused by the stenotic valve leads to a significant risk of maternal death.[88] Experience

with balloon aortic valvuloplasty in pregnancy is limited and restricted to case reports, all of which had good results and outcomes for the mother.[88] Based on these reports, valvuloplasty may be considered as an alternative to surgical valve replacement in the pregnant woman with critical, symptomatic aortic stenosis.

Summary

Long-term event-free survival after balloon aortic valvuloplasty is poor and results in survival similar to the natural history of untreated aortic stenosis.[72] Current guidelines from the American College of Cardiology/American Heart Association suggest that the procedure should only be offered as palliation for patients that have symptomatic critical aortic stenosis and are not considered to be surgical candidates or as a bridge to surgery in patients with potentially reversible contraindications to immediate surgical correction.[50] Balloon aortic valvuloplasty may become more common place in the near future as an adjunct to transcatheter aortic valve implantation (TAVI) procedures.

PERCUTANEOUS AORTIC VALVE IMPLANTATION

A large portion of patients with symptomatic, severe aortic stenosis present a prohibitive risk for surgical aortic valve replacement and balloon valvuloplasty offers limited long-term results. The TAVI has emerged as a promising technology for providing treatment to this group of patients.

The first expandable artificial valve without thoracotomy was inserted in 1990 into pigs by the Danish cardiologist Dr. Henning Rud Andersen in his garage.[89] Since then, there has been tremendous interest in developing devices and techniques to accomplish percutaneous valve replacement. The first human percutaneous a TAVI was described in 2004.[90] The recipient was critically ill, hemodynamically, unstable patient judged not to be a candidate for a surgical aortic valve replacement. Cribier and his coworkers mounted three bovine pericardial leaflets in a balloon expandable stent. This was felt to be a last resort, potentially life-saving intervention that might be a bridge to surgery. The implantation resulted in marked immediate hemodynamic improvement lasting for 17 weeks when the patient died from a noncardiac cause. This was followed by a series of 6 patients with dramatic hemodynamic and functional improvements.[91]

A number of percutaneous valves and delivery devices are under development and in early clinical trials (Figs 6A to C). In contrast to surgical replacements, these devices are all placed without removing the native diseased valves. Currently, there are two major technologies that have passed the preclinical development stage: (1) the self-expanding CoreValve ReValving system (Medtronic, Inc., Minneapolis, MN) and (2) the balloon-expandable Edwards SAPIEN valve (Edwards Lifesciences Corp, Irvine, CA). The CoreValve prosthesis is a porcine trileaflet valve mounted on a self-expanding stent that is implanted via the transfemoral approach, whereas the Edwards SAPIEN valve is a bovine pericardial tissue valve mounted in a balloon expandable stainless steel stent placed either via transfemoral or transapical approaches. Grube et al. published the first clinical series using the self-expanding CoreValve system in 2006 including 25 high-risk surgical candidates with symptomatic aortic valve stenosis. Device success and procedural success were achieved in 22 (88%) and 21 (84%) of the patients. Successful device implantation resulted in a marked reduction in the gradient across the aortic valve. Major in-hospital cardiovascular and cerebral events occurred in 8 patients (32%) including mortality in 5 patients (20%).[92] A single center experience from Canada, including 168 cases of high surgical risk aortic stenosis patients, was reported with over 94% procedural success rate and with a 1.2% intraprocedural mortality using the Edwards valve.[93] Periprocedural complications as a consequence of pre-valve prosthesis placement valvuloplasty or prosthetic valve implantation were reported with the early experiences and including vascular access site complications, acute aortic regurgitation, conduction system abnormalities, arterial embolic events, displacement of the valve prosthesis and occlusion of coronary ostia during the valve deployment. These early experience studies have been followed by more recent information from many centers and registries utilizing second or third generation technology and greater operator experience leading to improved outcomes.[94]



FIGURES 6A TO C: Examples of devices for percutaneous aortic valve treatments: (A) The CoreValve system. (*Source:* Modified from Medtronic, Inc., Minneapolis, MN). (B) The Edwards SAPIEN valve. (*Source:* Modified from Edwards Lifesciences, Irvine, CA). (C) The AorTx valve. (*Source:* Modified from Hansen Medical Mountain View, CA)

The placement of aortic transcatheter (PARTNER) valves trial is the first prospective randomized clinical trial comparing transcatheter aortic valve implantation with standard therapy in high-risk patients with severe aortic stenosis.[95] In this trial, there was a prespecified cohort (cohort B) of 358 patients who were not considered to be surgical candidates. At 1 year, the rate of death from any cause was 30.7% with TAVI compared to 50.7% with standard therapy including balloon valvuloplasty. The rate of the composite end point of death from any cause or repeat hospitalization was 42.5% with TAVI as compared with 71.6% with standard therapy. However, at 30 days, TAVI, as compared with standard therapy, was associated with a higher incidence of major strokes 5.0% versus 1.1% and major vascular complications 16.2% versus 1.1%.[95]

The results from the second cohort (cohort A) of the PARTNER trial were recently presented (American College of Cardiology in New Orleans, April 2011). This part of the trial compared the safety and effectiveness of TAVI (either transfemoral or transapical) head to head to the traditional surgical treatment in operable, high surgical risk patients with symptomatic aortic stenosis. This was a prospective randomized trial with noninferiority design. About 699 patients were

randomized to a transfemoral arm (492 patients) or a transapical arm (207 patients) and then, randomized 1:1 to TAVI or AVR. All cause mortality was 24.2% in the TAVI group versus 26.8% in the AVR group. The transfemoral group was also noninferior to AVR when analyzed alone versus AVR. Major strokes and vascular complications rates tended to be higher in the TAVI group, but did not reach statistical significance. Major bleeding (9.3% vs 19.5%) and new atrial fibrillation (8.6% vs 16%) was significantly, higher in the AVR group versus TAVI. Symptom improvement assessed with a 6 minute walk test and NYHA class was similar at 1 year, but there was increased paravalvular regurgitation associated with TAVI.

There is increasing evidence that TAVI may be an attractive option for AS patients with high operative risk and may become the standard of care for inoperable patients. Early results from cohort A from the PARTNER trial show promising results comparing TAVI to AVR in high surgical risk patients with severe aortic stenosis. However, long-term data is lacking including the durability of the valve and significance of paravalvular leak. This technique and the device are still considered first generation and rapid evolvement may be expected. Many important questions regarding this technique and the role of TAVI in treating aortic valve disease remain unanswered. Future studies will likely be focused on lower risk patients who are candidates for surgery.

SUMMARY/FUTURE DIRECTIONS

Transcatheter valve therapies have evolved over the last few decades from palliative procedures in nonoperable patients to standard-of-care in appropriate, selected patient populations. Pulmonic and mitral valvuloplasty procedures are established as first line therapies for many patients. A valve for percutaneous pulmonary valve replacement has been recently approved to manage children and adults with congenital heart disease. While surgical intervention remains the gold standard for many other valve disorders, the field of percutaneous valve replacement and repair is developing rapidly. Transcatheter aortic and pulmonic valve replacement and a variety of mitral valve therapy approaches have been successfully performed in hundreds of patients. The patient populations who may, ultimately, benefit most from treatment using these new technologies will be defined in the next few years. These new transcatheter approaches may change the face of valve therapy and promise to extend treatment to a larger proportion of the valve disease population.

GUIDELINES
SELECTED AMERICAN HEART ASSOCIATION/ AMERICAN COLLEGE OF CARDIOLOGY GUIDELINES[96]

AORTIC BALLOON VALVOTOMY

Class IIb:

- Aortic balloon valvotomy might be reasonable as a bridge to surgery in hemodynamically unstable adult patients with aortic stenosis who are at high risk for aortic valve replacement.
- Aortic balloon valvotomy might be reasonable for palliation in adult patients with aortic stenosis in whom aortic valve replacement cannot be performed because of serious comorbid conditions.

Class III:

- Aortic balloon valvotomy is not recommended as an alternative to aortic valve replacement in adult patients with aortic stenosis; certain younger adults without valve calcification may be an exception.

INDICATIONS FOR PERCUTANEOUS MITRAL BALLOON VALVOTOMY

Class I:

- Percutaneous mitral balloon valvotomy is effective for symptomatic patients (New York Heart Association functional class II, III, or IV), with moderate or severe mitral stenosis and valve morphology favorable for percutaneous mitral balloon valvotomy in the absence of left atrial thrombus or moderate to severe mitral regurgitation.
- Percutaneous mitral balloon valvotomy is effective for asymptomatic patients with moderate or severe mitral stenosis, and valve morphology that is favorable for percutaneous mitral balloon valvotomy who have pulmonary hypertension (pulmonary artery systolic pressure greater than 50 mm Hg at rest or greater than 60 mm Hg with exercise) in the absence of left atrial thrombus or moderate to severe mitral regurgitation.

Class IIa:

- Percutaneous mitral balloon valvotomy is reasonable for patients with moderate or severe mitral stenosis who have a nonpliable calcified valve, are in New York Heart Association functional class III–IV, and are either not candidates for surgery or are at high risk for surgery.

INDICATIONS FOR BALLOON VALVOTOMY IN PULMONIC STENOSIS

Class I:

- Balloon valvotomy is recommended in adolescent and young adult patients with pulmonic stenosis who have exertional dyspnea, angina, syncope, or presyncope and an RV-to-pulmonary artery peak-to-peak gradient greater than 30 mm Hg at catheterization.
- Balloon valvotomy is recommended in asymptomatic adolescent and young adult patients with pulmonic stenosis and RV-to-pulmonary artery peak-to-peak gradient greater than 40 mm Hg at catheterization.

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Chapter 60

Infective Endocarditis

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Chapter Outline

- Epidemiology
  - Adults
  - Children
- Pathogenesis
  - Predisposing Cardiac Conditions and Contributions of Abnormal Flow
  - Non-Bacterial Thrombotic Endocarditis (NBTE)
  - Microbial Factors
  - Host Response
  - Manifestations of Infection
- Microbiology
  - Native Valve
  - Prosthetic Valve
  - Culture-Negative Endocarditis
- Patient Presentation and Diagnosis
  - Clinical Presentation
  - Blood Culture
  - Use of Echocardiography
  - Other Diagnostic Studies
  - Mimickers of Infectious Endocarditis
- Management
  - Empiric Medical Therapy
  - Definitive Medical Therapy
  - Surgical Therapy and Timing of Surgery
  - Persistent Fever
  - Anticoagulation
  - Prevention of Endocarditis

INTRODUCTION

In contrast to improved outcomes with other types of heart disease, the prognosis of endocarditis has appreciably not changed in the last few decades, with in-hospital mortality ranging from 15% to 30%. The increasing prevalence of healthcare-associated endocarditis, coupled with the rise of antibiotic-resistant microbial pathogens, means that endocarditis will continue to be associated with high morbidity and mortality in the foreseeable future.

EPIDEMIOLOGY

Depending on the population studied, endocarditis occurs with an incidence of 1.7–11.0 per 1,000 person-years, with much of the variability related to prevalence of intravenous drug use.[1-3] Endocarditis is approximately twice more common in men than in women. Rheumatic heart disease, formerly a major risk factor for endocarditis, is now an uncommon underlying predisposition for endocarditis in the United States and the Europe. Longitudinal studies of endocarditis in developed countries have shown a stable incidence over the past 50 years, but with an increasing percentage of cases occurring in the elderly.[1] Rheumatic heart disease remains a major predisposing factor for endocarditis in Africa and other developing nations.[4]

ADULTS

Among adults, endocarditis can be broadly divided into four major groups at risk of disease: (1) native valve endocarditis; (2) prosthetic valve endocarditis; (3) endocarditis in illicit drug users and (4) healthcare-associated endocarditis. These four categories have significantly different predisposing factors, microbiologic patterns and outcomes (Table 1). Endocarditis has also been categorized clinically as “acute” or “subacute”, a distinction that more often reflects the infecting organism (e.g. *Staphylococcus aureus* causing acute endocarditis) and the course of disease rather than the epidemiologic subgroup.

Native Valve Endocarditis

Native valve endocarditis represents the majority of endocarditis and reflects a spectrum of risk in the general community. Thirty to forty percent of patients with native valve endocarditis have no identifiable risk factor. In the remainder of patients anatomic predispositions may include mitral valve prolapse, rheumatic heart disease and congenital heart disease. Injection drug use is also an important risk factor in patients with anatomically normal valves (see section “Illicit Drug Use”). Case-control epidemiologic studies have also shown that patients with endocarditis are more likely to have chronic kidney disease or diabetes,[5] and prospective studies have shown that each is an independent risk factor for in-hospital mortality.[6]

Myxomatous degeneration of the mitral valve with prolapse and insufficiency predisposes to irregular valve thickening and disturbed flow, both of which can contribute to bacterial colonization and vegetation formation. Persons with mitral valve prolapse have a risk of endocarditis between 4.6 and 52 per 100,00 person-years,[7,8] with the majority of infectious risk

TABLE 1

Risk factors, microbiologic patterns and outcomes of endocarditis

	Types of Endocarditis			
	Native valve	*Prosthetic valve*	*Illicit drug use*	*Healthcare associated*
Risk factors	Mitral valve prolapse Rheumatic heart disease Congenital heart disease Chronic kidney disease Diabetes	Prior endocarditis Risk is higher during first 12 months for mechanical valve, greater for bioprosthesis after 12 months	Injection drug use (especially heroin)	Recent hospitalization or interaction with healthcare system
Most common microbiologic patterns	*Viridans group Streptococci* *Staphylococcus aureus* *S. gallolyticus* (formerly *bovis*) Enterococci	Early: *S. aureus* Coagulase-negative *Staph* *Enterococcus* *Streptococci* Late: Coagulase-negative *Staph* *S. aureus* *Enterococcus*	*S. aureus* *Streptococci*	*S. aureus* *Enterococci* Coagulase-negative *Staph* *Streptococci*
In-hospital mortality	15–20%	20–30%	5–10%	20–30%

Endocarditis in adults has four major patterns of presentation: (1) native valve endocarditis; (2) prosthethic valve endocarditis; (3) endocarditis associated with illicit drug use and (4) healthcare-associated endocarditis. These subgroups are associated with different risk factors, microbiologic patterns and mortality. (*Source:* Murdoch et al.[20] and Wang et al.[13])

confined to the subgroup of patients with thickened leaflets and mitral regurgitation.[9]

Rheumatic heart disease was historically the most common predisposing cause of endocarditis, but in developed countries now accounts for less than 10% of cases. Among persons with rheumatic heart disease, the mitral valve is most frequently involved, followed by the aortic valve.

Congenital heart disease is increasingly prevalent in adults due to advances in medical and surgical management. High-flow lesions (e.g. ventricular septal defect) can lead to disturbed flow; in some cases, the jet itself may injure the endothelial surface, leading to so-called jet lesions. In comparison, low-flow lesions, such as atrial septal defect, rarely lead to endocarditis. Due to its high prevalence, a bicuspid aortic valve may be the predisposing condition in middle aged to elderly patients with endocarditis.[10] Elderly patients may also be at risk due to senescent changes such as valvular sclerosis and insufficiency.

Prosthetic Valve Endocarditis

Prosthetic valve endocarditis occurs with actuarial rates of approximately 1% at 1 year and 3–5% after 5 years.[11] Mechanical bioprostheses have a higher rate of infection during the first 3 months, but bioprosthetic valves appear to have a higher late risk of infection, resulting in similar long-term risk of endocarditis regardless of prosthetic valve type.[12] A recent multinational cohort study found that prosthetic valve endocarditis now accounts for 20% of all cases of endocarditis, with *S. aureus* the predominant infecting organism.[13] The mortality of prosthetic valve endocarditis remains more than 20%, with *S. aureus* and healthcare-associated infections independently predicting in-hospital mortality.

Endocarditis in Illicit Drug Use

Injection drug users have an annual incidence of endocarditis ranging from 2% to 5% per year. The tricuspid valve is most commonly involved, although any valve or combination of valves can be affected.[14,15] The *S. aureus* is the major microbial species in injection drug use endocarditis and accounts for more than half the cases, but other organisms, such as *Pseudomonas* and *Candida* spp., occur with increased frequency compared to other groups, likely reflecting contamination of and additives to the injectate. Studies have suggested a rising incidence of injection drug-associated endocarditis despite stable rates of drug abuse; this may be due to increased use of methamphetamines and/or more frequent injection by current users.[16] Patients with HIV have a higher incidence of endocarditis, but much of this risk is attributable to associated injection drug use among subgroups of patients; patients with advanced immunosuppression may be at somewhat higher risk than the general population and have more than 50% one-year mortality from endocarditis. The incidence of endocarditis among patients infected with HIV had declined significantly in recent years, possibly due to development of highly active antiretroviral therapies.[17]

Healthcare-Associated Endocarditis

Healthcare-associated endocarditis (i.e. acquired in the hospital or as a complication of a medical intervention) is an increasingly important risk factor for infection, accounting for 25% of endocarditis in a recent international series.[18] Patients with healthcare-associated endocarditis are generally older than patients with community-acquired endocarditis and have a higher prevalence of comorbidities. Healthcare-associated endocarditis has high (20–30%) inpatient mortality. The *S. aureus*, coagulase-negative staphylococci, and *Enterococcus* spp. are the most common etiologic organisms. The prevalence of antibiotic-resistant strains of these organisms, including methicillin resistant *S. aureus* (MRSA) and vancomycin-resistant *Enterococcus* (VRE), is higher than in the general population.

Cardiac device-related infection represents an increasingly important subgroup of healthcare-associated endocarditis,

occurring with an incidence of 1–2% of all pacemaker implants.[19] With the increasing use of pacemakers and intracardiac defibrillators, device infection now accounts for 7–8% of all cases of endocarditis.[20]

CHILDREN

Endocarditis in children occurs primarily in infancy and adolescence, reflecting newborns with predisposing factors and late sequelae of congenital heart disease.[21] Approximately 40% of children with endocarditis have pre-existing heart disease; indwelling venous catheters and premature birth are the other major epidemiologic factors associated with childhood endocarditis.[22] Staphylococcal infections are the most frequent etiologic organism, with viridans group streptococci being second most common.

PATHOGENESIS

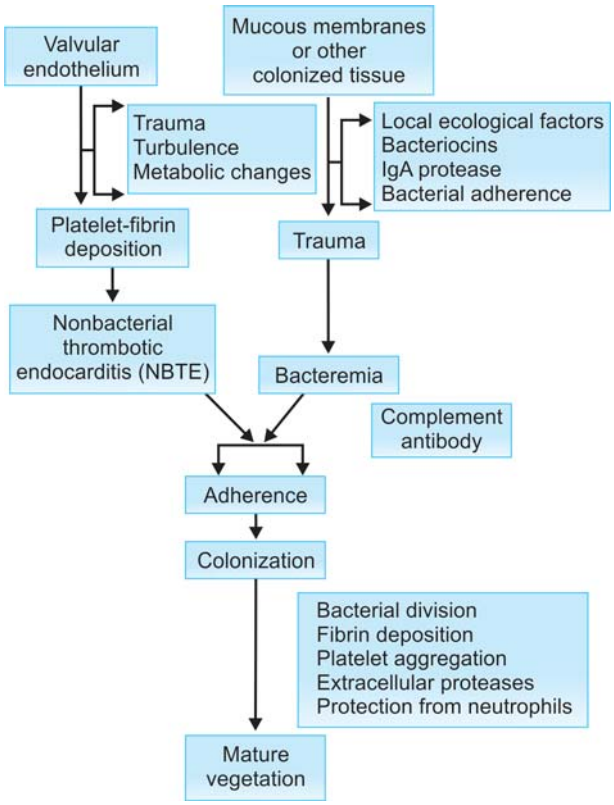
Patient and microbial factors both contribute to the propensity for development of endocarditis. Patient factors include pre-existing cardiac conditions that cause abnormal pressure-flow dynamics, leading to endothelial injury and development of non-bacterial thrombotic endocarditis (NBTE) or sterile vegetation, which is composed of a platelet-fibrin network at sites of endothelial injury. Sites of NBTE provide a nidus for bacterial adhesion and invasion, and microbial factors determine the likelihood of bacterial persistence and sustained infection. A working model for this process is shown in Flow chart 1.

PREDISPOSING CARDIAC CONDITIONS AND CONTRIBUTIONS OF ABNORMAL FLOW

Blood flow in the normal human heart is well organized and mostly laminar. The presence of a stenotic or regurgitant lesion with an associated pressure differential from a high-pressure to a low-pressure chamber results in blood acceleration and high velocities.[23] High velocity jets create a risk for endothelial infection by their associated turbulence. In some situations the accelerated flow may also create a jet that, by virtue of its direction and immediate proximity to a cardiac chamber wall or vessel, exerts sufficient mechanical fluid forces to result in endothelial injury and formation of a jet lesion. More commonly, high velocity jets are surrounded at their periphery by decreased pressure and eddy currents, exposing the adjacent endothelial surfaces on the low-pressure side of the valve lesion to the endothelial activation associated with turbulence (Fig. 1).

These hydrodynamic effects explain the finding that lesions of endocarditis tend to occur at specific anatomic sites (Table 2). For example, in patients with a ventricular septal defect, the high flow of blood directed from the left ventricle to the right ventricle can result in a characteristic jet lesion on the right ventricular wall. In patients with aortic regurgitation or mitral regurgitation, the lesion typically localizes to the low-pressure side of the valve (i.e. the ventricular surface of the aortic valve or the atrial surface of the mitral valve). Secondary "satellite" lesions can occur along the ventricular chordae or left atrium, either from embolization of the initial lesions or from jet effects of the regurgitant lesions.

FLOW CHART 1: Proposed pathogenesis of endocarditis. Patient factors and microbial factors interact to lead to develop endocarditis. Injury to the valvular endothelium from trauma, turbulence or metabolic changes leads to platelet-fibrin deposition and formation of NBTE. Trauma to mucous membranes or other compromised tissue allows bacterial entrance to the circulation and bacteremia. Bacterial adhesion factors promote adherence to NBTE, promoting further platelet aggregation, coverage of the bacteria by a platelet fibrin meshwork, and formation of mature vegetation



(*Source:* Modified from Mandell)

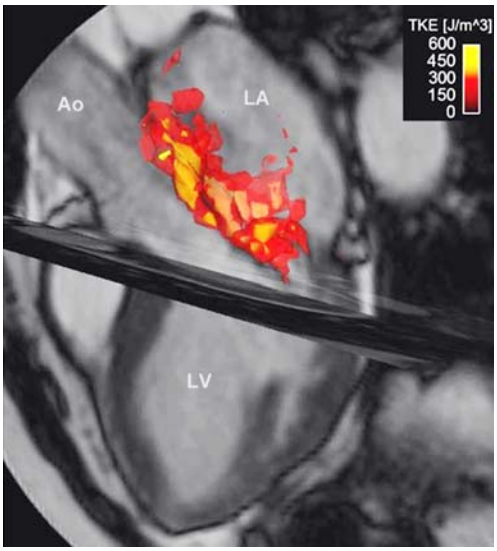


FIGURE 1: Turbulence and endothelial injury. Turbulence [demonstrated as turbulent kinetic energy (TKE)] related to mitral regurgitation is seen in the left atrium during systole. Endothelium in contact with turbulence that occurs at the periphery of high velocity jets has increased susceptibility to infection by circulating microorganisms; in this example, the atrial surface of the anterior mitral leaflet is exposed to disorganized flow as a result of the anteriorly directed mitral regurgitation jet. (Abbreviations: LA: Left atrium; LV: Left ventricle; Ao: Ascending aorta)

TABLE 2

Characteristic locations of endocarditis lesions

Predisposing condition	*Source (high pressure)*	*Sink (low pressure)*	*Location of lesions*	*Satellite lesion location*
Patent ductus arteriosus	Aorta	Pulmonary artery	Pulmonary artery	Pulmonary valve
Ventricular septal defect	Left ventricle	Right ventricle	Right ventricular surface of defect	Pulmonary artery
Aortic regurgitation	Aorta	Left ventricle	Ventricular surface of aortic valve	Mitral valve chordae
Mitral regurgitation	Left ventricle	Left atrium	Atrial surface of mitral valve	Atrium
Pulmonic regurgitaiton	Pulmonary artery	Right ventricle	Ventricular surface of pulmonary valve	
Tricuspid regurgitation	Right ventricle	Right atrium	Atrial surface of tricuspid valve	

(*Source:* Modified from Rodbard, 1963)[23]

NON-BACTERIAL THROMBOTIC ENDOCARDITIS (NBTE)

Local injury of the endocardial surface denudes the valvular endothelium exposing subintimal collagen. Circulating platelets and fibrin bind to this injured surface. In the majority of cases, local repair mechanisms reconstitute the endothelial lining. In the presence of hypercoagulability or repeated injury; however, the platelet-fibrin meshwork remains intact on the injured surface and forms a sterile vegetation referred to as NBTE. Autopsy studies have shown a high prevalence of clinically insignificant NBTE, suggesting that such lesions are part of the normal process of injury and repair. The NBTE provides a nidus for bacterial adhesion and subsequent conversion to infected vegetation.

MICROBIAL FACTORS

Transient bacteremia can occur after injury to any mucosal surface that is colonized with bacteria. Bacteremia is common after many daily activities including tooth brushing and flossing, but can also occur in the absence of any obvious trauma. The numbers of bacteria are generally quite low, and often the species of bacteria isolated typically do not cause clinical endocarditis.[24] Bacterial species that commonly cause endocarditis, e.g. *S. aureus* and alpha-hemolytic streptococci, produce specific factors that facilitate binding to injured endothelial surfaces. For example, as few as ten *S. aureus* bacteria may be sufficient to cause endocarditis.

Bacterial adherence to platelets is a first step in the initiation of endocarditis. By binding to platelets, bacteria initiate a procoagulant milieu and may preferentially localize with platelets to sites of NBTE, thereby establishing a specific locus of infection at sites of compromised endothelium. Glycocalyx is a bacterial polysaccharide that forms the outer capsule of bacteria such as streptococci. Glycocalyx mediates adhesion to tooth enamel and other inert substances. In experimental models, glycocalyx was shown to mediate binding to platelets of platelet-fibrin complexes (the constituents of NBTE).[25] The concentration of glycocalyx expressed by *Streptococcus pyogenes* correlates directly with propensity to cause endocarditis.[26] Other bacterial adhesins, including FimA,[27] have also been identified as virulence factors for development of endocarditis. In addition to binding platelets and fibrin at sites of NBTE, these adhesive factors also mediate binding to prosthetic materials.

S. aureus possesses numerous virulence factors, several of which interact with platelets. Virulence factors that interact with platelets include clumping factor A,[28] clumping factor B,[29] protein A,[30] fibronectin binding protein A[31] and serine-rich surface protein SraP.[32] *S. aureus* therefore has multiple redundant mechanisms that facilitate binding to platelets and areas of platelet-rich thrombi. *S. aureus* can also invade endothelial cells directly, possibly through interaction with fibronectin and active endothelial cell engulfment of staphylococci.[33,34] Bacterial engulfment initiates an inflammatory response of endothelial cells that includes endothelial expression of IL-1 and IL-6.[35] Infected endothelial cells also express increased levels of tissue factor and the adhesion molecules VCAM-1 and ICAM-1, which leads to monocyte adhesion and further activation of the inflammatory response.[36]

HOST RESPONSE

Once bacteria have adhered to a site of nascent endocarditis, they are covered by a platelet-fibrin mesh. Bacteria replicate within this space, reaching densities exceeding 10^9 organisms/gram. The combination of proliferating bacteria and a thrombotic meshwork overlying the bacteria constitutes a macroscopic vegetation. Bacteria within this vegetation may continue to replicate or may die and result in focal areas of necrosis.[37]

MANIFESTATIONS OF INFECTION

Once a vegetation is established, multiple mechanisms lead to pathologic sequelae of disease, including valve destruction and periannular extension, embolization of the vegetation or parts of the vegetation with end-organ damage or abscess formation, metastatic foci of infection from bacteremic seeding and deposition of immunologic complexes that result in further end-organ damage.

Valvular Destruction and Periannular Extension

Although valvular vegetations are the characteristic echocardiographic finding in endocarditis, the exuberant microbial infection often proceeds inward to the valve interstitium. In some cases, valve destruction and perforation may occur in the absence of a significant vegetation, especially in cases of infection with highly virulent organisms such as *S. aureus*. Valve perforation occurs in 30–40% of infective endocarditis (IE).[38]

Aortic valve perforation may be more common than mitral valve perforation.[39] Valve destruction results in incompetence and acute regurgitation that may be life threatening and require emergency surgery. Acute aortic regurgitation is usually less well tolerated hemodynamically than mitral regurgitation, but both lesions lead to eventual heart failure and need for valve replacement.

Periannular extension can result in formation of abscesses, pseudoaneurysms and fistulae. Periannular extension is more common in aortic than mitral valve endocarditis when assessed prospectively by transesophageal echocardiography (TEE) and in patients with a history of prior endocarditis.[40] Most cases of prosthetic valve endocarditis begin as a periannulitis at the suture line. As a result, periannular involvement is observed in 60–80% of cases of prosthetic valve endocarditis.[41]

The aortic and mitral valves lie in a plane of anatomic continuity. Extension of bacterial infection from either valve can interrupt the cardiac conduction system, leading in severe cases to complete heart block.[42] Cardiac conduction anomalies are therefore a common clinical finding in cases of confirmed periannular extension. Extension into the myocardium may result in electrocardiographic findings suggesting ischemia; further extension can lead to formation of a pseudoaneurysm and/or pericarditis. Extension of aortic valve endocarditis into the membranous interventricular septum may lead to a ventricular septal defect.

Periannular extension of endocarditis is generally considered an indication for surgery (see section "Management").

Embolization

Clinically apparent embolism of vegetation occurs in 20–40% of patients with endocarditis, although the rate of subclinical embolization is substantially higher.[43] The majority of clinically apparent emboli occur in the central nervous system, but emboli may also occur to the coronary arteries, spleen, kidneys and digits. Patients with right-sided endocarditis frequently develop septic pulmonary emboli. Approximately two-thirds of embolic complications occur prior to diagnosis and initiation of antibiotic therapy; 10–15% of patients will develop an embolic complication during antibiotic therapy.[44] Risk factors for embolism include large vegetations (over 10 mm), a highly mobile vegetation and infection with *S. aureus*.[45,46] Some studies have suggested that endocarditis of the mitral valve is also an independent risk factor for embolization.[44]

Magnetic resonance imaging (MRI) of patients with endocarditis reveals that 50% or more of patients without clinical neurologic signs have evidence of subclinical brain embolism; this finding is associated with mortality rates similar to patients with clinically evident stroke.[43] The prevalence of acute brain embolism may approach 95% in patients with left-sided endocarditis caused by *S. aureus*. Emboli to the central nervous system usually occur in a cortical or subcortical pattern and may be distributed across multiple vascular beds (so-called "shower" emboli). Embolic infarcts may transform to hemorrhagic strokes, and in some cases may cause secondary seeding and development of intracranial abscess and/or meningitis.

Septic embolization to the central nervous system may lead to mycotic aneurysm, a localized dilation of the arterial wall due to infection and destruction of the arterial wall media. Continued destruction of the arterial wall eventually leads to rupture and intracerebral hemorrhage. Mycotic aneurysms, present in only 2–5% of cases, are associated with mortality of 50–60%.[47] Patients with mycotic aneurysm may present with headache and/or or focal neurologic signs due to impending subarachnoid hemorrhage. Computed tomography (CT) and MRI have a high sensitivity for detecting mycotic aneurysms and associated bleeding, but invasive angiography remains the diagnostic gold standard. Intracranial mycotic aneurysms may heal with medical therapy, but some aneurysms continue to enlarge and require surgical ligation. In some cases, endovascular therapy may be feasible.[48] Extracranial mycotic aneurysms (e.g. aorta, splenic artery) are rare but almost universally necessitate surgery.

Septic embolism to the coronary arteries occurs rarely but can be difficult to manage, due to the relative contraindication to systemic anticoagulation in such patients, who frequently have concomitant central nervous system emboli.[49] Case reports have described aspiration thrombectomy in the management of embolic myocardial infarction.

Clinically apparent splenic infarcts occur in approximately 20% of patients with left-sided endocarditis; CT imaging suggests the actual prevalence of splenic infarcts is 40%.[50] Emboli to the spleen may result in secondary seeding and abscess formation, with rupture in extreme cases. Surgery may be required for management of large splenic infarcts.

Renal emboli may cause cortical infarcts and hematuria but rarely cause renal failure. Instead, renal failure associated with endocarditis is more often the result of immune-complex deposition and glomerulonephritis, or a complication of antibiotic therapy (such as aminoglycoside toxicity).

Other peripheral manifestations of embolism may include Janeway lesions (nontender macules on the hands or feet), Osler nodes, splinter hemorrhages in distal nail beds, conjunctival petechiae and Roth spots (retinal hemorrhages with a clear center).

Since vegetation formation and growth are associated with formation of platelet aggregates, antiplatelet agents have been studied in the prevention of embolic complications. Laboratory studies suggested that aspirin reduces vegetation density and emboli in animal models.[51] A randomized trial in humans failed to show a benefit of aspirin, with a trend toward increased hemorrhagic complications in patients randomized to aspirin therapy.[52] These findings have led to the recommendation that antiplatelet agents be avoided in patients with active endocarditis unless a compelling indication exists for continued use of an antiplatelet agent.

Metastatic Foci of Infection

Bacteremia in endocarditis is high-grade and continuous, creating the potential for seeding of virtually any tissue and for subsequent development of metastatic foci of infection. Osteomyelitis, usually of the vertebral body; epidural abscess; paraspinous abscess; septic arthritis, including non-synovial

joints such as the sacroiliac and sternoclavicular joints; urinary tract infection; endophthalmitis; and meningitis are some of the more common secondary infections. *S. aureus*, due to its invasive nature, is more likely than other bacterial species to be associated with metastatic infections. Recognition of these complications and treatment with surgical or percutaneous drainage is important for prevention of treatment failure or relapse.

Immunologic Manifestations

Persistent bacteremia from endocarditis constitutes a considerable antigen load leading to a host antibody response with development of circulating immune complexes. These may deposit in joints or in the kidney and manifest clinically as a sterile, inflammatory arthritis, often involving several joints, or hypocomplementemic glomerulonephritis, respectively. Immune complexes may also be found in cutaneous lesions of endocarditis, e.g. Osler nodes or Janeway lesions, although these are primarily caused by microembolization rather than immune complex deposition. They may also be associated with cutaneous vasculitis, a rare peripheral manifestation of IE.

MICROBIOLOGY

The microbiology of endocarditis varies widely depending on the presence of a native or prosthetic valve and whether the patient is an injection illicit drug user. These epidemiologic factors have important implications for empiric therapy of endocarditis. Culture-negative endocarditis accounts for 5–10% of cases and usually is due to administration of antibiotics prior to obtaining blood cultures. Culture-negative endocarditis may also be caused by fastidious organisms that grow poorly in blood culture, as well as by diseases that may mimic IE.

NATIVE VALVE

Streptococci and staphylococci account for 80–90% of cases of native valve endocarditis. Streptococci were until recently the most common cause of endocarditis in the absence of drug use, but staphylococci have become increasingly common due to healthcare-associated infections. The majority of endocarditis cases in injection drug users are caused by *S. aureus*, but important albeit less frequent organisms also contribute to the microbiology of intravenous drug use-associated endocarditis.

Non-Drug Users

Streptococci: Viridans streptococci (Table 3), so-called due to the green hemolysis produced by colonies on blood agar, are the most common cause of streptococcal native valve endocarditis. These are a group of commensal organisms inhabiting the oropharynx that include several distinct species, including *Streptococcus sanguis*, *Streptococcus mutans*, *Streptococcus mitis;* and the milleri group (*Streptococcus anginosus*, *Streptococcus constellatus* and *Streptococcus intermedius*).

A number of other streptococci may cause endocarditis. Beta-hemolytic streptococci, typically group B, comprise the next largest group of organisms. Group B *Streptococcus* endocarditis is associated with a high risk of emboli and end-organ complications. Endocarditis caused by *Streptococcus bovis,* (now *Streptococcus gallolyticus*) a group D streptococcal species, is associated with colonic malignancy or other underlying bowel disease and patients with *S. gallolyticus* endocarditis should undergo colonoscopy. *Streptococcus pneumoniae*, an uncommon cause of endocarditis, causes acute disease with high risk of valve perforation and more than 50% mortality; most patients have concomitant meningitis. *Gemella* spp. and *Abiotrophia* spp., although not members of the streptococcal family of organisms, may resemble streptococci on Gram stain and often are grouped together as streptococci that infrequently cause endocarditis.

Staphylococci: Staphylococci are an increasingly common cause of endocarditis and in many developed countries *S. aureus* is the most common cause of endocarditis. This is due primarily

TABLE 3
Epidemiology and microbiology of native valve endocarditis

Etiologic organism	*Epidemiologic notes*
Streptococci (25–35%)	
Viridans group streptococci	Most common cause of endocarditis
S. gallolyticus (formerly *bovis*)	Associated with colonic malignancy
S. pneumoniae	Highly virulent
Strep groups B, C and D	Group B associated with emboli
Staphylococci (30–40%)	
S. aureus	Highly invasive
Coagulase-negative Staph	Associated with indwelling catheters
Enterococcus (10–15%)	
E. faecalis	
E. faecium	
Gram-negative (2–3%)	
E. coli	
Salmonella	Also associated with parenteral drug use
Haemophilus	
Neisseria	
HACEK group	Previously considered culture-negative
Gram-positive rods (1–2%)	
Corynebacterium	More commonly seen in prosthetic valve endocarditis
Listeria	
Fungi/yeast (1–2%)	
Candida	Fungemia often persistent
Aspergillus	Difficult to isolate
Histoplasma	
Culture-negative (3–5%)	
T. whippelei	Causative microbe of Whippelei's disease
C. burnetii	Causative microbe of Q fever
Bartonella	*B. henselae* associated with cats *B. quintana* associated with homelessness

to increased technological developments including dialysis and indwelling catheters that act as a transcutaneous portal of entry.[53] In addition, the increased use of ancillary health services, including rehabilitation centers, visiting nurses and outpatient procedures, means that a greater proportion of patients may be exposed to healthcare-related organisms. *S. aureus* causes an acute infection of native valves with a high morbidity and mortality. Coagulase-negative staphylococci infrequently cause true native valve endocarditis; these infections typically have a more indolent course and are more likely to occur in patients with indwelling catheters, pacemakers or other intravascular devices. Coagulase-negative staphylococcal species are also an important cause of prosthetic valve endocarditis. Treatment of these infections is difficult due to the increasing prevalence of isolates that are methicillin resistant (i.e. resistant the beta-lactam class antibiotics).

Enterococci: Enterococcal endocarditis represents 10–15% of native valve endocarditis in recent series. *Enterococci* reside in the genitourinary tract, and bacteremic seeding is thought to occur after genitourinary or obstetrical procedures. The majority of infections occur in young women or elderly men. *Enterococcus faecalis* causes 85% of enterococcal endocarditis; *E. faecium* accounts for the other 15% of cases. Enterococcal endocarditis can be challenging to cure with medical therapy, due to the intrinsic resistance of enterococcus to many antibiotics (see section "Patient Presentation and Diagnosis") and increasing frequency of isolates that are resistant to ampicillin, vancomycin and gentamicin, which are agents of choice for treating enterococcal infections.

Gram-negative species: Gram-negative species are an uncommon cause of endocarditis, accounting for 5% or less of cases. Among the gram-negative bacilli, *Escherichia coli* and *Salmonella* more frequently cause endocarditis than other enteric organisms. *Salmonella* endocarditis is frequently associated with myopericarditis. Most cases of gram-negative endocarditis are healthcare-associated and may frequently involve the presence of prosthetic material.[54] The HACEK organisms (*Haemophilus* species other than *H. influenzae*, *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens* and *Kingella* species) are anaerobic gram-negative coccobacilli that are part of the oral flora. Previously considered as a cause of culture-negative endocarditis, the HACEK organisms now grow on most bacterial culture systems.

Fungi: Fungal infections are an uncommon cause of endocarditis, accounting for 1–2% of all cases. The majority of fungal endocarditis is healthcare-associated; a prosthetic heart valve is another epidemiologic risk for fungal endocarditis. *Candida* and *Aspergillus* spp. account for most cases of fungal endocarditis. *Candida* is relatively easily recovered in blood culture, whereas aspergillus is particularly difficult isolated in blood culture, even if special media and isolator tubes are used. Consequently, aspergillus infection is a consideration in patients with culture-negative endocarditis. Diagnosis usually requires culture of valve material or a thromboembolus.

Injection Drug Users

Endocarditis in recreational injection drug users has a distinct microbiology. *S. aureus* represents 60–80% of cases. Despite the high rates of staphylococcal endocarditis, the mortality of parenteral drug use-associated endocarditis is only 8–10%, since the majority of cases involve the tricuspid valve,[55] a hemodynamically less morbid condition and associated with low rates of system embolization, and these individuals tend to be young and therefore have a lower rate of concomitant medical illness.

The same organisms that cause native valve endocarditis in non-drug users are also common causes of endocarditis in injection drug users, particularly if there is aortic or mitral valve involvement. Intravenous drug use has also been associated with endocarditis from otherwise uncommon pathogens. These cases may be due to contamination of injectate, or the relatively immunosuppressed status of patients. These organisms include *Candida albicans* and other candidal species, *Salmonella*, *Serratia* and *Corynebacterium*. Endocarditis from injection drug use is also associated with polymicrobial infections.

PROSTHETIC VALVE

Prosthetic valve endocarditis has a distinct microbiology depending on the timing of presentation (Table 4). Endocarditis

TABLE 4

Epidemiology and microbiology of prosthetic valve endocarditis. Early prosthetic valve endocarditis is defined as endocarditis occurring within sixty days of prosthetic valve implantation

Early prosthetic valve endocarditis	
Etiologic microorganism	*Prevalence (%)*
Staph aureus	36
Coagulase-negative Staph	17
Culture negative	17
Fungal	9
Enterococcus	8
S. gallolyticus	2
Viridans group streptococci	2
E. coli	2
Pseudomonas	2
Serratia marcescens	2
Late prosthetic valve endocarditis	
Coagulase-negative Staph	20
Staph aureus	18
Enterococcus	13
Culture negative	12
Viridans group streptococci	10
S. gallolyticus	7
Fungal	2
Polymicrobial	2
Other streptococci	2
Listeria	1
Mycobacteria	1

(*Source:* Modified from Wang, 2007)[13]

occurring within 60 days of valve implantation is categorized as "early" prosthetic valve endocarditis and is considered nosocomial in etiology. Endocarditis occurring more than 1 year post-implantation is categorized as "late" and more generally reflects community acquisition. Cases occurring between 60 days and 1 year have microbiologic patterns that overlap with early and late prosthetic valve endocarditis.

Early Prosthetic Valve Endocarditis

The majority of early prosthetic valve endocarditis historically has been caused by coagulase-negative staphylococci, but recent series suggest that *S. aureus* is now the most common cause of early prosthetic valve endocarditis, with more than 50% of these infections caused by methicillin-resistant *S. aureus*.[13] Coagulase-negative staphylococci remain an important causative agent in this group as the second-most common microbe and infection is associated with a high incidence of heart failure and in-hospital mortality.[56]

Unique to early prosthetic valve endocarditis is a high proportion of fungal endocarditis (up to 9% of all cases), often necessitating re-operation.[57] A large proportion of patients (up to 17%) may be culture-negative due either to recent administration of antibiotics or infection with less common organisms. *Legionella* has also been rarely reported as a cause of early prosthetic valve endocarditis. It considered a nosocomial infection and has in some cases been isolated from the water source used for the hospital.[58]

Late Prosthetic Valve Endocarditis

S. aureus and coagulase-negative staphylococci are both frequent causes of late prosthetic valve endocarditis; the frequency of methicillin-resistant organisms is lower than with early prosthetic valve endocarditis, but still exceeds 30%. The microbiology of late prosthetic valve endocarditis begins to resemble that of native valve endocarditis, the farther the patient is out from valve implantation. Fungal infection is much less common in later prosthetic valve endocarditis, but many cases remain culture-negative.

CULTURE-NEGATIVE ENDOCARDITIS

Culture-negative endocarditis occurs in 5–10% of cases of suspected endocarditis. The most common reason for negative blood cultures is that the patient has received antibiotics prior to obtaining blood cultures. The organisms in most of these "culture-negative" cases are probably viridans group streptococci or HACEK species, as these are relatively fastidious organisms that are easily inhibited by antimicrobial agents. Staphylococci and enterococci, in contrast, are hardy organisms that better tolerate exposure to antibiotics.

The other reason for negative blood cultures is that the endocarditis is caused by an organism that grows poorly or not all in artificial media and requires serologic diagnosis or special culture techniques. Non-infectious causes of apparent endocarditis must also be considered when cultures are negative (see section "Patient Presentation and Diagnosis"). The patient with suspected endocarditis who does not have a history of recent antimicrobial therapy may be infected by one of these unusual organisms. A history of occupational or environmental exposures may provide clues to the diagnosis. For example, a history of exposure to cats is suggestive of *Bartonella hensalae*; homelessness, alcoholism, and exposure to body lice is associated with *Bartonella quintana*. Contact with psittacine birds is associated with *Chlamydophila psittaci*, whereas occupational exposure to animals (e.g. veterinarians, farmers, residence on or visitor to a farm) or unpasteurized milk or milk products is a risk factor for *Brucella* spp. or *Coxiella burnetii*, the agent of Q fever.

Diagnosis of endocarditis caused by these agents requires serological testing, polymerase chain reaction (PCR) or use of special culture media. *Legionella* is a cause of culture-negative, nosocomial prosthetic valve endocarditis. *Aspergillus*, the second most common cause of fungal endocarditis after *Candida*, causes an endocarditis characterized by bulky vegetations on echocardiogram in which systemic embolization is a prominent feature; diagnosis usually requires culture or histopathological diagnosis of valvular vegetation or a thromboembolus.

Whipple's disease is caused by *Tropheryma whippelei*. Systemic Whipple's disease is characterized by chronic and progressive development of weight loss, diffuse arthralgias and anemia. Endocarditis may occur as part of a systemic disease, or endocarditis may be the only presentation or infection.[59] In cases of systemic disease, biopsy of another affected tissue (e.g. small bowel) followed by periodic-acid Schiff staining and PCR analysis may aid in diagnosis. Noninfectious causes that may mimic culture-negative endocarditis are discussed below.

PATIENT PRESENTATION AND DIAGNOSIS

Presence of a pathological murmur, blood cultures and echocardiography are the mainstays of diagnosis for endocarditis. The symptoms and signs of endocarditis may be related to the valve infection itself, embolic phenomena and immunologic effects of prolonged infection. In straightforward cases, the presence of fever, a murmur, positive blood cultures and echocardiographic visualization of vegetation confirms the diagnosis. Many cases, however, may be initially indeterminate and require the use of more focused tests (such as specialized blood cultures or assays and/or use of TEE) to reach a diagnosis. The propensity for endocarditis to cause symptoms and signs possibly referable to other organ systems may result in initial clinical suspicion for other etiologies (e.g. malignancy). Conversely, other systemic disease may initially be mistaken for endocarditis (see section "Mimickers of Infectious Endocarditis").

The modified Duke criteria are a widely accepted set of criteria for establishing a diagnosis of endocarditis. These criteria categorize endocarditis as definite, possible or rejected based on certain clinical findings principal among which is a new regurgitant murmur, blood cultures or serologies, and echocardiography (Table 5).[60] Pathologic specimens or histology may also be utilized in cases where surgery or a biopsy is performed. The modified Duke criteria have a high sensitivity and specificity for diagnosis of endocarditis but strict use of these criteria may result in misclassification of culture-negative endocarditis or endocarditis due to less common pathogens.

TABLE 5

Modified Duke criteria for diagnosis of endocarditis

Definite endocarditis

Pathological criteria
- Microorganisms demonstrated by culture or histological culture of a vegetation, embolism or abscess OR
- Pathological lesions; vegetation or intracardiac abscess confirmed by histology showing active endocarditis

Clinical criteria
- 2 major criteria OR
- 1 major criterion and 3 minor OR
- 5 minor criteria

Possible endocarditis
- 1 major and 1 minor criterion OR
- 3 minor criteria

Rejected endocarditis
- Firm alternate diagnosis OR
- Resolution of endocarditis syndrome after 4 days or less of antibiotics OR
- No pathologic evidence for endocarditis at surgery or autopsy, if 4 days or less of antibiotics OR
- Does not meet criteria for possible endocarditis

Major criteria

Blood cultures positive
- Typical microorganisms consistent with endocarditis from 2 separate blood cultures:
  - Viridans group streptococci
  - *S. gallolyticus*
  - HACEK organisms
  - *Staphylococcus aureus*
  - Community-acquired enterococcus (in absence of primary focus)
- Microorganisms consistent with endocarditis from persistently positive blood cultures, defined as:
  - at least 2 blood cultures drawn > 12 hours apart or all of 3 or majority of ≥ 4 separate cultures of blood (with first and last sample drawn at least an hour apart)
- Single blood culture positive for *C. burnetii* or anti-phase I IgG antibody titer > 1:800

Evidence of endocardial involvement
- Positive echocardiogram:
  - Oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted prosthetic material in absence of an alternative anatomic explanation
- Abscess
- New partial dehiscence of a prosthetic valve
- New valvular regurgitation (worsening, changing or pre-existing murmur not sufficient)

Minor criteria
- Predisposition, predisposing heart condition or parenteral drug use
- Fever, temperature > 39°C
- Vascular phenomena, major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages and Janeway's lesions or Osler's nodes
- Immunologic phenomena: glomerulonephritis, Roth's spots and rheumatoid factor
- Microbiologic evidence: positive blood culture but does not meet a major criterion as above or serological evidence of active infection with an organism consistent with endocarditis

(*Source:* Modified from Li et al. 2000)[60]

Clinical judgment is therefore paramount for arriving at a final diagnosis.

CLINICAL PRESENTATION

Fever is present in 90% or more of patients with endocarditis, but patients with underlying heart failure, chronic kidney disease or immunosuppression may not develop significant fever. Prosthetic valve endocarditis may present with an indolent course, and any fever or new findings of heart failure in a patient with a prosthetic valve should prompt consideration of prosthetic valve endocarditis. Patients with endocarditis also develop other symptoms and signs resulting from chronic infection, including anorexia, weight loss and malaise. Arthralgias and muscle pains may result from immune complex deposition but, if focal, should raise concern for secondary bacteremic seeding.

A new or changing heart murmur may be present in a patient with suspected endocarditis, but the absence of a murmur does not exclude nascent endocarditis. Patients with tricuspid or pulmonic valve endocarditis frequently do not have an audible murmur. When a new murmur is recognized during therapy, it often presages the development of heart failure.

Any patient with suspected endocarditis should be examined carefully for evidence of vascular or immunologic phenomena. A thorough neurologic examination should be performed to identify focal neurological deficits, and any symptoms of a headache should raise suspicion for possible associated mycotic aneurysm or meningeal spread. Conjunctival or gingival petechiae may be present, as well as splinter hemorrhages in the proximal nailbed. Janeway lesions are nonpainful, macular spots on the hands and feet resulting from septic emboli; Osler nodes are painful nodules, pathologically indistinguishable from Janeway lesions, but located distally on the fingers and toes are also caused by microembolization. Immune complexes may contribute to the vasculitic nature of these lesions. Although these findings are not pathognomonic for endocarditis and may be found in other conditions (e.g. vasculitis), they are highly suggestive of the diagnosis.

BLOOD CULTURE

Patients with endocarditis have sustained bacteremia.[61] Blood cultures at the first suspicion of endocarditis and before administration of antibiotics are paramount in making the diagnosis. Three sets of blood cultures, both aerobic and anaerobic, should be drawn within the first 24 hours. The volume of blood obtained will depend on the blood culture system being used, but in general at least 10 ml is recommended to optimize recovery of the organism.[62] If initial cultures are negative, the microbiology laboratory should also be informed of the suspicion for endocarditis, in order to facilitate further subculture.

Since the bacteremia of endocarditis is continuous in most cases, the majority and typically all blood cultures will be positive. In the absence of prior antibiotics, one of the first two cultures is positive in 95–98% of cases.[61] Prior antibiotic therapy lowers the rate of positive blood cultures to 60–90%. In a recent international study, elderly patients (> 65 years of age) with endocarditis were more likely to have positive blood cultures, primarily due to higher rates of nosocomial and enterococcal infections.[63]

The modified Duke criteria define a positive blood culture as two separate cultures obtained at different times and from different sites that are positive for a typical causative agent of endocarditis [e.g. infection with viridans group streptococci, *S. gallolyticus* (formerly *bovis*), *S. aureus*, *Enterococcus* or HACEK organisms]. In the case of blood cultures positive for

other organisms, the requirement is for two blood cultures more than 12 hours apart, all three of the initial cultures positive or the majority of more than four cultures positive in the first 24 hours. If none of these criteria are met and infectious endocarditis still suspected, a positive blood culture may still be considered a minor criteria toward diagnosis (Table 5).

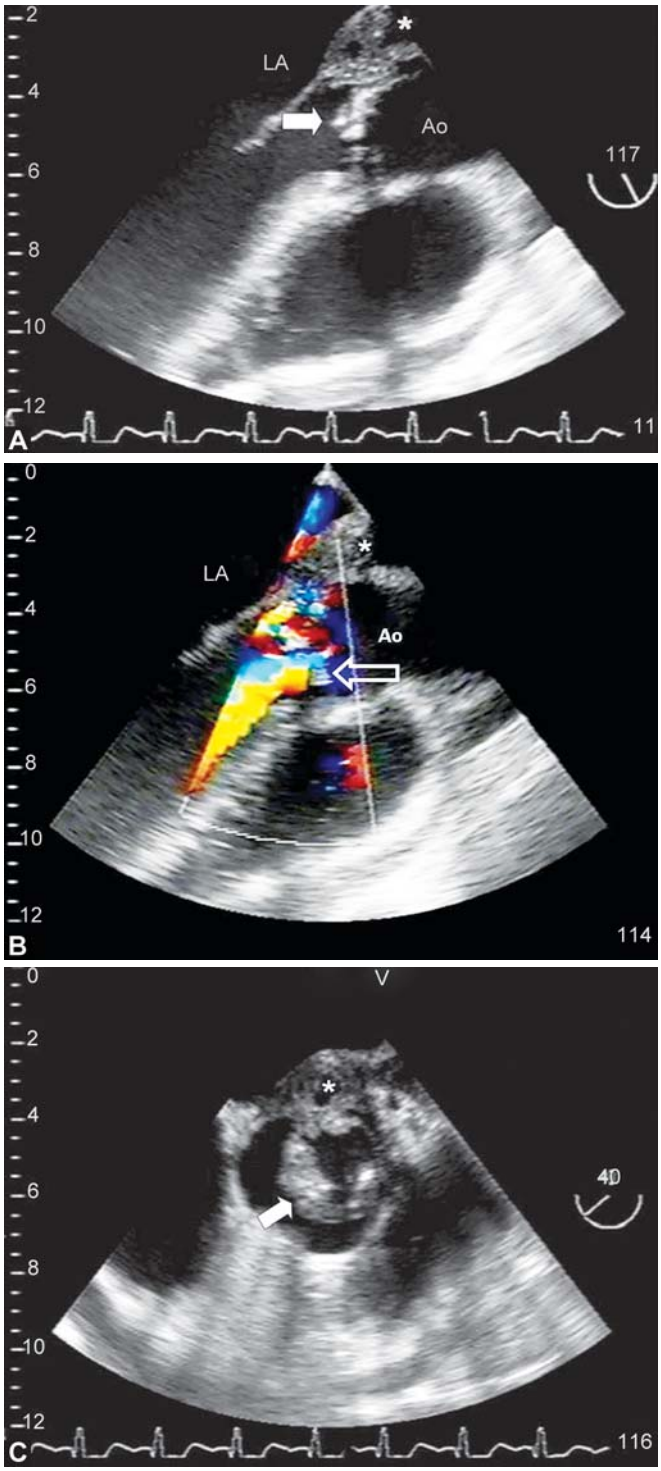
USE OF ECHOCARDIOGRAPHY

Echocardiography is integral to the diagnosis and prognostic assessment of endocarditis. Some form of echocardiography should be performed as soon as possible, and within the first 12 to 24 hours, if endocarditis is suspected. If the patient's pre-test likelihood for endocarditis is not high and there is no valvular prosthesis in place, initial transthoracic images may be obtained. The modified Duke major criteria for the diagnosis of IE include echocardiographic evidence of vegetation, annular abscess, dehiscence of a prosthetic valve, or new valvular regurgitation.[60] Even without such findings, a clinical picture that is strongly suggestive of endocarditis is compelling and should lead to treatment and further imaging with higher resolution tools such as transesophageal echocardiography.

The presence of physiologically significant valvular insufficiency is a powerful predictor of a patient's eventual need for surgery (either during the treatment of the infection or during longer-term follow-up). Large vegetations of 10 mm or more in maximal diameter have been associated with increased risk for embolization and may prompt early surgery to avoid stroke or other vascular catastrophe.

The views obtained with transthoracic echocardiography (TTE) are often inadequate for clear visualization of valvular structures, including the periannular tissues. TEE is performed with higher imaging frequencies and therefore has better spatial resolution and consequently improved detection of small vegetations. In addition, there are fewer impediments between the probe and the cardiac structures to obscure findings. The TEE is usually the only modality that can clearly demonstrate perivalvular extension of infection, fistulae and abscess formation (Figs 2A to C).[64]

The choice between initial TTE and TEE echocardiography must be based on the initial clinical suspicion of IE. If the suspicion is relatively low (perhaps due to an alternative site of infection or the absence of predisposing factors for endocarditis), TTE may be an adequate first diagnostic test. For low-likelihood patients with excellent image quality, a negative TTE may be sufficient. A high quality study that demonstrates neither vegetation nor valvular dysfunction does not definitively "rule out" endocarditis, but does effectively risk stratify the patient if they do have IE by other clinical criteria. Initial imaging with TEE should be performed in patients with high-risk clinical features, such as new atrioventricular block or *S. aureus* bacteremia, in patients with prosthetic valves (where the infection is likely to involve perivalvular extension) and in patients where chest wall imaging will likely result in low quality images. If a TEE cannot be obtained within the first 24 hours, an initial TTE should be performed in the interim to avoid missing an opportunity to recognize a large vegetation or significant valvular insufficiency that might predict embolism or need for early surgery.[65-67]



FIGURES 2A TO C: Aortic valve endocarditis with paravalvular abscess. (A and C) Transesophageal two-dimensional and (B) color Doppler flow imaging views of aortic valve endocarditis. Vegetation (open arrow) and paravalvular abscess (asterisk) are seen in the long axis and short axis views (A and C); the abscess comprises irregular tissue and fluid filled cavities in the periannular region between the aorta and the left atrium. Color Doppler flow imaging demonstrates a wide jet of severe aortic valve regurgitation in diastole (open arrow). (Abbreviations: LA: Left atrium; Ao: Ascending aorta)

Even in patients with IE confirmed by TEE, a baseline TTE can be helpful for comparison of vegetation size and valvular regurgitation in future patient management, as repeat TTE imaging is often performed either during treatment or at the completion of therapy.

False negative TTE and TEE studies may occur in patients with endocarditis. Vegetations below the resolution of the modalities will only be suggested by nonspecific valve thickening. Alternatively, prior embolization of vegetative material may leave only the thickened attachment region. If clinical suspicion for IE remains high after an initial negative TTE, TEE should be performed. If the initial TEE is negative, a repeat study after 7–10 days may demonstrate the interim development of vegetation or abscess. Such repeat imaging can also have important prognostic contributions: progression of vegetation size despite appropriate antibiotic therapy is highly predictive of a complicated clinical course and the need for surgery.[68]

False positive findings suggestive of endocarditis include any form of valvular thickening or distortion. These are extremely common and include myxomatous degeneration of the mitral valve and Lambl's excrescences, as well as scarring from previous endocarditis, and rheumatic and degenerative changes, among others (see below). Vigilance for independent motion that implies excessive tissue is helpful in trying to differentiate these valve changes from infection, but clear distinction is often not possible. In the final analysis, IE is a clinical diagnosis, and any echocardiographic finding must be interpreted in light of the patient's characteristics and condition.

OTHER DIAGNOSTIC STUDIES

Although clinical presentation, blood cultures and echocardiography are the mainstays of diagnosis in most cases of endocarditis, other ancillary studies may be useful. In cases of initially culture-negative endocarditis, testing for *C. burnetii* serologies may establish Q fever as an etiology, and this is now considered a major criterion for the diagnosis of endocarditis. In cases of suspected fungal endocarditis, testing for *Candida* antigenemia or *Aspergillus*-associated galactomannan levels may aid in diagnosis.[69]

Approximately 50% of patients with endocarditis have elevated levels of rheumatoid factor; levels are more frequently elevated in patients with a prolonged course of disease or subacute presentation.[70] Serum complement levels may be depressed in patients with immune complex disease, especially glomerulonephritis. C-reactive protein and erythrocyte sedimentation rate (ESR) are frequently elevated in patients with endocarditis, but these tests lack specificity.[71]

A number of other diagnostic tests have been proposed for identification of endocarditis but are not yet used on a routine basis. Culture, histopathologic examination or PCR-based assays of explanted heart valve tissue may be useful for identification of the causative microorganism in cases where blood cultures were negative.[72] The PCR analysis of blood and of explanted valves may identify culture-negative streptococci, *Bartonella spp.*, *T. whippelei* and fungi.[73] These assays have been optimized for detection of bacterial 16S and 23S ribosomal RNA,[74] and recent studies have reported the use of fluorescent in situ hybridization for direct visualization of bacteria on explanted valves.[75]

Other imaging modalities may complement echocardiography in diagnosis of endocarditis. A study of multislice CT in a population of patients at moderate or high risk of IE suggested that CT has similar sensitivity and specificity to that of TEE in identifying large vegetations and perivalvular extension of infection. Vegetations, smaller than 4 mm, and leaflet perforations were not detected due to limitations in spatial and temporal resolution.[76] Cardiac CT may be useful in evaluating presence of coronary artery disease in patients requiring surgery for endocarditis, especially if there is concern about causing iatrogenic vegetation embolism during cardiac catheterization. Combining anatomic data from CT with gallium-67 SPECT imaging of inflammation may also assist in localizing infection.[77]

MIMICKERS OF INFECTIOUS ENDOCARDITIS

In cases where blood cultures and other diagnostic tests are inconclusive, a noninfectious etiology of apparent endocarditis should also be considered. These etiologies include Libman-Sacks endocarditis, intracardiac tumors, marantic endocarditis, and Lambl's excrescences.

Libman-Sacks endocarditis is noninfectious endocarditis associated with lupus and the antiphospholipid antibody syndrome. Cardiac involvement may consist of nonspecific valve thickening or vegetations that are morphologically similar to those of infection. The majority of patients with lupus have thickened cardiac valves, and approximately one-third of patients have characteristic vegetations when assessed by TEE.[78] The association between cardiac lesions in lupus and presence of antiphospholipid antibodies remains controversial, as many patients with lupus may have valvular lesions but low or undetectable antiphospholipid antibodies.[79] In patients with antiphospholipid antibody syndrome, autoantibodies recognize protein-phospholipid complexes and β2-glycoprotein; these autoantibodies and/or circulating immune complexes may accelerate endothelial cell injury and the development of NBTE.[80] Libman-Sacks lesions occur most frequently on the ventricular surface of the mitral valve.

Intracardiac tumors may sometimes mimic endocarditis. Cardiac myxomas may cause valve obstruction or insufficiency. Since myxomas elaborate high levels of interleukins, cardiac myxomas may also be accompanied by fevers and anorexia otherwise characteristic of endocarditis. Papillary fibroelastomas have a frond-like appearance and, if located near or on a heart valve, may have an echocardiographic appearance similar to that of infectious vegetation. Both myxomas and papillary fibroelastomas may embolize, leading to a clinical presentation that could be confused with infectious endocarditis.

Patients with systemic cancers may develop hypercoagulability and extensive endothelial cell injury leading to valve vegetations (so-called marantic endocarditis). Lesions of marantic endocarditis have a high rate of embolism and in some cases may necessitate valve replacement.

Lambl's excrescences are small fibrinous thrombi that occur at the valve closure line, typically of the aortic valve. Their small size and lack of associated valve dysfunction distinguishes them from infective vegetations. The majority of Lambl's excrescences are benign and do not embolize.[81]

MANAGEMENT

Medical therapy with antibiotics targeted to the infectious organism is the mainstay of treatment for endocarditis. When

medical therapy fails or in certain clinical circumstances, surgical excision and replacement of the infected valve is the treatment of choice. Other important clinical considerations include management of persistent fever and, especially in subjects with prosthetic valves, whether to continue anticoagulation.

EMPIRIC MEDICAL THERAPY

Medical therapy of endocarditis is determined principally based on the organism isolated from the blood and whether it is susceptible to beta-lactam antibiotics. Empiric therapy may be withheld in a patient who is not acutely ill in order to obtain blood cultures and even while awaiting results of those cultures. It also may be appropriate to discontinue empiric antimicrobial therapy in a stable patient in order to obtain blood cultures and observe the patient if pre-treatment blood cultures were not obtained or are negative. Empiric antimicrobial therapy should be initiated as soon as possible after three blood cultures have been obtained for acutely ill patients, including those who are hemodynamically unstable, those who have evidence of heart failure or end-organ dysfunction, or those who appear septic.

Empiric therapy for native-valve endocarditis should provide coverage for staphylococci, streptococci, enterococci, and HACEK organisms, as these are the most likely infectious etiologies. Two commonly recommended regimens are nafcillin plus penicillin plus gentamicin and vancomycin plus gentamicin, but given the prevalence of methicillin-resistance among *S. aureus* strains, vancomycin plus gentamicin is preferable. An alternative regimen that avoids the issue of aminoglycoside toxicity is vancomycin plus ceftriaxone. Vancomycin plus gentamicin is the preferred regimen for the patient with serious allergy to beta-lactam antibiotics. The recommended empiric regimen for the patient with suspected prosthetic valve endocarditis is vancomycin plus rifampin plus gentamicin.

DEFINITIVE MEDICAL THERAPY

Once a causative organism for endocarditis has been identified and its antimicrobial susceptibility determined, a standardized regimen should be used to treat the patient (Table 6). A beta-lactam antibiotic, the preferred agent for treatment of endocarditis, should be used whenever possible. Experience is greatest with beta-lactam antibiotics and no other class of antibiotics is safer or more effective. The addition of low-dose gentamicin (i.e. 3 mg/kg per day), formerly recommended in official guidelines, is now considered optional.[82] In the authors' opinion, such low dose regimens of gentamicin are best avoided except in select situations given lack of data for a mortality benefit or improved cure rates compared to single drug regimens and clear evidence of increased toxicity.[83] The three situations in which gentamicin combination therapy should be used are: endocarditis caused by a strain of viridans streptococci with an MIC more than 0.5 mg/ml; enterococcal endocarditis and prosthetic valve endocarditis.

Streptococcal Endocarditis

Given its ease of administration and proven efficacy ceftriaxone is a preferred agent for treatment of uncomplicated endocarditis caused by highly penicillin susceptible strains of viridans streptococci or *S. gallolyticus* (formerly *bovis*). Ceftriaxone is administered as a once daily dose, facilitating its use in the outpatient setting and no dosage adjustment is required. The addition of low-dose gentamicin to either ceftriaxone or penicillin permits shortening the duration of therapy to two weeks, but a shorter course combination regimen should be reserved for those with uncomplicated endocarditis at low risk for gentamicin toxicity (e.g. younger patients with no pre-existing renal disease), if it is used at all. Vancomycin is the recommended alternative for cases with severe allergy to beta-lactam antibiotics. Depending on the penicillin MIC and whether endocarditis is native or prosthetic valve, longer durations of therapy and gentamicin combination therapy may be indicated (Table 6).

Staphylococcal Endocarditis

A beta-lactam antibiotic, as a single agent, is the drug of choice for treatment of *S. aureus* native valve endocarditis caused by a methicillin-susceptible strain. There is no evidence that the addition of gentamicin or other aminoglycoside improves outcomes, but toxicity is definitely greater than with single drug therapy. Vancomycin is inferior to beta-lactams and should be used only in cases of severe beta-lactam allergy or toxicity.

Vancomycin, as a single agent, is the drug of choice for treatment of native valve endocarditis caused by methicillin resistant strains. Daptomycin is an acceptable alternative, although it is FDA approved only for treatment of right-sided endocarditis.[84] Regardless of the regimen, persistent bacteremia or relapse occur in a quarter or more of patients. These patients often have secondary foci of infection, which should be aggressively sought and eliminated. Early valve replacement should also be considered, particularly if other sources of persistent bacteremia have been ruled out. There is no consensus as to how antimicrobial therapy should be modified; consultation with an infectious diseases expert is strongly advised to assist in management of antimicrobial therapy.

Combination therapy is recommended for treatment of prosthetic valve endocarditis due to *S. aureus* or coagulase-negative staphylococci. Nafcillin (or oxacillin) for endocarditis caused by methicillin-susceptible strains or vancomycin for methicillin-resistant strains plus both gentamicin and rifampin are indicated.

Enterococcal Endocarditis

Penicillin (or ampicillin), vancomycin and gentamicin are primary agents for treatment of enterococcal endocarditis. Treatment of enterococcal endocarditis is one of the few instances in which outcomes are improved for combination compared to single agent therapy. The optimal regimen depends on the susceptibility of the clinical isolate to penicillin, vancomycin and gentamicin (Table 6).

Culture-Negative Endocarditis

Therapy of endocarditis in the absence of positive blood cultures is guided by whether there is a history of prior antimicrobial therapy that could have rendered cultures negative and the

TABLE 6

Antimicrobial therapy of bacterial endocarditis*

Clinical setting	*Regimens*	*Comments*
Empirical therapy, once blood cultures have been obtained	Vancomycin 15 mg/kg IV q12h + gentamicin 3 mg/kg IV q24h OR Vancomycin 15 mg/kg IV q12h + ceftriaxone 2g IV q24h OR Nafcillin 2g IV q4h + penicillin 3 million units IV q4h + gentamicin 3 mg/kg IV 24h	Not recommended if MRSA is a consideration
Viridans group streptococci or *S. gallolyticus* (formely *bovis*), penicillin MIC ≤ 0.12 µg/ml, native valve	Ceftriaxone 2 gm IV q24h for 4 weeks OR Penicillin 3 million units IV q4h for 4 weeks OR Vancomycin 15 mg/kg IV q12h for 4 weeks OR Penicillin 3 million units IV q4h for 2 weeks + gentamicin 3 mg/kg IV q24h for 2 weeks OR Ceftriaxone 2 gm IV q24h for 2 weeks + gentamicin 3 mg/kg IV q24h for 2 weeks	Vancomycin should be used only if a beta-lactam cannot be used Two-week gentamicin combination regimen not recommended for elderly patients; patients with underlying renal disease, impaired hearing or other eight cranial nerve deficit; patients with complicated endocarditis; target peak gentamicin serum concentration of 3-4 µg/ml and trough of < 1 µg/ml
Viridans group streptococci or *S. gallolyticus*, penicillin MIC > 0.12 and ≤ 0.5 µg/ml, native valve	Ceftriaxone 2 gm IV q24h for 4 weeks + gentamicin 3 mg/kg IV q24h for 2 weeks OR Penicillin 3 million units IV q4h for 4 weeks + gentamicin 3 mg/kg IV q24h for 2 weeks OR Vancomycin 15 mg/kg IV q12h for 4 weeks	See above for target gentamicin concentrations Vancomycin should be used only if a beta-lactam cannot be used
Viridans group streptococci or *S. gallolyticus,* penicillin MIC > 0.5 µg/ml, native valve	Ampicillin 2 gm IV q4h for 4-6 weeks + gentamicin 1 mg/kg IV q8h for 4-6 weeks OR Penicillin 4 million units IV q4h for 4–6 weeks + gentamicin 1 mg/kg IV q8h for 4–6 weeks OR Vancomycin 15 mg/kg IV q12h for 6 weeks + gentamicin 1 mg/kg IV q8h for 6 weeks	Vancomycin should be used only if a beta-lactam cannot be used
Viridans group streptococci or *S. gallolyticus* (formely *bovis*), penicillin MIC ≤ 0.12 mg/ml, prosthetic valve	Penicillin 4 million units IV q4h for 6 weeks OR Ceftriaxone 2 gm IV q24h for 6 weeks OR Vancomycin 15 mg/kg q12h IV for 6 weeks	Although some authorities recommend addition of gentamicin 3 mg/kg IV/IM q24h to penicillin or ceftriaxone, evidence of improved outcome is lacking Vancomycin should be used only if a beta-lactam cannot be used
Viridans group streptococci or *S. gallolyticus* (formely *bovis*), penicillin MIC > 0.12 µg/ml, prosthetic valve	Ceftriaxone 2 gm IV q24h for 6 weeks + gentamicin 1 mg/kg IV q8h for 6 weeks OR Penicillin 4 million units IV q4h for 6 weeks + gentamicin 1 mg/kg IV q8h for 6 weeks OR Vancomycin 15 mg/kg q12h IV for 6 weeks	Vancomycin should be used only if a beta-lactam cannot be used
S. pneumoniae, beta-hemolytic *streptococci*, native valve	Ceftriaxone 2g IV q24h for 4 weeks OR Penicillin 4 million units IV q4h for 4 weeks OR Vancomycin 15 mg/kg q12h IV for 4 weeks	Vancomycin should be used only if a beta-lactam cannot be used
Staphylococcus aureus, or coagulase-negative staphylococci, methicillin susceptible, native valve	Nafcillin or oxacillin 2 gm q4h IV for 4–6 weeks OR Cefazolin 2 gm q8h IV for 6 weeks OR Vancomycin 15–20 mg/kg q8–12h IV for 6 weeks	Two weeks of nafcillin or oxacillin therapy may be sufficient in patients with isolated tricuspid valve endocarditis and no metastatic foci of infection Vancomycin should only be used if a beta-lactam is contraindicated; target trough concentrations of 15–20 µg/ml

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Clinical setting	*Regimens*	*Comments*
Staphylococcus aureus or coagulase-negative staphylococci, methicillin susceptible, prosthetic valve	Nafcillin (or oxacillin) 2 gm q4h IV for 6 weeks + rifampin 600–900 mg in two divided doses for 6 weeks + gentamicin 1 mg/kg q8h IV for 2 weeks OR Vancomycin 15-20 mg/kg q8h-12h IV for 6 weeks + rifampin 600-900 mg in two divided doses for 6 weeks + gentamicin 1 mg/kg q8h IV for 2 weeks	Use vancomycin only if use of nafcillin or oxacillin is contraindicated; target vancomycin trough concentrations of 15–20 µg/ml
Staphylococcus aureus, or coagulase-negative staphylococci, methicillin resistant native valve	Vancomycin 15–20 mg/kg q8–12h IV for 6 weeks OR Daptomycin 6 mg/kg IV q24h for 6 weeks	Target vancomycin trough concentrations of 15–20 µg/ml Equivalent to vancomycin for right-sided endocarditis; not FDA approved for left-sided endocarditis
Staphylococcus aureus or coagulase-negative staphylococci, methicillin resistant prosthetic valve	Vancomycin 15–20 mg/kg q8h–12h IV for 6 weeks + rifampin 600–900 mg in two divided doses PO/IV for 6 weeks + gentamicin 1 mg/kg q8h IV for 2 weeks	
Enterococcus faecalis or *E. faecium*, susceptible to penicillin, gentamicin, and vancomycin; native or prosthetic valve	Ampicillin 2g q4h IV for 4–6 weeks + gentamicin 1 mg/kg q8h IV for 4–6 weeks OR Penicillin 4 million units q4h IV for 4–6 weeks + gentamicin 1 mg/kg q8h IV for 4–6 weeks OR Vancomycin 15 mg/kg q12h IV for 6 weeks + gentamicin 1 mg/kg q8h IV for 6 weeks	6 weeks of therapy recommended for prosthetic valve infection Use of vancomycin not recommended unless penicillin or ampicillin cannot be used
Enterococcus faecalis or *E. faecium*, susceptible to penicillin and vancomycin, resistant to gentamicin; native or prosthetic valve	Ampicillin 2 gm q4h IV or penicillin 4 million units q4h IV for 4–6 weeks+ streptomycin 7.5 mg/kg q12h IV for 4–6 weeks OR Vancomycin 15 mg/kg q12h IV for 6 weeks + streptomycin 7.5 mg/kg q12h IV for 6 weeks	6 weeks of therapy recommended for prosthetic valve infection Confirm susceptibility to streptomycin; if resistant then use ceftriaxone 2g q12h IV instead of streptomycin and treat for a total duration of 8 weeks
Enterococcus faecalis or *E. faecium*, susceptible to vancomycin and gentamicin, resistant to penicillin; native or prosthetic valve	Vancomycin 15 mg/kg q12h IV for 6 weeks + gentamicin 1 mg/kg q8h IV for 6 weeks	
E. faecium resistant to penicillin, vancomycin, gentamicin, native or prosthetic valve	Linezolid 600 mg q12h IV/PO at for least 8 weeks OR Quinupristin-dalfopristin 7.5 mg/kg q8h IV for at least 8 weeks	Cure rates < 50% with medical therapy alone; valve replacement therapy may be necessary for cure
E. faecalis resistant to penicillin, vancomycin, gentamicin, native or prosthetic valve	Ampicillin 2 g q4h IV for at least 8 weeks + ceftriaxone 2 g q12h IV for at least 8 weeks	
HACEK	Ceftriaxone 2g q24h IV for 4 weeks OR Ciprofloxacin 500 mg q12h PO or 400 mg q12h IV for 4 weeks	
Culture-negative endocarditis, native valve	Ampicillin-sulbactam 3 g q6h IV for 4–6 weeks + gentamicin 1 mg/kg q8h IV for 4–6 weeks OR Vancomycin 15 mg/kg q12h IV for 4–6 weeks + gentamicin 1 mg/kg q8h IV for 4–6 weeks + ciprofloxacin 500 mg q12h PO or 400 mg q12h IV for 4–6 weeks	
Culture-negative endocarditis, prosthetic valve, implanted ≤ 1 year	Vancomycin 15 mg/kg q12h IV for 6 weeks + gentamicin 1 mg/kg q8h IV for 2 weeks + cefepime 2 gm IV 8h for 6 weeks + rifampin 600–900 mg in two divided doses PO/IV for 6 weeks	
Culture-negative endocarditis, prosthetic valve, implanted > 1 year	Ampicillin-sulbactam 3 g q6h IV for 4–6 weeks + gentamicin 1 mg/kg q8h IV for 4–6 weeks OR Vancomycin 15 mg/kg q12h IV for 4–6 weeks + gentamicin 1 mg/kg q8h IV for 4–6 weeks + ciprofloxacin 500 mg PO q12h or 400 mg IV 12h for 4–6 weeks	
*Recommended doses for patients with normal renal function.		

presence of epidemiologic or other risk factors suggestive of unusual organisms. In the absence of risk factors or serologic evidence for unusual, non-cultivable organisms, and particularly if antimicrobial therapy was administered prior to appropriate blood being obtained, antimicrobial therapy should be directed against streptococcal or HACEK organisms, or in the case of culture-negative prosthetic valve endocarditis, coagulase-negative staphylococci (Table 6).

SURGICAL THERAPY AND TIMING OF SURGERY

In the recent international collaboration on endocarditis study, 40% of patients underwent surgical therapy during the index hospitalization.[85] Despite the increasing utilization of surgery, there remains significant uncertainty regarding optimal timing of surgery and identification of subgroups that preferentially benefit from early surgical intervention. The decision to proceed with surgery is complex. The major indications for surgery are development of heart failure, a structural deterioration of the valve, annulus, or prosthesis, and failure of antibiotic therapy. Relative indications include embolization and large vegetation size (Table 7, Fig. 3).

Worsening congestive heart failure may ensue despite antibiotic therapy due to valve destruction, rupture of chordae, development of a fistula or valve obstruction. The development of Class III–IV heart failure is associated with mortality rates in the range of 70–90% in the absence of surgery. Among valve lesions, aortic insufficiency is the least well tolerated and may necessitate urgent or emergent surgery. Although patients with heart failure from mitral insufficiency may stabilize with medical therapy only, the majority eventually require surgery. In some cases, mitral valve repair may be feasible, avoiding the need for placement of prosthesis.[86]

Patients with prosthetic valve endocarditis require surgical intervention more frequently than those with native valve endocarditis.[87] Antibiotic therapy alone is often ineffective for PVE because of failure to eradicate organisms within micro-abscesses at the suture lines and destabilization of the prosthesis. Prosthetic valve dehiscence may be more common in endocarditis occurring in the first year after implantation and in prostheses in the aortic position. Due to the high mortality associated with medical treatment of *S. aureus* prosthetic valve endocarditis, surgery may have particular benefit in this high-risk subgroup.[13]

TABLE 7

Indications for surgical therapy of endocarditis

- Indications
  - — Worsening heart failure
  - — Failure of antibiotic therapy: especially fungal infection, left-sided infection with gram-negative bacteria or persistently positive blood cultures after > 1 week of antibiotics
  - — Disrupted valve or prosthesis: valve perforation, annular extension, fistula or unstable prosthesis
- Relative indications
  - — Risk of embolization: large vegetation > 10 mm, persistent vegetation after embolization, or enlarging vegetation despite antimicrobial therapy

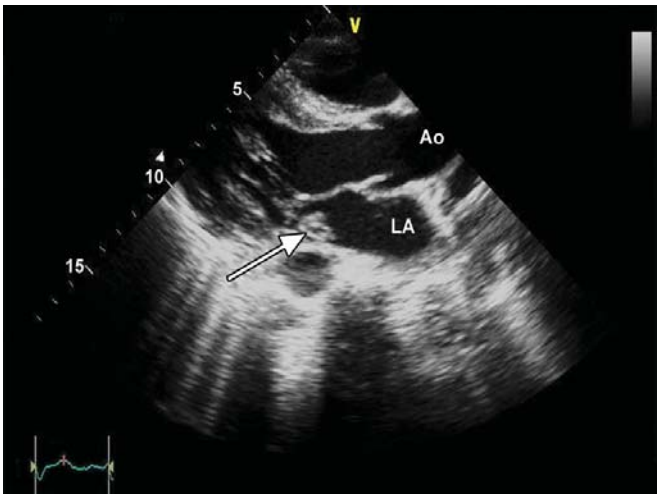


FIGURE 3: Mitral valve endocarditis. Transthoracic echocardiography demonstrates a large, 1.6 mm diameter vegetation (arrow) on the mitral valve in a 23-year-old patient with methicillin-resistant *Staphylococcus aureus* endocarditis

Despite advances in antimicrobial therapy, a subset of infections persists due to ineffective antibiotic penetration, resistant organisms, or an indolent course. Surgery is necessary to achieve cure of most cases of fungal endocarditis. Endocarditis due to drug-resistant organisms (e.g. vancomycin resistant enterococci), and gram-negative bacilli are also common microbiologic indications for surgery.

Systemic emboli are an independent predictor of in-hospital death from endocarditis.[88] To achieve maximum benefit, surgery should be performed prior to significant embolism. Several echocardiographic predictors of embolism have been identified, including mobile vegetations more than 10 mm,[46] vegetation located on the anterior leaflet of the mitral valve, and enlargement of a vegetation during antimicrobial therapy. Each of these findings is a relative indication for early surgery. Surgery can be performed with low neurologic complication rates in patients with transient ischemic attack (TIA) or subclinical brain emboli;[89] the development of intracranial hemorrhage is generally considered a contraindication to surgery for 1 month (Fig. 4).

The continued high mortality of endocarditis despite improved diagnostic tools and aggressive antibiotic therapy has led investigators to examine whether early surgery might confer a mortality benefit in patients with endocarditis. Analysis of this question is difficult due to lack of randomized data and the inherent survivor bias of surgery (i.e. patients who live longer are more likely to undergo surgery).[90] Propensity analyses addressing early use of surgery have yielded conflicting results, with some studies suggesting no benefit to surgery and others suggesting significant benefit of early surgery.[85,91-94] The largest of these studies found that surgery performed during the initial hospitalization was associated with decreased mortality among patients with paravalvular complications, stroke, systemic embolization, and *S. aureus* endocarditis.[94] Further prospective studies will continue to define the role of early surgery for reducing morbidity and mortality from infectious endocarditis;

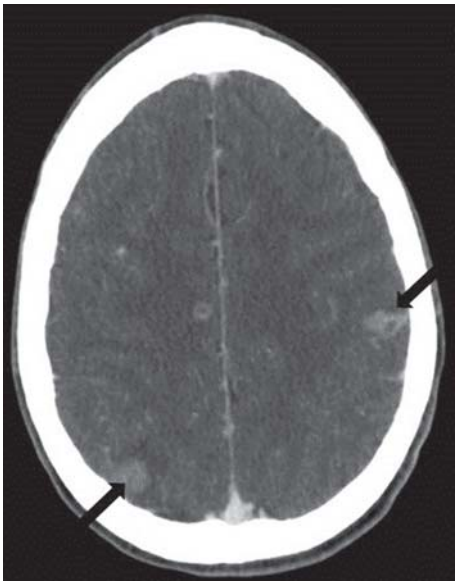


FIGURE 4: Intracranial emboli from endocarditis. Multiple bilateral cortical emboli with hemorrhage (arrows) in the patient shown in Figure 3

additionally, a randomized trial is underway comparing early surgery to medical therapy for certain high-risk subgroups.[95]

PERSISTENT FEVER

Continued fever despite antibiotic administration often raises the issue of possible failure of medical therapy. Fifty percent of patients will become afebrile within three days of antimicrobial therapy;[96] fever of more than two weeks' duration should raise suspicion for periannular extension, secondary seeding, or an alternative diagnosis.[97]

ANTICOAGULATION

Two major issues arise regarding anticoagulation in a patient with endocarditis: anticoagulation in the presence of a mechanical prosthetic valve, and use of antiplatelet agents. Anticoagulation in the presence of a prosthetic valve is controversial and requires balancing the risk of valve thrombosis with intracranial bleeding from subclinical emboli. With a rate of 50% for stroke or intracranial hemorrhage and a 70% mortality rate in patients with *S. aureus* prosthetic valve endocarditis, strong consideration should be given to discontinuation of anticoagulation during the early, septic phase of the infection.[98] In the presence of known intracranial embolization, anticoagulation should be discontinued for a minimum of two weeks. Anticoagulation in the presence of native valve endocarditis has never been shown to reduce the risk of embolization. Although aspirin had apparent benefit in preventing embolization in animal models of endocarditis, randomized trials showed no benefit and suggested an increased risk of intracranial bleeding.[52] For this reason, antiplatelet agents should be stopped in a patient with infectious endocarditis unless there is a clinical indication (e.g. recent intracoronary stenting).

PREVENTION OF ENDOCARDITIS

Transient bacteremias with oral organisms including *viridans* streptococci occur multiple times every day. Despite this, endocarditis remains a rare occurrence, possibly due to low intensity and transient nature of bacteremia, low virulence of most bacteria, and absence of a predisposing lesion for bacterial adherence. These randomly occurring bacteremias are of similar duration, magnitude and microbiology to the bacteremias that occur predictably during many dental interventions, including tooth cleaning.[99] The optimistic strategy of avoiding endocardial infections by using prophylactic antibiotics against oral organisms during the very small percentage of predictable bacteremic episodes in a patient's life was abandoned for most patients in 2007 when the IE prophylaxis guidelines published by the American Heart Association (AHA) were modified to exclude all but patients at the highest risk for adverse outcomes from IE (i.e. patients with prosthetic heart valves, complex congenital heart disease, previous endocarditis, and cardiac allografts).[100] In 2008, guidelines in the UK eliminated the recommendation for IE prophylaxis in all patients irrespective of predisposing conditions.[101]

These changes in prophylactic recommendations followed a thorough re-review of all relevant published data. Very little robust data on endocarditis prevention was available from humans; the bulk of the data was uncontrolled or based on animal models of disease. In retrospective reviews and case-control studies, use of periprocedural antibiotics and improved oral hygiene were associated with decreased risk of endocarditis among high-risk groups of patients with congenital heart disease.[102,103] More current data includes a study of endocarditis in the Netherlands which suggested that periprocedural bacteremia might account for only a small percentage of endocarditis even when the temporal window for association was greater than 3 months, that periprocedural antibiotic prophylaxis did not definitely reduce the odds of endocarditis, and that even if prophylaxis were effective, the greatest efficacy attributable to antibiotic administration would be less than 50%.[104]

These findings were confirmed by a French population-based study of 39 million adults in 1999.[105] The study estimated that 2.7 million at-risk dental procedures were performed on

TABLE 8

ACC/AHA guidelines for antibiotic prophylaxis for the prevention of endocarditis

- Class I: No class I guidelines for antibiotic prophylaxis
- Class IIa: It is reasonable to administer antibiotics to the following group of patients prior to a dental procedure that involves manipulation of the gingival tissues, periapical region of the teeth, or perforation of the oral mucosa:
  - — Patients with prosthetic cardiac valves or prosthetic material used for cardiac valve repair
  - — Patients with previous infective endocarditis
- Patients with congenital heart disease, unrepaired congenital heart disease, including palliative shunts and conduits, completely repaired congenital heart defect repaired with prosthetic material or device, whether placed by surgery or by catheter, during the first 6 months post-procedure. Repaired congenital heart disease with residual defects at the site of or adjacent to the site of a prosthetic patch or prosthetic device
- Cardiac transplant recipients with valve regurgitation due to a structurally abnormal valve

(*Source:* Taken from Nishimura et al. 2008)[107]

TABLE 9

Antibiotic regimens for prevention of endocarditis during dental procedures

Clinical situation	*Antibiotic*	*Adult*	*Children*
Able to take oral antibiotics	Amoxicillin	2 gram	50 mg/kg
Unable to take oral medication	Ampicillin OR Cefazolin OR Ceftriaxone	2 gram IM or IV 1 gram IM or IV 1 gram IM or IV	50 mg/kg IM or IV 50 mg/kg IM or IV 50 mg/kg IM or IV
Allergic to penicillins or ampicillin—oral	Cephalexin OR Clindamycin OR Azithromycin OR Clarithromycin	2 gram 600 mg 500 mg 500 mg	50 mg/kg 20 mg/kg 15 mg/kg 15 mg/kg
Allergic to penicillins or ampicillin—unable to take oral medications	Cefazolin OR Ceftriaxone OR Clindamycin	1 gram IM or IV 1 gram IM or IV 600 mg IM or IV	50 mg/kg IM or IV 50 mg/kg IM or IV 20 mg/kg IM or IV

(*Source:* Modified from Nishimura et al. 2008)[107]

patients with cardiac predisposition in 1 year. They estimated that of the 1,370 cases of IE cases in 1 year (1 in 28,500 adults), 714 (52%) occurred in pts with pre-existing cardiac conditions that would put them at increased risk of IE. Of all cases, 44 could have been related to at-risk dental procedures. This study concluded that prophylaxis reduced IE prevalence in patients with pre-existing cardiac conditions from 1/46,000 to 1/149,000; therefore, a huge number of doses of prophylaxis would be needed to prevent a low number of cases.

Similarly, a US-based case-control study of endocarditis prophylaxis in the Delaware Valley used structured interview and medical/dental record reviews to evaluate dental prophylaxis and cardiac risk factors for community-acquired IE. This study determined that preceding dental treatment was not a risk factor of IE, and that few cases of IE could be prevented with prophylaxis even they were 100% effective.[106]

Current AHA and ACC/AHA prophylaxis guidelines are based on these human studies, combined with the lack of prospective evidence supporting periprocedural antibiotic prophylaxis of endocarditis. Antibiotic prophylaxis is recommended based on patient-specific risk of poor IE outcome, rather than based on the lifetime incidence of IE (Table 8).[100,107] Antibiotics are recommended only for dental surgery, and no longer for gastrointestinal or genitourinary procedures (Table 9). The clinical strategy for avoiding endocarditis in patients at more than baseline risk for endocarditis hinges on maintenance of excellent oral health, and advice to contact the health care provider for sustained fever before beginning antibiotic therapy, so that reliable blood cultures can be obtained if endocarditis is suspected.

SUMMARY AND CONCLUSION

Endocarditis remains a common clinical problem with a high morbidity and mortality. The development and refinement of echocardiography and clinical criteria over the past three decades have made it possible to diagnose endocarditis in the majority of cases, but a number of uncertainties remain for the prevention and treatment of endocarditis. Important areas for future research will include better understanding of the virulence factors that predispose to endocarditis, which may lead to novel therapeutics that inhibit bacterial virulence. Advanced imaging technologies, such as MRI, will also assist in identifying hemodynamic influences predisposing to endocarditis. Given the continued high mortality of endocarditis, several treatment questions remain to be answered. These include the difficult task of surgical timing and identification of high-risk subgroups that may benefit from early surgery. Due to the high morbidity associated with embolization, better understanding of the factors that lead to and might prevent embolization could also provide significant clinical benefit. Multidrug resistance and healthcare-associated endocarditis will remain important public health issues in endocarditis for the foreseeable future. With the continued rise of medical devices, engineering of coatings that reduce the rates of device infection will also have important public health implications. Coupled to issues of drug resistance are validation and safety of the new guidelines for prophylaxis, which may limit the exposure of the general population to antibiotics.

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Chapter 61

Prosthetic Heart Valves

Byron F Vandenberg

Chapter Outline

- Risk of Valve Replacement
- Types of Prosthetic Valves
  - Mechanical Valves
  - Bioprosthetic Valves
  - Homograft
  - Ross Procedure (Pulmonic Valve Autotransplantation)
- Selecting the Optimal Prosthesis
- Prosthesis-Patient Mismatch
- Long-term Management
  - Antithrombotic Therapy
  - Echocardiography Follow-up
- Long-term Complications
  - Thromboembolic and Bleeding Complications
  - Structural Valve Deterioration
  - Paravalvular Regurgitation
  - Hemolysis

Approximately 90,000 valve prostheses are implanted in the United States and 280,000 worldwide each year.[1] While the goals of valve surgery are to improve functional status and longevity, valve replacement does not provide a cure. Rather, native valve disease is exchanged for prosthetic valve disease.[1,2] Optimal management of these patients includes knowledge of prostheses and current guidelines for long-term management.

RISK OF VALVE REPLACEMENT

A number of risk models for predicting operative mortality that include the EuroSCORE, the New York Model[3] and the Society of Thoracic Surgeons (STS) Database. The EuroSCORE model has been shown to over predict risk, presumably since other models are more recent and reflect improvements in valve surgery.[4,5] The New York Model may need regional correction to maintain its accuracy.[3]

The STS Database has identified clinical variables that independently influence operative mortality (Table 1).[6,7] According to STS data from 2002 to 2006 (including 67,292 isolated aortic valve replacements and 21,229 isolated mitral valve replacements), unadjusted operative mortality for isolated valve procedures was 3.4%. The unadjusted hospital morbidity rates ranged from 0.3% for deep sternal wound infection to 11.8% for prolonged ventilation.[6] A model for predicting risk for patients undergoing combined valve surgery and coronary artery bypass grafting has also been reported using data (i.e. 101,661 procedures) from the same time period.[7] An online risk calculator is available through a link from the STS website.[8]

Perioperative stroke occurs in 2.2% after AVR and in 5.4% after combined AVR and MVR. Multivariate predictors are calcified ascending aorta, LV ejection fraction less than 0.30, diabetes mellitus, age greater than 70 years, female gender, ejection fraction less than 30%, and bypass time greater than 120 minutes. Stroke risk may be reduced with the use of periaortic ultrasound imaging for guiding the location of aortic cross-clamping and cannulation.[9]

TABLE 1

Clinical variables that influence valvular heart surgery risk estimated by the Society of Thoracic Surgery database

• Status of procedure (i.e. elective, urgent, emergent)
• Age
• Gender
• Race/ethnicity
• Diabetes mellitus and whether therapy is diet, oral agent or insulin
• Creatinine level
• Dialysis
• Hypertension
• Infectious endocarditis
• Chronic obstructive pulmonary disease and severity
• Peripheral vascular disease
• Immunosuppressive therapy
• Cerebrovascular disease
• Prior cardiac surgery
• Preoperative myocardial infarction
• Presentation with acute coronary syndrome (e.g. unstable angina, non-ST elevation myocardial infarction, ST elevation myocardial infarction)
• Congestive heart failure and New York Heart Association functional class
• Preoperative inotropes
• Intra-aortic balloon pump
• Atrial fibrillation/flutter or other arrhythmias
• Number of diseased coronary arteries at cardiac catheterization
• Left ventricular ejection fraction
• Severity of regurgitant valve lesions (mitral, aortic or tricuspid valves)
• Severity of stenotic valve lesions (aortic or mitral valves)
Adapted from: www.sts.org/sections/stsnationaldatabase/riskcalculator/

Operative mortality in high-risk patients undergoing combined coronary revascularization and valve surgery can be reduced by "hybrid" operations of percutaneous coronary intervention followed by the valve surgery. In a group of high-risk patients with STS predicted mortality of 22%, "hybrid" operations resulted in an observed mortality of 3.8%.[10] A minimally invasive approach (i.e. full sternotomy and cardiopulmonary bypass support are not performed) provides an alternative for standard approaches in cardiopulmonary bypass cannulation, aortic occlusion and cardioplegia delivery. However, there is no significant reduction in mortality or stroke incidence. After previous cardiac surgery, minimally invasive surgery is associated with reduced blood loss, fewer transfusions and faster recovery compared to repeat sternotomy.[11]

TYPES OF PROSTHETIC VALVES

The ideal valve prosthesis should have excellent hemodynamics, long durability, high thromboresistance and excellent implantability.[1] The currently available prostheses are not ideal: Mechanical valves are durable but require chronic anticoagulation because of thrombogenicity. Biological valves do not require anticoagulation (unless there are other compelling reasons, such as atrial fibrillation) but durability is limited. Examples of mechanical and biologic valves are given in Figures 1A to H.

MECHANICAL VALVES

Mechanical valves have three key components: occluder (i.e. the closure mechanism), housing and sewing ring. All have some degree of regurgitant flow (i.e. the washing jet) that prevents thrombus formation on the surface of the valve.[12]

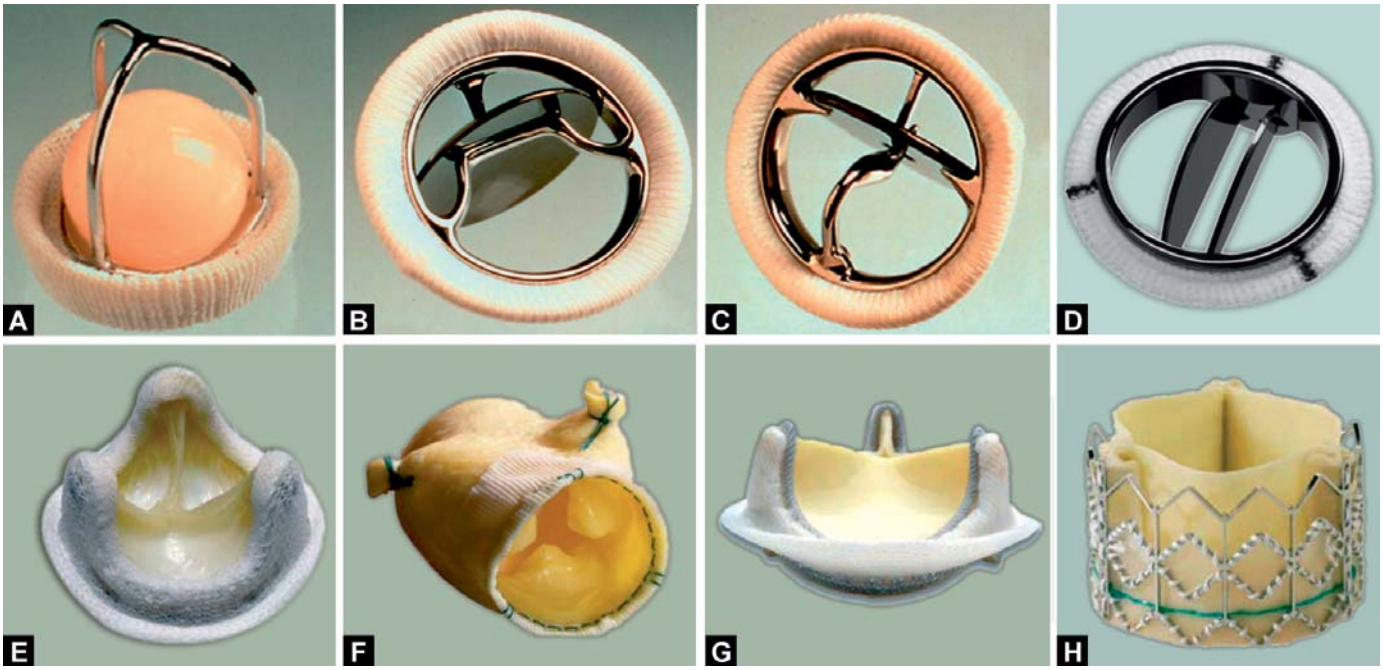
Caged-ball Design

The Starr-Edwards caged-ball valve was first implanted in 1960, and the design has essentially been unchanged since 1965. Production of the valve was discontinued in 2007 and there have been no deaths related to structural valve deterioration. Survival to 40 years after implantation has been reported.[13] The original design had a silicone rubber (silastic) ball that freely moved within a three-strut alloy cage. Subsequent models have had a metal ball and a four-strut cage.[12] While these valves are durable, they have a tendency to form blood clots and require full-dose anticoagulation with goal INR of 2.5–3.5.[2]

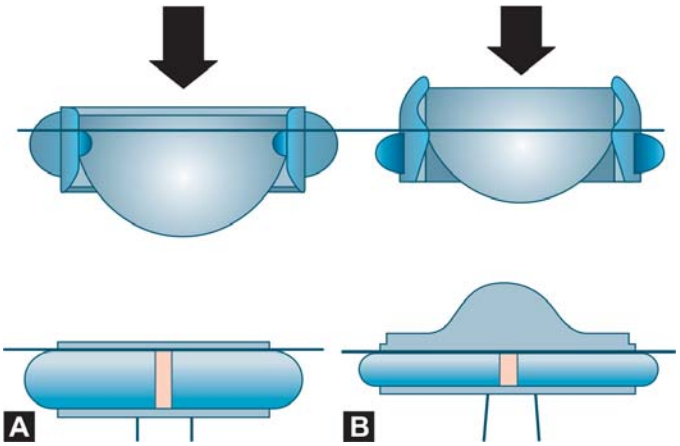
Single Tilting-disk Design

Bjork-Shiley: The original single tilting disk was the Bjork-Shiley valve initially introduced in 1969. Multiple design changes were introduced after the original delrin disk model, including a pyrolitic conical disk, a spherical disk, a 60° convexo-concave disk, a 70° convexo-concave disk and a monostrut valve (with a 70° opening angle). The convexo-concave valve was withdrawn in 1986 due to several cases of strut fracture and embolization of the disk.[12] The later models were designed with pyrolitic carbon disks and cobalt-chromium alloy orifice rings and struts. Long-term durability has been demonstrated in randomized studies including the VA and Edinburgh Heart Valve trials.[14,15]

Medtronic-Hall: The Medtronic-Hall tilting disk was introduced into clinical practice in 1977 and was a commonly implanted single disk valve. The disk was made of tungsten-impregnated graphite with a carbon pyrolitic coating and is supported in titanium housing. It tilts to an opening angle of 70° in the mitral position and 75° in the aortic position on a central metal post via



FIGURES 1A TO H: Different models of prosthetic heart valves. (A) Starr-Edwards caged-ball valve. (B) Bjork-Shiley tilting disk valve. (C) Medtronic-Hall tilting disk valve. (D) St Jude Medical bileaflet valve. (E) Medtronic Hancock II porcine valve. (F) Medtronic Freestyle porcine valve. (G) Carpentier-Edwards Perimount bovine pericardial valve. (H) Edwards SAPIEN transcatheter pericardial aortic valve. (*Source:* Sun JCJ, Davidson MJ, Lamy A, et al. Antithrombotic management of patients with prosthetic heart valves: current evidence and future trends. Lancet. 2009;374:565-76)



FIGURES 2A AND B: Design modifications of bileaflet mechanical valves demonstrating valves without pivot guards (A) and with pivot guards (B). Arrows denote direction of flow. (*Source:* ATS Medical, Inc.)

a central disk perforation. This results in two different size orifices for flow. In comparison with previous tilting disk designs, the relative size of the minor orifice was increased and the disk was made to lift out of the housing and to rotate on it, features to improve washing of points vulnerable to thrombosis. In addition, the housing cross member was placed in the center to avoid flow disturbances. Twenty year follow-up series have reported low valve thrombosis rates of 0.03–0.04% per year.[16] Durability is excellent and no mechanical failures were identified in a group of patients followed for 25 years after aortic valve replacement.[17]

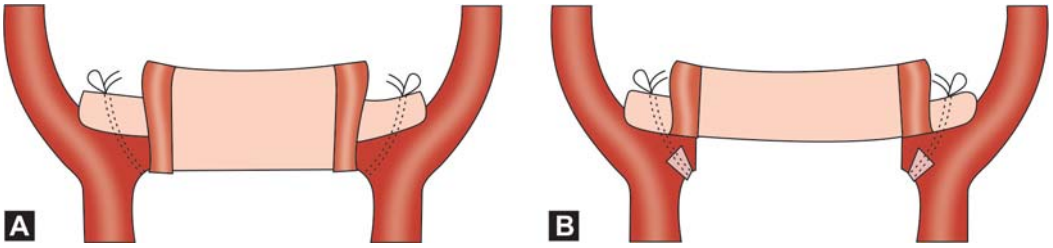
Bileaflet Tilting-disk Design

The introduction of a bileaflet design allows excursion of the two leaflet to 75°–90°, so there is near unimpeded flow through a central orifice and two lateral orifices. The effective orifice area (EOA) approaches the native valve. There is a central orifice and two larger lateral orifices. In addition, they are more resistant to thrombosis, so lower dose anticoagulation is feasible with goal INR of 2.0–3.0. The St Jude, CarboMedics, ATS and On-X valves are examples of bileaflet tilting disk valves. Design modifications have focused not only on improved hemodynamic performance but also on minimizing the risks of valve-related thrombosis. These design modifications have included the use of pure pyrolitic carbon, minimizing areas of stasis by altering or removing pivot guards (Figs 2A and B) and changes in the hinge mechanisms and hinge was jets. For larger annular size (i.e. > 23 mm in the aortic position), the differences in hemodynamic performance among the currently available bileaflet prostheses are probably negligible. However, in smaller sizes, the St Jude Medical Regent and On-X valves offer the potential for superior hemodynamic performance.[18]

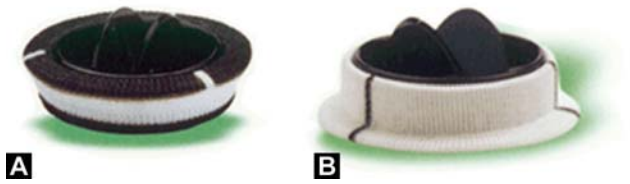
St Jude Medical (St Paul, MN): The Masters Series valves have been implanted since 1977, the same year as the Medtronic Hall valve. Two pyrolitic carbon leaflets, coated with graphite, open to an angle of 85°. The leaflets are contained in pyrolite-covered graphite housing which is attached to a Dacron ring.[18] Freedom from reoperation was 98% in a group of 4,480 patients undergoing single valve replacement from 1977 to 2002 and followed for an average of 7±5 years.[19] Durability was similar to a caged ball valve design in a randomized trial of the St Jude and Starr-Edwards valves.[20] The Masters HP Series design is the same as the Masters Series except that the sewing cuff is designed to facilitate supra-annular placement in the aortic or mitral position and therefore the orifice size is larger.

The Regent aortic valve is designed for supra-annular valve implantation. The sewing ring is modified to allow placement of a larger prosthesis into a smaller annulus, increasing the EOA (Figs 3A and B). The valve is seated in a supra-annular position, and the pivot guards are directed into the aortic annulus.[18] In 23 patients undergoing aortic valve replacement for aortic stenosis with a 17-mm regent valve, echocardiography at 14±10 months demonstrated an indexed EOA of 0.95±0.25 cm^2/m^2 and a decrease in LV mass.[21] The importance of the indexed EOA is discussed in the section on prosthesis-patient mismatch (PPM).

Sorin Group (Milano, Italy): The CarboMedics valve leaflets are made of pyrolitic carbon and a carbon coated polyester sewing cuff is secured to a titanium ring that surrounds the valve. The opening angle of the leaflets is slightly less than the St Jude Medical valve and this difference may explain the slightly higher pressure gradients across the valve. The titanium stiffening ring can be rotated *in situ* to avoid interference by the subvalvular tissue. In a prospective, randomized trial comparing CarboMedics and St Jude Medical bileaflet mechanical valves, there was no difference in clinical outcomes (i.e. survival and complications) at 10 years.[22] The Reduced Series aortic valve has a smaller sewing ring and is specifically designed for patients with a narrow, rigid annulus that would not permit placement of a supra-annular valve. The Top Hat aortic valve was introduced in 1993 and is designed for supra-annular placement in patients with a small annulus (Figs 4A and B). The Opti Form mitral valve design allows the



FIGURES 3A AND B: Intrasupra-annular (A) versus complete supra-annular (B) position. The positions of pledgets and the noneverting suture technique are visualized. By using ventriculoarterial mattress sutures combined with the special valve design, complete supra-annular placement is achieved (*Source:* Ruzicka DJ, Hettich I, Hutter A, et al. The complete supraannular concept: in vivo hemodynamics of bovine and porcine aortic bioprostheses. Circulation. 2009;120(Suppl. 1):S139-45)



FIGURES 4A AND B: Design modification of bileaflet mechanical valve demonstrating variation in location of valve housing relative to sewing ring. (A) CarboMedics standard aortic valve. (B) CarboMedics Top Hat bileaflet valve with housing above sewing ring (*Source :* The Sorin Group)

valve to be placed in a supra-annular or sub-annular position, by varying the suture entry and exit sites. This flexibility in implantation may be suited for a heavily calcified annulus or mitral valve reoperation.

ATS Medical (Minneapolis, MN): The ATS valve leaflets are pyrolitic carbon with a graphite substrate and the design allows supra-annular implantation. The opening angle is similar to the St Jude valve. However, valve noise appears to be reduced for this valve.[18,23] No structural valve deterioration, valve thrombosis or operative valve endocarditis was reported in a series of 231 patients followed for 6.9±3.8 years.[23]

On-X LTI [(Life Technologies, Inc.), Austin, TX]: The FDA approved the On-X aortic valve in 2001 and the mitral valve in 2002 for use in the United States. In the closed position each leaflet forms an angle of 40° relative to the orifice plane. In the open position, the leaflet forms an angle of 90°, larger than the other bileaflet valves. The leaflets consist of a patented unalloyed form of pyrolitic carbon deposited on a graphite substance, and impregnated with tungsten to provide radiopacity. The orifice is composed of a graphite substance coated with the carbon. The sewing ring sits in a supra-annular position and the housing is seated within the annulus.[18] A reduced anticoagulation regimen is being studied in the Prospective Randomized On-X Valve Anticoagulation Clinical Trial (PROACT), and the estimated study completion is 2015.[24]

BIOPROSTHETIC VALVES

Bioprosthetic valves are considered heterograft (i.e. from porcine or bovine tissue) or homograft (i.e. human cadaver). Porcine valves may be stented with the valve tissue mounted on supportive prosthetic material or stentless in the aortic position with the valve tissue supported by the donated annulus and aortic root. Bovine pericardial valves are manufactured from sheets of bovine pericardium mounted inside or outside of a supporting stent.[1]

The stented valve design requires a mounting platform which may be polypropylene (e.g. Carpentier-Edwards valve) or a wire backbone (e.g. Medtronic Hancock valve). The valves have relatively ease of implantation by stitching the sewing ring to the annulus. However, the EOA may be reduced by the thick sewing ring. Heterograft porcine or bovine stented valves are options for the aortic and mitral valve position. Stented valves have undergone changes in fixation and preparation since their introduction. First generation valves were treated with glutaraldehyde and fixed under high pressures. Due to concerns that high pressure causes collagen cross-linking, early matrix fragmentation and premature valve deterioration from calcification, second and third generation valves are fixed under low pressure. In addition, contemporary valves are subjected to anticalcification treatments such as alpha-oleic acid and polysorbate (Tween) 80. AOA bonds to the bioprosthetic tissue and inhibits calcium flux. The mechanism of calcification suppression by the nonionic surfactant polysorbate 80 is unclear.[17]

Stented valves are less thombogenic than mechanical valves and do not require long-term anticoagulation.[12]

Stented Porcine Valves

Edwards lifesciences (Irvine, CA): The Carpentier-Edwards (C-E) standard prosthesis was introduced in 1975. The valves are designed with a flexible Elgiloy wire stent to minimize tissue stress. The muscle shelf is incorporated into the stent wall to prevent the obstruction of the primary orifice. The valve is an intra-annular prosthesis with glutaraldehyde tissue fixation at approximately 60 mm Hg pressure. Since its introduction, there have been design changes in 1976, 1980 and 1982, when treatment with surfactant, polysorbate (Tween) 80 was added to prevent mineralization. In a follow-up of valves implanted prior to the addition of polysorbate 80, freedom from structural valve deterioration (SVD) at 15 years was 58% for aortic and 21% for mitral valves. Freedom from SVD at 12 years in the mitral position was greater for patients with advancing age 85% for patients greater than or equal to 70 years versus 54% for patients 65–69 years. In the aortic position, freedom from SVD at 12 years was 96% for patients greater than or equal to 70 years versus 92% for patients 65–69 years.[25] In a retrospective analysis of patients receiving 1,119 standard C-E valves implanted between 1975 and 1995, actual freedom from reoperation at 10 years was 83±2% for aortic valves versus 65±3% for mitral valves. Young age was a strong risk factor for reoperation, with the risk progressively decreasing with increasing age.[26]

The Supra-annular Aortic Valve (SAV) prosthesis was introduced in 1981. The second generation valve is fixed with glutaraldehyde at 2 mm Hg and is treated with polysorbate 80, and ethanol to reduce SVD.[27] The SAV was designed for supra-annular inplantation to optimize hemodynamics over first generation intra-annular valves. However, the low profile configuration of the SAV may contribute to altered stresses and premature SVD when implanted in the mitral position, especially in patients less than 70 years.[27,28] In a follow-up of 1,823 patients after aortic valve replacement, reoperation was more common in younger patients. The actuarial freedom from reoperation at 18 years was 97±1% for patients greater than 70 years, compared to 44±6% for patients 51–60 years.[27] SVD presented as stenosis in 28% and regurgitation in 72%. Pathological evaluation demonstrated that calcification with leaflet tear is the most common finding in young patients.

Medtronic: The original Hancock standard valve was introduced in 1971 and the second generation Hancock II valve entered clinical trials in 1982. The Hancock II has a lower profile and a minimized right coronary septal muscle shelf. The preparation process includes anticalcification treatment with the surfactant sodium dodecyl sulfate and a two stage fixation process (i.e. low pressure followed by high pressure).[29] Rates of structural

valve deterioration and reoperation rates are higher for younger patients. In the aortic position, freedom from reoperation at 20 years was 52±10% for patients under 60 years versus 87±5% for patients 60 years or older. In the mitral position, the rates were 41±10% for patients under 60 years and 62±8% for patients 60 years or older.[29] Increased risk of SVD in younger patients at 20 years following valve replacement was demonstrated in another study as well.[30]

The Mosaic valve is a third generation supra-annular valve that was introduced in 1994. The preparation process includes predilation of the porcine aortic root at the time of preservation. Fixation is performed at zero pressure and the valves receive anticalcification treatment with AOA.[31] In the aortic position, the 13-year survival was 63±4% and freedom from explantation was 73±7%. The freedom from SVD was 86% and similar for patients less than 65 compared to patients greater than 65 years. In the mitral position, 13-year survival was 51±14% and freedom from explanation was 89±6%, suggesting improved durability compared to first generation valves. While the goal of supra-annular valves is to increase EOA, very small valves may not provide an adequate orifice area for cardiac output. In a study of patients receiving 19 mm Mosaic valves, severe PPM occurred in 50%. In addition, the 30 day mortality was 9.9% and the 2-year survival was only 69.1±5.5%.[32]

St Jude Medical: The Biocor valve is designed with three separate porcine leaflets, crosslinked using low pressure fixation, and attached to a polymer stent. A pericardial shield on the outflow edge of the stents is designed to prevent the risk of abrasion. In the aortic position, the valve can be implanted in supra-annular or intra-annular positions. Durability is demonstrated at 20 year follow-up in elderly patients. In aortic valve recipients less than or equal to 65 years, actuarial freedom from reoperation due to structural valve deterioration was 44±9% versus 92±4% in patients greater than 5 years. In mitral valve recipients, the equivalent values were 75±8% versus 88±8%.[33] Thus, the Biocor valve has comparable durability in the aortic and mitral positions in the elderly. The improved durability in the mitral position may be related to the tri-composite leaflet configuration with stress reduction.[28]

The Epic valve design is the same as the Biocor valve except that the valve undergoes a proprietary anticalcification treatment. The valve received FDA approval in 2007 and there are no long-term studies of durability.

Stented Bovine Pericardial

The hemodynamic performance of pericardial valves is superior to recent generation stented porcine valves in the aortic position. However, long-term studies have not consistently demonstrated improved durability.

Edwards lifescience: The C-E Perimount valve was introduced into clinical use in 1981 and approved for the US commercial distribution in 1991. Bovine pericardium is mounted in a polypropylene stent and a sewing ring. They are second generation pericardial valves, with design changes (i.e. improved tissue fixation, improved leaflet-mounting and enhanced stent flexibility) intended to minimize the SVD of the first generation, Lonescu-Shiley pericardial valves.[34] In a prospective trial of 100 patients undergoing aortic valve replacement with Perimount or Medtronic Mosaic porcine valves, the mean gradients were lower at follow-up for 23 mm and 25 mm pericardial valves. LV mass regression was more significant for the 23 mm pericardial valve but there was no difference with the 25 mm valves.[35] In another prospective study, the C-E Perimount aortic valve had lower gradients than the Mosaic supra-annular valve at 1 year.[36]

The Perimount Magna aortic valve was introduced in 2003 as a modification of the standard Perimount valve and is designed for supra-annular positioning. It has a lower profile to ease insertion and aortotomy closure. The lower stent base maximizes coronary ostia clearance. In patients with small annulus sizes (i.e. < 23 mm), mean gradients were reported to be lower with Perimount Magna valves compared to Medtronic Mosaic and St Jude Epic stented porcine valves.[37] In another study, comparing the hemodynamics of the Perimount Magna with the standard Perimount and Medtronic Mosaic valves, mean gradient and PPM incidence was lower for the Magna valve in patients receiving 21–23 mm valves. However, there was no difference in mean gradients in patients receiving 18–20 mm valves and the incidence of PPM was high in all of these valves.[38] Lower gradients were also demonstrated in a retrospective study comparing Perimount Magna valves with Hancock II porcine valves.[39]

In a study comparing durability of C-E pericardial with C-E porcine aortic valves, the 10-year freedom from SVD for the C-E pericardial valve was 98.5% versus 92% for the C-E porcine aortic valves.[40] However, the porcine valves were implanted between 1974 and 1996, so first generation porcine valves were included in the comparison with pericardial valves implanted from 1991 to 2002. In a retrospective comparison of patients receiving Perimount and C-E SAV porcine aortic valves, there was no difference in actuarial freedom of valve-related reoperation at 15 years (74±2% for the SAV valve and 82±4% for the Perimount valve). While the freedom from SVD in patients less than 60 years was higher for the Perimount valve, SVD is still more common in younger patients.[41] In a series of 1,000 patients having aortic valve replacement with C-E pericardial valves, actuarial freedom from SVD at 15 years was 35% for patients less than 65 years compared to 89% for patients 65–75 years.[34]

Stentless

Aortic stentless valves were designed to improve hemodynamic performance of stented valves. They are made of a preparation of porcine aortic root and do not have the obstructive stent and sewing cuff of stented valves, allowing for a larger flow area and lower transvalvular gradients.[42] Three different techniques for implantation have been described (Fig. 5): (1) subcoronary (used for pure aortic valve pathologies); (2) root inclusion (i.e. the bioprosthesis is placed as a tube inside the native aorta in an attempt to reduce distortion of the graft) and (3) root replacement (used in the presence of associated aortic root pathology). In all three implantation techniques, sizing is undertaken at the sinotubular junction, rather than the annulus.[42] Early in the experience with the Toronto stentless porcine valve, sizing was done at the aortic annulus; however, mild aortic

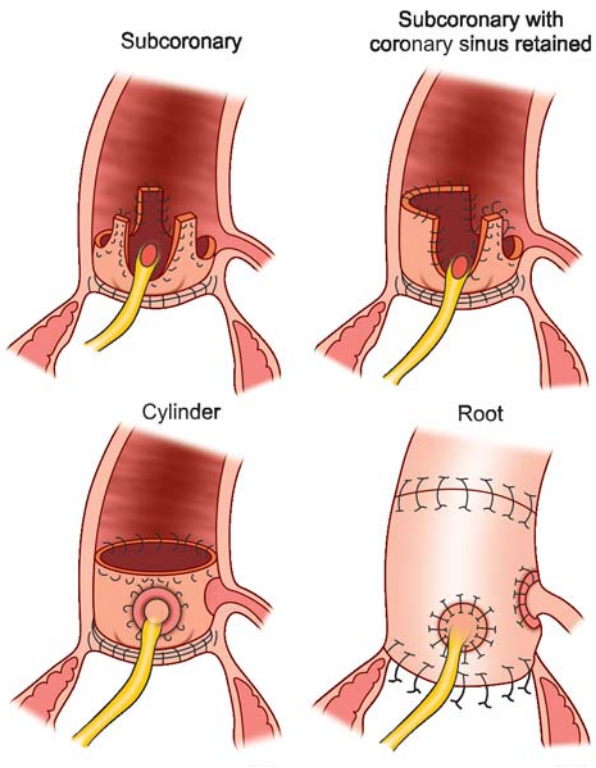


FIGURE 5: Implantation techniques possible with Medtronic Freestyle stentless valve (*Source:* Reardon MD, David TE. Stentless xenograft aortic valves. Curr Opin Cardio. 1999;14:84-9)

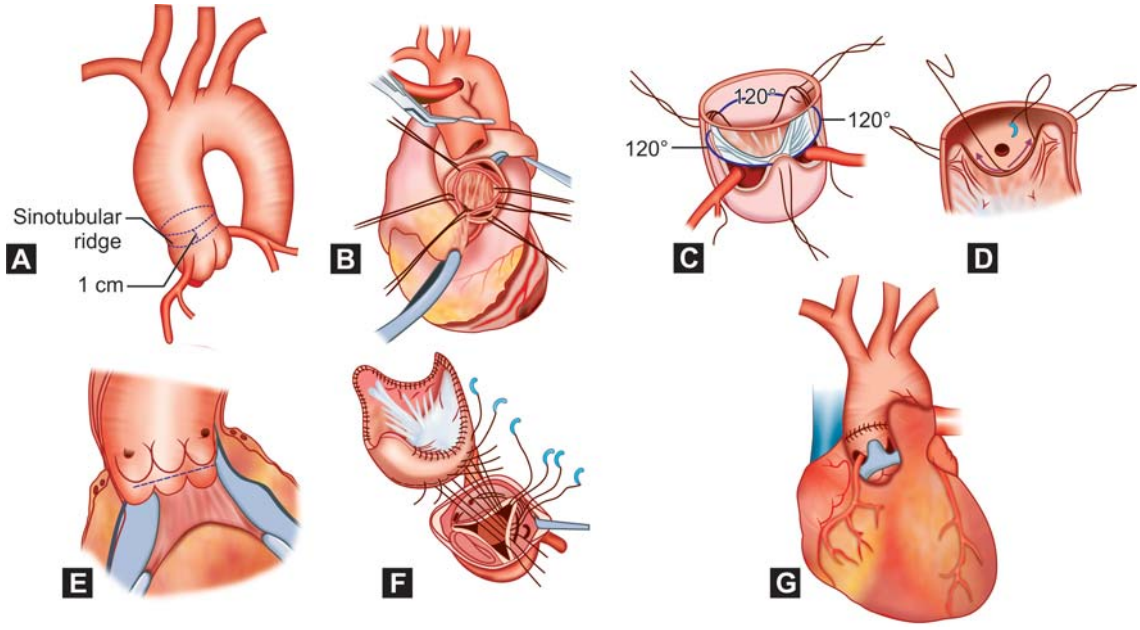
regurgitation was noted in follow-up. Since the sinotubular junction is usually larger than the annulus, it is usual to implant a stentless valve that is larger than a stented valve for the same annular diameter.

However, the procedure is more complicated and requires additional time. Two suture lines are usually required in stentless valve implantation (Figs 6A to G) making the procedure more time-consuming compared with stented valve implantation, with reported aortic cross clamp times of 20–30 minutes longer for stentless valve implantation. Mortality is increased with full aortic root implantation compared to subcoronary implantation.[42,43] In addition, in patients undergoing reoperation for structural valve deterioration of stentless valves, operative mortality was 11% (with a higher mortality of 67% if redo surgery was within 1 year vs 7% after 1 year).[44]

Almost all studies comparing stentless valves with second and third generation stented porcine valves show significant hemodynamic superiority of stentless valves. In contrast, almost all trials comparing stentless porcine valves with stented pericardial valves show equivalent hemodynamic performance.[42] In a meta-analysis comparing stentless and stented valves, left ventricular mass was reduced at 6 months compared with stented valves, but the difference was less significant when comparisons were made with pericardial valves. However, at 12 months, there was no significant difference in LV mass regression between valves. In addition, there was no difference in mortality at one year follow-up.[45]

Studies of follow-up at midterm length follow-up (i.e. 5–8 years) have suggested a survival advantage of stentless valves compared to stented valves (Hancock II, C-E SAV and Perimount valves), but long-term studies of greater than 10 years show no advantage.[42]

St Jude Medical: The Toronto Stentless Porcine valve is fixed with glutaraldehyde at a pressure of 1.5 mm Hg without anti-calcification treatment.[46] It is designed for subcoronary implantation and has excellent hemodynamic performance but not clearly superior to other valves. In a comparison with the C-E supra-annular Perimount valve in the aortic position, there was no difference in valve area at 6 months or LV mass regression at 1 year.[47]



FIGURES 6A TO G: Toronto stentless porcine valve implantation technique. (A) Opening the aorta distal to the sinotubular junction. (B) Exposure of the aorta and trachea structures. (C) Plane of proximal suture line. (D) Proximal suture line below coronary arteries. (E) Orientation stay sutures for commissural ports. (F) Distal suture lines. (G) Completed valve (*Source:* Reardon MD, David TE. Stentless xenograft aortic valves. Curr Opin Cardio. 1999;14:84-9)

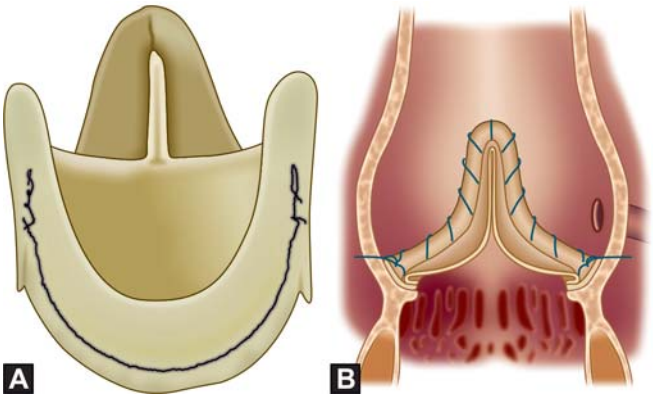
Suboptimal durability in younger patients has been demonstrated in long-term follow-up. In a study of 200 patients (mean age, 65±11 years) undergoing aortic valve replacement with the Toronto SPV, actuarial freedom from SVD was 99% at 5 years, but 78% at 10 years.[48] In another study, the 12-year survival was 69±4% in 357 patients undergoing the surgery from 1991 to 2004. Freedom from structural valve deterioration at 12 years was 52±8% for patients under 65 years and 85±4% for patients 65 years or older. Thus, the valve is probably best suited for the older patient with a small annulus.[46]

Medtronic: The Freestyle aortic root bioprosthesis is a stentless porcine aortic root, prepared using a proprietary low-pressure and zero-pressure fixation process and anticalcification treatment with alpha-amino oleic acid.[49] The full root design provides multiple implant options (e.g. complete root or subcoronary). The Prestyled Freestyle bioprosthesis is pretrimmed. The initial implantation in humans began in 1992 and was approved for use in the United States in 1997. In a review of experiences from multiple medical centers, the 10-year survival was similar for implantation groups: subcoronary, 44±4%; full root 47±8%; root inclusion 45±14%. The 10-year actuarial freedom from reoperation was also similar for the three techniques (97±2%, 96±4% and 91±11%, respectively). However, freedom from moderate or more aortic regurgitation was higher for full root (98±2%) compared to subcoronary (87±3%), possibly related to more stable valve geometry because of retention of the porcine aortic root.[49] In general, the mechanism of valve deterioration was related to leaflet tear, rather than calcification. Aortic regurgitation appears less common compared to the Toronto valve presumed related to the full root and root inclusion techniques for the Freestyle valve, which may prevent dilation of the sinotubular junction.[49]

In the ASSERT trial (Aortic Stentless vs Stented valve assessed by Echocardiography Randomized Trial), patients undergoing aortic valve replacement for aortic stenosis with annulus less than or equal to 25 mm in diameter were randomized to a stentless Freestyle valve or to a supra-annular stented Medtronic Mosaic porcine valve. There was a greater increase in the EOA and decrease in peak gradient in the stentless group but no difference in survival or LV mass regression at 12 months,[50] similar to findings of the meta-analysis of stentless valves discussed in the chapter's introduction section of stentless valves.[45]

Edwards lifescience: The Prima porcine prosthesis received FDA approval in the United States in 2001 and long-term durability studies are limited. In a study of 154 patients, aged 71±9 years and followed for 48±19 months, 7-year freedom from structural failure was 99±1% and survival was 97±3%.[51] When compared with C-E Perimount valves in 161 patients undergoing valve replacement for aortic stenosis, there was no difference between groups in LV mass regression at 1 year. However, in patients with LV ejection fraction (EF) less than 60% at baseline, EF increased more in patients with stentless valves.[52]

Sorin group: The Sorin group stentless valves are available for international distribution but not in the United States. The Pericarbon Freedom valve is made of two sheets of bovine pericardium sutured together without synthetic fabric reinforcement and prepared with an anticalcification treatment



FIGURES 7A AND B: (A) The SOLO stentless bovine pericardial aortic prosthesis. (B) Technique of implantation with a single supra-annular suture line (*Source:* Aymard T, Eckstein F, Englberger L, et al. The Sorin Freedom SOLO stentless aortic valve: technique of implantation and operative results in 109 patients. J Thorac Cardiovasc Surg. 2010;139: 775-7)

of homocysteic acid, which neutralizes residues of unbound aldehyde groups remaining after fixation.[53] In a study of 130 patients (mean age, 76±5 years) undergoing aortic valve replacement from 1999 to 2005, overall hospital mortality was 8.4% and freedom from valve-related deaths was 91±4%. The slope of the survival curve was similar to that of a population matched for age and sex and the difference between the two curves was related the early mortality of the operative cohort.[53] The design of the Freedom Solo valve differs from other stentless valves because the outside pericardial support is eliminated and allows a supra-annular position with a single suture line, rather than separate suture lines at the annulus and above[54] (Figs 7A and B).

Cryolife (Atlanta, GA): The O'Brien valve was introduced into clinical practice in 1992. The valve is less obstructive than the Toronto SPV valve, possibly related to differences in design and implantation site. The O'Brien valve has no Dacron lining and is composed of three porcine noncoronary cusps and therefore has no muscle bar (which is present at the base of the right coronary cusp). The O'Brien valve is sited just above the annulus while the Toronto valve is sewn at the annulus.[55] In a single institutional experience report, the actuarial survival at 10 years was 40% and freedom from reoperation at 10 years was 57%.[56]

HOMOGRAFT

Homograft aortic valves are available through cooperative ventures with tissue banks (e.g. St Jude Medical cooperates with LifeNet, a not-for-profit tissues bank that provides centralized procurement, processing and distribution of allografts in the United States).

Homografts may be chosen for patients with active endocarditis, associated abscess or uncontrolled infection.[57] This indication is at least partly attributed their preincubation in antibiotics. In addition, the long-term risk of endocarditis is low.[58] However, in two retrospective studies of patients undergoing aortic valve replacement, there were no differences in survival or recurrent infection.[59,60] In both studies more patients with annular disease underwent replacement with homograft,

potentially introducing selection bias of favoring homografts in more complicated cases. Due to limited durability, patients with homografts are more likely to undergo reoperation compared to patients undergoing replacement with a mechanical valve.[60]

Homografts and bioprostheses have similar rates of structural valve deterioration.[57,61] However, the versatility in dealing with acquired and congenital aortic root pathology by using the inclusion cylinder or full root replacement makes homografts a good second option to the Ross procedure in the young and heterografts in adults not felt to be candidates for long-term anticoagulation.[61] Predictors of poor outcome are older donor age, young recipient age, size-mismatching and full-root versus non-root replacement.[58] The impact of young age on reduced durability has been confirmed by others, demonstrating at least a trend for increased risk of SVD with younger age at implantation.[62] Hospital mortality is in the range of 3–6% and cumulative 20-year survival ranges 35–52%.[61] Using subcoronary replacement, 20-year survival of 58±4% has been reported with freedom from reoperation of 86±3% at 10 years and 40±5% at 20 years.[58]

ROSS PROCEDURE (PULMONIC VALVE AUTOTRANSPLANTATION)

In the Ross Procedure, the patient's pulmonary valve and main pulmonary artery are removed and replace the diseased aortic valve and the proximal aorta with reimplantation of the coronary arteries.[63] Then, a pulmonary or aortic homograft is inserted into the pulmonary position. The procedure is most commonly performed in children and young adults and there is some controversy about indications in adults.[61] In a cohort of 212 patients with a mean age of 34±9 years, with congenital aortic valve disease and followed for 10±4 years, the optimal outcomes were in female patients with aortic stenosis and an aortic annulus less than 27 mm.[64] Male sex and primary diagnosis of aortic regurgitation have been associated with autograft failure in other studies as well.[65]

Advantages of the procedure include: (1) the autograft may grow in children; (2) warfarin is not required; (3) favorable hemodynamic characteristics; (4) low incidence of thromboembolism and (5) low endocarditis risk. Disadvantages include: (1) a complex operation which is technically demanding; (2) in-hospital mortality of 3–5%; (3) risk of early aortic valve failure; (4) the homograft used to replace pulmonary valve is subject to stenosis and failure and (5) the procedure is not recommended for patients with bicuspid valve and dilated aorta, since a bicuspid valve may be associated with degenerative changes in the pulmonary root.[61,64,66]

In a systematic review and meta-analysis, the early mortality for adult patients was 3.2%, autograft deterioration rate was 0.78% per patient-year, and right ventricular outflow tract conduit deterioration was 0.55% per patient-year. Durability limitations become apparent after 10 years.[66] Aortic root dilatation or aneurysm is proving to be progressively more frequent late after the Ross procedure. Risk factors for root dilatation are preoperative aortic aneurysm, aortic insufficiency and the root replacement technique.[61]

In a retrospective review of outcomes after allograft or autograft aortic valve or root replacement in young adults, age 16–55 years, with congenital heart disease, 13-year survival was 97% for autograft and 93% for allograft recipients.[63] In addition, the 13-year freedom from valve-related reoperation was similar for both prostheses (i.e. 63% for autografts and 69% for allografts). While the risk of SVD was similar for both procedures, the risk of reoperation after an initial Ross procedure is significant.[57]

Absolute contraindications include recognized connective tissue disease (e.g. Marfan's syndrome) and chronic inflammatory disorders because of the potential involvement of the pulmonary valve/root in the disease process.[61]

SELECTING THE OPTIMAL PROSTHESIS

An optimal valve prosthesis is characterized by excellent hemodynamics, long durability, high thromboresistance and ease of implantability. Unfortunately, none of the currently available prostheses have all these features and the selection of a prosthetic valve for the individual is determined by the relative importance of these characteristics.[1]

Improved mortality with mechanical valves compared to porcine valves has been demonstrated in early randomized trials. In the VA randomized trial, male patients were randomized between 1977 and 1982. Patients receiving aortic valve replacement with Bjork-Shiley single leaflet tilting disk valves had improved survival and lower reoperation rates after 10 years compared to patients receiving porcine bioprosthetic valves. However, mortality rates for mitral valve replacement were similar. Primary valve failure rates between mechanical and bioprosthetic valves were not significantly different in patients greater than or equal to 65 years old (i.e. complications with porcine valves were more common in patients less than 65 years). At 11 years after randomization, mechanical valves had an increased risk of bleeding complications (related to anticoagulation) but a decreased risk of structural risk of valve failure.[14]

In the Edinburgh Heart Valve trial, patients were randomized between 1975 and 1979 to Bjork-Shiley single leaflet tilting mechanical valves or porcine bioprostheses. There was a trend toward improved survival with the Bjork-Shiley valve with an average follow-up of 12 years in an early report,[67] and similar findings were obtained at 20-year follow-up.[15] However, survival without a major event (i.e. death, reoperation, major bleeding, major embolism and endocarditis) was better for patients having mechanical valve compared to porcine valves for patient having mitral valve replacement. The difference in survival without a major event was almost entirely accounted for by the need for reoperation in patients with bioprostheses. In addition, the bleeding risk was higher with the mechanical valves versus the porcine valves after aortic valve replacement but not after mitral valve replacement, presumably due to increased warfarin use in mitral bioprostheses (i.e. 57% of patients with a mitral bioprosthesis were taking warfarin by 15 years).

In a more recent randomized trial comparing contemporary mechanical and bioprosthetic aortic valves, the differences in mortality were not significant at 13 years. There was no difference in cardiac related mortality between newer generation bioprostheses (i.e. C-E SAV and pericardial) and mechanical bileaflet valves implanted between 1995 and 2003 with a mean

TABLE 2

Comparison of complications in patients with mechanical and biological prostheses in randomized trials

	Systemic emboli				*Bleeding*				*Reoperation*			
	Aortic		*Mitral*		*Aortic*		*Mitral*		*Aortic*		*Mitral*	
Study	Mech	Bio	Mech	Bio	Mech	Bio	Mech	Bio	Mech	Bio	Mech	Bio
VA[14](%)	18±4	18±4	18±5	22±5	51±4**	30±4	53±7*	31±6	10±3	29±5*	25±6	50±8
Edinburgh[15](%)	24±6	39±9	53±7	32±6	61±8**	42±12	53±8	37±11	7±3	56±8***	13±4	78±7***
Tassano[68] (Linearized rate, %/pt-yr)	0.54	0.24			1.47†	0.72			0.62	2.32**		

(Abbreviations: Mech: Mechanical valve, Bio: Biological valve)
*0.001 < p ≤ 0.01, **0.0001 ≤ p ≤ 0.001, ***p < 0.0001
†21% in the bioprosthesis group were taking warfarin. Bleeding occurred in 3.4% of bioprosthesis patients not taking warfarin, compared to 12.7% of patients with mechanical valves (p = 0.001)

follow-up of 106 months. The randomized patients were in the age range of 55–70 years and the perioperative mortality of less than 4% was similar in both groups; however, reoperation and valve failure were more common in the bioprosthesis group. While the difference in bleeding risk was not significant (p = 0.08), bleeding in the bioprostheses group was likely related to warfarin use in 21% of patients. When the subset of patients with bioprostheses on warfarin were excluded, bleeding was more common in the mechanical valve group.[68]

Nonrandomized trials demonstrate that the survival rates and risk of complications are dependent on patient-related factors, such as age, left ventricular dysfunction, heart failure, coronary artery disease, coronary artery bypass grafting, arrhythmias, pulmonary hypertension, and coexistent conditions such as renal failure, lung disease, hypertension and diabetes.[69] Thus, comparison of outcomes between mechanical and biological valves requires caution unless baseline characteristics of patients are similar.[57] However, the choice between mechanical and bioprosthetic valves is largely related to a trade-off between the durability advantages of mechanical valves compared to lower bleeding risk of bioprostheses (Table 2).

A retrospective review compared outcomes of patients age 50–70 years having aortic valve replacement with St Jude Medical bileaflet mechanical valves versus C-E bioprostheses (including first generation and pericardial), implanted between 1991 and 2000. After adjusting for unmatched variables, including diabetes, renal failure, lung disease, NYHA functional class, ejection fraction and stroke, the use of a mechanical valve was protective against late mortality.[70] In addition, the patient with bioprostheses had higher perioperative mortality (5.5% vs 1.8%, p < 0.04) which included hemorrhagic stroke, lung and liver complications. The findings suggest the importance of favoring mechanical valves in younger patients.

In a review of Medicare data (i.e. patients age of 65 years or older) of over 300,000 patients undergoing aortic valve replacement from 1991 to 2003, bioprostheses had higher risk of reoperation while mechanical valves had higher risk of hemorrhage, stroke or embolism.[71] In addition, improved life expectancy with bioprosthetic valves was demonstrated in elderly patients undergoing aortic valve replacement compared to mechanical valves, likely related to the increased bleeding risk associated with anticoagulation use[72] (Figs 8 and 9).

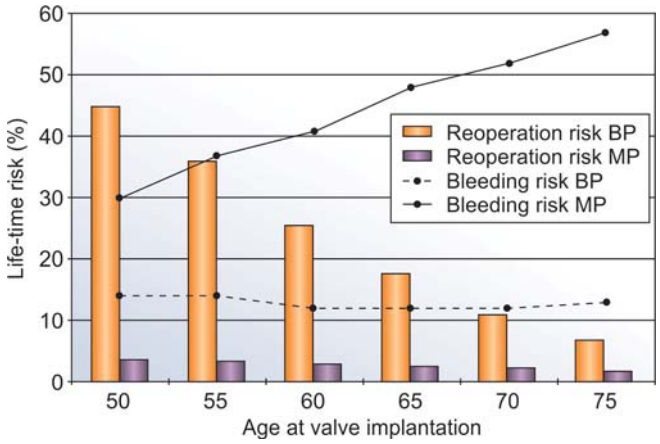


FIGURE 8: Lifetime risks of reoperation and bleeding after aortic valve replacement with mechanical and bioprostheses. BP, biological prosthesis; MP, mechanical prosthesis line (*Source:* van Geldorp MWA, Jamieson WRE, Kappetein AP, et al. Patient outcome after aortic valve replacement with mechanical or biologic prosthesis. Weighing lifetime anticoagulant related event risk against reoperation risk. J Thorac Cardiovasc Surg. 2009;137:881-6)

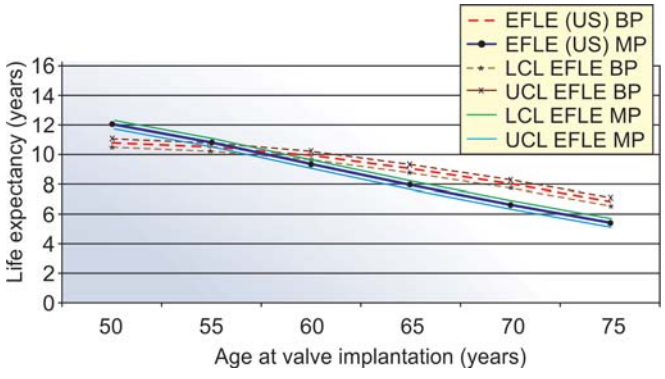
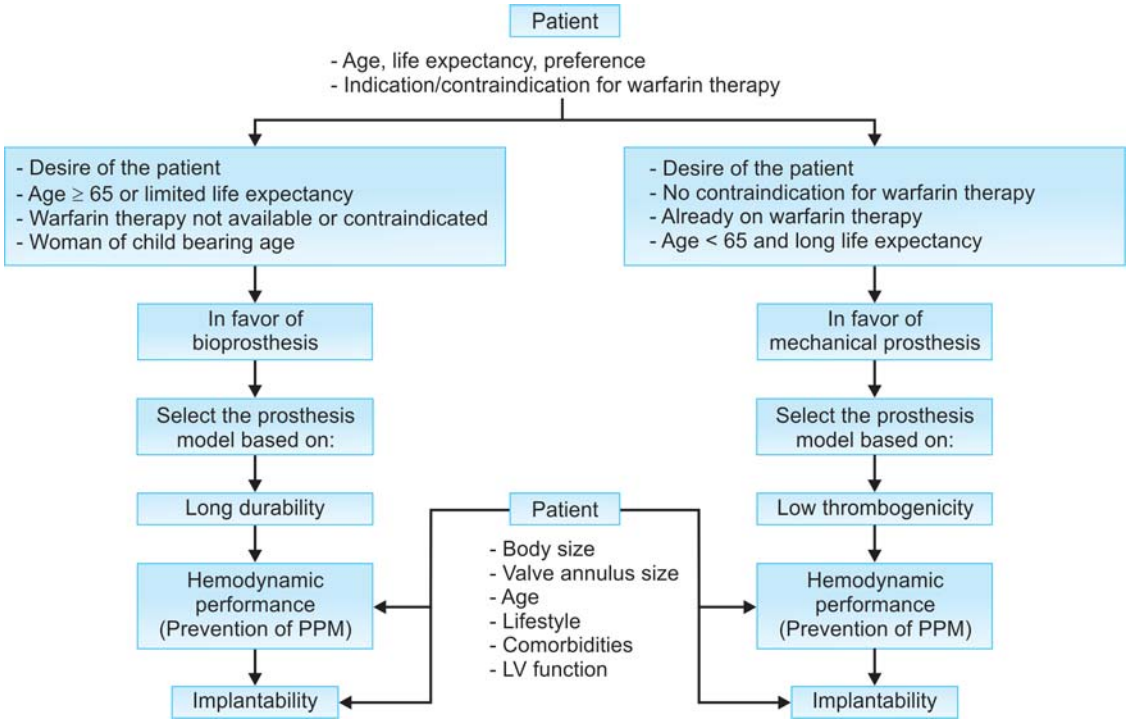


FIGURE 9: Event-free life expectancy (with 68% confidence limits in gray) after AVR with mechanical and bioprosthesis in the United States. MP, mechanical prosthesis; BP, biological prosthesis; EFLE, event-free life expectancy; UCL, upper confidence limit; ICL, lower confidence limit (*Source:* van Geldorp MWA, Jamieson WRE, Kappetein AP, et al. Patient outcome after aortic valve replacement with mechanical or biologic prosthesis. Weighing lifetime anticoagulant related event risk against reoperation risk. J Thorac Cardiovasc Surg. 2009;137:881-6)

FLOW CHART 1: Algorithm for the selection of the optimal prosthesis in the individual patient



(*Source:* Pibarot P, Dumesnil JG. Prosthetic heart valves: selection of the optimal prosthesis and long-term management. Circulation. 2009;110: 1034-48)

The selection of prosthetic heart valves for women of childbearing age is difficult. Mechanical bileaflet valves may be favored because of durability. They may be a reasonable choice for women who are compliant and committed to careful anticoagulation. However, a biological valve prosthesis may be preferred in young women who are not interested in anticoagulation or for whom close follow-up is not possible.[73] Unfortunately, pregnancy in a woman with a bioprosthetic valve is associated with SVD and the incidence may average 24% during or shortly after the pregnancy.[74]

The selection of the optimal prosthesis depends on a number of clinical variables including age, ability to tolerate full dose oral anticoagulation, comorbidities, LV function, body size and valve annulus size[1] (Flow Chart 1).

PROSTHESIS-PATIENT MISMATCH

Prosthesis-patient mismatch (PPM) occurs when the EOA of a normal functioning valve is too small in relation to the patient's body size and cardiac output requirements, resulting in abnormally high transvalvular gradients.[1,75] Criteria for PPM have been established and are based on the EOA indexed for body surface area. The projected indexed EOA is typically determined from reference values published by echocardiography labs[1,92] (Tables 3 and 4). Reference valve areas obtained by Doppler echocardiography in normal valves 6 months after valve replacement are superior to geometric orifice areas calculated from internal diameters.[76] Methods for calculating EOA are discussed in the echocardiography section of this chapter. Severe PPM is estimated to occur in 2–10% of patients and is defined as an EOA/m^2 less than or equal to 0.65 for aortic valve prostheses and less than or equal to 0.9 for mitral. Moderate PPM may be frequent in both the aortic (20–70%) and mitral (30–70%) positions and is defined as EOA/m^2 of less than or equal to 0.85 for aortic valve prostheses and less than or equal to 1.2 for mitral.[1]

PPM in the aortic position is associated with less improvement in symptoms and functional class, less regression of LV hypertrophy and more adverse cardiac events including mortality.[1] Preoperative left ventricular function is predictive of a combined endpoint of increased incidence of heart failure symptoms or death related to heart failure at three years in patients with moderate PPM after aortic valve replacement.[77] The incidence of the combined endpoint was 30.3% in patients with moderate PPM and left ventricular EF less than 50% compared to 14.9% in patients with PPM and normal left ventricular EF (Fig. 10). Thus, the increased hemodynamic burden of increased afterload is less well tolerated by a poorly functioning left ventricle than by a normal ventricle.[1]

In a retrospective review of patients with 19 or 21 mm St Jude Medical mechanical prostheses, severe PPM (defined as indexed EOA $\leq$ 0.6 cm^2/m^2) was associated with a higher incidence of mortality and congestive heart failure compared to patients with moderate PPM.[78] In a follow-up long-term survival study, the same authors determined that age less than 70 years and body mass index less than 30 kg/m^2 were associated with increased mortality in patients with PPM.[79] Finally, the presence of PPM (defined as indexed EOA less than 0.85 cm^2/m^2 and valve size less than 21 mm bioprosthetic aortic valve prosthesis) may be predictive of SVD due to stenosis.[80]

The incidence of mitral position PPM (defind as indexed EOA < 1.25 cm^2/m^2) was 32% in the series reported by Lam et al.[81] Predictors of recurrent congestive heart failure were low indexed EOA, low ejection fraction, elevated

TABLE 3

Normal reference values of EOAs for aortic prostheses

	19	21	23	25	27	29
Stented porcine						
Mosaic (Medtronic)	...	1.4 ± 0.4	1.5 ± 0.4	1.8 ± 0.5	1.9 ± 0.1	2.1 ± 0.2
Hancock II (Medtronic)	...	1.3 ± 0.4	1.3 ± 0.4	1.6 ± 0.4	...	1.6 ± 0.2
Intact (Medtronic)	...	1.6 ± 0.4	1.6 ± 0.4	1.7 ± 0.3	...	...
Biocor (St Jude Medical)	...	...	1.3 ± 0.3	1.7 ± 0.4	2.2 ± 0.4	...
C-E Standard (Edwards Lifescience)	0.9 ± 0.2	1.5 ± 0.3	1.7 ± 0.5	1.9 ± 0.5	2.3 ± 0.6	2.8 ± 0.5
C-E Supra-annular	1.1 ± 0.1	1.4 ± 0.9	1.6 ± 0.6	1.8 ± 0.4	1.9 ± 0.7	...
Stented bovine						
C-E Perimount	1.1 ± 0.3	1.3 ± 0.4	1.5 ± 0.4	1.8 ± 0.4	2.1 ± 0.4	2.2 ± 0.4
C-E Perimount Magna	1.3 ± 0.3	1.7 ± 0.3	2.1 ± 0.4	2.3 ± 0.5	...	...
Mitroflow (Sorin)*	1.1 ± 0.1	1.3 ± 0.1	1.5 ± 0.2	1.8 ± 0.2	...	...
Labcor-Santiago	1.2 ± 0.1	1.3 ± 0.1	1.8 ± 0.2	2.1 ± 0.3	...	...
Stentless bioprosthesis						
Freestyle (Medtronic)	...	1.4 ± 0.3	1.7 ± 0.5	2.1 ± 0.5	2.5 ± 0.1	...
Toronto SPV (St Jude Medical)	...	1.3 ± 0.6	1.6 ± 0.6	1.8 ± 0.5	2.0 ± 0.3	2.4 ± 0.6
O'Brien (Cryolife)	1.5 ± 0.3	1.7 ± 0.4	2.3 ± 0.2	2.6 ± 0.2	2.8 ± 0.3	...
Prima (Edwards)	...	1.4 ± 0.7	1.5 ± 0.3	1.8 ± 0.5	...	...
Pericarbon (Sorin)	1.2 ± 0.5	1.3 ± 0.6	1.5 ± 0.5	...	...	...
Caged-ball mechanical						
Starr-Edwards	...	...	1.1 ± 0.2	1.1 ± 0.3	...	...
Single leaflet tilting disk mechanical						
Bjork-Shiley	...	1.1 ± 0.3	1.3 ± 0.3	1.5 ± 0.4	1.6 ± 0.3	...
Medtronic-Hall	...	1.1 ± 0.2	1.4 ± 0.4	1.5 ± 0.5	1.9 ± 0.2	...
Bileaflet tilting disk mechanical						
Standard (St Jude Medical)	1.5 ± 0.1	1.4 ± 0.4	1.6 ± 0.4	1.9 ± 0.5	2.5 ± 0.4	2.8 ± 0.5
Regent (St Jude Medical)	1.6 ± 0.4	2.0 ± 0.7	2.3 ± 0.9	2.5 ± 0.8	3.6 ± 0.5	...
CarboMedics standard (Sorin Group)	1.0 ± 0.3	1.5 ± 0.4	1.4 ± 0.3	1.8 ± 0.4	2.2 ± 0.2	3.2 ± 1.6
Top Hat CarboMedics (Sorin Group)	...	1.2 ± 0.3	1.4 ± 0.4	1.6 ± 0.3	...	...
ATS Standard (ATS)	1.1 ± 0.3	1.4 ± 0.5	1.7 ± 0.5	2.1 ± 0.7	2.5 ± 0.1	3.1 ± 0.8
On-X (MCRI)	1.5 ± 0.2	1.7 ± 0.4	1.9 ± 0.6	2.4 ± 0.6	...	...

*Data limited
(*Source:* Zoghbi et al.[92] and Pibarot and Dumesnil[1])

TABLE 4

Normal reference values of EOAs for mitral prostheses

	23	25	27	29	31	33
Stented porcine						
Hancock I or not specified (Medtronic)	...	...	1.3 ± 0.8	1.5 ± 0.2	1.6 ± 0.2	1.9 ± 0.2
Hancock II (Medtronic)	...	...	2.2 ± 0.1	2.8 ± 0.1	2.8 ± 0.1	3.1 ± 0.2
Mosaic (Medtronic)	...	1.5 ± 0.4	1.7 ± 0.5	1.9 ± 0.5	1.9 ± 0.5	...
Stented bovine						
Carpentier-Edwards Perimount*	...	1.6 ± 0.4	1.8 ± 0.4	2.1 ± 0.5	...	...
Single leaflet tilting disk mechanical						
Bjork-Shiley	...	1.7 ± 0.6	1.8 ± 0.5	2.1 ± 0.4	2.2 ± 0.3	...
Bileaflet tilting disk mechanical						
Standard (St Jude Medical)	1.0	1.3 ± 0.2	1.7 ± 0.2	1.8 ± 0.2	2.0 ± 0.3	...
CarboMedics Standard (Sorin Group)	...	2.9 ± 0.8	2.9 ± 0.7	2.3 ± 0.4	2.8 ± 1.1	...
On-X (MCRI)	...	1.9 ± 1.1	2.2 ± 0.5	2.2 ± 0.5	2.5 ± 1.1	2.5 ± 1.1

*Data limited
(*Source:* Zoghbi et al.[92] and Pibarot and Dumesnil[1])

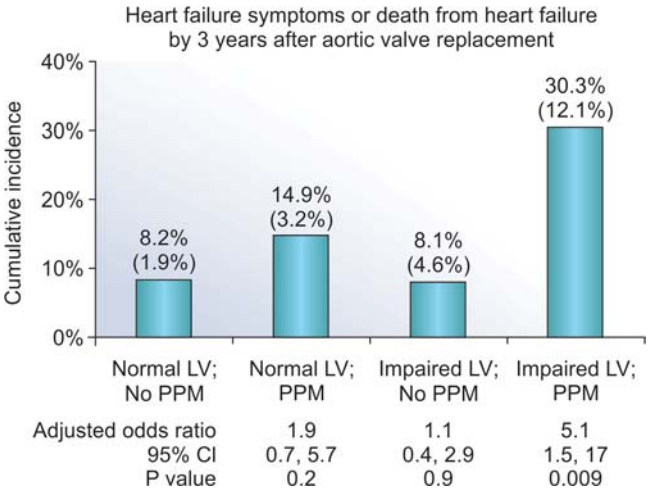


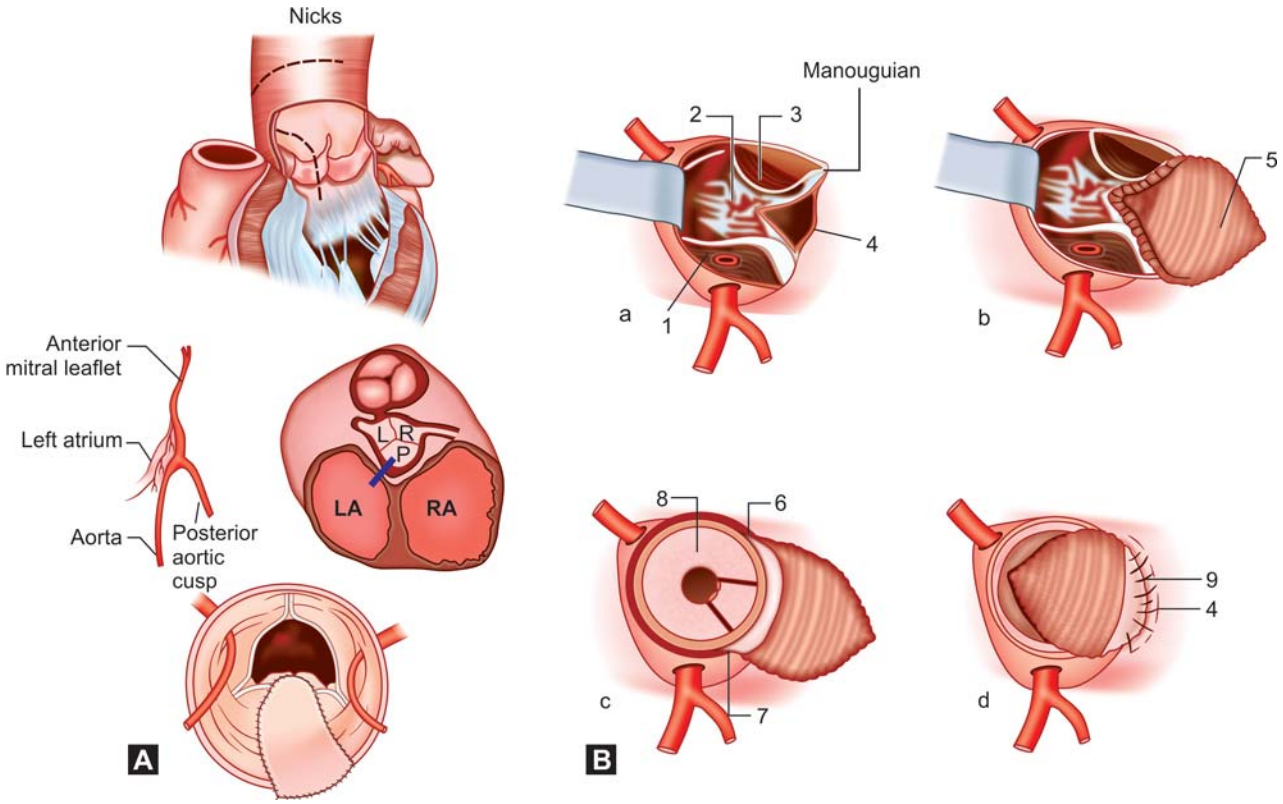
FIGURE 10: Effect of prosthetic-patient mismatch and preoperative LV function on cumulative incidence of congestive heart failure symptoms or death related to congestive heart failure at 3 years after aortic valve replacement. PPM: EOA index < 0.85 cm²/m². Impaired LV: EF < 50%. (*Source:* Ruel M, Al-Faleh H, Kulik A, et al. Prosthesis-patient mismatch after aortic valve replacement primarily affects patients with pre-existing left ventricular dysfunction: impact on survival, freedom from heart failure and left ventricular mass regression. J Thorac Cardiovasc Surg. 2006;131:1036-44)

postoperative mean gradient and use of a bioprosthesis. Ten-year survival was reduced in patients with PPM compared to patients without PPM (65% vs 75%). Others have also demonstrated reduced survival with PPM after mitral valve replacement. Magne et al. retrospectively identified 81 patients with severe PPM (defined as indexed EOA $\leq$ 0.9 cm^2/m^2) and 664 patients with moderate PPM (defined as indexed EOA $>$ 0.9 and $\leq$ 1.2 cm^2/m^2). The 12-year survival for severe PPM was 63$\pm$7%, compared to 76$\pm$2% with moderate PPM and 82$\pm$4% with nonsignificant PPM.[82] However, Jamieson et al. found no difference in mortality to 15 years between groups of PPM severity although pulmonary hypertension influenced mortality by severity of PPM.[83]

PPM in the mitral position can be equated to residual mitral stenosis with similar consequences (i.e. persistence of abnormally high mitral gradients and increased left atrial and pulmonary arterial pressure). Pulmonary pressures are higher in patients with severe PPM.[84] Unfortunately, when PPM after mitral valve replacement is predicted on the basis of projected EOA, options are limited. No alternative techniques exist to implant a larger prosthesis and durability of homografts and stentless valves are not optimal.[69,82]

Management of PPM is directed at avoiding severe mismatch in patients undergoing aortic and mitral valve replacement and avoiding moderate mismatch in patients with pre-existing LV dysfunction and/or severe LV hypertrophy and in patients engaging in regular and/or intense physical activity (especially younger patients).[1]

If the projected indexed EOA predicts significant PPM in the aortic position, an alternate prosthesis or aortic root enlargement provide options. Several approaches (Figs 11A and B) for posterior aortic root enlargement have been described and both involve suturing a pericardial patch to the posterior



FIGURES 11A AND B: In posterior root enlargement techniques, the aorta is excised posteriorly across the aortic annulus to the anterior leaflet of the mitral valve. The defect is closed with autologous or bovine pericardium is placed as a patch. The Nicks enlargement (A) involves extension of an oblique aortotomy and the Manouguian enlargement (B) involves extension of a transverse aortotomy. The valve prosthesis is sutured in a supra-annular position (*Source:* Dhareshwar J, Sundt TM, Dearani JA, et al. Aortic root enlargement: what are the operative risks? J Thorac Cardiovasc Surg. 2007;134:916-24)

root to allow enlargement of the annulus without compromising the coronary ostia.[85] Enlargement before valve replacement is associated with a lower postoperative gradient, but the survival benefit is uncertain.[86] In addition to aortic root enlargement, alternate procedures include a supra-annular stented bioprosthesis, stentless bioprosthesis, newer generation mechanical valve, homograft or the Ross operation.[69] A lower occurrence of PPM in stentless valves is reported in studies comparing them with stented porcine valves. However, when comparing stentless valves with stented pericardial valves, studies are mixed with either reduced or equivalent rates of PPM with stentless valves.[42]

LONG-TERM MANAGEMENT

ANTITHROMBOTIC THERAPY

General Management

Mechanical valves are prone to thrombus formation and all such patients require warfarin therapy.[2] For example, lack of prophylaxis in patients with St Jude Medical bileaflet valves is associated with a risk of embolism or thrombosis in the aortic position of 12% per year and 22% per year in the mitral position.[87] However, even with warfarin, the thromboembolic risk is 1–2% per year.[2] In patients with bioprosthetic valves and in sinus rhythm, the risk is 0.7% per year.

Mitral prostheses have increased risk of thromboembolic events compared to aortic valves. In addition, the risk of a thromboembolic event is higher in the initial three months of implantation (before the valve is endothelialized) compared to later. Risk factors associated with an increased risk of thromboembolism include atrial fibrillation, LV dysfunction, left atrial dilation, previous history of thromboembolism and hypercoagulable condition.[2]

Current ACC/AHA guidelines recommend a relatively low goal INR of 2.0–3.0 for bileaflet or Medtronic-Hall single leaflet aortic valve prostheses, when no risk factors, for thromboembolism are present.[2] During the initial 3 months however, a goal INR of 2.5–3.5 can be considered (due to the increased risk of thromboembolism early after valve replacement). A goal INR of 2.5–3.5 is recommended if patients with these valves have risk factors associated with increased thromboembolism. In addition, the goal INR of 2.5–3.5 is recommended in patients with Starr-Edwards cage-ball valves, single-leaflet valves (other than Medtronic-Hall) in the aortic position without risk factors and mechanical valves in the mitral position[2] (Flow Chart 2).

In those patients with a high-risk of thromboembolism and in whom aspirin cannot be used, there is a suggestion of benefit for INR goals of 3.5–4.5 or to add clopidogrel to warfarin therapy. However, the higher INR goal is associated with an increased risk of bleeding.[2]

Aspirin is recommended in a dose of 75–100 mg a day as an addition to warfarin in patients with mechanical heart valves.[2] Turpie et al. demonstrated that the addition of 100 mg of aspirin to warfarin reduced death and embolism in patients with mechanical valves (14.3% vs 2.8%), although bleeding risk was increased.[88]

In patients with aortic or mitral valve bioprostheses, warfarin is indicated to achieve a goal INR of 2.0–3.0 if there are risk factors for increased risk of thromboembolism. In the absence of risk factors, warfarin for the initial 3 months after surgery is considered "reasonable" by current guidelines, although most centers use only aspirin in the aortic position. In the absence of risk factors for thromboembolism, aspirin 75–100 mg is recommended chronically.[2]

Self-management of oral anticoagulation therapy improves survival and lowers thromboembolic risk, presumed related to a reduction in INR variability.[89,90]

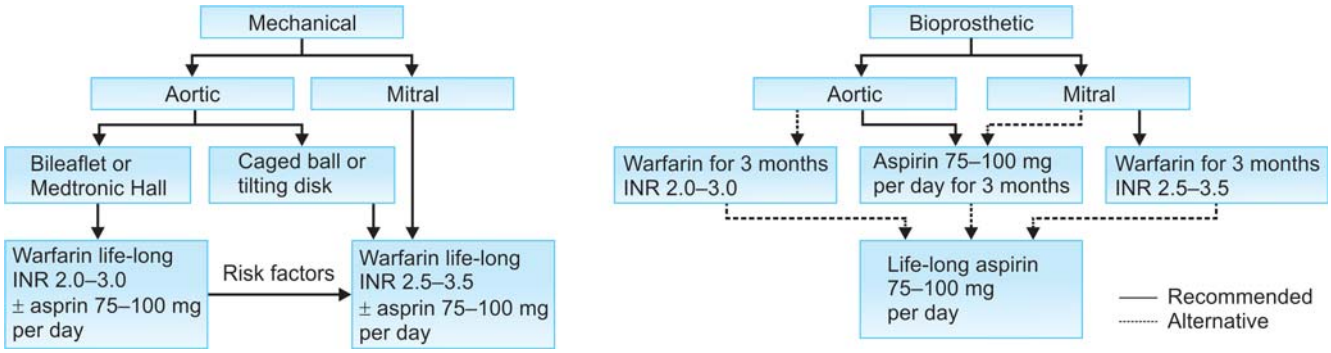
Guidelines for the management of excessive anticoagulation are discussed in the section on long-term complications.

Pregnancy

Warfarin use during pregnancy is associated with a 20–50% rate of spontaneous abortion in the first trimester (i.e. the initial 6–12 weeks of pregnancy). The incidence of a characteristic fetal embryopathy when the fetus goes to term is approximately 4–10%.[2,74] The embryopathy is characterized by nasal hypoplasia and/or stippled epiphyses.[91] Limb hypoplasia has been reported in up to one third of cases. The embryopathy can be prevented if warfarin is not taken during the first trimester and fetal complications are less common with warfarin doses under 5 mg per day.[2] Frequent pregnancy tests are recommended in women taking warfarin who are attempting pregnancy.[2,91]

Three anticoagulation regimens have been proposed in the ACC/AHA Valvular Heart Disease Guidelines for use in pregnant patients with mechanical valves as an alternative to warfarin:[2]

FLOW CHART 2: Algorithm for antithrombotic therapy for prosthetic heart valves. Risk factors: atrial fibrillation, previous thromboembolism, left ventricular ejection fraction < 35% and hypercoagulable state



(*Source:* Modified from Lancet[12])

- Continuous, intravenous dose-adjusted unfractionated heparin (UFH). While the fetal risk is lower compared to the other regimens, the maternal risks of prosthetic valve thrombosis, systemic embolization, infection, osteoporosis and heparin-induced thrombocytopenia are relatively higher.
- Subcutaneous dose-adjusted unfractionated heparin with the PTT at least twice control. Heparin is initiated at 17,500 to 20,000 U q 12 hours with PTT check at 6 hours.
- Subcutaneous dose-adjusted low molecular weight heparin (LMWH) administered twice daily to maintain the anti-Xa level between 0.7 and 1.2 U per ml 4 hours after administration.

The suggested dosing regimens are:

- Either LMWH or UFH between 6 and 12 weeks and close to term only, with warfarin at other times
- Aggressive, dose-adjusted UFH throughout pregnancy
- Aggressive, dose-adjusted LMWH throughout pregnancy

Besides, the addition of low-dose aspirin (i.e. 75–100 mg per day) in the second and third trimesters of pregnancy is reasonable.[2]

For women with high-risk mechanical valves (e.g. older generation valve in the mitral position or history of thromboembolism), the American College of Chest Physicians Practice Guidelines suggest the use of oral anticoagulants over heparin, in an effort to avoid maternal complications, recognizing the potential risk of fetal complications.[91] During warfarin use in pregnancy, the INR goal is 3.0 (range 2.5–3.5).

Warfarin is relatively safe during the second and third trimesters of pregnancy, but starting 2–3 weeks before planned delivery, warfarin should be discontinued and continuous intravenous UFH given. It is reasonable to resume UFH 4–6 hours after delivery and begin oral warfarin in the absence of significant bleeding.[2]

Noncardiac Surgery

Bridging therapy with intravenous anticoagulation may be needed in patients with mechanical valves who require interruption of warfarin therapy for noncardiac surgery, invasive procedures, or dental care. However, antithrombotic therapy should not be stopped for procedures in which bleeding would be unlikely or inconsequential.[2]

In patients at low-risk of thrombosis, defined as those with a bileaflet mechanical AVR with no risk factors for increased risk of thromboembolism (i.e. atrial fibrillation, previous thromboembolism, LV dysfunction, hypercoagulable conditions, older generation thrombogenic valves, mechanical tricuspid valves or more than 1 mechanical valve), it is recommended that warfarin be stopped 48–72 hours before the procedure (so the INR falls to less than 1.5) and restarted within 24 hours after the procedure since intravenous heparin is usually unnecessary.[2]

In patients at high-risk of thrombosis (defined as those with any mechanical mitral or tricuspid valve replacement or a mechanical AVR with any risk factor for increased risk of thromboembolism), therapeutic doses of intravenous UFH should be started when the INR falls below 2.0 (typically 48 hours before surgery), stopped 4–6 hours before the procedure, restarted as early after surgery as bleeding stability allows, and continued (with a goal PTT of 55–70 seconds) until the INR is again therapeutic with warfarin therapy.[2]

The use of LMWH in the perioperative period is associated with cost savings related to reduced in patient days. However, concerns about the use of LMWH in patients with mechanical valves persist and according to the FDA package insert: "The use of Lovenox has not adequately been studied for thromboprophylaxis in patients with mechanical prosthetic heart valves". Close monitoring with anti-Xa assays is therefore recommended when LMWH is used in patients with mechanical valves.[2]

In the event of emergency surgery, it is reasonable to give fresh frozen plasma to patients with mechanical valves who require interruption of warfarin. Fresh frozen plasma is preferable to high dose vitamin K which may create a hypercoagulable state.[2]

Prior to cardiac catheterization, in patients taking warfarin, the drug is stopped approximately 72 hours before the procedure to achieve an INR under 1.5 (unless trans-septal puncture or LV puncture is planned, then the goal INR is < 1.2). Following catheterization, warfarin is restarted as soon as the procedure is completed. However, if the patient has more than one risk factor for thromboembolism, heparin is started when the INR is under 2.0. Following catheterization, warfarin is restarted with an overlap of 3–5 days until the desired INR goal is achieved.[2]

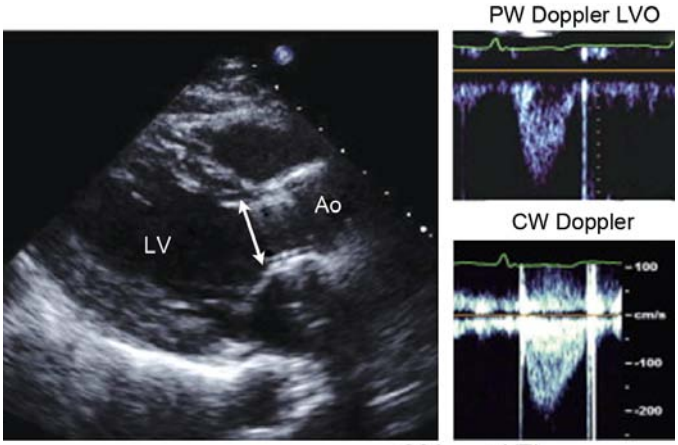
ECHOCARDIOGRAPHY FOLLOW-UP

After valve surgery, current guidelines recommend an echo Doppler at the first postoperative visit (i.e. 2–4 weeks after discharge) if a baseline study was not obtained during hospitalization. The echocardiogram in addition to an interval or complete history and physical examination indicates laboratory evaluation (e.g. complete blood count, BUN, creatinine, electrolytes, LDH or INR). Routine visits annually are recommended, but with a repeat echocardiogram only if there is a change in clinical status (e.g. new murmur, concern for prosthetic valve or LV dysfunction). However, an annual echocardiogram may be considered in patients with a bioprosthetic valve after the first 5 years.[2]

Echo parameters of interest include leaflet morphology and mobility, as well as measurement of transprosthetic gradients and EOA, estimation of the degree of regurgitation, evaluation of LV size and function and calculation of pulmonary arterial systolic pressure.[92] Transesophageal echocardiography can provide improved image quality and detection of cusp calcification and thickening, valvular vegetation, thrombus or pannus, and reduced leaflet mobility.[1,92] Mechanical valves are limited by reverberations and "shadowing" of the prosthesis. In this case, fluoroscopy may be preferred for leaflet motion assessment.

Quantitative Doppler parameters are useful in determining the intrinsic gradient of the valve, providing a comparison for subsequent studies[92] (Table 5). They include:

- Gradients, calculated by the Bernoulli equation. Jets may be eccentric in mechanical valves, and therefore technically difficult to measure.
- EOA, calculated by continuity equation (Fig. 12). For aortic prostheses, this includes velocity measurements in the LV outflow tract and across the prosthesis, as well as the LV outflow tract diameter. For mitral prostheses, the continuity equation calculation uses stroke volume, also estimated from



$$\text{Effective orifice area} = \frac{CSA_{LVO} \times VTI_{LVO}}{VTI_{JET}}$$

FIGURE 12: Derivation of EOA of a prosthetic valve in the aortic position by Doppler echocardiography. The diameter of the LV outflow tract, just below the insertion of the prosthetic aortic valve, is shown. Once the diameter has been measured, cross-sectional area of the LV outflow tract is calculated (CSA_{LVOT}) is calculated. Pulsed Doppler in LV outflow tract from the apical window is combined with the continuous wave Doppler recording to complete the data acquisition for EOA calculation. (*Source:* Zoghbi W, Chambers JB, Dumesnil JG, et al. Recommendations for evaluation of prosthetic valves with echocardiography and Doppler ultrasound. J AM Soc Echocardiogr. 2009;22:975-1014)

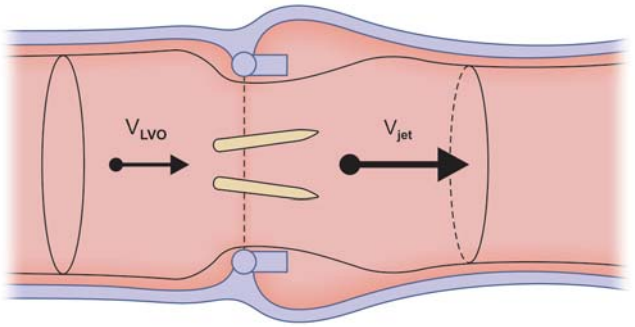


FIGURE 13: Schematic representation of the concept of the Doppler velocity Index (DVI). Velocity across the prosthesis is accelerated through the jet from the left ventricular outflow (LVO) tract. DVI is the ratio of the velocity in the LVO tract (V_{LVO}) to the velocity of the jet (V_{jet}) calculation (*Source:* Zoghbi W, Chambers JB, Dumesnil JG, et al. Recommendations for evaluation of prosthetic valves with echocardiography and Doppler ultrasound. J AM Soc Echocardiogr. 2009;22:975-1014)

the LVOT velocity and diameter, in addition to the velocity measurement across the mitral prosthesis.

- Doppler velocity index, calculated from the ratio: $Velocity_{LVOT}/Velocity_{Prosthetic\ Valve}$ (Fig. 13). This is a dimensionless index, useful in screening for obstruction when LV outflow tract measurements cannot be obtained.[1,92]

When an elevated gradient is obtained, the differential diagnosis is Flow Chart 3:

- Pathological valve obstruction
- LV outflow tract obstruction
- PPM
- High flow state
- Localized high gradient in presence of bileaflet mechanical valve

PPM is suspected if the reference index EOA is low (see previous section in this chapter on PPM for criteria used to define moderate and severe PPM). If there is no significant PPM and the DVI is normal (due to an elevated LVOT velocity), then there is probably a high flow state or LV outflow obstruction. If the measured EOA is less than the reference EOA, then pathological valve obstruction (Figs 14 and 15) or a localized high gradient associated with a bileaflet valve are suspect and fluoroscopy may help in the distinction by determining adequacy of leaflet motion. In the presence of a bileaflet mechanical valve,

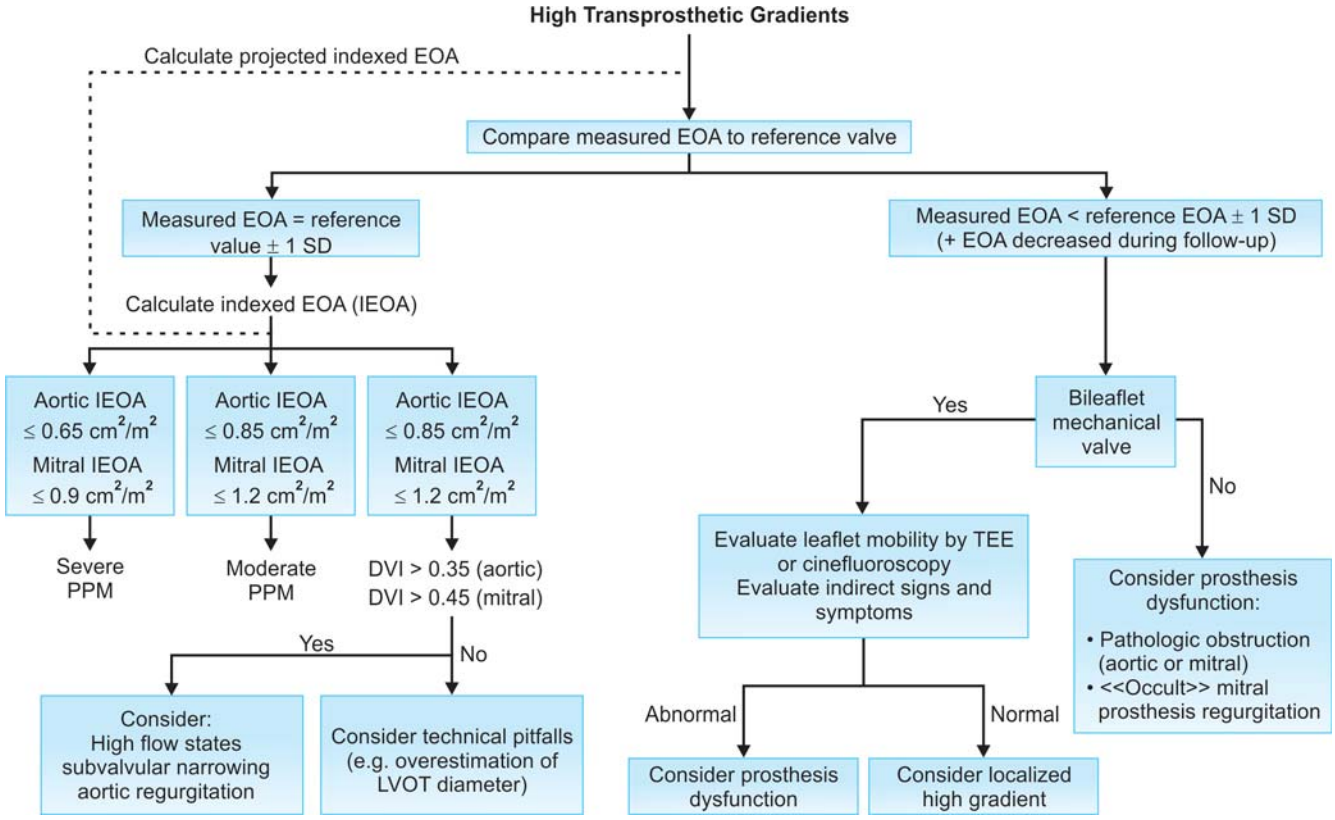
TABLE 5

Parameters for evaluation of the severity of prosthetic aortic valve regurgitation

Parameter	*Mild*	*Moderate*	*Severe*
Valve structure and motion	Usually normal	Abnormal*	Abnormal*
LV size	Normal	Normal or mildly dilated	Dilated
Color Doppler jet width of central jets (% LVOT diameter)	Narrow (< 25%)	Intermediate (26–64%)	Large (≥ 65%)
Jet density of CW Doppler spectrum	Incomplete or faint	Dense	Dense
Jet deceleration rate (PHT, ms) by CW Doppler	Slow (> 500)	Variable (200–500)	Steep (< 200)
LVOT flow vs pulmonary flow by PW Doppler	Slightly increased	Intermediate	Greatly increased
Diastolic flow reversal in the descending aorta by PW Doppler	Absent or brief early diastolic	Intermediate	Prominent, holodiastolic
Diastolic flow reversal in the descending aorta by PW Doppler	Absent or brief early diastolic	Intermediate	Prominent, holodiastolic
Regurgitant volume (ml/beat) by Doppler	< 30	30–59	> 60
Regurgitant fraction (%) by Doppler	< 30	30–50	> 50

*Abnormal: Dehiscence or rocking, immobile mechanical occluder, thickened or prolapse of bioprosthetic leaflets
Abbreviations: PHT: Pressure half-time; LVOT: Left ventricular outflow tract
(*Source:* Zoghbi et al[92])

FLOW CHART 3: Algorithm for the interpretation of high transprosthetic gradients. IEOA: indexed effective orifice area



(*Source:* Pibarot P, Dumesnil JG. Prosthetic heart valves: selection of the optimal prosthesis and long-term management. Circulation. 2009;119: 1034-48)

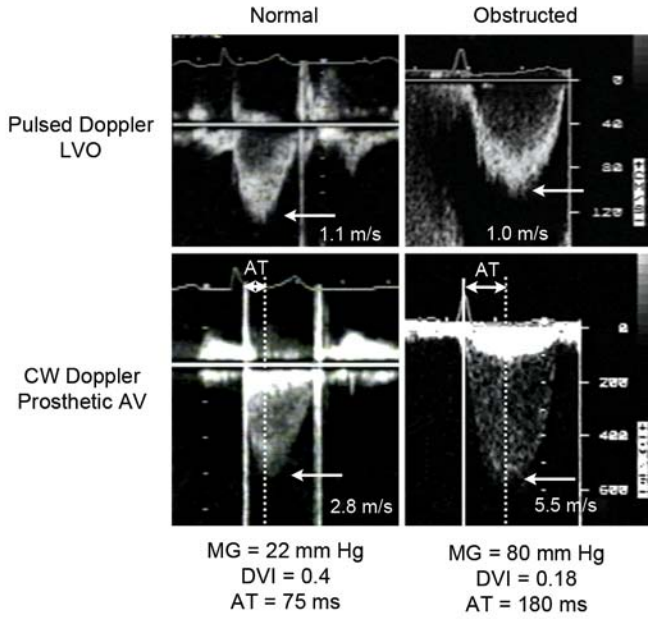


FIGURE 14: Doppler velocity recordings of a normal and an obstructed prosthetic valve in the aortic position. With obstruction, the velocity of the jet is increased along with changes in the contour of the jet velocity to that of a parabolic, late peaking profile. The acceleration time (AT) and the mean gradient are increased and the Doppler velocity index (DVI) is decreased with obstruction (*Source:* Zoghbi W, Chambers JB, Dumesnil JG, et al. Recommendations for evaluation of prosthetic valves with echocardiography and Doppler ultrasound. J AM Soc Echocardiogr. 2009;22:975-1014)

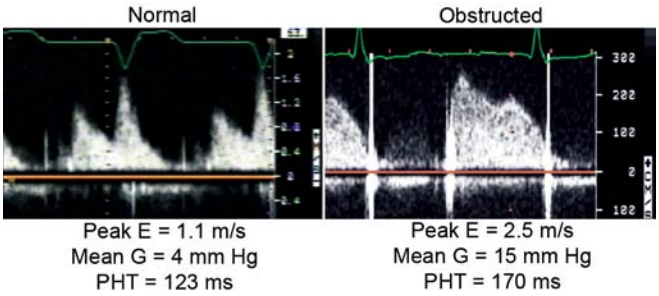
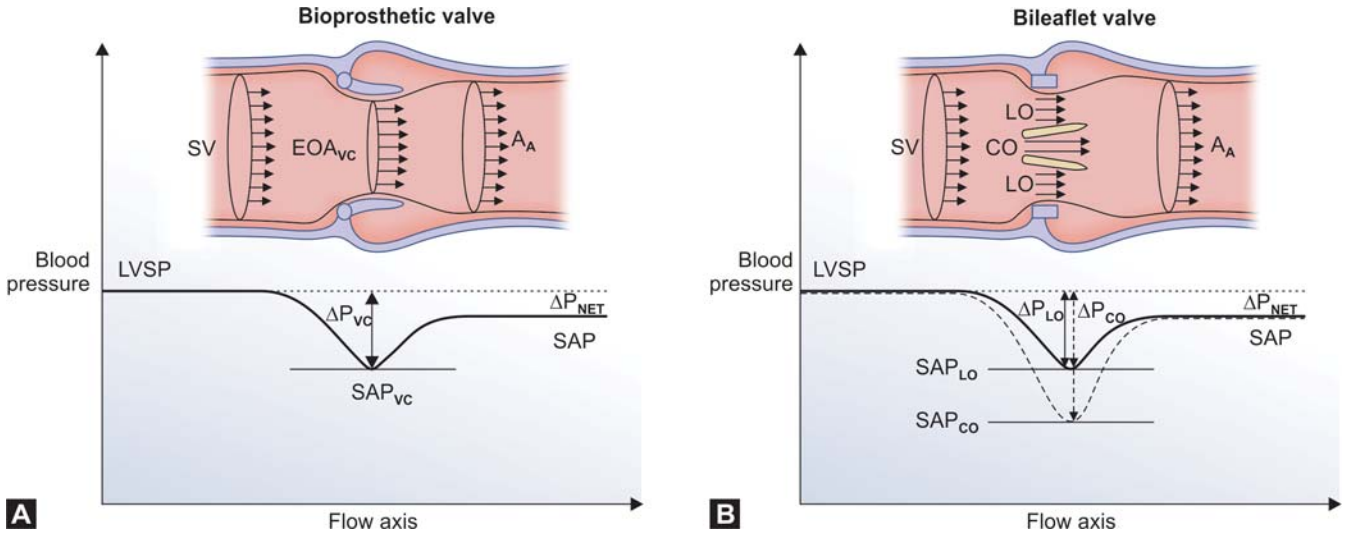


FIGURE 15: Doppler velocity recordings of a normal and an obstructed prosthetic valve in the mitral position. The peak E (early) velocity, mean G (gradient) and PHT (pressure half-time) are increased with obstruction (*Source:* Zoghbi W, Chambers JB, Dumesnil JG, et al. Recommendations for evaluation of prosthetic valves with echocardiography and Doppler ultrasound. J AM Soc Echocardiogr. 2009;22:975-1014)

the smaller central orifice may give rise to a high velocity jet that corresponds to a localized pressure drop that is largely recovered once the central flow reunites with flows originating from the two lateral orifices[92] (Figs 16A and B). A continuous wave Doppler recording includes this high-velocity jet, which leads to overestimation of gradients and underestimation of EOA compared to hemodynamics obtained at cardiac catheterization. Finally, the jet contour from the Doppler spectral recording may be helpful in discriminating prosthesis stenosis from other causes of elevated gradients since an acceleration time greater than 100 millisecond suggests stenosis[92] (Figs 17 and 18).

Pathological regurgitation may be central (i.e. transvalvular) or paravalvular. In general, the criteria for grading severity of regurgitant lesions in prosthetic valves (Tables 6 and 7) are similar to native valves largely related to the paucity of studies in patients with prosthetic valves.[92] In the presence of mitral



FIGURES 16A AND B: Schematic representation of velocity and pressure changes from the LV outflow tract to the ascending aorta in the presence of a stented bioprosthetic valve (A) and a bileaflet mechanical valve (B), illustrating the phenomenon of pressure recovery. Due to pressure recovery, velocities are lower and systolic arterial pressure is higher at the distal aorta than at the level of the vena contracta obstruction. (*Source:* Zoghbi W, Chambers JB, Dumesnil JG, et al. Recommendations for evaluation of prosthetic valves with echocardiography and Doppler ultrasound. J AM Soc Echocardiogr. 2009;22:975-1014)

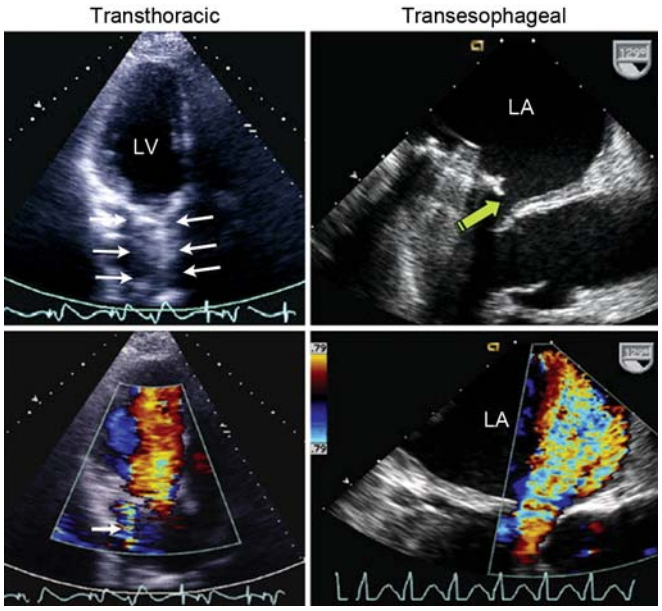


FIGURE 17: Transthoracic (TTE) and transesophageal (TEE) echocardiographic and Doppler images in a patient with severe paravalvular mitral regurgitation. On the TTE image (upper left), there is shadowing (arrows) of the left atrium from the mechanical prosthesis so that the severity of mitral regurgitation (single arrow) cannot be assessed by color Doppler imaging (lower right). The extent of valve dehiscence is shown by the green arrow on the TEE (upper right) as well as severity of regurgitation by color Doppler (lower right). (*Source:* Zoghbi W, Chambers JB, Dumesnil JG, et al. Recommendations for evaluation of prosthetic valves with echocardiography and Doppler ultrasound. J AM Soc Echocardiogr. 2009;22:975-1014)

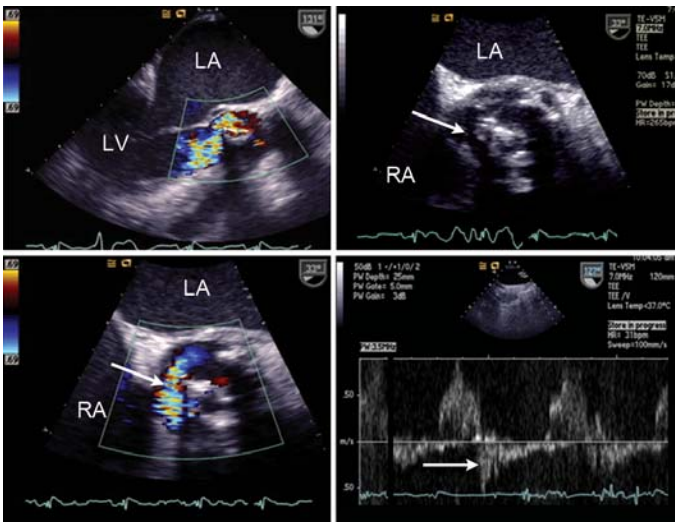


FIGURE 18: Transesophageal images of a patient with perivalvular significant aortic regurgitation demonstrating (arrow) the extent of dehiscence and regurgitation in cross-section (upper right) and diastolic flow reversal (arrow) in the descending aorta (lower right). Aortic regurgitation is demonstrated by color Doppler (left upper and lower). (*Source:* Zoghbi W, Chambers JB, Dumesnil JG, et al. Recommendations for evaluation of prosthetic valves with echocardiography and Doppler ultrasound. J AM Soc Echocardiogr. 2009;22:975-1014)

regurgitation, the largest diameter of the regurgitant jet emerging through the prosthesis has optimal diagnostic accuracy in comparison with other Doppler variables[93] (Fig. 19). However, care is needed to separate physiological from pathological regurgitation since mechanical valves have normal leakage backflow to prevent blood stasis and thrombus formation (Fig. 20). Two types of "physiological" regurgitation may be seen: (1) a closing volume (i.e. displacement of blood caused by the motion of the occluder) and (2) true trivial or mild regurgitation at the hinges of the occluder. Single tilting disk valves have both types of regurgitation, but the patterns may vary (e.g. Bjork-Shiley valves have small jets just inside the sewing ring where the closed disk meets the housing while Medtronic-Hall valves have a large jet through the central hole in the disk). Bileaflet valves typically have multiple jets located inside the sewing ring, and centrally, where the closed bileaflets meet each other.[92] The distinction between paravalvular and transvalvular regurgitation may require transesophageal echocardiography.

TABLE 6

Parameters for evaluation of the severity of prosthetic mitral valve regurgitation

Parameter	*Mild*	*Moderate*	*Severe*
Valve structure and motion	Usually normal	Abnormal*	Abnormal*
LV size	Normal	Normal or dilated	Usually dilated
Jet area by color Doppler (cm^2)	< 4 sq cm or < 20% of LA area	Variable	> 8 sq cm or > 40% of LA area (if central jet)
Flow convergence (at Nyquist limit of 40 cm/s)	None or minimal i.e. (radius < 4 mm)	Intermediate	Large (i.e. radius > 9 mm)
MR Jet density on CW Doppler	Incomplete or faint	Dense	Dense
Jet contour on CW Doppler	Parabolic	Usually parabolic	Early peaking, triangular
Pulmonary venous flow	Systolic dominance	Systolic blunting	Systolic flow reversal
Vena Contracta width by color Doppler (cm)	< 0.3	0.3–0.59	≥ 0.6
Regurgitant volume (ml/beat) by Doppler	< 30	30–59	≥ 60
Regurgitant fraction (%) by Doppler	< 30	30–49	≥ 50
Effective regurgitant orifice area (cm^2)	< 0.20	0.20–0.49	≥ 0.50

*Abnormal: Dehiscence or rocking, immobile mechanical occluder, thickened or prolapse of bioprosthetic leaflets
(*Source:* Zoghbi et al[92])

TABLE 7

Doppler parameters of prosthetic aortic and mitral valve stenosis

Parameter	*Normal*	*Possible stenosis*	*Suggests significant stenosis*
Aortic valve			
Peak velocity (m/sec)	< 3	3–4	> 4
Mean gradient (mm Hg)	< 20	20–35	> 35
DVI	≥ 0.30	0.25–0.29	< 0.25
EOA (cm^2)	> 1.2	0.8–1.2	< 0.8
Jet contour	Triangular, early peaking	Triangular to intermediate	Rounded, symmetrical contour
AT (ms)	< 80	80–100	> 100
Mitral valve			
Peak velocity (m/sec)	< 1.9	1.9–2.5	≥ 2.5
Mean gradient (mm Hg)	≤ 5	6–10	> 10
EOA (cm^2)	> 2.0	1.0–2.0	< 1.0
PHT (ms)	< 130	130–200	> 200

Source: Zoghbi et al.[92]

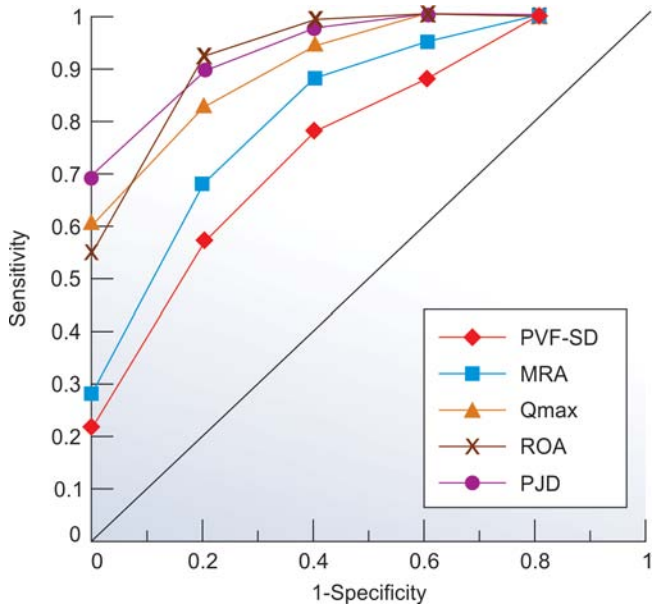


FIGURE 19: Comparison of the receiver operating characteristic curves obtained for transesophageal echo Doppler variables in the prediction of angiographically significant prosthetic mitral regurgitation. Proximal jet diameter (PJD) had optimal accuracy compared to PVF-S/D (pulmonary vein flow-systolic/diastolic), MRA (mitral regurgitant area), Qmax (maximum instantaneous regurgitant flow), ROA (regurgitant orifice area). (*Source:* Vitarelli A, Conde Y, Cimino E, et al. Assessment of severity of mechanical prosthetic mitral regurgitation by transesophageal echocardiography. Heart. 2004;90:539-44)

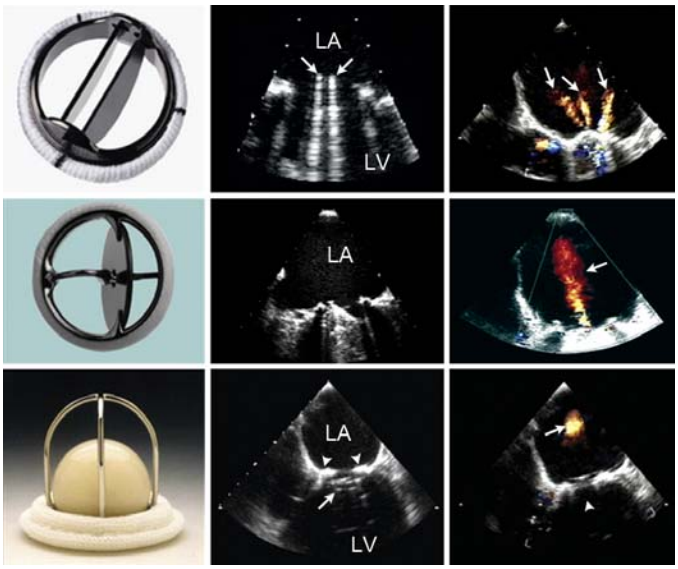


FIGURE 20: Examples of bileaflet (top row), single leaflet Medtronic-Hall (middle row) and caged ball mechanical valves and their transesophageal color Doppler echo characteristics in the mitral position in diastole (middle column) and in systole (right column). The arrows in diastole point to the occluder mechanism of the valve and in systole to the characteristic physiologic regurgitation observed (*Source:* Zogbhi W, Chambers JB, Dumesnil JG, et al. Recommendations for evaluation of prosthetic valves with echocardiography and Doppler ultrasound. J AM Soc Echocardiogr. 2009;22:975-1014)

LONG-TERM COMPLICATIONS

THROMBOEMBOLIC AND BLEEDING COMPLICATIONS

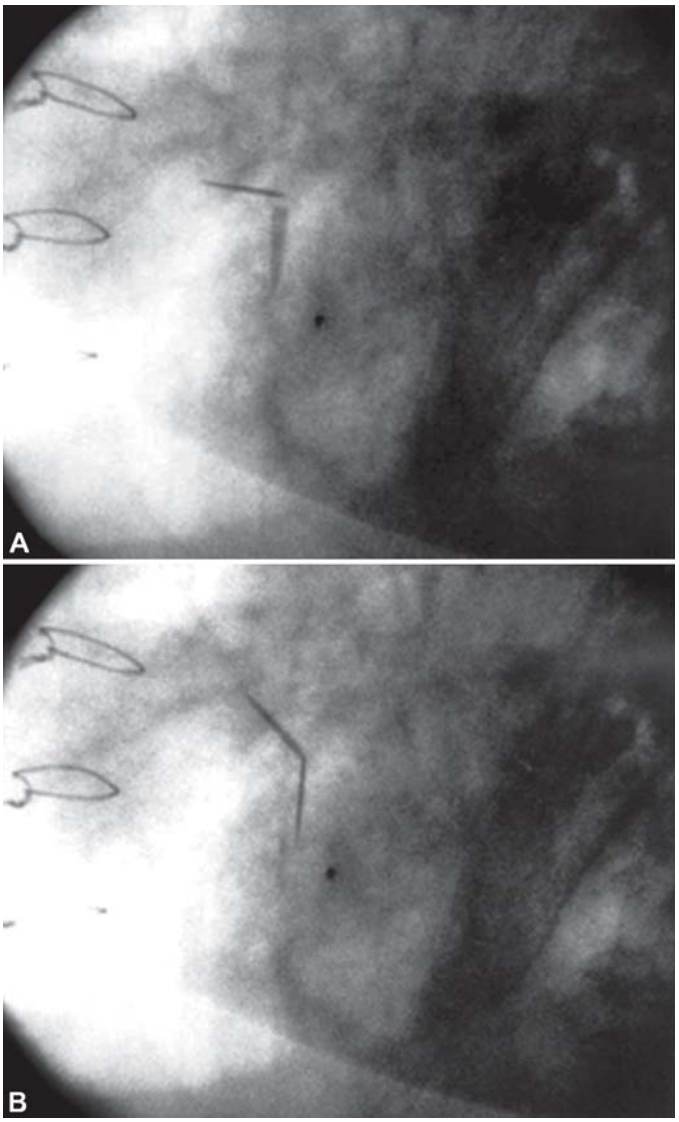
When a patient has a systemic embolic event, the adequacy of anticoagulation control should be assessed. If inadequate, therapy is adjusted to maintain therapeutic goals. If anticoagulation is adequate, the dosage of antithrombotic therapy should be increased, when clinically safe, as follows:[2]

- If the patient is not taking aspirin, add aspirin 75–100 mg per day.
- If the patient is taking aspirin alone, the aspirin dose may need to be increased to 325 mg per day, clopidogrel 75 mg per day added, and/or warfarin added.
- If current warfarin INR goal is 2.0–3.0, then increase the warfarin dose to achieve INR goal of 2.5–3.5.
- If current warfarin INR goal is 2.5–3.5, then increase the warfarin dose to achieve INR goal of 3.5–4.5.
- If the patient is taking warfarin plus aspirin 75–100 mg per day, the aspirin dose may also need to be increased to 325 mg per day if the higher dose of warfarin is not achieving the desired clinical result.

More aggressive goals for anticoagulation are expected with associated risk of increased bleeding. Besides, in the presence of recent cerebral infarction, anticoagulation may need to be held to avoid hemorrhagic transformation.

Prosthetic Valve Thrombosis

Obstruction of a prosthetic valve may be caused by thrombus, pannus ingrowth or a combination of both.[2] Prosthetic valve thrombosis has an incidence of 0.3–1.3% per patient-year with mechanical valves, but can occur early postoperative after bioprosthetic valves as well, usually in the early postoperative period.[94]



FIGURES 21A AND B: Cinefluoroscopy showing impaired motion of the two leaflets (A and B) of a thrombosed bileaflet mechanical mitral valve. (*Source:* Roudaut R, Serri K, Lafitte S. Thrombosis of prosthetic heart valves: diagnosis and therapeutic considerations. Heart. 2007;93:137-42)

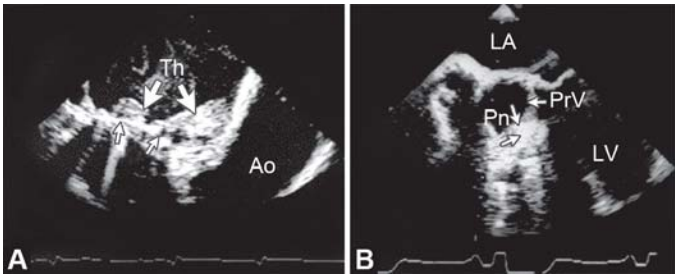
When prosthetic valve obstruction is suspected, transthoracic Doppler echocardiography is indicated to assess the hemodynamic severity of the obstruction. Transesophageal echocardiography and/or fluoroscopy may be useful to assess valve motion and/or clot burden.[1,2,94,95] In the presence of obstruction, fluoroscopy demonstrates restricted leaflet motion, which may be due to thrombus or pannus[94] (Figs 21A and B). The TEE and CT may be helpful in distinguishing pannus ingrowth from thrombus[96,97] (Figs 22A and B). Increased high-intensity transient signal due to emboli from thrombus may be detected by transcranial Doppler.[98] Clinical history may be helpful in distinguishing thrombus from pannus ingrowth. Symptoms of obstruction are more typically gradual with pannus ingrowth[96] (Table 8). The etiology of obstruction is more likely thrombotic if anticoagulation is interrupted or subtherapeutic.[2]

TABLE 8

Recommendations for managing elevated INRs or bleeding in patients receiving warfarin: Clinical practice guidelines from the American College of Chest Physicians

INR more than therapeutic range but < 5.0; no significant bleeding	Lower dose or omit dose; monitor more frequently and resume at lower dose when INR therapeutic; if only minimally above therapeutic range, no dose reduction may be required.
INR ≥ 5.0, but < 9.0; no significant bleeding	Omit next one or two doses, monitor more frequently, and resume at an appropriately adjusted dose when INR in therapeutic range. Alternatively, omit dose and give vitamin K (1–2.5 mg po), particularly if at increased risk of bleeding. If more rapid reversal is required because the patient requires urgent surgery, vitamin K (≤ 5 mg po) can be given with the expectation that a reduction of the INR will occur in 24 hr. If the INR is still high, additional vitamin K (1–2 mg po) can be given.
INR ≥ 9.0; no significant bleeding	Hold warfarin therapy and give higher dose of vitamin K (2.5–5 mg po) with the expectation that the INR will be reduced substantially in 24–48 hr. Monitor more frequently and use additional vitamin K if necessary. Resume therapy at an appropriately adjusted dose when INR is therapeutic.
Serious bleeding at any elevation of INR	Hold warfarin therapy and give vitamin K (10 mg by slow IV infusion), supplemented with FFP, PCC, or rVIIa, depending on the urgency of the situation; vitamin K can be repeated q12h.
Life-threatening bleeding	Hold warfarin therapy and give FFP, PCC, or rVIIa supplemented with vitamin K (10 mg by slow IV infusion). Repeat, if necessary, depending on INR.
Administration of vitamin K	In patients with mild to moderately elevated INRs without major bleeding, give vitamin K orally rather than subcutaneously.

(*Source:* Salem DN et al[87])



FIGURES 22A AND B: Transesophageal echocardiogram showing: (A) A thrombus (large arrows) visualized as a soft mass on the atrial side of a bileaflet mitral prosthetic valve. There is extension of the thrombus to the left atrial wall. Small arrows indicate the level of the prosthesis. (B) A pannus (large arrows) visualized as a dense mass on a tilting-disk aortic prosthesis. Small arrow indicates the valve ring (Abbreviations: Ao: Aorta; LA: Left atrium; LV: Left ventricle; Pn: Pannus; PrV: Prosthetic valve; Th: Thrombus. (*Source:* Barbetseas J, Nagueh SF, Pitsavos C, et al. Differentiating thrombus from pannus formation in obstructed mechanical prosthetic valves: an evaluation of clinical, transthoracic and transesophageal echocardiographic parameters. J Am Coll Cardiol. 1998;32:1410-7)

Recommendations for management have been provided by the ACC/AHA Guidelines on Valvular Heart Disease.[2] Emergency operation is reasonable for patients with a thrombosed left-sided prosthetic valve and NYHA functional class III–IV symptoms or a large clot burden. However, operative mortality approaches 15–20% with functional class IV patients.[1]

Thrombolytic therapy is an alternative to surgery in left-sided valve thrombosis, but there is a 12–15% risk of systemic embolism and a 5% risk of major bleeding. The repeat thrombosis rate is as high as 15–20%.[1] Mortality associated with fibrinolytic therapy is 6%.[99] Fibrinolytic therapy may be considered as a first-line therapy for patients with a thrombosed left-sided prosthetic valve, a small clot burden and NYHA functional class I–II symptoms, or if surgery is high-risk or not available for patients with NYHA functional class III–IV symptoms. In cases with a large clot burden (i.e. > 5–10 mm), fibrinolytic therapy may be considered for patients who have NYHA functional class II–IV symptoms if emergency surgery is high-risk or not available. However, fibrinolytic therapy is not effective if obstruction is due to pannus ingrowth.[2]

In the PRO-TEE Registry, 107 patients with prosthetic valve thrombosis, documented by TEE, were reported from 14 centers. The mitral valve was affected in 74%, the aortic in 12% and the tricuspid in 14%. Thrombolytic therapy resulted in return of the transvalvular gradient to normal range in 76% of obstructed valves and was similar among different valve and lytic agents. Independent predictors of successful thrombolysis were small size (i.e. < 0.8 cm^2), and lack of previous history of stroke.[100] Complications, including emboli and bleeding, occurred in 17.8%.

An algorithm for management was recently proposed by Pibarot and Dumesnil[1] (Flow Chart 4).

Fibrinolytic therapy is also reasonable for thrombosed right-sided prosthetic heart valves with NYHA functional class III–IV symptoms or a large clot burden.[2]

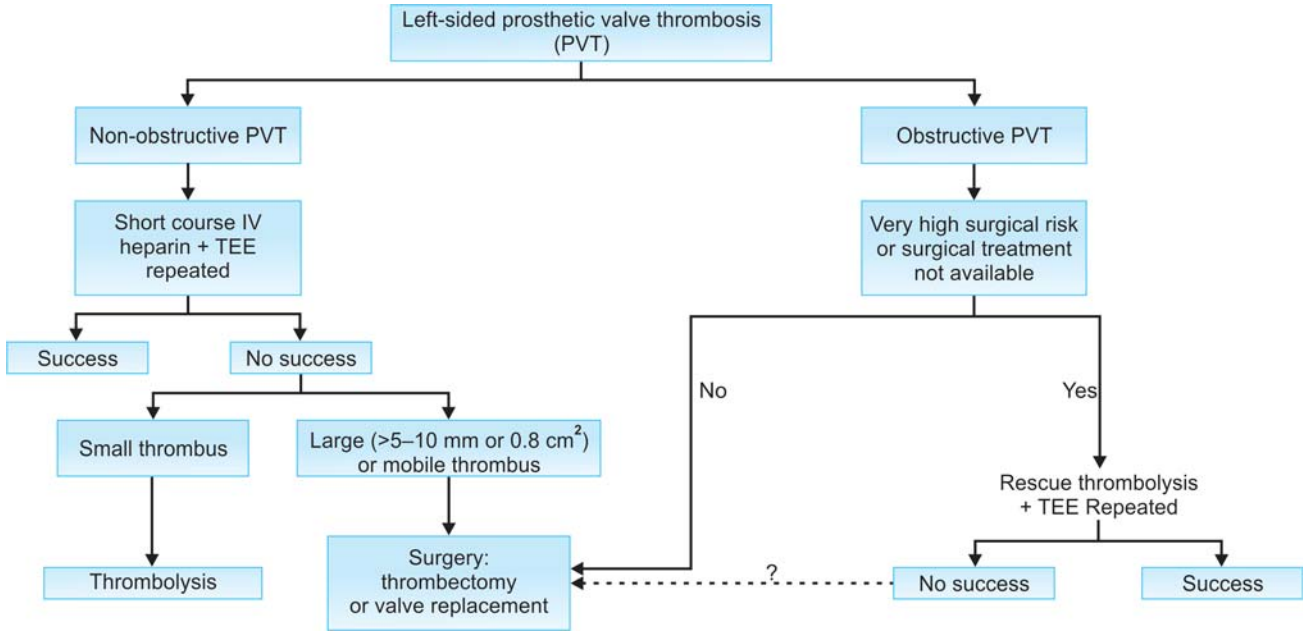
If fibrinolytic therapy is successful, it should be followed by intravenous UFH until warfarin achieves an INR of 3.0–4.0 for aortic prosthetic valves and 3.5–4.5 for mitral prosthetic valves. These patients should also receive aspirin.[2]

Intravenous UFH is an alternative to fibrinolytic therapy and may be considered for patients with a thrombosed valve who are in NYHA functional class I–II and have a small clot burden. A trial of continuous infusion fibrinolytic therapy may be helpful if the initial UFH trial is not successful.[2]

Bleeding Complications

The annual risk of bleeding in randomized trials is 1–3%[14,15] and is more common in mechanical valves and in patients over 65 years of age.[57] Bleeding is often due to excessive anticoagulation and can be managed by withholding warfarin and monitoring the level of anticoagulation with serial INR determinations.[1,87] Guidelines for managing bleeding complications are provided by the American College of Chest Physicians[87] (Table 9).

FLOW CHART 4: Algorithm for the management of patients with left-sided prosthetic valve thrombosis



(*Source:* Pibarot P, Dumesnil JG. Prosthetic heart valves: selection of the optimal prosthesis and long-term management. Circulation. 2009;119:1034-48)

TABLE 9

Differentiating thrombus from pannus formation (data from 24 obstructed valves in 23 patients)

	Thrombus	*Pannus*	*P*
Duration from implant to reoperation (days)	62	178	0.0006
Duration of symptoms to reoperation (days)	9	305	0.0006
Rate of adequate anticoagulation (%)	21	89	0.003
Aortic position (%)	21	70	0.035
Abnormal valve motion on TEE (%)	100	60	0.021
Length (cm)	2.8±2.5	1.2±0.04	0.038
Soft ultrasound density (%)	92	29	0.007
Videointensity (mass/prosthesis)	0.46±0.14	0.71±0.17	0.006

(*Source:* Barbetseas J et al[96])

STRUCTURAL VALVE DETERIORATION

Mechanical prostheses have excellent durability, and SVD is rare with contemporary valves.[1] The SVD after bioprosthetic valve replacement begins at about 5 years for mitral position and at about 8 years for aortic position.[57] The percentage of freedom from valvular deterioration and valve-related death decreases at a faster rate after 5 years compared with the first 5 years (i.e. there appears to be an almost exponential rate of decline over time). With conventional stented bioprostheses, the freedom from structural failure is 70–90% at 10 years and 50–80% at 15 years.[1] However, certain pericardial valves have improved durability compared to porcine valves.[40] Unfortunately, reoperation for bioprosthetic valve failure has a significantly higher mortality than the initial valve replacement.

Approximately three-quarters of porcine valve degenerative failures manifest as regurgitation, usually related to cusp tears in calcified cusps. Pure stenosis due to calcific cuspal stiffening and tears occur in 10–15% and perforations unrelated to calcification occur in about 10–15%. Calcification is a major contributor to bioprosthesis failure to such an extent that it is considered one of the predisposing causes of cusp tears.[101]

Premature deterioration of bioprostheses may be related to tissue fixation methods. Glutaraldehyde reduces antigenicity of heterografts; however, membrane damage may predispose to calcium crystal nucleation, contributing to subsequent calcium crystal growth. Additional mechanisms include atherosclerosis and immune rejection (due to residual antigens).[1] Host IgM/IgG antibodies enter the valve matrix, leading to macrophage deposition on the valve surface, followed by collagen breakdown and finally calcification.[101] Randomized trials are needed to address the potential benefits of interventions that may slow the progression of SVD.

Risk factors associated with bioprosthetic SVD include:[1]

- Younger patients, related to the heightened and more effective immune response in response to residual animal antigens. However, very early SVD of bioprostheses can

TABLE 10

Microbiology profiles of early (< 12 months) versus late (> 12 months) prosthetic valve endocarditis

Organism	*Early*	*Late*
Strep. Viridans	1%	18%*
Staph. Aureus	24%	17%
Methicilin-sensitive coagulase negative staphylococci	9%	12%
Methicilin-resistant coagulase negative staphylococci	28%	5%*
Negative cultures	16%	12%

*p < 0.05
(*Source:* Lopez J et al[106])

occur in elderly patients. Of 122 Metronic Mosaic porcine valves implanted from 2001 to 2005 in patients over 68 years, 4 developed severe stenosis, requiring replacement at 3, 14, 19, 44 months.[102]

- Mitral position which is related to higher closure pressure and increased stress on the valve.
- Renal insufficiency.
- Hyperparathyroidism.
- Hypertension: In the aortic position, SVD of bioprostheses may be related to stress from elevated diastolic BP.

Endocarditis

A diagnosis of infective endocarditis (IE) is based on the presence of either major or minor clinical criteria and is discussed in the chapter on IE. Refinements have been made to the Duke Criteria and include echocardiographic criteria. However, TEE is recommended in patients with prosthetic valve endocarditis (PVE).[103] The incidence of PVE is about 0.3–1.2% per patient-year and accounts for 10–30% of all cases of IE.[104]

Overall, *S. aureus* is the most common causative organism of PVE followed by coagulase-negative staphylococci, streptococci and enterococci.[105] However, the microbiology varies according to time of developing endocarditis after valve surgery. In patients with PVE within 1 year of surgery and no drug abuse, methicillin-resistant coagulase negative *staphylococcus* was the most common organism in a recent series,[106] followed by *S. aureus* (Table 10). For late PVE, Strep viridans and *S. aureus* were the most common organisms.[60] However, cultures may remain negative in both early and late PVE.[104]

In cases of early endocarditis, the infection usually involves the junction between the sewing ring and annulus, leading to perivalvular abscess, dehiscence and fistula. Surgery is frequently required in these patients. In later PVE, similar sites of infection occur in mechanical valves, but infection is more frequently located on the leaflets of patients with bioprostheses.[103]

Echocardiographic criteria for IE include: (1) an oscillating intracardiac mass on the valve, supporting structures (including implanted material) or in the path of regurgitant jet; (2) abscess, usually manifest as echolucency or echodensity in the valve ring (and they may infiltrate the septum and conduction systems or result in fistula formation); (3) new partial dehiscence of prostheses and (4) new valvular regurgitation.[2,103]

If the initial TEE is negative and clinical suspicion persists, a repeat TEE in 7–10 days may be advisable. In addition, repeat TEE may be useful when there is a change in clinical status during antibiotic therapy (e.g. progression in heart failure symptoms, change in murmur, new atrioventricular block or arrhythmia).[103]

Medical therapy alone is more likely to succeed in late PVE and non-staphylococcal infections. Antibiotic treatment regimens are summarized in Table 11. Specific details regarding antibiotic doses and dosing intervals are available elsewhere.[103]

Anticoagulation is controversial in mechanical valve endocarditis. Some authorities recommend continuation of therapy, but the general advice is to discontinue all anticoagulation in patients with *S. aureus* PVE who have experienced a recent central nervous system event for at least the first 2 weeks of antibiotic therapy, to prevent hemorrhagic transformation.[103]

In-hospital mortality of PVE is 23% in some series and predictors are old age, health-care associated infection, *S. aureus* infection and complicated endocarditis.[105]

Indications for cardiac surgery include heart failure, valve dehiscence, abscess formation and persistent bacteremia or recurrent emboli despite appropriate antibiotics.[2] Although mortality remains high, early surgery is recommended when the infection is due to *S. aureus* or if there is a complication of PVE. The choice of the optimal valve substitute is controversial. For the mitral position, mechanical or biological prostheses are usually placed. In the aortic position, homografts have been utilized. However, some authors believe that the success of homografts is related to the surgeon's ability to remove infected tissue.[59,104] A homograft valve may be preferred for reconstruction of the aortic root in the presence of abscess because it is easier to handle than conventional prostheses, and its anterior leaflet can be used to patch the defect created by resection of abscess.[104]

Endocarditis Prophylaxis

The ACC/AHA 2008 update on IE recommended antibiotic prophylaxis of endocarditis for dental procedures in prosthetic valve patients, that involve manipulation of either gingival tissue or the periapical region of teeth or perforation of oral mucosa. In addition, prophylaxis is no longer recommended for procedures that involve the respiratory tract, unless the procedure involves incision of the respiratory tract such as tonsillectomy and adenoidectomy. Prophylaxis is no longer recommended for GI or GU procedures, including diagnostic esophagogastroduodenoscopy or colonoscopy. However, in high-risk patients with infections of the GI or GU tract, it is reasonable to administer antibiotic therapy to prevent wound infection or sepsis. For high-risk patients undergoing elective cystoscopy or other urinary tract manipulation who have enterococcal urinary tract infection or colonization, antibiotic therapy to eradicate enterococci from the urine before the procedure is reasonable.[107] Similar guidelines for prophylaxis are recommended by the European Society of Cardiology.[108]

Regimens for prophylaxis are administered 30–60 minutes before the procedure and they include amoxicillin 2 gm PO. For penicillin allergic patients, the recommendation is to substitute cephalexin 2 gm (although cephalosporins are not recommended if allergy is manifest as anaphylaxis), clindamycin

TABLE 11

Antibiotic regimens for treating prosthetic valve endocarditis

1. Viridans group *streptococcus* and *streptococcus bovis*
   - A. Penicillin-susceptible strains (minimum inhibitory concentration ≤ 0.12 µg/ml)
     Aqueous crystalline penicillin G sodium
     or ceftriaxone x 6 weeks,
     with or without gentamicin x 2 weeks
     Vancomycin x 6 weeks (if unable to tolerate penicillin or ceftriaxone)
   - B. Penicillin relatively or fully resistant strains (minimum inhibitory concentration > 0.12 µg/ml)
     Aqueous crystalline penicillin G sodium
     or ceftriaxone x 6 weeks,
     plus gentamicin x 6 weeks
     Vancomycin x 6 weeks (if unable to tolerate penicillin or ceftriaxone)
2. *Staphylococcus*
   - A. Oxacillin-susceptible strains
     Nafcillin or oxacillin x ≥ 6 weeks (penicillin G may be substituted if penicillin susceptible [i.e. minimum inhibitory concentration ≤ 0.1 µg/ml]),
     plus rifampin x ≥ 6 weeks,
     plus gentamicin x 2 weeks
     For penicillin allergic: Substitute cefazolin (if non-anaphylactoid reaction) or vancomycin (if anaphylactoid reaction)
   - B. Oxacillin-resistant strains
     Vancomycin x ≥ 6 weeks,
     plus rifampin x ≥ 6 weeks,
     plus gentamicin x 2 weeks
3. Enterococcal
   - A. Susceptible to penicillin, gentamicin and vancomycin
     Ampicillin or aqueous crystlalline penicillin G x ≥ 6 weeks,
     plus gentamicin x ≥ 6 weeks
     Vancomycin x 6 weeks (if unable to tolerate penicillin or ampicillin),
     plus gentamicin x 6 weeks
   - B. Susceptible to penicillin, streptomycin and vancomycin, but resistant to gentamicin
     Ampicillin or aqueous crystalline penicillin G x ≥ 6 weeks,
     plus streptomycin x ≥ 6 weeks
     Vancomycin x 6 weeks (if unable to tolerate penicillin or ampicillin),
     plus streptomycin x 6 weeks
   - C. Susceptible to aminoglycoside and vancomycin, but resistant to penicillin
     1. β-lactamase producing strain
        Ampicillin-sulbactam plus gentamicin x 6 weeks (if gentamicin resistant, then > 6 weeks of ampicilin-sulbactam will be needed)
        Vancomycin plus gentamicin x 6 weeks (if unable to tolerate ampicillin-sulbactam)
     2. Intrinsic penicillin resistance
        Vancomycin x 6 weeks,
        plus gentamicin x 6 weeks
   - D. Resistant to penicillin, aminoglycoside and vancomycin
     1. *E. faecium:* Linezolid x ≥ 8 weeks or quinupristin-dalfopristin x ≥ 8 weeks
     2. *E. faecalis:* Imipenem/cilastatin plus ampicillin sodium x ≥ 8 weeks
        or ceftriaxone sodium plus ampicillin sodium x ≥ 8 weeks
4. HACEK microorganisms
   Ceftriaxone or ampicillin-sulbactam or ciprofloxacin (if unable to tolerate ceftriaxone or ampicillin-sulbactam) x 6 weeks
5. Culture negative
   - A. Early (≤ 1 year)
     Vancomycin x 6 weeks,
     plus gentamicin x 2 weeks,
     plus cefepime x 6 weeks,
     plus rifampin x 6 weeks
   - B. Late (> 1 year)
     Ampicilin-sulbactam x 6 weeks,
     plus gentamicin x 6 weeks,
     plus rifampin x 6 weeks
     Vancomycin x 6 weeks (if unable to tolerate penicillin),
     plus gentamicin x 6 weeks,
     plus ciprofloxacin x 6 weeks,
     plus rifampin x 6 weeks
   - C. Bartonella
     1. Suspected
        Ceftriaxone x 6 weeks,
        plus gentamicin x 2 weeks,
        with or without doxycycline
     2. Documented, culture positive
        Doxycycline x 6 weeks,
        plus gentamicin x 2 weeks

(*Source:* Baddour LM et al[103])

600 mg, azithromycin 500 mg or clarithromycin 500 mg. If the patient is NPO, cefazolin or ceftriaxone 1 gm IM/IV or clindamycin 600 mg IM/IV can be given.[107]

PARAVALVULAR REGURGITATION

Small paravalvular jets are common on intraoperative TEE, occurring in 10–25% of cases. These leaks typically resolve with healing and less than 1% require reoperation at 1–2 years. Moderate or severe regurgitation on postoperative TEE is rare (i.e. 1–2%) and requires correction, which can be performed by repair alone in about 50% of cases. The etiology of paravalvular regurgitation is likely due to infection, dehiscensce or fibrosis and calcification of the annulus leading to inadequate contact between the sewing ring and the annulus.[1]

HEMOLYSIS

Hemolysis is usually associated with either structural deterioration or paravalvular leak and due to turbulence through the valve or between the sewing ring and the native ring.[109,110] A paravalvular leak may be visualized with TEE. However, the severity of hemolysis is related to the eccentricity of the jet having contact with the chamber wall, rather than the severity of the regurgitation. While subclinical hemolysis can be detected in 18–51% of patients with mechanical prosthetic valve, serious hemolysis occurs in less than 1% due to improvements in valve design.[109]

The hallmark of mechanical hemolytic anemia is the presence of fragmented erythrocytes in the peripheral blood smear. Other findings include reticulocytosis, low haptoglobin levels, elevated lactic dehydrogenase, indirect hyperbilirubinemia and urinary excretion of hemosiderin. The anemia is due to the inability of the bone marrow to compensate for the shorted lifespan of the erythrocytes.[109]

Medical management is limited but there are reports of benefit with beta-adrenergic blockers, presumed related to reduced shearing forces on the erythrocytes. Pentoxifylline may reduce hemolysis by improving erythrocyte deformability. Iron, folate and erythropoietin supplementation may be necessary. Reoperation is warranted if hemolysis is severe enough to require repeated blood transfusions, or if the paravalvular leak is symptomatic. Percutaneous closure of leaks with coils or ventricular septal defect occluders has emerged as a potential option in patients who are not surgical candidates.[109]

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Chapter 62

Antithrombotic Therapy in Valvular Heart Disease

Michael H Crawford

Chapter Outline

- General Considerations
- Prophylactic Antithrombic Therapy
- Native Valvular Heart Disease
- Rheumatic Valvular Heart Disease
- Mitral Valve Prolapse
- Calcified or Degenerative Valvular Disease
- Prosthetic Valves
  - Mechanical Valves
- Bioprosthetic Valves
- Valvuloplasty and Valve Repair
- Management Issues
  - Diagnosis of Thrombotic Valve Complications
  - Valve Thrombosis
  - Pregnancy
  - Elective Surgery
  - Endocarditis

INTRODUCTION

Disease of the heart valves, both stenosis and regurgitation, can lead to turbulent blood flow. Eddy currents can form along the sides of turbulent blood flow, leading to areas of stagnant blood flow within the cardiac chambers and the proximal great vessels. Stagnant flow may precipitate blood coagulation and thrombus formation, especially in the low pressure atria. Thrombus formation may cause embolization to either the pulmonary or systemic circulation with potentially disastrous consequences such as stroke. Prosthetic heart valves are often smaller than the native orifice in which they are placed and they frequently exhibit regurgitation. Thus eddy currents can form around prosthetic valves. Also the closure of prosthetic valves with larger occluders, such as mono-disk and ball valves, can result in a wake of stagnant blood flow near the valve.[1] All prosthetic valves contain foreign material in the sewing ring and mechanical prosthetic valves are entirely composed of non-biological material. Such foreign material may also precipitate thrombus formation even in the absence of stagnant flow or eddy currents. Finally, disease of native valves may lead to endothelial or epicardial degeneration which can be a nidus for platelet activation and deposition. If sufficiently exuberant, this can lead to platelet emboli and thrombus formation.

Valvular heart disease may be caused by other conditions which increase the propensity for intracardiac thrombus formation. For example, myocardial infarction or dilated cardiomyopathy can lead to a significant reduction in left ventricular performance and stagnation of blood flow in certain parts of the left ventricle, which can lead to left ventricular thrombus formation. These conditions can also lead to mitral regurgitation and the formation of atrial thrombi. Thus the source of an embolus in these complicated conditions where valve disease is secondary to another condition is complicated. Also, valve disease may lead to conditions which increase the risk of thromboemboli such as atrial fibrillation. Thus a major component of the management of patients with valvular heart disease is the prevention of distal emboli of thrombotic or platelet rich material by the use of antithrombic therapy.

The purpose of this chapter is to discuss the pharmacologic antithrombotic therapy used in valvular heart disease to prevent distal emboli of thrombotic material. The vast majority of situations where thrombus risk is present involve chronic valvular heart disease, which will make up the bulk of this discussion. In this setting oral antithrombotic agents are the major form of therapy and include vitamin K antagonists such as warfarin and antiplatelet drugs (e.g. aspirin, clopidogrel and dipyridamole). Less commonly acute valvular disease is associated with thrombus formation. In these settings intravenous anticoagulation is often employed with agents such as heparin. A full discussion of the pharmacology of these various drugs is beyond the scope of this chapter. Also, there are numerous alternative agents for special situations that will not be discussed in detail.

GENERAL CONSIDERATIONS

The risk of thromboembolic events is related to patient specific factors and valve characteristics.[2] Patient factors include atrial fibrillation, heart failure and left atrial size, which are frequently associated with valvular heart disease (Table 1). Some of these factors or combinations of them may be indications for antithrombic therapy regardless of the presence of valve disease. In native valve disease with normal sinus rhythm, antithrombic therapy would not be considered unless other high-risk features are present. For example, in severe mitral stenosis anticoagulants would only be given if one or more of the following were present: advanced age; large left atrium especially with spontaneous echo contrast or frank thrombi present; reduced cardiac output; heart failure or a prior embolic event.

TABLE 1

Patient factors that increase the risk of thromboembolism in valvular heart disease

- Advanced age
- Atrial fibrillation
- Heart failure
- Reduced left ventricular systolic performance
- Enlarged atria
- Previous thromboembolic events
- Coagulation abnormalities

TABLE 2

Relative thrombogenicity of prosthetic valves

Prosthesis category	*Valve type*	*Thrombosis risk*
Mechanical	Caged-ball	High
	Mono-disk	Intermediate
	Bileaflet	Intermediate
	Annuloplasty ring	Low
Biological	Heterograft	Low
	Homograft	Low
	Percutaneous valve	Low

Prosthetic valves fall into two broad categories: (1) biological valves and (2) mechanical valves; although the former often have non-biological components. In general, biological valves are less thrombogenic and less durable. Mechanical valves are more durable, but more thrombogenic (Table 2). Annuloplasty rings and the sewing rings of most prosthetic valves require up to 3 months to endothelialize and then the risk of thrombosis decreases. Valvuloplasty and valve repair damage valve surfaces which creates a short-term concern for thrombus formation.

PROPHYLACTIC ANTITHROMBIC THERAPY

The major benefit of antithrombic therapy in valvular heart disease is the prevention of systemic or pulmonary emboli. Other benefits include preservation of normal valve function in prosthetic valves and reduction in the risk of infective endocarditis. The major risk of anticoagulant therapy is bleeding and this risk needs to be balanced against the potential benefits.[3] Some of the risk factors that increase the likelihood of bleeding on anticoagulant therapy are shown in Table 3. They mitigate against antithrombic therapy in borderline cases, but in certain types of valvular heart disease, antithrombic therapy is mandatory. In these cases, the presence of risk factors for bleeding may direct the selection of the antithrombic agent, since some have a higher risk of bleeding than others. Certain antithrombic agents have risks that are specific to the particular agents such as heparin induced thrombocytopenia and the teratogenic effects of warfarin. At this time warfarin or other coumarins are the most effective agents for chronic anti-coagulation in valvular heart disease.[4] Unfortunately warfarin has several drawbacks:

- A slow onset and offset
- A narrow therapeutic window

TABLE 3

Factors that increase the risk of bleeding on anticoagulants

- Bleeding diatheses
- History of GI bleeding
- Genetic variations in warfarin metabolism
- Advanced age
- History of hemorrhagic stroke
- Chronic kidney disease
- Excess alcohol use
- High risk for trauma
- Diabetes
- Unreliable in taking medications

- A variable dose response
- Interactions with food and other drugs, and the need for costly monitoring.[5]

Several new oral anticoagulants are being tested, and there is hope that a better agent will be available soon.

Several studies have shown that warfarin is significantly superior to antiplatelet agents, such as aspirin, dipyridamole and pentoxifylline, either used singularly or in combinations.[6] Thus, these agents would only be used in situations where there was a very high risk of bleeding on warfarin, or when antiplatelet therapy alone was felt to be adequate. Often warfarin needs to be combined with antiplatelet therapy due to other comorbidities such as coronary artery disease. In these situations, the risk of bleeding is increased. The most feared bleeding complication of antithrombic therapy is acute intracerebral hemorrhage. This condition often presents acutely with rapid progression of neurologic symptoms and a very high mortality. However any episode of major bleeding causing hemodynamic compromise or requiring transfusion is an adverse prognostic event for the patient. Thus every effort must be taken to treat only those in whom the potential benefits of antithrombic therapy outweigh the risks, and to monitor those on the most potent antithrombic agents carefully. Anticoagulation intensity is usually measured by the international normalized ratio (INR) which represents the partial thromboplastin time (PTT) of the patient divided by the PTT of the international reference standard. A normal ratio (no anticoagulant effect) is 1.0. Other conditions besides anticoagulant drugs can affect this ratio such as liver disease. Table 4 shows the recommended anticoagulation intensity by INR for the various valve diseases which are discussed below.

TABLE 4

Chronic anticoagulation recommendations and INR range for the following native valve diseases

Valve disease	*INR*
• Mitral stenosis and high-risk factors	2–3
• Mitral regurgitation and high-risk factors	2–3
• Mitral valve prolapse and TIA or stroke	2–3
• Valve disease and atrial fibrillation	2–3
• Valve disease and prior embolic event	2–3
• Mitral valvuloplasty, 1 month before and after	2–3

NATIVE VALVULAR HEART DISEASE

The two most common causes of native valvular heart disease are degenerative or calcific valve disease and rheumatic heart disease. Next in prevalence would be congenital valvular heart disease. Less common causes of valvular heart disease include rheumatologic diseases, trauma and infective endocarditis. In addition, other cardiovascular diseases can cause secondary valvular abnormalities, such as coronary artery disease and cardiomyopathies. In general, rheumatic valvular heart disease has the highest incidence of thrombotic complications followed by degenerative or calcific disease, then cardiomyopathies and coronary artery disease.

RHEUMATIC VALVULAR HEART DISEASE

The most common condition associated with thrombotic emboli in rheumatic valvular disease is patients with mitral valve disease. The risk is greatest in patients with mitral stenosis and atrial fibrillation. Such patients have an 18-fold increase in their incidence of systemic emboli as compared to patients without these two conditions. In general, the risk of thromboembolic complications in patients with rheumatic mitral valve disease increases with advancing age and reduced cardiac output. Since mitral stenosis obstructs the flow of blood leading to a low cardiac output, left atrial dilatation and often atrial fibrillation, this explains the high propensity for thrombi in this condition. Rheumatic mitral regurgitation is known to have a lower risk of thrombotic complications unless there is concomitant mitral stenosis. Due to this low risk in pure rheumatic mitral regurgitation, there is no recommended prophylactic antithrombic treatment regimen for this condition. However any rheumatic mitral valve disease in the presence of atrial fibrillation or a prior embolic event would require anticoagulation with warfarin, with a target INR of 2–3. If, on this therapy, there is any recurrence of thrombi, it would be appropriate to add an antiplatelet agent such as aspirin, dipyridamole or clopidogrel. In rheumatic mitral stenosis when the patient is in normal sinus rhythm, anticoagulation is indicated if the left atrial size is greater than 5.5 cm in diameter. These patients would also be treated to an INR of 2–3. In rheumatic mitral stenosis patients who are peri-valvuloplasty, anticoagulation is usually done for 3 weeks prior to the procedure and for 4 weeks afterward. The treatment prior to the procedure is to eliminate any thrombi that might be dislodged by the placement of the valvuloplasty catheter in the left atrium. The post-procedure treatment protects the patient from any nidus for thrombus caused by the atrial septostomy or other trauma to the endocardium.

MITRAL VALVE PROLAPSE

Embolic phenomena are uncommon in this, often hereditary, degenerative valvular disease. There have been reports of amaurosis fugax, transient ischemic attacks (TIA) or frank strokes in patients with mitral valve prolapse in the absence of atrial fibrillation. Pathologic studies in patients, who died of other causes with mitral valve prolapse, have shown that platelets can accumulate in clumps on the atrial side of the mitral valve leaflets. It has been hypothesized that these may produce small emboli in the brain, leading to acute neurologic abnormalities. The presence of overt thrombus is rare in mitral valve prolapse in the absence of atrial fibrillation. For asymptomatic mitral valve prolapse patients, no specific prophylactic therapy is recommended. Those who have had TIA or stroke should receive aspirin or another antiplatelet agent. If recurrent cerebral events occur then anticoagulation is recommended to an INR of 2–3. Prophylactic therapy should be indefinite and probably should be continued after valve repair in those with a prior history of TIA or stroke.

CALCIFIED OR DEGENERATIVE VALVULAR DISEASE

Calcification of the valve annuli or the leaflets and surrounding structures is most often associated with senescence. In younger patients, it can be seen with chronic kidney disease or Marfan syndrome. This process can lead to valvular dysfunction resulting in either stenosis or regurgitation. The incidence of calcific valve disease is most common in the aortic and secondly in the mitral valve. Both can lead to systemic emboli, either from calcium or thrombotic material. The past occurrence of calcific emboli can sometimes be detected by examination of the eyegrounds. Embolized cholesterol plaques resemble small mirrors in the retinal arteries. This is most often seen in patients with aortic valve disease, since aortic valve calcification bares a close resemblance to atherosclerosis and patients with calcific aortic valve disease often have the same risk factors as patients with atherosclerosis. Thrombotic emboli can also occur, especially in patients with calcific mitral valve disease. If thrombotic emboli are suspected or proven then anticoagulation with an INR of 2–3 is recommended. Patients with atherosclerosis and associated valvular calcifications are often on aspirin or other antiplatelet therapy and this should be continued.

PROSTHETIC VALVES

MECHANICAL VALVES

In general, the risk of thrombus formation is highest in mechanical prosthetic valves as compared to bioprosthetic valves. The risk of thromboemboli with mechanical prosthetic valves has been observed in studies of patients in whom contraindications to anticoagulation prevented their use. Overall valve thrombosis is unusual (1.8/100 patient years). Major emboli (4.0/100 patient years) and total emboli (8.6/100 patient years) are more common. Mitral valve thrombosis is more common than aortic valve thrombosis (0.9 vs 0.5/100 patient years). Ball valves have the highest incidence of thrombosis (2.5/100 patient years) as compared to mono-disks (0.7/100 patient years) and bileaflet (0.5/100 patient years) valves.[1]

The risk of thromboemboli can be augmented by other risk factors such as reduced left ventricular function and atrial fibrillation. As a general rule, all mechanical prosthetic heart valves in any valvular position in the heart are anticoagulated, unless there is a contraindication. The guidelines for anticoagulation of mechanical prosthetic valves varies somewhat between Continental Europe, the United Kingdom and the United States, possibly due to variations in the predominant valves available in the different locals and differences in the coumarins that are used.[7-9] The recommendations below and in Table 5 are based

TABLE 5

Recommended chronic anticoagulation INR range for the following valve prostheses

Valve type	*INR*
• Mechanical valves:	
— Aortic caged-ball	3–4
— Aortic mono-disk	2–3
— Aortic bileaflet	2–3
— Mitral caged-ball	3–4
— Mitral mono-disk	2.5–3.5
— Mitral bileaflet	2.5–3.5
• Annuloplasty ring	
— First 3 months	2–3
• Biological valves	
— First 3 months	2–3

upon the American College of Cardiology and American Heart Association Guidelines.[10] Although the following recommendations are quite specific, it may seem fanciful to the practitioner to think that differences of 0.5 INR units is a clinically meaningful target given the difficulties in adjusting INR with coumarins. In the aortic position, bileaflet or tilting mono-disks should have an INR of 2–3. Some believe in the first 3 months that a range of 2.5–3.5 is desirable. In the mitral position, bioleflet and tilting disk valves should have an INR of 2.5–3.5 due to the higher propensity for thrombus formation in the mitral position. If patients are at particularly high risk for thrombus, have had recurrent thrombosis or have coronary artery disease, then aspirin or another antiplatelet agent should be added. If aspirin cannot be taken, then clopidogrel is a reasonable alternative, or some have suggested increasing the INR to the 3–4 range. For caged ball valves, which are not commonly seen today, the range of INR is 3–4, unless they are a high-risk patient, in which case it should be 3.5–4.5. These values reflect the higher incidence of thrombosis with such valves.

BIOPROSTHETIC VALVES

Bioprosthetic valves generally have a lower risk of thrombosis than mechanical valves. The 1-year thromboembolism rate of bioprosthetic valves not on therapy is about 1.3% for aortic valves at 1 year and 1.5% for 7 years. Mitral bioprosthetic valves have an untreated rate of 1.7% per patient year.[1] The highest risk of thrombosis is early after surgery due to the sewing ring. Since complete endothelialization of the sewing ring may take up to 3 months, it is recommended that bioprosthetic valves receive anticoagulation for the first 3 months at an INR of 2–3. It is also recommended that heparin bridging be started as soon as feasible after surgery and continued until the INR is above 2.[11] This approach is always taken in the mitral position, but some surgeons do not anticoagulate aortic bioprosthetic valves given the lower incidence of thrombus with them.[12-14] Long-term anticoagulation is not indicated for these valves unless there is a high-risk situation such as atrial fibrillation. However aspirin is recommended for all patients with bioprosthetic valves, unless they cannot take aspirin.[15] There are no recommendations for percutaneously delivered bioprosthetic aortic valves, but most operators put them on lifelong aspirin. Some use aspirin plus clopidogrel for the first month.

VALVULOPLASTY AND VALVE REPAIR

Percutaneous mitral balloon valvuloplasty for mitral stenosis is a high-risk situation for dislodging any atrial thrombi. Consequently, patients should be anticoagulated prior to the procedure for 3–4 weeks. Prior to atrial puncture a transesophageal echocardiography (TEE) should be done to confirm that no thrombi are present. Heparin should be given during the procedure and long-term anticoagulation should be given if indicators are present. Mitral valve repair almost always includes placement of an annuloplasty ring, which is similar to the sewing ring of a prosthetic valve. Most recommend anticoagulation for 6 weeks to 3 months after mitral valve repair. Long-term anticoagulation would depend on other risk factors.

MANAGEMENT ISSUES

DIAGNOSIS OF THROMBOTIC VALVE COMPLICATIONS

Echocardiography is the key to the diagnosis of thrombotic complications of valvular heart disease. Patients at high risk for intracardiac thrombosis, who have known or suspected valvular disease, should have echocardiographic imaging, even if treatment is indicated without such imaging, because it is useful to have baseline images to compare subsequent images taken when thrombotic events are suspected. In native valvular disease, echocardiography is done following national guidelines to assess the initial severity and progress of the disease. Thrombi may be detected incidentally during such echocardiograms. Also, an echocardiogram should be done in native valvular disease when embolic phenomena are known or diagnosed by other means. These echocardiograms should include an assessment of the presence or absence of a patent foramen ovale as paradoxical emboli are possible. Occasionally, TEE will be indicated to clarify whether or not thrombi are present, especially in the left atrium. Echocardiography guidelines should be consulted in determining when TEE is appropriate.

Prosthetic valves should have echocardiographic imaging in the first 3 months after surgery to establish a new baseline for comparison to future studies. In mechanical valves, follow-up echocardiograms are not usually done unless there is some indication such as suspected thromboemboli. In such cases, TEE is almost always indicated due to the difficulty in detecting thrombi due to shadowing and poor lateral resolution of the mechanical valve parts, which may obscure thrombi. Bioprosthetic valves should also have a postoperative baseline echocardiogram. Bioprosthetic valves are known to deteriorate over time, so after 5 years a sequence of routine echocardiography is often instituted to detect deterioration of the valves. These echocardiograms may incidentally pick up thrombi formation. The detection of left ventricular thrombi is often aided by a contrast echocardiography. The detection of left atrial thrombi almost always requires TEE.

Computed tomography (CT) scans and magnetic resonance imaging (MRI) can also be used to detect intracardiac thrombi. Both require contrast administration and CT involves exposure to radiation. Both are expensive relative to echocardiography. Thus, they are usually used in special circumstances, where this type of imaging would be expected to be superior to

echocardiography, or when echocardiographic images are not adequate to resolve the clinical issue. Cardiac fluoroscopy is also useful for detecting thrombus induced mechanical valve dysfunction. The mechanical leaflet apparatus is radio-opaque, and derivations from normal positions during the cardiac cycle can readily be detected.

It should be remembered that echocardiography cannot reliably identify the type of tissue in an intracardiac mass. The density of the mass in question, its mobility and location may give clues as to the origin, but only extraction of the embolic material and its pathological examination is definitive. The differential diagnosis of valve disease related cardiac masses includes vegetations from infective endocarditis, thrombi, calcific deposits, tumors and atherosclerotic lesions in the aorta. In addition, any of these conditions may lead to distal embolization. This differential diagnosis is not trivial since some of these conditions are better treated by surgical excision rather than antithrombic therapy.

VALVE THROMBOSIS

The development of thrombus can obstruct a mechanical prosthetic valve or prevent its closure resulting in regurgitation. The differential diagnosis includes pannus formation, which is a form of exuberant scar tissue around the sewing ring which encroaches on the valve orifice and sometimes impinges on leaflet function. Although not highly accurate, a softer appearance of the mass on echocardiography suggests thrombus, especially if it is mobile, whereas pannus is usually a denser structure that is not mobile. Although sometimes difficult, this distinction is important due to the implications for treatment. Also, infective endocarditis should be excluded because treatment would be different.

Thrombus can often be treated medically, whereas pannus ingrowth would require repeat surgery. Thrombus may respond to an infusion of heparin, and this would be indicated for patients without symptoms or hemodynamic compromise who have demonstrated valve thrombus. In symptomatic patients, the severity of the symptoms and the size of the clot determine the approach. With mild symptoms and a clot area of less than 0.8 cm^2, thrombolysis can be considered.[16] The risk of thrombolysis in addition to bleeding is breaking up of the thrombus, resulting in emboli. Studies have shown that this is less likely with small thrombi. In those with more profound symptoms or hemodynamic collapse and a larger clot (> 0.8 cm^2) surgery is the preferred treatment. There are two caveats to this recommendation. First, if the risk of surgery is deemed to be too high then thrombolysis can be attempted. For dysfunctional right heart valves with thrombus, thrombolysis can be attempted, since the risk of a small pulmonary embolus causing death is much less likely than that of a systemic embolus going to the brain. The protocol used for thrombolysis of a thrombosed valve is the same as the protocol for pulmonary embolus. Do not use the protocol for myocardial infarction. The overall efficacy of thrombolysis for thrombosed prosthetic valves is about 80%, but complications occur in 15–20% and mortality in 3–12%. However surgical mortality has been reported to be 12–46%.

PREGNANCY

Since warfarin is teratogenic, its use in the first trimester is not recommended. After the first trimester warfarin is much safer, but not necessarily desirable. However it is safe during lactation. The ideal management of pregnancy in patients, who need to be on chronic oral anticoagulation, is to switch them to heparin preconception, and either continue it throughout pregnancy or switch to warfarin after the first trimester. There is no data in pregnancy with low weight molecular heparin, although some organizations recommend it due to the convenience of administration subcutaneously compared to heparin. In high-risk patients for whom it is necessary, aspirin is acceptable during pregnancy. Anticoagulation with warfarin should be discontinued prior to delivery, which is easy to do if the delivery is planned. If it is not going to be an induced delivery, the patient should switch to heparin for the last 6 weeks then resume warfarin after delivery. Heparin can be stopped just prior to delivery or reversed with protamine if necessary.[17]

ELECTIVE SURGERY

This is another situation where the risk of thrombus must be balanced against the risk of bleeding.[18] Since surgery induces a hypercoagulable state, the risk of thrombosis is elevated during surgery. It has been observed that the risk of thrombosis in patients not on anticoagulation during surgery with a bileaflet prosthesis is about 10% per patient year. With a mitral ball or mono-disk mechanical prosthesis, it is 13–18%, and if the patient has two mechanical prosthetic valves, the rate of thrombosis is even higher. Thus, all mechanical prosthetic valve patients, including those with aortic bileaflet valves, are at intermediate to high risk of having thrombosis and heparin bridging is required. This is accomplished by discontinuing warfarin for 4 days prior to surgery, starting heparin 2 days later and stopping it 4 hours prior to surgery, then restarting it as soon as it is safe postoperatively.[19] In patients at especially high risk one can monitor the INR and start the heparin as soon as it hits 2.0, rather than just starting the heparin arbitrarily on day 2. There is experience in using low molecular weight heparin which is easier to administer to outpatients awaiting surgery, but safety data is limited so the major guidelines do not recommend its use.[20] Some surgical procedures are so minor that it is not worth the risk of stopping anticoagulation. An example of this would be most dental surgery. Alternatively, for somewhat higher risk minor surgery, warfarin can be stopped 1–3 days before or until the INR is 1.5–2. Endoscopy with biopsy has the same bleeding risk as major surgery, so warfarin should be stopped 4–5 days prior or until the INR is 1.0. If it is necessary to perform emergency surgery, then warfarin should be discontinued and fresh frozen plasma or prothrombin concentrate administrated. Do not use vitamin K as this might induce a prothrombotic state, unless heparin is co-administrated.

ENDOCARDITIS

Infective endocarditis most commonly occurs on diseased or prosthetic valves, but can occur in structurally normally valves with aggressive organisms. Emboli are a frequent complication and often go to the brain, causing immediate cerebral hemorrhage

or sometimes mycotic cerebral arterial aneurysms, which can rupture years after the endocarditis event. For these reasons, anticoagulation in infective endocarditis patients is controversial. This is a situation where the risk versus potential benefits need to be carefully weighed. In general, patients at high risk of emboli to the systemic circuit should be continued on anticoagulation even if they develop infective endocarditis. Such patients include those with mitral stenosis and atrial fibrillation; mechanical prosthetic valves; and previous embolic strokes. However careful attention should be given to keeping the INR in the recommended range, if patients are on warfarin or keeping the activated clotting time in the therapeutic range, if they are on heparin, is important. As soon as antibiotic therapy is started in infective endocarditis the risk of stroke decreases quickly and is low after 2 weeks of effective treatment. In patients who have cerebral embolism it would be prudent to stop anticoagulation for 7–14 days to reduce the likelihood of massive intracerebral bleeding.

In marantic endocarditis, emboli are frequent. The basic treatment is trying to control the underlying disease, but if emboli occur, then heparin therapy is indicated unless there is a contraindication, such as a recent intracerebral bleed. Whether long-term anticoagulation therapy with warfarin is indicated for such patients after they leave the hospital is unclear. This decision would require the careful balancing of potential benefits versus risks with the physician who is taking care of the patients underlying disease.

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Section 7

VASCULAR DISEASES

Chapter 63

Evaluation and Management of the Patient with Essential Hypertension

Edward D Frohlich

Chapter Outline

- Evaluation of the Patient with Hypertension
  - Clinical Manifestations
  - Physical Findings
  - Laboratory Studies
  - Chest Roentgenogram
  - Electrocardiography
- Antihypertensive Therapy
  - Lifestyle Management
  - Pharmacological Therapy
- Hemodynamic Concepts
- Clinical Pharmacologic Concepts
  - Diuretics
  - Thiazides and Congeners
  - Mechanisms of Action
  - Metabolic Effects
- Treatment Algorithms Advocated Over the Years
  - Stepped Care Approach
  - Individualized Stepped-care Approach
  - Hypertensive Emergencies

INTRODUCTION

With the establishment of the National High Blood Pressure Education Program by the National Heart Institute (of the National Institutes of Health) in 1972, there were approximately 23 million people with hypertension accounting for 2% of cardiovascular deaths in the United States. Today, the death rate from cardiovascular diseases has fallen from 54% of all deaths to less than 50%. Notwithstanding, hypertension—accounts for most of the deaths from stroke (the third most common cause of deaths), is one of the major risk factors underlying coronary heart disease and its associated deaths; and is the most common cause of cardiac failure which is the most common cause of hospitalization of patients older than 65 years; and is the major cause of end-stage renal disease in industrialized societies. Yet, the latest data continue to point out that most of the patients with hypertension are still either unrecognized or untreated or, if they are under treatment, have uncontrolled blood pressure elevation. It, therefore, goes without saying that over these 40 years, we have performed poorly in aggressive management of the hypertension problem and its consequences. At present, there are over 60 million people with this potentially lethal problem. This chapter addresses the overall problem of hypertension, its evaluation, treatment and its associated comorbid conditions.

EVALUATION OF THE PATIENT WITH HYPERTENSION

CLINICAL MANIFESTATIONS

In most patients with systemic hypertension, there are no clinical manifestations other than the elevated blood pressure. Therefore, unless blood pressure is measured routinely in all patients, hypertension, will remain unrecognized. Not infrequently it is said that the most common symptoms related to hypertension are fatigue, headache and epistaxis; however, these symptoms are among the most common and important complaints offered by any patient seeking medical attention. In contrast to the foregoing nonspecific complaints, the most common and important symptoms are related to the "target organs" of hypertension and include decreased exercise tolerance, fatigue and nocturia as early evidence of cardiac and renal involvement, respectively. In addition, patients with mild hypertension may describe symptoms of cardiac awareness (e.g. palpitations and tachycardia) that may persist inordinately long after exertion or stress. Chest discomfort may occur in patient with cardiac involvement as a consequence of the increased myocardial oxygen demands associated with high pressure, left ventricular hypertrophy (LVH), or as a manifestation of coexistent epicedial coronary arterial (atherosclerotic) heart disease.

Transient symptoms of sensatory or motor deficit should suggest occlusive carotid or vertebral arterial occlusive disease; and, clearly, more lasting or recurrent symptoms would suggest occlusive and thrombotic basilar or cerebral arterial lesions.

PHYSICAL FINDINGS

Blood Pressure Measurement

The indirect technique of blood pressure measurement is described in detail in all guidelines (e.g. Joint National Committee, World Health Organization, American Heart Association, most national reports on evaluation of hypertension, etc.). The key advice is to use a sphygmomanometer which is calibratable has an inflatable cuff which can be placed with ease around the arm, and the readings should be easily read. The

TABLE 1

Classification of blood pressure for adults

Class	*Systolic pressure (mm Hg)*	*Diastolic pressure (mm Hg)*
Normal	< 120	and < 80
Prehypertension	120–139	or 80–89
Stage 1	140–159	or 90–99
Stage 2	> 160	or > 100

patient should be relaxed in a supine or seated position and standing, if there is concern about postural blood pressure changes. The patient should be as undisturbed as possible, not talking and should not be holding an object (such as a briefcase, luggage at an airport pressure measuring instrument, etc.). The patient should not have been smoking (within 30 minutes) and, if taking antihypertensive medications, it should be so noted. The readings should be taken multiple times and the readings averaged. If the pressure is elevated, it should be confirmed on at least three occasions, if possible. However, if there is concern about the severity of the reading, the managing healthcare professional should refer or initiate therapy, if indicated. The classification of blood pressure measurement and severity of pressure elevation are presented in Table 1.

Optic Fundi

The small vessels of the optic fundus provide an excellent means to assess the degree of systemic vasoconstriction; this examination should be performed routinely. The earliest state (Group 1) of hypertensive vascular disease is recognized by increased arterial tortuosity and mild constriction. Coexisting arteriosclerotic changes are manifested by the discontinuity of the arterioles at arteriovenous (AV) crossings (i.e. AV nicking; Group II). Appearance of exudates and hemorrhages (Group III) represents accelerated hypertension and/or renal disease. The appearance of papilledema (Group IV) permits the diagnosis of malignant hypertension.

Peripheral Pulses

One should always compare the simultaneous palpations of femoral and brachial arterial pulsations in all patients with hypertension in a search for a delay in the propagation of the aortic pulse wave as a manifestation of coarctation of the aorta (particularly in young patients) or, for evidence of atherosclerotic occlusive processes in older patients. Auscultation of the carotid arteries (for bruits) may provide signs of preventable strokes and transient ischemic attacks. Funduscopic examination may reveal cholesterol emboli in the retinal arterioles. Renal arterial bruits on examination of the abdomen, flanks and back provide an important sign of occlusive renal arterial disease and renovascular hypertension. Systolic bruits are commonly detected in young, as well as in older patients. In the older patients, one should be careful to listen for a diastolic component to the bruit which provided a more significant relationship to atherosclerotic occlusive renal arterial disease.

Cardiac Examination

Even before cardiac structure is altered, careful palpation may reveal a hyperkinetic apical impulse and a faster heart rate as

TABLE 2

Clinical classification of hypertensive heart disease

Stage 1
Normal-sized heart without evidence of cardiac enlargement (by chest film, electrocardiogram or echocardiogram)

Stage II
Early left ventricular hypertrophy as detected by a fourth heart sound and two of the following ECG criteria:
- P wave in lead II ≥ 0.3 mV and ≥ 0.12 sec Bipeak interval in notched P wave ≥ 0.04 sec
- Ratio of P wave duration to PR segment ≥ 1.6 (lead II)
- Terminal (negative) atrial forces (in V) ≥ 0.04 sec
- Echocardiography of LVH

Stage III
Clinically evident left ventricular hypertrophy as evidenced by:
- ECG criteria of LVH
- Sum of tallest R and deepest S waves ≥ 4.5 mV (precordial)
- LV "strain"—that is QRS and T wave vectors 180° apart
- QRS frontal axis < 0°
- All three ECG criteria (above)
- Echocardiographic evidence of LVH

Stage IV
- Left ventricular failure
- Systolic or diastolic dysfunction with preserved systolic function

evidence of early functional hyperdynamic cardiac changes. But, as the heart adapts structurally with LVH from its increasing afterload, this increased left ventricular mass may not always be detectable by the chest roentgenogram and electrocardiogram. The earliest clinical index of cardiac involvement in hypertension is left atrial enlargement, which may be suspected by an atrial diastolic gallop rhythm (fourth heart sound). This auscultatory finding is highly concordant with at least two of four conventional electrocardiographic criteria of left atrial abnormality (Table 2). Hemodynamic and echocardiographic studies have demonstrated that when both the fourth heart sound (the bruit de Gallop) and the electrocardiographic findings of left atrial abnormality are present (even without clinical indication of LVH), there is clear-cut physiologic evidence of impaired left ventricular structure and function. As LVH becomes more evident by chest roentgenogram and electrocardiogram, a louder aortic component of the second heart sound is heard, the fourth heart sound is almost always present, and there is a palpable and sustained left ventricular lift. These findings have been confirmed echocardiographically. Clearly, the presence of a third heart sound, this ventricular diastolic gallop rhythm, connotes the presence of left ventricular failure.

LABORATORY STUDIES

It is important for the physician to discuss the appropriate preparation for laboratory tests with the patient (Tables 3 to 5). If possible, these should be done with the patient of all medications. Even a sodium-restricted diet will stimulate the adrenal cortex sufficiently to suggest the possibility of hyperaldosteronism. Dietary sodium intake in excess of 100 mEq/day (2,300 mg) will obviate this possibility. Oral contraceptives may not only obscure the baseline arterial pressure readings, but may also alter intravascular volume, hemodynamics and plasma rennin activity. Diuretics, laxatives and even intercurrent viral infections (causing nausea, vomiting and diarrhea) may produce secondary hyperaldosteronism and

TABLE 3

Laboratory studies that may be of value in the evaluation of the patient with hypertension

I. Complete blood count:
- White blood cell count (and differential)
- Hemoglobin concentration
- Hematocrit
- Adequacy of platelets

II. Blood chemistries:
- Glucose (fasting, 2-hr postprandial, or glucose tolerance test)
- Hemoglobin A1c
- Uric acid
- Cholesterol concentration (total, high-density lipoprotein and low-density lipoprotein fractions)
- Renal function (serum creatinine and/or blood urea concentrations)
- Serum electrolytes (Na, K, Cl, CO_2) concentrations
- Calcium and phosphorus concentrations
- Total protein and albumin concentration
- Hepatic function (alkaline phosphatase, bilirubin, serum glutamic oxaloacetic transaminase
- Serum glutamic pyruvic transaminase, lactic acid dehydrogenase)

III. Urine studies:
- Urinalysis
- Urine culture
- A 24-hour collection (protein, Na, K, creatinine)

TABLE 4

Factors responsible for hypokalemia

I. Dietary sodium excess associated with diuretic therapy
II. Chronic gastrointestinal potassium losses:
- Vomiting
- Diarrhea
- Laxative abuse
- Pyloric obstruction
- Nasogastric suction
- Villous adenoma (colon)
- Malabsorption syndrome
- Ureterosigmoidoscopy

III. Adrenocortical excess:
- Primary aldosteronism (adenoma or hyperplasia)
- Cushing's syndrome and disease
- Other adrenal steroidal hormone excess

IV. Drug therapy and food:
- Diuretics
- Licorice
- Adrenal steroids
- Salicylate intoxication
- Outdated tetracycline

V. Renal disease (chronic):
- Potassium-wasting nephropathy
- Nephrotic syndrome
- Renal tubular acidosis

VI. Secondary hyperaldosteronism:
- Renal arterial disease
- Congestive heart failure
- Cirrhosis

VII. Diabetes mellitus (acidosis)
VIII. Primary periodic paralysis (hypokalemic type)

TABLE 5

Specialized studies of value in evaluating patients with hypertension

Study	*Indications*
Intravenous urography	Consideration of renal parenchymal disease
	History of urinary tract infections, renal stones or obstructive uropathy
	Persistence of hypertension after toxemia of pregnancy
Renal arterography	Abdominal, flank or back bruit (see text)
	Sudden onset of hypertension
	Sudden severity of known hypertension (loss of blood pressure control on prior adequate therapy)
	Disparity in renal lengths (by urography or scintigraphy) of $\geq$ 1 cm
	Renal venous renin activities functional assessment of the arterial lesions(s) at the time of selective renal arteriography
	Noninvasive arteriograms demonstrating renal arterial disease
	Evaluation of progression of known renal arterial disease
Isotope renography and renal scans	Follow-up of patient with renal arterial disease (e.g. to assess reduction in renal size or to compare postoperative to preoperative studies)
	Postoperative assessment of the patency of renal blood supply
	Use in conjunction with digital subtraction arteriography
Plasma renin activity (peripheral venous blood)	Assessment of low-renin forms of hypertension (e.g. primary aldosteronism, volume-dependent hypertension)
	Assessment of high-renin forms of hypertension in association with pharmacologic provocative studies to aid in selecting therapeutic programs
Hormonal studies	Catecholamines for pheochromocytoma or with clonidine suppression test
	Aldosterone levels for hyperaldostronism aldosteronism
	Corticosteroid levels for Cushing's disease or syndrome
	Thyroid function studies for hyperthyroidism or hypothyroidism
	Parathormone for hyperparathyroidism
	Growth hormone for acromegaly
	Insulin levels for associated diabetes mellitus
Blood (i.e. plasma) volume	Determination of volume expansion and confirmation of "Pseudotolerance" to antihypertensive therapy
	Preoperative assessment of patient with pheochromocytoma

associated hypokalemia. Certain antihypertensive drugs may have effects lasting for as long as four weeks, thereby providing a false concept of "baseline" pressure levels. Even the thiazide diuretics may have persistent effects for as long as two weeks following their discontinuation. Other common medications, including sympathomimetics, nose drops containing sympathomimetics, nonsteroidal anti-inflammatory compounds, monoamine oxidase inhibitors and tricyclic antidepressant drugs, as well as excessive dietary sodium intake, may contribute to the high pressure reading or antagonize prescribed antihypertensive drugs.

The following discussion is offered to provide a rationale for interpretation of those laboratory studies that may be ordered in the evaluation of the patient with hypertension. Clearly, not all of these studies are necessary in the routine evaluation of a patient with hypertension; however, this discussion is offered to permit a means for understanding and evaluating a patient with hypertension. It is also for the pertinence and significance for the patient who may have one or more of those diseases that frequently coexist with hypertension. For the uncomplicated patient, the minimal evaluation, usually, includes: complete blood count (without differential); determination of serum creatinine, potassium blood sugar, uric acid and cholesterol (with high and low density cholesterol) concentrations; and an electrocardiogram. It is clear that the fewer the number of laboratory studies, the more cost effective, but there are certain studies that will enhance the evaluation. However, modern automated laboratory testing techniques provide more measurements and a more comprehensive laboratory evaluation.

Complete Blood Count

In addition to assessing the hematologic status of a new patient, the complete blood count (CBC) is of broad significance. Firstly, if anemia is present, the physician should determine whether it is a complication of the hypertensive disease (e.g. renal involvement), a result of therapy (e.g. methyldopa-induced hemolysis) or related to an associated problem (e.g. a hemoglobinopathy). Conversely, an elevated hemoglobin concentration or hematocrit occurs not infrequently in hypertension. The Gäisbock Syndrome is manifested by elevated arterial pressure and by "polycythemia" but with splenomegaly, leukocytosis, or thrombocytosis; and it may be explained physiologically, as a "relative" or "stress" polycythemia, since, red cell mass and erythropoietin levels are actually normal. Therefore, the "polycythemia" of hypertension frequently explains the "ruddy" complexion of the hypertensive patient and can be confirmed by a contracted plasma volume.

Blood Chemistries

Several laboratory chemistry tests may be of value in evaluating the patient with hypertension (Table 3). The fasting blood sugar value may be abnormal; and diabetes mellitus is an exceedingly common coexistent disease. Alternately, the fasting blood sugar value may be normal, but results of a 2- or 4-hour glucose tolerance test may be abnormal. This finding should alert the clinician for other manifestations of diabetes and should suggest those patients who might develop hyperglycemia, glycosuria or overt diabetes mellitus while receiving diuretic therapy. The determination of the glycosylated hemoglobin (HbA1c) level is of great value, especially, if the blood sugar is elevated. However, it is unnecessary to order a 2- or 4-hour glucose tolerance test in all patients with hypertension; in those in whom diabetes mellitus is suspected (e.g. patients with a family history of diabetes or who develop abnormal carbohydrate tolerance while receiving a thiazide), it may be of value. In most experts' experience, for example, diabetes does not develop *de novo* in the patient with hypertension and an abnormality in carbohydrate metabolism frequently preceded the use of the diuretic. Furthermore, when associated with overweight or exogenous obesity (especially in those patients with the metabolic syndrome), consideration of potential diabetes is important.

The serum uric acid determination should also suggest which patients may develop more severe hyperuricemia or even clinical gout with diuretic therapy. In addition, Author his colleagues and have reported that the higher the uric acid concentration in patients with otherwise uncomplicated essential hypertension, the lower will be the renal blood flow and the higher the renal vascular resistance. Uric acid obviously, is transported via the blood to the kidney, filtered (also dependent on renal blood flow), and the absorbed and secreted by the tubules (also dependent on blood flow). This rise in serum uric acid levels, reflecting early involvement of renal hemodynamic function in hypertension, follows the earliest echocardiographic changes of LVH (the reader is referred to a longer discussion on this topic below). Clinicians are also advised to screen their patients for hyperlipidemia. The blood cholesterol determination (with high- and low-density lipoprotein concentrations) is of value for detecting hyperlipidemia, and the physician is cautioned to advise the patient to remain fasting from after dinner to the evening before this test.

The kidney is a prime target organ of hypertension, and renal functional impairment is a major complication. Therefore, it is of value to measure the serum creatinine and/or blood urea nitrogen concentrations in all patients. Author usually obtains both tests; and by using the serum creatinine along with urinary creatinine excretion, it is possible to calculate the creatinine clearance (glomerular filtration rate) in those patients in whom impaired renal function is of concern. Measurement of serum electrolyte values, particularly serum potassium concentration, is valuable in excluding secondary forms of hypertension, steroidal hormone excess, and the effects of diuretic therapy. Many factors may produce hypokalemia (Table 4), and very few non-renal factors (other than laboratory error and red cell hemolysis) are responsible for hyperkalemia. Determination of serum calcium concentration will exclude hypercalcemia, an alteration that is associated with a high incidence of hypertension; its correction may reduce an abnormally elevated pressure to normal levels.

Routine measurement of serum protein concentrations and hepatic function are usually, part of the automated serum chemistry determination. Although these tests may be of little value for the patient with hypertension, they may confirm hemoconcentration (i.e. plasma protein concentrations) or may provide a baseline for later possible coexisting problems (e.g. myocardial infarction, hepatic diseases). Baseline hepatic function data could be of great value in evaluating intercurrent and incidental problems (e.g. hepatitis, drug hepatotoxicity or even the possible low-grade elevation of serum billirubin with Gilbert's disease).

Urinary Studies

Of prime importance in all patients with hypertension is the routine urinalysis to detect the glycosuria of diabetes mellitus, the impaired renal function of advancing nephrosclerosis (diminished concentratability), the alkaline urine of primary hyperaldosteronism and the abnormal sediment in renal parenchymal disease. A 24-hour urine collection is most valuable in determining creatinine clearance as well as dietary sodium intake. If the urinary sodium excretion is greater than 100 mEq/24 hr (demonstrating adequate sodium intake and there is no dietary factor to explain increased aldosterone secretion), and if the urinary excretion of potassium is less than 40 mEq/24 hr, the measured hypokalemia (< 3.5 mEq/liter) is not likely to be the result of excessive adrenal cortical hormone excretion. On the other hand, if the 24-hour potassium excretion is excessive (i.e. > 50 mEq) in the presence of adequate sodium intake and there is no other obvious explanation for the demonstrated hypokalemia (< 3.5 mEq/liter; Table 4), there is a definite need to consider the possibilities of hyperaldosteronism.

Further, the normal kidney should not excrete more than 200–300 mg protein daily. Any amount in excess suggests either renal parenchymal disease (including nephrosclerosis) or an effect of the elevated blood pressure itself. Nephrosclerosis itself is not the sole cause associated with protein excretion in excess of 400–500 mg daily. Although a severely elevated arterial pressure may be associated with massive proteinuria, it should remit with reduction of pressure to normal levels. Thus, if urinary protein excretion persists or remains in excess of 400–500 mg in 24 hours, the physician should consider other causes of renal parenchymal (e.g. chronic pyelonephritis, glomerulonephritis) and cardiovascular (e.g. cardiac failure) diseases. If daily protein excretion exceeds 2 or 3 g, the physician should conclude that chronic pyelonephritis alone is an unlikely cause and a more rational diagnosis will include the various causes of nephrotic syndrome. Urine culture and sensitivity are always wise, if there is suspicion of a urinary tract infection.

CHEST ROENTGENOGRAM

Routine chest roentgenographic examination is a worthwhile baseline study for any patient with a chronic illness and is of particular value in the patient with hypertension. It permits recognition of cardiac enlargement, the stigmata of aortic coarctation (rib notching), and complications of hypertension (e.g. pulmonary congestion, aortic widening). It also provides evidence for associated diseases. The extent of cardiac enlargement is easily quantified by chest film and electrocardiogram, thus, providing a means to assess changes with therapy.

ELECTROCARDIOGRAPHY

The electrocardiogram is of particular value in determining the degree of cardiac involvement from hypertensive vascular disease. As indicated, left atrial abnormality is the first electrocardiographic sign of cardiac enlargement. Although the electrocardiographic literature is replete with criteria for diagnosis of LVH, each criterion has its own false-negative and false-positive results. The McPhie criterion (the sum of the tallest R-wave and deepest S-wave in any of the precordial leads achieving a total voltage of 4.5 mV) has the lowest false-positive result (1.5%). The criteria that we have used are detailed in Table 2, and when used with measurements determined from chest roentgenograms are of value in classifying the severity of hypertensive heart disease. These criteria have been confirmed by echocardiography and provide an excellent means to describe functional progression of hypertensive heart disease.

There is a large variety of specialized diagnostic tests available to evaluate the patient with hypertension. As a rule, none needs to be performed routinely. However, the major specialized tests are presented in Table 5, each with its major indications. For a more detailed discussion of these tests, the reader is referred to specialized texts dealing with them in greater detail.

ANTIHYPERTENSIVE THERAPY

LIFESTYLE MANAGEMENT

Ever, since, the Third Joint Coordinating Committee Report (JNC-3) of the High Blood Pressure Education Program specific recommendations were made with respect to the various nonpharmacological approaches for the treatment of hypertension (later termed lifestyle modifications). Each of these major national reports has been repeated and they all update their recommendations in subsequent reports (including the present JNC-7). At present, they include recommendations for the management of overweight/obesity, dietary salt (i.e. sodium) excess, tobacco smoking, alcohol abuse, a regular exercise program, the role of potassium and other electrolyte substances, and the adverse effects of non-antihypertensive drugs on blood pressure. These recommendations continue to be of increasing importance; and they have been re-emphasized to control or normalize blood pressure in normotensive and pre-hypertensive individuals. Moreover, they add to the antihypertensive effectiveness of prescribed antihypertensive agents in the overall management of hypertensive patients.

At present, the non-drug treatments of lifestyle modifications have been increasingly emphasized in specific clinical recommendations and/or disease guidelines, and they have been emphasized as well, in public education and publications in the lay-media.

Obesity

The problem of overweight and obesity has become a major national health, social and economic concern of our society today. Focus on this problem, especially in children, has been brought to central attention today, but it is clear that, like many other biological problems, the underlying mechanisms are complex and multifactorial, especially as new information is obtained through investigation. Until relatively, recently, we believed that the problem was related simply to overeating and assimilation of excessive amounts of calories and foods that were not nourishing and healthy. However, we now appreciate that fatty tissue is a veritable organ and that the adipocyte is the source of a multiplicity of humoral and hormonal substances that affect the overall metabolism. Indeed, this new knowledge has promoted a sophisticated expansion of an overall

understanding of the metabolic syndrome which includes a myriad of mechanisms that interact with one another. These considerations include such comorbid conditions as hypertension, diabetes mellitus, obesity (and its inherent aspects including abdominal versus truncal obesity), and each interplays with aging, racial, gender and, no doubt, many other factors. In addition to the foregoing consideration, we have known for over 80 years of the striking coincidence of hypertension and diabetes mellitus. On the other hand, it is clear that, if we are to do something about our genuine concern of overweight and obesity, we must follow the earlier proscribed measures, and that is to reduce body mass by a wise diet consisting of reduced caloric intake, and to carefully control the daily intake of fatty and fried foodstuffs as well as carbohydrates. These recommendations must relate to the individual's age, gender, body surface area (relating to height and weight) and, of course, any associated comorbid complicating factors which are not within the purview of this overall discussion.

Salt

As with the foregoing discussion on obesity, the issue of salt and hypertension is vastly complex. We frequently, hear of the association of the salt intake as it seems to be related directly to hypertension. However, this relationship is far too simple for us to relate to the oft-repeated epidemiological association of the salt intake of populations with its prevalence of hypertensive disease. We are well aware of the similar experience that not all hypertensive patients are overweight (or obese) and that not all patients with hypertension are "salt sensitive" (whatever the definition of this term means).

We know that only about 35% of patients demonstrate an elevated arterial pressure when given a proscribed salt load. However, we must remember that hypertension is not defined as, solely, by an increased arterial pressure. It is a disease which is manifested on physical examination by an increased pressure, but it is also associated with generalized target organ disease involvement; involving the large and small vessels, heart, kidneys, and brain. Therefore, it is with a lifetime of salt excess which produces structural and functional involvement of these target organs that may or may not be manifested solely by an increased blood pressure. These manifestations of dietary salt excess may involve normotensive individuals as well as hypertensive patients and, therefore, may explain their common hospitalizations due to cardiac failure, end-stage renal disease, stroke and large vessel disease involving both classes of patients. Pathophysiologically, these events may result in severe functional and structural involvement of these target organs. In any event, the present basic recommendations stated for hypertension, diabetes, obesity and other guidelines today are reasonable. One should maintain and follow a diet chart with consumption not greater than 2,300 mg of sodium (or 5.0 grams of salt) per day. One must, therefore, be particularly careful to read the food labels since, the food companies are making efforts to reduce the amount of calories and, consequently, the taste of these foods is frequently enhanced with the addition of salt. Hence, it is wise to compare the labels of low caloric food content and with those of the same foods, but without caloric restriction.

With respect to implementation of low-sodium diet therapy for hypertension, it also serves to enhance the effectiveness of antihypertensive drugs. Thus, dietary sodium should be held to less than 2,300 mg/day. Furthermore, one should be keenly aware that, over one-half the dietary sodium intake is provided by sodium chloride and the other half is included in the many food additives and preservatives listed on their food labels.

Other Electrolytes

One other electrolyte demonstrated to reduce arterial pressure in several studies (included in a meta-analysis) relates to increased potassium intake. In those few controlled studies, it appears that dietary intake of 90 mmol daily has been effective in reducing blood pressure. In this regard, consumption of fruit juices and uncooked vegetables will enhance this effectiveness and, to the contrary, prolonged boiling tends to leach out their necessary potassium content.

Magnesium is another electrolyte that may reduce pressure; however, this depends on the route and amount administered. Thus, intravenous administration of magnesium sulfate is well-known to decrease blood pressure (and was effective in this regard in pregnant patients with eclampsia). Further, when administered orally in sufficiently high doses, it, frequently produces diarrhea, thereby affecting antihypertensive effectiveness. Finally, a calcium enriched diet has been said to be associated with a lower blood pressure, but, at this time, this assertion still remains controversial.

Exercise

Numerous studies have demonstrated that a regular program (e.g. 20–30 minutes five days a week) of aerobic (isometric) exercise will be associated with a pressure reduction. This involves such forms of exercise as walking, jogging, bicycling, treadmill exercise or swimming. In contrast, isotonic exercises (such as weight lifting and rowing) tend to increase total peripheral resistance which is already elevated by the hypertensive disease and, therefore, Author does not encourage this type of exercise with his patients. The degree of blood pressure reduction varies depending upon what the height of the pre-exercise pressure and whether this program is regularly maintained and is associated with antihypertensive drug therapy. In any exercise program, involving patients currently receiving antihypertensive or vasodilator medications, the exercise-mediated reduction vasodilation may promote further reduction pressure (during or after the exercise), thereby possibly provoking symptoms associated with the exercise-induced hypotension.

Alcohol Restriction

Many studies have demonstrated that the quantity of daily alcohol ingested (in excess of one ounce of ethanol or its equivalents) is directly related to the height of arterial pressure. For this reason, the guidelines have continued to recommend that daily ethanol intake in excess of one ounce should be limited carefully (particularly in patients with hypertension).

Cigarette Smoking

National guidelines are not clear with respect to the effect of cigarette smoking on blood pressure. These guidelines point to

the clear-cut observations, that in measuring an individual's blood pressure, that person to be examined should not have been smoking for 15–30 minutes, since, pressure may be elevated for that time. Furthermore, if an individual is a habitual smoker by consuming several packages of cigarettes daily, one cannot be certain as to the effect of the habit on the patient's baseline pressure (since, it may be continually elevated throughout the day). Furthermore, a number of large multicenter trials have clearly demonstrated that the smoker who receives only a beta-adrenergic blocking drug and who may have the same reduction of blood pressure, as the patient who receives only a diuretic will not have the same protection from death or occurrence from myocardial infarction or stroke. For this reason, Author takes these observations into consideration before prescribing specific antihypertensive drugs to all hypertensive patients who smoke. Unfortunately, the national and international guidelines have avoided comment on the specific effect of smoking on blood pressure; but they carefully state that smoking is known to have adverse cardiovascular and other health effects in all patients. In this respect, the awareness of the importance of the foregoing statement is emphasized by recent federal and local legislation, changes in smoking regulations in public workplaces and restaurants and, as a result, reducing the number of smokers in today's societies. Notwithstanding, there is far too many smokers in this country and elsewhere. Specifically, as the numbers of cigarette smokers have decreased in general and more certainly in adults and men, the prevalence of cigarette smoking in women and young people (even sub-teenagers) in Asian and other countries continue to increase alarmingly. These observations add to the health, economic and other social burdens of these societies.

Non-antihypertensive Drugs

A number of other drugs which may be prescribed or available "over-the-counter" or as the so-called "street drugs" are known to elevate blood pressure. A number of reports have been published that identify those drugs and update their specific names and actions. However, in general, among the more common agents are those that: include catecholamines (or related compounds), such as in nose drops, steroidal substances, non-steroidal anti-inflammatory agents, certain oral contraceptives, licorice, chewing tobacco, neuropsychiatric agents, that interfere with reuptake of pressor amines, and many other substances. To be certain about the potential of any agent, it is wise for the prescriber and patient to be familiar with the package insert of all agents used by (or prescribed for) patients.

PHARMACOLOGICAL THERAPY

Initially, the individual antihypertensive drug classes include the diuretics, antiadrenergic compounds, vasodilators and beta-adrenergic receptor blocking agents. In more recent years, the calcium antagonists, angiotensin converting enzyme (ACE) inhibitors, angiotensin II (type 1), receptor blockers (ARB) and renin inhibitors have been included.

In Table 6, JNC-7 (see references) provides a detailed listing of all the available antihypertensive drugs, their respective classes, the different agents and their respective trade names with their usual doses prescribed. Other classes of agents are presently under study, but, none has been released for general use and prescription in the United States for the treatment of hypertensive diseases. In the following discussion, we shall describe the hemodynamic concepts involved in understanding the mechanisms of their hemodynamic and antihypertensive actions and certain thoughts related to our current understanding of what constitutes an "ideal" antihypertensive therapeutic agent. In discussing the specific drug classes, of necessity, the diuretics, beta-adrenergic receptor blockers (beta-blockers), calcium antagonists, and those agents that inhibit the action of the renin-angiotensin system (RAS) will be emphasized. The adrenergic inhibitors and the smooth muscle vasodilators will be discussed with restriction, primarily, because they are of "historical interest", although they are still used for antihypertensive therapeutic as well as other cardiovascular indications.

TABLE 6

Classes of antihypertensive agents

Diuretics:
• Thiazide congeners
• Loop-acting agents
• Potassium-sparing agents
• Aldosterone antagonists
• Sodium pump inhibitors
β-Adrenergic receptor antagonists:
• Cardioselective (β_1) inhibitors
• Nonspecific ((β_1, β_2) inhibitors
• Complex molecules
• α-β-blockers
• β-blockers-vasodilators
Adrenergic inhibitor:
• Centrally acting agents
• Peripherally acting agents
• α-Adrenergic receptor antagonists
• Complex molecules (central and peripheral actions)
Direct-acting vasodilators:
• Direct vascular smooth muscle relaxing agents act primarily on arteriolar or smooth muscle
Renin-angiotensin system inhibitors:
• Agents that inhibit renin release from the kidney
• Inhibitors of the angiotensin converting enzyme
• Angiotensin II receptor antagonists
• Renin inhibitors
Calcium antagonists:
• Agents that inhibit calcium entry into cardiac and vascular myocytes
• Agents that inhibit calcium entry into vascular myocytes

HEMODYNAMIC CONCEPTS

Most clinical forms of hypertension are characterized hemodynamically, as being produced by a generalized increase in the tone of vascular smooth muscle. The resulting vasoconstriction explains the increased systemic arteriolar resistance and a reduced venular capacitance. Consequently, the hemodynamic hallmark of hypertensive disease is an increased total peripheral resistance throughout the organ circulations. Increased venular smooth muscle tone serves to redistribute the circulating intravascular volume from the peripheral to the central (i.e. cardiopulmonary) circulation. Thus, early in the development of hypertension, this intravascular volume shift is manifested by an increased cardiac output. Later, in more established hypertension, the cardiac output returns toward the

normal and the regional or organ blood flows are normal and may even become reduced. This decreased cardiac output toward the normal (or lower) is reflect in a contracted intravascular (i.e. plasma) volume and a lesser return of the circulating volume to the cardiopulmonary area and the heart as the pre- and postcapillary vascular resistances increase. As hypertensive disease progresses in severity, vascular resistance increases, thereby raising the arterial pressure further. Two primary cardiovascular adaptations result from these changes. First, the heart and vessels adapt structurally to their increasing workloads, thereby increasing cardiac (i.e. left ventricular) mass and vascular wall thickness. The second adaptive change is a further contraction of intravascular (i.e. plasma) volume in most non-volume dependent forms of hypertension. When the heart and vessels, no longer can adapt structurally and functionally, secondary humoral and/or hormonal mechanisms (e.g. renin-angiotensin-aldosterone, vasopressin, catecholamines) come into play. Eventually, cardiac and circulatory failure ensues with an associated further expansion of effective circulating blood volume and its attendant impaired renal excretory function. The sequence of these pathophysiological changes has been well-documented in most patients with essential hypertensive disease.

CLINICAL PHARMACOLOGIC CONCEPTS

An "ideal" antihypertensive agent should be one that: (1) reduces vascular smooth muscle tone in order to reduce total peripheral and organ vascular resistances; (2) maintains cardiac output and organ blood flows (especially to the heart, brain and kidneys) at normal levels; (3) does not inordinately, reflexively, stimulate the heart (in response to the induced hypotension) to increase its rate, contractility or ejection, and metabolism and (4) does not expand intravascular volume in response to the reduced hydrostatic and renal perfusion pressures.

When assessing the hemodynamic effects of any antihypertensive drug, it is essential that the physician should be aware that discrepancies in published reports may reflect: (1) differences in the route of that drug's administration used by the different investigators; (2) the dose used; (3) the time elapsed after drug administration before observations were made; (4) whether a single dose was administered or the patient was treated over a more extensive time; (5) the age, race and gender of the treated subjects (recent reports emphasized the importance of these factors); (6) the severity of the hypertensive diseases; (7) previous drug therapy and (8) whether other medications have been administered concomitantly or recently enough to alter the hemodynamic responses to the therapeutic agent in question. These points are of great significance as are other factors, even though, they may not seem to have vasoactive action. Such factors include use of tranquilizers or anesthetic agents; the time of day; time since, the last meal and ingestion of commonly used self-medications (e.g. oral contraceptives, nose drops, steroidal compounds, and even such "non-drugs" as coffee, tea, tobacco, snuff, vitamin tablets, and laxatives).

DIURETICS

Until relatively recently, most authorities have considered the diuretics as the initial step (and mainstay) of antihypertensive therapy. However, with the advent of the beta-blockers and the other newer classes of drugs suitable for initial monotherapy of hypertension, there has been a reconsideration of the general primary need for the diuretic as the mainstay of antihypertensive therapy. Thus, the diuretic is not necessarily prerequisite for the beta-blocker, calcium antagonist, ACE inhibitor, ARB or renin inhibitor to include a diuretic in the overall antihypertensive therapeutic program. The discussion that follows provides current thinking on the various sub-classes and clinical considerations related to the diuretics, their mechanisms of action and their varied side effects (Table 7).

TABLE 7

Clinical considerations of diuretic therapy

- Dose of agent
- Hypokalemia
- Cardiac dysrhythmias, sudden death
- Carbohydrate intolerance
- Hyperuricemia
- Lack of uniformity of response in all patients with hypertension
- Hyperlipidemia (cholesterol, low-density, lipoprotein cholesterol, triglycerides)

THIAZIDES AND CONGENERS

These agents include chlorothiazide and hydrochlorothiazide as well as a large number of other chemical congeners of hydrochlorothiazide which are very similar in action and side effects, although their dosages are not identical in equivalence. Thus, unfortunately, there have been no prospective, large scale, double-blinded, and controlled studies that have demonstrated equivalent doses, side effects and end-points comparing any two or more agents of this grouping of diuretics (including, for example, the various thiazides as they are said to have been compared with chlorthalidone). This assertion is all the more pertinent, since, it is important to be aware that the specific equivalence in potencies and effects of these two common diuretics frequently employed in large multicenter antihypertensive drug trials have not been reported (although their bioequivalence is frequently stated). However, in general, one tablet of any one compound is generally, considered to be similar to each other (especially by investigators of those large scale multicenter trials).

MECHANISMS OF ACTION

The thiazides and their congeners produce natriuresis through inhibition of carbonic anhydrase as well as by active sodium reabsorption in the proximal and distal renal tubules. With resulting natriuresis, diuresis and volume contraction, the enzyme renin is released from the juxtaglomerular apparatus resulting in the generation of angiotensin II and the adrenal cortical release of aldosterone, thereby providing a negative feedback mechanism for the natriuretic stimulus. Further, potassium, magnesium and chloride ions are also lost concurrently in the urine, thus, inducing a hypokalemic alkalosis (and secondary hyperaldosteronism) that may be confused with other causes of the other forms of hyperaldosteronism (e.g. primary aldosteronism, renal arterial disease and cardiac failure). Most notable, is the secondary hyperaldosteronism that

can be exacerbated by diuretic-induced hypokalemia by means of favoring a sodium-for-potassium exchange at the distal tubule. As the blood pressure is reduced initially, intravascular (plasma) volume and cardiac output are reduced and total peripheral resistance increases. Later, after about 6–12 weeks, the cardiac output normalizes. It also shows that the total peripheral resistance and plasma volume increase. These changes appear to be maintained thereafter.

METABOLIC EFFECTS

Hypokalemia

A major side effect associated with the thiazides is that of hypokalemia (Table 4). In this regard, is the consequence of excessive dietary sodium intake associated with acceptable doses of the thiazides that produce hypokalemia. Thus, a secondary hyperaldosteronism is produced by the thiazide or their congeners, thereby facilitating further potassium wasting from body stores as the excessive dietary sodium filters through the kidney and is exchanged for potassium at the level of the distal tubule. Reduction of the dietary sodium intake will facilitate the overall effectiveness of the diuretic and minimizes concern for the induced hypokalemia. Another concept related to the diuretics is their potential to produce cardiac dysrhythmias (and, perhaps, sudden death) resulting from the induced hypokalemia and possibly, also hypomagnesemia. In one important trial, reduction of the hydrochlorothiazide dose and, consequently, protection from cardiac arrest and sudden death were remarkably reduced. Since, publication of that important report, routine use of reduced doses of thiazide doses (and, thus, consequent sudden death) has notably occurred. Other signs or complications of hypokalemia include cardiac dysrhythmias, polyuria, nocturia, muscle weakness, skin rash and suppression of bone marrow cellular elements.

Hyperuricemia

The thiazides increase the tubular reabsorption of urate and, hence, affect plasma uric acid concentration. If the hyperuricemia is severe enough, symptomatic gout may result. Therefore, if the uric acid concentration is borderline or elevated at the outset of the diuretic therapy (or if there is a personal or family history of gout), the uric acid should be monitored intermittently during treatment, anticipating potential gout. If the uric acid concentration exceeds levels that may produce symptomatic gout, specific therapy may be prescribed with a uricosuric agent (e.g. probenecid, allopurinol) or an inhibitor of the enzyme xanthinne oxidase (e.g. allopurinol) that reduces urate synthesis.

Over six decades ago (before the era of diuretic therapy), Stanton and Freis made the observation that hyperuricemia is a frequent biochemical finding in patients with essential hypertension. Subsequently, Ferris and his co-workers found that serum uric acid concentration increased simultaneously with an acute rise in arterial pressure produced by the intravenous infusion of either norepinephrine or angiotensin II. These changes were also coincident with a reduction in renal blood flow; and these changes were immediately reversed with discontinuance of either of the pressor substances. In subsequent studies, two decades later, we demonstrated highly significant relationships between the serum uric acid concentration and the renal hemodynamic findings in untreated patients with essential hypertension without gout or other factors associated with uric acid concentration. Thus, the higher their serum uric acid concentration, the lower was the renal blood flow and the higher their renal vascular resistance in the patients with essential hypertension having normal excretory function. We have reproduced these findings in many subsequent experimental and clinical studies and have found that hyperuricemia develops as renal functional impairment occurs in patients with hypertension (and in normotensive individuals) even in the absence of diuretic therapy, providing a very useful concept of the relationship of uric acid, renal hemodynamics and hypertensive disease.

The thiazdes may also induce carbohydrate intolerance or hyperglycemia of varying degrees. When using lower dosages, risk of development of diabetes requiring hypoglycemic therapy may not be any greater than with other antihypertensive drug classes. However, a number of mechanisms may be associated with the development of hyperglycemia during diuretic therapy (especially with the higher doses) including: hypokalemia; inhibition of pancreatic islet beta-cells; induction of hyporesponsiveness or insensitivity to insulin; pre-existing carbohydrate intolerance exacerbated by the diuretic and, of course, coexisting diabetogenic factors including obesity, impaired carbohydrate intolerance prior to the thiazide and possibly, coexistent hyperlipidemia. Other metabolic side effects related to the thiazide diuretics and congeners include hypercalcemia, hypomagnesemia, hyperlipidemia and, of course, dehydration and thirst.

Loop Diuretics

Furosemide is the most common loop acting diuretic in clinical use, and, unlike the thiazides, they promote natriuresis by inhibiting sodium transport at the ascending limb of the loop of Henle. Since, more of the filtered sodium is delivered to the distal tubule for exchange, a greater amount of potassium wastage will result naturally. The onset of action is more immediate (frequently within 20 minutes) and, consequently, the initial diuresis is more rapid than the thiazides, rebound sodium and water retention is more pronounced, and there may be greater potassium wastage. Thus, these agents should be reserved for: intravenous necessities; patients with renal functional impairment or cardiac failure; or when the thiazides cannot be administered. In those patients with impaired renal function, the dose-response curve is linear unlike the thiazides. For these foregoing reasons, the “loop diuretics” are not generally recommended for patients with uncomplicated essential hypertension and patients with secondary hyperaldosteronism in order to prevent further, hypokalemia and its complications.

Potassium-sparing Agents (Spironolactone and Eplerinone)

These agents are discussed separately because they promote diuresis very specifically, by inhibition of the distal tubular action of aldosterone of sodium-for-potassium inhibition. Since, much of the obligate sodium ion transport occurs at the level of the proximal tubule, their potency is not as great as the thiazides.

Thus, they are particularly useful, alone or when combined with a thiazide, for patients with primary or secondary hyperaldosteronism; and they are particularly effective in patients with cardiac failure. Mastodynia or gynecomastia may be more common with these agents, in particular spironolactone; but these effects have not been related to induction of breast neoplasia.

Particular care should be emphasized, clearly, that when using these (and other) potassium sparing agents in patients predisposed to develop hyperkalemia. This caution should be heeded particularly in those patients with impaired renal function or with cardiac failure, especially, if these patients are receiving an ACE inhibitor or an ARB or if they are receiving supplemental potassium.

Amiloride and Triamterene

These two agents are structurally related and act on the same non aldosterone-dependent sodium-for-potassium renal tubular transport mechanism. Therefore, their action is entirely different from that of spironolactone or eplerinone as discussed above. Both of these agents reduce pressure with a thiazide and are frequently jointly compounded to preserve potassium. Nevertheless, these agents should be used with caution in patients with impaired renal function or when receiving an ACE inhibitor or an ARB due to the potential for severe hyperkalemia.

Beta-Adrenergic Receptor Blockers (Beta-Blockers)

The beta-blockers have been considered important alternative agents for the initial treatment of hypertension for over 50 years. However, in their long history, their role in treatment of hypertension has been fraught with many controversies. The first compound studied had severe untoward effects until propranolol was introduced. Although it was found first to be effective for the treatment of patients with angina pectoris, not all patients with hypertension responded to beta-blocker monotherapy with a meaningful pressure reduction. In particular, they were found to be most effective in younger patients, especially those with a hyperkinetic circulation, and for patients with such comorbid diseases as: coronary arterial disease (with or without myocardial infarction) or when used with a diuretic. With the advent of meta-analysis to evaluate more generalized and overall therapeutic experience, controversy resumed with arguments to exclude the beta-blockers for initial treatment. Support for this concept was gained with reports of "dysglycemia" with treatment; however, to Author's way of thinking, exclusion of any one class of therapeutic agents for a multifactorial disease such as hypertension is unrealistic since, the meta-analysis studies included few young patients or those patients with hypertension having coexistent coronary artery disease with or without a prior myocardial infarction, or those beta-blockers having been found to be effective in the treatment of cardiac failure (primarily the newer agents so approved by the regulatory agency). Moreover, those arguing for the broad initial therapeutic exclusion of the beta-blockers frequently, cite the NICE report from Great Britain whose recommendations were less specific, but more reasoned. Thus, this class of agents is discussed to permit the reader to arrive at a personally reasoned conclusion as to the rationale for their selection.

Postulated Mechanisms of Action of the Beta-Blockers (Table 8)

With respect to the foregoing discussion, it is most important to have a clear understanding of the hemodynamic actions of the various beta-blockers presently available (Table 9). Thus, the arterial pressure reduction produced by most beta-blockers is often associated with a decreased cardiac output, although the calculated total peripheral resistance may increase. With this class of agents, heart rate, myocardial tension and contractility and metabolism are usually reduced. However, their effects on vascular resistance have often been misinterpreted since, the usual reduction in cardiac output (20–25%, not infrequently) is not usually associated with proportionate reductions in all organ blood flows and, conversely, increased vascular resistances. Thus, the changes in organ flow depend upon the number and affinity of beta-adrenergic receptor sites in the respective organ circulation. For example, in the renal circulation, where the number of arteriolar beta-receptors are relatively few blood flow is not necessarily reduced (and, reciprocally, renal vascular resistance not increased) in patients with uncomplicated essential hypertension. Moreover, their hemodynamic effects on heart and kidney may not be as detrimental as assumed; myocardial oxygen demand and renal blood flow may be more beneficial than simple inferences suggested. By contrast, the blood flows to skeletal muscle and the splanchnic circulation are usually reduced.

TABLE 8

Beta-adrenergic receptor blockers

Generic name	*Trade name*	*Pharmacologic and clinical features*
Acebutolol	Sectral	Cardioselective; possesses intrinsic sympathomimetic activity
Atenolol	Tenormin	Cardioselective; given once daily
Metoprolol	Lopressor	Cardioselective; may be given once daily
Nadolol	Corgard	Nonselective; given once daily
Pindolol	Visken	Nonselective; possesses intrinsic sympathomimetic activity
Propranolol	Inderal	Nonselective; available longest; may be given once daily; approved for angina pectoris, migraine
Timolol	Blocadren	Nonselective; approved for glaucoma and prevention of myocardial reinfarction
Labetalol	Normodyne; trandate	Nonselective; α-β-blockade
Carvedilol	Coreg	Once daily; generic twice daily (also probable endothelial action
Bistolic	Nebibolol	Once daily

TABLE 9

Postulated antihypertensive mechanism of β-blocking drugs

- Reduced cardiac output
- Readjustments of blood flow
- Preferential responses of component regional circulations
- Total body autoregulation ("reverse Guyton")
- Reduced vessel distention ("reverse Bayliss")
- Readjusted baroreceptors
- Altered high-pressure cardiovascular reflexes
- Reduced plasma rennin activity
- Altered catecholamine biosynthesis
- Inhibited presynaptic β-receptors
- Central action of an active metabolite of the agent

Several beta-blockers, however, have more complex hemodynamic actions. For example, labetalol possesses alpha- as well as beta-adrenergic receptor blocking effects and, hence, there is a more generalized and profound reduction in organ vascular resistances. Furthermore, the newer agent carvedilol appears to have additional hemodynamic effects on the vascular endothelium promoting effects generating nitric acid and vasodilation. Other differences among the broad group of beta-blockers (including acebutolol, betaolol, bisoprolol, carteolol, penbutolol and pindolol) relate to their inherent intrinsic sympathomimetic activity (ISA) and, consequently, they may not reduce heart rate and cardiac output as much as those agents without ISA. In addition, some beta-blockers are said to be cardioselective (acebutolol, atenolol, celiprolol and metoprolol), but in the doses used for treating coronary artery disease or hypertension, they are just as effective as the non-cardioselective agents (nadolol, propranolol or timolol). Some agents may have a more prolonged duration of action (e.g. long-acting metoprolol) than others (e.g. atenolol), but the latter agent may be prescribed twice daily, if drug cost should be a factor.

In more recent years, the beta-blockers have been strongly advocated for the treatment of patients with cardiac failure; but particular care must be considered not to exacerbate the condition in patients with hypertensive heart disease. Moreover, some of the older and newer agents may be of particular value in patients with cardiac failure. For example, they may be effective not only in reducing arterial pressure, but the newer agents may be particularly beneficial if there is a prolonged QRS period and ventricular asynchrony in patients with hypertensive heart disease. Finally, another concern may relate to the hypertensive patient with coexisting diabetes. Under these circumstances, caution must be exercised in using these agents since their hemodynamic effects may alter the hemodynamic effects of hypoglycemic agents. Thus, in summary, Author suggests that it is unwise to make sweeping and broad conclusions about an entire drug class which may not serve patient's specific problems unless a clearer and wise understanding about that patient's clinical situation and the specific drug's applications are carefully considered.

For the foregoing reasons, Author believes that the beta-blockers are indicated in the hypertensive patients with a hyperdynamic beta-adrenergic circulation or other hyperkinetic circulatory states. These are also indicated certainly in patients with hypertension and a prior myocardial infarction, those with cardiac dysrhythmias responsive to beta-blockers (e.g. catecholamines), idiopathic mitral prolapse syndrome and the patients who are already receiving a beta-blocker in lower doses than for treating hypertension (e.g. migraine, muscle tremor, glaucoma). Sweeping conclusions as to the merits (or lack thereof) of any drug class are not at all justified.

Calcium Antagonists

The calcium antagonists have been available for over 50 years and, perhaps, the most heterogeneous antihypertensive drug class in terms of chemical structure, mode of action and clinical indications. Nevertheless, there is a certain similarity in their actions: inhibition of availability of the calcium ions cardiac and vascular smooth muscle cells that serve to inhibit myocytic contractility and reducing heart rate (particularly, the dihydropyridines). At least four receptors of calcium channels have been cloned, each responding by calcium ion inhibition. This may explain some of their heterogeneity and the synergism enabling two calcium antagonists to be used concomitantly. Additionally, these agents may also differ with respect to their intracellular actions (e.g. release of calcium ions from the intracellular mitochondria, sarcoplasmic reticulum and specific proteins like calmodulin, etc.). As vascular resistance is reduced, arterial pressure falls in response to most agents; although, one calcium antagonist (nimodipine) has little effect on pressure and is useful intraoperatively for patients with cerebral bleeding.

In general, the common term for these agents is the calcium channel blockers; but the term favored by the International Union Pharmacology (IUPHAR) is calcium antagonists inhibitors. Thus, each of these compounds may have different actions on their respective channel receptor sites (whether the channel is L, T, N or any other types) and the intracellular events which their inhibition subserves. For example, even though most of the L type channel inhibitors belong to the dihydropyridines, within this group nifedipine also has additional alpha-adrenergic receptor inhibiting action. The verapamil (a non-dihydropyridine) in addition to its vasodilating property has a cardioinhibitory action, thereby diminishing myocardial conduction/transmission and suggesting its value for the treatment of supraventricular tachyarrhythmias. Indeed, this latter property suggested, in its early investigative days, a possible beta-blocking action. All calcium antagonists reduce arterial pressure without expanding intravascular volume, explaining why they may be used as a monotherapeutic agent without a diuretic. The natriuretic effect of the calcium antagonists is explained, in part, due to their ability to inhibit renal sodium reabsorption through the sodium-for-calcium exchange mechanism. The foregoing statement should not be construed to relate to the development of pedal edema with higher doses of the calcium antagonists to renal sodium and fluid retention. This side effect is produced by their potent precapillary arteriolar dilation as well as reflexive postcapillary venular constriction which primarily promote increased capillary hydrostatic pressure in the dependent position, thereby favoring transcapillary fluid migration into the extravascular space and, thus, edema formation. Another common side effect of the calcium antagonists is gingival hyperplasia.

Calcium antagonists are of particular value for initial treatment when there is need for immediate pressure reduction, for promotion of coronary vasodilation in patients with angina pectoris unresponsive to beta-adrenergic receptor blockade; when an ACE inhibitor or ARB is contraindicated due to occlusive bilateral renal arterial disease or unilateral arterial disease of a solitary kidney; and have been shown to reduce development of stroke and non-fatal stroke with a dihydropyridine in the large multicenter Syst-Eur trial. Finally, Author has found that rather than increasing the dose of one calcium antagonist to control pressure better, the addition of a second calcium antagonist may obviate development of peripheral edema. Finally, the calcium antagonists have been formulated with ACE inhibitors and ARBs and more recently with a third agent, the diuretic. In the past, the calcium antagonist was not formulated with a diuretic due to its renal sodium-for-calcium exchange mechanism; but the natriuretic action with an ARB presumably suggested this triple combination.

Angiotensin Converting Enzyme (ACE) Inhibitors

The ACE inhibitors are also effective for monotherapy with all degrees of severity including: refractory hypertension, severe cardiac involvement (including LVH, angina pectoris, cardiac failure, and for secondary prevention and death after myocardial infarction), and for prevention of end-stage renal disease (particularly in patients with diabetes mellitus). These agents work by inhibiting the ACE, thereby reducing the generation of angiotensin II as well as the inactivation of the very potent vasodilator bradykinin (which may explain another antihypertensive action). Inhibition of the role of angiotensin II interacting with norepinephrine in specific brain centers and at peripheral nerve endings may explain why reflexive cardiac stimulation is not usually observed with these agents. The effect of these agents on promoting the effects of bradykinin may be explained by stimulation of endothelial nitric oxide production in vascular endothelium, cardiac myocyte and in the kidney.

Hemodynamically, the ACE inhibitors reduce arterial pressure though arteriolar dilation and consequent reduction of total peripheral resistance without associated increased cardiac output, reflexively. Renal blood flow increases through reduction of pre- and postglomerular arteriolar resistances and, thereby decreases glomerular hydrostatic pressure. This action explains their usefulness in patients with severe proteinuria and with end-stage renal disease associated with severe essential hypertension or diabetes. Additionally, it inhibits the mitogenic effects of angiotensin II and reduces cardiac remodeling and apoptosis, thereby explaining its usefulness in preventing and/or reducing severity of cardiac failure.

A number of ACE inhibitors are available and their antihypertensive effects are enhanced by diuretics which are frequently provided when co-formulated. Thus, several ACE inhibitors (captopril, benazepril, enalaparil, lisinopril, moexipril and quinapril) have been formulated with a diuretic. Once again, it is worthwhile to emphasize the potential of this combination to augment pressure reduction and postural hypotension. Their side effects, notably, are few. Nevertheless, they may enhance proteinuria, induce leukopenia by bone marrow suppression, produce skin rashes (usually better explained by their vasodilating action), angioneurotic edema, fetal abnormalities when given to a pregnant woman and, far more commonly, a bothersome cough in 8–13% of patients (presumably related to the enhanced amount of bradykinin produced by ACE inhibition). (Perhaps, the latter complaint has not prompted discontinuation of the drug in many patients.)

Angiotensin II Receptor Blockers (ARB) or Antagonists

These agents act by inhibiting the type 1 angiotensin II receptors' action in vascular smooth muscle, heart, kidney, adrenal cortex, brain and other organs. The ARBs, like the ACE inhibitors, have similar clinical indications and have been useful, particularly in those patients who cannot use the ACE inhibitor due to side effects (most notably, angioneurotic edema and the cough produced by ACE inhibition). Controversy currently, exists as to whether there are quantitative or synergistic clinical benefits of the ARB when used concurrently with the ACE inhibitor. A number of ARBs are available clinically and are active orally. As with the ACE inhibitors, the action of the ARBs are markedly enhanced when given with a diuretic and several compounds are available when co-formulated. The anti-hypertensive and hemodynamic effects of these compounds are very similar to the ACE inhibitors. Since, not all angiotensin II generation is inhibited by ACE inhibition, an additional mode of action occurs by the antagonism of generated throughout incomplete ACE inhibition, or by generation of angiotensin II by another enzyme (i.e. chymase) which is present in human myocardium in greater amounts than in experimental animals. Nevertheless, they produce the same side effects as the ACE inhibitors (except, perhaps, that of cough).

Renin Inhibitors

At present, there is only one renin inhibitor available for clinical use (aliskiren). The agent directly inhibits the rate-limiting biochemical step in angiotensin II generation by impairing the action of renin that leads to the subsequent conversion of angiotensin I. The drug reduces arterial pressure in a dose-dependent fashion, suppresses plasma renin activity, and its action is enhanced by a diuretic and can also be used with a calcium antagonist. There have been no major side effects with the renin inhibitors; and, because it has no effect on the ACE, it does not produce a cough although angioneurotic edema and hypokalemia are still possibilities. Thus, it is clear that this agent has been shown to be useful in patients with essential hypertension, with renal protection in patients with proteinuria, diabetes and cardiac failure.

Adrenergic Inhibitors

This class of antihypertensive agents is included in this discussion primarily for historical purpose, although some of the subgroups of adrenergic inhibitors still have some clinical pertinence today. The present array of sympatholytic compounds is so varied in mechanisms, that it is possible at this time to dissect pharmacologically many levels of the autonomic nervous system. Cardiac and vascular autonomic inhibitions attenuate the reflexes and, consequently, are important concepts as we consider hemodynamic actions, clinical responses to therapy, and enlightened selection of drugs. Thus, hypotension usually results from reduction of venous return to the heart, attenuation

of reflexive increases in heart rate and myocardial contractility. Other evidence of inhibited compensatory reflexes results from the abolition of the overshoot phase of the Valsalva maneuver, augmentation of postural hypotension, the "tilt-back" overshoot of arterial pressure which occurs when a patient returns to the supine position from the upright tilted position, or with the post-exercise hypotension. These phenomena result from those physiological or pharmacological interventions which redistribute circulating intravascular volume. An understanding of these phenomena is, therefore, important for comprehending many cardiovascular disease mechanisms and the mechanisms associated with this broad group of drug classes which will be discussed briefly.

Ganglion Blockers

Although these drugs were the mainstay of treatment of severe hypertension many years ago, they are now used rarely, usually with intravenous formulations for immediate and controlled hypotension in certain severe hypertensive emergencies or for control of arterial pressure during certain operative (e.g. neurosurgical) procedures. Thus, trimethaphan camsylate is infused intravenously (1 mg/ml) to produce instantaneous pressure reduction; and the pressure will immediately increase after dose reduction or discontinuance of the infusion. Antihypertensive effectiveness is enhanced during upright posture (e.g. elevation of the head of the bed) and with concomitant use of diuretics or when associated with blood loss. Conversely, with expansion of intravascular volume after control of pressure by these agents, pseudotolerance (intravascular volume expansion) will occur unless a diuretic is administered. Since, the ganglion blocking drugs also inhibit parasympathetic nerve activity, intestinal and urinary bladder smooth muscle function is also inhibited, thereby predisposing the patient to ileus and urinary retention. Loss of penile erectile function is another side effect.

Rauwolfia Alkaloids

This group of drugs has varying potency to deplete brain, adrenal glands and postganglionic sympathetic nerve ending of their natural biogenic amines (catecholamines and serotonin). These agents were used with great frequency in the early years of antihypertensive drug therapy and are still, commonly used in many areas around the world. When given by injection (e.g. reserpine 1.0–5.0 mg) they have been useful in treating hypertensive emergencies and the cardiovascular related symptoms of thyrotoxicosis. A "test" injection of 0.25 or 0.50 mg is worthwhile to avoid excessive hypotension. When administered orally, they serve as mild antihypertensive compounds, although their antihypertensive effect is minimal unless used with a diuretic and/or a vasodilator. Side effects include nasal stuffiness, postural hypotension, bradycardia, overriding parasympathetic gastrointestinal stimulation, mental depression which may be subtle and behavioral changes.

Postganglionic Neuronal Depletors

Among these agents are guanethidine and guanadrel. The former agent has been available for 50 years for treatment of patients with severe hypertension. It has a prolonged delay (48–72 hours) in action; and, once achieved, its hypotensive action may persist for days or weeks (and as much as one month) after discontinuance. Their hemodynamic action is similar to the ganglion blockers: reduction in arteriolar resistance, peripheral venodilation with peripheral pooling of blood, decreased cardiac venous return, cardiac output and reduced organ (e.g. renal) blood flow. Side effects include bradycardia, postural hypotension, increased frequency of bowel movements (or diarrhea), and retrograde ejaculation. As already indicated, these compounds are taken up by the postganglionic nerve endings, thereby inhibiting norepinephrine reuptake and depleting them of these agent. This concept is very important clinically today since, the same mechanism is involved with the similar ability of the nerve endings to take up tricyclic antidepressants, thereby producing unwanted effects. When these agents are discontinued, the arterial pressure may fall precipitously.

Centrally-acting Postsympathetic Alpha-adrenergic Agonists

Methyldopa has been available for clinical use for almost 50 years and is still used widely, throughout the world. Present concept of its hypotensive action is by false neurotransmission that stimulates postsynaptic alpha-adrenergic receptor sites in brain, thereby reducing adrenergic outflow from brain medullary centers to the cardiovascular system and kidney. As a result, arteriolar resistance falls, and a reduced venous resistance results in reduced venous return to the heart although cardiac output and renal blood flow are not reduced as much as the foregoing described sympatholytics. The most common side effects include dry mouth, lethargy, fatigability, somnolence and sexual dysfunction.

Clonidine, although chemically different from methyldopa, shares certain pharmacological actions. They reduce arterial pressure through a decreased vascular resistance as a result of central stimulation of alpha-adrenergic receptor sites in medullary centers and reducing brain adrenergic outflow. The side effects of these agents are similar to other adrenergic inhibitors; however, one more common associated with clonidine is the possibility of a precipitous rebound of pressure with an abrupt withdrawal of the drug. When this occurs, the beta-adrenergic symptoms should be treated with a beta-blocker and the rise in pressure with an alpha blocker (e.g. phentolamine). The more recent availability of the clonidine patch has apparently reduced the occurrence of the rebound phenomena.

Postsynaptic (Peripheral) Alpha-receptor Antagonists

There are two types of peripheral alpha-adrenergic receptors. When postsynaptic alpha-adrenergic receptors are stimulated by catecholamines released from the nerve endings, arteriolar and venular constriction result. When presynaptic alpha-2 receptors are stimulated further release of norepinephrine from the nerve ending into the synaptic cleft is inhibited, making alpha-1 receptor blockers (doxazosin, prazosin, terazosin) not to prevent alpha-2 receptor stimulation. These agents reduce arterial pressure as a result of a decreased vascular resistance (without associated increased heart rate, cardiac output or myocardial contractility). As a result, they may produce postural

hypotension (often after the first dose administered), strongly suggesting that this first dose should be the lowest dose available and cautionary advice to the patient (most frequently the man with prostatic hyperplasia) who takes this medication at bedtime. Pseudotolerance can be offset by the addition of a diuretic; however, this may exacerbate the potential for postural hypotension. This volume expansion with pseudotolerance may be associated with edema and perhaps shortness of breath suggesting cardiac failure. This problem was frequently observed during the ALLHAT multicenter trial prompting discontinuing the prazosin limb due to possible cardiac failure.

Smooth Muscle Vasodilators

These agents (hydralazine and minoxidil) have been used with a resurgence associated with the introduction of the beta-blockers and with varying success rates in patients with cardiac failure. They reduce blood pressure associated with a fall in vascular resistance and reflexive stimulation of the heart by increasing heart rate, myocardial contractility and increased myocardial oxygen demand. These undesirable reflex actions (which may be associated with chest discomfort or aggravation of a dissecting aortic aneurysm) may be offset with the concomitant use of a beta-blocker. The intravenous agent diazoxide is a non-natriuretic thiazide congener must be injected rapidly in 300 mg (or smaller dose) bolus may be used for rapid reduction of pressure in an emergent situation but, again, caution must be kept in mind since, reflex cardiac and aortic stimulation may result in those unwanted events described above.

TREATMENT ALGORITHMS ADVOCATED OVER THE YEARS

STEPPED CARE APPROACH

Early in the long-term experience of therapy with the antihypertensive agents, a so-called stepped care approach was advocated. The historical background to this approach dates back to the multicenter and placebo-controlled Veterans Administration Cooperative Study which was the first study to demonstrate the efficacy and safety of an antihypertensive drug therapy. Initially, this was demonstrated in patients receiving a ganglion blocking agent with a diuretic and, later, in the placebo-controlled studies with a combination of the diuretic chlorothiazine and, later, hydrochlorothiazide and reserpine and, if necessary, with the addition of the smooth muscle relaxant hydralazine. Most noteworthy, this triple therapeutic combination was shown to be highly effective, especially in hypertensive patients whose diastolic pressures were greater than 114 mm Hg and in later reports in the 90–114 mm Hg range. This concept of introducing therapy with the simplest agent and later, with other agents that acted additively or synergistically, was employed by other specialties in medicine for its simple rationale and effectiveness.

INDIVIDUALIZED STEPPED-CARE APPROACH (TABLE 10)

Later, as other agents became available which, by practicality, they were used by adding to the diuretic (if not initially), and with the addition of other agents. This therapeutic concept was presented in the later JNC recommendations and a very practical approach to the management of the hypertensive patient was practicable. Thus, a nonpharmacological or lifestyle management approach to treatment was advocated for all patients (even if normotensive, but with a strong family history of hypertension, "high normal" blood pressures, and more recently with those patients with pre-hypertension). If this non-drug treatment was found to be adequate, the patient would be followed carefully with periodic monitoring of blood pressure. If, however, this approach was found to be of an inadequate response, introduction of a pharmacological agent was instituted. Usually, this would be a diuretic, although with the introduction of one of the newer antihypertensive agents (calcium antagonist, ACE inhibitor, ARB, and more recently, the renin inhibitor). If a second or third agent were indicated, this might be done first with the addition of the drug or, later, with a combination drug. Experience has taught us that following this approach upward of 85% of patients would respond to this approach. As recently as the publication of JNC-7, selection of one of the recommended drugs alone or in combination may be dictated by the patient's so-called "compelling indications for the selected individual drug class" (reference JNC-7 and Table 6). Support for its recommended advice was based upon experiences gained from the large number of clinical trials which have become available.

TABLE 10

Individualized stepped-care approach to antihypertensive therapy

Nonpharmacologic approaches (baseline) *Initial selection*	
Adequate response	*Inadequate response*
Increase dosage	Add second agent
Substitute another agent	Add third (or more) agents

HYPERTENSIVE EMERGENCIES

In the years prior to antihypertensive therapy, a large number of hospitalized patients were encountered. But, progressively,

TABLE 11

Hypertensive emergencies

- Hypertensive encephalopathy
- Hypertension with intracranial hemorrhage
- Malignant (and accelerated) hypertension
- Hypertensive heart failure
- Hypertension with dissecting aortic aneurysm
- Severe hypertension associated with myocardial infarction
- Systolic hypertension (160–170 mm Hg) following vascular surgery and/or vascular grafting
- Pheochromocytoma crisis
- Clonidine withdrawal
- Hypertensive crisis during cardiovascular catheterization
- Food-related hypertension (associated with tyramine or with monoamine oxidase inhibiting drugs)
- Hypertension (in children) with acute glomerulonephritis
- Acute glomerulonephritis with oliguria or anuria
- Eclampsia

the number of these patients with these problems has been reduced; but, sadly, a review of Table 11 will reveal that their numbers are still far too high. The reader has to refer to JNC-7 or Author's recent reference for the various forms of hypertensive emergencies, the rationale for selecting the most reasonable agent, its dose range and frequency (as well as selection thinking for additional drugs).

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Chapter 64

Peripheral Vascular and Cerebrovascular Disease

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Chapter Outline

- Peripheral Arterial Disease
  - Epidemiology
  - Vascular History and Physical Examination
  - Risk Factors for PAD
  - Clinical Presentation and Natural History
  - Diagnosis
  - Management
- Carotid Artery Disease
  - Pathophysiology
  - Natural History and Risk Stratification
  - Screening
  - Diagnosis
  - Management
- Renal Artery Stenosis
  - Epidemiology and Natural History of ARAS
  - Screening and Diagnostic Tests
  - Medical Management
  - Revascularization
- Subclavian Artery Stenosis
- Vertebrobasilar Artery Stenosis
- Mesenteric Ischemia

INTRODUCTION

Peripheral vascular disease (PVD) includes myriad pathophysiological syndromes that affect arterial, venous and lymphatic circulation, essentially all vascular disease that alters end-organ perfusion. In contrast, peripheral arterial disease (PAD) involves disorders that jeopardize blood supply to the upper or lower extremities. The most common cause of PAD is atherosclerosis, although it less commonly results from embolism, vasculitis, fibromuscular dysplasia (FMD), entrapment or thrombosis.

The PAD is considered a major risk factor for cardiovascular mortality and morbidity. Intermittent claudication (IC) jeopardizes quality of life in many patients. In contrast to coronary artery disease (CAD), PAD is often underdiagnosed by cardiologists and primary care physicians. There has been increasing focus on the diagnosis and management of PAD over the last decade.

In this chapter we have comprehensively reviewed the natural history, diagnosis and management of PAD as well as renovascular, mesenteric, subclavian, carotid and vertebrobasilar artery disease.

PERIPHERAL ARTERIAL DISEASE

EPIDEMIOLOGY

PAD affects a large number of people throughout the world. The prevalence of PAD in the general population varies widely despite a consensus on appropriate diagnostic criteria (Table 1), which could be explained by age of cohort studied, underlying atherosclerotic risk factors or presence of concomitant coronary or cerebrovascular disease (CVD).[1-11] In the United States, PAD is estimated to affect more than 5–8 million adults.[6,10] The prevalence of PAD based on ankle-brachial index (ABI) varies from 3 to 11%[1-4,9,10] in adults who are more than 40 years old and increases to 14.5–20% in the elderly (Fig. 1),[1,8,10] and 12.6–30.9% in patients with risk factors for CAD.[6,11] Prevalence is even higher (up to 40%) in patients with established vascular disease other than PAD.[11] Despite the high prevalence, classic symptoms of IC present in less than 6% of the general population and about 12% of patients with established PAD.[4,6-8,12]

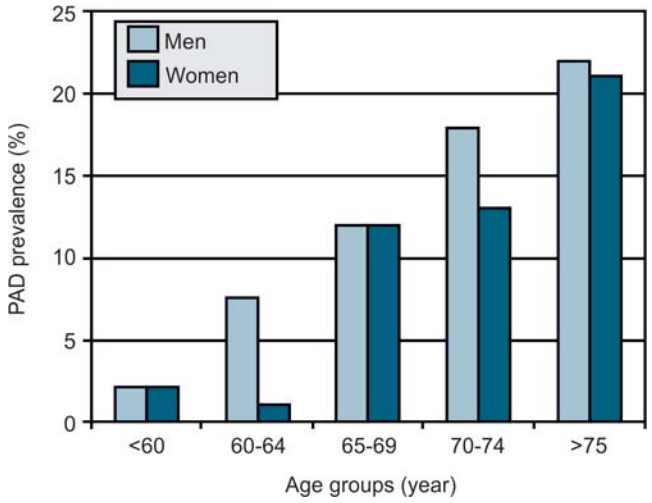


FIGURE 1: Prevalence of large-vessel peripheral arterial disease (PAD) by age. (*Source*: Modified from Criqui MH, Fronek A, Barrett-Connor E, et al. The prevalence of peripheral arterial disease in a defined population. Circulation. 1985;71:510-5)

TABLE 1

Prevalence of PAD† based on ankle-brachial index and intermittent claudication

Study	*Population*	*No. of subjects*	*Age (years)*	*Prevalence per ABI* < 0.9*	*Intermittent claudication*	*Comment*
Criqui et al.[1] San Diego study (1985)	General	613	38–82	11.7% Age > 70: 20%	Male: 2.2% Female: 1.7%	Small vessel disease in 5.2%
Fowkes et al.[2] Edinburgh artery study (1991)	General	1,592	55–74	9%	4.5%	Prevalence of claudication equal in male and female
Newman et al.[3] Cardiovascular health study (1993)	General	5,084	≥ 65	12.4%	N/A	
Hooi et al.[4] Limburg PAOD study (1998)	General	3,650	40–78	8.6%	3.8%	Abnormal ABI defined as < 0.95
Meijer et al.[5] Rotterdam study (1998)	General	7,715	≥ 55	19.1%	1.6% Male: 2.2% Female: 1.2%	
Hirsch et al.[6] PARTNERS program (2001)	Primary care practice‡	6,979	50–≥ 70	29%	5.5%; 12.6%§	
Murabito et al.[7] Framingham offspring study (2002)	General	3,313	≥ 40	3.6%	1.3%	
Diehm et al.[8] (2004)	Primary care practice	6,880	≥ 65	18%	2.8%	
Resnick et al.[9] Strong heart study (2004)	General	4,393	45–74	4.9%		Prevalence of 9.2% with ABI > 1.4
Selvin et al.[10] NHANES‖ (2004)	General	2,174	≥ 40	4.3% Age ≥ 70: 14.5%		
Fowkes et al.[11] AGATHA study (2006)	General¶	8,891	≥ 55	30.9–40.5%**		

*ABI—Ankle-brachial index. Abnormal defined as < 0.9
†PAD—Peripheral artery disease
‡Risk factors—Smoking or diabetes
§5.5% in newly diagnosed patients and 12.6% in patients with established PAD
‖NHANES—National Health and Nutrition Examination Survey
¶Patients with two or more risk factors (diabetes mellitus, dyslipidemia, smoking habit) or with vascular disease
**30.9% in patients with risk factors and 40.5% in patients with established vascular disease

Cost analysis from Medicare data and claims in 2001 showed that a total of $4.37 billion was spent in the United States on PAD-related treatment and 88% of those expenditures were for inpatient care.[13]

PAD also impairs functional status and quality of life, even for patients who do not report leg symptoms.[14,15]

VASCULAR HISTORY AND PHYSICAL EXAMINATION

A comprehensive and detailed patient history, review of the cardiovascular system and thorough physical examination are keys in the diagnosis and management of vascular disease.

Patients often underreport symptoms that may give a clue to the diagnosis of PAD. American College of Cardiology/American Heart Association (ACC/AHA) guidelines[16] strongly recommend a comprehensive review of systems with a focus on the vascular system in individuals at risk or with symptoms suggestive of underlying vascular disease. Table 2 represents the key points in review and physical examination of the vascular system.

RISK FACTORS FOR PAD

The major risk factors for PAD are the same as for CAD and include age more than or equal to 50 years (striking evidence, see epidemiology section), male gender, race, smoking, diabetes mellitus, dyslipidemia and hypertension (HTN). The risk is significantly higher in smokers [odds ratio (OR) 4.46], diabetics (OR 2.71) and black ethnicity (OR 2.83).[10] Smoking, but not diabetes, seems to be a stronger risk factor for development of PAD rather than CAD, whereas diabetes is shown to be the only predictor in the progression of small-vessel PAD as opposed to other traditional risk factors that contribute to the progression of large-vessel PAD.[27] Odds ratios for the major risk factors of PAD are depicted in Figure 2.

CLINICAL PRESENTATION AND NATURAL HISTORY

Clinical presentation, natural history and outcome of patients with PAD are summarized in Flow chart 1.

TABLE 2

Focused review of system and vascular examination

Review of system	
Exertional lower extremity pain or impairment	• Can be described as: fatigue, aching, numbness or pain • Primary site: buttock, thigh, calf or foot
Nonhealing ulcer	(See critical limb ischemia section)
Postprandial abdominal pain	• Provoked by eating and is associated with weight loss (mesenteric ischemia)
Physical examination	
Blood pressure	• In both arms and notation of asymmetry. Difference > 20 mm Hg indicates innominate, subclavian or axillary disease
Palpation of carotid pulse and notation of the carotid upstroke and presence of bruit	• Carotid bruit should be described as systolic, diastolic or both • Sensitivity of bruits is low in detecting high-grade lesion in asymptomatic patients (56%)[17] and slightly better in symptomatic patients (63%)[18] • Carotid bruit is a poor predictor of underlying carotid stenosis and risk of stroke in asymptomatic patients[19] • Carotid bruit is a prognostic indicator of cardiovascular death and myocardial infarction[20]
Auscultation of flank and abdomen	• Prevalence of bruit in general population: 6.5–27%[21] • Sensitivity for detection of renal artery stenosis: 39–77.7%[21]
Allen test	• False-positive result with overextension of the wrist[22]
Abdominal palpation	• Sensitivity for detection of AAA is 33%. Even lower in obese patients[23]
Physical examination of lower-extremity PAD	
Inspection	• Gangrene, ulcers with necrotic base involving distal foot • Distal hair loss, atrophic skin changes and foot discoloration (All low yield for clinical diagnosis of PAD)[24]
Palpation of pulses	• Brachial, radial, ulnar, femoral, popliteal, dorsalis pedis and posterior tibial site • Pulse intensity should be recorded numerically: 0 = absent; 1 = diminished; 2 = normal; 3 = bounding • Abnormal pedal pulses have high specificity for presence of PAD[24] • In a small number of normal individuals, dorsalis pedis pulse is absent (debranching from anterior tibial at the ankle) • Patients with isolated occlusion of internal iliac may present with impotency, buttock claudication (Leriche's syndrome) and sometimes normal femoral and pedal pulses • Absent of pedal pulses: physicians tend to overdiagnose PAD[25]
Buerger test	• Elevate the supine patient's foot perpendicular to the horizontal plane, which will cause foot pallor in those with vascular disease. Then, by slowly lowering the limb, record the angle at which a reddish hue returns (resolution of pallor below the horizontal plane is considered abnormal)[26] • Low sensitivity[25]
Capillary refill test	• Digital pressure to the plantar skin of the distal great toe for 5 minutes, local pallor > 5 seconds is regarded as delayed refill • Low yield for diagnosis of PAD
Auscultation of both femoral arteries	• For detection of bruits
(Abbreviations: AAA: Abdominal aortic aneurysm; PAD: Peripheral arterial disease)	

Asymptomatic and Symptomatic (IC) PAD

The term "claudication" is derived from the Latin word *caudicatio*, translated as "to limp," in vascular medicine it is defined as fatigue, discomfort or pain that occurs in specific limb muscle groups during exertion due to exercise-induced ischemia. Individuals with claudication have sufficient blood flow at rest, so ischemic symptoms are absent. With exertion, demand and supply of blood flow mismatch and, along with acquired metabolic abnormality in affected muscle groups, causes discomfort that resolves with rest. Most patients with PAD are asymptomatic (defined as absence of claudication), and among those with leg symptoms, the majority have atypical symptoms; and only less than 20% of patients present with classic IC.[14,28]

Patients with limited daily activity may never develop symptoms suggestive of IC and may never get diagnosed. In the PAD Awareness, Risk and Treatment: New Resources for Survival (PARTNERS) trial, close to 50% of newly diagnosed patients with PAD using ABI had no symptoms, and only 5.5% presented with classic IC.[6] Furthermore, evidence suggests that the progression of underlying PAD is identical regardless of presence or absence of symptoms in the legs and that development of critical leg ischemia (CLI) is independent of presenting symptoms.[12]

Nonvascular causes that may mimic claudication (pseudoclaudication), like spinal stenosis (worsens with standing up/changing position), nerve root compression, venous congestion (relief with leg elevation), compartment syndrome

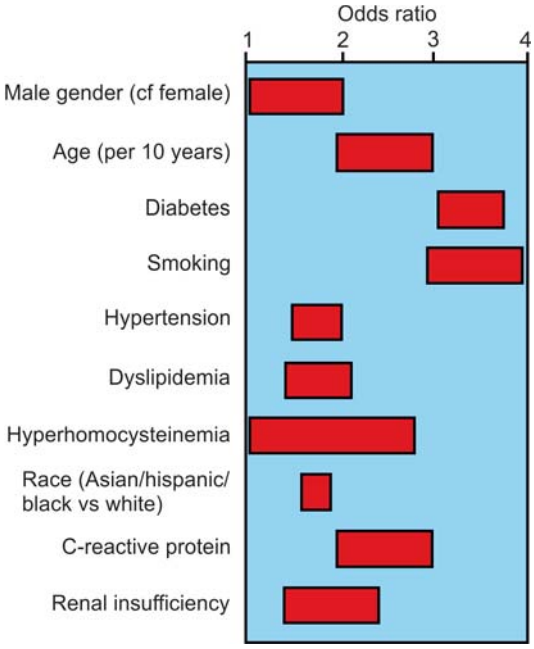


FIGURE 2: Approximate odds ratio for risk factors for symptomatic peripheral arterial disease. (*Source*: Modified from Norgren L, Hiatt WR, Dormandy JA, et al. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). J Vasc Surg. 2007;45:S5-67)

and arthritis, should be distinguished with careful history and physical examination.[12]

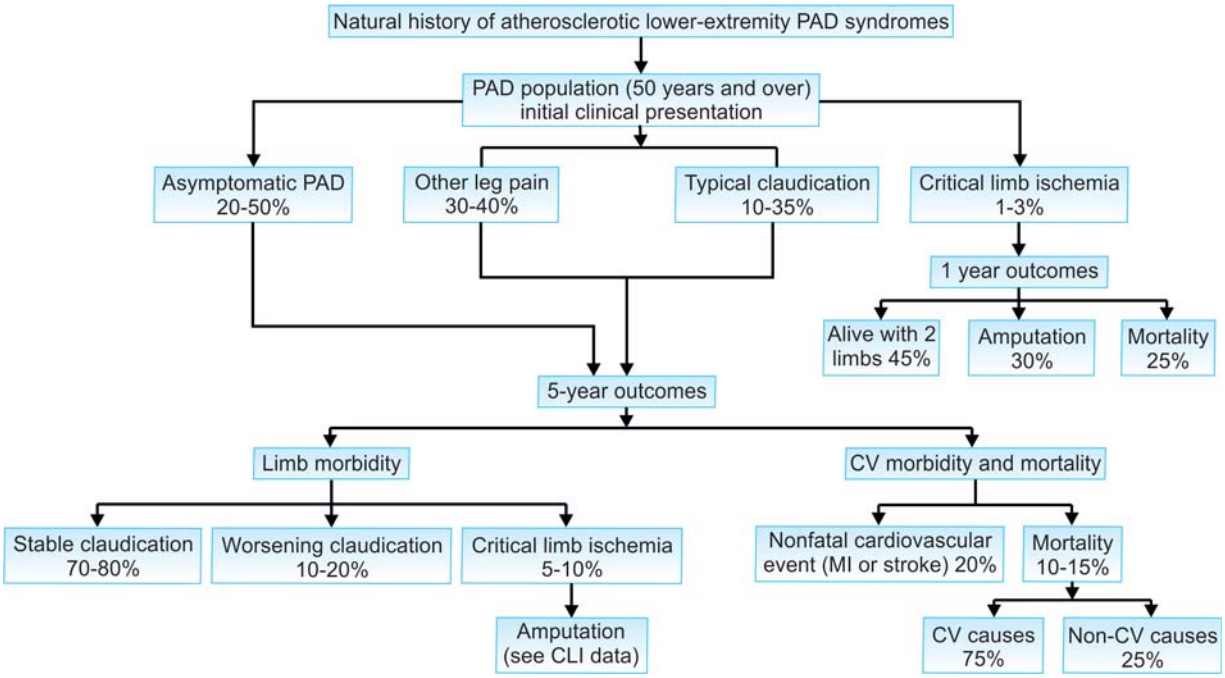
Critical Limb Ischemia

Critical limb ischemia is defined as chronic ischemic rest pain (more than two weeks), ulcers or gangrene attributed to objectively proven PAD (abnormal ABI < 0.5; toe pressure < 50 mm Hg; transcutaneous O_2 < 30 mm Hg).[12] The clinical severity of ischemia can be classified according to either Fontaine or Rutherford classifications (Table 3).

Ischemic rest pain usually begins distally in the toes and foot, which is worse when the leg is elevated (e.g. at night in supine position) and is relieved with dependency (e.g. sitting or standing up). As the disease progresses, the patient may experience paresthesia, coldness or weakness of extremities. Lower-extremity edema is a major concern in patients with CLI, thought to be secondary to vasomotor paralysis. This phenomenon is a result of chronic ischemia causing chronic exposure to vasorelaxing factors in patients with diseased vessels.[29]

Patients with CLI may present with ischemic ulcers or gangrene (defined as focal or extensive necrosis of the skin and underlying tissue). Clinicians should pay special attention to patients with diabetic neuropathy (silent progression of

FLOW CHART 1: Fate of claudication over 5 years



(Abbreviations: CLI: Chronic limb ischemia; CV: Cardiovascular; MI: Myocardial infarction; PAD: Peripheral arterial disease). (*Source*: Reproduced with permission from Hirsch AT, Haskal ZJ, Hertzer NR, et al. ACC/AHA 2005 guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): executive summary a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients with Peripheral Arterial Disease) endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; and Vascular Disease Foundation. J Am Coll Cardiol. 2006;47:1239-312, and Weitz JI, Byrne J, Clagett GP, et al. Diagnosis and treatment of chronic arterial insufficiency of the lower extremities: a critical review. Circulation. 1996;94:3026-49)

TABLE 3

Classification of peripheral arterial disease (PAD): Fontaine's stages and Rutherford's categories

Fontaine		*Rutherford*		
Stage	*Clinical*	*Grade*	*Category*	*Clinical*
I	Asymptomatic	0	0	Asymptomatic
IIa	Mild claudication	0	1	Mild claudication
IIb	Moderate to severe claudication	I	2	Moderate claudication
		I	3	Severe claudication
III	Ischemic rest pain	II	4	Ischemic rest pain
IV	Ulceration or gangrene	III	5	Minor tissue loss
		III	6	Major tissue loss

(*Source*: Reproduced with permission from Norgren L, Hiatt WR, Dormandy JA, et al. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). J Vasc Surg. 2007;45:S5-67)[12]

ischemia), since their first presentation could be ulcers or amputation. Therefore, all diabetes patients with foot ulcer should be ruled out for evidence of PAD using ABI. Ischemic foot ulcers are painful (not so in diabetic neuropathy), cold, pale and have irregular margins (Figs 3A and B). Other causes of foot and leg ulcers include venous insufficiency, skin infarct secondary to embolism (severe pain, ulcer located in lower third of leg) and neuropathy (painless, normal pulses, regular margins, located in weight-bearing area and associated with deformity).



FIGURES 3A AND B: (A) Ischemic ulcers are usually painful, cold and pale with irregular margins. (B) Ulcers secondary to venous insufficiency are usually painless, with regular margins located in medial malleolar (Photographs Courtesy of Dr Jeffrey Niezgoda)

Patients with PAD will have a poor prognosis if they develop CLI, with a 25% risk of amputation and 25% risk of cardiovascular mortality in one year (Flow chart 1). The rate of amputation remains high even after bypass surgery compared to patients who present with IC (12% vs 1% in one year).[30]

Acute Limb Ischemia

Acute limb ischemia (ALI) is defined as any sudden decrease in limb perfusion causing a potential threat to limb viability.[12] The distal tissue bed in the limb becomes ischemic with energy metabolism shifting from an aerobic to an anaerobic process. Progressive ischemia leads to cell dysfunction and death. Nervous tissue cells, skin and subcutaneous tissue are the most susceptible, followed by muscle cells. It is accepted that a patient without underlying vascular disease and an acute arterial blockage has approximately six hours for revascularization before irreversible functional damage occurs; however, the exact time frame depends on the degree of collateral perfusion in any given patient.

Causes for ALI include native thrombosis, embolism primarily from cardiac source and graft thrombosis. Other less common causes include peripheral aneurysm with embolism or thrombosis, vasculitis, aortic dissection causing obstruction and iatrogenic trauma.[12,31]

Physical findings of ALI may include the 5 Ps: Pain, Pulselessness, Pallor, Paresthesia and Paralysis (poor prognostic sign). It is very important to differentiate threatened extremities from viable extremities since the former is a medical emergency. Presence of rest pain, sensory loss and muscle weakness are all characteristics of threatened limb. Due to inaccuracy of physical examination, all patients with suspected ALI should have Doppler assessment of peripheral pulses at bedside to determine the presence of flow. If confirmed, all patients should be started on intravenous (IV) heparin and referred immediately for further vascular evaluation (see Management section).

Mortality rates for patients presenting with ALI range from 15% to 20%. Major morbidities reported are as follows: major bleeding and/or operative intervention in 10–15%; major amputation in up to 25%; fasciotomy in 5–25% and renal insufficiency in up to 20%.[12]

Despite the fact that patients with asymptomatic PAD have a threefold to sixfold increased risk of death from CAD and CVD,[32] there is no general agreement among major professional organizations, including the US Preventive Task Force, regarding screening of the general population, since there is no evidence that screening this population will have survival benefit.[33] However, based on the Inter-Society Consensus for PAD (TASC II),[12] ACC/AHA guidelines[16] and American Diabetes Association (ADA) guidelines,[34] screening ABI is strongly recommended for the following populations:

- Leg symptoms suggestive of IC or rest ischemia
- All patients with abnormal pedal pulses
- All patients between 50 years and 69 years of age who have a cardiovascular risk factor (particularly diabetes and smoking)
- All patients age more than or equal to 70 years regardless of risk factor status
- All patients with Framingham score 10–20%
- All patients with diabetes and age less than 50 years, if they have at least one additional cardiovascular risk factor
- Known CAD, carotid artery stenosis (CAS) or renal artery stenosis (RAS).

Among patients presenting with lower-extremity PAD, about one-third to one-half have evidence of CAD based on clinical history and electrocardiogram, and two-thirds based on abnormal stress test.[35] Angiographically significant CAD (> 50%) is reported in the range of 50–70% in the literature.[36,37] Therefore, it is reasonable to consider screening for CAD in patients with the aforementioned risk factors, findings and presentation.

DIAGNOSIS

Ankle-Brachial Index

The ankle-brachial index (ABI) is a simple, noninvasive test that is used for both screening and establishing diagnosis of PAD with a high degree of accuracy. It is simply calculated by dividing the highest ankle pressure (mm Hg) by highest arm pressure (mm Hg) in both limbs (Fig. 4). In normal individuals without PAD, ankle systolic pressure is usually 10–15 mm Hg higher than arm brachial pressure due to the effect of pulse wave reflection. A truly normal ABI is greater than 1.10 and abnormal ABI is defined as less than or equal to 0.90. Use of the ABI level of 0.90 or less has proved to have a sensitivity and specificity of 95% and 100%, respectively, for detecting angiographically positive PAD.[12,16]

Low ABI (< 0.9) is strongly associated with the risk of stroke, transient ischemic attack (TIA), worsening creatinine levels and cardiovascular mortality (threefold to sixfold),[9,38,39] and an ABI decline of more than 0.15 over 3–6 years from baseline is independently associated with increased cardiovascular risk.[40]

In patients with diabetes or renal insufficiency, measured ABI level could be falsely high (> 1.40), mainly due to calcified vessels. In this situation toe-brachial index (TBI) can be measured. The abnormal value for TBI is less than 0.70 because toe pressure is approximately 30 mm Hg less than ankle pressure. Exercise testing is recommended in patients with high pretest probability of PAD and a normal resting ABI. A decrease in ABI of 15–20% from baseline would be diagnostic for PAD.[12]

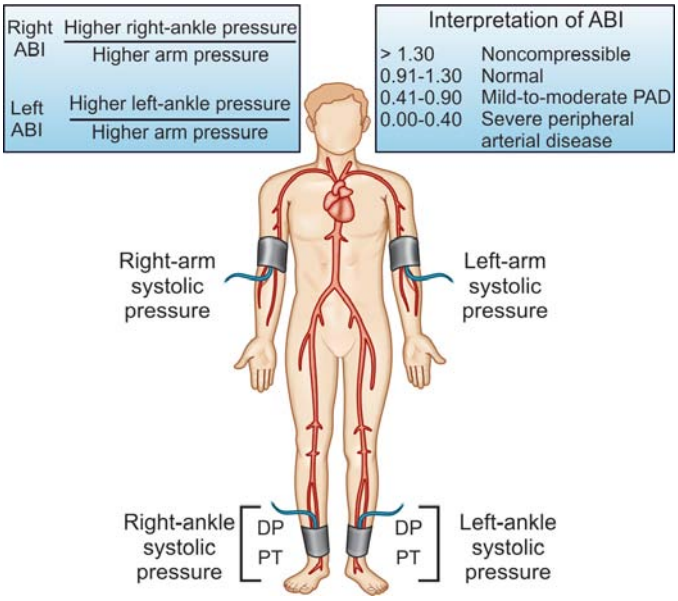


FIGURE 4: Performing pressure measurements; calculation and interpretation of the ankle-brachial index (ABI). (Abbreviations: DP: Dorsalis pedis; PT: Posterior tibial). (*Source*: Modified from Hiatt WR. Medical treatment of peripheral arterial disease and claudication. N Engl J Med. 2001;344:1608-21)

Other Noninvasive Vascular Modalities

- *Duplex ultrasound (DUS)*: Doppler velocity consists of three waveforms: a systolic peak, early diastole reversal flow and forward flow in late diastole. In severe PAD, there is a decrease in peak systolic flow, absence of reversal flow and increase of flow in late diastole. The sensitivity and specificity of duplex for detecting more than 50% stenosis is 86% and 97%, respectively, for aortoiliac, and 80% and 98%, respectively, for femoropopliteal disease.[41]
- *Computed tomography angiogram (CTA)*: It has sensitivity and specificity of 87% and 96%, respectively, for detection of more than 50% angiographic stenosis.[42]

  The CTA's primary limitation is the evaluation of severely calcified lesions. Beam-hardening artifacts from calcification make interpretation difficult. Other limitations include the use of a relatively large amount of IV contrast. This is a real concern in patients with borderline renal function, renal insufficiency or acute renal failure.
- *Magnetic resonance angiogram (MRA)*: It has been demonstrated to have sensitivity and specificity of 92% and 94%, respectively, for significant (> 50%) stenosis.[43] The MRA cannot be used in patients with contraindication to magnetic resonance (e.g. those with defibrillator, pacemaker, or metallic stents, coils and clips). Finally, the US Food and Drug Administration (FDA) has issued a warning on the use of gadolinium for patients with renal impairment because it has been linked to the development of nephrogenic systemic fibrosis, also known as nephrogenic fibrosing dermopathy.[44]

- *Digital Subtraction Angiography (DSA)*: It is considered the "gold standard" imaging test. Using DSA techniques remains the preferred method in most cases. A direct assessment of pressure gradient (more than 5–10 mm Hg) across the stenotic lesion will provide more information regarding the need for intervention. In patients with ALI, angiography remains the procedure of choice for intra-arterial lytic therapy. On the other hand, angiography is an invasive procedure and carries certain risk (e.g. mortality, dissection, bleeding, renal failure), and it should only be performed in appropriate clinical scenarios.

MANAGEMENT

Management of PAD includes management of atherosclerotic risk factors, an exercise training program, pharmacotherapy for IC and, finally, endovascular or surgical intervention for patients in whom revascularization is necessary.

Management of Atherosclerotic Risk Factors

The PAD is considered a CAD "risk equivalent," therefore aggressive risk-factor modification is strongly recommended. A summary of recommended interventions with supporting data is depicted in Table 4.

Management of Symptoms

Exercise therapy: The role of an exercise program in the management of IC has been studied extensively. A review of 22 randomized controlled trials with 1,200 participants with PAD showed that an exercise program significantly improves maximal pain-free walking time and distance irrespective of symptoms (Table 5).[59] Supervised exercise therapy is shown to improve maximal treadmill walking distance over unsupervised exercise therapy.[60]

Both ACC/AHA and TASC II strongly recommend supervised exercise as initial treatment for all patients with PAD (Class I, Level of evidence: A).

Pharmacologic treatments: Cilostazol (Pletal) is a phosphodiesterase type-3 inhibitor with vasodilator and mild antiplatelet properties. The superiority of cilostazol in increasing maximal and pain-free walking distance is established in randomized trials. In a meta-analysis of eight randomized trials, cilostazol increased maximal and pain-free walking distance by 50% and 67%, respectively.[62] Cilostazol (100 mg twice daily) is shown to be superior to pentoxifylline (400 mg three times daily) in increasing walking distance.[63] After endovascular treatment (EVT), cilostazol was associated with better freedom from target vessel revascularization (TVR) (84.6% vs 62.2%, P = 0.04) and lower rate of restenosis (43.6% vs 70.3%, P = 0.02) compared to a control group.[64,65] The most common side effects of cilostazol are headache, palpitations and diarrhea. Current guidelines recommend the use of cilostazol 100 mg twice daily in all patients with PAD and lifestyle-limiting claudication in the absence of heart failure to improve symptoms and walking distance.[12,16]

Pentoxifylline (Trental) is a methylxanthine derivative with hemorheological properties. Its possible mechanism of action includes an increase in red blood cell deformity and decreases in fibrinogen concentration, platelet adhesiveness and whole-blood viscosity. Available data indicate that the benefit of pentoxifylline is marginal and is not well established. The ACC/AHA guidelines assign a Class IIb indication for the use of

TABLE 4

Summary of medical management for PAD

Management of atherosclerotic risk factors	*Recommendation/Comment*
Smoking cessation[12,16,45-47]	• Physician advice • Nicotine replacement therapy • Bupropion • Improvement of leg symptoms and preventing systemic complication • Associated with significant reduction in all-cause mortality, rate of amputation, progression of PAD and graft failure
Lipid-lowering therapy (statins)[12,16,48-51]	• Dietary modification • LDL goal < 70 mg/dL • Benefit beyond LDL level
Blood pressure lowering drugs[12,16,52-54]	• BP goal < 140/90 mm Hg, or < 130/80 mm Hg in patients with DM and CKD • Benefit of ACE-I beyond antihypertensive effect • Consider using beta-blockers in patients with PAD and CAD (No data supporting worsening of symptoms with its use)
Antithrombotic therapy[12,16,55-58]	• Aspirin (81–325 mg) as first choice, consider clopidogrel (75 mg) as suitable alternative • No benefit with combination of aspirin and clopidogrel unless for patients undergoing stenting • Reduce risk of ischemic stroke, myocardial infarction or vascular death • Warfarin: No proven benefit except for IC
Management of Symptoms	
Exercise therapy[12,16,59-61]	• Strong data based on randomized controlled trials • Consider supervised exercise therapy three times per week for 30–60 minutes as initial treatment for all patients with PAD • Maintain high physical activity during daily life
Cilostazol[1,16,62-65]	• Use in all patients with life-limiting intermittent claudication • Improves symptoms and increases pain-free walking distance • Avoid in patients with congestive heart failure* • Increased plasma concentration with concomitant use of CYP450 3A4 inhibitors • Proven benefit over pentoxifylline
Pentoxifylline[12,16,63]	• The benefit is marginal • Tachyphylaxis with long-term use • Not commonly used in US.

*As noted by a US Federal Drug Administration black box warning.
Abbreviations: ACE-I: Angiotensin-converting enzyme inhibitor; CAD: Coronary artery disease; CKD: Chronic kidney disease; DM: Diabetes mellitus; IC: Intermittent claudication; LDL: Low-density lipoprotein; MI: Myocardial infarction; PAD: Peripheral arterial disease.

TABLE 5

Exercise regime compared to usual care

Outcome or subgroup title	*No. of studies*	*No. of participants*	*Mean difference (95% CI)*
Maximum walking distance (m)	6	391	113.20 (94.96–131.43)
Pain-free walking distance (m)	6	322	82.19 (71.73–92.65)
Maximal walking time (min)	7	255	5.12 (4.51–5.72)
Pain-free walking time (min)	3	150	2.91 (2.51–3.31)

(Abbreviations: CI: Confidence interval; m: Meter; min: Minute). (*Source*: Watson L, Ellis B, Leng GC. Exercise for intermittent claudication. Cochrane Database Syst Rev. 2008;CD000990)[61]

pentoxifylline (400 mg twice daily) as a second-line alternative to cilostazol.[16]

Other reported medical therapies: A long list of medical and natural therapies, including L-arginine, propionyl-L-carnitine, *Ginkgo biloba*, oral vasodilator prostaglandins, chelation (may be harmful), vit E and avasimibe, are studied in the literature without showing significant efficacy for treatment of PAD; therefore, their use is currently not recommended.[12,16]

Revascularization: There are three clear indications for revascularization in patients with PAD:

1. Life-limiting claudication despite aggressive risk-factor modification, supervised exercise program and trial of cilostazol;
2. Critical limb ischemia and limb salvage; and
3. Acute limb ischemia.

Endovascular interventions for revascularization include angioplasty, stent, stent grafts, plaque-debulking procedure, thrombolysis and percutaneous thrombectomy. Surgical options include autogenous or synthetic bypass, endarterectomy or an intraoperative hybrid procedure.

Catheter-based revascularization was first described by Dotter and Judkins[66] in 1964. Endovascular therapy offers several distinct advantages over open-surgical intervention for selected lesions. Lower morbidity and mortality rates, shorter hospital stay and patient preference, along with remarkable technological advances (especially stents), have all resulted in the selection of endovascular therapy as a first-line invasive strategy in suitable lesions. In addition, use of endovascular therapy generally does not preclude or alter subsequent surgery, if needed. An analysis of Medicare beneficiaries between 1996 and 2006 showed that endovascular intervention increased more than threefold while bypass surgery declined by 42%. The same report showed a significant decline in the rate of amputation (more than 25%).[67]

Patency post-percutaneous intervention is related to anatomic factors and clinical variables. Sustained patency is highest for lesions in the common iliac artery (CIA) and progressively worsens for more distal vessels. Other anatomic factors affecting patency include severity of the disease in run-off arteries, length of the stenosis and number of lesions treated. During lower-extremity angiography, it is always recommended to measure the gradient across the stenotic lesion if its significance is in doubt. Clinical variables with impact on outcome include diabetes, smoking, renal failure and severity of ischemia.

Suprainguinal (aortoiliac) revascularization: Patients with aortoiliac occlusive disease (AIOD) may present with buttock, thigh or hip claudication, CLI or impotence and absent femoral pulses, a condition named Leriche's syndrome after the surgeon who described this condition in the 19th century. The catheter-based percutaneous approach has become the procedure of choice in patients with aortoiliac/iliac disease, and is associated with lower mortality and morbidity rates.[68] The TASC II document describes characteristic lesion morphology from ideal (Type A) to unfavorable (Type D) for iliac lesions (Fig. 5). The recommended initial approach for Type A and B, and for selected C lesions of the iliac artery is catheter-based intervention. Patients with Type D lesions generally will be considered surgical candidates, but with newer technologies, such as reentry devices and covered stent grafts, these patients are increasingly considered for endovascular approach on a case-by-case basis.[12] Primary stent placement in iliac artery is now recommended as a Class I indication, given its higher procedural success rate and lower risk of long-term failure compared to percutaneous transluminal angioplasty (PTA) alone (Figs 6A and B) (Table 6),[68] and without the associated 8.3% surgical morbidity and 3.3% surgical mortality.[69]

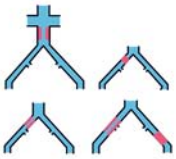
Surgical intervention is reserved for lesions that are not amenable to percutaneous intervention. As a general rule, a bilateral surgical bypass from the infrarenal abdominal aorta to both femoral arteries is usually recommended for diffuse disease throughout the aortoiliac system. While aortobifemoral bypass sustains the highest patency rate, patency rate is significantly lower in infrainguinal and post extra-anatomic bypasses[69] (Fig. 7).

Infrainguinal revascularization: Infrainguinal disease is divided and treated on the basis of three anatomic segments:

1. Common and deep femoral artery disease: It is best treated with an iliofemoral bypass operation or endarterectomy with patch angioplasty.[70] Since this vessel lies over the hip joint, placement of the stent is usually suboptimal and can be associated with stent thrombosis or restenosis causing acute limb-threatening ischemia, whereas atherectomy or cutting balloon PTA is reserved for patients who are not surgical candidates.
2. Superficial femoral and popliteal artery disease: Stenosis of the superficial femoral artery (SFA) is the most common form of PAD associated with claudication. Like aortoiliac disease, the TASC II group has classified lesion morphology from ideal (Type A) to unfavorable (Type D) for SFA lesions (Fig. 8). Safety and efficacy of PTA versus surgery was



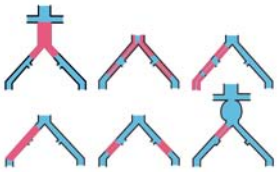
TASC A
Unilateral or bilateral stenoses of CIA
Unilateral or bilateral single short (≤3 cm) stenosis of EIA



TASC B
Short (3 cm) stenosis of infrarenal aorta
Unilateral CIA occlusion
Single or multiple stenosis totalling 3-10 cm involving the EIA not extending into the CFA
Unilateral EIA occlusion not involving the origins of internal iliac or CFA

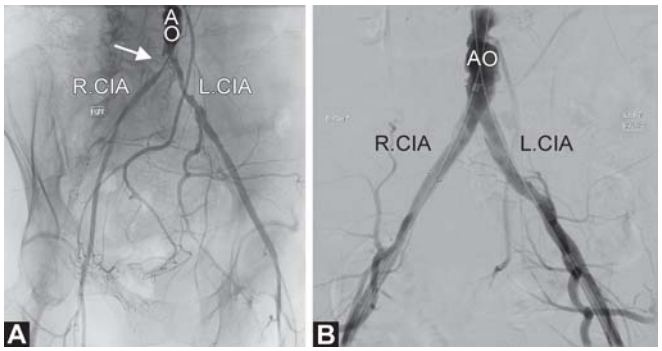


TASC C
Bilateral CIA occlusions
Bilateral EIA stenoses 3-10 cm long not extending into the CFA
Unilateral EIA stenosis extending into the CFA
Unilateral EIA occlusion that involves the origins of internal iliac and/or CFA
Heavily calcified unilateral EIA occlusion with or without involvement of origins of internal iliac and/or CFA



TASC D
Infrarenal aortoiliac occlusion
Diffuse disease involving the aorta and both iliac arteries requiring treatment
Diffuse multiple stenoses involving the unilateral CIA, EIA and CFA
Unilateral occlusions of both CIA and EIA
Bilateral occlusions of EIA
Iliac stenoses in patients with AAA requiring treatment and not amenable to endograft placement or other lesions requiring open aortic or iliac surgery

FIGURE 5: TASC classification of aortoiliac lesions. (Abbreviations: AAA: Abdominal aortic aneurysm; CFA: Common femoral artery; CIA: Common iliac artery; EIA: External iliac artery). (*Source*: Modified from Norgren L, Hiatt WR, Dormandy JA, et al. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). J Vasc Surg. 2007;45:S5-67)



FIGURES 6A AND B: A 60-year-old man with severe bilateral life-limiting gluteal and lower-extremities claudication on maximal medical management. (A) Angiogram shows severe distal aortoiliac disease (white arrow). (B) Final result after angioplasty and stenting with two self-expanding SMART® Control stents (Cordis Corp., Bridgewater, NJ) employed in kissing fashion. (Abbreviations: AO: Aorta; CIA: Common iliac artery; R: Right; L: Left)

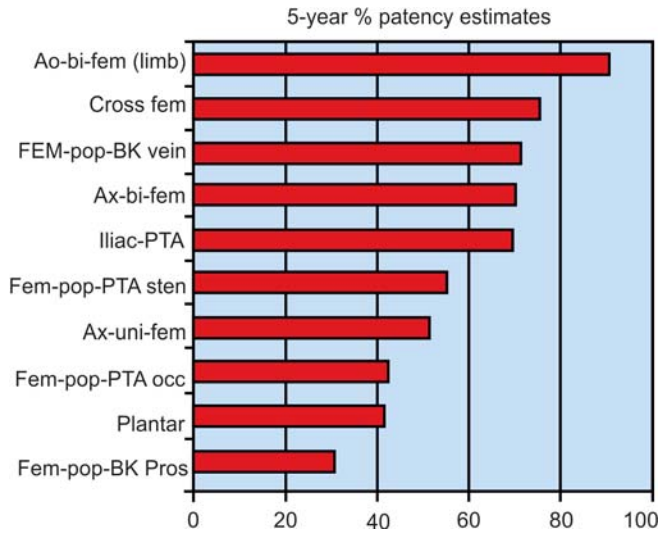


FIGURE 7: Average result for surgical treatment. (Abbreviations: Ao-bi-fem: Aortobifemoral bypass; Fem-pop-BK: Femoropopliteal below knee; Ax-bi-fem: Axillobifemoral; PTA: Percutaneous transluminal angioplasty; Ax-uni-fem: Axillounifemoral bypass; pros: Prosthetic). (*Source*: Modified from Norgren L, Hiatt WR, Dormandy JA, et al. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). J Vasc Surg. 2007;45:S5-67)

evaluated in the Bypass versus Angioplasty in Severe Ischemia of the Leg (BASIL) trial, which prospectively assigned patients with severe limb ischemia caused by infrainguinal disease to undergo either angioplasty or bypass surgery. At the end of the 5.5-year study, there was no significant difference in amputation-free survival between the two groups. However, in the angioplasty group, rates for morbidity and length of hospital stay were significantly

TABLE 6

PTA versus PTA plus stenting in iliac occlusive disease: results of meta-analysis of 14 studies

	PTA		*PTA + STENT*	
	Stenosis	*Occlusion*	*Stenosis*	*Occlusion*
Immediate technical success	96%	80%	100%	80%
Primary patency*	65%	54%	77%	61%
Secondary patency	80%		80%	
Major complications	4.3%		5.2%	

*4-year patency rate. Abbreviation: PTA: Percutaneous transluminal angioplasty.

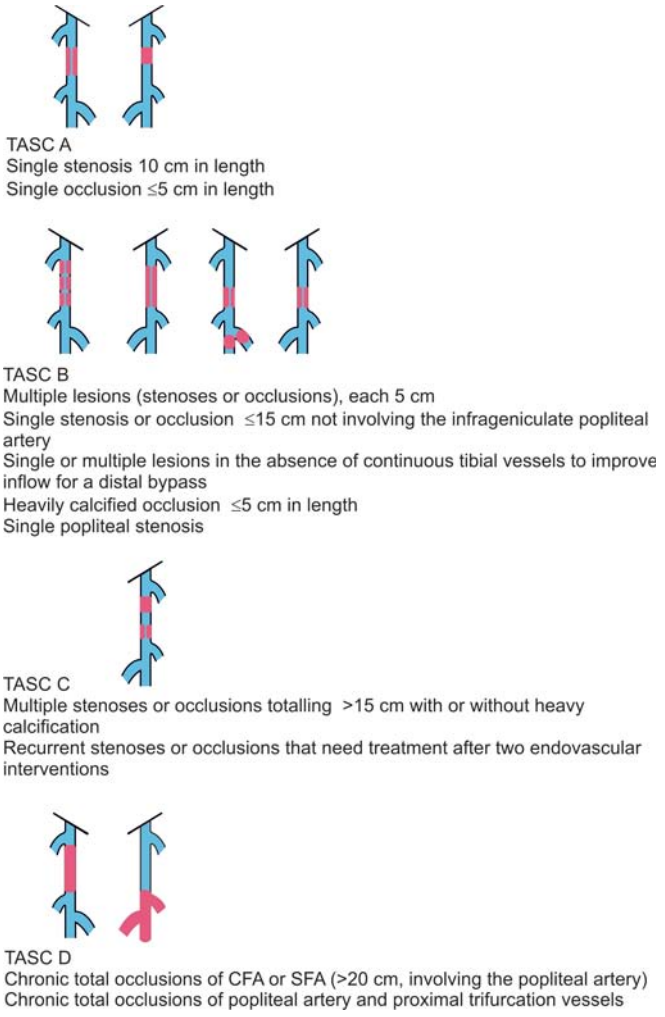
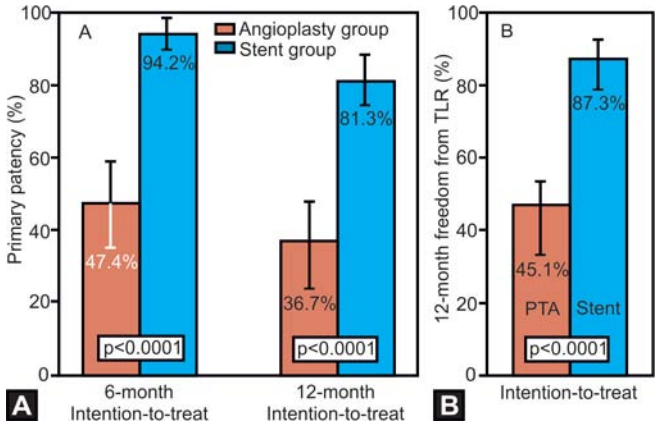
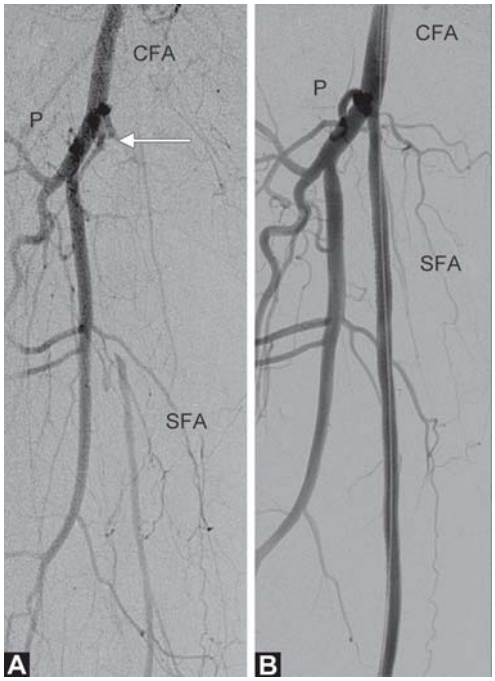


FIGURE 8: TASC classification of femoral popliteal lesions. (Abbreviations: CFA: Common femoral artery; SFA: Superficial femoral artery). (*Source*: Reproduced with permission from Norgren L, Hiatt WR, Dormandy JA, et al. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). J Vasc Surg. 2007;45:S5-67)



FIGURES 9A AND B: (A) Duplex ultrasound-derived primary patency (< 50% stenosis) for stent group and percutaneous transluminal angioplasty (PTA) group at 6 months and 12 months by intention-to-treat analysis. (B) Freedom from target lesion revascularization (TLR) is presented at 12 months for the PTA group and stent group by intention-to-treat analysis. [*Source*: Modified from Laird JR, Katzen BT, Scheinert D, et al. Nitinol stent implantation versus balloon angioplasty for lesions in the superficial femoral artery and proximal popliteal artery: twelve-month results from the RESILIENT randomized trial. Circ Cardiovasc Interv. 2010;3:267-76]



FIGURES 10A AND B: A 60-year-old woman with severe life-limiting claudication of right lower extremity. (A) Angiogram shows total occlusion of proximal right superficial femoral artery (SFA) (white arrow) after branching off the profunda artery (P). (B) Successful angioplasty and stenting of right SFA with two stents (Viabahn®, WL Gore and Associates, Newark, DE) in overlapping fashion, resulting in restoration of flow into the distal SFA. (Abbreviation: CFA: Common femoral artery)

lower, and total cost was significantly less.[71] Despite a success rate of about 88% in most PTA series,[72,73] the long-term patency rate is significantly lower than PTA of AIOD.[74] A pooled analysis by TASC II shows a patency rate of 77%, 61% and 55% for stenosis and 65%, 48% and 42% for occlusion at 1, 3 and 5 years, respectively.[12] The role of stent placement in revascularization of the SFA remains controversial. Classically, stenting has been reserved for patients with poor angiographic outcome after angioplasty, more than 30% residual stenosis following angioplasty or flow-limiting dissection. However, with newer generations of stents (such as nitinol stents and covered stent-grafts), primary stenting is becoming the procedure of choice in femoropopliteal disease, especially for intermediate- to long-length lesions. In the most recent randomized study—comparing the Edwards Self-Expanding LifeStent versus Angioplasty alone in LEsions INvolving the SFA or Proximal Popliteal Artery (RESILIENT)—Katzen et al. reported 1-year patency of 81% versus 37% for the stent group and balloon angioplasty group, respectively ($P < 0.0001$).[75] Freedom from target lesion revascularization (TLR) at 12 months was also significantly better for stent group (Figs 9A and B). While there is no strong data supporting routine use of cryoplasty, laser and mechanical atherectomy, percutaneous intervention using PTA and/or stent is recommended for Types A, B and most C lesions (Figs 10A and B), whereas surgical approach is considered

for Type D lesions not amenable to percutaneous intervention.

3. Infrapopliteal occlusive disease: Endovascular procedures below the popliteal artery are usually reserved for CLI and limb salvage. With angioplasty, technical success may approach 90% with resultant clinical success of approximately 70–90% in some series.[12] The role of balloon-expandable drug-eluting stents (DES) for infrapopliteal occlusive disease was recently evaluated in the Preventing Amputations Using Drug-Eluting Stents (PaRADISE) trial in patients with CLI, and showed a higher rate of amputation-free survival (68% ± 5%) in 3 years compared to the historic control.[76] In contrast, there is insufficient evidence to support such an intervention in patients with IC.

Regarding surgical bypass for infrainguinal occlusive disease, an adequate greater saphenous vein (vs prosthetic materials) is recommended as the best conduit for bypass surgery (5-year patency 74–76% vs 39–52%, respectively). In femorodistal bypass, any artery may serve as the inflow vessel as long as the origin of the graft is not compromised. Regarding outflow, the least diseased distal artery with the best continuous run-off should be used.[12]

Treatment of acute limb ischemia: Once the diagnosis of acute arterial occlusion has been made, immediate administration of IV unfractionated heparin (UH) followed by continuous UH infusion is recommended per TASC II.[12] Anticoagulation will prevent further propagation of thrombus and inhibit thrombosis distally in the arterial and venous systems due to low flow and stasis. Time is crucial; the decision to administer UH is based on the clinical evaluation and should not be delayed awaiting results of further diagnostic procedures. Following the initiation of heparin, treatment varies depending on the viability of the limb. Patients with ALI should undergo intervention to restore flow. Options include surgery and catheter-directed thrombolysis (CDT) therapy. Data from randomized prospective studies of ALI, although taken from groups with different baseline characteristics, suggest reduced rates of mortality and major amputation and shorter hospital stay with CDT compared to surgery.[77-79] Therefore, TASC II recommends CDT as the method of choice in patients in whom the degree of severity allows this more time-consuming approach (Category I: viable; Category IIa: marginally threatened) (Figs 11A to E), whereas a surgical approach is recommended in patients with profound limb ischemia (Category IIb: immediately threatened).

CAROTID ARTERY DISEASE

Stroke is the third-leading cause of death just after heart disease and cancer. In 2006, approximately 140,000 deaths were attributed to stroke, and it accounts for 1 of every 18 deaths in the United States.[80] In the United States, the direct and indirect cost of stroke in 2010 was estimated to be $73.7 billion[81] by year's end. The majority of strokes are caused by embolic events due to atheroemboli from the carotid artery, the ascending aorta and arch vessels, or cardiac thromboembolism from the left atrium or ventricle. It is estimated that CAS is responsible for 15–20% of all strokes, depending upon population studied.[82]

PATHOPHYSIOLOGY

Atherosclerosis is the most common disease of the carotid circulation. Other conditions associated with cerebral ischemia and infarction include: diseases of the aorta (dissection, aneurysm and aortitis), arteritis, FMD, dissection, primary vascular tumors, trauma and complication of head and neck cancer. Atherosclerosis in the carotid bed is mostly unifocal and 90% of lesions are located within 2 cm of the internal carotid artery (ICA) point of origin.[83] Atheromatous plaques progress over time. Ulceration, attachment of platelets and thrombi to crevices in plaques, and hemorrhage into plaques become more common as the arterial lumen becomes increasingly narrowed.

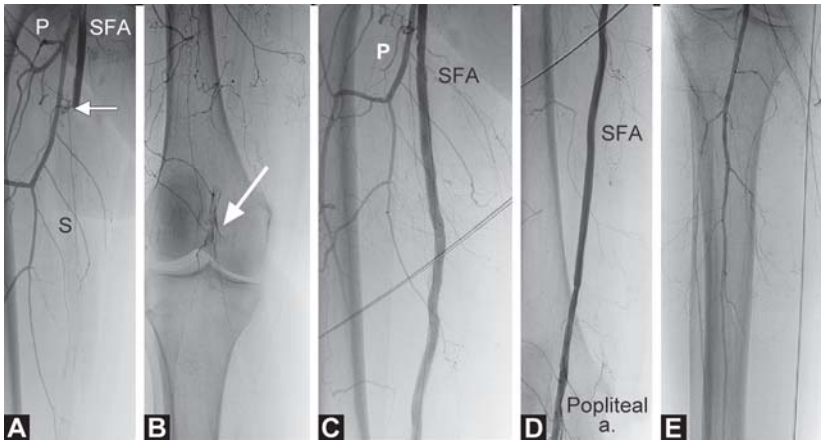
NATURAL HISTORY AND RISK STRATIFICATION

The prevalence of asymptomatic moderate (≥ 50%) and severe (≥ 70%) CAS is reported as 0.2–7.5% and 0.1–3.1%, respectively.[84] Risk factors for CAS are the same as risk factors in other vascular beds and this, population carries the same risk for future cardiac events as the presence of coronary heart disease (CHD), thus, it is classified as CHD equivalent.[50]

The annual stroke risk in asymptomatic patients is about 1% for carotid stenosis less than 60% and 1–2.4% for carotid stenosis more than 60%.[85]

SCREENING

Currently, there is no consensus to support routine screening of asymptomatic patients with noninvasive modalities,[86] except for



FIGURES 11A TO E: A 71-year-old woman with history of peripheral vascular disease and stenting of right superficial femoral artery (SFA) with two heparin-coated stents (Viabahn®) presented with ALI after stopping clopidogrel. (A) Digital subtraction angiography shows acute occlusion of proximal right SFA (white arrow) a few centimeters above the edge of the stent (S) and (B) clot burden in popliteal artery (white arrow). (C) Proximal SFA and (D) Distal SFA: final result after power-pulse urokinase spray, mechanical thrombectomy, percutaneous transluminal angioplasty and stenting with two stents (Protégé®, ev3 Endovascular Inc., Plymouth, MN), with (E) one-vessel run-off below the knee. (Abbreviations: P: Profunda artery; a: Artery)

patients undergoing coronary artery bypass graft (CABG). A carotid DUS is recommended prior to CABG in asymptomatic patients age more than 65 years or with left main coronary stenosis, PAD, history of smoking, TIA or stroke, or carotid bruits.[87] Patients with ischemic stroke and those with both CAS and a high CHD risk factor based on the Framingham algorithm (≥ 20%) should undergo noninvasive evaluation to rule out significant underlying obstructive epicardial disease.[88]

DIAGNOSIS

Noninvasive Testing

While major randomized trials utilized angiographic criteria to assess stenosis severity, noninvasive testing is usually recommended. It is more effective in assessing the severity and guiding decision-making regarding revascularization as the first choice of therapy.

DUS, computed tomography angiography and magnetic resonance angiography are recommended by ACC/AHA guidelines as Class I (Level of evidence: A) for the initial evaluation of carotid artery disease in patients presenting with acute stroke.[89] DUS is considered as the first choice in most centers. In asymptomatic patients, MRA or CTA could be considered, if results from DUS are inconclusive.

Conventional Angiogram

Cerebral angiogram is considered the gold standard for imaging carotid arteries. Development of digital subtraction angiography reduces the dose of contrast and shortens the length of the procedure. On the other hand, it carries a higher cost and estimated risk of neurological complication, and death is reported as 4% and 1%, respectively.[90] With the advance of noninvasive modalities, cerebral angiogram is rarely used as the first diagnostic approach nowadays.

MANAGEMENT

Treatment of CAS includes risk-factor modification and medical treatment alone, medical treatment plus carotid endarterectomy (CEA) or medical treatment plus carotid stenting. Prompt evaluation of patients with symptomatic CAS is essential to minimize the risk of early recurrent cerebrovascular event. Studies show that the risk of stroke is significantly greater 30–90 days after TIA and that immediate initiation of treatment can reduce this risk by up to 80%.[91] For risk-factor modification and treatment of hypertension, dyslipidemia and diabetes, recommendations from major societies should be followed.[64,92,93]

Antiplatelets, Dipyridamole and Warfarin

Initial therapy for all patients with noncardiac ischemic stroke should involve aspirin (ASA 50–325 mg) or the combination of ASA and extended-release dipyridamole, or clopidogrel monotherapy (Class I, Level of evidence: A).[94] Asymptomatic patients with one or more atherosclerosis risk factors should be started on antiplatelets as well. In symptomatic patients, ASA results in relative risk reduction of 16% for fatal stroke and 28% for nonfatal stroke,[55] while extended-release dipyridamole plus ASA is shown to be superior to ASA alone for secondary prevention in patients with minor stroke or TIA.[95] Clopidogrel has largely replaced ticlopidine due to its superior safety profile and once-daily dosing. In the Clopidogrel versus Aspirin in Patients at High Risk of Ischemic Events (CAPRIE) trial, the benefit of clopidogrel was mostly observed in patients with PAD; and the difference in composite outcome between clopidogrel and ASA treatment in patients with recent stroke, and myocardial infarction was not significant.[56] The combination of ASA and clopidogrel also carries no additional benefit for secondary prevention of stroke.[57] Finally, extended-release dipyridamole plus ASA therapy was tested against clopidogrel in the Prevention Regimen for Effectively Avoiding Second Stroke (PRoFESS) trial, which showed the same rate of recurrent stroke in both arms.[96]

Regarding warfarin, there is no data suggesting benefit over ASA in patients with noncardioembolic stroke.[97]

Carotid Endarterectomy

In patients with symptomatic moderate-to-severe CAS, CEA is recommended for prevention of future ipsilateral ischemic stroke.[98] Based on randomized control trials (RCTs), the number needed to treat (NNT) with CEA for patients with severe (> 70%) CAS in order to prevent one ipsilateral stroke in a 2-year period is eight.[99]

The benefit of CEA for asymptomatic patients with moderate-to-severe carotid stenosis was proved to be marginal in RCTs, reducing the risk of stroke from 2% per year to 1% per year. This benefit was shown to be even lower in women.[85,100,101] The AHA recommends CEA in symptomatic and asymptomatic patients with stenosis of 50–99% and 60–99%, if the risk of perioperative stroke or death is less than 6% and 3% (life expectancy at least 5 years), respectively.[98,102,103]

Carotid Stenting

Kerber et al. reported the first EVT of the carotid artery with balloon angioplasty in 1980.[104] New advances in self-expanding stents and the recent adoption of embolic protection devices (EPDs), in addition to patient preference, resulted in carotid artery stenting becoming an emerging and less-invasive revascularization method to prevent stroke, especially in patients at high risk for surgery. The Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial was a multicenter, prospective randomized trial that enrolled a majority of asymptomatic patients (70%) who were determined to be high risk for CEA. The 30-day rate of ipsilateral major stroke or death was virtually identical for carotid stenting (2.6%) and CEA (2.5%), and major composite endpoints at 30 days, 1 year and, more recently, 3 years (stroke and other major adverse events) demonstrated statistically significant noninferiority for stenting. Interestingly, in asymptomatic high-risk surgical patients, there were significantly fewer major adverse events following revascularization by stenting [driven by a lower rate (10.5%) of non-Q-wave myocardial infarction (MI)] than by CEA (20.1%).[105,106] Based on the 1-year result of SAPPHIRE trial, the US FDA granted approval for the stent and protection devices used in

TABLE 7

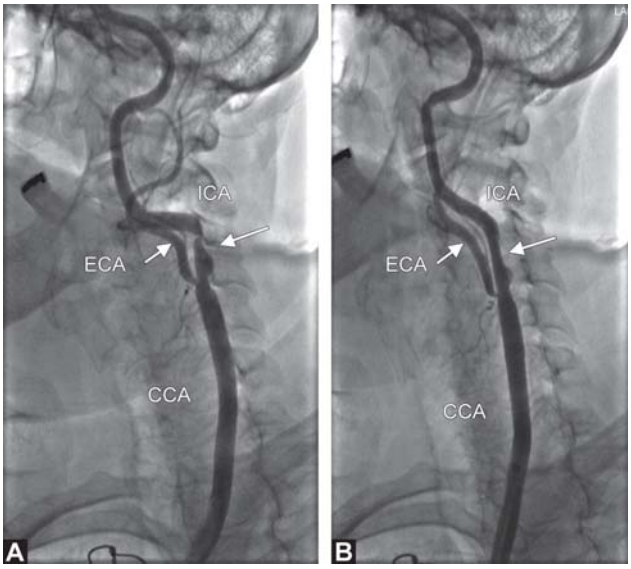
Clinical and anatomical features associated with increased procedural risks after carotid stenting and carotid endarterectomy

	Carotid stenting	*Carotid endarterectomy*
Clinical	Age ≥ 80 years	Age ≥ 80 years
	Recent stroke	Recent stroke
	Multiple lacunar infarcts	Severe heart disease
	Intracranial microangiopathy	Severe pulmonary disease
		Concomitant cardiac surgery
		Renal insufficiency or failure
Anatomic	Ulcerated plaque/thrombus	Ulcerated plaque/thrombus
	Long subtotal ICA lesion (string sign)	Long subtotal ICA lesion (string sign)
	Excessive tortuosity	Prior CEA
	Calcification	Prior neck radiation/surgery
	Multiple lesions	Contralateral ICA occlusion
	Contralateral carotid occlusion	High ICA lesion
		Low CCA lesion

Abbreviations: CEA: Carotid endarterectomy; ICA: Internal carotid artery; CCA: Common carotid artery.

SAPPHIRE, but only for symptomatic patients with high risk features for CEA. Regarding low/average-surgical-risk patients, two clinical trials—Endarterectomy versus Angioplasty in Patients with Severe Symptomatic Carotid Stenosis (EVA-3S) and Stent-Protected Angioplasty versus Carotid Endarterectomy (SPACE)—failed to demonstrate noninferiority for stenting over CEA in 30 days, with an increase in the rate of death or stroke seen in the EVA-3S study.[107,108] Lack of experience of the operators was the major criticism of the EVA-3S trial, whereas in the SPACE trial, the use of EPDs was left to the discretion of the interventionalist. EPDs are thought to reduce the risk of stroke in patients undergoing carotid stenting, and their use is strongly recommended in all cases. Recently published results of the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST) showed a similar composite endpoint of stroke, MI or death during the periprocedural period or ipsilateral stroke after a median follow-up of 2.5 years in stenting (7.2%) and CEA (6.8%) (P = NS), in 2,502 symptomatic and asymptomatic patients labeled low surgical risk.[109]

The US Centers for Medicare and Medicaid services only reimburse the cost of carotid stenting for patients with symptomatic CAS more than 70% and who are at high risk for CEA. For the rest, the procedure is reimbursed only in the setting of clinical trials or registries (Figs 12A and B). High-risk features for carotid stenting and CEA are shown in Table 7.



FIGURES 12A AND B: A 59-year-old woman with severe asymptomatic left carotid artery stenosis (CAS). (A) Angiogram of left carotid system shows high-grade stenosis of internal carotid artery (ICA) (large arrow). (B) Carotid angiogram after angioplasty and stenting using embolic protection device (ACT I trial) (small arrow). (Abbreviations: ECA: External carotid artery; CCA: Common carotid artery)

RENAL ARTERY STENOSIS

Renal artery stenosis (RAS) is the most common cause of secondary hypertension and is described as a narrowing of one or both renal arteries or their branches.[110] Atherosclerosis involving the ostium and proximal third of the main renal artery and perirenal aorta accounts for 90% of cases of RAS and is called atherosclerotic renal artery stenosis (ARAS).[111] Less frequently, RAS is caused by FMD. ARAS and FMD have distinct presentation and clinical consequences (Table 8). Although, there is debate regarding optimal management of ARAS, patients with FMD and resistant HTN can be treated successfully with balloon angioplasty.

TABLE 8

Characteristics of atherosclerotic renal artery stenosis and fibromuscular dysplasia

Variable	*Atherosclerosis*	*Fibromuscular dysplasia*
Age at presentation	Older (> 50 years)	Usually young (< 40 years)
Sex	Either	Usually female
Lesion location	Ostial, proximal, middle*	Middle or distal
Blood pressure response to revascularization	Unclear	Normotension in most patients

*Locations are listed in descending order of likelihood. (*Source:* Dworkin LD, Cooper CJ, et al. Clinical practice. Renal-artery stenosis. N Engl J Med. 2009;361:1972-8)[112]

In most patients, renovascular disease is accompanied by macrovascular pathology in several other important vascular beds, especially the coronary, aortoiliac and iliofemoral circulation. Given the asymptomatic nature of ARAS, its true prevalence in general population of the United States is not known. Prevalence of ARAS in more than 1.2 million Medicare recipients older than 65 years in 1999 was 0.54%.[113] Patients with ARAS have a markedly lower rate of survival, partly due to their extensive vascular comorbidities.[114] Progression of stenosis is reported in one-third to one-half of ARAS cases, primarily in patients with bilateral RAS, with occlusion occurring in 10–15% of cases.

In contrast, the likelihood of progression is lower in patients with FMD, and occlusion is rare.[115,116] The RAS is also associated with loss of renal size and function.[117]

Renal Artery Stenosis and Hypertension

The role of the renin-angiotensin system in the generation of HTN is well recognized, this mechanism is complex in patients with RAS since not all patients have renin-dependent HTN. There are two main mechanisms underlying how HTN develops in patients with RAS. In patients with unilateral RAS and normal functioning kidneys, blood pressure is renin dependent and characterized by increased vascular resistance. In this circumstance, renin and angiotensin levels remain elevated, and natriuresis from the contralateral kidney prevents volume expansion;[118] therefore, the value of renin level in diagnosis of RAS is limited in these patients.[119] When stenosis is bilateral or the contralateral kidney is not functioning, renin secretion decreases without a natriuretic effect from the contralateral kidney; therefore, HTN is maintained by volume expansion (one-kidney one-clip Goldblatt hypertension).[118,120]

Fibromuscular Dysplasia

Fibromuscular dysplasia is a nonatherosclerotic, non-inflammatory vascular disease that accounts for 10% of RAS cases. Renovascular FMD tends to affect women ages 15–50 years.

The pathologic classification scheme for renal FMD is based on arterial layers—intima, media or adventitia—in which a lesion is predominant. Medial fibroplasias represent the most common dysplastic lesion and are characterized by its classic "string of beads" appearance. Typically, the beading is larger than a normal-caliber artery and is located in the middle-to-distal segment of the artery without involvement of intima and adventitia. Intimal fibroplasia accounts for less than 10% of patients with arterial fibrodysplasia, and angiographically, it may appear as focal, concentric stenosis. Adventitial (periarterial) hyperplasia is the rarest type of fibrodysplastic lesion.[121,122]

SCREENING AND DIAGNOSTIC TESTS

Clinical situations suggesting high likelihood of RAS include:

- Onset of hypertension before age 30 or after 55 years
- Accelerated, resistant or malignant HTN
- Development of new azotemia or worsening renal function after administration of an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocking (ARB) agent
- Unexplained atrophic kidney or asymmetry in renal sizes is more than 1.5 cm
- Recurrent episodes of acute (flash) pulmonary edema, in the presence of normal left ventricular ejection fraction
- Refractory angina or unexplained congestive heart failure.

Current ACC/AHA guidelines recommend screening for renovascular disease only if finding of significant stenosis would change the management (i.e. a corrective procedure will be undertaken).[16] Once RAS is suspected, it is confirmed by imaging. Captopril renal scintigraphy, selective renal vein renin measurements, and plasma renin activity are not useful screening tools for RAS. Digital subtraction angiography remains the gold standard imaging modality for diagnosis of RAS. Noninvasive imaging modalities have been introduced for detection of RAS. DUS provides a functional assessment of the severity of stenosis, and higher velocity correlates with a greater stenosis. It has reported sensitivity, specificity and positive or negative predictive values of 89%, 92%, 92% and 88%, respectively;[123] however, its use requires a skilled technician and is limited by obesity or bowel gas. In a large imaging study, the sensitivity and specificity of CTA for detecting stenosis more than or equal to 70% was 62% and 90%, respectively, for all lesions and 28% and 99%, respectively, for fibromuscular disease.[124] The risk of contrast-induced nephropathy remains high in patients with chronic kidney disease undergoing CTA.

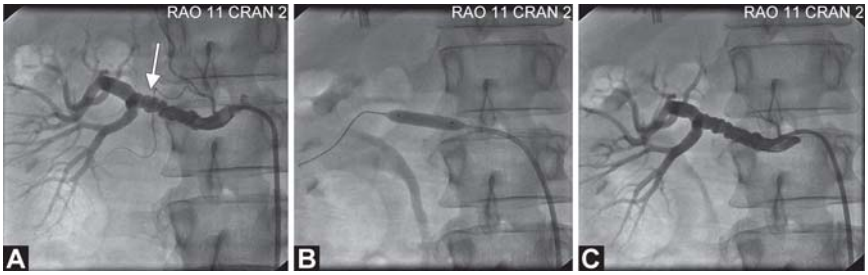
Taken from multiple studies, the median sensitivity and specificity of magnetic resonance angiography with contrast as compared to conventional catheter angiography with contrast were 96% and 93%, respectively.[125] However, MRA is contra-indicated in patients with claustrophobia and/or a metallic implant (e.g. pacemaker, aneurysm clip). In addition, among patients with an estimated glomerular filtration rate (GFR) less than 30 ml/min, the administration of gadolinium during MRA has been strongly linked to nephrogenic systemic fibrosis (also known as nephrogenic fibrosing dermopathy) and should be avoided.[44]

MEDICAL MANAGEMENT

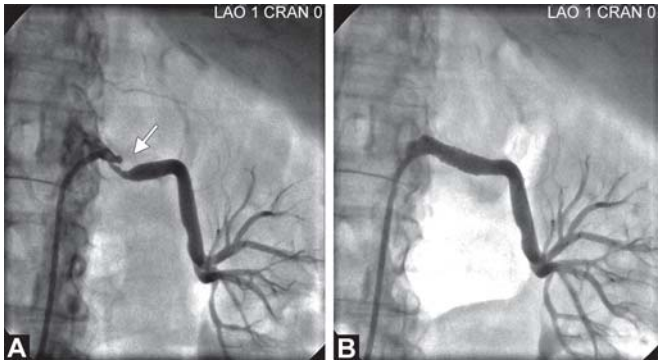
Pharmacologic therapy for HTN in patients with ARAS and FMD should follow the Joint National Committee (JNC7) guidelines.[52] Use of renin-angiotensin-aldosterone inhibitors can be associated with acute renal failure, especially in patients with bilateral RAS, advanced kidney disease or high-grade stenosis in one kidney.[126] The probability of the latter complication is low and, in most cases, reversible with discontinuation of treatment. ACE inhibitors also have shown mortality benefit in a large cohort study; therefore, the presence of RAS is not a contraindication for the use of renin-angiotensin inhibitors if patients are carefully monitored.[127]

REVASCULARIZATION

Angioplasty and/or stenting has become the procedure of choice over surgical approach for ARAS revascularization.[16] Recent results from the Medicare population suggest an in-hospital mortality rate close to 10% after surgical intervention,[128] and balloon angioplasty has shown comparable results with lower



FIGURES 13A TO C: Fibromuscular dysplasia of right renal artery in a 52-year-old woman with resistant hypertension. (A) Notice "string of beads" appearance in the mid-distal segment of renal artery (white arrow). (B) Balloon angioplasty. (C) Final angiogram with significant improvement in hypertension



FIGURES 14A AND B: An 82-year-old woman with resistant hypertension. (A) Renal angiogram showing severe ostial atherosclerotic renal artery stenosis of left renal artery (white arrow). (B) Final result after percutaneous transluminal angioplasty and stenting of ostial lesion using Herculink Elite® (Abbott Vascular, Abbott Park, IL) stent

mortality and morbidity.[129] In patients with FMD, when the lesion meets clinical criteria for intervention, angioplasty is the procedure of choice (Figs 13A to C) as it is associated with low mortality and morbidity.[16,130,131] The use of stents in patients with FMD has been reserved as a "bailout" procedure for suboptimal results when dissection occurs after PTA.[16,131] In contrast, balloon angioplasty alone has resulted in suboptimal results in patients with ARAS and ostial renal lesion compared to stenting, with a higher rate of restenosis in long-term follow-up. Therefore, renal stent placement is indicated for ostial ARAS lesions that meet the clinical criteria for intervention (Figs 14A and B).[16,132]

Two recent randomized trials failed to demonstrate any mortality benefit, better blood pressure control and renal protection with percutaneous intervention and medical management versus medical management alone.[133,134] It should be noted that both of these trials were limited by inclusion of patients with clinically insignificant RAS, imprecise definition of RAS, inadequate medical intervention and high crossovers from medical therapy alone to the intervention/stenting arm.

Based on ACC/AHA guidelines on RAS, percutaneous intervention should be considered for the following scenarios only when medical management fails:[16]

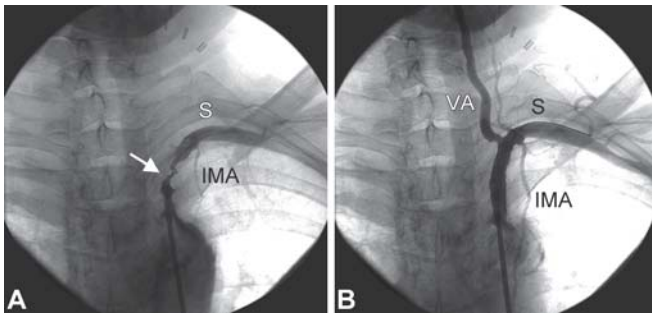
- Class I: Unexplained congestive heart failure of recurrent pulmonary edema
- Class IIa: Accelerated, malignant or resistant HTN
  - HTN with medication intolerance or unilateral small kidney
  - Chronic renal failure with bilateral RAS or unilateral solitary kidney
  - Recurrent unstable angina
- Class IIb: Asymptomatic bilateral or solitary viable kidney with severe RAS
  - Asymptomatic unilateral significant RAS in a viable kidney
  - RAS and chronic renal failure when unilateral stenosis is present.

SUBCLAVIAN ARTERY STENOSIS

Atherosclerosis is the most common cause of subclavian artery stenosis (SAS). Other causes should be included in differential diagnosis such as vasculitis, congenital malformations (e.g. following surgical repair of aortic coarctation), thoracic outlet syndrome, or sequel from radiation. The prevalence of SAS for patients undergoing CABG is reported as 0.5–1.0%.[135] SAS is associated with atherosclerosis involving other large vessels (e.g. coronary, carotid), and is a predictor of total and cardiovascular mortality independent of the presence of underlying cardiovascular disease and risk factors;[136] therefore, aggressive secondary prevention is strongly recommended in this population.

Hemodynamically significant SAS proximal to ipsilateral vertebral artery results in lower pressure in distal subclavian artery. As a consequence, with repetitive arm movement, reversal of flow occurs from the contralateral vertebral artery and brain stem, resulting in neurological symptoms (e.g. drop attacks, dizziness). This is referred to as "subclavian steal syndrome."[137,138] The same "stealing" phenomenon could cause significant ischemia in patients with history of CABG utilizing internal mammary artery (IMA). Therefore, patients with high-grade SAS should be treated (surgically or percutaneously) prior to CABG.[139]

Physical examination in patients with SAS typically reveals a significant difference in brachial systolic blood pressure (> 15 mm Hg differential) between the affected and normal arms and lower amplitude with delayed pulse in the affected arm. While DUS, MRA and CTA are postulated as diagnostic tools for detection of hemodynamically significant SAS, contrast angiography is considered the gold standard and "confirmatory" procedure of choice in this population. The surgical approach for treatment of symptomatic SAS has shown reasonable long-term patency[140] but, among other complications, carries a mortality rate of about 2% and a stroke rate of about 3%.[141] Percutaneous intervention with stenting has shown high procedural success rate (> 90%) with good long-term patency rate (> 89%) and lower rate of major complications (1%);[142,143] therefore, it should be considered as the primary treatment in patients who need revascularization for SAS (Figs15A and B).



FIGURES 15A AND B: A 78-year-old woman with history of left arm claudication associated with severe dizziness. (A) Selective angiogram of left subclavian artery (S) demonstrates severe proximal stenosis (white arrow) with no flow into left vertebral artery (VA). (B) Angioplasty and stent of proximal subclavian artery using two Genesis™ stents (Cordis Corp. Bridgewater, NJ) in overlapping fashion with restoration of flow into left VA. (Abbreviation: IMA: Internal mammary artery)

VERTEBROBASILAR ARTERY STENOSIS

Among patients with ischemic stroke, about 20–25% suffer strokes located in posterior circulation involving the vertebrobasilar system.[144] The prognosis of patients with atherosclerotic occlusion or thrombosis of vertebrobasilar system is poor with mortality rate of 80–100%.[145,146] Patients with atherosclerotic PAD have a 40% incidence of vertebral artery stenosis (VAS).[147] In a large angiographic study of 3,800 patients who presented with symptomatic CVD, the incidence of VAS was reported as high as 40%.[148] Patients may present with vertigo, loss of balance, gait problems and visual disturbances. Medical therapy, including antithrombotics, is indicated in all patients with VAS. Arch- and four-vessel angiography is considered the gold standard for diagnosis of VAS. The combined mortality and morbidity rates of VAS surgical therapy range from 10% to 20%.[149,150] Therefore, management of VAS has shifted to percutaneous techniques with high rates of success (> 95%) and no major complications.[151,152]

MESENTERIC ISCHEMIA

Mesenteric ischemia is caused by reduction in intestinal blood flow due to occlusion, vasospasm or hypoperfusion of mesenteric vasculature. Acute mesenteric ischemia (AMI) most commonly occurs due to emboli or thrombosis of mesenteric arteries and could result in a mortality rate exceeding 60%.[153] Risk factors for developing AMI include: advanced age, atherosclerosis, cardiac arrhythmias, low cardiac output state, valvular heart disease, recent myocardial infarction and intra-abdominal malignancy.[153] In acute ischemic injury, the intestine is able to compensate for a 75% acute reduction in mesenteric blood flow for up to 12 hours by increased oxygen extraction.[154] However, after several hours, vasoconstriction may persist even after blood flow has been restored, leading to continued intestinal ischemia. In addition, it is postulated that reperfusion injury of an ischemic intestine—mediated by both reactive oxygen metabolites and activated polymorphonuclear leukocytes—could result in significant microvascular and parencymal cell injury.[155]

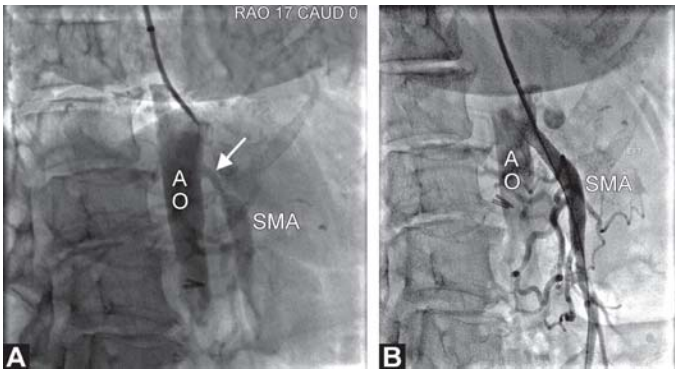
Diagnosis of AMI depends on strong clinical suspicion, especially in patients with risk factors (see previous paragraph). Classically, patients present with rapid onset of severe preumbilical pain, which is often out of proportion to findings on physical examination. In contrast, the pain may occur more insidiously (hours to days) in patients with thrombotic causes, vasculitis or nonocclusive ischemia. Normal laboratory values do not exclude AMI. However, marked leukocytosis with predominance of immature white blood cells, elevated hematocrit and metabolic acidosis would support clinical diagnosis. Mesenteric angiography remains the gold standard diagnostic study for AMI, and has resulted in the decline in mortality of patients with AMI over the past 30 years.[156] On the other hand, CTA appears to be an acceptable alternative in settings where obtaining angiography is impractical or there is only moderate suspicion of AMI.

The ultimate goal of treatment in patients with AMI is to restore intestinal flow as rapidly as possible. Initial management should include aggressive hemodynamic monitoring and support, gastric decompression, broad-spectrum antibiotics, correction of acidosis and systemic anticoagulation. Vasoconstricting agents and digitalis should be avoided. Patients suspected of having intestinal infarction or perforation should undergo surgery on an emergency basis regardless of the cause for AMI, whereas the endovascular approach (including transcatheter thrombolytic therapy, balloon angioplasty and stenting) is reserved for patients with AMI in the absence of peritoneal signs or subjects with peritoneal signs who are poor candidates for surgery.[16]

Chronic mesenteric ischemia (CMI) (also called intestinal angina) refers to episodic or constant intestinal hypoperfusion.[157] Atherosclerosis is the most common cause for CMI. In rare cases, CMI may be associated with fibrovascular dysplasia, vasculitis, ergotamine intoxication, radiation injury and mesenteric venous thrombosis. Patients with CMI are mostly female (70%) and about 30–50% have had prior coronary or peripheral intervention.[158,159] Typical patients have history of smoking and underlying atherosclerotic vascular disease and classically complain of dull, crampy, postprandial epigastric pain that increases after large meals with high fat content.[160] Other symptoms include: nausea, vomiting, early satiety, weight loss and cachexia. The diagnosis of CMI is supported by the demonstration of high-grade stenosis in multiple mesenteric vessels in patients with unexplained chronic abdominal pain, weight loss and food aversion. Angiography is currently considered to be the gold standard diagnostic test. Therapeutic options for patients with CMI include surgical reconstruction or PTA with or without placement of stents. Although surgical reconstruction has shown to have a reasonable success rate and graft patency, it is associated with perioperative mortality of up to 11%.[161] The endovascular approach has become an alternative to surgery, with lower morbidity and shorter hospital stay (Figs 16A and B).[162] Current ACC/AHA practice guidelines recommend percutaneous endovascular approach as a Class I indication for treatment of CMI.[16]

SUMMARY

Peripheral arterial disease is prevalent in the general population (especially in those with cardiovascular risk factors) and carries significant cardiovascular mortality and morbidity. However,



FIGURES 16A AND B: (A) Selective abdominal angiogram of 71-year-old woman with symptomatic ostial/proximal superior mesenteric artery (SMA) stenosis (white arrow). (B) Angiographic result after percutaneous transluminal angioplasty and stenting with an express stent. (Abbreviation: AO: Suprarenal aorta)

awareness among health care providers and the general public regarding its presence, early detection and management is lacking, partly due to the asymptomatic nature of the disease. Screening ABI in patients with risk factors (smokers, diabetics, elderly) or those with symptoms of claudication is recommended. As discussed in this chapter, the presence of atherosclerotic disease in one vascular bed is equivalent to its presence in others; therefore, we screen our patients with PAD for the presence and extent of CAD and vice versa. Upon diagnosis, early risk-factor modification, an exercise program and close follow-up to detect progression of the disease should be initiated. Revascularization is recommended for lifestyle-limiting symptoms or critical limb ischemia. Within the last decade, endovascular intervention has become the method of choice for revascularization over surgical approach, with lower morbidity and mortality and shorter hospital stay.

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Chapter 65

Aortic Dissection

Ariane Neyou

Chapter Outline

- Predisposing Factors
  - Atherosclerosis
  - Inherited Disease
- Classification
  - Stanford Classification
  - DeBakey Classification
  - Anatomical Classification
  - New Classification
- Clinical Manifestations
  - Clinical Symptoms
  - Physical Findings
- Diagnosis
  - Chest X-ray
  - Electrocardiography
  - D-Dimer
  - Imaging
- Treatment
  - Initial Treatment
  - Endovascular Repair
  - Acute Aortic Dissection: Outcome

INTRODUCTION

Acute aortic dissection (AAD) is a catastrophic illness that occurs with an incidence of 5–30 cases per million people per year leading to at least 7,000 cases per year in the United States.[1] This wide range of incidence is mostly related to the prevalence of risk factors of aortic dissection which varies in different study populations. Several studies from international registry of aortic dissection (IRAD) which is the largest international registry of AAD have shown that two-thirds of patients with AAD are male and 62% have documented type A dissection.[2,3]

The symptoms might mimic myocardial ischemia and physical findings in aortic dissection may be absent or could be suggestive of a diverse range of other conditions. The diagnosis of aortic dissection has been missed in up to 38% of patients in initial evaluation and in up to 28% of patients, the diagnosis has been first established at the postmortem examination.[4] Such challenges in clinical diagnosis make aortic dissection largely undiagnosed (or diagnosed late) by clinicians leading to a very high mortality. Early mortality in dissection involving the ascending aorta is as high as 1% per hour if untreated in the first 24 hours after symptom onset.[1]

Aortic dissection occurs secondary to different mechanisms.[5] Either it is related to a tear in the intima, which directly opposed a diseased medial layer (commonly called cystic medial degeneration) or from intramural hemorrhage and hematoma formation in the media subsequently followed by perforation of the intima or, it could be secondary to a perforating penetrating ulcer. Cystic medial degeneration is an intrinsic feature of several hereditary defects of connective tissue disease, notably Marfan and Ehlers-Danlos syndromes, and is also common in patients with bicuspid aortic valve (Fig. 1).[1]

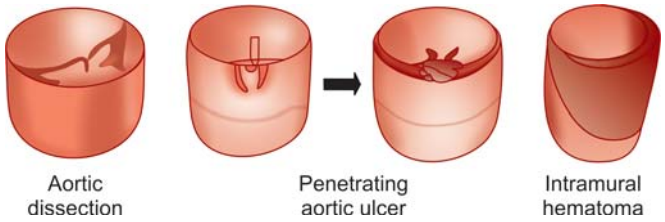


FIGURE 1: Aortic dissection, penetrating aortic ulcer, intramural hematoma. (*Source:* Ramanath VS, et al. Acute aortic syndromes and thoracic aortic aneurysm. Mayo Clin Proc. 2009;84:465-81.)

Chest traumas as well as pregnancy in the third trimester and early postpartum period are also risk factors for aortic dissection. New diagnostic imaging including computed tomography (CT) scan, magnetic resonance imaging (MRI) and echocardiography have all contributed to early diagnosis and decision making even in emergency situations.[6] Patient outcome is dependent of the type of dissection, underlying comorbidities, diagnostic delay and treatment modalities.

PREDISPOSING FACTORS

ATHEROSCLEROSIS

The peak incidence of AAD is in the sixth and seventh decades of life, with men affected twice as often as women.[7] About 75% of patients with aortic dissection have a history of hypertension. Atherosclerosis leads to thickening of the intima. The intima develops fibrosis and calcification, and increased amount of extracellular fatty acids. The integrity of this layer can be compromised by the extracellular matrix being degraded by

histiocytes cells. Additional changes are characterized by reduced cellularity and collagen fiber hyalinization. Both mechanisms are thought to lead to plaque intima rupture, most often at the edge of the plaques. Intimal thickening also increases the distance between the endothelial layer and the media, compromising the nutrient and oxygen supply of the aortic wall, leading to cystic medial necrosis. When the event of intima rupture occurs in the setting of cystic media necrosis, this results in intrusion of blood between the two layers leading to aortic dissection.[8]

INHERITED DISEASE

Thoracic Aortic Aneurysms and Dissections

It is a very important and often unappreciated condition with highly lethal consequences. The majority of the cases are sporadic, but more than 20% are inherited as a single gene disorder.[9] The most common familial thoracic aortic aneurysms and dissections (TAAD) is Marfan's syndrome which is caused by mutations in fibrillin-1 gene (FBN-1), the less common Loeys-Dietz syndrome (caused by mutations in TGFBR1 and 2) as well as the non-syndromic thoracic aortic aneurysm.[10] The mode of inheritance in most cases is autosomal dominant with variable penetrance.

Marfan's Syndrome

Marfan's syndrome is an autosomal dominant connective tissue disorder with an estimated incidence of 1/5,000. The syndrome involves many systems: skeletal, ocular, cardiovascular and pulmonary. There are criteria called the 'Ghent nosology' which help to distinguish Marfan's syndrome from related disorders. Both skeletal and cardiovascular features are major diagnostic criteria (Table 1). Marfan's syndrome is secondary to a defect in an extracellular matrix protein named fibrillin. This protein is a major constituent of microfibrils found in the extracellular matrix, either isolated or closely associated with elastin fibers. To date, more than 100 different mutations have been identified in the fibrillin-1 gene in patients with Marfan's syndrome. The mutations are found in complete and incomplete forms of Marfan's syndrome but also in a spectrum of overlapping diseases, some of which are associated with aortic dissection as: Shprintzen-Goldberg syndrome, familial or isolated forms of aortic aneurysms and the mitral-aortic-skin-skeletal (MASS)' phenotype. The common denominator of these diseases is the dedifferentiation of vascular smooth muscle cells leading to classic progression of atherosclerosis and aneurysm formation as well as enhanced elastosis of aortic wall component as shown in a fibrillin-q-deficient animal model. Enhanced expression of metalloproteinases in vascular smooth muscle cells of the Marfan aorta promotes fragmentation of medial elastic layers and elastosis. Also, peroxisome proliferators-activated receptor-gamma (PPar gamma) is upregulated leading to cystic media necrosis and correlates with disease severity. In IRAD, Marfan's syndrome accounts for 5% of all aortic dissections.[11] Patients with Marfan's syndrome are at higher risk for proximal aortic dissection at a younger age. Marfan's syndrome accounts for majority of dissection cases in patients less than 40 years of age (Table 2).[8]

TABLE 1

The revised Ghent nosology for Marfan's syndrome

Revised Ghent criteria for diagnosis of Marfan's syndrome and related conditions

In the absence of family history:

1. Ao (Z ≥ 2) and EL = MFS*
2. Ao (Z ≥ 2) and *FBN1* = MFS
3. Ao (Z ≥ 2) and Syst (≥ 7 pts) = MFS*
4. EL and *FBN1* with known Ao = MFS

EL with or without Syst and with an *FBN1* not known with Ao or no *FBN1* = ELS

Ao (Z < 2) and syst (≥ 5 with at least one skeletal feature without EL = MASS

MVP and Ao (z < 2) and syst (< 5) without EL = MVPS

In the presence of family history:

5. EL and FH of MFS (as defined above) = MFS
6. Syst (≥ 7 pts) and FH of MFS (as defined above)—MFS*
7. Ao (Z ≥ 2 above 20 years old, ≥ 3 below 20 years) + FH of MFS (as defined above) = MFS*

Scoring of systemic features

- Wrist and thumb sign—3 (wrist or thumb sign—1)
- Pectus carinatum deformity—2 (pectus excavatum or chest asymmetry—1)
- Hindfoot deformity—2 (plain pes planus—1)
- Penumothorax—2
- Dural ectasia—2
- Protrusio acetabuli—2
- Reduced US/LS and increased arm/height and no severe scoliosis–1
- Scoliosis or thoracolumar kyphosis—1
- Reduced elbow extension—1
- Facial features (3/5)—1 (dolichocephaly, enophthalmos, down-standing palpebral fissures, malar hypoplasia, retrognathia)
- Skin striae—1
- Myopia > 3 diopters—1
- Mitral valve prolapse (all types)—1

Maximum total: 20 points; score ≥ 7 indicates systemic involvement; US/LS, upper segment/lower segment ratio

*Caveat: without discriminating features of SGS, LDS or vEDS (as defined in Table 1) and after *TGFBR1/2*, collagen biochemistry, COL3A1 testing if indicated. Other conditions/genes will emerge with time.
Ao, aortic diameter at the sinuses of valsalve above indicated Z-score or aortic root dissection; EL, ectopia lentis; ELS, ectopia lentis syndrome; *FBN1*, fibrillin-1 mutation, *FBN1* not known with Ao, *FBN1* mutation that has not previously been associated aortic root aneurysm/dissection; *FBN1* with known Ao, *FBN1* mutation that has been identified in an individual with aortic aneurysm; MASS, myopia, mitral valve prolapse, borderline (z < 2) aortic root dilatation, striae, skeletal findings phenotype; MFS, Marfan syndrome; MVPS, mitral valve prolapse syndrome; Syst, systemic score and Z, Z-socre.
(*Source:* Loeys, et al. The revised Ghent nosology for the Marfan's syndrome.J Med Genet. 2010;47:476-85.)

Loeys-Dietz Syndrome

Patients with this syndrome manifest thoracic aortic aneurysms as well as dissections in an autosomic dominant pattern and at an early age. It is associated with sequence variations in the transforming growth factor beta receptors 1 and 2.

Non Syndromic Familial Thoracic Aortic Aneurysms and Dissections

Multiples mutations in fibrillin-1 gene have been identified in patients which present with sporadic forms of aortic dissection. Cystic medial necrosis as well as elastolysis and deposits of

TABLE 2

Commonly used classification systems to describe aortic dissection

Type	*Site of origin and extent of aortic involvement*
DeBakey:	
Type I	Originates in the ascending aorta, propagates at least to the aortic arch and often beyond it distally
Type II	Originates and is confined to the ascending aorta
Type III	Originates in the descending aorta and extends distally down the aorta or, rarely, retrograde into the aortic arch
Stanford:	
Type A	All dissections involving the ascending aortal, regardless of the site of origin
Type B	All dissections not involving the ascending aorta
Descriptive:	
Proximal	Includes DeBakey types I and II or Stanford type A
Distal	Includes DeBakey type III or Stanford type B

(*Source:* Libby P. Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine, 8th edn.)

mucopolysaccharide-like materials are seen as the common features of this syndrome. No abnormal type I and type III collagen or fibrillin are found in fibroblast culture. Other genetic mutations thus far identified in this category include ACTA2, MYH II, TGFBR1/2, MYLK and others.

Ehler-Danlos Syndrome

It is a heterogeneous group of hereditable connective tissue disorders characterized by articular hypermobility, skin hyperextensibility and tissue fragility. The estimated incidence is 1/5,000 births. This disease is caused by structural defect in the pro-alpha (III) chain of collagen type III. Aortic involvement is seen primarily in Ehler-Danlos syndrome (EDS) type IV. Cystic media necrosis is also an intrinsic feature of this disease leading to aortic dissection.

Bicuspid Aortic Valve

Cystic medial necrosis is common in patients with bicuspid aortic valve disease, leading to an increased risk of ascending aortic enlargement and/or aortic dissection. Bicuspid aortic valve related aortic disease accounts for 5% of cases of aortic dissection.

Other Conditions

Pre-existing aortic aneurysm, congenital vascular disorders as coarctation of the aorta and Turner syndrome are also risk factors for aortic dissection. Rarely aortic dissection complicates inflammatory disorders as Takayasu's arteritis, syphilic aortitis, rheumatoid arthritis and more often, giant cell arteritis involving the aorta. Cocaine abuse accounts for less than 1% of the cases. In IRAD, the largest registry for AAD, the percentage of patients with cocaine-related AAD was 0.5%. Most IRAD patients with cocaine-related dissection had underlying hypertension and were long-time smokers, suggesting that cocaine exacerbates the increase in shear stress that already exists from chronic hypertension. The risk of aortic dissection increases during pregnancy. In women less than 40 years old, 50% of aortic dissections occur during pregnancy. Hypertension has been reported in 25–50% of cases of aortic dissection in pregnant women. The most common site of pregnancy-associated dissection is the proximal aorta. The aortic dissection generally occurs during the third trimester or during the first phase of labor.[8]

Indirect trauma, such as sudden deceleration, and direct trauma, as trauma induced by catheter-based diagnostic and therapeutic interventions, account for 5% of the cases of aortic dissections.[12]

CLASSIFICATION

STANFORD CLASSIFICATION

The Stanford classification of aortic dissection distinguishes between type A and type B. Type A includes all dissections involving the ascending aorta regardless of the site of origin and type B all dissections not involving the ascending aorta.[13]

DEBAKEY CLASSIFICATION

Type I originates in the ascending aorta, propagates at least to the aortic arch and often beyond it distally; type II originates and is confined to the ascending aorta and type III originates in the descending aorta, extends distally down to the aorta, or rarely retrograde into the aortic arch and ascending aorta, involves the descending aorta.

ANATOMICAL CLASSIFICATION (FIG. 2)

Proximal dissection includes DeBakey type I and II or Stanford A. Distal dissection includes DeBakey type II or Stanford B.

NEW CLASSIFICATION

New studies have demonstrated that intramural hematoma and aortic ulcers may be signs of evolving dissections or dissections subtypes. A new differentiation of acute aortic syndromes has thus been proposed by the following classes:[14]

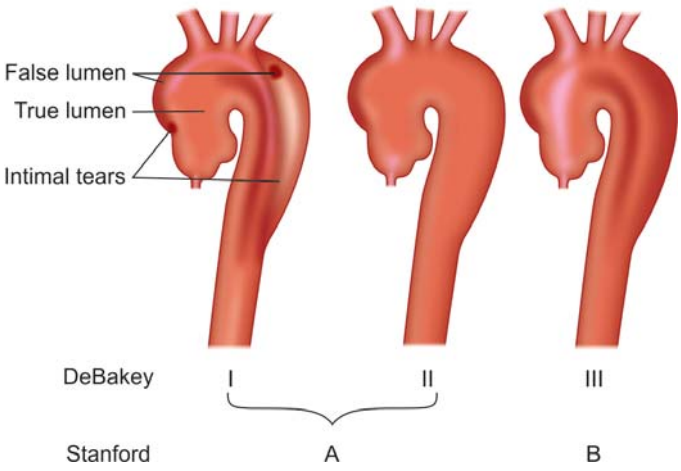


FIGURE 2: Anatomy and classification of aortic dissection (*Source:* Libby P. Braunwald's Heart Disease. A Textbook of Cardiovascular Medicine, 8th edn.)

Class I

Aortic dissection with a flap: The AAD is characterized by the rapid development of an intimal flap separating the true and the false lumen. Intimal flap tears characterize communicating dissections but are not always found, and non-communicating dissections are common. The dissection can spread from diseased segments of the aortic wall in an antegrade or retrograde fashion, involving side branches and causing other complications.

Class II

Intramural hematoma: This is probably the initial lesion in many cases of cystic medial necrosis, leading to aortic dissection where the intimal tear seems to be secondary to preceding intramural dissection.[15,16] Intramural hematoma may be the result of ruptured normal-appearing or diseased vasa-vasorum. As a dissection, the hematoma can expand along the aorta. The weakened inner wall is subjected to the elongating force of the diastolic recoil which can result in intimal tears only visible at surgery or autopsy. The prevalence of intramural hematoma in patients with suspected aortic dissection is in the range of 10–30%. Intramural hematoma can lead to acute dissection in 28–48% of the cases and is associated with aortic rupture in 21–47% of the cases. Regression is seen in 10% of the patients. Involvement of the ascending aorta is usually an indication for emergent surgery due to the risk of rupture, tamponade or compression of coronary ostia. Distal or descending aorta intramural hematoma warrants watchful waiting, medical therapy and occasional elective or emergent interventional stent-graft placement. There are two distinct types of intramural hematoma:

Type I: It shows a smooth inner aortic lumen, the diameter is usually less than 3.5 cm and the wall thickness greater than 0.5 cm. The mean longitudinal extent of the hematoma is 11 cm and the echo-free spaces show no signs of flow.

Type II: It occurs in atherosclerosis. A rough inner aortic surface with severe aortic sclerosis is characteristic. The aorta is more than 3.5 cm dilated and calcium deposits are frequently found. The longitudinal extend is also around 11 cm.

Overall, intramural hemorrhage is seen more frequently in descending than ascending aortic dissection.[17]

Class III

Subtle-discrete aortic dissection: There is a partial or linear tear of the vessel wall covered by thrombus. When the partial tear forms a scar, this is called an abortive or discrete dissection. Partial ruptures of the inner layer allow blood flow to enter the damaged media and thus cause dissection of the aortic wall.

Class IV or Plaque Ulceration

Ulceration of atherosclerosis plaques can lead to aortic hematoma, dissection and/or aortic perforation. The ulcers seem to affect the descending thoracic aorta as well as the abdominal aorta and are not usually associated with extensive longitudinal propagation or branch vessel compromise.

Class V

Blunt chest trauma usually causes dissection of the ascending aorta and/or the region of the ligamentum botalli at the aortic isthmus. Iatrogenic dissection can also occur during heart catheterization, after cross-clamping of the aorta and after intra-aortic balloon pumping. Most catheter induced dissections are retrograde dissections. They tend to decrease in size as the false lumen thromboses.[1,2,8]

CLINICAL MANIFESTATIONS

CLINICAL SYMPTOMS

The main challenge in managing patients with AAD is to suspect and diagnose it as early as possible. Aortic dissection is characterized by sudden onset of chest pain present in nearly 90% of the cases in patients from IRAD registry. The chest pain is described as sharp more often than tearing, ripping or stabbing. In contrast to acute myocardial infarction, the chest pain of dissection is often maximal at the time of onset. In acute myocardial infarction, the chest pain starts slowly and tends to gain intensity over time. In proximal dissections, the chest pain is usually located proximally, whereas distal dissections are characterized by interscapular as well as back pain.

The chest pain of aortic dissection may migrate from the point of origin to other sites, following the path of the extension of the dissection. Migratory pain is found in 17% of the cases. The presence of any neck, jaw and throat pain is highly suggestive of proximal dissection whereas pain involving the back, abdomen and lower extremities is suggestive of dissection involving the descending aorta. In some cases, the patient will present with pleuritic chest pain secondary to hemorrhage or inflammation in the pericardial space from the dissected aorta. Further propagation of the dissection may result in repetitive bouts of pain.

Chest pain may be absent and this is usually indicative of chronic aortic dissection or occurs in a patient with prior cardiac surgery.

Other symptoms present at presentation but less frequent are: syncope (13%), cerebrovascular accident (6%), congestive heart failure (7%), ischemic peripheral neuropathy or paraplegia, cardiac arrest and death. Patients with syncope have a higher mortality rate and are more likely to have cardiac tamponade or stroke.[11]

PHYSICAL FINDINGS

Hypotension occurs more commonly in patients with proximal aortic dissection whereas hypertension occurs in patients with distal aortic dissection. Hypertension is seen in 70% of the patients with distal aortic dissection, but only in 36% of the patients with proximal aortic dissection. Other clinical findings are pulse deficits related to the extension of aortic dissection found in 20% of the cases, a murmur of aortic valve regurgitation is seen in 40–50% of the cases of type A dissection. Congestive heart failure may occur secondary to acute valve aortic regurgitation. Pulse deficits are more characteristic of proximal aortic dissection occurring in 30% of the cases versus 15% of the cases in patients with distal aortic dissection. An impaired

pulse is secondary to diminished arterial flow and may result in visceral ischemia if mesenteric arteries are involved. This may be related to obstruction caused by the intimal flap. When spinal artery perfusion is compromised, ischemic spinal cord damage may result in paraparesis or paraplegia.

In 1–2% of the cases, the dissection may involve the ostium of a coronary artery and cause myocardial infarction. Most proximal dissections arise above the right sinus of valsalva explaining why the right coronary artery is more involved than the left. This may cause an acute myocardial infarction and the resulting use of thrombolytic and/or anticoagulation may be catastrophic in such patients.

Other arteries may include any arterial branch of the aorta such as the renal and the mesenteric arteries resulting in renal ischemia, acute renal failure and mesenteric ischemia.

Other associated clinical findings include pleural effusions seen on the left side, hemothorax secondary to the rupture of the aortal into the pleural space, hemoptysis and hematemesis secondary to rupture in the tracheobronchial tree or in the esophagus, superior vena cava syndrome, Horner's syndrome and unexplained fever due to the release of pyogenic substances from the aortic wall.

The diagnosis of AAD should always be considered in patients presenting with unexplained syncope, chest pain, back pain, abdominal pain, stroke, acute onset of congestive heart failure, pulse differentials or malperfusion syndrome of extremities and viscera.

The differential diagnosis includes myocardial ischemia, pulmonary embolism, pericarditis, non-dissecting thoracic and abdominal aneurysms and mediastinal tumors.[1,18,19]

DIAGNOSIS

CHEST X-RAY

The most common abnormality seen on chest X-ray is mediastinal enlargement seen in 60–90% of the cases. Other chest X-ray findings not uncommon are pleural effusions. If calcification of the aortic knob is present, separation of the intimal calcification from the outer aortic soft tissue border by more than 1 cm is called the "calcium sign" and is suggestive of aortic dissection.

ELECTROCARDIOGRAPHY

The electrocardiography (ECG) is frequently abnormal, showing signs of left ventricular hypertrophy, myocardial ischemia, non-specific ST-T wave deviations, or myocardial infarction, more frequently involving the inferior wall. Only a third of patients presenting with AAD have a normal ECG. The association of chest pain without any ischemic changes should prompt one to consider aortic dissection in the differential diagnosis.

D-DIMER

A prospective multicenter study of 220 patients from the Bio-IRAD registry with initial suspicion of AAD included 87 diagnosed with dissection and 133 with some other final diagnosis, including myocardial infarction, pulmonary embolism and angina.[4,20] D-dimer was markedly elevated in patients with AAD.[21] The cutoff level of 500 ng/ml used to "rule out" pulmonary embolism was also reliable to rule out AAD. At this cutoff level, sensitivity was 96.6% (95% CI, 90.3, 99.3) and specificity 46.6% (95% CI, 25.1, 54.6).

While D-dimer was found to be very sensitive it is not specific for the diagnosis of AAD. Also, the criteria of enrollment in this study was the suspicion of aortic dissection, So there was a selection bias which limits the generalization of the study other patients presenting with thoracic pain.[22-24] Gottfried et al. reported in a systematic review that D-dimer levels less than 0.1 µg/ml would exclude AAD in all cases.

A new biomarker calponin, a troponin counterpart of smooth vessel, has potential for the early diagnostic study of AAD within 24 hours of presentation.[25] A substudy of Bio-IRAD comparing 59 patients with confirmed AAD and 158 with suspicion of AAD at presentation (but whose final diagnosis was not AAD) showed an area under the curve of 0.63 and 0.58 respectively for both acidic and basic calponin.[20] Acidic calponin had a sensitivity of 58% and specificity of 72% at 24 hours and basic calponin had a sensitivity of 50% and specificity of 66% at 24 hours.[26]

IMAGING

Transthoracic Echocardiogram

Transthoracic echocardiogram (TTE) has a sensitivity of 60–85% and specificity of 93–96% for the involvement of the ascending aorta. The value of TTE is limited in patients with abnormal chest configuration, obesity, emphysema and in patients on mechanical ventilation.

Transesophageal Echocardiogram

Transesophageal echocardiogram (TEE) has a sensitivity of 90% in patients with type A aortic dissection and sensitivity of only 80% in type B.[27] Although TEE can be performed quickly in the emergent setting, it should only be interpreted by an experienced echocardiographer. One of the limitations of TEE is the use of conscious sedation which can cause bradycardia and elevate systemic blood pressure as the result of patient gagging. Another limitation is difficulty in visualization of small aortic segments within the distal part of the ascending aorta and the anterior portion of the aortic arch, a region known as the "blind spot". Artifacts due to reverberation within the lumen of the ascending aorta may be a problem to non-experienced echocardiographers. Plaque ulceration after plaque rupture is typically visualized. Dissection extending to the ostium of coronary arteries can be visualized in TEE (Fig. 3).

CT Angiogram

In CT angiogram (CTA), AAD is diagnosed by the presence of two different lumina separated by an intimal flap. Helical CT has improved CT diagnostics because it minimizes motion artifacts and eliminates respiratory misregistration. The diagnosis is based on the demonstration of an intimal flap which separates the true from the false lumen. The flap is identified as a low attenuation linear structure in the aortic lumen. Anterograde, retrograde or delayed flow is identified in the false lumen. Non-communicating aortic dissections cannot always be differentiated from

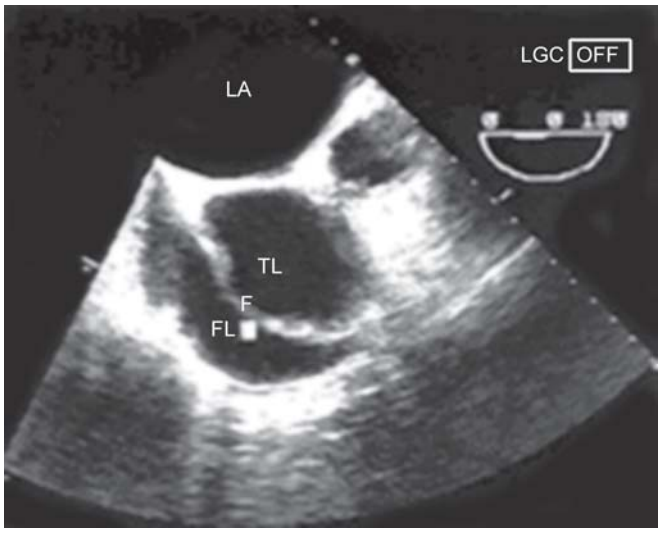


FIGURE 3: TEE of dissection of descending aorta in the horizontal plane (*Source:* Khan IA, Nair CK. Clinical, diagnosis and management perspective of aortic dissection. Chest. 2002;122:311-28.)

intramural hematoma. The CTA has a sensitivity of 83–94% and specificity between 87% and 100%. A limitation of CTA is that it does not characterize aortic regurgitation or coronary artery involvement well, and may predispose to contrast nephropathy secondary to iodine injection.[12]

Magnetic Resonance Imaging

Although magnetic resonance imaging (MRI) is both highly sensitive and specific in the diagnosis of AAD, the technique is not always available on an emergency basis and is difficult to execute on a hemodynamically unstable patient. The MRI sensitivity exceeds 90%. Despite its accuracy, artifacts might occur in as many as 64% of the cases. The MRI demonstrates the extent of the disease, pericardial involvement and aortic valve regurgitation.[1]

Aortography

The angiographics signs of aortic dissection include visualization of two lumina or an intimal flap, or indirect findings such as deformity of the aortic lumen, thickening of the aortic walls, branch vessels abnormalities and aortic regurgitation. The true lumen is typically compressed and tends to adopt a spiral configuration down the aorta. Injections in false lumen are characterized by the absence of branch vessels. Contrast aortography accurately identifies branch vessel involvement.

Aortography had long been considered the diagnostic standard for the evaluation of aortic dissection. However, prospective studies have shown that the sensitivity of aortography is 88% and falls to 77% when the definition of aortic dissection includes intramural hematoma and noncommunicating disease. The specificity of aortography is 94%. False negative aortograms occur due to thrombosis of the false lumen, equal and simultaneous opacification of the true and false lumina, or the presence of intramural hematoma. Aortography helps in the diagnostic of coronary artery involvement as well as aortic valve regurgitation. But it is an invasive procedure which carries a risk of contrast nephropathy.[1]

Coronary Angiography

Although new imaging techniques are gaining an emerging role in the assessment of coronary ostial involvement by the dissecting flap, coronary angiography remains the gold standard of evaluation of coronary arteries. Coronary artery disease is present in 25% of the patients with aortic dissection and may worsen the surgical outcome. However, mortality after surgery for AAD does not seem to be related to myocardial ischemia, therefore it is unclear if routine coronary angiogram changes the prognosis. Many aortic centers advocate emergent surgery without coronary angiography for type A dissection, using manual inspection or epicoronary ultrasound to decide when coronary bypass is also needed.[1,8]

TREATMENT

INITIAL TREATMENT

Admission to ICU, blood pressure regulation and hemodynamic stabilization are critical in the initial treatment of aortic dissection. The initial goal should be to reduce the blood pressure to 100–120 mm Hg (mean 60–75 mm Hg) or the lowest level commensurate with adequate vital organ function (cardiac, cerebral and renal) perfusion. Beta-blockers and vasodilators are the two medications used to control the blood pressure and to reduce the force of left ventricular ejection (dp/dt). Vasodilators should not be used as monotherapy because they can abruptly raise dp/dt, potentially worsening the dissection. The use of long acting β blockers should be avoided in patients who are surgical candidates secondary to untoward influences intraoperative blood pressure which could be complicated. A short acting β blocker, such as esmolol, would be more appropriate in this case.

Nitroprusside sodium and labetalol are very helpful agents. Adequate β blockade is achieved when the heart rate is close to 60/min. Among β blockers, labetalol is often used secondary to its α and β blockade properties resulting in ability to lower both left ventricular contractility and systemic arterial blood pressure. A trial of esmolol in patients with COPD is adequate to judge their ability to tolerate β blockers without bronchospasm. If β blockers are contraindicated, then a calcium channel blocker, such as verapamil ordiltiazem, is frequently used.

Refractory hypertension may result when a dissection flap compromises one or both renal arteries. In this case, the most effective antihypertensive medication may be the use of intravenous angiotensin-converting enzyme inhibitor.

Hypotension should raise the suspicion of cardiac tamponade or aortic rupture. Pseudohypotension resulting from altered arm circulation due to the dissection should always be excluded. In the case of hypotension, volume expansion should be initiated. If hypotension persists, pressors of choice are norepinephrine or phenylephrine. Dopamine should be reserved for improving renal perfusion and only at low doses given the fact that it may raise the dp/dt and theoretically extend the dissection.

It complicates proximal aortic dissection and is one of the mechanisms of death of these patients. Urgent pericardiocentesis might be performed, but may be harmful rather than beneficial because it can precipitate hemodynamic collapse and death. If the patient is relatively stable, emergent surgery with intraoperative pericardium decompression is the treatment of choice. However, if the patient has marked hypotension, aspiration of the minimum volume of fluid to raise the blood pressure to the lowest level acceptable should be the treatment of choice.[12]

Type A Acute Aortic Dissection

Type A aortic dissection is a surgical emergency with a mortality rate of 1– 2% per hour after onset.[28] At 24 hours of presentation, medical management alone results in mortality rate of 20%, 30% at 48 hours of presentation and 50% at 1 month.[29-31] Patients with intramural hematoma of the ascending aortal should be treated surgically. Current surgical techniques include resection of the intima tear, replacement or resuspension of the aortic valve if it has been disrupted by the dissection, coronary artery bypass if necessary and replacement of the ascending aorta. If the dissection involves the aortic arch, partial or total replacement of the aortic arch may be necessary. After the diseased segment containing the intimal tear is resected, aortic continuity is reestablished by interposing a prosthetic sleeve graft between the two ends of the aorta.

Several studies have shown that patients' immediate and long-term survival was not affected by the resection of the intimal tear. In particular, aortic arch intimal tear repair might increase morbidity and mortality; so many surgeons opt not to repair the arch secondary to risk of complications. If there is any aortic regurgitation, decompression of the false lumen usually allows for resuspension of aortic leaflets and restoration of the valvular competence. Placement of a prosthetic aortic valve is occasionally necessary because the valve repair is unsuccessful or in the setting of preexistent valvular disease as in Marfan's syndrome.[32-36]

Type B Acute Aortic Dissection

Patients with uncomplicated type B acute aortic dissection and intramural hematoma of the descending aorta are typically managed medically.[37] These patients have a high surgical mortality rate due to comorbidities and underlying atherosclerosis which is often present. There is a risk of both spinal injury and postoperative mortality associated with both open and endovascular repair. Routine surgical repair has not been shown to be beneficial in stable patients. In 384 patients in IRAD registry, the in-patient overall mortality was 13% and 32% in patients treated medically versus surgically. Aggressive medical management consists of maintaining the systolic blood pressure at or below 120 mm Hg with β blockers and other agents. Surgical treatment is indicated in patients presenting with complications as refractory pain, malperfusion of vital organs, dissection progression, aneurysm expansion and refractory hypertension.[38]

ENDOVASCULAR REPAIR

Endovascular repair may retard the progression of disease in patients who are not open surgical candidates or who refuse open surgical repair. Patients with renal and visceral artery compromise have more than 50% mortality rate with open surgery. Endovascular repair is often used in high risk patients with type B dissection and consists of either fenestration that helps to relieve malperfusion by decompressing the false lumen (equalizing the pressure between the false and the true lumen) or more frequently stent placement that seeks to redirect flow into the true lumen and facilitate the closure of the entry tear into the false lumen, and promotes healing of the involved segment .The fenestration of the intimal flap involves crossing an intact flap with a wire, passing a ballon-tipped catheter over the wire and then expanding the balloon to create one or more holes in the intimal flap. The hole(s) promotes equalization of pressures in the true and false lumen. Stent placement is a percutaneous deployment of a goretex graft over the affected arterial branch whose flow has been compromised by the dissection process.[39]

Intraluminal stent graft placement represents an attractive alternative to open aortic repair. The US Food and Drug administration has not yet approved the use of endovascular grafts in the chronic phase of aortic dissection.[40] Some of the current indications of endovascular procedures include obstruction of aortic branch arteries, descending dissection with intractable pain, periaortic hematoma as a sign of impeding rupture and an expanding false lumen.[41,42]

ACUTE AORTIC DISSECTION: OUTCOME

Type A Dissection

In IRAD registry (303 patients), 273 (90.1%) were managed surgically and 30 (9.9%) were managed medically. Long-term survival rate (after hospital discharge) for patients treated surgically was 96% at 1 year and 90% at 3 years versus 88% and 66% at 1 and 3 years for patients treated medically, mean follow-up overall 2.8 years.[43] A history of previous cardiac surgery as well as history of atherosclerosis was independent predictor factors of mortality.[44] Women tend to have more inpatient mortality and poorer surgical complications than men,[(OR of death 1.4), surgical mortality 32% vs 22%]. Late complications include aortic regurgitation, recurrent dissection and aneurysm formation or rupture. The incidence of subsequent aneurysm formation is 17–25% and is usually the consequence of the dilation of residual false lumen in the distal aortic segments not resected at the time of surgery. The presence of a patent false lumen is one of the strongest predictors of adverse late outcomes, including more rapid aortic dilation, a greater likelihood of requiring subsequent aortic surgery and late mortality. Late aortic aneurysm is 10 times more common in patients with poorly controlled blood pressure; so long-term blood pressure control to reduce dp/dt is mandatory. Systolic blood pressure should be maintained at less than 130 mm Hg.[2]

Secondary to the high incidence of late aneurysm, follow-up imaging is recommended, including CT scan, MRI and/or TEE at 1, 3 and 6 months initially, then every 6 months for 2 years, then every year thereafter.[2,45-47]

Type B Dissection

Seventy eight percent of type B dissection patients in IRAD registry received medical therapy while 11% underwent surgery

and 11% endovascular treatment.[48] In hospital mortality was 29% in patients treated with surgery, 11% in patients treated with endovascular treatment and 10% in patients treated with medical therapy alone.[49]

Three years survival for patients treated medically, surgically or with endovascular repair was 77% versus 82% and 76%. Independents predictors of inpatient mortality were female gender, a history of prior aneurysm, history of atherosclerosis, in-hospital renal failure, pleural effusion on chest X-ray, in-hospital hypotension or shock. In a risk prediction model controlling for age and gender, the authors showed the "deadly triad: absence of chest/back pain at presentation, branch vessel involvement, hypotension/shock" to be independent predictors of in-hospital death. Between 31% and 66% of follow-up deaths are due to aorta rupture, extension of dissection, or perioperative mortality during or after subsequent vascular repair.

Small retrospective studies have shown that type B intramural hematoma may have a better prognosis than classic type B dissection. In a study on 53 patients with intramural hematoma and 57 patients with type B aortic dissection, the survival rates were 100%, 97% and 97% at 1, 2 and 5 years in patients with intramural hematoma versus 83%, 79% and 79% in patients with type B acute aortic dissection. In this study, the new appearance of an ulcer-like lesion was the strongest predictor of progression in patients with intramural hematoma.[19,49]

CONCLUSION

The diagnosis of aortic dissection is challenging. If diagnosed late, AAD has a very poor prognosis, especially in type A dissection. Prompt imaging at presentation is key to initiation of life saving therapy. Urgent surgical treatment is standard of care in type A. Medical management and endovascular treatment are used initially in type B dissection. Endovascular procedures are being used for certain higher risk subgroups and appear to be an important advance for managing complicated type B dissection.

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Chapter 66

Endovascular Treatment of Aortic Aneurysm and Dissection

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Chapter Outline

- History of Endovascular Aortic Repair
  - Devices
- Stent Graft Design: The Lessons of Experience
- Anatomic Substrate for Endovascular Aneurysm Repair
- Current Stent Graft Designs for Abdominal Aortic Aneurysm (AAA)
  - Modular Z-stent-based Stent Grafts
  - Unibody Stent Grafts
  - Uni-iliac Stent Grafts
  - Ringed Stent Grafts
  - Polymer Filled Stent Grafts
- Adjunctive Devices and Techniques
  - Narrow Iliac Arteries
  - Angulated Neck
  - Short Neck
  - Iliac Aneurysm
- Endoleak
- Late-occurring Complications of Endovascular Aneurysm Repair
  - Migration
  - Endotension
  - Neck Dilatation
- Follow-up Imaging
- Branched and Fenestrated Stent Grafts
- Current Thoracic Aortic Stent Graft Designs
- Endovascular Repair of Thoracic Aortic Aneurysms
- Thoracic Aortic Dissection
- Acute Type B Dissection
- Chronic Type B Dissection
- Complications of Thoracic Endovascular Aortic Repair
  - Endoleak
  - Neurological Complications
  - Failed Insertion
- Intramural Hematoma
- Penetrating Aortic Ulcer

INTRODUCTION

Although aortic aneurysm sometimes causes aortic dissection and visa versa, these are two very different diseases. What they have in common is structural failure of the aortic wall. Of the two, aneurysm is less likely to present as an acute aortic emergency and more likely to be treated by endovascular means. In addition, aortic aneurysm is a simpler problem than aortic dissection. Consequently, far more is known about the endovascular repair of aortic aneurysm than the endovascular treatment of aortic dissection.

Aneurysms are caused by proteolytic degradation of adventitial elastin, among other things. The weakened aortic wall dilates, increasing wall tension, accelerating dilatation and increasing the risk of rupture. In most cases, the process is painless up to the point of rupture, hemorrhage and death. The goal of aneurysm repair is to connect the non-dilated segments proximal and distal to the aneurysm using an impervious conduit, which isolates the aneurysm from flow and pressure, thereby preventing dilatation and rupture. In the elective setting, this is a prophylactic operation with no short-term benefits, only risks. The long-term benefit, freedom from risk of rupture, depends on the size of the aneurysm and the life expectancy of the patient, together with the efficacy and durability of the repair.

Dissection occurs when blood enters the aortic wall through a tear in the intima and propagates along the aorta, shearing the inner layers from the outer layers. Unlike aneurysm, which is a slow process with very little risk of rupture in the early stages, dissection has a variety of dire short-term effects. In the absence of a route of egress, high diastolic pressure causes the false lumen of the aorta to expand, compressing the true lumen (dynamic obstruction). False lumen expansion also narrows the true lumen of the aorta's branches (static obstruction). Both forms of true lumen compression compromise flow to indispensable branches feeding the brain and the abdominal viscera. Dissection of the ascending aorta (type A) is a particularly bad actor: it has to be treated promptly to prevent serious cardio-aortic complications and it is not currently amenable to endovascular repair. Dissection of the descending thoracic aorta (type B) is usually more benign, at least in the short term. Early repair, using an endovascular stent graft, often results in false lumen thrombosis and true lumen expansion. Even when the restoration of the aortic true lumen fails to correct visceral perfusion, various other endovascular interventions, involving stents and man-made connections between the true and false lumens (fenestrations) are often effective.

HISTORY OF ENDOVASCULAR AORTIC REPAIR

The first case of endovascular aneurysm repair was performed by Volodos et al. in 1986,[1] but not widely reported outside the Ukraine. The approach first came to public attention in 1990 with the publication of Parodi's work, using a balloon-expanded stent to attach a woven Dacron graft below the renal arteries.[2]

All the repairs in Parodi's initial series failed for lack of a secure hemostatic distal attachment site. Indeed, no aorto-aortic stent grafts work well in the infrarenal location because there is rarely enough non-dilated aorta above the bifurcation.[3] The development of a bifurcated stent graft, first used clinically in 1993,[4] overcame this limitation by moving the site of distal implantation into the common iliac arteries. This particular bifurcated stent graft was of a unibody design, meaning that the entire graft was inserted whole and manipulated into position using catheters. It was soon followed by several modular alternatives, in which at least one limb of the stent graft was inserted separately and attached to the short stump of a limb on the body of the device. Meanwhile, tubular aorto-aortic stent grafts found applications in the descending thoracic aorta where there are no indispensable branches.[5]

Early delivery systems were bulky, stiff and blunt ended. They tracked poorly through the tortuous atherosclerotic iliac arteries of the typical elderly aneurysm patient. As a result, iliac rupture, dissection and failed insertion were common.[6] These were soon displaced (in Europe at least) by narrower, more trackable, over-the-wire systems.[7]

DEVICES

Once in place, the early grafts worked reasonably well in the short term, but they proved incapable of withstanding the repetitive stresses and strains of the endovascular environment. High rates of structural failure, migration, re-intervention, conversion and aneurysm rupture prompted some endoskeptics to pronounce endovascular aneurysm repair "a failed experiment".[8] However, the commoner forms of failure were not intrinsic to the endovascular approach: they were the device-specific consequences of identifiable design features.[9] Manufacturers subsequently identified and eliminated many of the causes of late failure. By 1999, when the prospective randomized endovascular aneurysm repair studies (EVAR-1[10] and EVAR-2[11]) began, the most widely used stent grafts were already safe, effective and durable.

The EVAR-2 study compared endovascular repair with no repair in patients considered too sick for open repair. The results showed no significant difference in mortality between the two groups. However, several design flaws undermined the significance of the findings. For example, roughly half of the deaths in the treatment group were caused by aneurysm rupture during the long interval between randomization and operation. Patients who crossed over from the observation arm to the treatment arm fared surprisingly well, probably because the delay in treatment allowed for optimization of cardiopulmonary condition.

EVAR-1 compared endovascular aneurysm repair with open repair in patients who were suitable for either. The perioperative mortality rate following endovascular repair (1.7%) was significantly lower than the rate following open repair (4.7%). In the medium term, this advantage of EVAR was reflected as a lower rate of *aneurysm-related mortality*, yet the difference in *overall mortality disappeared*. The observed "catch up" mortality in the EVAR group has been the subject of much speculation. One explanation is that high-risk patients with a short life expectancy were "culled" from the open repair group. When these patients died in follow-up, the all-cause mortality gap narrowed. Other prospective randomized studies, such as the Dutch randomized endovascular aneurysm management (DREAM) study[12] and the veterans' administration open surgery versus endovascular repair (OVER) study[13] had similar findings. The relatively small DREAM study proved to be somewhat underpowered. The remarkably low mortality rates seen in the OVER study may well reflect advances in the state of the art between 1999 and 2002 when the OVER study began. Meta-regression analysis[6] shows that the rates of mortality and endoleak declined well into the current decade. The field of endovascular aneurysm repair also advanced through the development of endovascular treatments for aneurysms of the aortic arch,[14,15] the pararenal aorta[16] and the thoracoabdominal aorta.[17,18]

STENT GRAFT DESIGN: THE LESSONS OF EXPERIENCE

It is important to recognize that endovascular aneurysm repair is a relatively new technique that depends heavily on the performance of a relatively new technology; both are still improving. Definitive pronouncements regarding the limitations of endovascular aortic repair are often invalidated by subsequent advances in the field. The best anyone can do is to describe the short-term performance of current devices, or the long-term performance of old devices. Since the product cycle is still relatively short, and early devices may no longer be in use, data do not have to be old to be out of date.

It is also important to recognize the limits of preclinical testing. Most improvements in stent graft design resulted from the elimination of failure modes that were not apparent until the devices had been used clinically. As a rule, short-term problems become apparent quickly, but long-term problems go unrecognized for years. No device can be considered durable until it has been in use for many years, by which time it may be obsolete.

Nevertheless, most stent grafts employ the same basic principles as their predecessors, and elements that worked before will probably work again, while those that failed before have generally been eliminated. We know, for example, that movement between the apex of a stent and a graft causes fabric erosion,[9] loosely woven grafts develop suture holes,[19] porous grafts transmit pressure,[20] compression loaded Nitinol struts fracture, unsupported graft limbs occlude and friction alone is not enough to prevent migration.[21] These features of the Ancure (Endovascular Technologies, Menlo Park, CA), Vanguard (Boston Scientific, Natick, MA), AneuRx (Medtronic, Minneapolis, MN) and early Excluder (WL Gore, Flagstaff, AZ) stent grafts[22] are absent from current devices.

Most of what we do not know relates to the fundamentally different mechanisms of action employed by some new devices. We do not know, for example, whether neck dilatation will cause

leakage around the proximal end of the fixed diameter polymer balloons of the Nellix stent graft (Nellix, Palo Alto, CA) and Ovation (Trivascular, Santa Rosa, CA) stent grafts. If so, these devices will soon disappear. If not, they may be the stent grafts of the future.

ANATOMIC SUBSTRATE FOR ENDOVASCULAR ANEURYSM REPAIR

The basic requirements for successful endovascular aneurysm repair include: a route of aortic access through the iliac arteries and non-dilated implantation sites of sufficient length between the aneurysm and the orifices of indispensable arteries. Whatever the device, straight wide iliac arteries are less likely to impede device insertion and long cylindrical implantation sites are less likely to disrupt the seal. Various authors have tried to categorize arterial anatomy as a way to predict the likelihood of complications. However, the threshold values that divide favorable anatomy from unfavorable anatomy are always arbitrary and non-predictive for several reasons. First, some devices cope with unfavorable anatomy better than others. The Aorfix stent graft (Lombard Medical Technologies, Didcot, England), for example, is flexible enough to accommodate angulated necks. Few other stent grafts bend so easily.[23] Second, adjunctive maneuvers (see below) alter either stent graft performance or arterial anatomy in ways that can make the difference between success and failure. Third, unfavorable features have compounding effects. An angulated neck is much more likely to cause leakage if it is also short. The anatomic selection criteria described in the instructions for use should not be regarded as absolute requirements for safe effective aneurysm repair, but they cannot be ignored because they defined the patient populations of industry-sponsored IDE studies, and those studies provided much of the published literature on device performance.

CURRENT STENT GRAFT DESIGNS FOR ABDOMINAL AORTIC ANEURYSM (AAA)

The evolutionary process which yielded most of the current stent grafts was more for convergent than divergent. Families of devices share certain defining features and performance characteristics. One can often predict the behavior of a new device by examining the behavior of other members of the same family.

MODULAR Z-STENT-BASED STENT GRAFTS

Most of the stent grafts in this family have a woven polyester graft supported by an exoskeleton of self expanding Z-stents, one of which projects beyond the proximal margin of the graft into pararenal aorta where its barbs ensure secure attachment. The Zenith stent graft (Cook Medical, Bloomington, IN) was arguably the most stable of the second generation of stent grafts.[24] The sutured attachment between the proximal stent and the rest of the stent graft was augmented in 2002. Very little else has changed since the original Zenith stent graft was first used in 1998. Other stent grafts of its generation lacked a suprarenal stent (AneuRx, Excluder), or barbs (Talent, Medtronic, Minneapolis, MN), and were subject to higher rates of migration. The latest generation includes the Zenith Low Profile, the Endurant (Medtronic, Minneapolis, MN), the Incraft (Cordis, Miami, FL). All three have tightly woven thin walled fabrics, Nitinol stents and slippery kink-resistant introducer sheaths suitable for percutaneous insertion.

UNIBODY STENT GRAFTS

Unibody bifurcated stent grafts have no inter-component connections and no risk of component separation, but they tend to be more difficult to insert and less versatile than modular stent grafts. The only unibody stent graft currently marketed for clinical use is the Powerlink (Endologix, Irvine, CA), but even this is not truly unibody in that most repairs employ more than one component. The original bifurcated part of this stent graft has no proximal attachment means. It sits on the bifurcation of the aorta, like a rider in a western saddle, relying on its stiffness to support the position of the proximal component. Since the renal to bifurcation distance varies, while the length of the stent graft is fixed, accurate proximal implantation requires the routine use of an aortic extension. In the absence of active proximal fixation, this type of stent graft has to be stiff; otherwise, it would collapse into the aneurysm. One might think that such a rigid stent graft would have a hard time accommodating the bends of the typical aneurysmal aorta, but the long-term results have been surprisingly good, even in aneurysms with short angulated necks.

UNI-ILIAC STENT GRAFTS

Uni-iliac stent grafts are useful when one of the iliac arteries is too narrow or too small for delivery system insertion, or there is insufficient space below the renal arteries to construct a bifurcated stent graft. This group includes versions of the Powerlink, Unifit (LeMaitre, Burlington, MA) and Zenith stent grafts. The latter, known as the Renu stent graft, is used to re-line previously placed stent grafts that have either migrated (usually AneuRx), or become too porous to prevent aneurysm dilatation (see section Endotension).

RINGED STENT GRAFTS

Instead of stents, the Aorfix and Anaconda (Vascutek, Glasgow, Scotland) stent grafts have multiple loops of Nitinol wire. In their fully expanded state, these wire loops do little to constrain the longitudinal dimensions of the stent graft, allowing differential shortening between opposite sides. The resulting flexibility allows a stent graft of this type to match the orientation of the most angulated necks. Both devices rely for attachment on short curved barbs at the proximal orifice. The graft limbs are even more flexible than the trunk. In theory, they should resist kinking, even in the presence of severe iliac angulation. In practice, limb thrombosis rates have been surprisingly high, perhaps because the wire loops function well only when they have the space to expand fully, which may not be the case in an iliac artery of variable diameter.

POLYMER FILLED STENT GRAFTS

Most stent grafts employ a metal framework to hold the fabric of a graft against the wall of the non-dilated aorta and isolate

the aneurysm from the circulation, but not all. The Ovation and Nellix stent grafts rely instead on polymer filled balloons. The Ovation stent graft has Nitinol stents at its ends for attachment and a series of narrow interconnected balloons encircling the polytetrafluoroethylene (PTFE) fabric. The attachment stent of the original unibody version of the device was prone to fracture, but the balloon-mediated seal apparently stood the test of time.

The Nellix has a unique mode of action. Most stent grafts aim to isolate the aneurysm from the circulation, whereas the Nellix aims to fill the aneurysm with a bag of polymer, through which two stent-supported lumens carry blood to the iliac arteries.

Both devices depend on the fate of the neck. If the neck dilates, as it does with all the usual self-expanding stent grafts, blood will find its way into the aneurysm sac and the repair will fail.

ADJUNCTIVE DEVICES AND TECHNIQUES

Aneurysms fall into four groups depending on the state of the neck proximally and the iliac arteries distally:

1. Treatable using standard stent grafts.
2. Treatable using standard stent grafts with the help of additional devices and techniques.
3. Treatable using complex fenestrated or branched stent grafts.
4. Untreatable by purely endovascular means.

In the days of aorto-aortic AAA repair, 80–90% of cases were in group 4, but the number has been dwindling steadily with every advance in the field. These days, few patients lack the anatomic substrate for some form of endovascular repair. However, the laudable desire to spare the patient the discomfort, morbidity and disability of conventional open repair can be carried to excess. In most high volume centers, the open surgical repair of juxtarenal and pararenal aortic aneurysms is associated with low mortality rates and predictable long-term efficacy. In contrast, less than a dozen centers have the means to perform complex endovascular repairs and the long-term results of these investigational procedures are unknown.

NARROW ILIAC ARTERIES

Although modern delivery systems are narrower and more flexible than they used to be, patients still die from ill-advised attempts to traverse the iliac arteries. The damage done during device insertion may only become apparent when the sheath is removed and the site of injury exposed. The quickest and safest way to obtain control of a ruptured iliac artery is to inflate a balloon at, or proximal to, the site of injury. Unless the artery is totally destroyed, a covered stent can be used for repair. If the problem is anticipated, the covered stent can be implanted before either device insertion or balloon angioplasty stretches the iliac artery beyond its limits. This method of "paving and cracking" creates an endovascular conduit. However, the approach is not applicable in every case of iliac narrowing. For example, when the proximal external iliac artery is involved there is a risk of internal iliac artery occlusion. Under these circumstances, a surgically created conduit may be better, especially for a complex thoracic (or thoracoabdominal) reconstruction, which relies on the internal iliac artery as a source of collateral flow to the spine. At UCSF we prefer permanent ilio-femoral or ilio-iliac bypass to the use of a temporary, blind-ended conduit. We create the bypass at a preliminary operation, often weeks before the endovascular repair. To avoid competitive flow we perform an end-to-end anastomosis proximally and an end-to-side anastomosis distally. The external iliac artery then serves as a route for retrograde flow to the internal iliac artery.

ANGULATED NECK

The combination of a short, angulated neck and a stiff stent graft often results in axial misalignment, loss of contact and endoleak.[23] The device selection is as important as patient selection in these cases because some devices, such as the Endurant or Aorfix stent grafts, tolerate neck angulation better than others. Balloon-driven realignment of the proximal stent graft helps to establish coaxial orientation with the neck, and a Palmaz stent helps to maintain coaxial orientation upon balloon deflation.

Anterior angulation of the neck calls for craniocaudal angulation of the image intensifier. Otherwise, the neck appears foreshortened and the renal arteries are difficult to locate with any precision. When the image intensifier is in the correct orientation all the stent apices line up across the aorta.

SHORT NECK

The neck of an abdominal aortic aneurysm is bounded proximally by the renal arteries and distally by the aneurysm. The implantation site can be lengthened by covering the renal arteries, but something must be done to preserve renal perfusion. The endovascular options include renal stenting, and stent graft fenestration (see below).

Inadvertent coverage of a renal artery can be treated by inserting a stent with one end in the renal artery and the other in the aorta, pushing the proximal margin of the stent graft inward, or downward, away from the renal orifice. While complete renal artery coverage is easy to recognize but difficult to treat, partial coverage is difficult to recognize but easy to treat. In cases of partial coverage, completion angiograms often show no filling defects and no delay in renal artery filling. One has to look carefully at the position of the markers with the image intensifier at the proper angle. A high frame rate helps.

The transbrachial implantation of a renal stent alongside the stent graft creates a route for flow from the proximal margin of the stent graft to the renal arteries.[25] Even if this stent (known as a snorkel or chimney graft) has a PTFE lining to channel all luminal flow into the renal artery, periluminal flow through gutters between the stent, the aorta and the stent graft are potential routes of leakage into the aneurysm. The resulting type I endoleak can be difficult to treat. Options include: the simultaneous deployment of a Palmaz stent within the aorta with or without a balloon within the renal stent to preserve renal flow, and coil embolization of the gutters and the proximal aneurysm. At UCSF we often remove the stent graft from its delivery system before insertion and sew a carpet of coils to the outside of the stent graft in the area designated for the snorkel. The goal is to fill potential gutters and interrupt the route of leakage.

ILIAC ANEURYSM

Iliac arteries up to 22 mm in diameter can be used as sites for stent graft implantation without fear that they will dilate, leading to aneurysm formation or endoleak.[26] If the common iliac artery is wider than the widest available iliac stent grafts, one has to look to the external iliac artery for a distal implantation site, and perform branched iliac repair or accept the loss of prograde flow into the internal iliac artery. Following unilateral internal iliac occlusion, buttock claudication is common but self-limited, and severe ischemic complications, such as colon necrosis, paraplegia or lumbosacral plexopathy, are rare.[27] Opinions vary regarding the consequences of bilateral internal iliac occlusion, but most agree that bilateral internal artery occlusion should be avoided, or at least staged. The kind of distal internal iliac embolism used for control of pelvic hemorrhage in trauma is not appropriate. More proximal internal iliac occlusion using Gianturco coils or an Amplazer plug preserves collaterals and minimizes pelvic ischemia.

ENDOLEAK

Since the primary goal of endovascular aneurysm repair is to isolate the aneurysm from the circulation, persistence of perigraft perfusion (endoleak) has to be regarded as a sign of failure.[28-30] However, an endoleak's effect on sac pressure,[31] dilatation[32] and risk of rupture[33] depends very much on the source.

In the absence of an endoleak, the sac pressure is low, the aneurysm shrinks and there is no risk of rupture. Untreated leakage directly into the aneurysm either around the end of the stent graft (type I) or through a defect in the wall of the stent graft (type III) is associated with high sac pressure, rapid dilatation and a high rate of rupture. Leakage into the aneurysm sac by an indirect route through lumbar or inferior mesenteric branches (type II) occupies an intermediate position between direct leakage and no leakage. Most type II endoleaks resolve spontaneously within 6 months, and in the absence of aneurysm dilatation,[34] rupture is rare. Moreover, type II endoleaks are notoriously difficult to treat by transarterial means, especially when the lumbar arteries are involved. It is not enough to occlude the ascending iliolumbar feeders because other collateral routes soon develop. One has to completely obliterate the endoleak cavity within the aneurysm. Then at least an endoleak will be rendered invisible on computed tomography (CT). Type IV endoleak is a form of type III endoleak through tiny defects in the graft which sealed upon heparin reversal.[29] However, continued transmission of pressure to the aneurysm sac often leads to aneurysm dilatation (type V endoleak, or endotension). The substitution of a more tightly woven graft fabric seems to have eliminated this complication of repair with the AneuRx stent graft.[19] Graft porosity on a microscopic level appears to have been responsible for a similar phenomenon following repair with the original excluder stent graft, requiring changes in the graft fabric.[20]

LATE-OCCURRING COMPLICATIONS OF ENDOVASCULAR ANEURYSM REPAIR

The aortic pulse subjects the stent graft to a relentless hemodynamic pounding, which eventually degrades stent graft position, structure and function. Although modern stent grafts appear to be more durable than their predecessors, the complications of stent graft instability will continue to be present for years as patients outlast their devices.

MIGRATION

Effective endovascular repair lowers the pressure within the aneurysm and generates a pressure gradient across the wall of the stent graft. The pressure-related forces on a straight untapered segment of the stent graft are in balance, but when the cross-sectional area or axial orientation of the stent graft change, unbalanced forces destabilize stent graft attachment. Since the cross-sectional area of the trunk of a bifurcate stent graft is larger than the cross-sectional area of the limbs, pressure-related forces push the bifurcation in a caudal direction. A large-diameter bifurcated stent graft can generate caudally directed forces as high as 20 N. Bends in the trunk or limbs of a stent graft tend to generate transaxial forces, pulling the center of the stent graft toward the anterior wall of the aneurysm and the ends of the neck and common iliac arteries.[35]

Experience has shown that friction,[36] arterial ingrowth,[37] and column strength[36] provide little protection against migration. The most stable stent grafts have barbs,[38] suprarenal stents[39] and a long-body/short-leg configuration.[40]

The commonest form of migration involves caudal displacement of the proximal end of the stent graft out of the neck and into the aneurysm. If detected in its early stages, the problem is easy to correct using a stent graft extension with active, barb-mediated attachment proximally and a long overlap with the original graft distally. Since unstable stent grafts tend to have short trunk, there is often only enough room to insert a uni-iliac extension. The resulting flow limitation may cause claudication in a very active patient.

ENDOTENSION

Aneurysm dilatation in the absence of endoleak (endotension) was a common problem after endovascular repair using first-generation AneuRx and Exluder stent grafts, but they are not the only stent grafts to fail in this way. Endotension occurs with increasing frequency once any stent graft has been in place 5 years, or more. Troubling as this may be, death from hemorrhage is unlikely in the absence of perigraft flow, even if the aneurysm were to rupture. Nevertheless, the safest course of action is to re-line the original stent graft.[41] The combination of an endotension prone stent graft and a persistent type II endoleak presents a more difficult dilemma. At UCSF we tend to treat both potential causes of aneurysm pressurization, because perigraft perfusion raises the possibility of true hemorrhagic rupture.

NECK DILATATION

The observation that neck dilatation inevitably follows endovascular aneurysm repair with just about any self-expanding stent graft[42] led some endoskeptics to predict that type I endoleak and migration would be the eventual outcome in any patient who lived long enough. Experience has proved them wrong,[40] probably because the fully expanded stent graft protects the neck.

For self-expanding stent grafts, the amount of neck expansion depends on the degree of oversizing. When the diameter of the neck equals the unconstrained diameter of the stent graft (full expansion) dilatation ceases and the diameter plateaus. One occasionally sees stent migration in patients with neck dilatation, but most such cases occur following repair with a device that lacks active barb-mediated fixation.

Balloon-expanded stent grafts behave differently. Balloon-driven expansion initially stretches the neck, but then neck diameter stablizes because the balloon-expanded stent will expand no further.[43] In addition, uncovered portions of a balloon-expanded stent often become incorporated into the surrounding aortic tissue, stabilizing the dimensions of the proximal part of the implantation site.

FOLLOW-UP IMAGING

The purpose of follow-up imaging is to detect impending failure while the underlying problem remains amenable to endovascular correction. The choice of imaging modality and follow-up interval depends on the late failure mode of the particular stent graft. In the United States, where a migration-prone stent graft was once in widespread use, the imaging modality has to be sensitive to small changes in stent graft shape or position. Contrast-enhanced CT scan is not the only suitable means of surveillance.[44] Significant migration is always associated with anterior displacement of the graft within the aneurysm, which can be seen by comparing serial non-contrast CT scans or lateral X-rays of the abdomen.[45]

Stent grafts with a track record of stability do not need frequent follow-up, if an initial study shows no cause for concern.[46] If, on the other hand, the initial imaging shows a type I endoleak, immediate corrective measures are indicated, and if initial imaging show a type II endoleak, more frequent assessment of aneurysm size is warranted.

BRANCHED AND FENESTRATED STENT GRAFTS

Fenestrations are simply holes in the wall of the graft for flow to an important aortic branch. The risk of endoleaks is lowest when the margin of a relatively small fenestration is brought into close apposition with the orifice of the corresponding artery. Accurate alignment is achieved using a bridging catheter to guide the fenestration to the target artery during staged stent graft expansion, and maintained using a bridging stent to hold the fenestration in place.[16] The technique is most useful in the treatment of juxtarenal aortic aneurysms.

The substitution of a covered stent for the typical uncovered bridging stent turns a fenestration into a branch,[47] where upon the seal no longer depends on contact between the stent graft and the aortic wall, but on contact between the margin of the fenestration and the covered stent. Augmenting the margin of the fenestration with a cuff or a short branch increases inter-component contact and improves the seal. Branched stent grafts can therefore be used to treat aneurysms of the thoracoabdominal aorta[47] and aortic arch[14] where conventional surgery produces high rates of death and disability.

Although fenestrated and branched stent grafts remain unapproved for sale in the United States, they are far from new. The first fenestrated stent grafts were used clinically more than a decade ago. At the time of writing, over 5,000 have been inserted worldwide with remarkably good results. The basic technique, involving staged deployment, bridging catheter guidance and bridging stent fixation, has not changed since 1998, but the approach has evolved through a series of small refinements. In the current device, fenestrations are reinforced with loops of Nitinol wire. Indwelling catheters and sheaths facilitate access through the fenestrations into the target arteries. These days, most users prefer covered bridging stents which minimize the risk of type III endoleak. The most common long-term problem has been branch occlusion, due to stent graft migration. Unstented fenestrations and scallops do not only migrate down the aorta; they can also migrate in a transverses plane as differential expansion twists the stent graft.

The first 4-branch repair of a thoracoabdominal aortic aneurysm was performed in 2000.[18] The main design features of that stent graft, with a tapered trunk, barbed proximal stent, and caudally oriented cuffs, are present in modern devices. The cuffed stent graft has proven to be easier to plan, easier to insert, more forgiving and more versatile than the fenestrated equivalent. At UCSF we have gradually transitioned from custom made stent grafts to standard off-the-shelf stent grafts. The off-the-shelf system is used in 50–80% of cases depending mainly on the extent of the TAAA. Having treated over 100 TAAA patients using caudally oriented cuffs, only once we have failed to insert all the branches as planned, and we have never seen kinking, component separation, or stent graft migration.

Endovascular repair of the aortic arch has progressed more slowly. In the first case reported in 2003,[14] the bifurcated stent graft was inserted through the right carotid artery. Of the short wide trunk and the short wide limb stent graft were deployed in the ascending thoracic aorta, and the long narrow limb deployed in the innominate (brachiocephalic) artery. The main limitation of this approach has been a diameter mismatch between the delivery system (22–24 French) and the carotid artery. In such cases the creation of a conduit to the innominate artery provides a route of access for device insertion, but reduces the minimally invasive aspects of the approach.

We recently (past 6 months) started to use an alternative system in which a cuffed stent graft is inserted into the arch through a surgically exposed femoral artery using a curved self-orienting delivery system. The cuffed stent graft is deployed during a brief period of rapid ventricular pacing or adenosine-induced cardiac standstill. Modular branches are inserted through the supra-aortic trunks and deployed within the cuffs of the stent graft. In this regard, the system resembles the one that proved to be so successful in the thoracoabdominal aorta (Fig. 1). One important difference is the route of branch insertion. The branches of an arch device inserted through the supra-aortic trunks into the cuffs without first passing through the primary stent graft. The worldwide experience of 20 cases is still too limited to comment on the potential role this device might play in the management of arch aneurysms and dissections. All we can say is that the approach has promise, and that the results of conventional repair with hypothermic circulatory arrest leave considerable room for improvement.



FIGURE 1: CTA of a patient who underwent 4-branch endovascular repair of a thoracoabdominal aortic aneurysm, followed 3 years later by 2-branch endovascular repair of an aortic arch aneurysm

CURRENT THORACIC AORTIC STENT GRAFT DESIGNS

Although stent grafts have evolved to meet the special demands of thoracic aortic repair, progress has been slow because the relatively small market commands little funding. Most current thoracic aortic stent grafts are basically scaled-up versions of designs developed for use in the abdominal aorta, and many companies have not entered the field at all. There are, for example, no thoracic aortic versions of the Nellix, Powerlink, Ovation, Aorfix and Anaconda stent grafts. Up to now, most progress in this area has involved the elimination of design features that clearly hurt device function. For example, the longitudinal struts of the original TAG device were eliminated when medium-term clinical experience showed them to be fracture prone. The switch to a more robust fabric made the longitudinal struts redundant, while also reducing the porosity of the TAG stent graft and eliminating a potential cause of aneurysm pressurization.

Most of the currently available stent grafts (TX2, Cook Medical; Relay, Bolton; Valiant, Medtronic; Talent, Medtronic; ELLA, Hradec Kralove, Czech Republic) are simple tubes of polyester fabric (Dacron) sutured to a series of Z-stents. In some devices the Z-stents project out of the proximal end of the fabric, in some the Z-stents carry barbs, in some the Z-stents are made of stainless steel, and in others they are made of Nitinol. The TAG (WL Gore) differs from most of the others in that the Nitinol stents are sandwiched between layers of a PTFE fabric tube and constrained, not by a sheath but by a PTFE corset, which opens upon the removal of the PTFE lacing. The TX2 stent graft is unique in having two distinct classes of components, used routinely as the proximal and distal parts of a composite. The distal TX2 component has an uncovered distal stent with cranially directed barbs. Indeed, one version of the distal TX2 component has a petticoat of uncovered stents to support the true lumen in cases of aortic dissection.

Three recent entries to the market promise to simplify endovascular repair in patients with less than ideal anatomy. The C-TAG (WL Gore, Flagstaff, AZ) is more flexible than the standard TAG. It also has a partially uncovered proximal stent. Both features encourage the orientation of the stent graft to match the orientation of an angulated neck. The C-TAG should not be used in cases with a short angulated neck close to a large aneurysm. The TX2 Pro-Form delivery system. It works by constraining the initial expansion of the proximal stent, encouraging it to rotate away from the superior surface of the distal aortic arch. The low profile TX2 thoracic aortic stent graft is a more fundamental departure from earlier technology. Specially designed stents and fabrics allow a broad range of stent graft diameters to fit inside 18 and 20 French sheaths. The asymmetric proximal stent serves the same purpose as the uncovered proximal stent of the C-TAG, but its rounded apices have less potential (in theory at least) for erosion/injury to the distal aortic arch.

ENDOVASCULAR REPAIR OF THORACIC AORTIC ANEURYSMS

Like the descending thoracic aorta, a thoracic aortic stent graft has no major branches and no bifurcations. Endovascular repair of a thoracic aortic aneurysm starts and ends in the aorta. When the implantation sites are long and the access arteries wide, the implantation procedure is often quick, bloodless and uncomplicated. Industry sponsored studies in carefully selected patients have generally shown endovascular to be far safer than open surgery and just as effective.[48] However, none of these comparisons was randomized and there are few long-term (more than 3 years) data. In addition, the results may not apply to patients with unfavorable anatomic features such as short, wide, angulated implantation sites, and stenotic, tortuous iliac arteries. Wide aortic implantation sites require wide stent grafts and delivery systems, which often have difficulty traversing the iliac arteries, especially in women who make up a large section of the thoracic aortic aneurysm patient population.

THORACIC AORTIC DISSECTION

Endovascular repair has no role in the management of aortic dissection involving the arch and ascending thoracic aorta (type A) which often originates close to the sinotubular junction and often propagates proximally into the aortic root, causing coronary occlusion, aortic regurgitation and pericardial tamponade. The treatment is prompt surgical repair under hypothermic circulatory arrest.

Endovascular treatment also has a limited role in the management of uncomplicated acute aortic dissection involving the descending thoracic and abdominal aortic segments of the aorta (type B). The primary treatment is medical using combinations of beta-blockers and vasodilators. Endovascular intervention is however indicated for the treatment of acute type B dissection (less than 2 weeks) complicated by visceral malperfusion, rupture, rapid false lumen expansion, or unremitting pain. Endovascular repair is also used to treat cases of chronic type B dissection in which the false lumen has dilated to the point of aneurysm formation.

Regardless of whether treatment occurs in the acute or chronic phase, the goal of endovascular repair is true lumen

expansion and false lumen thrombosis. In this regard the endovascular repair of acute dissection is more likely to succeed that endovascular repair of chronic dissection;[49] hence, the argument for treating acute dissection even in the absence of complications in the hope of preventing aneurysm formation. The observation that a large false lumen (or combined lumen) at the time of presentation was associated with a high rate of aneurysm formation also provides the rationale for a more aggressive approach in which rapid dilatation is regarded as an indication for repair, even in the absence of other complications.

ACUTE TYPE B DISSECTION

Endovascular intervention for acute type B dissection usually entails endovascular stent graft implantation, fenestration or some combination of the two. The goal of endovascular stent graft implantation is to close the inter-luminal connections (tears or fenestrations) and channel flow away from the false lumen into the true lumen. The goal of fenestration is to open inter-luminal connections, provide a route of egress for false luminal flow and equalize pressure between the true and false lumens. Although some authors endeavor to eliminate false lumen flow completely using stent grafts in the aorta and stents within the visceral branches, a more typical approach is to use endovascular aortic repair and inter-luminal fenestration in different segments of the aorta. Endovascular repair is often confined to the proximal descending thoracic aorta where the dissection originates and where aneurysms occur most often, whereas fenestrations are confined to the proximal abdominal aorta where the visceral arteries preclude the implantation of an unbranched aortic stent graft.

It is still unclear whether endovascular intervention has a role in the management of uncomplicated acute type B dissection. However, intervention can be life-saving when acute type B dissection is complicated by rupture or, more commonly, visceral malperfusion. The signs of visceral malperfusion include: abdominal pain, ileus, renal failure, lactic acidosis, sepsis and diminished femoral pulses. Renal function is probably the most sensitive of these with many patients showing only a steady rise in serum creatinine, at which point contrast-enhanced CT scans add nephrotoxicity to renal ischemia. Visceral malperfusion has two main causes: (1) compression of the aortic true lumen (dynamic obstruction, Fig. 2A) and (2) compression of the visceral artery true lumen (static obstruction, Fig. 2B). Both result from an imbalance of pressure between the true lumen and the false lumen.

A properly functioning endovascular stent graft helps to restore flow through the true lumen by closing inflow to the false lumen through the proximal tear.[50] Not that the proximal tear is the only inter-luminal connection (fenestration). There are often other fenestrations at the level of the visceral arteries, but these are not usually a problem. Indeed they may help true lumen expansion by decompressing the false lumen.

The initial intraoperative angiograms help to distinguish the true lumen from the false lumen, identify the proximal fenestration, confirm the true luminal position of the guidewire at the level of the aortic arch and the level of the visceral arteries, and confirm the diagnosis of true lumen compression. The typical appearance is of multiple relatively normal visceral arteries arising from a tiny aortic true lumen. Our usual practice at UCSF medical center is to leave the guidewire in place and obtain multi-level angiograms using a 90 cm-long 5 French sheath. A transesophageal color flow ultrasound provides a lot of information regarding the state of the aortic arch and proximal descending thoracic aorta. Intravascular ultrasound is sometimes used to identify flaps and fenestrations in and around the visceral arteries. Catheters and guidewires can easily pass through a fenestration from the true lumen into the false lumen and back again during insertion. Wherever else the stent graft goes, one has to be sure that the top and bottom are in the true lumen of the aorta.

Once the stent graft is in place, the true lumen and visceral branches are reassessed. The result is often better than one would expect based on preoperative imaging (Fig. 2C). The static obstruction of a visceral artery is not necessarily a fixed lesion, and branches that appeared to be fed exclusively by the false



FIGURE 2A: CTA in a case of acute type B aortic dissection, showing the tiny true lumen (white arrow) and large false lumen (black arrow) of the proximal abdominal aorta



FIGURE 2B: CTA from the same case, showing total occlusion of the superior mesenteric artery (white arrow)

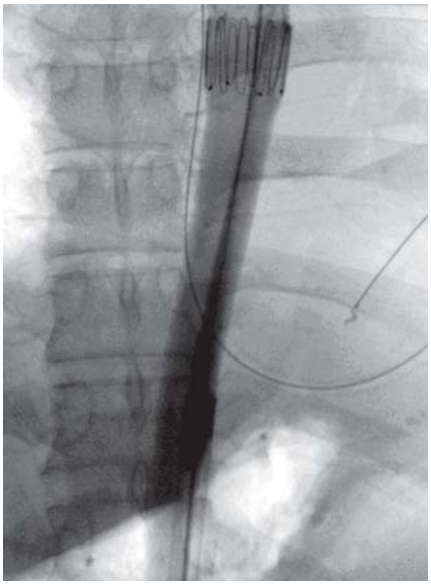


FIGURE 2C: Intraoperative angiogram from the same case, showing expansion of the aortic true lumen below a proximal thoracic aortic stent graft

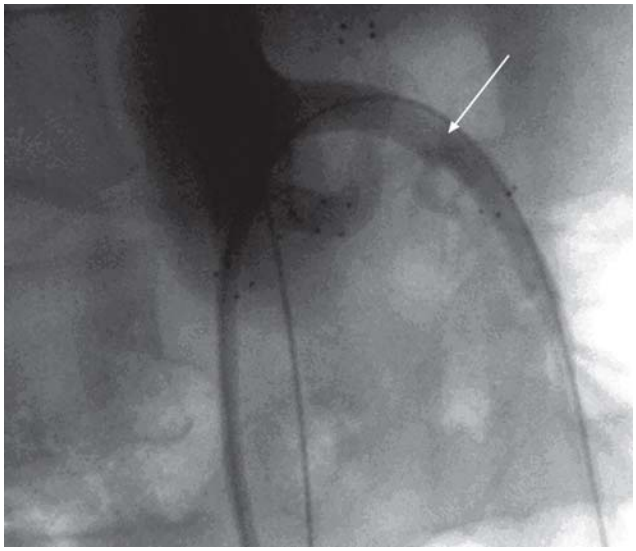


FIGURE 2D: Intraoperative angiogram from the same cases, showing a stent in the superior mesenteric artery (white arrow)

lumen often perfuse well through a newly pressurized true lumen. Nevertheless, persistent obstruction of a visceral artery may require the insertion of a stent (Fig. 2D). It can be difficult to know where to place the proximal end of the stent to be sure that it occupies the true lumen. When in doubt, longer is better. If the goal is to completely isolate the false lumen from the circulation, covered stents can bridge the gap between the true lumen of the aorta and the true lumen of the branch. These may be inserted at a second operation, based on the findings of the first postoperative computed tomographic angiography (CTA).

CHRONIC TYPE B DISSECTION

The excess mortality seen in the years after aortic dissection is attributable to false lumen dilatation and rupture.[51] These false lumen aneurysms are slightly more likely to rupture and far more difficult to treat that atherosclerotic aneurysms of similar size. The length of the proximal implantation site may be short, depending on the location of the primary tear, but the real problem is often the lack of a distal implantation site above the celiac artery. The aortic dissection usually extends into the abdominal aorta with multiple fenestrations at the level of the visceral arteries. Implantation of the stent graft into the true lumen of the supra-celiac aorta leaves the false lumen as a potential route of retrograde flow into the aneurysm. More complete aneurysm exclusion requires thoracoabdominal repair, which can be difficult to accomplish by endovascular means when the true lumen is small and the false lumen gives rise to some of the branches.

Nevertheless, unbranched repair of the proximal aortic true lumen may have a role when only the proximal portion of the



FIGURE 3A: Sagittal reconstruction of CTA in a case of chronic dissection, showing the primary tear (fenestration) between the true lumen (white arrow) and the false lumen (black arrow)

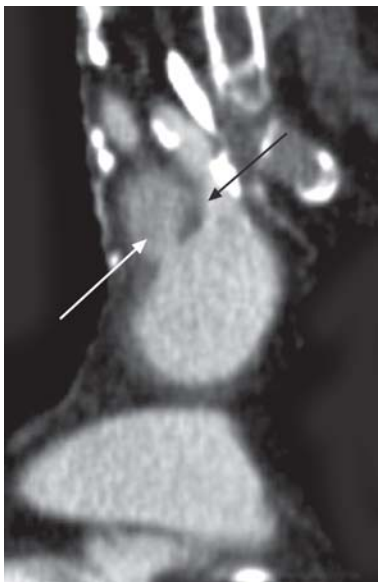


FIGURE 3B: Coronal reconstruction of the same CTA showing the proximity of the primary tear (white arrow) to the origin of the subclavian artery (black arrow)

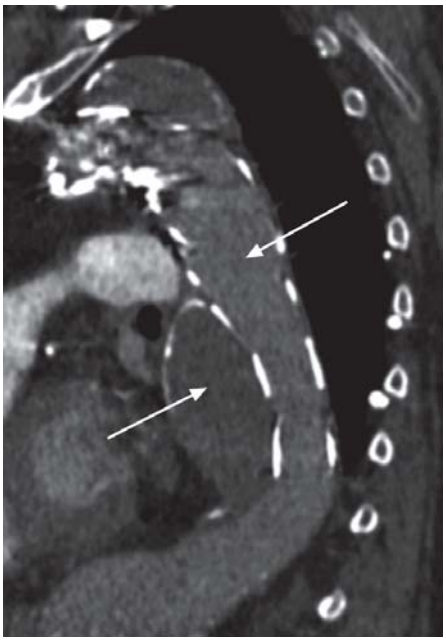


FIGURE 3C: CTA from the same case after implantation of a stent graft, showing contrast enhancement of the true lumen and thrombosis of the false lumen

descending thoracic aorta is wide enough to represent a risk of rupture and there are no significant fenestrations within the distal descending thoracic aorta. Under these circumstances, the goal is to occlude the primary tear and create a static column of thrombus, extending up the false lumen from the paravisceral true lumen to the aneurysm (Figs 3A to C). Although far from definitive, this form of repair may be the least risky option when the only alternatives are open TAAA repair and observation.

COMPLICATIONS OF THORACIC ENDOVASCULAR AORTIC REPAIR

The complications of endovascular repair represent a mismatch between the arterial anatomy and the functional capabilities of the stent graft. Given the specific challenges of thoracic endovascular aortic repair (TEVAR) and the limitations of most currently available stent grafts, TEVAR would be fraught with complications were it not for the widespread use of various adjunctive maneuvers.

ENDOLEAK

Type I endoleaks are likely when the neck is short, angulated or conical. The problem can usually be overcome by covering one, or more, of the supra-aortic trunks after first "de-branching" the distal aortic arch or proximal abdominal aorta. One cannot occlude the left subclavian artery when the left internal mammary artery feeds a coronary artery, the left vertebral artery is the dominant source of flow to the posterior circulation of the brain, or the left vertebral and costocervical arteries provide collateral flow to the spine. To do so, without first creating a carotid-subclavian bypass, risks myocardial infarction, stroke or paraplegia. Nor can one occlude the celiac artery unless angiography demonstrates adequate filling through collaterals from the superior mesenteric artery.

Type II endoleaks are relatively uncommon following TEVAR and most are benign. Type III endoleaks complicate multi-component repair when the aneurysm is large, the overlap short and the implantation sites are angulated, creating a bend in the stent graft. Under these circumstances, hemodynamic forces push the center of the stent graft toward the outer curve of the aneurysm, pulling one component out of the other as the overall length increases. Treatment is relatively easy using an additional stent graft, if the problem is identified early, but prevention is easier still. A long overlap stiffens the central portion of the stent graft, stops it bending into the aneurysm and helps maintain continuity, even when bending does occur. Experience at UCSF medical center, in large numbers of TAAA cases, has shown barb mediated inter-component attachment to be very effective. The potential for damage to the outer stent graft is mitigated by the presence of the inner stent graft.

NEUROLOGICAL COMPLICATIONS

Stroke is the most common neurological complication of TEVAR, although the rate appears to be falling with recent series reporting rates of 2–4%. Most are thought to be caused by emboli dislodged from the ascending aorta and arch by guidewires and the stent graft delivery system. Advanced age, and repeated proximal aortic instrumentation are risk factors. One can only hope that the latest generation of flexible, narrow, smoothly tapered delivery systems helps to minimize aortic instrumentation and eliminate the kind of high-energy insertions that used to be the norm.

Paraplegia is caused by the occlusion of the segmental arterial supply of the anterior spinal cord. Risk factors include: an extensive field of repair (especially below T8), prior (or simultaneous) AAA repair, occlusion of the subclavian artery and hypotension. Preventative/remedial measures include: carotid-subclavian bypass, blood pressure support and cerebrospinal fluid (CSF) drainage. Lower extremity weakness following endovascular aortic repair is often partial, reversible and delayed, unlike lower extremity weakness following open repair, which is usually complete, permanent and apparent as soon as the patient wakes from anesthesia. The recruitment of collaterals produces clear effects within a day or two of surgery, allowing supportive measures, such as CSF drainage, to be withdrawn without causing recurrent symptoms. The process continues for months, as evidenced by the dilatation of lumbar and intercostals arteries above and below the stent graft.

FAILED INSERTION

The most common impediment to device insertion is a size mismatch between the delivery system and the external iliac artery of a female patient (see section Narrow Iliac Arteries). The next most common cause of failed insertion is aortic tortuosity. The supra-aortic trunks of the arch and the crura of the diaphragm are points of aortic fixation that yield very little during delivery system insertion. A stiff guidewire (Lunderquist, Cook Medical, Bloomington, IN) helps a thoracic aortic delivery systems conform to the shape of the aorta, and a tensioned right brachial-femoral wire helps even more. This is another area where the trackability and flexibility of new delivery systems will reduce the incidence of traumatic device insertion.

INTRAMURAL HEMATOMA

Intramural hematoma (IMH) can be regarded as a form of aortic dissection, in which the intramural cavity is filled with thrombosed blood and separated from the lumen of the aorta by an intact intima.[52] However, the underlying pathologic similarity of the two diseases is demonstrated by frequent progression of IMH to frank aortic dissection. In the absence of true dissection, there is little risk of rupture or visceral malperfusion. The IMH of the descending thoracic aorta requires nothing more than blood pressure control, whereas IMH of the ascending thoracic aorta requires open surgical repair.

PENETRATING AORTIC ULCER

These localized mushroom-like aneurysms occur at sites of plaque rupture. Some patients have many such lesions in the descending thoracic and abdominal aorta. The management of a penetrating aortic ulcer (also known as an ulcer-like projection) is controversial. Although penetrating aortic ulcers often appear ideal for endovascular treatment, their natural history is unknown. Moreover, they tend to occur in elderly patients with advanced atherosclerosis and reduced life expectancy.

CONCLUSION

The treatment of aortic aneurysm and dissection has been changed forever by the shift from maximally invasive surgery to minimally invasive intervention. The reduced physiological impact of the endovascular approach has simplified postoperative management, but complicated preoperative decision by adding another dimension to the matrix of therapeutic options. To complicate things further, data regarding the results of endovascular intervention are somewhat lacking. Most short-term data apply to a narrow range of selected patients, and most long-term data apply to obsolete devices or practices. Nevertheless, one can say with certainty that endovascular repair of abdominal aortic and descending thoracic aortic aneurysms is safer than open surgical repair, at least in the short term. Long-term comparisons between endovascular aneurysm and surgical repair are less conclusive.[53] Meanwhile, the only proven indications for endovascular repair of type B aortic dissection are visceral malperfusion and aneurysm formation.

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Chapter 67

Autonomic Dysfunction and the Cardiovascular System

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Chapter Outline

- Autonomic Regulation of the Cardiovascular System
  - Regulation of Blood Pressure
  - Heart Rate Control
  - Chemoreflex Influence on Heart Rate and Blood Pressure
  - Orthostatic Hypotension
- Autonomic Testing
  - Orthostatics
  - Valsalva Maneuver
  - Resting Heart Rate
  - Baroreflex Sensitivity
  - Heart Rate Variability
  - Heart Rate Recovery
  - Catecholamine Blood Measurement
  - Cardiac Sympathetic Imaging
- Primary Chronic Autonomic Failure
  - Pure Autonomic Failure
  - Multiple System Atrophy
- Secondary and Congenital Autonomic Failure
- Chronic Orthostatic Intolerance
  - Postural Orthostatic Tachycardia Syndrome
  - Treatment of Orthostatic Hypotension/ Intolerance
- Syndromes Associated with Episodic Autonomic Failure
  - Hemorrhage
  - Neurocardiogenic Syncope
  - Inferior Wall Myocardial Ischemia/Infarction
  - Carotid Sinus Hypersensitivity
- Autonomic Perturbations Associated with Cardiovascular Conditions
  - Baroreflex Failure: Neurogenic Hypertension
  - Heart Failure and Ischemic Heart Disease
  - Obstructive Sleep Apnea
  - Pheochromocytoma
  - Cardiac Arrhythmias

INTRODUCTION

The functions of our autonomic nervous system (ANS) are often taken for granted. And yet, every time we rise from a recumbent to a standing position, our cardiovascular system must undergo instantaneous adaptations, otherwise we will faint and fall. Besides maintaining hemodynamic competency during postural changes, the ANS continuously responds to a variety of internal and external cues to regulate other equally vital physiological functions—most of which occurs without us being conscious of it. These include such important homeostatic functions as regulation of blood pressure, circulatory volume, respiration, temperature, gastrointestinal activity and metabolism. Thus, when the ANS fails, the consequences can be devastating. Some of the most common manifestations of autonomic dysfunction are alterations in heart rate and blood pressure, and so cardiologists are often called upon to diagnose and treat these patients. Moreover, many common cardiovascular diseases are associated with concomitant alterations in the ANS, and the prognosis with these diseases is often directly linked to the degree in which the ANS is perturbed. In fact, many of the most common pharmacological therapeutic agents to treat heart disease are directed toward these alterations in the ANS.

Compared with the central nervous system, the peripheral nervous system is relatively simple and accessible for experimentation. Thus, we know more about the ANS than other parts of the nervous system, and it has served as a key model to further our understanding of neuronal function, synaptic transmission and neural networks. Still, it becomes readily apparent to the clinician who has faced a patient with ANS dysfunction that our understanding is far from complete. Over the past several decades, knowledge of various abnormalities of the ANS has evolved significantly. In this chapter, we have categorized and defined clinical perturbations of the ANS in accordance to our current understanding of the underlying disease mechanisms. In addition, we have focused on the role that ANS dysfunction plays in more common cardiovascular diseases such as heart failure and arrhythmias.

AUTONOMIC REGULATION OF THE CARDIOVASCULAR SYSTEM

Classically, the ANS can be divided into three components: (1) the sympathetic, (2) parasympathetic and (3) enteric systems. More recently, it has been appreciated that sensory input from various organs and tissues via afferent neuronal pathways is a

critical component of autonomic function. Afferent neurons possess special receptive terminals that sense mechanical forces (such as pressure, stretch, shear, etc.), or the chemical milieu (such as pH, P_{O_2}, P_{CO_2}, noxious irritants, etc.). In this broader sense, the ANS consists of a series of feedback loops whereby afferent pathways provide continuous information regarding the state of the body. This information is integrated in central autonomic control centers, and then motor output, via the parasympathetic and sympathetic efferent pathways, is adjusted to maintain homeostasis. In humans, the major centers of cardiovascular autonomic nervous integration and control are in the medulla and include the nucleus tractus solitarii (NTS) as well as motor output centers in the brainstem. In addition, feedback regulatory loops also occur at more peripheral sites including the spinal cord and autonomic ganglia. The two principle efferent pathways that control the cardiovascular system—the sympathetic and parasympathetic pathways—often, but not always, have opposite influences on target tissues; and the resultant effect on cardiovascular responses represents the relative balance between the two pathways. Although, homeostasis of all basic bodily functions can be maintained with just the medulla, spinal cord and peripheral ANS, higher forebrain regions, including the hypothalamus, limbic system, and cortex—which control complex behaviors including exercise, as well as fear, other emotions and motivations—play an important role in coordinating and modulating autonomic output.

REGULATION OF BLOOD PRESSURE

One of the most critical functions of the ANS is to maintain adequate blood flow to the various organs and tissues of the body, and to do so, the mean systemic arterial pressure must be regulated within an optimal range. Long-term regulation of arterial pressure—on the time scale of hours to days—involves humoral regulation of the effective circulatory volume; although neural actions on the kidney also play a role.[1] On the other hand, short-term regulation of arterial pressure—on the time scale of seconds to minutes—is almost exclusively under autonomic control. Collectively, the principle autonomic reflexes that regulate blood pressure are referred to as the baroreflex.

Arterial baroreceptors are specialized stretch-activated sensory nerves located on the carotid sinuses and the aortic arch that sense distension of the vessel wall induced by pressure changes (Fig. 1). The carotid sinuses are highly compliant portions of the internal carotid arteries located at the branching of the internal and external carotid arteries, and the aortic arch distends with each ejection of blood from the left ventricle. Distension of these arterial walls causes depolarization of

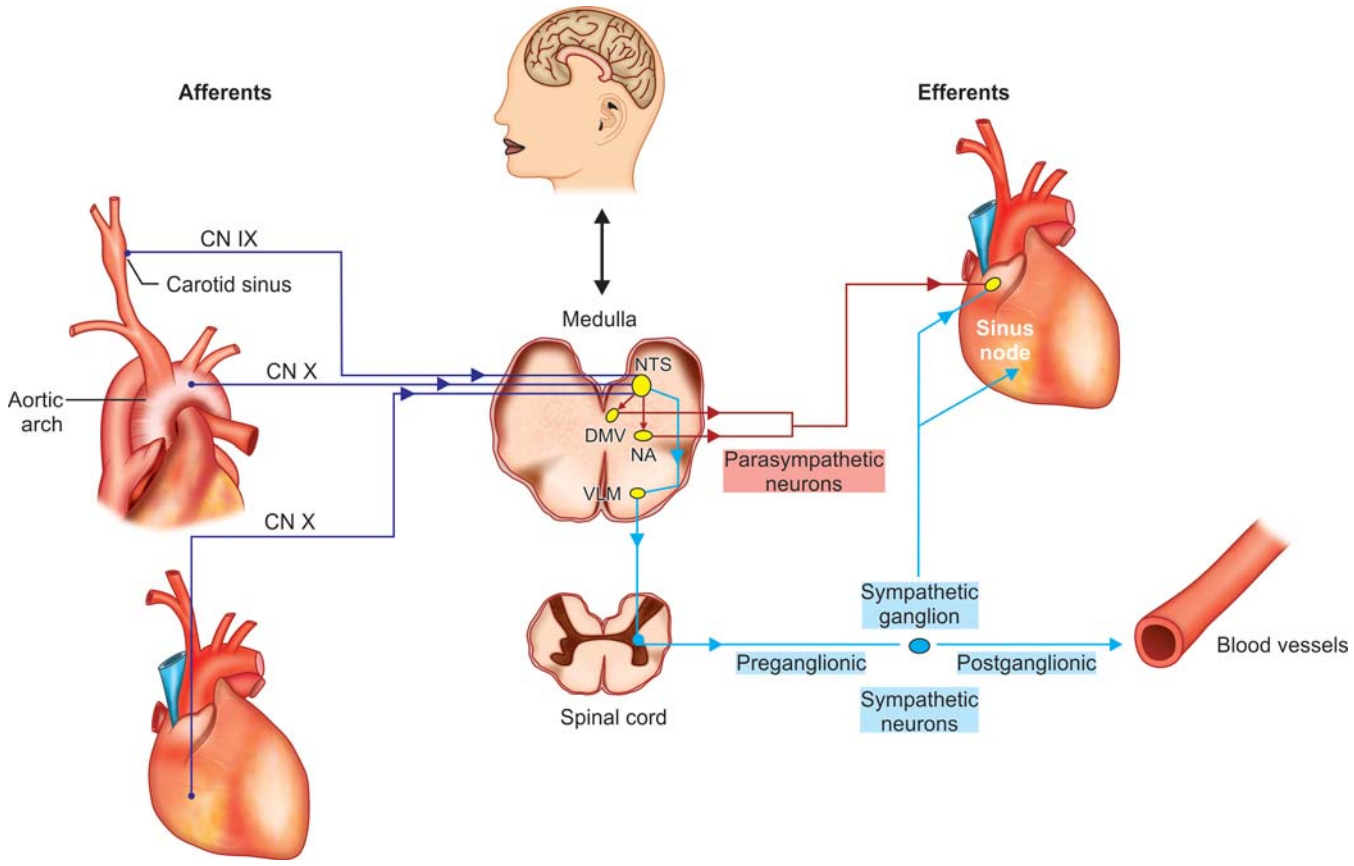


FIGURE 1: Schematic representation of the baroreflex. Afferent pathways (blue) from arterial and cardiopulmonary baroreceptors follow the glossopharyngeal (CN IX) and vagus (CN X) nerves to the NTS in the medulla. Excitatory interneurons project from the NTS to the cardioinhibitory regions including the DMV and NA which mediate parasympathetic output (brown pathways) to the heart. The NTS also sends projections to the vasomotor and cardioacceleratory regions in the VLM which control sympathetic output (sky blue pathways) to the vasculature and heart respectively (Abbreviations: CN: Cranial nerve; NTS: Nucleus tractus solitaries; NA: Nucleus ambiguous; DMV: Dorsal motor nucleus of the vagus; VLM: Ventrolateral medulla)

stretch-activated baroreceptor nerve terminals, which then generate action potentials of varying firing frequency. Normal blood pressure is associated with a baseline level of spike frequency; lowering of pressure causes a decrease in firing frequency, while an increase in blood pressure causes an increase in firing frequency. Baroreceptor afferent fibers innervating the carotid sinuses travel in the glossopharyngeal nerve, and those innervating the aortic arch are located in the vagus nerve. The NTS in the brainstem receives and integrates these incoming afferent signals, and then signals to the sympathetic and parasympathetic output centers that control vascular tone and heart rate. For example, in response to an increase in blood pressure, baroreceptors will increase their firing frequency to the NTS, which in turn, projects interneurons to inhibit sympathetic output from vasomotor centers, and excite the parasympathetic cardioinhibitory centers in the medulla. The net effects are: (1) vasodilation of arterioles and veins throughout the systemic peripheral circulation, and (2) a decrease in heart rate and ventricular contractility. Thus, blood pressure is reduced back to normal by a decrease in vascular resistance and a decrease in cardiac output. The opposite effects occur in response to a decrease in blood pressure. During postural changes, the baroreflex is the major mechanism to maintain cerebral blood flow. Immediately upon standing, gravity induces a significant pooling of blood in the lower extremities and arterial pressure drops in the head and upper body. The baroreflex when functioning properly can immediately counter these effects by increasing sympathetic discharge to maintain blood pressure and cerebral perfusion, and prevent loss of consciousness.

In addition to high-pressure arterial baroreceptors, the cardiac chambers and pulmonary vessels are innervated by low-pressure cardiopulmonary receptors that primarily serve to sense changes in circulatory volume. Cardiopulmonary receptor activation by volume expansion of the chambers leads to inhibition of arginine vasopressin release from the posterior pituitary and a decrease in sympathetic nerve activity, which lead to diuresis and natriuresis. Thus, by regulation of effective circulatory volume, cardiopulmonary baroreceptors indirectly contribute to maintenance of blood pressure.

HEART RATE CONTROL

A denervated heart, such as occurs with a transplanted heart, has an intrinsic sinus nodal heart rate of approximately 100 beats/minute. Deviations from this intrinsic rate are primarily under the influence of the ANS. When a healthy person is at rest, parasympathetic efferent input to the sinus node lowers the average heart rate to 60–70 beats/min, and the sympathetic input to the sinus node is essentially silent. Rapid changes in heart rate, such as occur with the respiratory cycle (sinus arrhythmia) and those induced by the baroreflex, are mediated by fluctuating parasympathetic input. During stress or exercise, sympathetic input to the heart becomes dominant and heart rate rises accordingly.

CHEMOREFLEX INFLUENCE ON HEART RATE AND BLOOD PRESSURE

The chemoreceptors, which consist of both peripheral and central components, are the major sensors that regulate respiration. However, chemoreflexes also influence both blood pressure and heart rate, and have a particularly important modulatory effect in some disease conditions such as sleep apnea. The peripheral chemoreceptors which primarily sense hypoxemia reside in the carotid bodies located near the carotid sinuses at the branching of the internal and external carotid arteries. The central chemoreceptors are located in the medulla, and they primarily sense hypercapnea or acidosis. Chemoreceptor afferents signal to the NTS and the respiratory control centers, and they also influence the cardiovascular output regions. However, whereas baroreceptor input exerts a negative drive on sympathetic vasomotor output centers, causing vasodilation, peripheral chemoreceptor stimulation results in a positive drive on the vasomotor center, resulting in vasoconstriction. The chemoreflex effect on heart rate is the same as the baroreflex; both exert a positive drive on the parasympathetic cardioinhibitory center to slow down the heart rate. The chemoreflex effects on the cardiovascular system are most apparent during forced apnea, such as occurs during submersion in water. This unique 'diving reflex' manifests as a simultaneous increase in sympathetic tone to the vasculature causing vasoconstriction, and an increase in parasympathetic drive to the heart causing bradycardia.

ORTHOSTATIC HYPOTENSION

Chronic upright posture is a uniquely human experience, and remarkable cardiovascular adaptations regulated in large part by the ANS, have evolved to compensate for the effects of gravity on the circulation. Thus, it is not surprising that the most common cardiovascular manifestations of autonomic dysfunction are those associated with abrupt changes in posture. Upon standing, there is a shift of up to a liter of blood from the upper body to the lower abdomen, buttocks, and legs. This results in diminished venous return to the heart, a reduction in stroke volume via the Frank-Starling mechanism, and a consequent drop in blood pressure.[2] Almost immediately, these changes are counteracted by the baroreflex with a corresponding increase in heart rate and vascular tone. After this initial pooling of blood, there is a more prolonged period in which there is a substantial transcapillary shift of fluid from the blood into the interstitial spaces of dependent tissues. In healthy subjects, there is a 15–20% fall in plasma volume within 10 minutes after assumption of the upright posture.[3] To counter these more prolonged orthostatic stresses, the renin-angiotensin-aldosterone system is activated, vasopressin is released and sympathetic output progressively increases. Thus, while an early drop in blood pressure during orthostatic testing is mostly reflective of a pure autonomic neurological abnormality, delayed hypotension can represent a malfunction of multiple different neuro-hormonal mechanisms.

Purely defined, orthostatic hypotension is a physical sign rather than a diagnosis, and patients may be symptomatic or asymptomatic. In fact, the degree of blood pressure drop does not correlate well with severity of symptoms.[4] As we have reviewed in later sections, some patients with chronic autonomic failure can tolerate profound blood pressure falls, perhaps due to a shift in cerebral autoregulation into a lower pressure range. On the other hand, patients with orthostatic intolerance syndromes can report severe symptoms with little orthostatic

hypotension. From a more physiological perspective, orthostatic hypotension can be viewed as an inability to maintain adequate perfusion pressure with changes in posture. Most often, the symptoms of orthostatic hypotension relate to inadequate cerebral perfusion, and manifest as dizziness, light-headedness, weakness, fatigue, presyncope and—in extreme cases—syncope. Visual changes are not uncommon, due to cortical or retinal ischemia. In addition, patients may report head and neck pain in the posterior cervical, suboccipital and shoulder regions (termed 'coat-hanger headache') presumably due to muscle ischemia in these regions. Finally, myocardial ischemia can result from orthostasis causing classic symptoms of angina pectoris, even in the absence of obvious coronary artery disease. On the other hand, orthostatic hypotension is most common in the elderly who are also at risk for coronary artery disease, and it is our experience that coronary intervention to relieve significant stenosis in such patients not only relieves angina but can also improve the symptoms of postural hypotension. The symptoms of orthostatic hypotension can be precipitated or exacerbated by dehydration, increases in ambient temperature, prolonged periods of standing in place, exertion and eating. In fact, the elderly seem to be particularly prone to postprandial symptoms associated with hypotension, presumably due to inadequate autonomic response to splanchnic blood pooling after meals.[5] In the following sections we addressed the causes, diagnosis and treatment of neurogenic orthostatic and postprandial hypotension.

AUTONOMIC TESTING

The functional effects of the ANS on the cardiovascular system can be tested by a variety of means. Some of these tests can be performed at the bedside or in the outpatient office setting; others require more sophisticated equipment and are primarily performed at specialized clinics and research centers of autonomic dysfunction. Here, we have reviewed a few of the more commonly used tests. Simple bedside orthostatic blood pressure measurements and Valsalva maneuvers are informative initial tests in the evaluation of patients presenting with symptoms precipitated by postural changes. In addition, baroreflex sensitivity, resting heart rate, heart rate variability and heart rate recovery provide further assessment of autonomic function, and have increased our understanding that autonomic disturbances are important predictors of risk in many common cardiovascular diseases. Finally, blood levels of norepinephrine and its metabolites, as well as functional imaging of the peripheral sympathetic nervous system may help to differentiate between different types of dysautonomias.

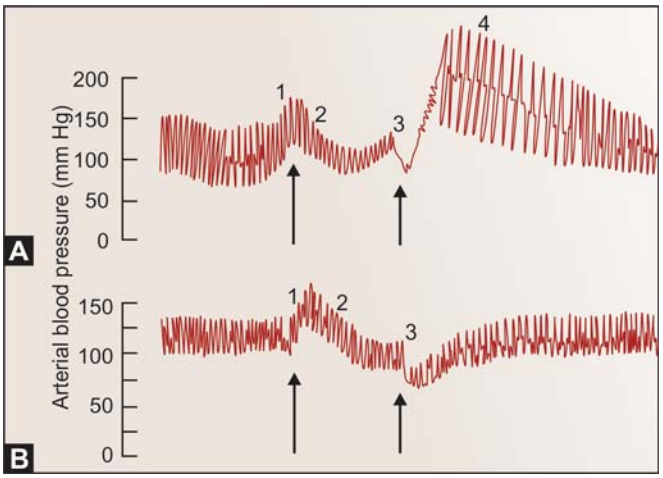
ORTHOSTATICS

Measurement of orthostatic blood pressure and heart rate response at the bedside is a simple and useful test that often recapitulates a patient's symptoms, and provides insight into the underlying pathophysiology. Orthostatic hypotension, as defined by a consensus statement in 1996, is a fall of systolic blood pressure of at least 20 mm Hg or a fall of diastolic blood pressure of at least 10 mm Hg within 3 minutes of standing or head-up tilt on a tilt table.[6] After careful measurement of supine blood pressure and heart rate, the patient is asked to stand, or sit with feet dangling over the bedside if standing is not possible. Blood pressure and heart rate is measured when the patient becomes symptomatic or at 3 minutes. In addition, orthostatics can be measured using a tilt-table in the head-up position, at an angle of at least 60 degrees. Interestingly, the correlation between orthostatic hypotension during active standing and tilt-table testing is not high.[4,7] There are multiple reasons why the two tests might not be equivalent including the fact that tilt-table testing significantly eliminates the pumping action of the leg muscles during standing on venous return to the heart.

A few caveats need to be addressed regarding the definition of orthostatic hypotension. First, this finding is very common in the elderly, occurring in up to 68% of some elderly debilitated populations.[8] Second, orthostatic blood pressure changes occur more frequently in patients with hypertension compared to normotensives or those with low supine pressure, leading some to propose that criteria for orthostatic hypotension be adjusted according to the recorded supine blood pressure.[9] Third, a phenomenon of "delayed orthostatic hypotension" has also been described with orthostatic blood pressure changes developing between 5 minutes and 45 minutes.[4] This delayed drop in blood pressure is generally associated with less severe forms of autonomic dysfunction, suggesting that this phenomenon may reflect milder or earlier impairment, or might reflect defective regulatory mechanisms other than autonomic dysfunction.

VALSALVA MANEUVER

In 1704, an Italian physician and anatomist from Bologna, Antonio Maria Valsalva, reported the use of forceful expiration against a closed mouth and nose as a useful maneuver to expel pus from the inner ear and test patency of the Eustachian tube.[10] Over the centuries, the "Valsalva maneuver", gained wider clinical significance. In addition to being used to complement the clinical diagnosis of left ventricular dysfunction, dyspnea, and to treat conduction abnormalities—it is used to assess autonomic function.[11] The test is typically performed in a supine position and patient is asked to blow into a closed tube at 40 mm Hg, or exhale forcefully against a closed glottis and maintain the strain for 10–15 seconds while blood pressure waveform and heart rate are analyzed. Adequate strain is assessed based on neck vein distension, increased tone in the abdominal wall muscles and a flushed face. The normal blood pressure and heart rate responses are divided into four phases (Figs 2A and B).[12] Phase 1 is associated with a brief increase in blood pressure due to mechanical compression of the great vessels. Blood pressure falls during the early part of phase 2 due to diminished venous return to the heart, and the later part of phase 2 is associated with a return of blood pressure and an increase in heart rate due to increased sympathetic activity. Blood pressure then briefly falls in phase 3 due to release of mechanical compression, and then is followed by a "blood pressure overshoot" in phase 4 that represents a normalization of venous return to the heart in the setting of persistently elevated sympathetic tone. The normal heart rate responses during Valsalva maneuver reflect baroreflex responses; the falls in blood pressure during phases 2 and 3 trigger an increase in heart rate, whereas the increase in blood pressure during phases 1 and 4 are accompanied by decrease in heart rate. The most



FIGURES 2A AND B: Four phases of arterial pressure responses during Valsalva maneuver—see text for details. (A) Normal control. (B) Absence of arterial pressure recovery during phase 2 and overshoot during phase 4 in a patient with autonomic dysfunction (*Source:* Modified from Zema MJ, Restivo B, Sos T, et al. Left ventricular dysfunction—bedside Valsalva manoeuvre. Br Heart J. 1980;44:560-9, with permission)

commonly seen abnormalities in patients with autonomic dysfunction are failure to correct hypotension in phase 2 and/or failure to overshoot blood pressure in phase 4.

RESTING HEART RATE

One of the simplest measures of autonomic function is resting heart rate, and it has gained increasing appreciation as an important prognostic indicator. Low resting heart rates are commonly seen in competitive athletes and are indicative of high parasympathetic tone. Conversely, higher resting heart rate is associated with multiple cardiovascular disease conditions, and it is characterized by loss of parasympathetic, and increasing sympathetic activity. The link between high resting heart rate and mortality associated with coronary artery disease, myocardial infarction and heart failure is well established.[13] While the use of beta-blocking agents to improve mortality is clear, it is particularly intriguing that the improved survival associated with beta-blockers in survivors of myocardial infarction is proportional to the magnitude of heart rate reduction.[14] Such results have led investigators to devise strategies to more selectively reduce heart rate. Ivabradine is a selective inhibitor of the I(f) current in the sinus node and appears to lower heart rate without other cardiovascular effects, and it has been shown to reduce atherosclerosis in a genetically susceptible mouse model.[15] In a large randomized clinical trial of patients with coronary artery disease and diminished left ventricular systolic function, ivabradine had no effect of overall cardiovascular outcomes; although it did reduce the incidence of myocardial infarction and need for coronary revascularization in a predefined subset of patients with heart rate of more than or equal to 70 beats/minute.[16]

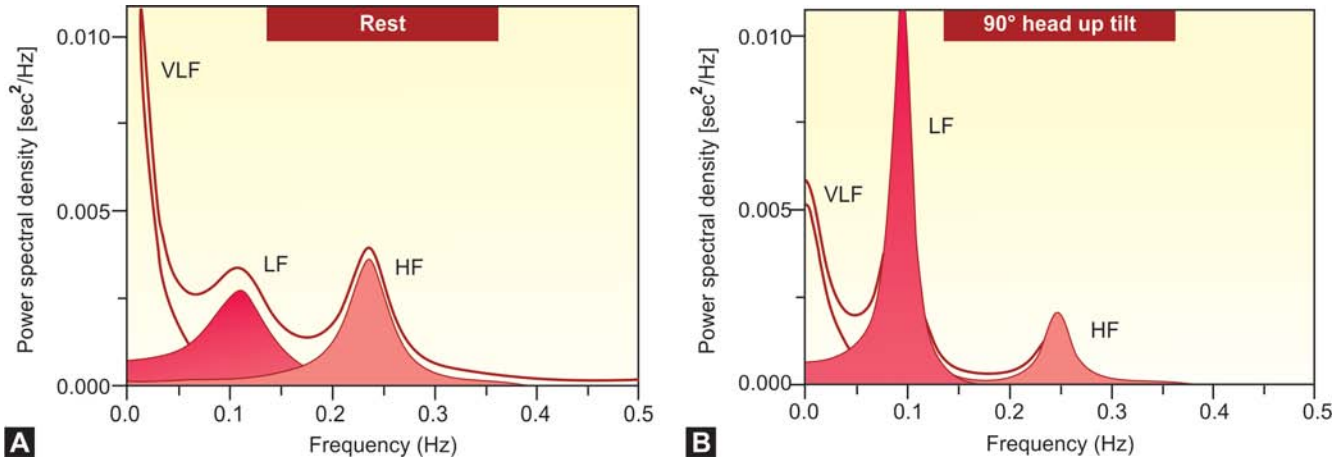
BAROREFLEX SENSITIVITY

As previously described, the baroreceptor reflex is the principal neural mechanism involved in short-term (seconds to minutes) blood pressure regulation. A sudden increase in blood pressure evokes a reflex increase in cardiovagal activity and a corresponding decrease in heart rate (or increase in R-R interval recorded with electrocardiography). Conversely, a sudden drop in blood pressure leads to an inhibition of cardiovagal tone and a corresponding increase in heart rate (or decrease in R-R interval). Generally the relationship between changes in systolic pressure and R-R interval is linear, and the slope of this relationship is a measure of baroreflex sensitivity. The slope is typically steep in young, healthy individuals and it decreases with age and cardiovascular diseases such as hypertension and heart failure. In general, baroreflex sensitivity is steep under conditions of high parasympathetic tone, flattens with high sympathetic tone and further flattens with autonomic failure.

One of the earliest devised methods used to interrogate the baroreflex is to give a bolus intravenous injection of vasoconstrictor (Oxford technique), such as the alpha-adrenergic agonist, phenylephrine, and plot the corresponding changes in R-R interval to the preceding systolic blood pressure changes.[17] Injection of the vasodilator nitroprusside before phenylephrine (modified Oxford technique) enables assessment over a broader blood pressure range, and sequential administration of multiple doses allows construction of the entire sigmoidal baroreflex function curve. The clinical application of the above techniques has been limited since they require intravenous drug administration and intra-arterial beat-to-beat blood pressure recording. Simpler, less invasive techniques have been developed for use in both laboratory animals and human clinical trials. Computer analysis of spontaneous fluctuations in blood pressure and heart rate enables calculations of spontaneous baroreceptor sensitivity. The most common analysis method (sequence method) involves identifying sequences of three or more consecutive beats where systolic blood pressure and R-R interval are positively correlated. "Up" sequences are defined by an increase in blood pressure and R-R interval, while "down" sequences represent a decrease in blood pressure and R-R interval. The average of the slopes for changes in blood pressure and R-R interval relationships define the baroreceptor sensitivity. Several recent clinical trials have made use of a noninvasive method to measure beat-to-beat changes in blood pressure during assessment of baroreflex sensitivity using a finger plethysmograph. This technique correlates well with invasive measurement of baroreflex sensitivity,[18] and has been used to demonstrate that impaired baroreflex sensitivity is an independent risk marker of mortality and major adverse cardiovascular events in patients with hypertension,[19] chronic heart failure,[20] and after myocardial infarction.[21]

HEART RATE VARIABILITY

Early in the 18th century it was appreciated that the respiratory cycle is linked to oscillations in the intervals between consecutive heart beats. Today, it is recognized that these normal R-R interval changes (decrease during inspiration and increase with expiration—the so-called respiratory "sinus arrhythmia") are predominantly mediated by oscillations in parasympathetic activity to the sinus node. In addition, heart rate variability is also under the control of other autonomic and homeostatic mechanisms.



FIGURES 3A AND B: Power spectral analysis of heart rate variability. (A) The heart rate variability spectra were calculated by parametric autoregressive modeling on 256 consecutive R-R values in a healthy subject at supine rest and (B) During head up tilt. At rest, two major components of similar power are detectable at LF and HF. During tilt, the LF component becomes dominant as the HF component is reduced, and absolute power (total area under the curve at all frequencies) is diminished (Abbreviations: VLF: Very low frequency, LF: Low frequency, HF: High frequency). (*Source:* Modified from Heart rate variability: standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Circulation. 1996;93:1043-65, with permission)

Heart rate variability measurement requires continuous electrocardiographic recording to measure R-R intervals over a period of time, and generally utilizes computer software for analysis by either time-domain or frequency-domain methods.[22] An example of a time-domain measurement is the variance (e.g. standard deviation) of the R-R intervals over a given period of time. Such time-domain measurements typically reflect overall heart rate variability. To better understand the contribution of the different oscillatory components that influence heart rate, frequency-domain measurements have been utilized. Power spectral density analysis provides information on how power (i.e. variance) is distributed across a range of frequencies. Those frequencies in the higher range are most useful in analyzing autonomic contribution to heart rate variability in humans (Figs 3A and B). The high frequency (HF) component (0.15–0.4 Hz) principally records the respiratory sinus arrhythmia contribution, and muscarinic receptor blockade or vagotomy demonstrates that parasympathetic efferents are the major contributor. The low frequency (LF) component (0.04–0.15 Hz) is more controversial; however, it is generally agreed that this component reflects the combined activity of both vagal and sympathetic activity, and the LF/HF ratio is often measured as an indicator of sympathovagal balance. The physiological determinants of the lower frequency components (< 0.04 Hz) are less understood. The time duration of recording has a large effect upon the interpretation of heart rate variability measurements; short-term 2–5 minutes recordings predominantly assess the high frequency components, whereas long-term 24 hours recordings also incorporate the lower frequency components, and thus the total heart rate variability increases over time.

Like baroreceptor sensitivity, heart rate variability diminishes with increasing age[23] and it has been used to predict adverse outcomes in cardiovascular disease. In the Framingham Heart study, both a decrease in the standard deviation of R-R intervals and reduction in low frequency power components were associated with increased mortality in an elderly population.[24] Moreover, decreased heart rate variability has been shown to predict cardiac mortality after myocardial infarction.[21]

HEART RATE RECOVERY

During exercise, the heart rate rises from both parasympathetic withdrawal and sympathetic activation. The rapid fall in heart rate that occurs within 30 seconds after stopping exercise is predominantly a function of the reactivation of the parasympathetic nervous system,[25] and is termed heart rate recovery. Based on a population-based cohort study, the failure of the heart rate to fall rapidly during early recovery after exercise stress testing was one of the strongest predictors of death, even after adjustments for cardiovascular risk factors including changes in the heart rate during exercise.[26]

CATECHOLAMINE BLOOD MEASUREMENT

Measuring plasma catecholamine levels is an important adjunct in diagnosing autonomic dysfunction. The most relevant endogenous catecholamines, their precursors and metabolites that can be detected in human plasma are 3,4-dihydroxy-L-phenylalanine (dopa), norepinephrine, dihydroxyphenylacetic acid (DOPAC) and dihydroxyphenylglycol (DHPG), as depicted on Figure 4.[27,28] The plasma levels of norepinephrine depend on the balance between its exocytotic release from sympathetic nerves and neuronal reuptake via the cell membrane norepinephrine transporter (uptake-1). In healthy subjects, the baroreflex mediates a twofold to threefold increase in norepinephrine levels upon standing from a supine position. Patients with orthostatic hypotension due to loss of peripheral sympathetic innervation have chronically low plasma levels of catecholamines. Other patients with orthostatic hypotension have an intact peripheral sympathetic system, but fail to appropriately activate it due to sensory or central defects in the baroreflex; these patients usually have normal catecholamine levels at rest, but they fail to increase upon standing. Since steady-state plasma

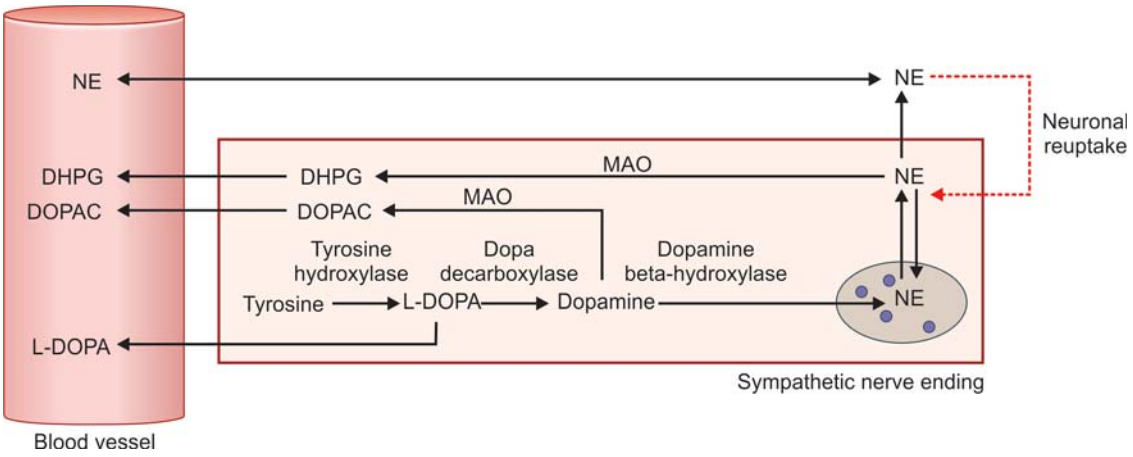


FIGURE 4: Major sources of plasma catecholamines, their precursors and metabolites. Within sympathetic nerves, tyrosine undergoes hydroxylation to dihydroxyphenylalanine (L-DOPA; levodopa), which is decarboxylated to dopamine and further hydroxylated to norepinephrine (NE). NE that enters the plasma is mainly from synaptic vesicle release; although the vast majority of NE is taken back up into the nerve terminals via an uptake-1 mechanism. Dopamine is metabolized to dihydroxyphenylacetic acid (DOPAC), and NE to dihydroxyphenylglycol (DHPG) through monoamine oxidase (MAO) activity (*Source:* Modified from Goldstein DS, Eisenhofer G, Kopin IJ. Sources and significance of plasma levels of catechols and their metabolites in humans. J Pharmacol Exp Ther. 2003;305:800-11, with permission)

levels of norepinephrine are dependent upon both its release and its clearance from plasma, researchers often measure norepinephrine "spillover" (the appearance rate of norepinephrine in the plasma) as a more accurate reflection of sympathetic function.[29] Using an "isotope dilution method", radiolabeled ^{3}H-norepinephrine is infused into the circulation and norepinephrine spillover is determined by measuring the amount of dilution of the isotope by endogenous norepinephrine. Measurement of regional norepinephrine spillover allows for assessment of sympathetic function in specific organs and tissues.

CARDIAC SYMPATHETIC IMAGING

Imaging of the postganglionic sympathetic catecholamine cardiac innervation has been used with increasing frequency both in research and clinical practice. The most commonly used radiotracer is ^{123}I-metaiodobenzylguanidine (^{123}I-MIBG), a sympathomimetic agent that is taken up into sympathetic nerves by the uptake-1 process and sequestered in storage vesicles. However, since it is not degraded like norepinephrine, it can be measured using single proton emission tomography (SPECT). The ^{123}I-MIBG was first used in diagnosing and localizing pheochromocytoma, neuroblastoma and carcinoid tumors. More recently, it has been used to determine cardiac sympathetic innervation and function, and has prognostic significance in a variety of cardiac diseases including diabetes, hypertension, heart failure, stress cardiomyopathy ("takotsubo"), coronary artery disease, cardiac hypertrophy and Brugada syndrome, as well as aiding in the diagnosis of various etiologies of autonomic failure.[30–32]

PRIMARY CHRONIC AUTONOMIC FAILURE

Chronic autonomic dysfunction or failure most commonly occurs as a secondary manifestation of other diseases that lead to peripheral neuropathy such as diabetes, amyloidosis or immune-mediated neuropathies. The term primary chronic autonomic failure is reserved for those rare cases where autonomic dysfunction dominates the clinical presentation, in the absence of an underlying cause. The terminology of the various syndromes continues to evolve, reflecting our improving understanding of the underlying pathophysiological mechanisms. The primary autonomic degenerative disorders are termed pure autonomic failure and multiple system atrophy. Parkinson's disease and Lewy body dementia are related diseases that primarily involve central neurodegeneration, although both commonly also have peripheral autonomic involvement. All of the above disorders are characterized by cytoplasmic inclusion bodies in degenerative neurons (called Lewy bodies) in the Lewy body disorders (pure autonomic failure, Parkinson's disease and Lewy body dementia) and in glia (in the case of multiple system atrophy). The major component of these inclusion bodies is precipitated α-synuclein and hence these disorders have been termed 'synucleinopathies'. Currently, the pathophysiological role of the α-synuclein protein aggregates is unknown.[33,34] While the clinical presentations of patients with the various syndromes can overlap, accurate diagnosis is important since treatment differs and their prognosis varies significantly.

PURE AUTONOMIC FAILURE

Pure autonomic failure is a rare, sporadic disorder characterized by orthostatic hypotension as well as bladder and sexual dysfunction—in the absence of other neurological deficits.[6] It generally presents in individuals in their sixties, is slowly progressive, and the prognosis is generally good. However, in severe cases the orthostatic hypotension can be so debilitating that it confines some patients to wheelchairs. Paradoxically, these patients often have hypertension when supine. This is a common feature of autonomic dysfunction of any cause and can confound the treatment of the orthostatic hypotension. The dysfunction in pure autonomic failure occurs at the level of peripheral autonomic neurons, and low norepinephrine levels due to inadequate sympathetic neuronal release are a defining characteristic. Therapy with norepinephrine precursor (Fig. 4) has been shown to be

effective in treating the orthostatic hypotension in these patients.[35] Neuropathological abnormalities have been described in both preganglionic and postganglionic sympathetic neurons in pure autonomic failure, and the presence of Lewy bodies led to the proposal that pure autonomic failure might be a peripheral, or early manifestation of Parkinson's disease.[36] Pure autonomic failure also resembles other Lewy body disorders in that SPECT scanning with ^{123}I-MIBG reveals diminished cardiac uptake, consistent with cardiac sympathetic denervation.[31]

MULTIPLE SYSTEM ATROPHY

The term multiple system atrophy was introduced in 1969 to combine the entities of striatonigral degeneration, olivopontocerebellar ataxia, and Shy-Drager syndrome.[37] It is a rare, adult-onset (usually mid 50s), sporadic, and rapidly progressive neurodegenerative disease characterized by autonomic failure in combination with motor dysfunction.[38] As with pure autonomic failure, the autonomic dysfunction associated with multiple system atrophy is characterized by profound orthostatic hypotension and urogenital dysfunction. However, unlike pure autonomic failure, patients with multiple system atrophy also develop severe movement disorders, which manifest as either Parkinsonism or cerebellar ataxia. The pathological features of multiple system atrophy include neuronal degeneration in the central nervous system, including preganglionic central autonomic neurons, while sparing peripheral postganglionic autonomic neurons. In addition to neuronal degeneration, the diagnostic hallmark of multiple system atrophy is glial cytoplasmic inclusion bodies. The orthostatic hypotension associated with multiple system atrophy is usually profound and debilitating, with drops in systolic pressure of up to 100 mm Hg not uncommon. Perhaps due to the chronic and progressive nature of the disease process, some patients tolerate these profound falls in blood pressure remarkably well. The clinical diagnosis requires a reduction in systolic blood pressure of 30 mm Hg systolic or diastolic pressure of 15 mm Hg (note that this is a more pronounced decrease of blood pressure than recommended previously in the American Autonomic Society consensus statement on the definition of orthostatic hypotension).[38] Similar to pure autonomic failure, patients can also suffer from supine hypertension. Since the peripheral sympathetic system is intact in multiple system atrophy, the orthostatic hypotension is believed to represent a failure to appropriately activate it, whereas the supine hypertension is due to a failure to inactivate it through normal regulatory mechanisms. It has been shown that ganglionic blockade with trimethaphan completely abolishes supine hypertension in multiple system atrophy, but had no effect in patients with pure autonomic failure.[39] The motor manifestations of multiple system atrophy present primarily as Parkinsonian features, including bradykinesia, rigidity, hypokinetic speech, postural instability, and tremor (60% of multiple system atrophy patients). Another group of patients with multiple system atrophy (40%) present mainly with cerebellar ataxia, including gait ataxia, dysarthria, limb ataxia and oculomotor dysfunction.

Distinguishing multiple system atrophy from Parkinson's disease and Lewy body dementia can be challenging.[33] Up to two-thirds of patients with Parkinson's disease have orthostatic hypotension, although the degree of the orthostatic pressure reduction and associated symptoms are rarely as severe as in multiple system atrophy. An important distinguishing characteristic is that Parkinsonism associated with multiple system atrophy, when present, is typically not responsive to levodopa, and often levodopa will worsen the orthostatic hypotension. Lewy body dementia is characterized by cognitive impairment as well as Parkinsonism, and many of these patients present with autonomic dysfunction early in their clinical course. Unlike the Lewy body syndromes, the peripheral autonomic neurons are spared in multiple system atrophy, and these patients can be often distinguished by normal or only slightly reduced plasma norepinephrine levels, as well as preserved catecholamine uptake by cardiac sympathetic neurons. Diagnosis of multiple system atrophy can be supported by neuroimaging, including MRI, where recent advances have identified distinguishing characteristics.[38] Multiple system atrophy is a devastating disease, with the age of onset usually decades earlier than that of Lewy body dementia (age 50s compared to 70s), and mean survival is only 6 years, which is significantly shorter than that in Parkinson's disease. At present, the therapy of multiple system atrophy is only symptomatic and mainly targets the autonomic failure.[40]

SECONDARY AND CONGENITAL AUTONOMIC FAILURE

Autonomic failure most commonly occurs in the setting of underlying systemic disease, with diabetes mellitus being the most common cause.[41] Although the incidence of autonomic dysfunction varies in different populations of type 1 and type 2 diabetic patients, and it depends on the criteria used to define autonomic dysfunction, the incidence can be as high as 90% in selective type 1 diabetics evaluated for pancreas transplantation.[42] Autonomic failure is predominantly a manifestation of a more generalized peripheral neuropathy, and similarly it generally begins distally and progresses proximally. The vagus nerve is the longest autonomic nerve, and the earliest manifestations of diabetic autonomic neuropathy are usually associated with parasympathetic denervation. A relative increase in sympathetic/parasympathetic balance ensues leading to an increase in resting heart rate, a decrease in heart rate variability, and blood pressure dysregulation due to baroreflex abnormalities.[43] Sympathetic denervation usually presents in a later stage of the disease and manifests as a further decline in exercise tolerance, and ultimately to the development of orthostatic hypotension. Autonomic dysfunction is associated with a very poor prognosis in patients with diabetes, and sudden death is common. In one large prospective study of type 1 diabetic patients, autonomic dysfunction was the strongest predictor of mortality, exceeding the effect of traditional cardiovascular risk factors.[44] There is no effective targeted treatment for diabetic autonomic neuropathy; however, optimal therapy of the underlying disease, specifically blood pressure and glycemic control, may prevent neuropathic and microvascular complications, and improve overall autonomic function.

Other systemic disorders that have been associated with autonomic failure are less common. Many of these disorders that affect the nervous system are immune-mediated, including acute inflammatory demyelinating polyneuropathy (Guillain-Barre syndrome), Lyme disease[45] and paraneoplastic proces-

ses.[46] Some immune-mediated processes involve the production of antibodies against acetylcholine receptors; thus, they disrupt synaptic transmission in both sympathetic and parasympathetic peripheral ganglia.[47] There may be a role for immune modulating therapies in some of these conditions. Processes involving infiltration of autonomic nerves include primary and hereditary amyloidosis; however, autonomic dysfunction is rarely associated with secondary amyloidosis.[48] A small number of elderly patients with reversible autonomic dysfunction due to vitamin B_{12} deficiency have been reported.[49] Based on a small prospective study, almost 65% of HIV antibody positive patients have been shown to have symptoms suggestive of autonomic dysfunction.[50]

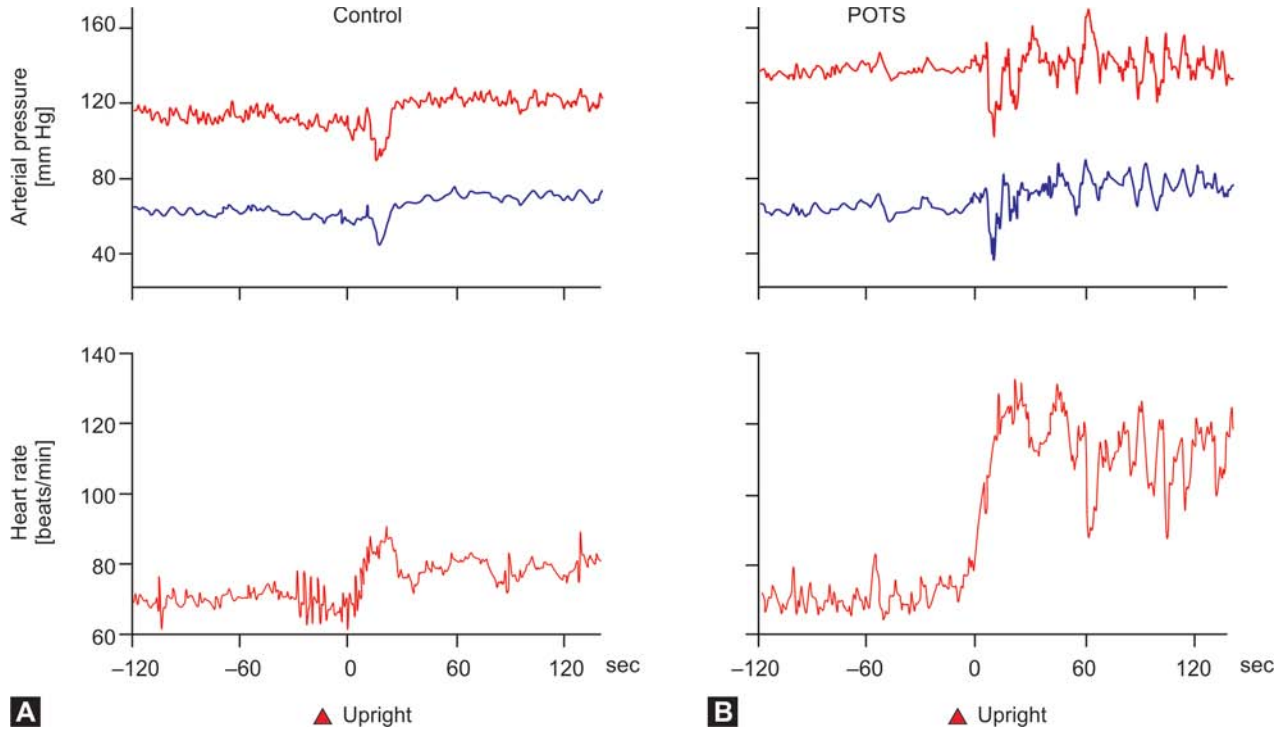
Several congenital disorders are associated with autonomic dysfunction. Some of these disorders, such as familial dysautonomia and Allgrove syndrome, occur as a result of developmental abnormalities of the ANS and present with profound dysautonomia and severe orthostatic hypotension that begins early in life.[51] Another group of autonomic developmental disorders, including Hirschsprung disease (an absence of enteric ganglia in the intestine), neuroblastomas derived from neural crest cells, and congenital central hypoventilation syndrome ("Ondine's curse"), result from mutations in the PHOX2B gene, which is critical for the development of the ANS from neural crest tissue.[52] Other congenital disorders result in neurotransmitter deficiencies and can present later in life and even into adulthood. One such rare, but informative, cause of primary autonomic failure is congenital dopamine beta-hydroxylase deficiency.[53] This enzyme converts dopamine to norepinephrine in sympathetic neurons. Therefore, patients have undetectable levels of norepinephrine and epinephrine, and increased levels of circulating dopamine. As a result, patients present with marked orthostatic hypotension with an insufficient heart rate response. Patients can also have ptosis, nasal stuffiness and retrograde ejaculation in men, as well as increased urinary sodium excretion resulting in volume depletion.[54] Orally administered droxidopa (L-DOPS) is taken up by sympathetic neurons, and directly decarboxylated into norepinephrine and has shown to be a particularly effective therapy in these patients.[55,56]

CHRONIC ORTHOSTATIC INTOLERANCE

POSTURAL ORTHOSTATIC TACHYCARDIA SYNDROME

One the most frequent complaints of patients that present to autonomic clinical centers is intolerance of postural changes. Yet, unlike the disorders of autonomic failure described previously, most patients do not, in fact, have orthostatic hypotension. Nevertheless, these patients do have autonomic abnormalities and the hallmark of this disorder is an exaggerated increase in heart rate upon standing or head-up tilt. The disorder has been termed postural orthostatic tachycardia syndrome or POTS.[57] POTS is most likely a syndrome with many etiologies and this has been reflected in the different names used to describe it, including orthostatic tachycardia, effort syndrome, idiopathic hypovolemia, sympathotonic orthostatic hypotension and mitral valve prolapse syndrome. Current thinking is that patients with mitral valve prolapse do not have an increased predilection to have autonomic dysfunction.[58] The symptoms associated with POTS are varied but most commonly include lightheadedness or dizziness, weakness, fatigue, blurred vision and possible presyncope, as well as palpitations, tremulousness and anxiety. Gastrointestinal symptoms are frequent, which include nausea, bloating, diarrhea and constipation. Symptoms are often episodic and cyclical, they often correlate with women's menstrual cycle, and are exacerbated by heat, exercise, and dehydration. The most commonly used diagnostic criteria for POTS include a sustained increase in heart rate of more than 30 beats/minute, or tachycardia more than or equal to 120 beats/minute within 10 minutes of standing or upright tilting, in the absence of orthostatic hypotension (Figs 5A and B). Unlike autonomic failure, which is characterized by loss of sympathetic activity, orthostatic symptoms in POTS are accompanied by elevated plasma norepinephrine (≥ 600 pg/ml) in about half of patients.[59,60] It is estimated that half a million Americans suffer from POTS. It generally occurs in young adults (age 15–50 years), and there is a female to male ratio of 5:1.

The cause of POTS is controversial, and most likely reflects the heterogeneous nature of the syndrome. We will highlight a few of the abnormalities that have been described in these patients that lend insight into potential etiologies. A percentage of POTS patients demonstrate evidence of selective lower extremity autonomic denervation. These patients have impairment of lower extremity norepinephrine spillover, and sudomotor denervation can cause anhidrosis of the feet and toes. Lower extremity sympathetic denervation causes venous pooling, and these patients can present with dependent lower extremity rubor, acrocyanosis and edema. Venous pooling will diminish venous return to the heart upon standing, decrease stroke volume, and subsequently prompt the observed tachycardia. Reduced blood volume has been observed in patients with POTS, as well as abnormalities in the renin-angiotensin-aldosterone axis leading to impaired sodium retention. Interestingly, this might reflect selective sympathetic denervation of the kidney, which is an important regulator of renin release.[61] Despite evidence of selective denervation, increased overall sympathetic activity is a common final pathway in POTS, and low dose beta-blockers improve tachycardia and symptoms in some patients. Measured abnormalities in baroreflex sensitivity, as well as responses to the Valsalva maneuver and lower body negative pressure suggest that patients with POTS have baroreflex dysfunction.[62] In some POTS patients there appears to be a familial component. One family was found to have reduced norepinephrine clearance due to a mutation in the gene encoding the norepinephrine-transporter responsible for norepinephrine re-uptake.[63] Other studies have found polymorphisms in the genes encoding the beta 2-adrenergic receptor and nitric oxide synthase that could predispose patients to having POTS.[64,65] Finally, some believe that there is significant overlap between patients that have POTS and those diagnosed with chronic fatigue syndrome and fibromyalgia, and that the common denominator in these conditions might be deconditioning.[66,67] In fact, many of the cardiovascular abnormalities in POTS are reproduced in patients having undergone deconditioning or extended space flight[68] and



FIGURES 5A AND B: (A) Arterial pressure and heart rate responses to the upright posture in a normal individual and (B) A patient with postural orthostatic tachycardia syndrome (POTS). In addition to having a more marked rise in heart rate during the upright posture, the POTS patient also showed much more variability in their heart rate and arterial pressure responses (*Source:* Modified from Joyner MJ, Masuki S. POTS versus deconditioning: the same or different. Clin Auton Res. 2008;18:300-7)

perhaps such patients may benefit from undergoing exercise training.[69,70]

TREATMENT OF ORTHOSTATIC HYPOTENSION/INTOLERANCE

Treatment of chronic orthostatic hypotension due to autonomic dysfunction is challenging. Although many therapeutic approaches have been proposed, no specific treatment has been proven to be effective. Because in most patients normotension cannot be usually restored, the goal of treatment is to improve quality of life by ameliorating symptoms using a combination of both non-pharmacological and pharmacological interventions.

Non-Pharmacologic Therapy

The first step in dealing with patients with orthostatic hypotension is to carefully review all medications and eliminate those that can potentially exacerbate symptoms; these include antihypertensive drugs, diuretics, nitrates and antidepressants. All patients and their families should be counseled regarding lifestyle modifications and simple maneuvers that might be very helpful on a daily basis. In particular, patients should be educated to arise slowly from supine to seated or standing position. Leg-crossing is another maneuver that has been shown to prolong the standing time in patients with autonomic disturbances. It causes compression of the muscles and veins in the upper legs and abdomen resulting in an increase in central blood volume and mean arterial pressure.[71] It is performed by firmly crossing one leg over another during active standing. Squatting, bending over, sitting in knee-chest position or placing one foot on a chair while standing are also very effective and may prevent from syncope and fall. Custom-fitted elastic stockings/girdles are also strongly advised in order to minimize peripheral blood pooling. Elevation of the head of the bed by 10–20 degrees decreases renal perfusion and activates the renin-angiotensin-aldosterone system, which decreases nocturnal diuresis and expands extracellular fluid volume. Patients should learn to avoid certain triggers including prolonged coughing, straining or walking in hot and humid weather. Regular exercise training involving aerobic exercise and lower limb resistance can increase sympathetic tone, promote blood volume expansion and reverse deconditioning. In a randomized controlled trial, endurance exercise training improved symptoms of orthostatic intolerance in POTS patients.[69] Adequate salt intake and hydration are paramount. Finally, patients with postprandial autonomic failure and hypotension should avoid large meals, be encouraged to consume low carbohydrate meals, minimize alcohol intake and avoid strenuous activities or sudden standing immediately after eating.

Pharmacologic Therapy

Pharmacologic therapies for chronic orthostatic hypotension and POTS syndrome are similar, and they will be discussed together. Although there are many drugs and supplemental agents available, mineralocorticoids, followed by sympathomimetics are the first line of therapy. Plasma volume expansion with high doses of fludrocortisone tends to improve symptoms both in patients with orthostatic hypotension and with POTS, although it can exacerbate associated supine hypertension.[72]

Midodrine is a peripheral selective alpha-1-adrenergic agonist that was approved in 1996 for the treatment of symptomatic orthostatic hypotension.[73] For unclear reasons, the above agents can significantly improve symptoms in patients with autonomic failure, even when they do not cause a reduction in the degree of orthostatic hypotension. Other sympathomimetics, such as ephedrine, pseudoephedrine, and phenylpropanolamine have also been used, but they are generally less effective. Some patients with POTS, particularly those troubled by prominent adrenergic symptoms, may benefit from low dose beta-blocking agents; however, they should be avoided in patients with chronic orthostatic hypotension. Beta-blockers should be started in low doses and increased gradually (e.g. propranolol 20–30 mg three or four times daily).[74] Some patients with orthostatic hypotension have a decreased red-cell mass that might compromise their effective circulating blood volume and aggravate the orthostasis; therefore, treatment with erythropoietin has been suggested.[75]

SYNDROMES ASSOCIATED WITH EPISODIC AUTONOMIC FAILURE

HEMORRHAGE

Studies conducted during World War II provided the basis for our understanding of the pathophysiology of cardiovascular collapse due to life-threatening hemorrhage. Barcroft and Edholm demonstrated that peripheral vasodilatation significantly contributes to cardiovascular collapse.[76] Under normal conditions, a gradual loss of central blood volume causes both central venous and arterial pressures to fall. As a result, the baroreflex is deactivated resulting in a reduction of parasympathetic outflow to the heart and increase in sympathetic outflow to the peripheral circulation. These adaptive mechanisms are responsible for maintaining blood pressure in spite of marked reductions in central blood volume. During extreme loss of blood volume, however, the low pressure cardiac mechanoreceptors send paradoxical signals to the cardiovascular centers of brainstem that trigger an increase in parasympathetic outflow to the heart and reductions in sympathetic outflow to the peripheral circulation—similar to the Bezold-Jarisch reflex. This so-called "empty heart syndrome" results in an abrupt vasodilation and bradycardia, and often—loss of consciousness. While this paradigm is most certainly an oversimplification,[77,78] it has provided a basis for understanding of other causes of neurally mediated syncope including that associated with aortic stenosis,[79] hypertrophic cardiomyopathy[80] and hemodialysis.[81]

NEUROCARDIOGENIC SYNCOPE

Neurocardiogenic syncope, also known as vasovagal syncope, is characterized by an autonomic neurally mediated loss of consciousness, with normal autonomic function between the episodes. It is the most common cause of syncope. The mechanism is thought to be secondary to diminished venous return to the heart resulting from increased peripheral venous pooling of blood. This leads to paradoxical activation of cardiac mechanoreceptors, resulting in bradycardia and decreased systemic vascular resistance, similar to the "empty heart syndrome" described for severe hemorrhage. Symptoms include weakness, lightheadedness, feelings of warm and cold, and ultimately a brief loss of consciousness. Classically, neurocardiogenic syncope is triggered by emotional or physical stress such as venipuncture, painful stimuli, fear, prolonged standing, heat exposure or exertion. However, in some patients recurrent episodes occur without an identifiable cause or trigger. Prognosis is benign aside from sequela of any falls that may occur with syncope. Tilt-table testing has good specificity, but uncertain sensitivity in diagnosis and is not always reproducible.[82] Implantable loop recorders may also be used; however, they are expensive and the diagnostic benefit is questionable. Treatment is usually conservative, and includes counseling and education, particularly in determining potential predisposing factors and early prodromal symptoms in order to prevent falls. Similar to POTS patients, increasing fluid and salt intake may be helpful in prevention of neurocardiogenic syncope. Pharmacological therapy includes beta-blockers that may work via inhibition of mechanoreceptor activation, fludrocortisone to expand plasma volume, vasoconstrictors and selective serotonin reuptake inhibitors that may have a role in regulating the sympathetic nervous system. The usefulness of cardiac pacing for the prevention of recurrences of vasovagal syncope remains controversial. According to the findings of the Second Vasovagal Pacemaker Study (VPS II), pacemaker therapy does not significantly reduce the risk of recurrent syncope in patients with vasovagal syncope and should not be recommended as first-line therapy.[83] However, in highly selected elderly patients without prodromal symptoms who are refractory to conservative therapy, pacemaker therapy could be effective in preventing syncope.[84]

INFERIOR WALL MYOCARDIAL ISCHEMIA/INFARCTION

Myocardial infarction or ischemia is usually associated with tachycardia, presumably due to diminished cardiac output leading to lowering of blood pressure and resultant activation of the baroreflex and possibly cardiac sympathetic afferents (see section Heart Failure and Ischemic Heart Disease). On the contrary, patients with inferior wall myocardial infarction or ischemia can experience episodes of profound, but usually transient, bradycardia and hypotension. This reflex activation of cardiac inhibitory signals also causes inhibition of sympathetic activity, further potentiating neurogenic hypotension. Studies have demonstrated that this inhibitory reflex is mediated by cardiac receptors that are preferentially located in the inferoposterior wall of the ventricle.[85] The stimulus during ischemia that actives this Bezold-Jarisch like reflex is not well understood.

CAROTID SINUS HYPERSENSITIVITY

Carotid sinus hypersensitivity is an important cause of syncope and falls in patients of age more than 50 years.[86] It is characterized by exaggerated response to stimulation of baroreceptor pathways. Carotid sinus sensitivity is diagnosed when either the history reveals syncope after mechanical manipulation of the neck (e.g. adjusting a tight collar, or pressure from shaving), or symptoms are reproduced by carotid sinus massage testing. Baring contraindications, carotid sinus massage should be done for at least 6 seconds on each side, and the test is considered positive if symptoms correlate with asystole for more than 3 seconds, or systolic blood pressure fall of more

than 50 mm Hg. Treatment is generally the same as for neurocardiogenic syncope; however, pacemaker implantation is recommended for patients with syncope with a history consistent with carotid sinus hypersensitivity and reproducible symptoms during carotid sinus massage testing.[87]

AUTONOMIC PERTURBATIONS ASSOCIATED WITH CARDIOVASCULAR CONDITIONS

BAROREFLEX FAILURE: NEUROGENIC HYPERTENSION

Chronic essential hypertension is primarily felt to be due to faulty sodium and volume regulation by the kidneys and associated hormonal regulatory systems. However, specific perturbations of the baroreflex can lead to profound hypertension, and highlights the potential role of the ANS in chronic control of blood pressure. The arterial baroreflex serves to buffer acute fluctuations of blood pressure that occur during posture changes and other physical and emotional stressors. The diagnosis of baroreflex failure is generally reserved for patients that have suffered physical damage to the afferent limb of the baroreflex. The damage can occur at the level of the baroreceptors themselves, the glossopharyngeal and/or vagus nerves, or the afferent brainstem nuclei. In some cases, when the damage is to the vagal nerves, the vagal efferents are also affected. The most common causes of baroreflex failure include neck surgery (e.g. carotid endarterectomy),[88] radiation therapy for neck cancers,[89] neck trauma, or stroke involving the brainstem.[90] A distinguishing characteristic of baroreflex failure is that the sympathetic efferents remain intact and poorly regulated. Thus, unlike autonomic failure where hypotension is the predominant feature, baroreflex failure is characterized by profound swings in blood pressure and heart rate, and profound episodic elevations in blood pressure are common.

The manifestations of baroreflex failure are most dramatic early after neck trauma or surgery, when patients can present with significant pheochromocytoma-like hypertensive crisis associated with palpitations, diaphoresis, and severe headaches. Profound elevation of blood pressure, with systolic blood pressures greater than 250 mm Hg, commonly occur requiring acute admission and treatment. Later in the course of disease, over days or weeks, the pressor crisis subsides and the blood pressure becomes more volatile. During this more chronic phase wide blood pressure swings are particularly under the influence of unregulated sympathetic system, with hypertension and tachycardia accompanying mental or physical stress. Particularly in cases where the vagal efferents are intact, patients with baroreflex failure can also manifest with episodes of orthostatic hypotension and bradycardia, particularly at rest, with some requiring pacemaker placement. However, orthostatic hypotension is not common, and it is interesting to speculate that other reflex mechanisms, including those initiated by cardiopulmonary and muscle afferents, are able to compensate and appropriately trigger sympathetic efferent activity upon standing.[91]

The diagnosis of chronic baroreflex failure is usually straightforward when a patient presents in hypertensive crisis after recent neck trauma or surgery. Usually such cases involve extensive bilateral damage to the baroreflex afferent pathways. However, the effect of unilateral or less extensive injury is less understood, and might play an important and unrecognized role in blood pressure regulation. In patients where the diagnosis is in question, 24 hours blood pressure monitoring can be useful to demonstrate volatile fluctuations. Also, pharmacological interrogation of baroreflex function can demonstrate profound blood pressure increases to vasoconstrictor agents, without an accompanying change in heart rate, although it is recommended to start with very low doses to avoid potential hypertensive crisis.[92] The extreme sensitivity to vasoactive agents makes treatment of patients with baroreflex failure very difficult. Pharmacological therapy is generally directed toward antagonizing sympathetic activity both centrally, such as clonidine and methyldopa, and in the periphery, with alpha- and beta-adrenergic receptor antagonists, as well as agents to block the peripheral release of catecholamines.[93]

HEART FAILURE AND ISCHEMIC HEART DISEASE

Heart failure and myocardial ischemia are associated with hemodynamic derangements that trigger activation of neurohormonal systems, including the sympathetic nervous system and the renin-angiotensin-aldosterone axis. In parallel, there is a concomitant withdrawal of parasympathetic tone. In the short-term, these mechanisms can help to support the acutely failing heart by increasing heart rate, myocardial contractility and effective circulatory volume. However, in the long-term, most of these "compensatory" mechanisms are deleterious; they cause congestion, increase cardiac metabolic demand, worsen myocardial ischemic, trigger tachyarrhythmias, and precipitate the progressive downward spiral commonly seen with cardiac pump failure. In fact, many of the pharmacological therapies used to treat heart failure and myocardial ischemia are directed at blocking these counterproductive neurohormonal systems.

There is clear evidence for increased sympathetic nerve activity in patients with heart failure as measured by plasma norepinephrine levels, sympathetic nerve recordings and regional norepinephrine spillover. Patients with heart failure can have up to a 50-fold increase in cardiac norepinephrine spillover compared to normal controls, with levels approximating those achieved with maximal aerobic exercise.[94] Moreover, the sympathetic hyperexcitation can be regional rather than generalized, particularly early in the disease course when norepinephrine spillover is greatest from the heart and kidneys.[95,96] Despite this sympathoexcitation, there is evidence of diminished cardiac neural density, especially early in the setting of ischemic cardiomyopathy.[97,98] The reason for this seeming paradox is unclear, but it might involve regional denervation of some areas of myocardium in association with hyperinnervation of other areas due to sympathetic nerve sprouting.[99] Such regional differences in sympathetic innervation could contribute to the heterogeneity of myocardial excitability and refractoriness associated with cardiomyopathies, and predispose to arrhythmias.

Besides altered cardiac innervation, there are multiple other mechanisms that can contribute to sympathetic hyperactivity in heart failure. Traditionally, sympathoexcitation has been attributed to diminished arterial baroreflex mediated sympathoinhibition due to low cardiac output and blood pressure. In

addition, baroreflex sensitivity is decreased in most patients with heart failure. While this is certainly true in patients with heart failure, and it predicts poor survival,[20] it may not account for the chronic elevation of sympathetic tone. More recently, other mechanisms have been proposed to account for sympathoexcitation in heart failure. Perhaps most importantly, increasing evidence suggests that elevated venous and cardiac chamber filling pressures activate a sympathoexcitatory reflex in the failing heart.[100] This response is the directly opposite of that observed under normal conditions, where loading of low pressure baroreceptors leads to sympathoinhibition. In support of this, the level of cardiac norepinephrine spillover correlates positively with the degree of pulmonary artery and atrial pressures in patients with heart failure[101] and is reduced after acutely lowering cardiac filling pressures.[102] What accounts for this paradoxical response in heart failure? Studies in animal models of heart failure have demonstrated increased excitation of cardiac sensory nerves, predominantly cardiac sympathetic afferents, which become sensitized to both mechanical and chemical stimuli in heart failure.[103,104] Blocking of these cardiac afferent pathways, reduces sympathoexcitation to a normal level. Other data demonstrate abnormal skeletal muscle afferent activity associated with skeletal myopathy[105] and abnormal chemoreflexes,[106] perhaps associated with sleep apnea, as contributors to the high sympathetic tone in heart failure. Finally, there is strong evidence that changes within the central nervous system, including brain angiotensin-II and aldosterone, contribute to sympathetic hyperactivity.[107]

The consequences of sympathoexcitation and parasympathetic withdrawal on the progression of heart failure and worsening outcomes has been well documented[108] The effects of an acute surge in sympathetic input to the heart are dramatically illustrated by the fulminate, life-threatening cardiomyopathies occasionally seen after major brain trauma or stroke, or during emotional stress. More chronic catecholamine exposure leads to interstitial fibrosis, myocyte apoptosis, beta 1-receptor downregulation, potentially fatal arrhythmias, as well as disadvantageous remodeling primarily through ventricular dilation. The effect of increased sympathetic input to the kidneys contributes to activation of the renin-angiotensin system and increases sodium retention.

The increasing use and understood benefits of beta-adrenergic receptor blocking agents are perhaps the best examples that therapy to alter the autonomic system can halt disease progression and improve survival in heart failure. The non-selective beta-blocker, carvedilol, has been shown to improve heart rate variability and baroreflex sensitivity, as well as decrease total body and cardiac spillover of norepinephrine in heart failure patients.[109,110] Conversely, beta-agonists, such as dobutamine and milrinone, while required at times to support the acutely failure heart, have proven to increase mortality when administered chronically. Both angiotensin-II and aldosterone enhance release and inhibit uptake of norepinephrine,[111,112] and so part of the beneficial effects of angiotensin-converting enzyme inhibitors, angiotensin-II receptor blockers, and aldosterone antagonists are due to their effect on the sympathetic nervous system. Patients with heart failure have poor exercise capacity and abnormal exercise-mediated reflexes which mediate sympathoexcitation.[105] In an animal model of heart failure, exercise training has been shown to normalize elevated sympathetic outflow.[113] A recent randomized trial of heart failure patients demonstrated that exercise training improved symptoms, reduced hospitalizations and improved mortality.[114] Given the high prevalence of obstructive or central sleep apnea in patients with heart failure, and the association of sleep apnea with autonomic derangement, treatment of sleep apnea is probably an underutilized strategy to correct dysautonomia and improve outcomes in heart failure. In addition to pharmacological means, investigators have tried to alter the ANS through device-based system. Implantable thoracic spinal cord stimulators have been used for years in the treatment of patients with refractory angina.[115] Recent trials in animal models of heart failure have demonstrated that modulation of the ANS by stimulation of either the spinal cord[116] or vagus nerve[117] can improve cardiac function and reduce the incidence of fatal arrhythmias, and preliminary studies in humans with heart failure suggest similar benefits.[118]

OBSTRUCTIVE SLEEP APNEA

Obstructive sleep apnea (OSA) is characterized by intermittent episodes of partial or complete obstruction of the upper airway during sleep, which leads to transient hypoxia and is typically associated with snoring and daytime somnolence. The OSA is known to have major adverse cardiovascular effects and sympathetic overactivity is thought to be one of the key mechanisms.[119] Increased sympathetic activity, supported by elevated plasma and urinary catecholamine levels,[120] as well as a reduction in heart rate variability,[121] have been reported in OSA. Interestingly, sympathetic outflow remains elevated throughout a 24 hours time period, even in the absence of underlying cardiovascular disease.[122] Furthermore, continuous positive airway pressure (CPAP) therapy effectively reduces muscle sympathetic nerve activity, plasma norepinephrine levels, and improves arterial baroreflex sensitivity during both wakefulness and sleep.[123,124]

PHEOCHROMOCYTOMA

Pheochromocytomas are catecholamine secreting neuroendocrine tumors originating from chromaffin cells of the adrenal medulla.[125] These tumors can also arise in extra-adrenal sympathetic ganglia in the thorax, abdomen or pelvis. Due to paroxysms of epinephrine or norepinephrine secretion from the tumors, the clinical hallmarks include episodic bouts of hypertension, tachycardia, panic or anxiety and flushing. Potentially lethal complications of pheochromocytomas are due to adverse cardiovascular effects of catecholamines leading to cardiac arrhythmia, myocarditis, dilated cardiomyopathy, cardiogenic shock and heart failure.[126] Anesthesia and tumor manipulation are well-known stimuli to elicit a catecholaminergic crisis. Diagnostic workup should be initiated by biochemical testing and should include measurement of plasma catecholamines, urinary metanephrines (normetanephrine and metanephrine) and urinary vanillylmandelic acid. Abnormal biochemical test results should be followed by radiological studies, with MRI providing the highest sensitivity. The MIBG scintigraphy has been used to detect particularly extra-adrenal tumors. Surgical resection of a hormonally active tumor is the

definitive treatment for pheochromocytoma; however, adequate blood pressure control with alpha- and beta-blocking agents preoperatively is necessary to prevent hypertensive crisis.

CARDIAC ARRHYTHMIAS

Heart rate and the electrical conduction through the heart are primarily controlled by the ANS. Thus, it is no surprise that perturbations of cardiac parasympathetic and sympathetic activity play a key role in the development of both supraventricular and ventricular cardiac arrhythmias. Conditions associated with high sympathetic tone predispose to ventricular arrhythmias and sudden death. However, the role of the two branches of the ANS as precipitators of atrial arrhythmias, and atrial fibrillation in particular, is less understood. Interestingly, the atria are more densely innervated with both parasympathetic and sympathetic fibers than the ventricles. Coumel was the first to propose dual mechanisms by which changes in autonomic activity can precipitate atrial fibrillation.[127] Some episodes appear to be triggered by high sympathetic activation; these include those associated with alcohol consumption, exercise and emotional stress and in the postoperative period. In addition, this adrenergic-mediated form of atrial fibrillation more commonly occurs in patients with associated heart disease. On the other hand, other bouts of atrial fibrillation seem driven by parasympathetic surges, such as occur during sleep. These cholinergic-driven episodes are more common in patients without concomitant structural heart disease—the so-called 'lone' atrial fibrillation. Excessive vagal stimulation to the atria can trigger atrial fibrillation by shortening action potential duration, and generate inhomogeneous shortening of the refractory period, producing a set-up for re-entry.[128] It has been proposed that while beta-blockers are beneficial in sympathetic-driven atrial fibrillation, they may also exacerbate parasympathetic-driven episodes. The fact that atrial fibrillation is common in patients after lung transplantation, but rarely seen in heart transplant recipients further suggests that cardiac autonomic innervation plays a crucial role in the mechanism of the arrhythmia.[129] This concept has led to attempts to treat atrial fibrillation by cardiac ganglion ablation. The intrinsic cardiac ganglia are the final relay station for sympathetic and parasympathetic efferent input to the heart. In addition, the ganglia receive information from cardiac sensory nerves, and together with interneurons serve to coordinate and modulate efferent outflow.[130] Of the multiple cardiac ganglia, each has variable effects on different regions of the heart, and thus it is not clear which of the multiple cardiac ganglia provide the autonomic input that predisposes to arrhythmia and should be targeted for ablation. Nevertheless, it has been proposed that pulmonary vein isolation and other left atrial ablative procedures to treat atrial fibrillation are more successful if they are accompanied by autonomic denervation.[131]

In contrast to atrial arrhythmias, there is compelling evidence that enhanced sympathetic activation and/or diminished parasympathetic tone predispose to ventricular arrhythmias and sudden death.[132] Large clinical trials, linking autonomic function and clinical outcomes, have shown that a reduction in baroreflex sensitivity and heart rate variability (reflecting sympathovagal imbalance) predicts fatal arrhythmias after myocardial infarction.[21,133] Sympathetic activation of ventricular myocardium leads to shortening of action potential duration, reduction in refractoriness and fibrillation thresholds, and can generate early after depolarizations. In addition, myocardial infarction causes initial nerve injury that is followed by sympathetic nerve sprouting and regional myocardial hyperinnervation, which further contributes to regional electrical heterogeneity of the myocardium and predisposes to re-entry. Finally, patients with some types of inheritable long QT syndrome are particularly prone to ventricular arrhythmia during times of sympathetic activation; beta-blockers being the mainstay of therapy and select patients have been shown to benefit from left-sided cardiac sympathetic denervation.[134]

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Section 8

HEART FAILURE

Chapter 68

Heart Failure: Epidemiology

Kanu Chatterjee

Chapter Outline

- Epidemiology
- Prevalence
- Incidence
  - Racial Differences
  - Geographic Differences
  - Gender Differences
- Secular Trends

INTRODUCTION

The incidence, prevalence and etiology of heart failure are variable and influenced by the definition of heart failure used and the relevant causes unique to the individual countries. For example, rheumatic heart disease as a cause of heart failure is more common in developing countries than in developed countries. However, irrespective of countries and the socio-economic status, there are some common epidemiologic factors.

Aging, hypertension, diabetes, obesity and increased body mass index are the major risk factors of heart failure.

Heart failure can result from primary valvular, pericardial or myocardial diseases. It can be acute or chronic. Heart failure complicating acute coronary syndromes or myocarditis are examples of acute heart failure. Heart failure complicating acute coronary syndromes, valvular, pericardial and myocardial diseases is discussed in different chapters. Decompensated heart failure is discussed in the chapter "Acute Heart Failure Syndromes".

Presently chronic heart failure is classified into two major clinical subtypes: (1) heart failure with reduced ejection fraction (HFREF) [also termed systolic heart failure (SHF)] and (2) heart failure with preserved ejection fraction (HFPEF) [also called diastolic heart failure (DHF)].

In this chapter, the epidemiology of HFREF and HFPEF has been discussed. In subsequent chapters, diagnosis, pathophysiology and management of HFREF and HFPEF have been discussed.

EPIDEMIOLOGY

The definition of HFREF is based on measurement of left ventricular ejection fraction. If the ejection fraction is 45% or less, HFREF is diagnosed. In HFPEF, left ventricular ejection fraction should be higher than 45%. For the diagnosis of heart failure based on signs and symptoms, a number of scoring systems have been proposed.[1] However, in practice and also in clinical trials, the Framingham system is most frequently used.

PREVALENCE

Prevalence is calculated by determining the number of total cases occurring in the population at risk. The 2011 American Heart Association update has reported that the prevalence of heart failure is approximately 2.4% of the adult population of the United States of America. In 2011, it was estimated that in the United States of America there were about 5.7 million people had an established diagnosis of heart failure.[2] By 2040, it is expected that approximately 10 million people will have heart failure (Tables 1 and 2).[2a] The worldwide prevalence of heart failure was estimated to be 23 millions.

The prevalence of heart failure increases sharply with age. The Framingham heart study reported the prevalence in men of

TABLE 1

Epidemiology of heart failure in the United States of America

- Estimated 5,50,000 new cases occur/year
- Estimated to rise to 7,72,000/year by year 2040
- More than 5 million Americans have heart failure
- Estimated to increase to 10 million by year 2040
- Among medicare beneficiaries, heart failure is the leading cause of hospitalization
- Cost of HF treatment is > 35 billion $ in 2007

TABLE 2

Prevalence of heart failure in the United States of America

- Heart failure is the third most prevalent cardiovascular disease
- Prevalence and age:
  20–39—less than 1%
  80 or older—about 20%
- Life time risk of developing heart failure
  20% for both women and men
- Life time risk of developing heart failure without coronary artery disease:
  Age 40—men—11.4%, women—15.4%

8/1,000 at age of 50–59 years which increased to 66/1,000 at ages 80–89 years.[3] In women, it was also 8/1,000 at age of 50–59 years and 79/1,000 at ages 80–89 years. In patients younger than 40 years, the prevalence is only 1%; in patients 80 years or older, it is 20%. The 2011 AHA update,[2] reported that in the American males the prevalence was 3%, in females 2%. In non-hispanic males, it was 2.7% and in non-hispanic females 1.8%. The prevalence is much higher in non-hispanic black males, 4.5% and in females, 3.8%. In Mexican-American males the prevalence of heart failure is 2.3% and in females 1.3%.[2] In Glasgow, Scotland, the estimated prevalence was 1.5% at ages 25–75 years.[4] The Rotterdam study reported a prevalence of HFREF of 0.7% in people at ages 55–64 years, 2.7% at 65–74 years and 13% at 75–84 years.[5] The similar rates of prevalence have been reported in other studies.[6-8] Redfield and colleagues reported a prevalence of 2.2% in the population at the age of 45 years or older. In this study, patients with both SHFand DHF were included.[9]

The lifetime risk for developing heart failure has been estimated, and it is about 20% for both men and women. In absence of coronary artery disease at age 40 years, it is 11.4% in men and 15.4% in women.[10]

It is estimated that the prevalence of heart failure in the United States will increase during next three decades. Currently, approximately 570,000 patients are diagnosed with heart failure per year, and it is estimated that the number will increase to 770,000 per year by the year 2040.[3]

There appears to be several reasons for this increase in prevalence of heart failure. The aging of the population, improvement in longevity due to salvage of a greater proportion of patients with acute coronary syndrome with the modern therapy and the increase in diabetes and obesity in the population are likely causes for the epidemic of heart failure. Along with the increase in prevalence of heart failure, the hospital admission and readmission rates have increased (Fig. 1). The increased hospital admission rates are not only due to increased frequency of advanced heart failure but also due to comorbidities (such as renal failure), electrolyte abnormalities and multiorgan systems failure.

Heart failure is the most common cause of hospital admissions in patients older than 65 years.[10] Heart failure is also the most common discharge diagnosis, and has increased by over 170% between 1979 and 2003 (Table 3).[10] The 2011 AHA update reported that in 2007, there were 990,000 patients were discharged with a diagnosis of heart failure.[2] In 1979, just over 1 million patients were admitted to hospital for heart failure; in 2004, it was close to 4 million. More than 80% of patients were 65 years of age or older.[11,12] The hospital readmission rates are also high. Approximately 20% of patients are readmitted within 30 days, and 50% within 6 months. The readmissions are also associated with high mortality (Fig. 2). The mortality of patients requiring readmissions is about 12% at 30 days, 33% at 12 months and 50% at 5 years.[13]

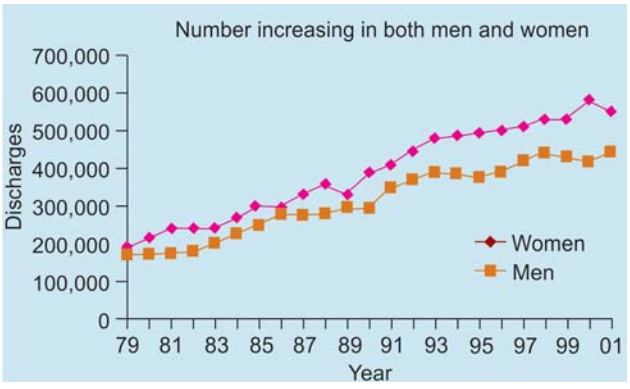


FIGURE 1: The increasing rates of hospital admission in women and men with discharge diagnosis of heart failure are illustrated. (*Source:* Modified from American Heart Association)

TABLE 3

Rate of hospitalizations, mortality and morbidity of heart failure in the United States of America

Prevalence
• Increasing rate of hospitalizations: 1979—1,274,000 2004—3,860,000
• More than 80% of patients were among 65 years or older
Prevalence and etiology
• Mortality: Nearly 50,000 annually
• Morbidity: 6.5 million days of hospital stay/year

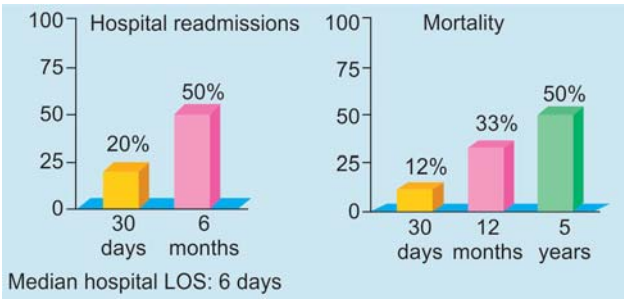


FIGURE 2: The readmission rates in heart failure and the prognosis of patients requiring readmission are illustrated. (*Source:* Modified from Jong P, et al. Arch Intern Med. 2002;162:1689-94)

The costs of management of heart failure also increase with number of hospitalizations. The total direct costs of heart failure are primarily related to number of hospitalizations and the length of hospital stay. In many developed countries, the cost of heart failure management is between 1% and 2% of the total health care budget.[14] In the United States, the costs of care for heart failure exceeded 35 billion dollars in 2007.

The prevalence of HFPEF (diastolic heart failure) appears to be similar to that of HFREF (systolic heart failure). Approximately 50% of patients with overt heart failure have preserved left ventricular ejection fraction. However there is a considerable variability in the reported prevalence of heart failure with preserved left ventricular ejection fraction, and it ranges between 13% and 74%.[15] Similar to HFREF, the prevalence of HFPEF increases with age. It has been estimated that the prevalence in patients younger than 50 years of age is approximately 15%, between 50 and 70 years 33% and older than 70 years 50%.[16] In Medicare-eligible patients hospitalized with the diagnosis of heart failure, 34% had preserved left ventricular ejection fraction.[17] The HFPEF is more common in women than in men. A multivariate analysis has reported that

the prevalence of HFPEF in women twofold higher than that in men (odds ratio 2.07, 95%, Confidence Interval 1.93–2.34).

INCIDENCE

Incidence is calculated with the number of patients with new onset of heart failure divided by the number of people at risk of developing heart failure.

The incidence of heart failure increases with increasing age. Over each successive decade of life the incidence almost doubles. In the Framingham study, the annual incidence of heart failure in men increased from 2/1,000 at the age 35–64 years to 12/1,000 at the age 65–94 years.[3] The lifetime risk (incidence) of developing heart failure is about 20% at all ages older than 40 years.[18]

There is controversy regarding the incidence of heart failure in relation to time. The Framingham study reported that there has been no change in the age-adjusted incidence of heart failure in men between the time periods 1950–1969 and 1990–1999. In women, there was a decline in the incidence of heart failure.[19] In another retrospective study, no change in the age-adjusted incidence of heart failure was found either in men or women between the time period of 1979 and 2000.[20] In another study, however, an increase in the age-adjusted incidence of heart failure was reported between the periods 1970–1974 and 1990–1994.[21] Among medicare beneficiaries, 65 years of age or older, the incidence of heart failure declined between 1994 and 2003. The decline was largest in people aged 80–84 years.[22]

The incidence of heart failure is lower in people of younger age. A five-year risk of developing heart failure in people 40 years of age is 0.1–0.2%.[18] In another study, a similar lower incidence of heart failure was observed in people younger than 50 years of age.[22] The 2011 AHA update reported that the incidence of heart failure in patients 45 years or older was 670,000, in males 350,000 and in females 320,000.[2]

The risk factors for developing heart failure are summarized in Table 4 and Figure 3. The conventional risk factors are age, gender, hypertension, diabetes, obesity and coronary artery disease. Insulin resistance, genetic factors and use of cardiotoxins are other risk factors that have been recognized. In patients with diabetes, the risk of developing heart failure in 10 years after the diagnosis is approximately 10% in men and 18% in women. In patients with hypertension it is 12% in men and 8% in women. In patients having a myocardial infarction approximately of 30% of men and women develop heart failure in 10 years.[23] Hypertension as a risk factor is now less common than coronary artery disease for developing heart failure (Table 5).[24,25]

TABLE 4

Risk factors for heart failure

Heart failure in the United States of America: Epidemiology
• Increasing age
• Hypertension
• Coronary artery disease
• Diabetes
• Obesity
• Insulin resistance
• Genetic factors
• Use of cardiotoxins

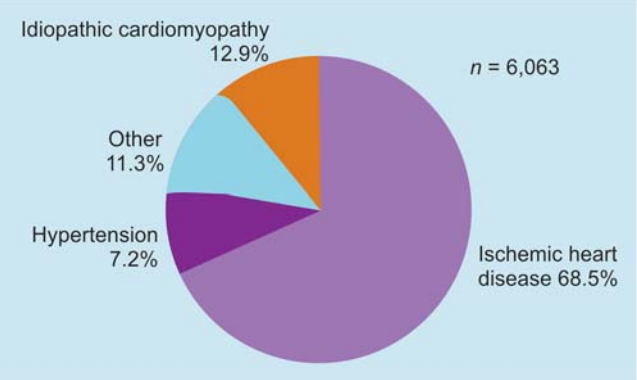


FIGURE 3: The etiology of systolic heart failure in the SOLVD registry is illustrated. The most common cause was ischemic heart disease. (*Source:* Modified from Bourassa, et al. J Am Coll Cardiol. 1993;22: 14A-19A)

TABLE 5

Risk of heart failure due to diabetes, hypertension or myocardial infarction

Over 10 years, heart failure develops in
• 10% of men
• 18% of women with diabetes
• 12% of men
• 8% of women with hypertension
• 30% of men
• 30% of women with myocardial infarction

In the studies of left ventricular dysfunction (SOLVD) registry, approximately 70% of patients had coronary artery disease and only 7% of patients had hypertension who developed SHF (Fig. 3).[24] The population attributable risk has been assessed to determine the relative contribution of the various risk factors for developing heart failure.[26] For coronary artery disease, the overall population attributable risk was 62%. It was 68% in men and 56% in women. For hypertension it was 10%, for cigarette smoking it was 17% and for diabetes it was 3%. The overweight was associated with the population attributable risk for developing heart failure of 8%. It is of interest that in patients with established heart failure the traditional risk factors appear to be associated with reduced risk of mortality which is called reverse epidemiology.[27] Newer risk factors for developing heart failure have been identified. Obesity and central adiposity,[28] high-normal albuminuria,[29] leukocytosis, particularly granulocytosis and increased levels of C-reactive protein[30] are associated with increased risk of heart failure .

RACIAL DIFFERENCES

Racial differences in the incidence of heart failure have been investigated (Table 6).[31] In the multi-ethnic study of atherosclerosis, the overall incidence rate of developing heart failure during a median follow-up of 4.0 years was 3.1/1,000 person-years. The incidence rate among African Americans, Hispanic, White and Chinese Americans were 4.6, 3.5, 2.4 and 1.0/1,000 person-years respectively. However, when hypertension and/or diabetes were included, the incidence of congestive heart failure

TABLE 6

Racial differences in the incidence of congestive heart failure

Over all incidence	3.1/1000 person-years
African American	4.6/1000 person-years
Hispanic	3.5/1000 person-years
White	2.4/1000 person-years
Chinese American	1.0/1000 person-years

TABLE 7

Gender differences in the incidence of congestive heart failure

Heart failure in the United States of America—Epidemiology

Age adjusted incidence rate 1/1000 person-years:

- Caucasian men: 6.0
- African-American men: 9.1
- Caucasian women: 3.4
- African women: 8.1

Lowest incidence is in Caucasian women

in African Americans were not statistically different compared to other ethnic population. The socioeconomic status also contributed to the higher incidence of congestive heart failure in the African Americans. The relative proportion of DHF was also higher in African Americans.

GEOGRAPHIC DIFFERENCES

The information about the prevalence or incidence of heart failure in the Asians or Southeast Asians is scarce. However as the incidence of coronary artery disease in these countries are increasing, it is very likely that the prevalence and incidence of heart failure resulting from coronary artery disease are also high. Furthermore, hypertension is very common in these countries and, therefore, hypertension-related heart failure is likely to be common as well.

It has been reported that in Chinese in China, hypertension is the predominant risk factor for developing heart failure.[32]

In Japan, the characteristics and outcomes of HFPEF and HFREF were compared by using the national registry database. This was a prospective observational study and 2,675 patients were enrolled. The average duration of follow-up was 2.4 years. The patients with HFPEF were more likely to be older female with a higher frequency of hypertension than coronary artery disease. The patients with HFREF were more likely to be male, younger and with a higher frequency of coronary artery disease than hypertension. The risk of mortality and rehospitalization rates were similar in patients with HFPEF and HFREF.[33]

In Pakistan, the prognosis of new or recent onset of HFREF was evaluated in a relatively small number (196) of patients. These patients were younger and had higher frequency of prior ischemic heart disease. During a follow-up period of 379 days, 27.5% of patients died and 52% had combined event of death or rehospitalization.[34]

In Singapore, the prognosis of patients with HFREF was evaluated in 225 patients hospitalized for heart failure. Malay and Indian patients had higher incidence of heart failure compared to Chinese. Ischemic heart disease was the most common cause. During 5 years of follow-up, the mortality was 67.5% and female gender, older age, renal failure and severe heart failure were important risk factors.[33]

In Malaysia, the prevalence and the risk factors of heart failure were assessed from acute medical hospital admissions of 1,435 patients in a busy hospital in Kuala Lumpur. The prevalence of heart failure was 6.7% and coronary artery disease was the major risk factor. In Malaysian Indians, diabetes was very prevalent.[34]

In Harrow, United Kingdom, the prevalence and the etiology of left ventricular systolic dysfunction among 1,392 patients who were 45 years of age or older were assessed. The incidence of probable and definite left ventricular systolic dysfunction was 5.5% and 3.5% respectively. The prevalence was similar in white Caucasians and South Asians.[35]

In Leicester, United Kingdom, the prognosis and predictive factors were studied among 176 South Asians and 352 age- and sex-matched white Caucasians with new onset of heart failure. The South Asians and white Caucasians had similar rates of coronary heart disease, but the South Asians had more hypertension, diabetes and preserved left ventricular ejection fraction. During follow-up, the mortality in South Asians was 41.2% and in white Caucasians 47.4%. At the time of first hospital admission, heart failure was less severe in South Asians compared to that in white Caucasians.[36]

Geographic variation in heart failure hospitalization has been recognized[37] Number of primary care physicians per population, regional income level have been associated with rate of hospitalization for the treatment of heart failure.[38]

GENDER DIFFERENCES

The gender differences in the incidence of heart failure have been studied.[39] The age-adjusted incidence/1,000 person-years was highest in African Americans men, 9.1, followed by African women, 8.1 (Table 7). The incidence in Caucasian men was 6.0, and 3.4 in Caucasian women. Thus, the lowest incidence was in the Caucasian women in this study.[40]

In the Malmö preventive project study, 33,342 heart failure subjects were enrolled between 1974 and 1992 to assess the gender differences in the incidence of heart failure.[41] In this community-based study, women had lower risk of developing heart failure than men. The incidence of all cause mortality and heart failure-related death was also lower in women than in men during follow-up of over 20 years.

In patients hospitalized with heart failure, in general women receive less appropriate hospital discharge instructions about follow-up management plans. The length of hospital stay is also longer in women than in men. Older patients, however, are less likely to receive guideline-recommended therapies irrespective of gender, and have higher risks of adverse outcomes.[42]

In patients hospitalized with decompensated heart failure, the incidence of HFPEF and reduced ejection fraction are very similar. The patient with HFPEF is more common in elderly women, and hypertension is more common etiology. Coronary artery disease is more common in HFREF. The incidence of diabetes and atrial fibrillation was slightly higher in HFPEF (Table 8).[43]

TABLE 8

Demographic differences between systolic (HFREF) and diastolic (HFPEF) from the ADHERE registry

ADHERE—All enrolled discharges		
Profile	*SHF*	*DHF*
	(59,523)	(50,497)
EF	< 40%	> 40%
Age	69.9	74.2*
Female	39%	62.2%*
CAD	63%	54%*
Diabetes	42%	46%*
AF	29%	33%*

*< 0.0001
(Abbreviations: EF: Ejection fraction; CAD: Coronary artery disease; AF: Atrial fibrillation)

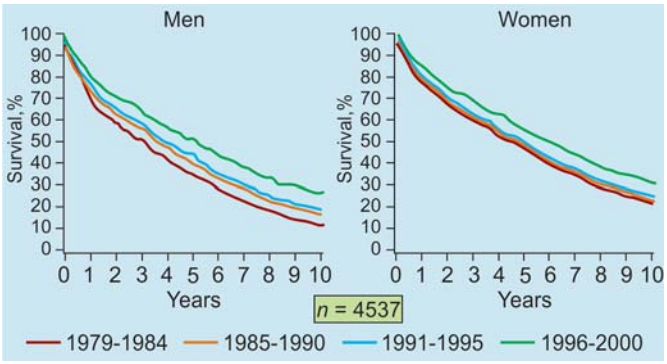
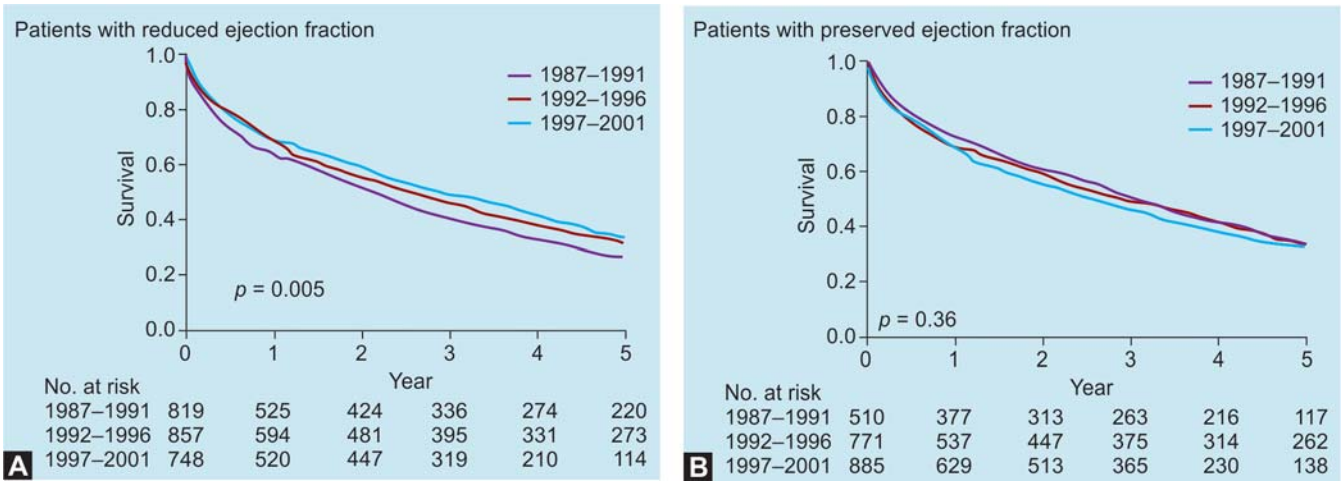


FIGURE 4: The mortality in men and women in relation to time. (*Source:* Published with permission from Roger, et al. JAMA. 2004;292:344-50)



FIGURES 5A AND B: The mortality in patients with (A) reduced ejection fraction and (B) preserved ejection fraction. (*Source:* Modified from Owan, et al. N Engl J Med. 2006;355:251-9)

SECULAR TRENDS

Very limited information is available regarding the secular trends in the incidence of heart failure. The mortality in men after the diagnosis of heart failure was approximately 70% between 1979 and 1984, 60% between 1985 and 1990 and 50% between 1991 and 1995, and 40% between 1996 and 2000 (Fig. 4).[44] In women it was 60% between 1979 and 1981, 55% between 1985 and 1990, 50% between 1991 and 1995, and 40% between 1996 and 2000.

In patients with HFREF, the 5-years mortality between 1987 and 1991 was approximately 70%, between 1992 and 1996 and between 1997 and 2001, 60% (Fig. 5A).[45] In patients with preserved ejection fraction, the mortality was approximately 60% during the same periods (Fig. 5B).[46]

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Chapter 69

Heart Failure: Diagnosis

Kanu Chatterjee

Chapter Outline

- Analysis of Symptoms
- Physical Examination
- Electrocardiogram
- Chest Radiograph
- Echocardiography
- Radionuclide Ventriculography
- Cardiac Magnetic Resonance
- Cardiac Tomography
- Routine Laboratory Tests
- Biomarkers
- Exercise Tests
- Six-minute Walk Test
- Coronary Arteriography
- Myocardial Ischemia
- Endomyocardial Biopsy
- Genetics Studies

The diagnosis of heart failure, irrespective of its etiology, should begin with taking history followed by clinical examination, and noninvasive and if required invasive tests.

ANALYSIS OF SYMPTOMS

Dyspnea is the most common presenting symptom of heart failure. Thus, it is desirable to enquire about the features of dyspnea that suggest heart failure. The typical history of paroxysmal nocturnal dyspnea is the characteristic of cardiac dyspnea. Orthopnea and exertional dyspnea have less diagnostic value. The Framingham criteria for diagnosis of heart failure are summarized in Table 1.[1]

The sensitivity and specificity of exertional dyspnea have been reported to be 100% and 17% respectively. The sensitivity and specificity of paroxysmal nocturnal dyspnea were 39% and 80% and of orthopnea 22% and 74%.[2] In another study of 1,306 patients with left ventricular ejection, a fraction of less than 40% undergoing cardiac catheterization, the sensitivity and specificity of symptoms of heart failure were determined.[3] The sensitivity, specificity and positive predictive value of exertional dyspnea were 66%, 52% and 23% respectively; of nocturnal dyspnea 33%, 76% and 26%; and those of orthopnea were 21%, 81% and 2% respectively.

In relatively elderly patients with documented left ventricular systolic dysfunction by echocardiography, exertional dyspnea and history of myocardial infarction or angina were associated with a higher independent predictive value for the diagnosis of left ventricular systolic dysfunction. However these symptoms were neither sensitive nor specific.[4]

Chest pain is an uncommon symptom of heart failure. However typical angina and atypical chest pain are present in some patients with heart failure with or without coronary artery disease.[5]

Patients with chronic heart failure do not usually present with history of frank syncope. However, in patients with previously undiagnosed left ventricular systolic dysfunction, syncope resulting from ventricular tachyarrhythmias may occur as the initial manifestation of heart failure. Dizziness and light headedness however are quite common and usually result from hypotension, and most frequently due to the medicines that are used for treatment of heart failure. Palpitations are also common symptoms in patients with heart failure but these symptoms are not of any diagnostic relevance.

Exertional fatigue is a common presenting symptom of patients with heart failure. However, like exertional dyspnea, it has a relatively low positive predictive value.

The other occasional symptoms of chronic heart failure are nocturnal cough, nocturia, right upper quadrant pain if

TABLE 1

Criteria of congestive heart failure—Framingham study

Major criteria
- Paroxysmal nocturnal dyspnea or orthopnea increased venous pressure > 6 cm
- Neck-vein distention
- Rales
- Cardiomegaly (circulation time > 25 sec)
- Hepatojugular reflux
- Acute pulmonary edema
- S_3 gallop

Minor criteria
- Ankle edema
- Night cough
- Dyspnea on exertion
- Pleural effusion
- Decreased vital capacity
- Sinus tachycardia (120 bpm or higher)

Major or minor criteria
- Weight loss > 4.5 kg in five days in response to treatment
- Two major or one major and two minor

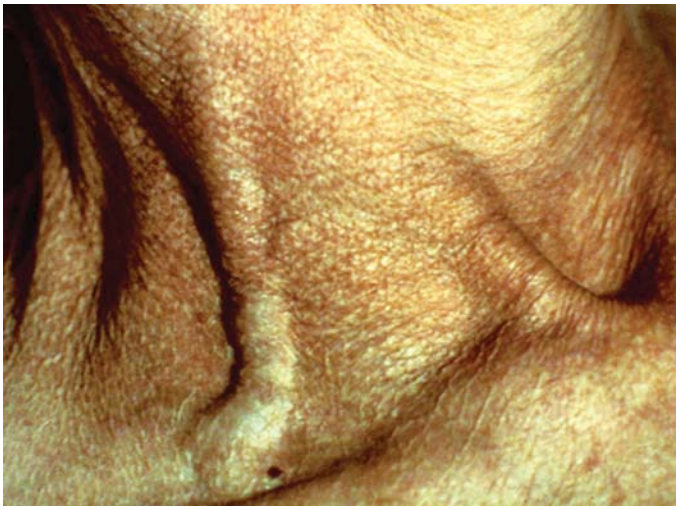


FIGURE 1: Distended right external and internal jugular veins in a patient with heart failure are illustrated

hepatomegaly is present, and disordered sleep. Anorexia is uncommon except in patients with end stage heart failure.

PHYSICAL EXAMINATION

Adequate physical examination is essential for the diagnosis of heart failure. The presence of abnormal physical findings not only establishes the diagnosis but also provides clues regarding the etiology of heart failure. Elevated jugular venous pressure has a specificity of 97%, sensitivity of 10% and a positive predictive value of 2% (Fig. 1). Lower extremity edema has a specificity of 99%, sensitivity of 13% and the positive predictive value of 6%. The S_3 gallop sound in patients older than 45 years has a specificity of 95%, sensitivity of 31% and a positive predictive value of 61%.[3] Thus the presence of an S_3 gallop sound has a significant diagnostic relevance. An S_3 gallop sound is associated with increased left ventricular end diastolic pressure, and increased levels of B-type Natriuretic Peptide (BNP).[6] An S_3 gallop sound has been reported to indicate left atrial pressure exceeding 20 mm Hg and left ventricular end diastolic pressure greater than 15 mm Hg. However considerable interobserver variability was observed in detection of S_3 gallop sound.[7,8]

In a phonocardiographic study[9] the hemodynamic correlation between gallop sounds and directly measured left ventricular end-diastolic pressure were determined. The sensitivity of an S_3 was 40–50% but specificity was 90%. It was also highly specific (90%) for elevated serum BNP.[10] A gallop rhythm almost always indicates heart failure with reduced ejection fraction (HFREF) due to dilated cardiomyopathy with increased end systolic and end diastolic volumes and end diastolic pressure. Presence of pulsus alternans is diagnostic of systolic heart failure (HFREF) (Fig. 2). Similarly a positive hepatojugular reflux is also very suggestive of systolic heart failure (HFREF) (Fig. 3).[7]

In patients with suspected or established heart failure, assessment of the character of the left ventricular apical impulse is useful to determine whether it is normal or sustained. A normal apical impulse is almost always associated with normal left ventricular ejection fraction, whereas a sustained impulse indicates reduced ejection fraction or severe left ventricular hypertrophy (Figs 4A to C). The hyperdynamic apical impulse is also associated with normal ejection fraction. Cardiac enlargement should be suspected if the apical impulse is displaced laterally past the left midclavicular line. A palpable right ventricular heave (left parasternal lift) usually indicates right ventricular failure and may be present in patients with advanced heart failure (See the chapter "Physical Examination").

The presence of pulmonary crackles during auscultation may indicate pulmonary venous congestion; however, in absence of other findings of heart failure pulmonary crackles have very little diagnostic value. The sensitivity, specificity and positive predictive value were reported to be 13%, 99% and 6% respectively.[3]

The signs of pulmonary arterial hypertension, such as an increased intensity of the pulmonic component of the second heart sound (P_2), may be detected during auscultation. It can be present both in patients with systolic or diastolic heart failure. Auscultatory signs of mitral regurgitation, when detected, usually indicate systolic heart failure. Tricuspid regurgitation is usually secondary to pulmonary hypertension and may be

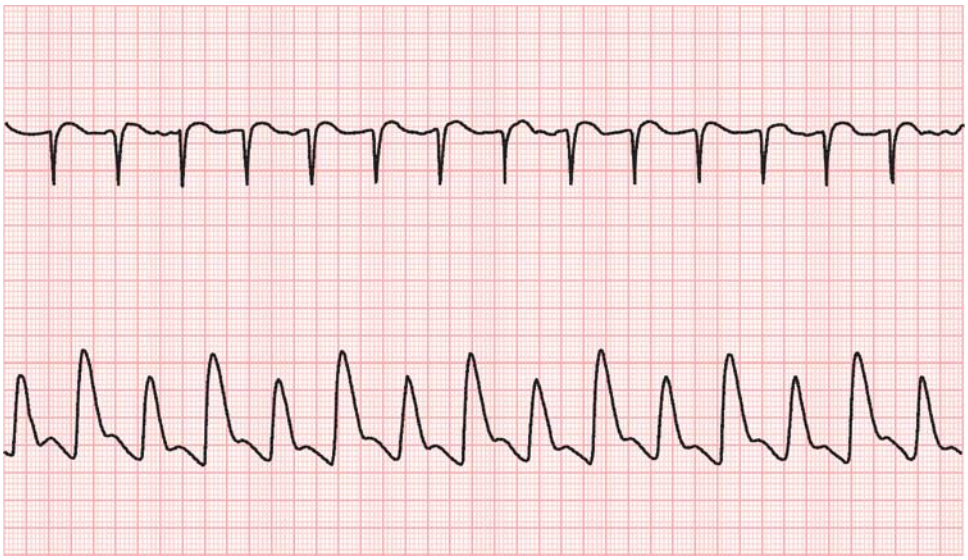


FIGURE 2: Direct arterial pressure recording showing pulsus alternans in a patient with systolic heart failure (HFREF) is illustrated

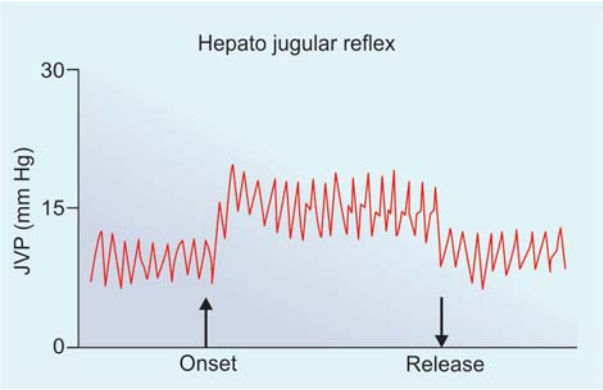


FIGURE 3: Schematic illustration of positive hepatojugular reflux which usually indicates systolic heart failure (HFREF). (*Source:* Published with permission from Ewy GA. Ann Intern Med. 1998;109:456)

TABLE 2

New York heart association functional classification

1. No limitations on physical activity, no symptoms with ordinary activities
2. Slight limitation, symptoms with ordinary activities
3. Marked limitation, symptoms with less than ordinary activities
4. Severe limitation, symptoms of heart failure at rest
Symptoms: Fatigue, dyspnea, palpitations, or angina

present both in systolic and diastolic heart failure (see the chapter "Physical Examination").

Marked loss of weight (cardiac cachexia), if present, indicates end stage heart failure. Similarly a marked elevation of systemic venous pressures, ascites and peripheral edema despite diuretic treatments usually indicates end stage refractory heart failure.

In patients with advanced heart failure, signs of low cardiac output often can be detected. Sinus tachycardia, narrow pulse pressure, and cool, clammy and pale skin indicate low cardiac output. The cool, clammy and pale skin results from reflex adrenergic stimulation and peripheral vasoconstriction in response to low cardiac output. Peripheral cyanosis also suggests low cardiac output and impaired tissue perfusion.

During clinical evaluation, it is highly desirable to assess the severity of symptoms and the stages of heart failure. To assess the functional class, the New York Heart Association (NYHA) classification is used (Table 2). NYHA functional class I indicates asymptomatic patients; class II when symptoms develop during more than usual activity. In NYHA class III

TABLE 3

Heart failure: new classification not based on the severity of symptoms

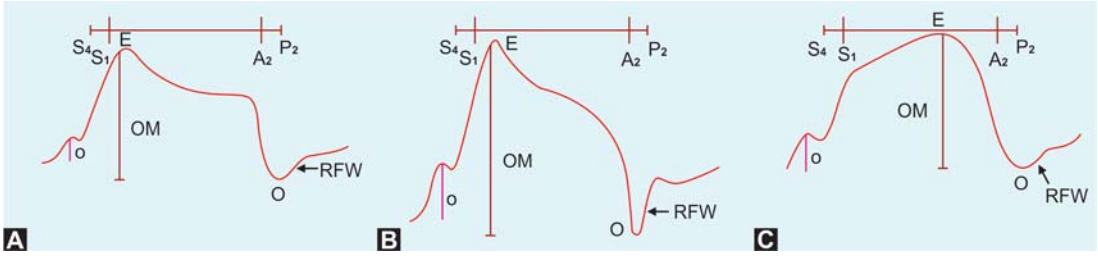
Stage A: At high risk for HF but without structural heart disease or symptoms of HF
Stage B: Structural heart disease but without symptoms of HF
Stage C: Structural heart disease with prior or current symptoms of HF
Stage D: Refractory HF requiring specialized interventions

patients, the symptoms develop during less than usual physical activity; in patients in NYHA IIIb, the symptoms develop with minimal activity. NYHA class IV patients are symptomatic at rest. Determination of functional class is important to assess prognosis. For the diagnosis of the potential etiology and the stages of heart failure the recommendations in the ACC/AHA guidelines are employed (Table 3).[5] In patients in stage A, there are risk factors for developing heart failure without structural heart disease. In stage B patients, there is asymptomatic left ventricular systolic dysfunction. Stage C patients are symptomatic heart failure and on recommended treatments for heart failure. Stage D patients have refractory heart failure who are candidates for heart transplantation and/or assist devices.

The noninvasive as well as invasive tests, if required, should also be considered during the diagnostic work up of patients with suspected heart failure.

ELECTROCARDIOGRAM

An electrocardiogram should be obtained in all patients. It may reveal arrhythmias, evidence of previous myocardial infarction, and left ventricular hypertrophy. The electrocardiographic evidence of old myocardial infarction with or without changes of chronic left ventricular aneurysm usually indicates systolic heart failure (Fig. 5). The evidence of left ventricular hypertrophy may be present in both systolic and diastolic heart failure (Figs 6 and 7). In elderly patients, however, electrocardiographic abnormalities of left ventricular hypertrophy are frequently present and their positive predictive value is low.[11] A completely normal electrocardiogram is very uncommon in patients with chronic heart failure.[11] A normal electrocardiogram has been reported to have a negative predictive value of 98%.[2] The electrocardiogram may reveal atrial fibrillation with rapid ventricular response which may be the etiology of heart failure (tachycardic cardiomyopathy) or the case of worsening heart failure. The electrocardiogram is useful for the diagnosis of myocardial ischemia which may cause dyspnea similar to



FIGURES 4A TO C: Schematic illustrations of a normal (A), hyperdynamic (B) and sustained (C) left ventricular apical impulse. (Abbreviations: OM: Outward movement; A_2: Aortic component of the second heart sound; P_2: Pulmonic component of the second heart sound; O: Opening of the mitral valve; RFW: Rapid filling wave; A: A wave; S_1: First heart sound; S_4: Fourth heart sound; E: E point). The illustrations represent apex cardiogram

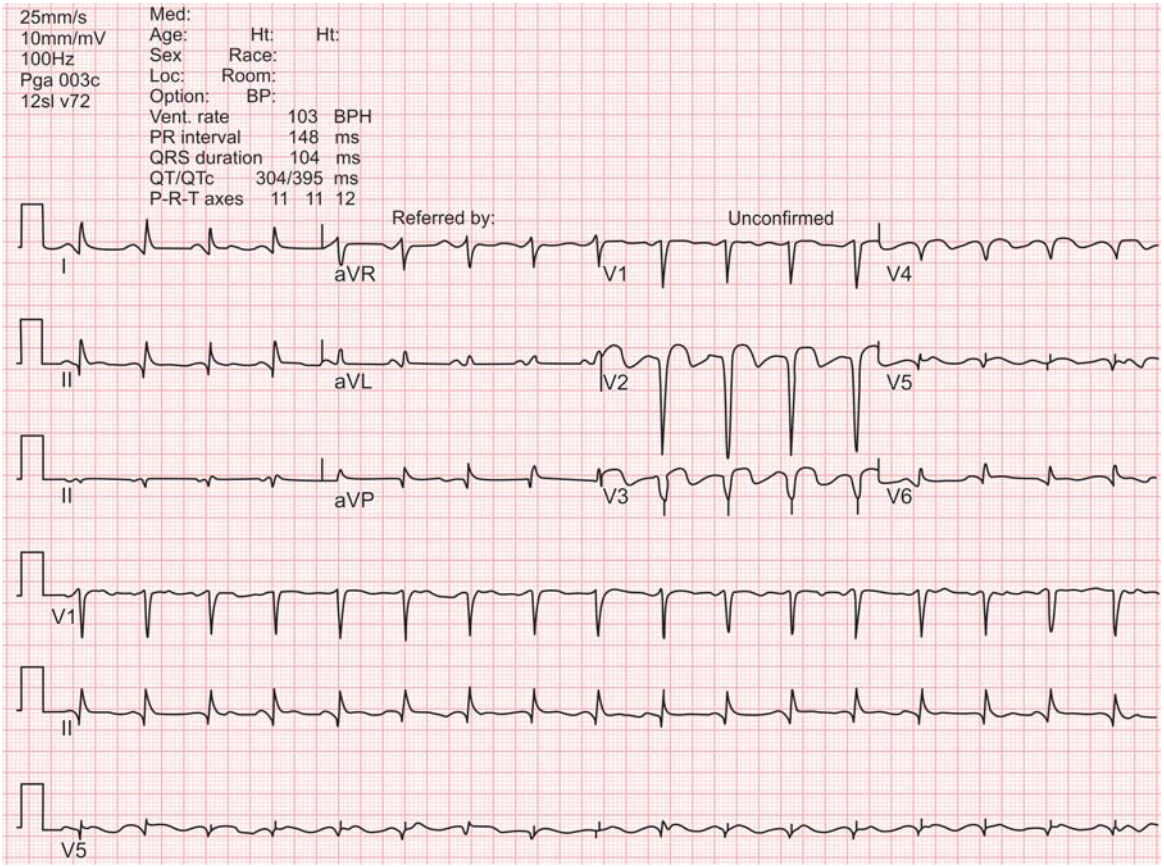


FIGURE 5: The electrocardiographic features of chronic left ventricular aneurysm are illustrated. Anterolateral myocardial infarction with Q waves in leads V2-V6 with persistent ST segments elevations are present. Localized slurring of ORS in V5 lead suggests peri-infarction block of "GRANT"



FIGURE 6: The electrocardiographic features of concentric left ventricular hypertrophy are illustrated. Left ventricular hypertrophy with repolarization abnormalities and normal frontal plane QRS axis are evident

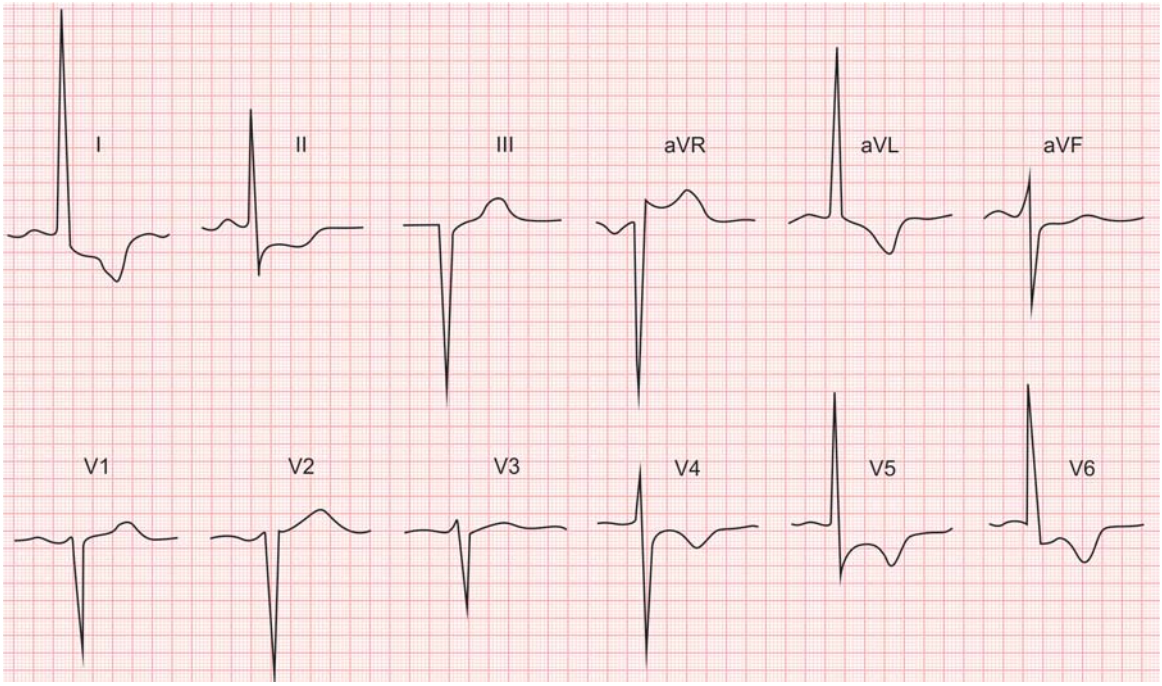


FIGURE 7: The electrocardiographic features of eccentric left ventricular hypertrophy are illustrated. Left ventricular hypertrophy with repolarization changes and left axis deviation of QRS complex are evident

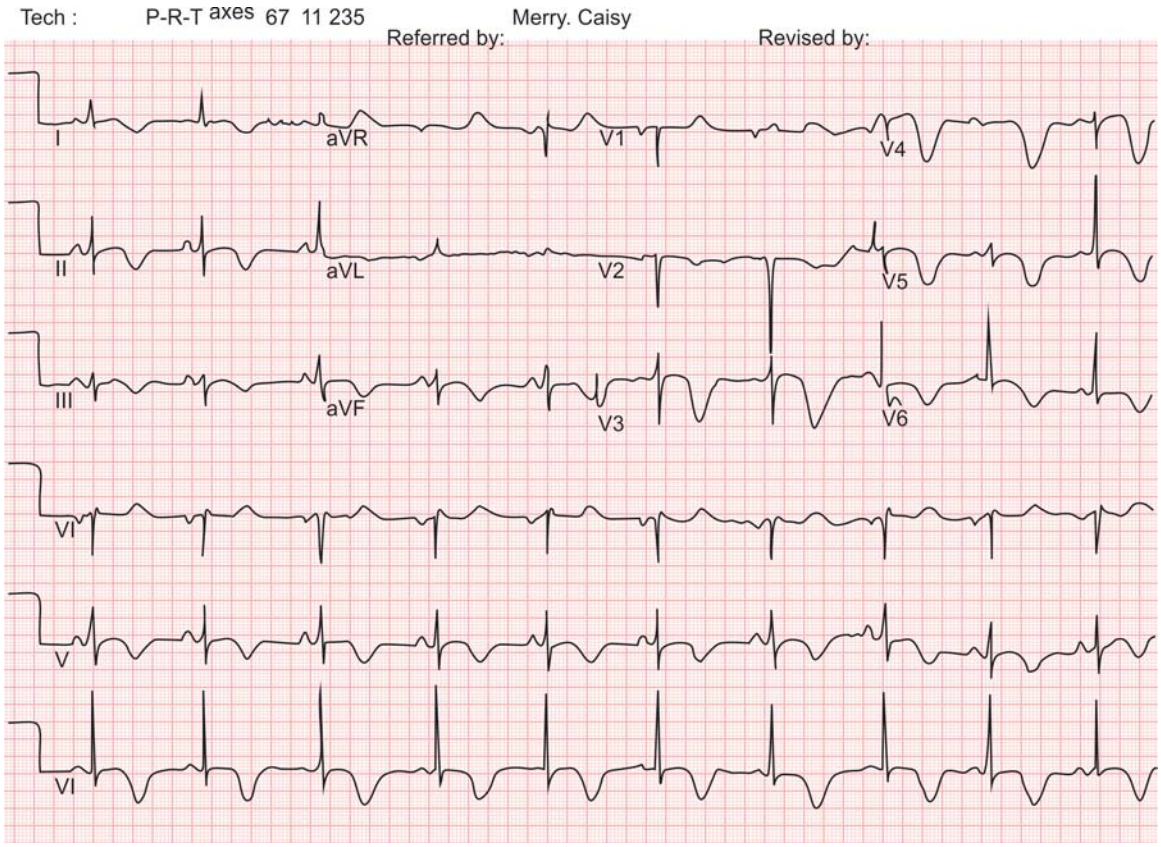


FIGURE 8: The electrocardiographic features of apical hypertrophic cardiomyopathy showing increased QRS voltage in lateral precordial leads with giant T wave inversions

heart failure. In patients with systolic heart failure electrocardiogram should be performed to detect the presence of left bundle branch block to decide whether chronic resynchronization treatment is necessary.

Electrocardiograms may reveal uncommon causes of heart failure such as apical hypertrophic cardiomyopathy (Fig. 8). The characteristic electrocardiographic features in this condition are large QRS voltage in the lateral precordial leads with

TABLE 4

A few causes of "giant T wave" inversions are summarized

- Intermittent left bundle branch block
- Post-pacing T wave changes (cardiac memory, Chatterjee syndrome)
- Post ablation of accessory pathway
- Subarracnoid hemorrhage
- Apical hypertrophic cardiomyopathy
- Hypertrophic obstructive cardiomyopathy
- Markedly prolonged QT
- Post Stokes-Adams-Morganni syndrome
- Post-right coronary artery contrast injection

deep T Wave inversions (giant T wave inversions). It should be appreciated that heart failure is much less common in apical hypertrophic cardiomyopathy than in hypertrophic obstructive cardiomyopathy. Giant T wave inversions may also be observed in hypertrophic obstructive cardiomyopathy. The causes of giant T wave inversions are summarized in Table 4.

CHEST RADIOGRAPH

In patients with suspected heart failure a plain chest radiograph should be obtained. The diagnosis of heart failure can be established if the radiologic findings of hemodynamic pulmonary edema are present. However, even in patients with decompensated chronic heart failure, the chest radiograph may be normal. The radiologic findings of hemodynamic pulmonary edema, such as prominent upper lobe vessels, perihilar haziness and Kerley's B lines, may be absent.

Cardiomegaly (cardiothoracic ratio of > 50%), left atrial enlargement, pleural effusions and right ventricular enlargement in patients with ejection fraction of 40% or lower identified patients with pulmonary capillary wedge pressure of less than 15 mm Hg from those patients with pulmonary capillary wedge pressure between 15 mm Hg and 24 mm Hg, but failed to identify patients with higher than 24 mm Hg (Fig. 9).[12] The usefulness of the chest radiograph for the diagnosis of increased pulmonary venous pressure and reduced left ventricular ejection fraction has been performed.[13,14] The pulmonary vascular redistribution and cardiomegaly were the best predictors of increased left ventricular diastolic pressure and reduced ejection fraction respectively. In a multicenter study of 880 patients, alveolar edema, interstitial edema and pulmonary vascular redistribution had a specificity of greater than 90% for the diagnosis of heart failure and cardiomegaly had a sensitivity of greater than 50%. However, even in patients with decompensated chronic heart failure, the chest radiograph may be negative and may not show evidence of heart failure.[15] In patients with chronic systolic heart failure, frank pulmonary edema can also occur which indicates hydrostatic pressure is considerably higher than the oncotic pressure (Fig. 10).

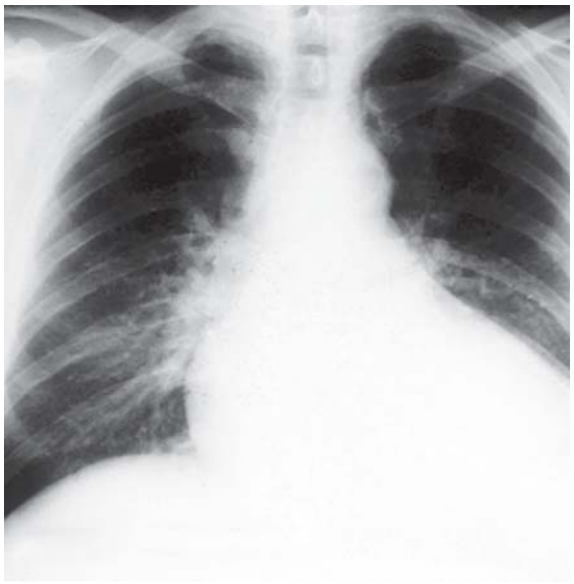


FIGURE 9: The chest radiograph of a patient with chronic systolic heart failure is illustrated. Cardiomegaly, left atrial enlargement and redistribution of pulmonary vascular distributions are evident. It is to be noted that despite a marked increase in pulmonary capillary wedge pressure there was no radiologic evince of florid pulmonary edema

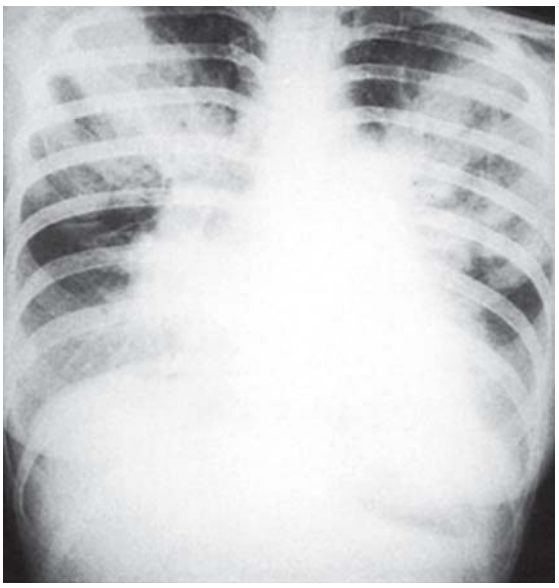


FIGURE 10: In a patient with chronic systolic heart failure frank pulmonary edema can occur which indicates pulmonary venous pressures are higher than 25 mm Hg

Evaluation of the character of the left ventricular apical impulse may be helpful to assess left ventricular ejection fraction. A sustained left ventricular apical impulse usually indicates reduced left ventricular ejection fraction provided the causes of severe left ventricular hypertrophy can be excluded. A displaced left ventricular apical impulse has a high sensitivity, specificity and positive and negative predictive values for the diagnosis of systolic heart failure.[2]

ECHOCARDIOGRAPHY

In all patients with suspected or established heart failure a transthoracic echocardiogram should be obtained. Echocardiography is the preferred method for assessment of cardiac dysfunction.[16] The guidelines recommend that echocardiography is appropriate for evaluation of cardiac dyspnea and other symptoms of heart failure.[16]

Echocardiography is less expensive, less time consuming and can easily be obtained. It is indeed should be considered as the initial noninvasive imaging test of choice. Echocardiography is useful to distinguish between systolic and diastolic heart failure.

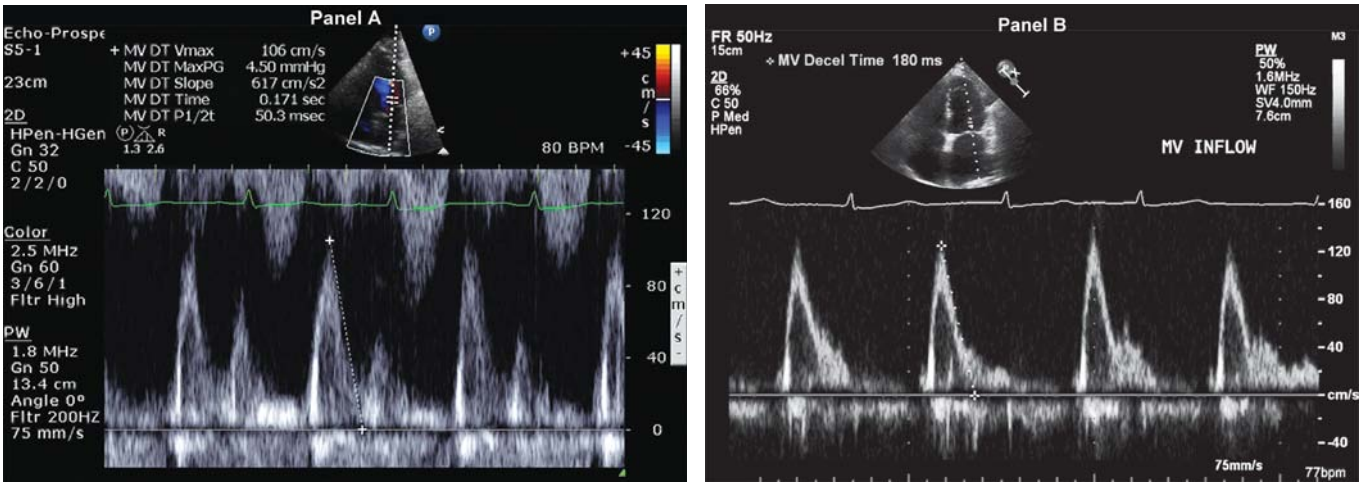


FIGURE 11: Transthoracic echocardiogram of a patient with systolic heart failure due to dilated cardiomyopathy is illustrated (Panel A and B). The left ventricle is dilated and its wall appears thinner than normal

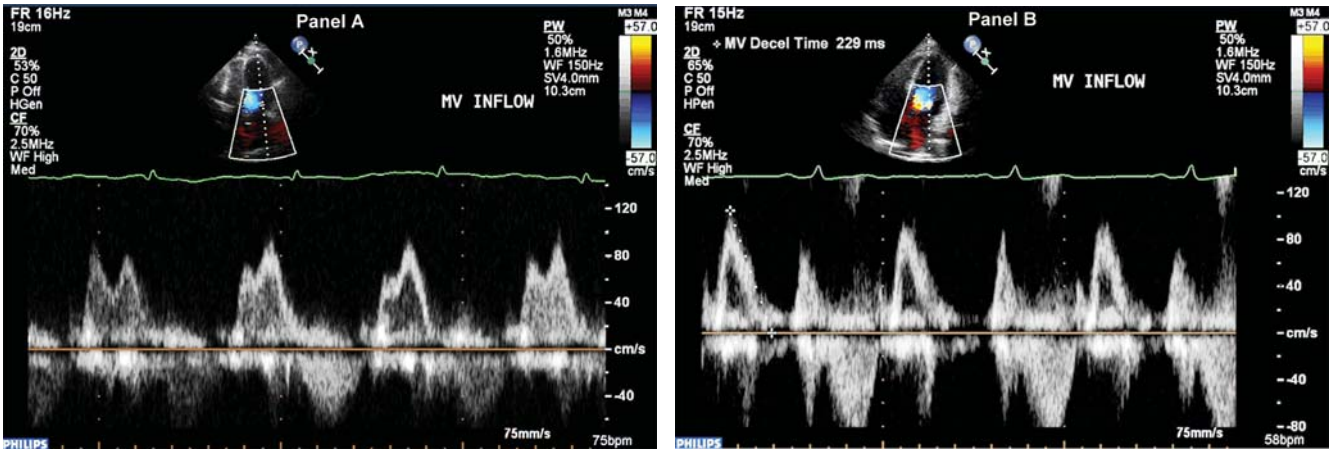


FIGURE 12: Transthoracic echocardiogram of a patient with diastolic heart failure is illustrated. The left ventricular cavity size is normal and its wall thickness is increased. Doppler echocardiographs show dominant "A" wave. Panel B shows normal transmitral flow pattern

In systolic heart failure left ventricle is dilated, end-diastolic and end systolic volumes are increased and the ejection fraction is reduced (Fig. 11). An ejection fraction of less than 45% by echocardiography is used for the diagnosis of systolic heart failure. Left ventricular ejection fraction of 45% or greater is used for the diagnosis of diastolic heart failure. In diastolic heart failure left ventricular size is normal and its wall thickness is increased (Fig. 12). Atrial enlargements can be present in both systolic and diastolic heart failure.

Doppler echocardiography is essential to assess left ventricular diastolic function. An early left ventricular diastolic dysfunction is characterized by a decrease in peak transmitral E-velocity, an increase in atrial-induced A-velocity and a decrease in E/A ratio. The early abnormal filling pattern is related to impaired left ventricular relaxation. In patients with advanced heart failure, the "restrictive filling pattern" is observed. A marked increase in E/A ratio with a short E-deceleration time is the major Doppler echocardiographic features of "restrictive filling pattern" (Fig. 13). The abbreviated duration of E wave velocity is related to elevated left ventricular end-systolic pressure and a rapid decrease in the transmitral pressure gradient during left ventricular filling.[17] The moderate left ventricular diastolic dysfunction is characterized by normal E/A ratio—"the pseudo-normalized filling pattern." This pattern can be distinguished from normal filling pattern by demonstrating the reduced E-velocity by Tissue Doppler Imaging[18] (see the chapter "Echocardiography and Doppler Echocardiography"). It should be appreciated that the abnormal left ventricular transmitral filling patterns can be present in both systolic and diastolic heart failure.

Echocardiography is also essential noninvasive test for evaluation of heart failure due to valvular heart disease. The signs and symptoms of heart failure in valvular heart disease may be similar to those of primary systolic or diastolic heart failure (Figs 14 and 15). The echocardiography is also essential for diagnosis of heart failure due to hypertrophic cardiomyopathy.

RADIONUCLIDE VENTRICULOGRAPHY

Radionuclide ventriculography can be used to assess left ventricular volumes and end ejection fraction. The advantage of this technique is its independence of geometric assumption for calculation of ventricular volumes. This technique can also

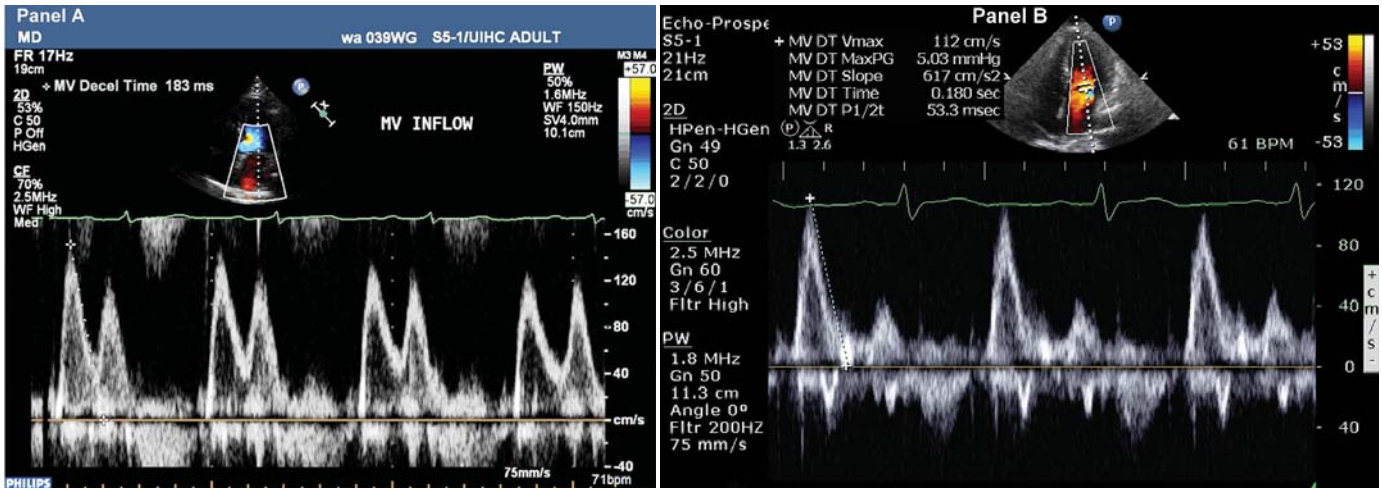


FIGURE 13: Doppler echocardiography of a patient with systolic heart failure is illustrated. It shows pseudonormalization of transmitral flow pattern

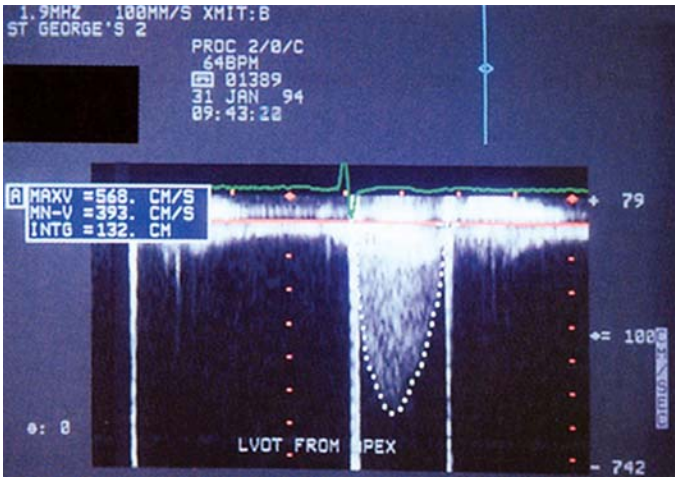


FIGURE 14: Doppler echocardiography in a patient with severe aortic valve stenosis

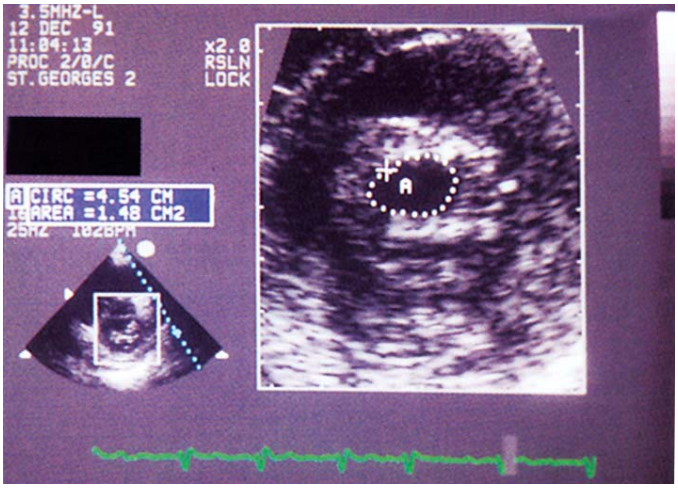


FIGURE 15: Transthoracic echocardiography in a patient with severe mitral stenosis showing markedly reduced mitral valve orifice (with permission)

be used to assess diastolic function by determining time to filling rate.[19] Radionuclide ventriculography, however, is infrequently employed in clinical practice for evaluation of patients with heart failure.

CARDIAC MAGNETIC RESONANCE

Cardiac magnetic resonance (CMR) imaging can also be used to assess left ventricular volumes and ejection fraction (Fig. 16).[20,21] In patients with systolic and diastolic heart failure the left ventricular volumes, size and ejection fraction can be determined by CMR. With the use of contrast agents such as gadolinium the other morphologic changes such as left ventricular mass and magnitude of fibrosis can be more accurately assessed by this technique. The CMR angiography is being also used for the detection of obstructive coronary artery disease. In presence of heavily calcified coronary artery segments, CMR imaging is a better noninvasive technique than computed tomography, as the images are not interfered by the presence of calcium.[22] It can be used to assess pericardial thickness to distinguish between constrictive pericarditis and the restrictive cardiomyopathy (Fig. 17) (see the chapter "Cardiac Magnetic Resonance").

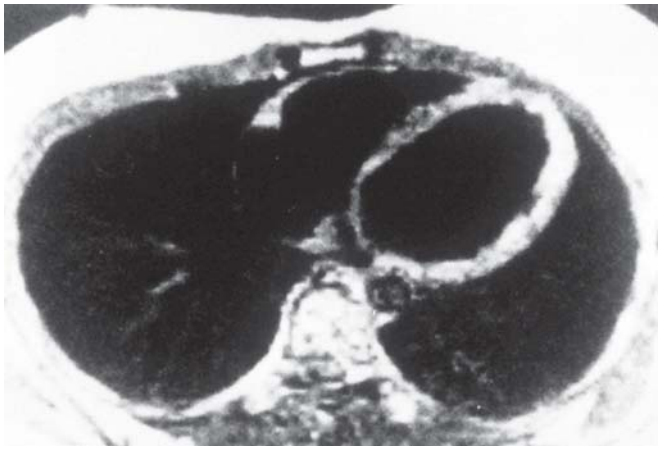


FIGURE 16: Cardiac magnetic resonance image of a patient with systolic heart failure is illustrated. The left ventricle is dilated and its wall is thin

CARDIAC TOMOGRAPHY

The electron beam computed tomography (EBCT) is useful for the diagnosis of presence of coronary artery calcium. A high coronary calcium score is associated with a greater likelihood

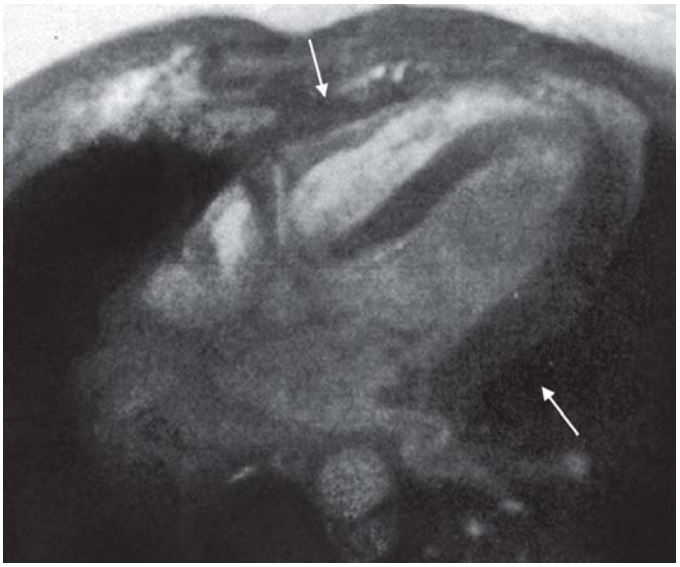


FIGURE 17: Cardiac magnetic resonance image of a patient with constrictive pericarditis is illustrated (spin-echo; horizontal long axis). The fibrous calcified nature of the pericardium is evident. (*Source:* Klein AL, Scalia GN)[23]

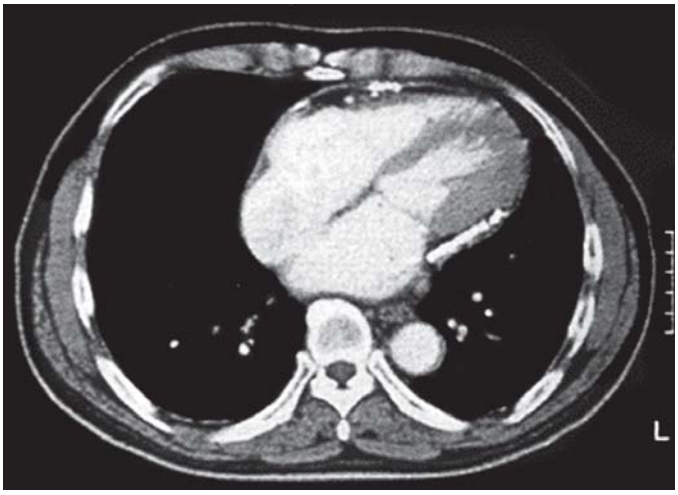


FIGURE 18: Computed tomographic image of a patient with constrictive pericarditis is illustrated. The calcium in the pericardium is evident

of atherosclerotic coronary artery disease. Coronary artery calcium detected by multidetector computed tomography (MDCT) also suggests coronary artery disease. However, in presence of coronary artery calcium, the specificity is reduced. The specificity is reduced from 86% to 53% for detection of 50% or greater degree of coronary artery stenosis with calcium scores of 400 or less versus greater than 400 Agatston units.[24-26] The contrast enhanced multislice computed tomographic coronary angiography is being increasingly used not only for detection of presence of coronary artery disease but also for diagnosis of ischemic and nonischemic dilated cardiomyopathy.[27] The contrast CT can be used for distinguishing between restrictive cardiomyopathy and constrictive pericarditis (Fig. 18) (see the chapter "Cardiac Computed Tomography").

ROUTINE LABORATORY TESTS

During initial work up of patients with suspected or established heart failure, blood tests should include a complete blood count, serum electrolytes, blood urea nitrogen and creatinine. Presently the creatinine clearance to assess glomerular filtration rate is automatically provided by the laboratory. It provides an estimation of renal function. Routine blood count is done to exclude significant anemia which can exacerbate heart failure. Renal failure can also exacerbate heart failure.

Liver function or thyroid function tests do not need to be routinely performed. However, in special circumstances such as in patients taking amiodarone, liver function and thyroid functions should be performed to exclude its toxicity. Lipid profiles and blood sugar levels should also be determined in the appropriate patients.

BIOMARKERS

A number of biomarkers can be elevated in heart failure (Table 5). Neurohormones including natriuretic peptides, biomarkers resulting from cardiac injury, biomarkers related to cardiac remodeling and oxidative stress and inflammatory markers can be increased in heart failure.

Natriuretic peptide serum levels, particularly of BNP or its counterpart aminoterminal pro-B-type natriuretic peptide (NT-proBNP), should be determined in all patients with suspected or established heart failure. The BNP was initially identified in the porcine brain, and thus it is also called brain natruretic peptide. The BNP hormone is physiologically active and is formed from the cleavage from its prohormone, pro-BNP. The N-terminal fragment, NT-proBNP is concurrently released into circulation. The NT-proBNP is not physiologically active, but it has a longer half-life of elimination; thus, it can be measured for a longer period than BNP.

The measurement of serum BNP and NT-proBNP is most useful in distinguishing between cardiac and non-cardiac dyspnea.

TABLE 5

The biomarkers in heart failure

Neurohormones
• Natriuretic peptides (ANP, BNP, CNP)
• Plasma renins and angiotensins
• Catecholamines
• Endothelins
• Arginine vasopressins
• Adrenomedullin
Cardiac injury biomarkers
• Troponins
• Heart-type fatty acid binding protein
• Apoptotic protein
• Growth differentiating factor-15
Inflammatory markers
• Tumor necrosis factor-alpha
• C-reactive protein
Matrix remodeling markers
• Matrix metalloproteinases
• Tissue inhibitors of metalloproteinases
• Telopeptides and propeptides of collagen type I and III
• Galectin
Oxidative stress markers
• Oxidized low-density lipoproteins
• Myeloperoxidase
• Plasma malondialdehyde
• Serum uric acid

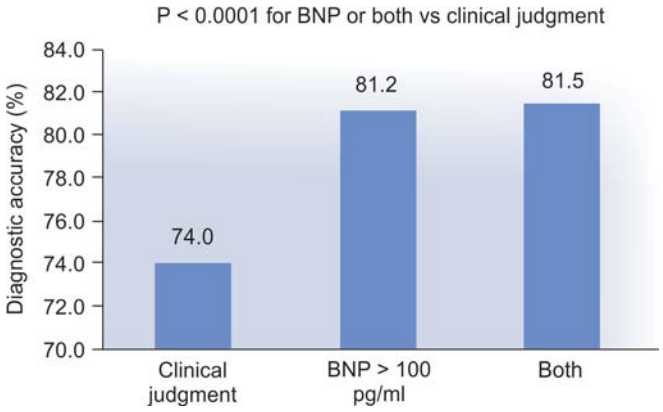


FIGURE 19: The B-type Natriuretic Peptide (BNP) levels in patients presenting to the emergency department with dyspnea are illustrated. The measurement of BNP levels was superior to clinical judgment. (*Source:* McCullough PA, Nowak RM, McCord J, et al. B-Type Natriuretic Peptide and Clinical Judgment in Emergency Diagnosis of Heart Failure: Analysis from Breathing Not Properly (BNP) Multinational Study. Circulation. 2002;106:416, with permission)

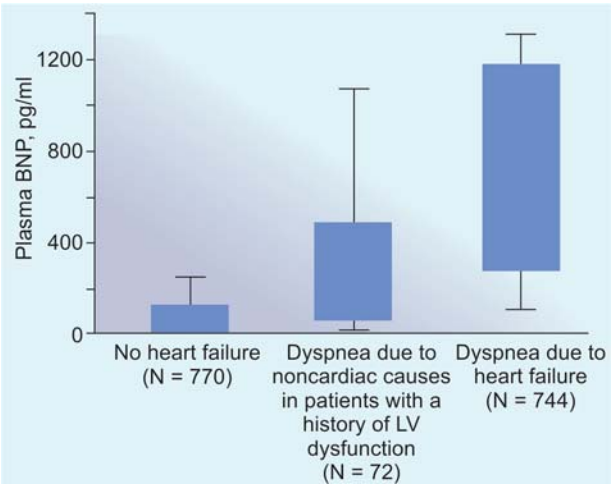


FIGURE 20: The BNP levels in patients presenting with dyspnea are illustrated. The BNP levels were higher in patients with overt systolic heart failure compared to those with asymptomatic left ventricular dysfunction and controls. (*Source:* Modified from Maisel AS et al. N Engl J Med. 2002;347:161)

In patients with non-cardiac dyspnea, the BNP levels are considerably lower than in patients with cardiac dyspnea.[28] In patients with cardiac dyspnea, the BNP levels are usually higher than 400 pg/ml. When the BNP concentrations are between 100 pg/ml and 400 pg/ml, the specificity and sensitivity for diagnosis of heart failure are not high. In patients presenting in the emergency care unit, the accuracy of measurement of BNP was superior to that of clinical judgment (Fig. 19). The combination of clinical judgment and measurement of BNP did not improve the diagnostic accuracy.[29] In patients with overt heart failure, the BNP levels are higher than those with asymptomatic left ventricular dysfunction (Fig. 20).

The levels of serum concentration of BNP are directly related to the severity of congestive heart failure. Both in males and females, the BNP levels progressively increase with the increasing severity of NYHA functional class (Fig. 21).

It should be appreciated that the level of natriuretic peptides can be elevated in absence of overt heart failure. In patients

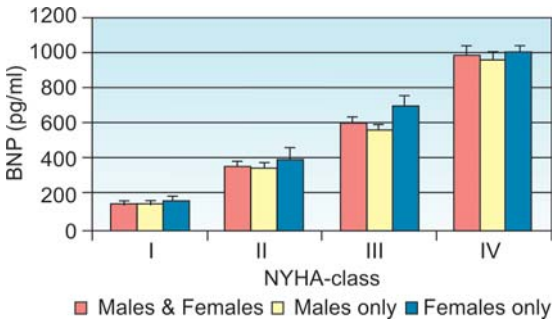


FIGURE 21: The relations between BNP levels and the severity of heart failure. Both in men and women, BNP levels increase with increasing NYHA class. (*Source:* Modified from Maisel AS et al. N Engl J Med. 2002;347:161-7)

with acute coronary syndromes, stable angina due to coronary artery disease, valvular heart disease, paroxysmal atrial fibrillation, isolated atrial enlargements and left ventricular hypertrophy (Table 5). Furthermore, the levels of BNP and NT-proBNP are also related to the age and genders. It is higher in elderly females than in younger males.[30]

In patients with obesity and increased body mass index BNP and NT-proBNP levels are lower than in nonobese patients.[31-33] Thus, in these patients with normal levels of these natriuretic peptides do not exclude heart failure. Furthermore, despite lower plasma levels of BNP in obese patients, worse prognosis is observed with higher plasma BNP levels within any body mass index category.[34] The mechanisms for decreased levels of natriuretic peptides in obese subjects have not been elucidated. Increased clearance and decreased production are possible mechanisms.

In renal failure the levels of BNP and NT-proBNP are higher than those of patients without renal failure.[35]

The BNP is cleared by the receptor mediated binding and removal, by enzymatic degradation by neutral endopeptidase and also by passive renal excretion.[36,37] Thus the glomerular filtration rate is inversely related to BNP concentrations.

The NT-proBNP is entirely cleared by kidney and its plasma concentrations are elevated with renal failure alone. In a review of 599 patients with a serum creatinine 2.5 mg/dl or less, the levels of NT-proBNP were correlated with estimated glomerular filtration rate. The sensitivity and specificity for diagnosis of heart failure were 85% and 88% for those with glomerular filtration rate 60 ml/min/1.73 m^2 and 89% and 72% in those with less than 60 ml/min/1.73 m^2.[35]

Troponins I and T are cardiac specific regulatory proteins.[38] After myocardial damage they are released into circulation and their levels can be detected within 3–12 hours of myocardial injury. The levels of troponins reflect the extent of myocardial injury. The troponins can be detected for 5–14 days after the initial insult. The elimination time is substantially prolonged in presence of renal failure.[39]

Troponins are released in patients with chronic heart failure even in absence of coronary artery disease.[40] Troponins are also elevated in patients with acute decompensated heart failure.[41] Myocyte damage is the principal mechanism for the elevated troponins in heart failure.[42] Stretching of cardiac myocytes may cause transient elevation of troponins[43] due to loss of cell membrane integrity. This mechanism may explain transient

TABLE 6

Elevated B-type natriuretic peptide (BNP) without clinical heart failure

- Acute coronary syndromes
- Chronic stable angina
- Left ventricular hypertrophy
- Asymptomatic LV dysfunction
- Isolated left atrial enlargement
- Paroxysmal atrial fibrillation
- Renal failure
- Valvular heart disease
- Very elderly, particularly females

TABLE 7

The clinical conditions in which cardiac troponins may be elevated

- Heart failure
- Acute coronary syndromes
- Chronic ischemic heart disease
- Isolated right ventricular failure
- Acute pulmonary embolism
- Chronic—precapillary pulmonary arterial hypertension
- Myopericarditis
- Periprocedural (angioplasty)
- Renal failure

increase in troponins in marathon runners and it can occur in absence of myocyte loss.

There are non-cardiac causes of elevation of troponins.[44] In patients with renal failure, the cardiac troponins levels are increased. In patients with heart failure and renal dysfunction, decreased renal clearance and increased production contribute to increased levels of troponins.

There are methodological causes of elevated troponins. For example, in patients with rheumatoid arthritis or history of mononucleosis the presence of antibodies may interfere with the assay.[43]

The cardiac troponins levels may be increased in patients with myocarditis, nonischemic dilated cardiomyopathy, and isolated chronic right heart failure. It can also be elevated in patients with sepsis, and pulmonary embolism, and following coronary angioplasty (procedural myocardial infarction). It should be appreciated that irrespective of the cause of elevated troponins, the long-term prognosis is worse in these patients compared to those with normal troponins levels.[45] In clinical conditions in which cardiac specific troponins levels may be increased are summarized in Table 6.

Cystatin C is an endogenous biomarker which is being used to assess renal function and it has been reported to be a more sensitive marker for detection of renal dysfunction than glomerular filtration rate.[46] The prognosis of patients with elevated cystatin C is worse than those with normal cystatin C levels.[47] It is also a risk factor for developing heart failure.[48]

Neutrophil gelatinase-associated lipocalin (NGAL) has been reported to be a predictor of increased risk of development of worsening heart failure.[49] However its diagnostic and prognostic values compared to other biomarkers have not been clearly established.

Although a large number of biomarkers are elevated in heart failure, for its diagnosis, only measurement of BNP or NT-proBNP is necessary. The ACC/AHA guidelines for indications of measurement of natriuretic peptides are summarized in Table 7.

Myeloperoxidase, a leukocyte derived enzyme, has been reported to play a mechanistic role for development of heart failure. Increased plasma levels of myeloperoxidase was associated with more severe symptoms diastolic dysfunction and higher clinical events.[50]

Inflammatory and oxidative biomarkers have been investigated in patients with heart failure.[51] The C-reactive protein has been used to distinguish between valve disease and heart failure.[51] In the Val-Heft trial, the higher levels of C-reactive protein were associated with more severe symptoms and worse prognosis.

EXERCISE TESTS

Reduced exercise tolerance is one of the major symptoms of heart failure. Although exercise tests are not necessary for the diagnosis of heart failure, they are useful to assess the functional class and prognosis. The NYHA classification is most frequently used to determine the functional class (Table 8). The prognosis is worse in class IV patients than in patients in classes II and III.

TABLE 8

ACC/AHA and HFSA guidelines on the use of natriuretic peptide measurement in patients with heart failure

ACC/AHA 2009 Heart Failure Guideline Update	*HFSA 2006 Practice Guideline: Acute Heart Failure Diagnosis*
Measurement of natriuretic peptides [B-type natriuretic peptide (BNP) and NT-proBNP] can be useful in the evaluation of patients presenting the urgent care setting in whom the clinical diagnosis of heart failure is uncertain. Measurement of natriuretic peptides (BNP and NT-proBNP) can be helpful in risk stratification (Level of evidence: A)	The diagnosis of decompensated heart failure should be based primarily on signs and symptoms (Level of evidence: C)
The value of serial measurements of BNP to guide therapy for patients with heart failure is not well established	When the diagnosis is uncertain, determination of plasma BNP or NT-proBNIP concentration should be considered in patients being evaluated for dyspnea who have signs and symptoms compatible with HF (Level of evidence: A)
	The natriuretic peptide concentration should not be interpreted in isolation, but in the context of all available clinical data bearing on the diagnosis of HF

Several methods can be used to assess exercise capacity. One method is cardiopulmonary exercise test.[50] During cardiopulmonary exercise test, peak exercise capacity is determined which is defined as the maximal ability of the cardiovascular system to deliver oxygen to the exercising muscles. Measurement of oxygen uptake (VO_2), carbon dioxide production (VCO_2) and minute ventilation during cardiopulmonary test allow quantitative measurement of exercise capacity (see the chapter "Cardiopulmonary Exercise Testing and Exercise Training in Heart Failure").

The ventilatory threshold formally called anaerobic threshold can be used to distinguish between non-cardiac and cardiac dyspnea. In patients with non-cardiac dyspnea, fatigue occurs before the ventilatory threshold is reached.[50] Maximal exercise testing with measurement of maximal oxygen consumption (VO_2 max) is frequently used to identify patients referred for cardiac transplantation or other treatments for advanced heart failure.[5]

SIX-MINUTE WALK TEST

The six-minute walk test measures the total distance that a patient can walk on the level surface with their maximal capacity, in six minutes. It is being increasingly used in clinical trials as well as in clinical practice to assess the functional capacity of a patient with heart failure.[51-55] This test is most applicable to distinguish between patients with NYHA classes III and IV heart failure. It correlates well with the NYHA functional class for the assessment of prognosis but correlates less well, with VO_2 particularly in patients in the NYHA functional Classes I and II.

It should be appreciated that exercise test is not essential for the diagnosis of heart failure but it is useful to assess the exercise capacity and prognosis.

During follow-up evaluation, a six-minute walk test along with measurements of natriuretic peptides is commonly employed to assess efficacy of interventions particularly in clinical trials. For routine follow-up of patients, however, exercise tests or measurements of natriuretic peptides are not necessary and only clinical evaluations appear to be adequate.

CORONARY ARTERIOGRAPHY

In patients with heart failure who present with chest pain, coronary arteriography may be considered if the etiology of chest pain remains uncertain and evaluation for obstructive coronary artery disease has not been done previously.[5] It should be also considered in patients who present with symptoms of heart failure without chest pain and have known or suspected coronary artery disease.[5]

Presently in many institutions, multi-slice contrast computed tomographic coronary angiography (CTA) is being performed instead of invasive coronary arteriography in patients with heart failure with similar clinical presentations. However the reliability of the contrast CTA has not been firmly established.

MYOCARDIAL ISCHEMIA

In patients with heart failure, with known or suspected coronary artery disease presence of myocardial ischemia should be assessed. The many noninvasive imaging techniques are available for the detection of myocardial ischemia. Pharmacologic or exercise stress thallium or Tc-99m sestamibi tomographic perfusion imaging can demonstrate reversible perfusion defects which indicate myocardial ischemia (Fig. 22).

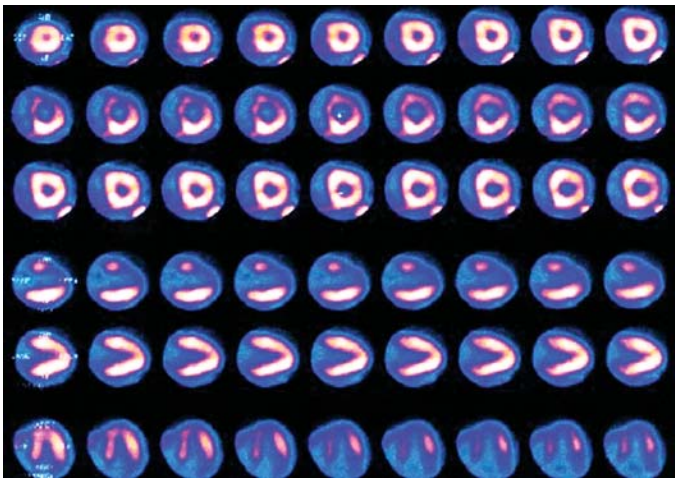


FIGURE 22: Gated perfusion single photon emission computed tomography dual isotope imaging using thallium-201 (rest, even rows) technetium-99m sestamibi (stress-related, odd rows) to detect the presence and extent of ischemic myocardium. The first four rows from the top show short axis slices from apex (left) to base (right). Rows 5 and 6 show vertical long axis slices from septum (left) to lateral wall (right) and rows 7 and 8 show horizontal long axis slices from inferior wall (left) to anterior wall (right). A large reversible perfusion defect in the anterolateral wall of the left ventricle (left anterior descending coronary artery territory) is evident, indicating the presence of ischemic myocardium. (*Source:* Dr Eli Botvinick, University of California/San Francisco)

Positron emission tomography with the use of fluorodeoxyglucose to assess myocardial metabolism and a blood flow agent, such as rubidium, can also demonstrate myocardial ischemia and viability (Fig. 23).

Cardiac magnetic resonance imaging (CMRI) with the use of contrast agent, such as gadolinium, can demonstrate myocardial fibrosis (Fig. 24).

Dobutamine stress echocardiography can be used for the diagnosis of myocardial ischemia (Fig. 25). With low dose dobutamine, thickening of the myocardium along with enhanced wall motion occurs. With a larger dose, wall motion abnormalities and thinning of the myocardial segments occur.

ENDOMYOCARDIAL BIOPSY

Endomyocardial biopsy should not routinely be performed for the diagnosis of the etiology of heart failure. However, when a specific cause such as giant cell myocarditis or cardiac amyloidosis is suspected, endomyocardial biopsy is indicated. It is also indicated for the diagnosis of fulminant myocarditis.

Endomyocardial biopsy can be used to assess presence and degree of myocardial fibrosis (Fig. 26).[5] Endomyocardial biopsy is also useful to distinguish between restrictive cardiomyopathy and constrictive pericarditis.[55,56]

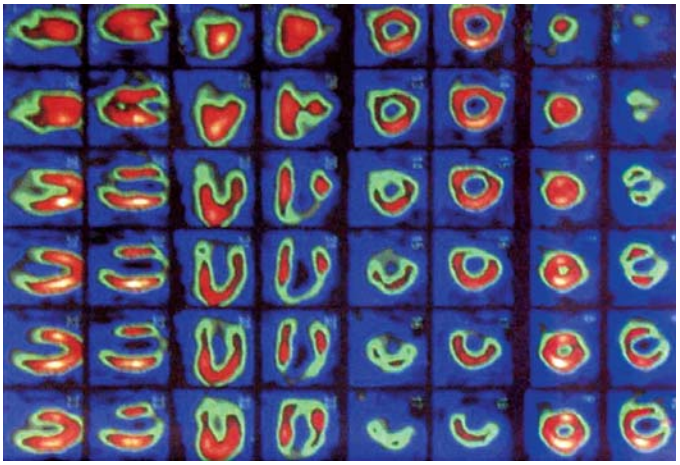


FIGURE 23: Radionuclide (scintigraphic) evaluation of the presence of ischemic but viable myocardium by positron emission tomography (PET) is illustrated. Short axis slices (rows 1–4), vertical long axis slices (rows 5 and 6), and horizontal long axis slices (rows 7 and 8) are shown. The resting perfusion images with rubidium-82 (rows 1, 3, 5 and 7) demonstrate a large lateral perfusion defect, but other areas take up rudium-82 indicating that these myocardial segments are perfused and viable. The fluor-deoxyglucose images (rows 2, 4, 6 and 8) show complementary uptake which indicates active myocardial metabolism and thus viability. (*Source:* Dr Eli Botvinick, University of California/San Francisco)

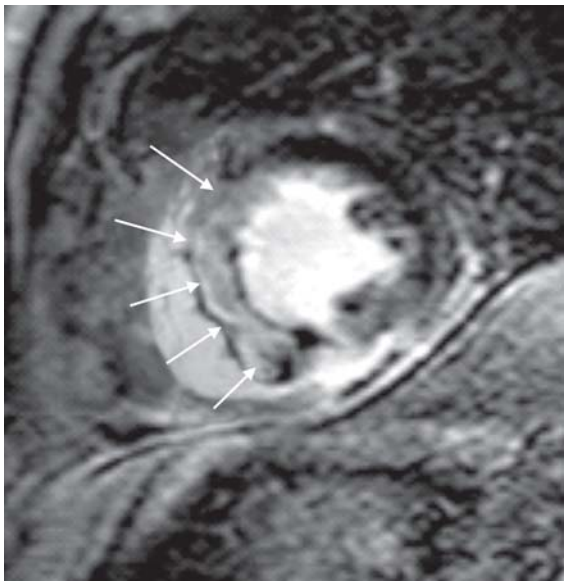


FIGURE 24: Cardiac magnetic resonance imaging with the use of the contrast gadolinium in a patient with heart failure is illustrated. The delayed enhancement image shows area of myocardial fibrosis (arrows)



FIGURE 25: Dobutamine stress echocardiogram in a patient with systolic heart failure is illustrated. With the low dose of dobutamine there was thickening of the antero-apical segment of left ventricle. With larger doses, there was thinning of the same segments

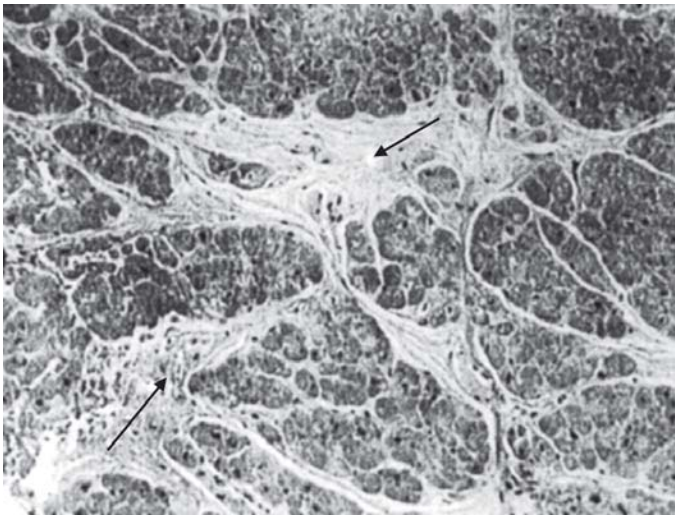


FIGURE 26: Endomyocardial biopsy in a patient with restrictive cardiomyopathy is illustrated. The extensive fibrosis with intact myocytes is evident. (*Source:* JD Hosenpud. 1989)

GENETICS STUDIES

Nonischemic dilated cardiomyopathy can be familial, and its frequency has been estimated to be about 11%.[57] It should be appreciated that the true incidence of familial dilated cardiomyopathy has not been firmly established. A prospective cohort study reported a genetic abnormality to be present in approximately 2.7% of patients with familial dilated cardiomyopathy.[57]

Endomyocardial biopsy usually shows myocyte hypertrophy and death with replacement fibrosis.[57] The guidelines recommend genetic evaluation in patients with suspected nonischemic dilated cardiomyopathy.[57] It should include obtaining careful family history of the patient, screening family members, genetic counseling and genetic testing.[58]

Approximately mutations of 30 genes have been identified in patients with familial dilated cardiomyopathy.[59-62] However it remains unclear whether genetic studies provide any benefit in the management of these patients. In clinical practice routine genetic studies are not necessary.

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Chapter 70

Systolic Heart Failure
(Heart Failure with Reduced Ejection Fraction)

Kanu Chatterjee

Chapter Outline

- Historical Perspective
  - — Definitions
  - — Risk Factors
- Ventricular Remodeling
- Functional Derangements and Hemodynamic Consequences
- Initial Treatment of Systolic Heart Failure
- Symptomatic Systolic Heart Failure
  - — Pharmacologic Treatments
  - — Non-pharmacologic Treatments
- Follow-up Evaluation

INTRODUCTION

Heart failure is a common clinical syndrome and its clinical presentations and etiology are protean. For example, it can be acute which is often defined when the symptoms of heart failure develop rapidly within hours or a few days. Frequently acute heart failure develops as complications of acute coronary syndromes or of valvular heart diseases. The syndromes of acute heart failure complicating acute coronary syndromes are discussed in the chapter "Cardiogenic Shock Complicating Acute Myocardial Infarction".

Chronic heart failure is defined when the symptoms of heart failure develop slowly in days and months and it may be caused by myocardial, pericardial or valvular heart diseases. Chronic heart failures resulting from pericardial and valvular diseases are discussed in the sections of pericardial and valvular heart disease. Heart failures due to primary cardiomyopathies, such as hypertrophic, dilated and restrictive cardiomyopathies, are discussed in the chapters of cardiomyopathies.

Systolic (Heart Failure with Reduced Ejection Fraction—HFREF) and diastolic heart failures (Heart Failure with Preserved Ejection Fraction—HFPEF) are two common clinical subsets of chronic heart failure. In this chapter systolic heart failure has been discussed.

HISTORICAL PERSPECTIVE

Existence of heart failure was known in the ancient Egyptian and Greek civilization.[1-3] In India, cardiac glycosides were used several centuries BC. In the Roman literature, benefits of the plant fox gloves have been mentioned.[4] *Digitalis purpura* was introduced by Withering in 1785.[5] Nitrates were introduced for the treatment of angina in 1853. For the treatments of various types of edema, a number of pharmacologic and non-pharmacologic treatments were used before the presently available treatment modalities for heart failure were introduced in clinical practice. Bloodletting and Southey's tubes were used for centuries. The only pharmacologic treatments for heart failure that were available in early 20th century were digitalis, nitrates, sulfonamides and mercurial diuretics. In 1956, intravenous hydralazine was introduced for the treatment of hypertensive congestive heart failure.[6] Oral hydralazine therapy for chronic heart failure was first introduced in 1976.[7] The few historical aspects of heart failure are summarized in Table 1.

Functional differences between systolic and diastolic heart failure ware recognized by Dr Fishberg and he wrote in 1937 that diastolic heart failure results from inadequate filling of the ventricle (hypodiastolic failure) and systolic heart failure from inadequate emptying (hyposystolic failure) of the heart.

TABLE 1

Heart failure

Historical perspectives
• Heart failure was known in the ancient Egyptian and early Greek civilizations
• Cardiac glycosides were probably used in India several centuries BC
• Reports of the benefits of foxglove exist in the Roman literature
• Blood letting, the use of leeches and Southey's tubes for treatment of edema have been used for centuries
• *Digitalis purpura* was introduced for treatment of dropsy by Withering in 1785
• Nitrates were introduced by Hering in 1853
• Diuretics (sulfonamides) were introduced in 1920
• Mercurial diuretics were introduced in 1949
• Thiazide diuretics were introduced in 1958
• Intravenous hydralazine for the treatment of hypertensive heart failure was introduced by Judson in 1956
• Oral hydralazine for the treatment of chronic heart failure was introduced by Chatterjee, Drew and Parmley in 1976

TABLE 2

Risk factors for developing systolic heart failure

- Hypertension
- Coronary artery disease
- Diabetes
- Insulin resistance
- Smoking
- Cardiotoxins
- Family history of cardiomyopathy

DEFINITIONS

Sir Thomas Lewis, in 1933, defined systolic heart failure as a condition in which heart fails to discharge its content. Professor Eugene Braunwald, in 1980, defined systolic heart failure as a pathophysiologic state in which an abnormality of cardiac function is responsible for the failure of the heart to pump blood at a rate commensurate with the requirements of the metabolizing tissues. Although these definitions provide precise pathophysiologic mechanisms, they are difficult to use in clinical practice.

The clinical definition of systolic heart failure is a "syndrome which results from reduced left ventricular ejection fraction". It should be appreciated that ejection fraction is not independent of loading conditions. A markedly reduced preload and increased afterload is associated with reduced ejection fraction without any changes in contractile function.

RISK FACTORS

A number of risk factors for developing systolic heart failure have been identified (Table 2). Coronary artery disease particularly a previous myocardial infarction is a major risk factor. Hypertension, obesity and diabetes are also important risk factors for developing systolic heart failure. Insulin resistance cardiomyopathy has also been identified. In these patients heart failure occurs in absence of frank diabetes and in presence of insulin resistance. The potential mechanisms are impaired phosphorylation of Akt-I, decreased inhibition of apoptosis, decreased production of nitric oxide and decreased hypertrophy and fibrosis. Use of cardiotoxins, such as chemotherapeutic agents, is a risk factor for developing systolic heart failure. The incidence of systolic heart failure in patients with a family history of dilated cardiomyopathy is higher. Smoking is also a risk factor for systolic heart failure.

VENTRICULAR REMODELING

In systolic heart failure the left ventricle is dilated and becomes more spherical. This altered shape and geometry is the principal mechanism for secondary mitral regurgitation. The increase in transverse diameter is greater than that of longitudinal axis. The distance between the anteromedial and posterolateral papillary muscles increases causing misalignment of the papillary muscles, chordae tendineae and mitral valve leaflets. Thus, the secondary or functional mitral regurgitation occurs without any structural changes of the mitral valve leaflets.

The left ventricular wall thickness either remains unchanged or decrease compared to normal controls (Fig. 1).[8,9] The left ventricular cavity size is substantially increased. As a result, left ventricular wall stress is increased which contributes to reduced ejection fraction. There is an inverse relation between wall stress and ejection fraction.

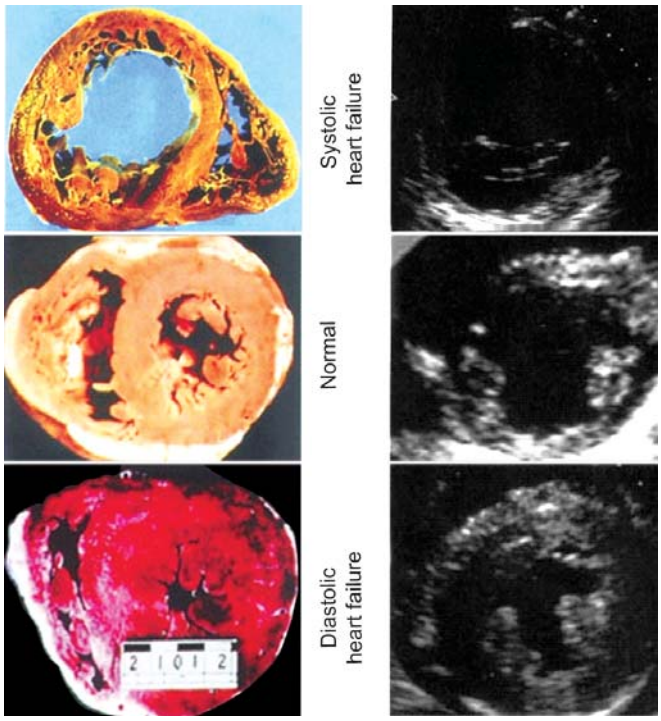


FIGURE 1: The left hand panel illustrates the transverse sections of the heart in a heart and in severe systolic heart failure, with diastolic heart failure. In the right hand panel two-dimensional echocardiographic cross-sectional views of the heart are shown. Compared to normal, in systolic heart failure, the left ventricle is dilated and spherical. The wall thickness is not increased. In diastolic heart failure, the left ventricular cavity is smaller than normal, and the left ventricular wall thickness is markedly increased. (*Source:* MA Konstam. JCF. 2003;9:1-3)

Both end-diastolic and end-systolic volumes are increased, but there is a greater increase in end-systolic than in end-diastolic volumes which is contributory to reduced ejection fraction. In systolic heart failure left ventricular hypertrophy is eccentric. The calculated left ventricular mass is increased, but as the cavity size is also increased, the cavity/mass ratio is increased. The echocardiographic left ventricular volumes, ejection fraction and mass in patients with systolic heart failure compared to normal controls are summarized in Table 3.[10]

In systolic heart failure synchronous contraction and relaxation of left ventricular walls are absent or impaired in a

TABLE 3

Systolic heart failure

	Controls	*SHF*
• LVEDV	102	192
• LVESV	46	137
• LVEF	54	31
• LVM	125	230
• LVM/V	1.49	1.22

(Abbreviations: LVEDV: Left ventricular diastolic volume; LVESV: Left ventricular end systolic volume; LVEF: Left ventricular ejection fraction; LVM: Left ventricular mass; LVM/V: Left ventricular mass/volume ratio)

TABLE 4

Systolic heart failure remodeling

- Usually eccentric hypertrophy
- Disproportionate increase in ventricular cavity size
- Increased ventricular mass
- Cavity/mass ratio increased
- Wall thickness—decreased or unchanged
- Increased wall stress
- Reduced ejection fraction
- Altered ventricular shape and geometry
- Frequent mechanical dyssynchrony with or without electrical dyssynchrony

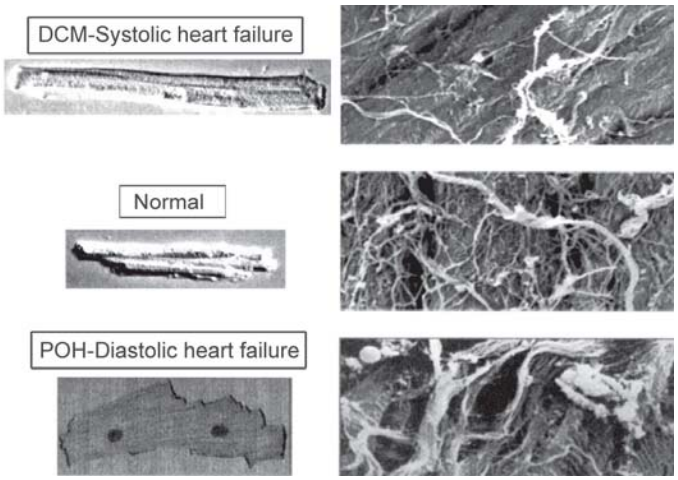


FIGURE 2: Changes in myocytes (left) and in extracellular matrix (right) in systolic heart failure resulting from dilated cardiomyopathy and diastolic heart failure resulting from pressure overload compared with normals in the animal models are illustrated. The myocyte length is increased in DCM-Systolic Heart Failure. In POH-Diastolic Heart Failure, the myocyte is thicker. In systolic heart failure, there is collagen disruption. In diastolic heart failure, the collagen bundles are thicker. (*Source:* GP Aurigema, et al. Circulation. 2006;113:296-304, with permission)

substantial number of patients.[11,12] This mechanical dyssynchrony occurs most frequently when the QRS duration is prolonged such as in left bundle branch block or in intraventricular conduction defect of left bundle branch block type. It should be appreciated that mechanical dyssynchrony can occur in presence of narrow QRS complex. Some of the features of left ventricular remodeling in systolic heart failure are summarized in Table 4.

The changes in the myocytes and myocardial architecture are illustrated in Figure 2.[9] In systolic heart failure the myocyte length is increased without any change in the thickness of the myocytes and the myocyte length/width ratio is increased. The sarcomeres are replicated in series. The myocardial architecture is also abnormal. There is an increase in collagen volume and fibrosis. The collagen bundles surrounding the myocytes are thinner than normal, and there is degradation and disruption of fibrillar collagen.[9] The total collagen content, however, is normal and not different from that in diastolic heart failure.[13] The collagen cross links are decreased in systolic heart failure. In general the matrix metalloproteinases are increased and the endogenous tissue inhibitors of metalloproteinase are decreased.[14,15] These changes in metalloproteinases metabolism may be contributory to the collagen disruption in systolic heart failure. Increased circulating levels of amino-terminal propeptide of type III procollagen have been observed in systolic heart failure which is another evidence of abnormal collagen metabolism.[16] In human left ventricular myocardial biopsy samples, titin isoforms were measured.[13] The N2BA isoform is more compliant collagen molecule than the N2B isoform. The N2BA/N2B ratio of collagen isoforms is increased in systolic heart failure.[13,17]

The mechanical and electrical functions of the myocytes of patients with severe systolic heart have been studied.[17] The tissue was obtained from the explanted heart. The developed force of the myocytes was decreased along with impaired relaxation. The action potential duration was prolonged. There was a blunted rise in intracellular calcium transient following depolarization suggesting slower delivery of calcium to the contractile proteins. During repolarization, the fall of intracellular calcium was also slower indicating slower reuptake of calcium by sarcoplasmic reticulum.[18]

It is generally agreed that myofibrillar function is depressed in heart failure. Upregulation of beta-myosin heavy chain and downregulation of alpha-myosin heavy chain have been observed.[19] In systolic heart failure there is loss of myocytes by necrosis and apoptosis. Necrosis results from myocyte injury when cell membrane is disintegrated. Following cell membrane rupture, the intracellular organelles and intracellular proteins are exposed which also promote inflammatory response. There is also leakage of intracellular calcium causing calcium overload which is associated with enhanced ischemia, worsening heart failure and propensity for developing arrhythmias. Necrotic myocyte death occurs in acute coronary syndrome, and in ischemic and non-ischemic dilated cardiomyopathy. The "troponin leaks" provide evidence for myocyte injury irrespective of clinical circumstances when it occurs.

Apoptosis also called programmed cell death is observed in systolic heart failure. The apoptotic cells are preprogrammed to be selectively eliminated. There is no cell swelling in apoptosis and the cell membrane remains intact. The nuclei are dense and fragmented. There is no pericellular inflammatory response. Both in ischemic and non-ischemic dilated cardiomyopathy, apoptopic cell death occurs. There is activation of cell death pathway and suppression of cell survival pathway.[20] The cellular and molecular changes in systolic heart failure are summarized in Table 5.

TABLE 5

Systolic heart failure

Myocyte	
Hypertrophy	+
Apoptosis	+
Necrosis	+
Fibrosis	+
Ca Regulation	–
MMPs/TIMPs	+
Collagen	
Cross-links	–
Titin isoforms	
N2BA/N2B	+

+: Increased; –: Decreased
(Abbreviations: Ca: Calcium; MMPs: Matrix metalloproteinases; TIMPs: Tissue inhibitors of metalloproteinases)

TABLE 6

Neurohormonal activation in systolic heart failure

- Vasoconstrictive, anti-natriuretic and mitogenic neurohormones:
  - Norepinephrine, epinephrine, dopamine
  - Renin and angiotensins
  - Aldosterone
  - Endothelin
  - Arginine vasopressin
  - Insulin
  - Cortisol
  - Growth hormone
  - Tumor necrosis factor-alpha
  - Interleukin-6
  - Cardiotropin-I
- Vasodilatory, natriuretic and anti-mitogenic neurohormones:
  - Atrial and B-type natriuretic peptides
  - Bradykinins
  - Prostaglandins
  - Neuropeptide Y
  - Adrenomedullin
  - Urodilantin
  - Endothelium derived relaxing factors
  - Nitric oxide

TABLE 7

Adverse effects of neurohormonal activation

- Adverse hemodynamic effects
- Vascular remodeling
- Ventricular remodeling
  - Myocyte hypertrophy
  - Extracellular matrix changes
- Promotes atherothrombosis
- Increased oxidative stress
- Endothelial dysfunction
- Myocardial necrosis
- Apoptosis

It has been suggested that in systolic heart failure oxidative stress contributes to the progression of heart failure. In oxidative stress, the free radicals, such as superoxide anion and hydrogen peroxide, are present in relative excess. These highly reactive molecules are referred as reactive oxygen species. The oxidative stress can promote atherosclerosis, myocyte necrosis and apoptosis.[21] Superoxide anion has been reported to reduce calcium-activated myocardial force development.[22] In animal studies, oxidative stress have been shown to contribute to development of heart failure both due to increased production of free radicals and decreased availability of free radical scavengers.[23,24] In rabbits with pacing induced heart failure, increased oxidative stress and myocyte apoptosis has been reported.[25]

In patients with chronic systolic heart failure an increase in oxidative stress has been observed. Both in patients with ischemic and non-ischemic dilated cardiomyopathy, increased plasma levels of malondialdehyde, a marker of lipid peroxidation, have been reported.[26,27] Another marker of oxidative stress, oxidized low density lipoprotein is elevated in patients with chronic heart failure and it is associated with worse prognosis.[28] Serum uric acid levels which reflects the degree of xanthine oxidase activation is elevated in patients with chronic heart failure and its level is directly proportional to the severity of symptoms.[29] It should be appreciated that the treatments designed to decrease oxidative stress have not been found effective in prospective randomized clinical trials.[30]

In systolic heart failure plasma levels of many neurohormones are elevated (Table 6).

Neurohormonal activation has been shown to be a major contributing mechanism for progression of heart failure. The activation of vasoconstrictive, antinatriuretic and antimitogenic neurohormones, such as catecholamines, angiotensins, aldosterone, vasopressin, endothelins and cytokines, is associated with adverse ventricular remodeling. The compensatory vasodilatory, natriuretic and antimitogenic neurohormones, such as natriuretic peptides, prostacyclins and endothelium derived relaxing factors and nitric oxide, are also increased. If a balance of these two systems is maintained, the progression of heart failure can be prevented. However, if there is more activation of neurohormones with the potential to produce adverse remodeling, progression of heart failure occurs (Fig. 3) (Table 7).

Angiotensin II is a potent vasoconstrictive, proinflammatory, mitogenic and prothrombotic hormone. It promotes atherosclerosis, and causes vascular smooth muscle cell proliferation and increases vascular intimal thickening. Angiotensin also promotes release of aldosterone which is associated with abnormal collagen synthesis and fibrosis. Angiotensins contribute to myocyte necrosis and apoptosis. Existence of tissue renin-angiotensin system in the myocardium has been documented and its activation is associated with myocardial hypertrophy and failure.[31]

The adverse vascular and cardiac effects of angiotensin are mediated by activation of angiotensin subtype 1 (AT1) receptors. Activation of angiotensin subtype 2 (AT2) receptors produce counter regulatory effects such as vasodilatation, decreased vascular smooth muscle cell proliferation and decreased myocardial hypertrophy. Both angiotensin I and angiotensin II can generate angiotensin-(I-VII) which also cause vasodilatation and decrease growth.[32] It also promotes formation and release of vasodilator prostaglandins and nitric oxide.

Endothelins are potent vasoconstrictors and are produced by vascular smooth muscle cells.[33a,b] Although its blood levels are increased in chronic systolic heart failure, the significance of increased endothelin remains uncertain.[34] Endothelin is produced by conversion of big endothelin-1 by an endothelin-converting enzyme. Endothelin synthesis and release are promoted by angiotensin II, norepinephrine, growth factors and oxidized low density lipoproteins.[35] Endothelin produces its pathophysiologic effects by stimulating endothelin A and B receptors. The activation of endothelin A receptors is associated with increased development of vascular smooth muscle cells tension, cell proliferation and hypertrophy. The endothelin-B receptor stimulation is associated with vasodilatation probably due to increased production of nitric oxide.[36] It should be appreciated that endothelin antagonists are not effective for the treatment of left heart failure but they are approved for the treatment of precapillary pulmonary hypertension.

The plasma arginine vasopressin levels are increased in patients with heart failure and the levels are higher in patients with symptomatic than in patients with asymptomatic left

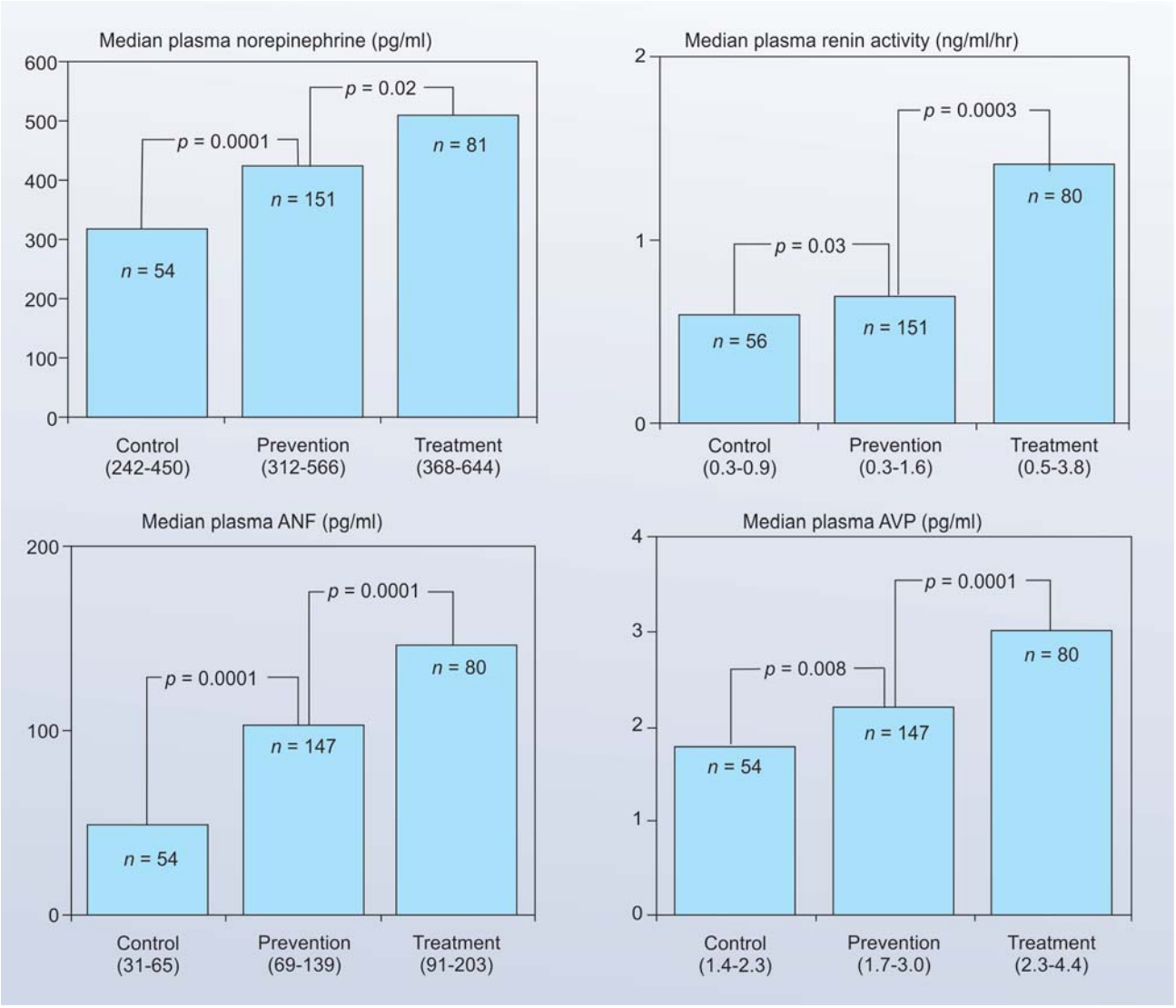


FIGURE 3: Neurohormonal activation in systolic heart failure is illustrated. The changes in plasma norepinephrine, rennin activity, atrial natriuretic factor and vasopressin in patients with asymptomatic left ventricular systolic dysfunction (prevention) and with overt clinical heart failure (treatment) compared with normal controls are illustrated. There is increasing levels of these neurohormones in patients with systolic dysfunction. (*Source:* GS Francis, et al. Circulation. 1990;82:1724-9, with permission)

ventricular systolic dysfunction (Fig. 3).[36] Arginine vasopressin is a nonapeptide and it is secreted from the posterior pituitary gland. The stimuli for the secretion are a fall in blood pressure, a reduction in plasma volume, arterial underfilling and a rise in plasma osmolality. It should be appreciated that in heart failure release of arginine vasopressin is not mediated by changes in plasma osmolality (Fig. 4).[37] In congestive heart failure, release of arginine vasopressin appears to be due to activation of baroreceptors.[38] Whether the patients are on diuretic therapy or not, the plasma levels of arginine vasopressin remain unchanged with changes in plasma osmolality.

The arginine vasopressin exerts its pathophysiologic effects by activation of vasopressin 1 and 2 receptors. The activation of V_{1a} receptors which are present in the vascular bed is associated with increased tension of the vascular smooth muscle cells and vasoconstriction. Systemic vascular resistance is increased which is associated with increased left ventricular afterload which impairs left ventricular pump function.[39] Systemic venoconstriction is associated with increased left ventricular preload. Coronary arterial vasoconstriction can induce myocardial ischemia. The V_{1a} receptors are also present in the myocardium and the activation of myocardial V_{1a} receptors is associated with myocardial hypertrophy.

The V_{1b} receptors are present in the anterior pituitary gland and its stimulation results in increased release of adrenocorticotrophic hormone and aldosterone. Increased aldosterone results in adverse vascular remodeling, myocardial hypertrophy and fibrosis. There is also impaired renal sodium and water clearance.

Vasopressin-2 receptors are located in renal distal tubule and collecting ducts. Its stimulation is associated with activation of water channel aquaporin-2.[40] There is decreased water permeability in the collecting duct resulting in water retention, volume overload and hyponatremia. The pathophysiologic effects of arginine vasopressin in heart failure are summarized in Table 8.

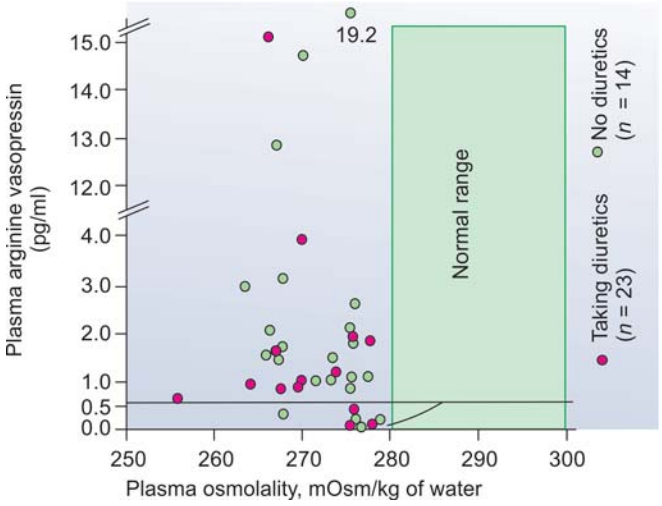


FIGURE 4: The changes in plasma arginine vasopressin in relation to changes in plasma osmolality in congestive heart failure are illustrated. Irrespective of diuretic therapy lack of correlation between arginine vasopressin levels and plasma osmolality is evident. (*Source:* Modified from Szatalowics, et al. N Engl J Med. 1981;305:263-6)

TABLE 8

Arginine vasopressin (AVP) in heart failure

AVP* is a nonapeptide secreted from the posterior pituitary gland

- Stimuli for secretion:
  - A decrease in blood pressure
  - A reduction in circulating blood volume
  - Arterial underfilling
  - A rise in plasma osmolality
- Activation of V_{1a} receptors
  - Vascular bed
    - Systemic arterial vasoconstriction
    - Increased SVR, increased LV afterload
    - Systemic venoconstriction—increased preload
    - Coronary vasoconstriction—myocardial ischemia
  - Myocardium
    - Myocyte hypertrophy
- Activation of V_{1b} receptors (anterior pituitary)
  - Increased release of ACTH
  - Increased release of aldosterone
    - Adverse vascular remodeling
    - Myocardial hypertrophy and fibrosis
    - Impaired renal water and sodium excretion
- Activation of V_2 receptors in renal collecting ducts and distal tubule
  - Activation of water channel aquaporin-2
  - Decreased water permeability in collecting duct
  - Increased water retention
  - Volume overload
  - Hyponatremia

*Also known as antidiuretic hormone (ADH)

In systolic heart failure, sympathoadrenergic activity is increased. The plasma levels of norepinephrine are substantially elevated (Table 9) (Fig. 3).[36,41,42] The level of norepinephrine is higher in patients with more severe heart failure.

There is not only increased synthesis and release of norepinephrine but there is also decreased norepinephrine reuptake by the presynaptic neuronal nerve endings. Increased plasma norepinephrine levels are associated with increased systemic vascular resistance which enhances left ventricular

TABLE 9

Circulating catecholamines and hemodynamics in patients with and without heart failure (HF)

	Patients with HF (n = 63)	*Patients without HF (n = 26)*
Norepinephrine (pg/ml)	665 ± 510*	184 ± 135
Dopamine (pg/ml)	407 ± 405†	197 ± 259
Epinephrine (pg/ml)	73 ± 98NS	55 ± 73
SWI (gm/m^2)	21 ± 9*	53 ± 13
PCWP (mm Hg)	27 ± 8*	11 ± 3

*p < .01
†p < .05

afterload which may cause impairment of left ventricular pump function. Increased sympathetic activity also causes systemic venoconstriction which increase left ventricular preload which may be initially beneficial to maintain stroke volume. However, increased ventricular volumes are associated with increased wall stress, which decreases forward stroke volume. Furthermore, due to its direct toxic effects, there is myocyte necrosis. It may also cause myocyte hypertrophy and contribute to adverse ventricular remodeling.

In congestive heart failure, increased centrally mediated muscle sympathetic nerve activity has been demonstrated by intraneural recordings which also indicates increased systemic adrenergic activity.[43]

That in systolic heart failure cardiac adrenergic activity is increased has been documented by studies measuring cardiac norepinephrine balance.[44,45] The concentration of norepinephrine in the coronary sinus venous blood is higher than its concentration in the coronary arterial blood. The calculated cardiac norepinephrine balance is approximately 40-fold higher in patients with heart failure than that in patients without heart failure. Myocardial oxygen demand is increased with increased cardiac adrenergic activity which may induce myocardial ischemia and may be contributory to myocyte necrosis and adverse ventricular remodeling. There is also an increase in renal sympathetic activity which is associated with efferent renal arterial vasoconstriction which initially maintain glomerular filtration rate. However, when compensatory mechanisms fail, glomerular filtration rate declines.

Activation of sympathetic adrenergic system is an independent prognostic factor in patients with congestive heart failure. The higher the plasma norepinephrine level, the worse is the prognosis.[46] The analysis of approximately 4,000 patients, reported that the plasma norepinephrine levels, equal to or higher than 572 pg/ml was associated with a significantly higher mortality at 2 years compared to patients with normal plasma norepinephrine levels.[46,47]

Aldosterone is a mineralocorticoid synthesized in zona glomerulosa of adrenal cortex. It is a trophic hormone for renin-angiotensin. It binds with the nuclear receptors in the renal tubular cells and myocardium.

Aldosterone level is elevated in systolic heart failure (Fig. 5). It promotes inflammation and increases oxidative stress. It also increases collagen synthesis and fibrosis. Aldosterone decrease arterial compliance which is associated with increased left ventricular afterload. Aldosterone impairs endothelial

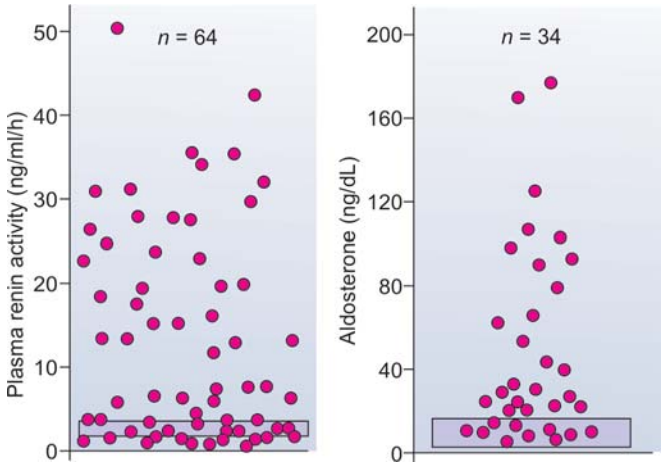


FIGURE 5: The changes in plasma rennin activity and aldosterone levels in patients with systolic heart failure are illustrated

function and promotes atherosclerosis. It also promotes thrombosis by increasing plasminogen activator inhibitor-1 and inhibiting tissue plasminogen activator. Increased levels of aldosterone are associated with water and salt retention and worsening heart failure. There is increased loss of potassium and magnesium which is associated with increased risks of arrhythmia. The potential adverse effects of aldosterone are summarized in Table 7 (Fig. 6).

Activation of cytokines, such as tumor necrosis factor-alpha and interleukin-1, may be contributory to the progression of heart failure. These cytokines have the proinflammatory and prothrombotic properties and they are also produced in the myocardium. These cytokines may cause direct toxic effects on the myocytes and cause myocyte necrosis and apoptosis. They also exert adverse effects on extracellular matrix and promote adverse ventricular remodeling.[48] Increased levels of these cytokines may cause impairment of left ventricular function. It should be appreciated, however, that any beneficial effect of pharmacologic interventions to counteract the adverse effects of these inflammatory cytokines has not been documented.

The counter regulatory neurohormones are activated as a compensatory mechanism to reduce the risks of adverse left ventricular remodeling. The brain natriuretic peptides (B-type) and atrial natriuretic peptides are activated to counteract the deleterious effects of renin-angiotensin and adrenergic systems on ventricular and atrial remodeling. The natriuretic peptides decrease myocyte hypertrophy, fibrosis and collagen synthesis. Atrial natriuretic peptides decrease atrial remodeling and B-Type natriuretic peptides reduce adverse ventricular remodeling. In physiologic conditions, the natruretic peptides promote diuresis and improve renal function. However, in heart failure, effects of natriuretic peptides on renal function is markedly blunted. The vasodilator prostacyclins, nitric oxide and endogenous antioxidants are increased in heart failure and they have the potential for decreasing adverse ventricular remodeling. The other neurohormones, such as adrenomedullin, which also has the potential to reduce progression of heart failure, have not been adequately investigated (please see the chapter on Vasodilators and Neurohormone Modulators).

The impaired left ventricular systolic function can establish a vicious cycle of adverse remodeling (Fig. 7). Decreased stroke volume and cardiac output activates the vasoconstrictive neurohormones which increase left ventricular afterload. Increased afterload is associated with a further decrease in stroke volume and cardiac output and thus a vicious cycle is established. The reduced cardiac output compromises renal perfusion which causes increased sodium and water retention, increased blood volume and increased left ventricular preload. Increased left ventricular volume without an increase in its wall thickness is associated with increased afterload which further impairs left ventricular pump function. Furthermore, these hemodynamic changes are associated with activation of sympathetic, renin-angiotensin and aldosterone systems which may cause a disproportionate increase in left ventricular afterload and preload which may cause further impairment of left ventricular function. The vasopressin is a potent vasoconstrictor and its plasma level is increased in heart failure. There is an increase in systemic vascular resistance which

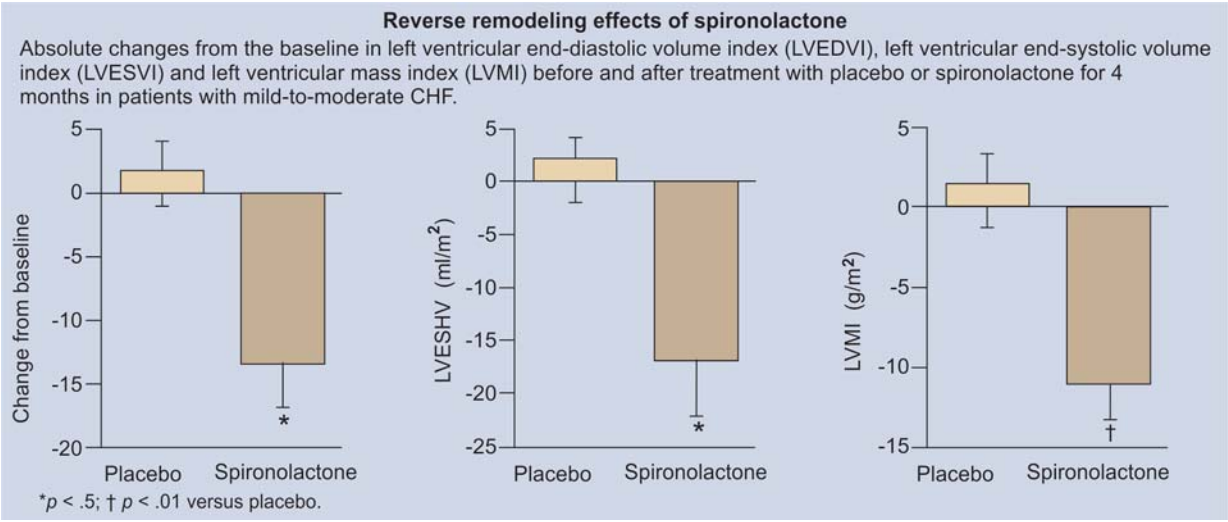


FIGURE 6: The effects of aldosterone on ventricular remodeling. (*Source:* Modified from Tsutamoto, et al. J Am Coll Cardiol. 2001;37:1228-33)

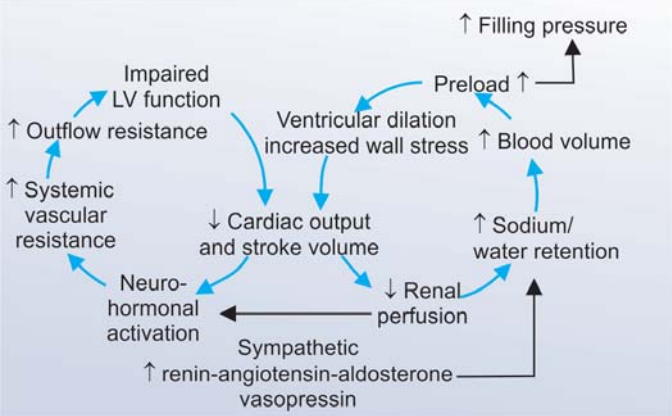


FIGURE 7: The vicious cycle of adverse left ventricular remodeling in systolic heart failure initiated by impaired systolic function is illustrated

decreases left ventricular systolic function. These neurohormonal changes also contribute to establish the vicious cycle.

The ischemic heart disease is the most common cause of systolic heart failure. In acute coronary syndromes, ventricular remodeling is initiated soon after the onset of myocardial infarction. The infracted segments expand due to stretching and thinning. There is myocyte necrosis and disruption of the extracellular matrix with disorganization of the collagen fibrils in the infracted segment. There is also accumulation of inflammatory cells which release cytokines and increase oxidative stress and promotes myocyte necrosis. There is also myocyte thinning and slippage. In the remote noninfarcted segments, there is myocyte hypertrophy, which can be eccentric and concentric. There is continued myocyte loss due to necrosis and apoptosis. The disruption of the collagen matrix in the noninfarcted segments occurs allowing these segments to stretch. The net effect of these morphologic changes in infarcted and noninfarcted segments is a dilated left ventricle with an increase in ventricular volumes and altered geometry. The features of the post-infarction left ventricular remodeling are illustrated in Figure 8.

It should be appreciated that the adverse left ventricular remodeling can occur despite adequate recanalization of the infarct related artery but a threshold magnitude of myocardium needs to be damaged. It is uncommon for the adverse remodeling to occur if the left ventricular ejection fraction is greater than 40% and the infarct size is relatively small.[49,50]

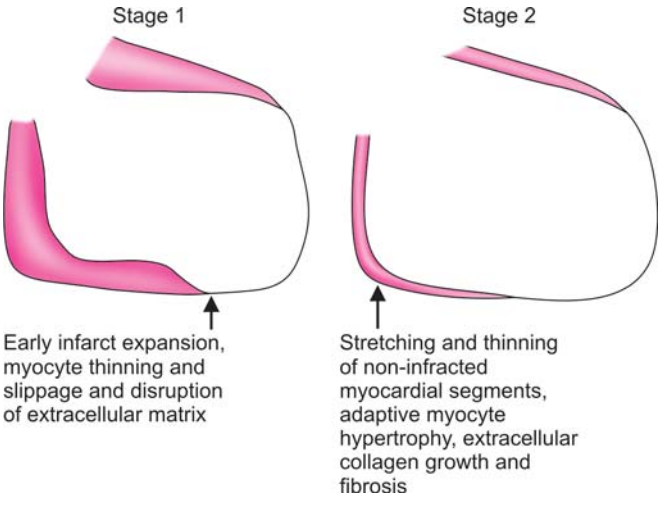


FIGURE 8: Schematic illustrations of left ventricular remodeling soon after acute myocardial infarction (stage 1) and late after myocardial infarction (stage 2) are shown

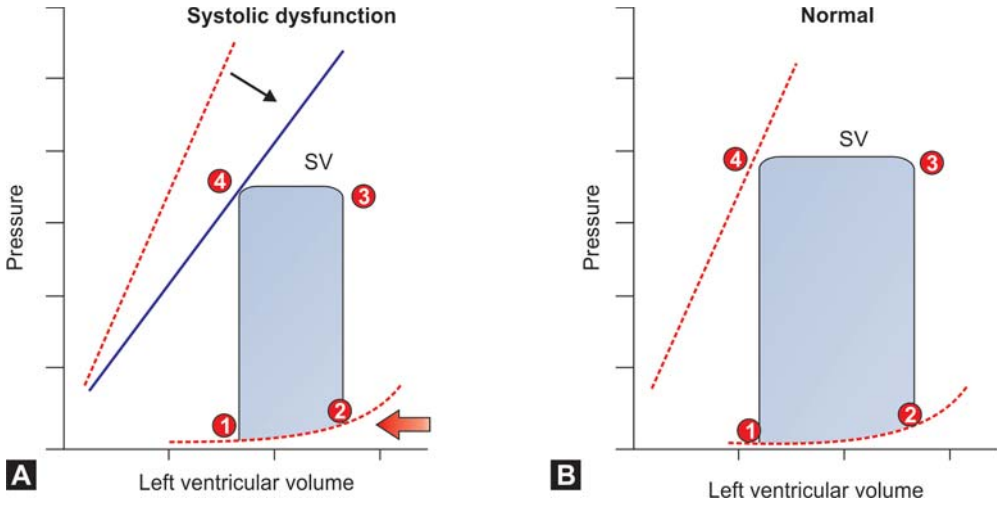
FUNCTIONAL DERANGEMENTS AND HEMODYNAMIC CONSEQUENCES

The principal myocardial dysfunction in systolic heart failure is impaired left ventricular contractility. The analysis of left ventricular pressure volume loop demonstrates a rightward and downward shift of the left ventricular end-systolic pressure volume line indicating reduced contractile function (Figs 9A and B). The stroke volume declines and there is an increase in end-systolic and end-diastolic volumes. Initially, stroke volume is maintained by Frank-Starling mechanism due to increased preload. With a further deterioration of ventricular function; however, stroke volume declines and there is an increase in residual volumes. The increase in left ventricular volume is associated with increased wall stress (afterload) which causes further impairment of left ventricular systolic function.

The hemodynamic consequences of impaired pump function in systolic heart failure are characterized by decreased stroke volume and cardiac output and increased left ventricular diastolic pressure. There is a passive increase in left atrial and pulmonary venous pressures which is associated with increased pulmonary artery pressure. The pulmonary arterial hypertension is predominantly post capillary. However, in chronic severe systolic heart failure, there is also an increase in pulmonary vascular resistance. This mixed type of pulmonary arterial hypertension increases right ventricular afterload and induce right ventricular failure. Thus there is an increase in systemic venous pressure with its hemodynamic consequences such as lower extremity edema.

INITIAL TREATMENT OF SYSTOLIC HEART FAILURE

The risk factors for developing heart failure (Stage A) are hypertension, diabetes, obesity, coronary artery disease, insulin resistance, male gender and age. Except age and gender, the other risk factors are modifiable and every effort should be made to treat these risk factors (Table 10). The patients in stage B have structural heart disease and have asymptomatic left ventricular systolic dysfunction. In time, these asymptomatic patients develop overt heart failure. The rate of development of symptomatic heart failure in untreated patients is approximately 10% per year.[51] Furthermore the mortality in the untreated patients is much higher. In the studies of left ventricular dysfunction (SOLVD) trial, the yearly mortality rate was about 5% per year in patients with asymptomatic left ventricular systolic dysfunction.[51] Large clinical trials have demonstrated that treatment with angiotensin-converting enzyme inhibitors in these patients is associated with decreased cardiovascular mortality and morbidity.[51] In post-infarction patients there is a substantial reduction in total mortality, cardiovascular mortality and the risk of developing heart failure with treatment with angiotensin-converting enzyme inhibitors compared to placebo.[52] The beta-blocker therapy also decreases morbidity and mortality in patients with acute



FIGURES 9A AND B: Schematic illustrations of left ventricular pressure-volume loops in normal individuals (B) and patients with systolic dysfunction (A) are shown. The straight dotted line is the end systolic pressure-volume line, and the curve dotted line represents the normal pressure volume relation in diastole. The area within the loop represents left ventricular stroke work. In patients with systolic heart failure, the end systolic pressure-volume line shifts downward and to the right due to reduced contractile function. There is a reduction in stroke volume and an increase in end systolic and end diastolic volumes. Initially, stroke volume is maintained by Frank-Starling Mechanism due to the increased end diastolic volume (preload). With further progression of heart failure, there is reduction in stroke volume and cardiac output

TABLE 10

Systolic heart failure

Management

- Stage A—treat hypertension
  - Encourage smoking cessation
  - Treat lipid disorders
  - Encourage regular exercise
  - Discourage alcohol abuse
  - Discourage illicit drug use
  - Angiotensin inhibition in appropriate patients
- Stage B—treatment for Stage A
- Angiotensin inhibition in appropriate patients
- Beta-blockers in appropriate patients

coronary syndromes irrespective of the symptomatic and functional status.[53] In the carvedilol post-infarction survival controlled evaluation (CAPRICORN) trial, a large number of patients with left ventricular ejection fraction of 40% or less were randomized to receive carvedilol or placebo. The patients were already being treated with angiotensin-converting enzyme inhibitors and received appropriate reperfusion therapy. There was a significant reduction in all cause mortality, cardiovascular mortality and nonfatal myocardial infarction during follow-up of about 15 months. The majority of patients were asymptomatic in this trial.[54] The treatment with aldosterone antagonist in post-infarction patients is also associated with decreased risks of developing heart failure, cardiovascular mortality, sudden cardiac death and ventricular remodeling. In the eplerenone post-acute myocardial infarction heart failure efficacy and survival study (EPHESUS) trial patients following myocardial infarction with ejection fraction of 40% or less was randomized to receive placebo or eplerenone, a selective aldosterone antagonist. Treatment with eplerenone was associated with a reduction in all cause mortality, cardiovascular mortality, sudden cardiac death and adverse ventricular remodeling.[55,56] The treatment of the risk factors for developing heart failure such as management of hypertension, diabetes and obesity are similar to those in patients in stage A heart failure (Table 11).[57] Increased systolic and diastolic blood pressures are major risk factors for developing heart failure.[58] The controlled studies have reported that adequate treatment of hypertension is associated with approximately 50% reduction of the risks of developing new heart failure.[59] For the treatment of hypertension, the use of angiotensin-converting enzyme inhibitors or angiotensin receptor blocking agents are preferable to alpha adrenergic blocking agents for reduction of the risk of development of heart failure.[60,61] Alpha-adrenergic blocking agents have the potential to increase the risk of heart failure. Obesity, insulin resistance and type 2 diabetes increase the risk of development of heart failure.[62,63] In the type 2 diabetes hypertension, cardiovascular events and ramipril (DIABHYCAR) study, in patients with type 2 diabetes and albuminuria about 5% of patients developed heart failure, but over 30% of these patients died during follow-up period.[64] The risk of developing heart failure is approximately threefold higher in women than in men with type 2 diabetes.[65] In patients with diabetes with or without hypertension, treatments with angiotensin-converting

TABLE 11

Systolic heart failure Stage C

- Angiotensin inhibition therapy
- Adrenergic blocking agents
- Aldosterone antagonists in severe heart failure
- Hydralazine-isosorbide dinitrate, in self reported blacks
- Diuretics to relieve congestive symptoms
- Digitalis in selected patients
- Treatments for Stage A

enzyme inhibitors or angiotensin receptor blocking agents should be considered not only to reduce the risk of end organ damage but also to reduce the risk of development of heart failure.[66-68] The metabolic syndrome is defined when there is clustering of risk factors for coronary artery disease and it is diagnosed when any three of the following criteria are present: abdominal adiposity, hypertriglyceridemia, low high density lipoprotein, hypertension and fasting hyperglycemia. The metabolic syndrome is associated with increased risk of developing heart failure.[69] Hyperlipidemia is one of the major risk factors of atherosclerotic vascular disease. In patients with history of myocardial infarction, adequate control of lipids particularly with the use of "statins" has the potential to decrease the risk of death and development of heart failure.[70] There is controversy regarding the use of aspirin concurrently with angiotensin-converting enzyme inhibitors. Angiotensin-converting enzyme inhibitors reduce degradation of bradykinin and bradykinin mediated vasodilatation has been postulated as one of the mechanisms of their beneficial effects. Aspirin inhibits synthesis of vasodilator prostaglandins and can interfere with the efficacy of angiotensin-converting enzyme inhibitors. It has been reported that the survival benefit of the angiotensin-converting enzyme inhibitors is reduced with concurrent treatment with aspirin.[71,72] However, in the meta-analysis involving 12,763 patients, the survival benefit of the angiotensin-converting enzyme inhibitors was not significantly reduced with aspirin treatment.[73] Thus, in patients with coronary artery disease, aspirin treatment is indicated. In absence of coronary artery disease, aspirin should be avoided.

SYMPTOMATIC SYSTOLIC HEART FAILURE

PHARMACOLOGIC TREATMENTS

In patients in stage C heart failure, angiotensin-converting enzyme inhibitors or angiotensin receptor blocking agents and beta-blocking agents are indicated. These therapies have been documented not only to ameliorate symptoms but also to improve morbidity and mortality (Figs 10 and 11) (Table 7). The angiotensin-converting enzyme inhibitors reduce the formation of angiotensin by blocking the angiotensin-converting

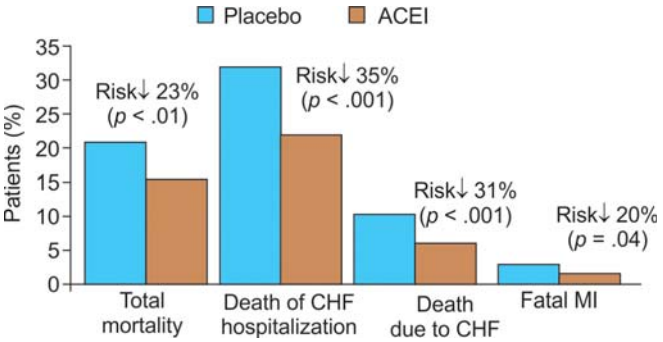
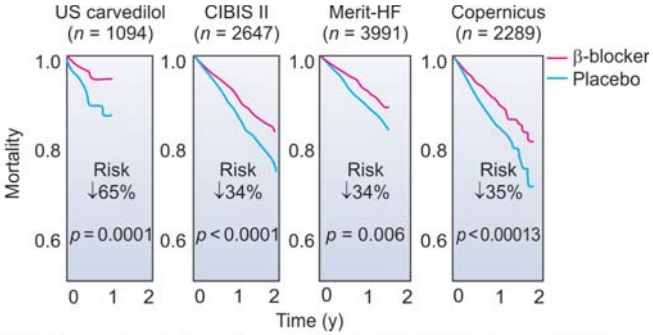


FIGURE 10: The effects of angiotensin-converting enzyme inhibitors on the mortality and morbidity of patients with systolic heart failure are illustrated. Compared to placebo there is a reduction in total mortality, death or hospitalizations for heart failure, death due to heart failure and fatal myocardial infarction. (Abbreviations: ACEI: Angiotensin-converting enzyme inhibitor; MI: Myocardial infarction). (*Source:* Modified from Garg, et al. JAMA. 1995;273:1450-6)



CIBIS: Cardiac insufficiency bisoprolol study; MERIT-HF: Metoprolol CR/XL randomized intervention trial in congestive heart failure; COPERNICUS: Carvedilol prospective randomized cumulative survival trial

FIGURE 11: The mortality benefit of beta-blocker treatment in the United States. Carvedilol, MERIT-HF, CIBIS-II and COPERNICUS trials are illustrated

enzymes. The use of angiotensin-converting enzyme inhibitors is associated with reverse ventricular remodeling, improved ventricular function and decrease in morbidity and mortality. To assess the effects of angiotensin-converting enzyme inhibitors on mortality and morbidity of patients with chronic systolic heart failure, the different types of angiotensin-converting enzyme inhibitors have been used in the randomized clinical trials.[74] The first placebo controlled randomized trial was with the use of enalapril. In the cooperative north scandinavian enalapril survival study (CONSENSUS), patients with severe heart failure, in NYHA class III B or IV, were randomized. There was a substantial survival benefit with enalapril compared to placebo.[75] Subsequently, a large number of randomized trials have been performed in patients with less severe heart failure and in patients with asymptomatic left ventricular systolic dysfunction. The results of 32 randomized clinical trials are summarized in the Figure 10. There was a substantial and statistically significant reduction in total mortality (23%), death or hospitalization for heart failure (35%), death due to heart failure (31%) and fatal myocardial infarction (20%). The magnitude of benefit in mortality and morbidity were similar with the various types of angiotensin-converting inhibitors that were used in these studies.[76-78] There was also amelioration of symptoms and improvement in exercise tolerance.[76] The commonly used angiotensin inhibitors and their doses are summarized in Table 12. The serious adverse effects of angiotensin-converting enzyme inhibitor therapy are uncommon. The most common complication is non-productive irritating cough which most patients tolerate. However, some patients get intolerant to cough and discontinue the therapy. The cough is mediated by bradykinin and is unrelated to the type of angiotensin-converting enzyme inhibitors used. Angioedema, which is also related to bradykinin is a rare complication of angiotensin-converting enzyme inhibitors. But it is a life threatening complication. The incidence of angioedema is about 1%. In patients with history of angioedema angiotensin-converting enzyme inhibitors should not be used. A significant hyperkalemia is another contraindication for treatment with angiotensin converting enzyme inhibitors. It should be appreciated that even severe renal dysfunction is not a contra-indication for use of angiotensin-converting enzyme inhibitors.

TABLE 12

Angiotensin inhibitors used in the treatment of heart failure

Agent	*Total Daily Dose (mg)*	*Frequency*
ACEI		
Captopril	75–150	Thrice daily
Enalapril	10–40	Twice daily
Fosinopril	10–40	Once daily
Lisinopril	10–40	Once daily
Quinapril	10–40	Once or twice daily
Ramipril	2.5–20	Once or twice daily
Trandolapril	1–4	Once daily
ARB		
Losartan	25–50	Twice daily
Valsartan	150–300	Once daily
Candesartan	4–16	Once daily

(Abbreviations: ACEI: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin receptor blocking agent)

Another contra-indication of angiotensin-inhibition therapy is during pregnancy as their use can be associated with fetal renal failure.

The starting dose of angiotensin-converting enzyme inhibitors should be low, particularly in hypotensive patients and the dose should be titrated slowly. If there is a rapid deterioration of renal function or marked increase in serum potassium, the angiotensin-converting enzyme inhibitors should be discontinued.

In patients intolerant to angiotensin-converting enzyme inhibitors or with contraindications for their use, angiotensin receptor blocking agents should be considered. The angiotensin receptor blocking agents exert their beneficial effects by blockade of the angiotensin II receptor subtype I and the angiotensin-converting enzyme pathway is not involved. The blockade of angiotensin receptors is associated with increased levels of angiotensin-converting enzyme due to activation of the negative feedback loop. Thus there is increased production of bradykinin which may be associated with increased incidence of both of its side effects and beneficial effects.

The three angiotensin receptor blocking agents that are used for the treatment of chronic heart failure are losartan, valsartan and candesartan. In the valsartan heart failure trial (Val-Heft), 5,010 patients were randomized to receive either valsartan or placebo. The patients were in NYHA Class II or III. The results showed that there was a slight but statistically significant reduction in a clinically composite endpoint consisting of all-cause mortality and hospitalizations for heart failure.[79] In the losartan heart failure survival study (ELITE II), the patients with left ventricular ejection fraction of less than 40% were randomized to receive losartan or enalapril. There was no difference between the angiotensin receptor blocking agents and the angiotensin-converting enzyme inhibitors.[80] In the candesartan in heart failure assessment of reduction in mortality and morbidity (CHARM) trial, the effects of candesartan was compared to those of angiotensin-converting enzyme inhibitors.[81,82] This study reported a small but statistically significant benefit of candesartan.[83]

That heart failure is a hyper-adrenergic state has been documented by many studies. The increased systemic and regional adrenergic activity is associated with deleterious hemodynamics and adverse vascular and ventricular remodeling.

In addition, there is downregulation of myocardial beta-adrenergic-1 receptors with little or no change of the beta-adrenergic-2 receptors. The clinical implication of these changes in myocardial adrenergic receptors subtypes density is that the myocardial contractile response to adrenergic stimulation is blunted in patients with heart failure.

The increased cardiac adrenergic activity is associated with increased myocardial oxygen demand, calcium overload, energy wastage, and myocardial ischemia. Myocyte hypertrophy occurs as well as disorganization of myocardial architecture. There is a direct toxic effect of catecholamines on the cardiac myocytes which may cause myocyte necrosis. This is similar to that of pheochromocytoma cardiomyopathy.[84]

The rational of beta-blocker therapy in systolic heart failure is to decrease the adverse effects of increased adrenergic activity. There are several potential mechanisms for the beneficial effects of beta-blocker therapy. There is a decrease in systemic vascular resistance which reduces left ventricular afterload and can improve left ventricular ejection fraction.[85-87] A decrease in heart rate is associated with a reduction in the reversed force frequency relation which enhances contractile function. Furthermore, there is improvement in ventricular filling and relaxation. During chronic beta-blocker therapy, left ventricular reverse remodeling occurs. There is reduction in left ventricular end-diastolic and end-systolic volume, and an increase in ejection fraction. There is also enhanced contractile response of the left ventricle. Reverse remodeling is also associated with improved survival. An adequate reduction in heart rate is necessary for the beneficial effects including survival benefit of beta-blocker therapy. The magnitude of decrease in heart rate but not the dose of beta blockers used is associated with the magnitude of decrease in mortality.[88] It should be appreciated that initially with introduction of beta-blocker therapy there may be deterioration of hemodynamics, and left ventricular function due to decrease in the contractile function. However, usually in 6–8 weeks, there is improvement in symptoms and left ventricular function.

Several prospective randomized trials have documented symptomatic improvement and prognosis with beta-blocker therapy (Fig. 11). In an earlier, the metoprolol in dilated cardiomyopathy (MDC) trial, 383 patients with non-ischemic dilated cardiomyopathy were randomized to receive metoprolol tartrate (50–75 mg) or placebo. During a follow-up period of approximately 12 months there was a significant improvement in hemodynamics and there was a trend for reduction in mortality and need for cardiac transplantation.[89] In another earlier, the cardiac insufficiency bisoprolol survival (CIBIS I) trial, 641 patients with either ischemic or non-ischemic dilated cardiomyopathy were randomized to receive bisoprolol (target dose, 5 mg), or placebo. During a follow-up of approximately 1.9 years, there was a trend to lower mortality and decreased rate of hospital admissions for worsening heart failure.[90]

A number of large prospective randomized clinical trials have been performed and all have demonstrated survival benefit

of long-term beta-blocker treatment in patients with chronic systolic heart failure.

In the US Carvedilol trial, 1,094 patients with left ventricular ejection fraction of 35% or less were randomized to receive either carvedilol or placebo. The patients were receiving angiotensin-converting enzyme inhibitors and diuretics before randomization. This trial reported a 65% reduction in all-cause mortality during the follow-up period.[91] In the carvedilol prospective randomized cumulative survival (COPERNICUS) trial, 2,289 patients in NYHA class III or IV, being treated with standard heart failure therapy, were randomized to receive carvedilol (target dose 25 mg twice daily) or placebo. During a follow-up of about 24 months, there was a 35% reduction in risk of death with carvedilol treatment.[92] In the metoprolol CR/XL randomized intervention trial in congestive heart failure (MERIT-HF), 3,991 patients with systolic heart failure, in NYHA class II and III with a mean ejection fraction of 28%, were randomized to receive either placebo or metoprolol succinate (target dose 200 mg a day). Patients in both groups received standard background treatment with angiotensin-converting enzyme inhibitor or angiotensin receptor blocking agent, diuretics and digoxin. During only about a follow-up period of 1 year, there was a 34% reduction in the risk of total mortality. There was also reduction in the risk of sudden cardiac death, heart failure hospitalization and functional class.[93] In the cardiac insufficiency bisoprolol survival (CIBIS II) trial, 2,647 patients with systolic heart failure with either ischemic or non-ischemic cardiomyopathy were randomized to receive either placebo or bisoprolol (target dose of 10 mg). During the follow-up period, there was 34% reduction in total mortality, 44% reduction in sudden cardiac death and 20% reduction in hospitalization with bisoprolol treatment.[94] In the Carvedilol Or Metoprolol European trial (COMET), more than 3,000 patients with moderately severe heart failure were randomized to receive metoprolol tartrate (target dose of 50 mg twice daily) or carvedilol (target dose of 25 mg twice daily). With carvedilol there was a 17% greater reduction in mortality.[95] It needs to be appreciated that all beta-adrenergic antagonists do not provide benefit. In the beta-blocker evaluation survival trial (BEST), 2,708 patients in NYHA class III or IV were randomized to receive bucindolol or placebo.[96] After about 2 years of follow-up, the trial was terminated as there was no probability of survival benefit with bucindolol. There was a trend towards improved survival in patients in NYHA class III and with left ventricular ejection fraction of greater than 20%. There was no benefit in patients with an ejection fraction of 20% or less. There was also no benefit in blacks.

It has been postulated that the differences in the pharmacologic properties may explain lack of benefit with bucindolol compared to that of bisoprolol, metoprolol and carvedilol. Bisoprolol is a selective beta-1 adrenergic receptor antagonist with a vasodilating property. Metoprolol is also a selective beta blocker but, unlike bisoprolol, it does not possess a vasodilating effect. Carvedilol is a non-selective beta-blocking agent and has weak alpha-1 blocking property. It also appears to have antioxidant effects and decrease oxidative stress. Bucindolol, although is similar to carvedilol, it has inverse agonist and intrinsic sympathomimetic activity.[97,98]

Nebivolol, a selective beta-1 adrenergic antagonist with nitric oxide-mediated vasodilating property, was used in the study of effects of nebivolol intervention on outcomes and rehospitalization in seniors with heart failure (SENIORS) trial. During the follow-up period of approximately 12 months, there was a significant reduction in the composite endpoint of death, or cardiovascular hospitalization in the elderly patients with left ventricular ejection fraction of less than 35%.[99]

That complete adrenergic inhibition may not be beneficial in patients with heart failure has also been documented.[100] Moxonidine, a centrally acting sympatholytic agent which decreases adrenergic activity substantially, was investigated in the moxonidine in heart failure (MOXCON) trial. The trial was prematurely terminated as there was a higher mortality in the patients treated with moxonidine. In clinical practice, presently bisoprolol, metoprolol succinate or carvedilol are recommended for the treatment of systolic heart failure. The optimal dose of bisoprolol is 10 mg once daily, of metoprolol succinate 200 mg once daily and of carvedilol 25 mg twice daily. During initiation of beta-blocker therapy, the dose of the beta blocker should be low and the dose should be increased slowly to the maximum tolerated dose. If the patients are admitted for the treatment of decompensated heart failure, the beta blockers should not be discontinued. The discontinuation of beta blockers is associated with worse prognosis.[101] It should be appreciated that the beta-blocker therapy is not contraindicated in patients with chronic obstructive pulmonary disease, renal failure or diabetes. It can also be used in combination with angiotensin-converting enzyme inhibitors or angiotensin receptor blocking agents and aldosterone antagonists. The beta-blocker therapy appears to be equally effective in men and women, in whites and blacks and in younger and older patients.[102]

The aldosterone receptor antagonists spironolactone and eplerenone are effective in producing left ventricular reverse remodeling and improving prognosis of patients with systolic heart failure. The efficacy of spironolactone was assessed in the Randomized Aldactone Evaluation Study (RALES) trial.[103a] In this study, 1,663 patients with systolic heart failure in NYHA III or IV were randomized to receive aldactone (target dose of 25–50 mg) or placebo. The left ventricular ejection fraction before randomization required to be 35% or less. The mean ejection fraction was 25% in the randomized patients. The patients with plasma concentration of creatinine of greater than 2.5 mg/dL or a plasma concentration of serum potassium greater than 5.0 mEq/l were excluded. After an average duration of follow-up of 24 months, the trial was prematurely discontinued because there was a 30% reduction in all-cause mortality which was due to reduction in risk of sudden cardiac death and death from heart failure (Fig. 12). There was also a 35% reduction in the rate of hospitalization for worsening heart failure. These benefits were observed in patients with ischemic or non-ischemic dilated cardiomyopathy.

The selective aldosterone antagonist eplerenone was also demonstrated to produce beneficial effects on survival and development of congestive heart failure in the post-infarction patients.[55] In the eplerenone post-acute myocardial infarction heart failure efficacy and survival study, 3–14 days after acute myocardial infarction with left ventricular ejection fraction of

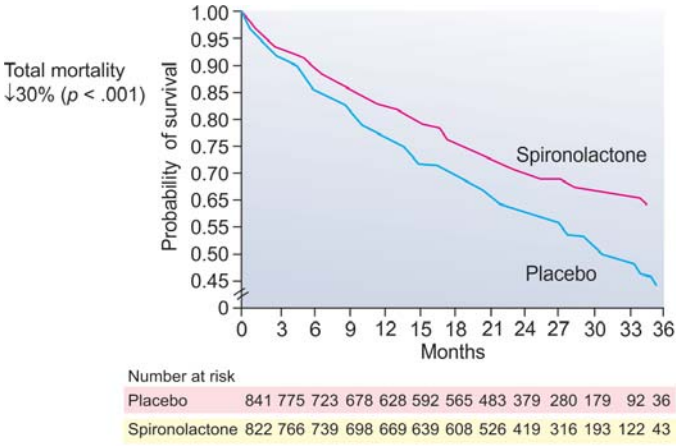


FIGURE 12: The effects of spironolactone on mortality of patients with severe chronic heart failure in randomized aldactone evaluation study (RALES). (*Source:* B Pitt, et al. N Engl J Med. 1999;341:709, with permission)

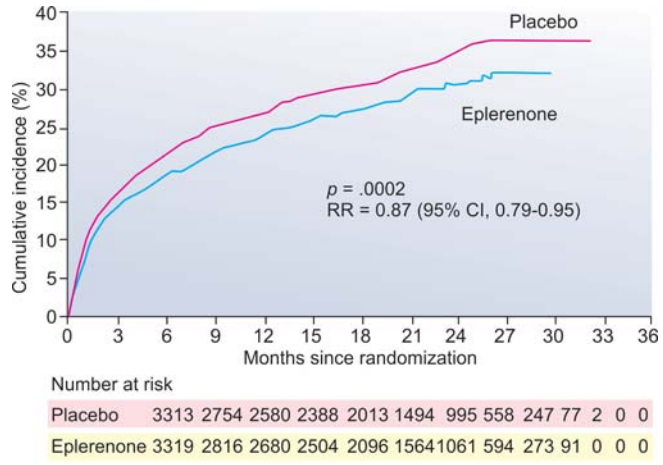


FIGURE 13: The effects of eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction (*Source:* B Pitt, et al. N Engl J Med. 2003;348:1309, with permission)

40% or less, 6,642 patients were randomized to receive eplerenone (target dose of 50 mg daily) or placebo. The patients were adequately treated with reperfusion therapy and angiotensin inhibition and beta-blocker therapy before randomization. There was a 15% reduction in all-cause mortality, sudden cardiac death, and hospitalizations for heart failure (Fig. 13).

Both spironolactone and eplerenone have been shown to exert beneficial effects on left ventricular remodeling. There is a reduction in left ventricular end-diastolic and end-systolic volumes and an increase in ejection fraction. There is also a reduction in the collagen turnover marker procollagen type I N-terminal propeptide, indicating reduced fibrosis.[103b,c]

Spironolactone and eplerenone are competitive antagonists of mineralocorticoid nuclear receptor aldosterone. Aldosterone receptors are present not only in the zona glomerulosa of the adrenal cortex but also in the myocytes and in the coronary vascular bed. The cardiac aldosterone synthesis by the aldosterone receptors is increased in heart failure and is mediated by enhanced activity of aldosterone synthase which is stimulated by angiotensin II.[104] The angiotensin II is the major stimulus for the aldosterone release. Thus theoretically inhibition of the formation of angiotensin may be associated with decreased level of aldosterone. However, the effects of aldosterone antagonists are not diminished with the concurrent use of angiotensin-converting enzyme inhibitors or angiotensin receptor blocking agents. Aldosterone antagonists decrease myocyte and vascular smooth muscle cell hypertrophy and decrease myocardial fibrosis, the principal mechanisms of their beneficial effects on ventricular remodeling.

Gynecomastia, painful breast enlargements in females, menstrual irregularities, impotence and decreased libido are the endocrine side effects specific to spironolactone. These side effects result from binding to androgen and progesterone receptors. Eplerenone is a selective aldosterone antagonist and is not associated with these side effects.[105]

The serious and potentially life-threatening complication of aldosterone antagonism is hyperkalemia. A number of risk factors contribute to hyperkalemia: increasing age, diabetes mellitus, pre-existing renal dysfunction, hypovolumia, and concurrent use of both an angiotensin-converting enzyme inhibitor and angiotensin receptor-blocking agent. Uses of potassium supplements or potassium containing salt substitutes are also contributory. Hyponatremia is also a side effect of aldosterone antagonism. Lack of monitoring of renal function and electrolytes may be associated with severe unexpected hyperkalemia and increased mortality.[106]

It is suggested that the starting dose of aldosterone antagonists should be low and the electrolytes and renal function should be evaluated at 1 week and then at 2 weeks before increasing the dose. After increasing the dose, the electrolytes and renal function should be repeated again after 1 and 2 weeks. It is advisable to monitor renal function and electrolytes more frequently in patients with relative hypotension and more severe heart failure. It is also important not to use aldosterone antagonists in patients with serum creatinine greater than 2.5 mg/dl or serum potassium greater than 5.0 mEq/l.

Aldosterone antagonists are usually used for the treatment of severely symptomatic patients (NYHA III) with systolic heart failure. However, it has been reported that eplerenone is effective in mildly symptomatic patients (NYHA II) in reducing mortality and morbidity. In the eplerenone in patients with systolic heart failure and mild symptoms (EMPHASIS–HF) trial, 2,737 patients with ejection fraction of not higher than 35% were randomized either to receive eplerenone (up to 50 mg daily) or placebo. The primary endpoint was a composite of death from cardiovascular causes or hospitalizations for heart failure. After a median follow-up period of 21 months, the primary outcome occurred in 25.9% in the placebo group and in 18.3% in the eplerenone treated group. The mortality was 12.5% in the eplerenone treated patients and 15.5% in the placebo group. These findings suggest that eplerenone decrease mortality and morbidity in mildly symptomatic patients with systolic heart failure.[107]

Omega-3 fatty acids have the potential to improve left ventricular ejection fraction and promote reverse remodeling in patients with non-ischemic systolic heart failure.[108] In the GISSI-HF trial, 133 clinically stable patients with non-ischemic dilated cardiomyopathy with an ejection fraction of 45 % or

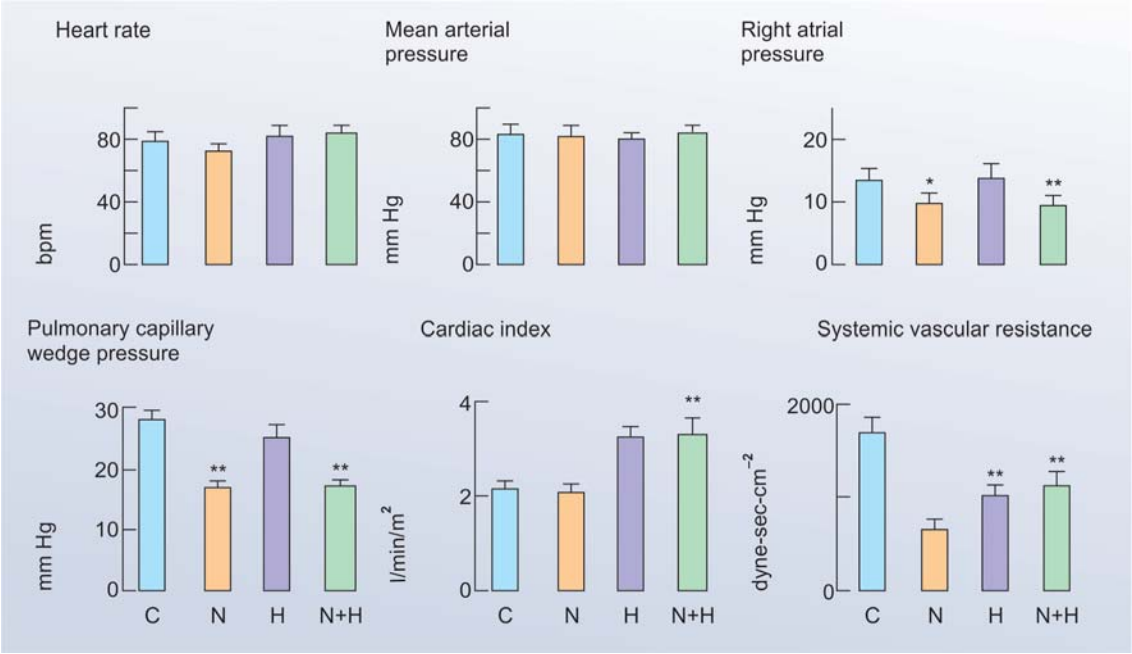


FIGURE 14: Hemodynamic effects of hydralizine alone, nitrates alone, and of combination of hydralazine and nitrates are illustrated. The combination therapy decreased pulmonary capillary wedge pressure and increased cardiac output. (Abbreviations: C: Control; H: Hydralazine; N: Nitrates; H+N: Hydralazine and nitrate combination). (*Source:* B Massie, et al. Am J Cardiol. 1977;40:794-801, with permission)

less were randomized to receive omega-3 (2 capsules/day) or placebo. After follow-up of approximately 11 months, there was a statistically significant increase in left ventricular ejection fraction. There was also an increase in peak maximal oxygen consumption (VO_2). There was no beneficial effect of statin rosuvastatin.

Hydralazine and nitrates are effective in improving symptoms and prognosis of patients with severe heart failure. Hydralazine is predominantly an arteriolar dilator and decrease systemic vascular resistance, increases stroke volume and cardiac output. Although it is a vasodilator antihypertensive agent, hydralazine does not decrease systolic arterial pressure in patients with heart failure. The systolic blood pressure may actually increase when there is increase in stroke volume. In patients with heart failure there is also no reflex increase in heart rate.[109] This is partly due to impaired baroreceptor sensitivity in heart failure. Furthermore, increased stroke volume is associated with loading of the baroreceptors. The nitrates are predominantly venodilators and decrease systemic and pulmonary venous pressures. The hemodynamic effects of combination of hydralazine and nitrate are characterized by a decrease in right atrial, pulmonary capillary wedge and mean pulmonary heart pressure. There is a reduction in systemic vascular resistance, increase in stroke volume and cardiac output without a significant change in heart rate and blood pressure (Fig. 14).[110]

A number of randomized clinical trials have been performed to assess effects of combination of hydralazine and isosorbide dinitrate on survival of patients with systolic heart failure. In the veteran administration heart failure I, 642 men in NYHA class II or III were randomized to receive placebo, prazosin or hydralazine and isosorbide dinitrate.[111] With hydralazine and isosorbide dinitrate there was a reduction in all-cause mortality compared to placebo. The survival benefit was found in blacks. There was no difference in mortality between prazosin and placebo. In the veterans administration heart failure trial II, hydralazine and isosorbide dinitrate combination treatment was compared to angiotensin-converting enzyme inhibitor.[112] The mortality rate was lower with angiotensin-converting enzyme inhibitors compared to hydralazine and nitrate.

In the African-American heart failure trial (A-HeFT), 1,050 self-reported blacks in NYHA III or IV receiving standard heart failure treatment including angiotensin-inhibition therapy (87%), beta blockers (74%), and spironolactone (39%) were randomized to fixed doses of hydralazine (37.5–75 mg three times daily) and isosorbide dinitrate (20–40 mg three times daily). The trial was terminated prematurely due to substantial survival benefit with hydralazine and isosorbide dinitrate (Table 13).[113]

TABLE 13

Results A-HeFT study

Endpoint	*Hydralazine nitrate (95% CI)*	*Hazard*	*Placebo*	*Risk Ratio*	*p value reduction*
Composite score	– 0.16 +/– 1.93	– 0.47 +/-2.04	N/A	N/A	< 0.021
All-cause mortality	6.2%	10.2%	0.57	43%	0.012
First hospitalization For heart failure	16.4%	24.4%	0.61	39%	< 0.001

(Abbreviation: NA: Not available)

It has been postulated that the increased nitric oxide availability may be contributory to the beneficial effects of hydralazine and nitrates-combination therapy. Nitrates are nitric oxide donor and improve endothelial function. Hydralazine may also be an antioxidant and it decreases nitrate tolerance.[114]

The guidelines recommend the use of hydralazine and nitrate combination therapy for all patients, irrespective of race or gender, with severe systolic heart failure who remain symptomatic despite standard therapy.[57]

The complications of hydralazine and nitrate therapy are uncommon. With the dose of hydralazine used for the treatment of heart failure, the lupus-like syndrome does not occur.

Amlodipine is a dihydropyridine calcium-channel blocker which has vasodilating property, and it has been tested in randomized clinical trials to assess its potential beneficial effects in patients with systolic heart failure due to ischemic or non-ischemic dilated cardiomyopathy. It is a long acting arteriolar dilator and decreases systemic vascular resistance. Like all calcium-channel blockers it also exerts a negative inotropic effect although its negative inotropic effect appears to be less compared to that of other calcium-channel blockers.

The effects of amlodipine were assessed in the two prospective randomized amlodipine survival evaluation (PRAISE) studies.[115] Although there was a trend for benefit in patients with non-ischemic dilated cardiomyopathy, the overall results were neutral. Thus there is no indication for its use in patients with systolic heart failure except for the treatment of associated hypertension or angina (please see the chapter on Vasodilators and Neurohormone Modulators).

Diuretics are essential to relieve congestive symptoms. In patients with signs and symptoms of pulmonary and systemic venous congestion, initially loop diuretics are used. The loop diuretics that are used in clinical practice are furosemide, ethacrynic acid, bumetanide and torsemide. Although furosemide is the most frequently used diuretic, it should be appreciated that when it is administered orally its bioavailability is only 50%. The absorptions of torsemide and bumetanide are greater and more predictable. Thus, in patients poorly responsive to furosemide, torsemide or bumetanide should be considered. The relative efficacy of furosemide and torsemide were compared in an open label randomized clinical trial. In this trial, 234 patients with heart failure were randomized.[116] The primary endpoint was the hospital admissions for heart failure. During a follow-up period of 1 year, the hospital admission rates with furosemide was 32%, and with torsemide 17%. There was also reduced incidence of fatigue with torsemide. The dose of the loop diuretics are increased according to the diuretic response. The daily dose of furosemide in heart failure is between 20 mg and 240 mg, of bumetanide 0.5 mg and 10 mg, of ethacrynic acid 50 mg and 200 mg and of torsemide 10 mg and 200 mg. However, the usual doses that are used initially for patients with normal glomerular filtration rate with mild to moderately severe heart failure are lower. In these patients the usual daily dose of furosemide is 40–80 mg, of bumetanide 2–3 mg and of torsemide 20–50 mg. In patients with renal failure larger doses of diuretics are required. For individual patients the diuretic doses should be determined based on clinical response.

During chronic diuretic therapy, there is potential for improvement in hemodynamics and left ventricular function. Left ventricular end diastolic volumes may decrease which is associated with decreased wall stress. Thus, there is reduction in afterload which is associated with an increase in stroke volume and cardiac output.[117] Chronic diuretic treatments may also improve exercise tolerance.[118]

Patients with severe heart failure may respond poorly to intermittent intravenous administration of furosemide. In these patients, a continuous infusion of furosemide is frequently employed. However, it appears that there is no difference in urine output between intermittent administration and continuous infusion of furosemide The more severe the heart failure is, the more likely that it will be necessary to use combination of diuretics with different sites of action on the nephrons. The loop diuretics are combined with thiazide diuretics and then with potassium sparing diuretics. The most frequently used oral thiazide diuretic is metolazone. The dose of metolazone is between 2.5 mg and 20 mg daily. Initially, a smaller dose, such as 2.5–5 mg twice or thrice per week, is employed. The dose and frequency can then be increased based on diuretic response. Intravenous thiazide diuretics are also used when oral therapy becomes ineffective. Acetazolamide is a proximal tubular diuretic, but it is less potent than the loop diuretics. It is seldom used except for severe diuretic induced metabolic alkalosis.

It should be appreciated that several complications may occur during aggressive diuretic therapy. Deterioration of renal function occurs in approximately 30% of patients with decompensated heart failure receiving diuretics.[119] An electrolyte imbalance, such as hypokalemia and hypomagnesemia, can occur which may induce life-threatening ventricular arrhythmias.[120] Impaired renal function is also associated with poor prognosis.[121,122] Thus, the careful monitoring of renal function and electrolytes are advisable during diuretic therapy. In patients with chronic heart failure, rapid intravenous administration of a loop diuretic is associated with adverse hemodynamic and neurohormonal effects.[123] There is a transient decrease in cardiac output and an increase in plasma norepinephrine, renin, aldosterone and vasopressin levels. In patients with chronic heart failure, however, the magnitude of reduction in stroke volume is small, as these patients are on the flat portion of the Frank-Starling curve. The other complications of diuretic therapy are hyponatremia, hyperuricemia and hyperglycemia. Deafness is a rare but reversible complication when large doses of furosemide or ethacrynic acid are used rapidly (please see the chapter on Diuretics).

The inadequate response to diuretics in heart failure is often called diuretic resistance or cardiorenal syndrome.[124] A number of factors appear to be contributory to the development of cardiorenal syndrome. Decreased renal perfusion due to low cardiac output, renal vasoconstriction and redistribution of cardiac output has been postulated. Inappropriate systemic and renal neuroendocrine activation are important mechanisms. The vasodilatation of the afferent renal arterioles is partly mediated by prostaglandins and non-steroidal anti-inflammatory agents (NSAIDS) which block the prostaglandins reduce the efficacy of the diuretics. The efferent arteriolar vasoregulation is mediated by the renin-angiotensin system. Diuretic therapy is associated with increased renin and angiotensin which may maintain renal blood flow and glomerular filtration rate. The use of angiotensin inhibitors which are indicated for the

treatment of heart failure may contribute to deteriorating renal function in heart failure (please see the chapter on Cardiorenal Syndrome). Another potential mechanism for inadequate response to diuretics in heart failure is decreased sodium load to the tubules due to low cardiac output and a marked reabsorption of sodium.

In patients with obvious volume overload and resistance to diuretic therapy, mechanical means for fluid removal may be employed. Ultrafiltration is effective in removing sodium and water. In the relief for acutely fluid-overload patients with decompensated congestive heart failure (RAPID-CHF) trial, 40 patients were randomized to receive diuretic treatment or ultrafiltration. The removal of fluid after 24 hours was about twofold greater with ultrafiltration.[124] In the ultrafiltration versus intravenous diuretics for patients hospitalized for acute decompensated congestive heart failure (UNLOAD) study, ultrafiltration was compared with intravenous diuretics. In this study, 200 patients were randomized to receive diuretic therapy or ultrafiltration. There was no difference in the dyspnea score, but ultrafiltration was associated with greater fluid loss at 48 hours[125] (please see the chapter on Cardiorenal Syndrome).

In patients with refractory heart failure, intravenous vasodilators are often used to improve hemodynamics and cardiac function. The intravenous vasodilators that are used in clinical practice are sodium nitroprusside, nitroglycerine and nesiritide. Sodium nitroprusside is a balanced vasodilator and causes arterial and venodilatation. The hemodynamic effects are characterized by a reduction in systemic vascular resistance, systemic and pulmonary venous pressures and an increase in cardiac output. Sodium nitroprusside is particularly useful in patients with mitral regurgitation. Thiocyanate toxicity is a rare complication of nitroprusside treatment. However, thiocyanate levels should be monitored when pronged and large doses of sodium nitroprusside are used. There is some evidence to indicate that in patients hospitalized with advanced heart failure stabilization with sodium nitroprusside may be associated with a better long-term prognosis.[126] The dose of nitroprusside for the treatment of advanced heart failure is much lower than for the treatment of hypertensive crisis. The usual dose is between 10 μg/min and 30 μg/min. Nitroglycerin is predominantly a venodilator and decreases systemic and pulmonary venous pressures with little or no change in cardiac output. The major disadvantage of nitroglycerin is the development of tolerance. The tolerance develops when large doses are used for more than 48 hours. The starting dose of nitroglycerin should be low, such as 10–20 μg/min, and gradually increased to the maximum dose of 200 μg/min. However, the dose does not need to be increased if the hemodynamic goals are achieved at a lower dose. Both sodium nitroprusside and nitroglycerin are used for improvement of hemodynamics in patients being considered for cardiac transplantation (please see the chapter on Cardiac Transplantation).

Nesiritide is a synthesized brain natriuretic peptide (BNP) that has been used for the treatment of refractory heart failure. In the vasodilation in the management of acute congestive heart failure (CHF) (VMAC) study, intravenous nesiritide was compared to intravenous nitroglycerin. In this study, nesiritide was reported to be better than intravenous nitroglycerin in improving symptoms and hemodynamics.[127] Nesiritide improves renal function and enhances diuresis in patients without heart failure. In patients with heart failure, however, there is usually little or no improvement in renal function or diuresis. Also, concerns have been expressed about safety of nesiritide as there were reports that nesiritide may be associated with increased risk of mortality.[128] However, a large randomized clinical trial has demonstrated that intravenous nesiritide does not cause increased mortality or deterioration of renal function. Its efficacy was similar to the placebo treatment. In a large multicenter, multinational prospective randomized clinical trial, the effect of nesiritide in patients with acute decompensated heart failure was evaluated.[128a] In the nesiritide group there were 3,496 patients and in the placebo group, 3,511 patients. Approximately 80% of patients had left ventricular ejection fraction less than 40% and 20%, greater than 40%. Nesiritide was not associated with any significant effect on dyspnea. Compared to placebo, it did not decrease or increase rate of death or rehospitalization. Use of nesiritide was not associated with worsening renal function but there were significantly higher number of patients who developed hypotension. Thus routine use of nesiritide cannot be recommended. To determine whether BNP-guided therapy is beneficial in the management of patients with advanced systolic heart failure, in the TIME-CHF trial, 251 patients were randomized to receive intensified BNP-guided therapy and 248 patients to receive standard therapy. There was no benefit in survival or quality of life with BNP-guided therapy.[128b]

In patients with advanced heart failure, the positive inotropic agents are used when there is poor response to standard pharmacologic treatments. Oral digoxin has been employed to improve hemodynamics and left ventricular function in patients with systolic heart failure.[129] In the digitalis investigation (DIG) trial, long-term oral digoxin therapy did not provide any survival benefit. In patients with digoxin blood level of 1.2 ng/ml or higher, there was an increased risk of arrhythmic death. Thus, if digoxin is used it is advisable to keep its blood level less than 1.2 ng/ml.[130]

Intravenous catecholamines and vasopressors are used as supportive treatments in patients with severe refractory heart failure (stage D). Dobutamine is predominantly a beta-1 adrenoreceptor agonist. It also stimulates beta-2 adrenergic receptors. The hemodynamic effects of dobutamine are characterized by an increase in stroke volume and cardiac output and a modest decrease in mean arterial pressure. Thus, if the main objective is to increase arterial pressure, dobutamine is not the drug of choice. The pulmonary capillary wedge and pulmonary artery pressures may not decrease significantly. The heart rate increases modestly.[131] It should be appreciated that as there is downregulation of the myocardial beta-1 receptors, contractile response to dobutamine is blunted.

Dopamine stimulates dopaminergic receptors (DA1 and DA2), and adrenergic receptors (beta-1, beta-2 and alpha). Neuronal release of norepinephrine and its reduced neuronal reuptake occur with dopamine. Thus, circulating norepinephrine levels are substantially increased.[132] The hemodynamic effects of dopamine are related to its dose. The lower dose (1–2 μg/kg/min) is associated with activation of DA1 and DA2 receptors. The stimulation of DA1 receptors causes dilatation of renal and mesenteric vascular system. With this dose, arterial pressure and

cardiac output remain unchanged. With the dose 4–10 μg/kg/min, beta receptors are activated and there is an increase in stroke volume, cardiac output and heart rate. With a further increase in the dose exceeding 10 μg/kg/min, the alpha receptors are stimulated which is associated with systemic vasoconstriction. The hemodynamic effects with higher doses are characterized by increased, systemic vascular resistance, arterial pressure and no further increase in cardiac output. Pulmonary capillary wedge and pulmonary artery pressures may also increase.[133] To increase arterial pressure with dopamine it is necessary to use the alpha receptors stimulating doses.

Norepinephrine and phenylephrine are also used in hypotensive patients to maintain arterial pressures. Norepinephrine is predominantly an alpha receptor agonist, and it does possess mild beta receptor agonist property. Phenylephrine is an alpha receptor agonist. Both norepinephrine and phenylephrine increase systemic vascular resistance and arterial pressure without inducing tachycardia. Stroke volume and cardiac output may decrease due to increased left ventricular afterload.

The relatively cardio-specific phosphodiesterase inhibitors (phosphodiesterase III and IV) milrinone and amrinone exert positive inotropic effect and increase stroke volume and cardiac output. Systemic vascular resistance and mean arterial pressure may decrease. There is also a substantial reduction of systemic and pulmonary venous pressures. However, these agents increase ventricular arrhythmias and may increase mortality.[134] The long-term effects of oral milrinone and other phosphodiesterase inhibitors have been evaluated in a few studies.[135,136] In one clinical trial, 1,088 patients in NYHA class III or IV systolic heart failure were randomized to receive either 40 mg of oral milrinone or placebo. There was a significant increase in the incidence of mortality and morbidity in patients treated with milrinone. Results of a meta analysis of the randomized clinical trials also reported a significant increase in the risk of mortality with the use of oral phosphodiesterase inhibitors.

The phosphodiesterase type V inhibitors are systemic and pulmonary vasodilators and are widely used for the treatment of precapillary pulmonary arterial hypertension and for erectile dysfunction. Preliminary studies indicate that these agents may be beneficial in patients with pulmonary hypertension due to left ventricular dysfunction.[137]

The clinical effects of the calcium sensitizing agents that increase myocardial response to a given concentration of calcium have been tested for the management of refractory heart failure. Levosimendan is an intravenous calcium sensitizing agent, and has been shown to produce beneficial hemodynamic effects which consist of increase in cardiac output and decrease in pulmonary capillary wedge pressure.[138] However, in a randomized clinical trial comparing levosimendan and dobutamine, there was no survival benefit with levosimendan[139] (please see the chapter on Positive Inotropic Drugs).

To assess the effects of reduction of heart rate alone without affecting the beta-adrenergic system in patients with systolic heart failure with left ventricular ejection fraction of less than 40%, a randomized clinical trial was performed with the use of ivabradine.[140] All patients had stable chronic coronary artery disease.

Ivabradine inhibits I(f) currents in the sinoatrial node and lowers the sinus rate. It does not possess any beta-adrenergic antagonist effect.

In the BEAUTIFUL trial, 5,479 patients received ivabradine (5–7.5 mg) and 5,438 patients received placebo during the median follow-up period of 19 months. The primary endpoint was a composite of cardiovascular death, admission to hospital for acute myocardial infarction, and admission to hospital for new onset or worsening heart failure. Ivabradine did not affect primary endpoint (hazard ratio 1.00; 95% confidence interval 0.91–1.1; $p = 0.94$). In the ivabradine group, all-cause mortality was 10.4% and in the placebo group 10.1%. The results of this study did not demonstrate any benefit of ivabrdine in the treatment of systolic heart failure.

In patients with dilated cardiomyopathy with heart failure a beneficial effect of trimetazidine, a metabolic modulator, has been observed.[140a] Trimetazidine increased cardiac and extracardiac metabolic effects. Cardiac free fatty acid oxidation decreased modestly and myocardial oxidative rate was unchanged. Trimetazidine also increased left ventricular ejection fraction. There was also a greater myocardial B1-adrenoreceptor occupancy suggesting a synergistic mechanism of improved metabolic and mechanical functions.

NON-PHARMACOLOGIC TREATMENTS

A number of non-pharmacologic treatments have been attempted for the treatment of refractory systolic heart failure (Table 14). The chronic resynchronization treatment (CRT) with or without implantable cardioverter-defibrillator (ICD) has been tested in patients with moderately severe and severe systolic heart failure. The CRT with or without ICD has the potential to improve symptoms, hemodynamics and prognosis of these patients. The CRT treatment is indicated in patients with QRS complex duration of 120 milliseconds or greater.[140b] The ICD treatment has been shown to decrease the risk of sudden cardiac death[141a] (please see the chapter "Device Treatments—Pacemakers, Defibrillators CRT").

Atrioventricular sequential dual chamber pacing with short P-R intervals have also been used in patients with dilated cardiomyopathy without success.

Left ventricular constrain devices, such as myosplints and mesh jackets, have been used to decrease left ventricular

TABLE 14

Non-pharmacologic interventions

- LV volume reduction surgery
  - Batista, Dore, Saver procedures
- Mitral valve repairs
- DDD-pacing with short P-R interval
- Ventricular assist devices
- Passive ventricular constraint devices
  - Myosplints
  - Mesh jacket
- Cardiac transplantation
- Revascularization in ischemic cardiomyopathy
- Resynchronization with or without ICD

remodeling Effectiveness of these procedures however has not been proven and is still experimental.

Left ventricular volume reduction surgery, such as the "Batista", "Dore" and "Saver" procedures, has been employed to decrease left ventricular volume and adverse remodeling. The long-term results of these surgical procedures have not been encouraging. Left ventricular remodeling is not prevented and outcomes are not improved. Surgical mitral valve repair in patients with significant secondary mitral regurgitation improves hemodynamics and has the potential to decrease progressive left ventricular dilatation. Whether long-term prognosis also improves or not has not been established. The catheter-based mitral valve repair is being performed, which is associated with less risk of mortality and morbidity than with surgical repair (please see the chapter "Revascularization and other surgical approaches for heart failure").

Left ventricular assist devices are primarily used to support patients waiting for cardiac transplantation. However, left ventricular assist devices are also being used as a destination therapy (please see the chapter "Cardiopulmonary Transplantation and Ventricular Assist Devices").

A regular exercise program should be implemented as part of the management strategy of patients with systolic heart failure. The moderate level of exercise is well tolerated, even by patients with severe heart failure. The regular exercise improves sense of well-being and also hemodynamics (please see the chapter "Cardiopulmonary Exercise Testing and Exercise Training in Heart Failure").

In a preliminary multicenter non-randomized clinical trial, chronic vagus nerve stimulation in patients with stage C systolic heart failure has been shown to decrease left ventricular end systolic volume and to increase left ventricular ejection fraction. There was also clinical improvement.[141b] However, without a large randomized clinical trial, the role of this new non-pharmacologic treatment remains unproven.

FOLLOW-UP EVALUATION

Heart failure is a chronic disease and is associated with a high mortality and morbidity rates. The unplanned hospital readmission rates for the treatment of heart failure and the visits to the emergency department are high.[142] The length of stay of the patients who require unplanned admissions to the hospital for the treatment of heart failure are usually longer.[143] In the United States of America, over 6.5 million hospital days are required for the treatment of patients with heart failure. Thus, the cost of care markedly increases, and in 2007, more than 35 billion dollars were spent for management of patients with heart failure.[142]

The quality of life of patients with chronic heart failure is also poor, particularly when adequate follow-up management is not provided.

Many therapeutic advances, as outlined in this chapter, have been made for the treatment of systolic heart failure. However, these life saving therapies continue to be underused, even in the developed countries.

Thus, a mechanism needs to be established for a greater use of these therapeutic agents. It has been suggested that patient education, evidence-based, guideline-recommended treatments should be initiated in the hospitals prior to discharge of the patients.[144] Heart failure disease management programs should be established and the team should include pharmacists.[145] Medicine management for heart failure is complex. Physicians are frequently unaware of drug-drug interactions, and inappropriate medicines and doses may be prescribed. Inappropriate medications have the potential to increase morbidity such as frequency of hospital readmissions.

Multidisciplinary chronic heart failure management programs should be established which allow implementation of appropriate therapy.[146-149] The team should consist of nurses trained in management of heart failure, heart failure specialists and pharmacists.[150] Some programs also include exercise and rehabilitation specialists.

The nurse specialists play the pivotal roles in these programs. Randomized clinical trials have reported that nurse-led, clinic- and home-based intervention programs reduce the rate of recurrent admissions to the hospitals.[147] The specialists can alter the dose of the diuretics, beta-blockers and angiotensin inhibitors. The patients are advised to weigh themselves every day and the diuretic doses are adjusted accordingly. The patients are seen in the clinic by the physicians and the nurse practitioners as needed. After the clinic visits, follow-up tests are performed if necessary. Nurse-led management program is also cost effective.[151] In this multicenter clinical trial, 1,163 patients were randomized to control group who received standard care and to specialist nurse-led management program. The nurse-led disease management program was associated with an increase in the economic evaluation of quality adjusted life years.

The prospective trial has reported that specialized heart failure programs can improve recovery and good health in the hospitalized veterans. The disease management programs can improve quality of life of patients with heart failure. It has been observed that patients younger than 65 years of age with chronic heart failure and poor quality of life are at a higher risk of adverse outcomes.[148] However, nurse-supported hospital discharge programs have been reported to decrease unplanned admissions to the hospitals, even in the relatively older populations with heart failure. It has been observed that the multidisciplinary home-based intervention programs can detect deterioration of heart failure earlier, and thus can facilitate earlier institution of appropriate treatments.[152] It has also been observed that specialist nurse management programs can substantially decrease the cost of the treatment of patients with heart failure.[153]

In a randomized clinical trial the efficacy of telemonitoring-guided heart failure care was assessed. There were 826 patients in the treatment group and 827 patients in the usual care group. The all-cause readmission/death was 52.3% in the treatment group and 51.5% in the usual care group. Thus this study demonstrated no benefit with telemonitoring-guided heart failure management program.[154]

In the telemedicine interventional monitoring in heart failure (TIM-HF) trial, the hazard ratio of all cause mortality was 0.97 (p-0.87) and of cardiovascular death/heart failure hospitalization was 0.89 (p-44). Thus this study also demonstrated that telemonitoring-guided heart failure treatment does not provide any benefit.[155]

TABLE 15

Potential mechanisms of benefits of exercise training in heart failure

- Reduction in sympathetic activity, increase in parasympathetic activity
- Decrease in circulating deleterious neurohormones
- Decrease generation of reactive oxygen species (ROS)
- Restore endothelial function
- Generation of more nitric oxide (NO)
- Exerts anti-inflammatory effect by reducing inflammatory cytokines, platelet-related inflammatory mediators and peripheral markers of endothelial dysfunction

TABLE 16

Potential mechanisms of benefits of exercise training in heart failure

- Improves oxygen consumption, and lactate threshold, delays onset of anaerobic metabolism in skeletal muscle
- Decreases systemic vascular resistance
- Decreases end-diastolic and end-systolic volumes and increases left ventricular ejection fraction

That physical activity may be associated with beneficial effects in patients with chronic heart failure has been documented.[156]

In this study, 28,334 Finish men and 29,874 women, aged 25–75 years, were followed for 18.4 years. During the follow-up period,1,868 men and 1,640 women developed heart failure. The multivariate adjusted hazard ratios for development of heart failure were determined. The results of this study showed that both men and women, moderate and high levels of occupational and leisure-time physical activity reduce risk of developing heart failure.

Exercise training is recommended in NYHA class II and III patients with chronic heart failure. Regular exercise can improve symptoms, exercise capacity, and quality of life. It can be associated with reduced hospitalization rates. The potential mechanisms of the benefits of exercise training in heart failure are summarized in Tables 15 and 16.

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Chapter 71

Diastolic Heart Failure
(Heart Failure with Preserved Ejection Fraction)

Kanu Chatterjee

Chapter Outline

- Definition
- Epidemiology
- Pathophysiology
  - Ventricular Remodeling
  - Neurohormonal Changes
  - Functional Derangements
  - Hemodynamic Consequences
- Clinical Presentation
- Diagnosis
- Prognosis
- Treatment Strategies
- Future Directions

INTRODUCTION

Diastolic heart failure as a clinical entity was recognized over 70 years ago by Dr. Fishberg, who wrote in 1937 that "this form of cardiac insufficiency results from inadequate filling of the heart" and he termed this form of heart failure as "Hypodiastolic failure".[1] However the syndrome of diastolic heart failure was not appreciated until about two decades ago when the cardiologists and the heart failure specialists recognized that diastolic heart failure is as common as systolic heart failure. The prevalence of diastolic heart failure appears to have also increased in recent years. In one community-based study, the prevalence of diastolic heart failure was approximately 35% in 1986, and it increased to over 50% in 2002.[2] It should also be appreciated that the recognition of this clinical subset of chronic heart failure by the physicians has also increased in recent years.

DEFINITION

There are not only confusions regarding the definition of diastolic heart failure but also for the timing of onset and duration of diastole. In the Webster Dictionary, diastole is defined as "the dilatation of the heart with blood: opposed to systole, or contraction".

The onset of diastole coincides with the closure of the aortic valve as it has been conventionally recognized as the onset of left ventricular relaxation.[3] However, as the left ventricular ejection influences its relaxation, it has been proposed that these phases should be regarded as part of systole and not of diastole.[4] In clinical practice the opening of the mitral valve is used as the beginning of diastole and the closure of the mitral valve as the end of diastole.[5] This phase is also called auxotonic relaxation phase.

One of the pathophysiologic definitions, as proposed by Brutsaert et al.[4] is that it is "a condition resulting from an increased resistance to filling of one or both ventricles leading to symptoms of congestion due to an inappropriate upward shift of the diastolic-pressure-volume relation (i.e. during the terminal phase of the cardiac cycle). Another proposed pathophysiologic definition is that it is a condition in which the "ventricular chamber is unable to accept an adequate volume of blood during diastole at normal diastolic pressures and at volumes sufficient to maintain an appropriate stroke volume".[6] Although these definitions describe the pathophysiologic characteristics of diastolic heart failure, they cannot be used in clinical practice.

A number of clinical definitions have also been proposed. One definition is that the diastolic heart failure is a "clinical syndrome characterized by the symptoms and signs of heart failure, a preserved ejection fraction (EF), and abnormal diastolic function".[6] Other definitions, such as "heart failure with normal or near normal ejection fraction", have also been used. In clinical practice most commonly used definition of diastolic heart failure (HFNEF) is when "the symptoms and signs of heart failure are present and the ejection fraction is greater than 45%". It should be appreciated that EF is load dependent. A lower preload and a higher after load are associated with a lower EF. Thus, at the time of measurement of EF, it is desirable to consider the determinants of preload (e.g. end-diastolic volume) and of afterload (e.g. blood pressure).

EPIDEMIOLOGY

The incidence and prevalence of diastolic heart failure have been studied in a number of epidemiologic studies.[2,7-12] These studies estimated the prevalence of diastolic heart failure between 50% and 55%. The prevalence increases with age, and it is more common in women than in men. In the cardiovascular health study,[11a,12] the risk of developing heart failure was higher in elderly women. In women at age between 65 and 69 years, the incidence was 6.6%, and it increased to 14% in women older than 85 years.[7,11a,12] That diastolic heart failure is more common in women than in men has been recognized in many studies.[13,14] In the cardiovascular health study, the prevalence of diastolic

TABLE 1

Systolic vs diastolic heart failure

ADHERE—All enrolled discharges		
Profile	*SHF*	*DHF*
EF	(59,523)	(50,497)
EF	< 40%	> 40%
Age	69.9	74.2*
Female	39%	62.2%*
CAD	63%	54%*
Diabetes	42%	46%*
AF	29%	33%*
BNP	1486	925*

*< 0.0001
(Abbreviations: EF: Ejection fraction; CAD: Coronary artery disease; AF: Atrial fibrillation; SHF: Systolic heart failure; DHF: Diastolic heart failure)

heart failure in women was 67% and that in men 42%.[11a,12] Similar findings were observed in the Framingham study.[13,14] In the Candesartan in Heart Failure-Assessment of Reduction in Mortality and Morbidity-Preserved (CHARM-Preserved) trial, the incidence of diastolic heart failure was higher in women than in men.[15] In this study, left ventricular EF needed to be greater than 40% to be included in the trial. The prevalence of women was 40% in the CHARM-Preserved study. In the "Irbesartan in patients with heart failure and preserved ejection fraction (I-PRESERVE)" trial, the prevalence of women was 60%.[16] The left ventricular ejection needed to be greater than 45% to be enrolled to the study. In patients hospitalized for the treatment of heart failure the prevalence of women with diastolic heart failure was approximately 60%.[17] Normal EF in this study was defined when the ejection was 55% or higher.

The echocardiographic studies have reported that the prevalence of diastolic heart failure in females is between 1.7% and 9.5% and in males between 2.7% and 6.6%.[10] In this study the prevalence of diastolic heart failure in men and women were similar.

The risk factors for diastolic heart failure are similar to those of systolic heart failure (Table 1).[17] Older age, female gender, diabetes, hypertension, obesity and the black race are the major risk factors for the development of heart failure. The incidence of coronary artery disease appears to be higher in systolic heart failure and obesity, diabetes and hypertension higher in diastolic heart failure. However, the incidence of coronary artery disease is still considerable in diastolic heart failure and diabetes and hypertension in systolic heart failure. In clinical practice therefore it is relevant to attempt to treat the modifiable risk factors in both diastolic and systolic heart failure.

PATHOPHYSIOLOGY

VENTRICULAR REMODELING

In diastolic heart failure, left ventricle is of normal size and its wall thickness is increased. Left ventricular hypertrophy is of concentric type. Left ventricular end-diastolic and end-systolic volumes are normal or decreased. Thus, left ventricular cavity size remains normal or even may be decreased. Left ventricular mass is increased and the mass/cavity ratio is increased. Due to

TABLE 2

Diastolic heart failure—remodeling

- Ventricular hypertrophy, usually concentric
- Increased ventricular mass
- Increased ventricular wall thickness
- Little or no increase in the cavity size
- Increased mass/cavity ratio
- Decreased wall stress
- Maintained ejection fraction
- Little or no change in ventricular shape
- Mechanical dyssynchrony with or without electrical dyssynchrony—present in approximately 1/3rd of patients

TABLE 3

Diastolic heart failure

	Controls	*DHF*
• LVEDV	102	87
• LVESV	46	37
• LVEF	54	60
• LVM	125	160
• LVM/V	1.49	2.12

(Abbreviations: LVEDV: Left ventricular end diastolic volume; LVESV: Left ventricular end systolic volume; LVEF: Left ventricular ejection fraction; LVM: Left ventricular mass; LVM/V: Left ventricular mass/volume ratio; DHF: Diastolic heart failure). (*Source:* Adapted from Kitzman DW, et al. JAMA. 2002;288:2144)

increased wall thickness without any change in the cavity size, left ventricular wall stress is decreased, which maintains normal EF.[18-23] Tissue Doppler imaging (TDI) studies have reported the prevalence of dyssynchrony in over 30% of patients with diastolic heart failure.[24,25] In patients with diastolic heart failure left ventricular mechanical dyssynchrony may occur with or without electrical dyssynchrony.[26] The morphologic changes in diastolic heart failure are summarized in Tables 2 and 3.[23,27]

The distinctive features of left ventricular remodeling in isolated diastolic and systolic heart failures are illustrated in Figure 1. In this example, compared to a normal heart, in diastolic heart failure the left ventricular wall thickness is markedly increased and the cavity is small. A cross sectional 2-dimensional echocardiographic view also demonstrates increased left ventricular wall thickness in diastolic heart failure. In contrast, in systolic heart failure the thickness of left ventricular wall is decreased and the cavity is dilated compared to normal wall. The cross sectional 2-dimensional echocardiogram demonstrates similar features.[28]

The characteristic changes in the myocytes and in the matrix in diastolic and systolic heart failure are illustrated in Figure 2.[19] Compared to normal myocyte, the myocyte in diastolic heart failure is thicker and there is increase in diameter without an increase in its length. The length/width ratio is decreased. There is increased myocyte protein synthesis. In systolic heart failure the myocyte length is increased without changing its diameter. The length/width ratio is increased. Left ventricular endomyocardial biopsy in patients with symptomatic diastolic and systolic heart failure demonstrates distinctive features in myocardial structure (Table 4).[23] Myocyte diameter

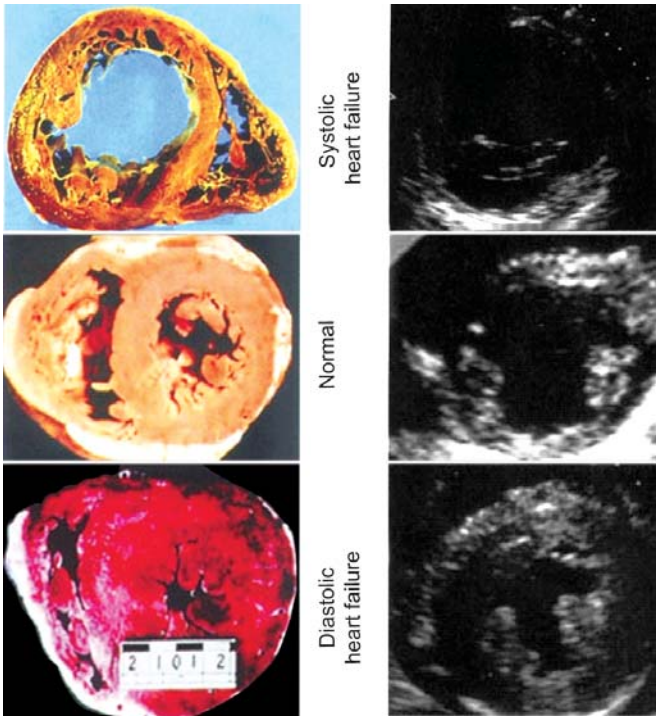


FIGURE 1: Autopsy examples of ventricular remodeling in diastolic and systolic heart failure are illustrated. Left-hand panel demonstrates gross pathology and right-hand panel 2-dimensional cross-sectional echocardiographic images. (*Source*: MA Konstam. J Cardiac Failure. 2003;9:1-3)

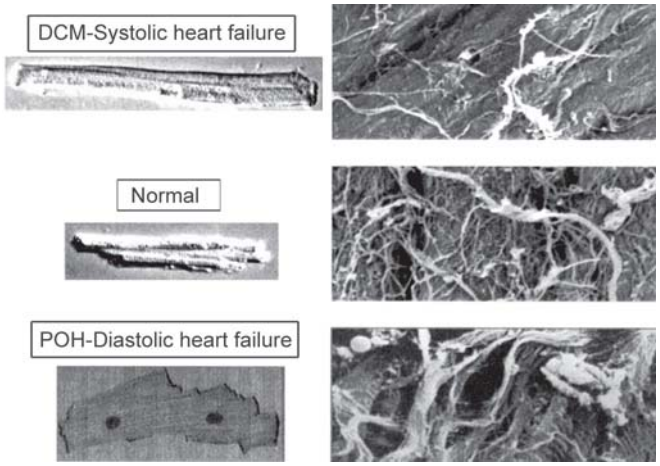


FIGURE 2: Changes in myocytes (left) and in extracellular matrix (right) are illustrated. (*Source*: Aurigemma et al. Circulation. 2006;113:296-304, with permission)

in diastolic heart failure is greater than that in systolic heart failure. Myofibrillar density is less in systolic than in patients with diastolic heart failure. There is, however, no difference in collagen volume in diastolic and systolic heart failure.

In both diastolic and systolic heart failure the collagen volume is increased.[19,22,23] In diastolic heart failure, the thickness of the collagen bundles and the continuity of the fibrillar components of the extracellular matrix surrounding the myocytes are increased. In systolic heart failure there is degradation and disruption in collagen.[19] The collagen cross links are increased in diastolic heart failure. The matrix

TABLE 4

Myocardial structure and function in diastolic and systolic heart failure

	DHF	*SHF*	*P*
MYD (microM)	20.3	15.1	< 0.001
CVF	+	+	NS
MFD %	46	36	< 0.001

(Abbreviations: MYD: Myocyte diameter; CVF: Collagen volume fraction; MFD: Myofibrillar density; DHF: Diastolic heart failure). (*Source*: Heerbeek LV et al. Circulation. 2006;113:1966-73)

metalloproteinases (MMPs) are reduced and the endogenous tissue inhibitors of metalloproteinases (TIMPs) are increased. Thus the ratio of the MMPs/TIMPs is decreased in diastolic heart failure.[29,30]

Abnormal calcium regulation has been observed in diastolic heart failure. The sarcoplasmic reticular reuptake of cytosolic calcium is abnormal and is associated with slower myocyte relaxation.[31,32]

Titin is a large myocyte protein which has a recoil spring property. It also desensitizes the myofilaments to calcium. The stiff titin isoform protein N2B is over expressed in human cardiac myocytes isolated by myocardial biopsy from patients with diastolic heart failure. The N2BA titin isoform protein is more compliant and the N2BA/N2B ratio is lower in the myocytes of patients with diastolic heart failure.[23,33] In diastolic heart failure, the procollagen type I and III aminoterminal peptides concentrations are increased suggesting the abnormalities of collagen metabolism. The changes in myocytes and extracellular matrix are summarized in Table 5.[34]

Myocardial ischemia impairs myocardial relaxation due to abnormality of calcium regulation. There is reduced reuptake of the cytosolic calcium by the sarcoplasmic reticulum.[35] Ischemia may induce myocyte necrosis and apoptosis.

NEUROHORMONAL CHANGES

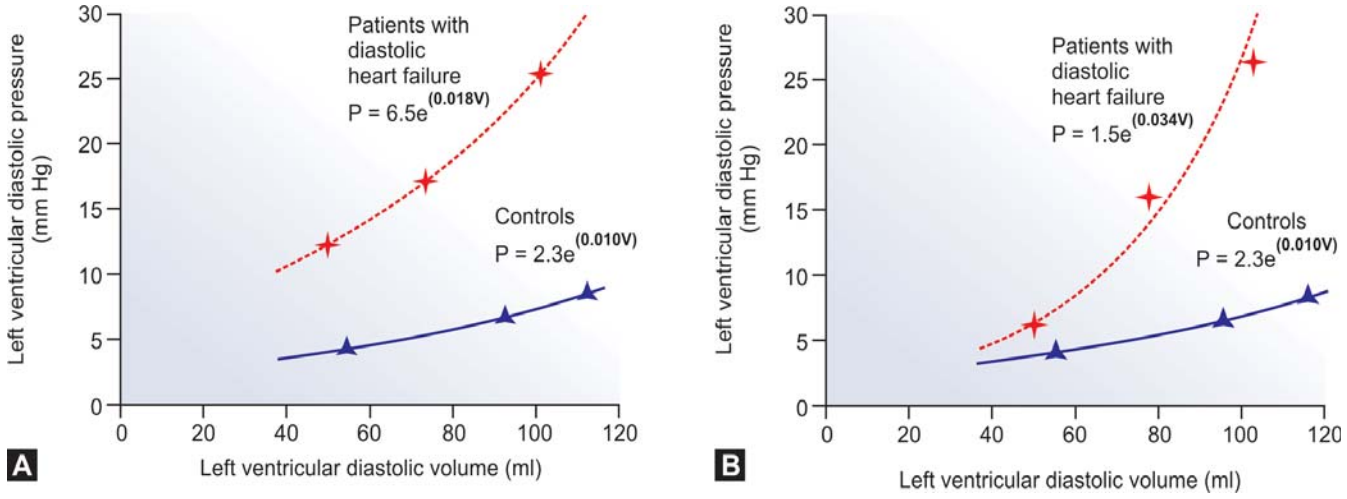
A number of neurohormonal abnormalities have been observed in diastolic heart failure. The plasma norepinephrine levels are increased.[27] The circulating levels of interleukin-6 and

TABLE 5

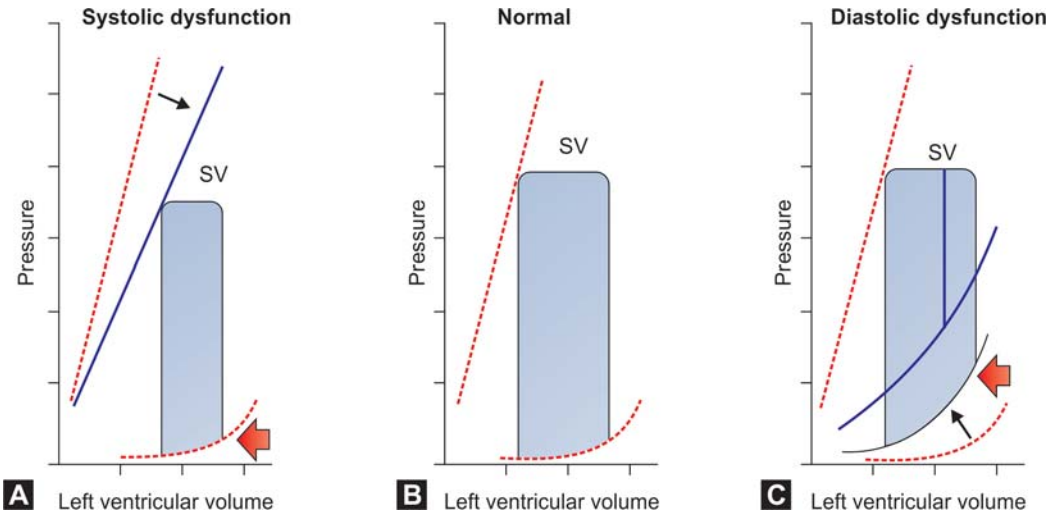
Diastolic heart failure

	DHF
• Myocyte	
hypertrophy	+
apoptosis	+
necrosis	+
• Fibrosis	+
• Ca regulation	–
• MMPs/TIMPs	–
• Collagen	
cross-links	+
• Titin isoforms	
N2BA/N2B	–

(Abbreviation: DHF: Diastolic heart failure)
+: Increased; –: Decreased



FIGURES 3A AND B: The changes in left ventricular diastolic pressure (mm Hg) (y-axis) and changes in left ventricular diastolic volume (ml) (x-axis) in groups of patients with diastolic heart failure and matched controls are illustrated. In patients with diastolic heart failure, the left ventricular-pressure volume relation is shifted upward and to the left. (*Source*: Zile et al. N Engl J Med. 2004;350:1953-9, with permission)



FIGURES 4A TO C: Schematic diagram of pressure-volume relations in Normal (B), Systolic dysfunction (A) and Diastolic dysfunction (C) are illustrated. In systolic heart failure, the end-systolic pressure-volume relation line (solid line) is shifted downward and to the right indicating reduced contractile function compared to normal (dashed line). In diastolic heart failure, there is no shift in the end systolic pressure-volume line indicating no change in contractile function. With a marked upward and leftward shift of the diastolic pressure-volume relation there is not only increased in left ventricular diastolic pressure but also a decrease in stroke volume (SV). (*Source*: Modified from GP Aurigemma. N Engl J Med. 2004;35:1097, with permission)

interleukin-8 and of tumor necrosis factor-alpha (TNFα) are increased.[34,36] These neurohormonal abnormalities may contribute to myocyte hypertrophy and myocardial inflammatory changes which may be associated with myocyte necrosis and apoptosis. The counter regulatory hormone B-type natriuretic peptide (BNP) is also increased. Despite increased levels of BNP, ventricular remodeling continues.

FUNCTIONAL DERANGEMENTS

The principal functional abnormality in diastolic heart failure is increased stiffness and decreased compliance of the left ventricle. The diastolic pressure-volume relation shifts upward and to the left. As a result, there is a disproportionate increase in left ventricular diastolic pressure for any increase in left ventricular diastolic volume (Figs 3 and 4). Myocardial hypertrophy, fibrosis and ischemia contribute to increased left ventricular fibrosis.

The analysis of left ventricular pressure-volume relations allows delineation of hemodynamic changes and their mechanisms (Fig. 4). Diastolic filling begins with the opening of the mitral valve. Normally, 70–80% of left ventricular filling occurs during the rapid filling phase. It should be appreciated that after the opening of the mitral valve left ventricular pressure continues to decline into the rapid filling phase. The early diastolic pressure gradient between the left atrium and the left ventricle is maintained without any increase in left atrial

pressure. During exercise which is associated with a need of a higher stroke volume, larger filling of the left ventricle is also required which is achieved with a more rapid decline and lower early diastolic pressure. The early diastolic pressure gradient is maintained without any significant increase in left atrial pressure. Thus, in presence of normal diastolic function, pulmonary venous congestion does not occur. In the presence of significant diastolic dysfunction as in patients with diastolic heart failure, left ventricular relaxation is impaired and left ventricular early diastolic pressure is elevated. Consequently left atrial pressure is also increased and there is a passive increase in pulmonary venous pressure which may be associated with signs and symptoms of pulmonary venous congestion. These hemodynamic abnormalities are accentuated during exercise. The rapid filling phase is not influenced by the increase in heart rate. During diastasis, that is the interval between the end of rapid filling phase and the beginning of the atrial filling phase, the relative amount of ventricular filling is small. During atrial filling phase, normally approximately 20% of ventricular filling occurs. In the presence of significant diastolic dysfunction as in patients with diastolic heart failure, the relative contribution of ventricular filling during atrial filling phase is greater as the degree of ventricular filling during the rapid filling phase is reduced. The atrial filling phase is influenced by heart rate, presence of sinus rhythm and effective atrial contraction. The presence of sinus rhythm and effective atrial contraction is more important in diastolic than in systolic heart failure to maintain adequate stroke volume.

After completion of ventricular filling with the closure of the mitral valve, the isovolumic systolic phase begins. During this phase, the left ventricular pressure increases without any change in ventricular volume. With the opening of the aortic valve left ventricular ejection begins and continues till the beginning of the hang-out time. The hangout time is the interval between the end of ejection and the closure of the aortic valve. With the closure of the aortic valve isovolumic relaxation phase begins and it ends with the opening of the mitral valve. At the end of ejection, the end-systolic pressure-volume relation remains unchanged and the end-systolic pressure-volume relation is independent of afterload and preload. With decreased contractile state, the end-systolic pressure-volume line shifts downward and to the right as in patients with systolic heart failure. In patients with diastolic heart failure the contractile function is usually preserved, and there is no shift of the end-systolic pressure-volume line.

Due to the upward and leftward shift of the diastolic pressure-volume relation, left ventricular diastolic pressure is increased and there is a passive increase in pulmonary venous pressure with signs and symptoms of pulmonary venous congestion. With a further upward shift of the diastolic pressure-volume relation left ventricular filling is compromised which is associated with decreased stroke volume and cardiac output (Fig. 4).

By definition diastolic heart failure is associated with normal or near normal left ventricular EF. However, controversy exists whether contractile function is entirely normal or not in patients with diastolic heart failure. The positive peak positive dp/dt, end-systolic elastance and endocardial stress-shortening relationships, which are indices of contractile function are not impaired in diastolic heart failure.[21] The TDI studies have reported that in some patients with diastolic heart failure the extent of midwall and long axis shortening is reduced indicating impaired contractile function. However it occurs in less than 50% of patients.[19]

TABLE 6

Changes in left ventricular volume and function in diastolic heart failure without coronary artery disease

	LVEDVI (ml/m²)	*LVEDP (mm Hg)*	*Stiffness-Mod (kn/m²)*	*LVEF (%)*
Init	68 ± 9	14 ± 3	3.4 ± 0.6	67 ± 3
End	76 ± 8	26 ± 2	6.3 ± 0.9	60 ± 4

(Abbreviations: LVEDVI: Left ventricular end diastolic volume index; LVEDP: Left ventricular end diastolic pressure; Stiffness-Mod: Stiffness modulus; Init: Initial study; End: End of follow-up of 64 ± 9 months). (*Source*: Handoko ML et al. Circulation. 2006;114:II-816)

There is also controversy whether left ventricle dilates in patients with symptomatic diastolic heart failure in absence of ischemic myocardial necrosis. In a study of only ten patients with overt diastolic heart failure without coronary artery disease, during over 5 years of follow-up, there was not any significant increase in left ventricular end-diastolic volume between the initial and the follow-up study. However there was a significant increase in left ventricular end-diastolic pressure and increase in the indices of left ventricular stiffness (Table 6).[37] This study indicates that left ventricle does not dilate in the absence of ischemic necrosis and the worsening symptoms are related to worsening left ventricular stiffness.

HEMODYNAMIC CONSEQUENCES

The hemodynamic consequences of advanced diastolic heart failure are characterized by an increase in left ventricular diastolic pressure and a passive increase in left atrial and pulmonary venous pressures. There is an obligatory increase in pulmonary arterial pressure which is associated with increased right ventricular afterload. Thus, right ventricular failure ensues with clinical manifestations such as dependant peripheral edema. The prevalence, severity and the hemodynamic mechanisms of pulmonary arterial hypertension have been investigated in a community based population study.[38] Transthoracic echocardiography and Doppler echocardiography was used to assess pulmonary artery systolic and pulmonary capillary wedge pressures. In 244 patients with diastolic heart failure, pulmonary arterial hypertension was detected in 83% of patients. The mechanism of pulmonary artery hypertension was due to both increase in pulmonary capillary wedge pressure and pulmonary vascular resistance. Pulmonary hypertension was a strong predictor of mortality.

CLINICAL PRESENTATION

Asymptomatic left ventricular diastolic dysfunction is far more common than symptomatic diastolic heart failure.[8] However, in symptomatic patients, the signs and symptoms of overt diastolic heart failure are similar to those of systolic heart failure

TABLE 7

Prevalence of specific symptoms and signs in systolic vs diastolic heart failure

	Diastolic HF (EF > 50%)	*Systolic HF (EF < 50%)*
Symptoms		
Dyspnea on exertion	85%	96%
Paroxysmal nocturnal dyspnea	55%	50%
Orthopnea	60%	73%
Physical examination		
Jugular venous distension	35%	46%
Rale	72%	70%
Displaced apical impulse	50%	60%
S3	45%	65%
S4	45%	66%
Hepatomegaly	15%	16%
Edema	30%	40%
Chest radiograph		
Cardiomegaly	90%	90%
Pulmonary venous hypertension	75%	80%

(Abbreviation: HF: Heart failure). (*Source*: Zile MR, Brutsaert DL. Circulation. 2002;105:1387-93)

(Table 7).[6] Exertional dyspnea is the most common presenting symptom and was present in 85% of patients. In more than 50% of patients, paroxysmal nocturnal dyspnea and orthopnea were present. Reduced exercise tolerance is also frequent in patients with diastolic heart failure.[27] The hemodynamic mechanisms of impaired exercise tolerance may be caused by disproportionate increase in pulmonary venous pressure and decreased cardiac output. Diastolic dysfunction was found to be an independent predictor of impaired exercise tolerance in a study of 2,867 patients undergoing exercise echocardiography.[39]

Physical findings indicative of right heart failure, such as elevated jugular venous pressure and peripheral edema, are present in approximately 30% of patients (Table 7).[6]

Postcapillary and mixed type of pulmonary arterial hypertension is the principal mechanism of right ventricular failure.

Evidence of left heart failure, such as signs of pulmonary venous congestion, left ventricular hypertrophy, left sided S_3 and S_4 gallops which indicate elevated left ventricular end-diastolic pressure are present in approximately 50% of patients with overt diastolic heart failure.

Cardiomegaly and signs of pulmonary venous hypertension are detected frequently in plain chest X-ray.

Sleep-disordered breathing has been reported to occur frequently in patients with overt diastolic heart failure.[40a] In a study of 244 consecutive patients sleep-disordered breathing was observed in approximately 70% of patients. About 40% of patients had obstructive and 30% central sleep apnea. The patients with sleep-disordered breathing had impaired exercise tolerance, and higher left ventricular end diastolic, pulmonary capillary wedge and pulmonary artery pressures.

DIAGNOSIS

The diagnosis of heart failure is made by the clinical evaluations, and the Framingham criteria are used for diagnosis. Once the diagnosis of clinical heart failure is established it is mandatory to assess left ventricular EF to distinguish between diastolic and systolic heart failure. Assessment of EF is usually done by transthoracic echocardiography; however, radionuclide imaging and contrast angiography can also be employed. The advantages of echocardiography are that it is a noninvasive and easily clinically applicable test, and also the diastolic function can be assessed concurrently. Determination of transmitral pulsed wave Doppler inflow with or without the Valsalva maneuver pattern can demonstrate severity of diastolic dysfunction. Measurement of isovolumic relaxation time, assessment of pulmonary venous flow, TDI and speckle tracking echocardiography can be employed to assess diastolic dysfunction.

Cardiac magnetic resonance imaging (CMRI) has also been used to assess diastolic function. The transmitral inflow velocities, pulmonary vein flow velocities and deceleration time can be measured by CMRI.[40b]

As coronary artery disease is present in approximately 50% of patients with diastolic heart failure,[17] an assessment of myocardial ischemia due to obstructive coronary artery disease is desirable. The stress radionuclide imaging or stress echocardiographic studies can be employed to assess myocardial ischemia. Presently coronary angiography is the gold standard to establish the presence of obstructive coronary artery disease. However, the contrast computerized tomographic studies (contrast CTA) is being increasingly used to exclude clinically significant obstructive coronary artery disease. It should be appreciated that the role of contrast CTA in the diagnosis of clinically relevant obstructive coronary artery disease has not been firmly established.

Measurement of BNP or N terminal pro-BNP is useful in excluding the diagnosis of heart failure. A normal plasma concentration of these natriuretic peptides virtually excludes the diagnosis of heart failure. However, elevated values cannot be used to distinguish between diastolic and systolic heart failure.

The routine hemodynamic measurements are not indicated for the diagnosis of heart failure. However, for clinical indication, such as for the diagnosis of obstructive coronary artery disease, if cardiac catheterization is required, a contrast ventriculogram can be performed to assess left ventricular EF. The hemodynamics can also be determined concurrently. A normal left ventricular EF along with elevated left ventricular end-diastolic pressure confirms the diagnosis of diastolic heart failure.

It should be appreciated that for clinical purposes, it is not necessary to determine left ventricular compliance or indices of stiffness, such as stiffness modulus, for the diagnosis of diastolic heart failure.

If a patient has signs and symptoms of heart failure and the left ventricular EF is normal or near normal and there is evidence of diastolic dysfunction diagnosis of diastolic heart failure is established.

Cardiopulmonary exercise or six minute walk tests are not necessary for the diagnosis of heart failure but they are performed to assess the results of therapy.

PROGNOSIS

The prognosis of patients with asymptomatic left ventricular diastolic dysfunction has not been extensively investigated. In a cross-sectional community based study of 2,042 patients, the severity of echocardiographic diastolic dysfunction was

evaluated. The mild dysfunction was present in 21%, moderate dysfunction in 7% and severe dysfunction in 1% of patients. During a median follow-up of 3.5 years, the risk of all-cause mortality increased by 8-fold in patients with mild diastolic dysfunction and by 10-fold in patients with moderate to severe diastolic dysfunction.[8]

In another study of 3,008 American Indians, diastolic dysfunction was assessed by Doppler echocardiography by measuring E/A ratio. In 16% of patients impaired relaxation pattern (E/A ratio, < 0.6) and in 3% of patients restrictive pattern (E/A ratio > 1.5) were detected. After adjustment of covariates, the restrictive patterns were found to be an independent risk factor for increased all-cause (relative risk 1.7) and cardiac mortality (relative risk 2.8).[41a]

In a study of 331 elderly patients requiring hospitalization for the treatment of heart failure, the relation between the severity of diastolic dysfunction and mortality was assessed. Severity of diastolic dysfunction was determined using established echocardiographic criteria. During follow-up of 378 days, the prevalence of systolic and diastolic heart failure was similar (12% vs 10%). Cardiovascular (18% vs 19%) and all-cause mortality (49% vs 50%) were also similar in patients with systolic and diastolic heart failure. With increasing severity of diastolic dysfunction, all-cause and cardiovascular mortality progressively increased.[41b]

In patients with chronic ischemic heart disease, asymptomatic left ventricular diastolic dysfunction is associated with worse prognosis. In a study of 693 patients with normal left ventricular EF, and without history of heart failure, diastolic function was normal in 66% of patients, mild dysfunction in 24% and moderate to severe dysfunction in 10% of patients. During follow-up of 3 years, the mortality in patients with moderate to severe diastolic dysfunction was higher than that of patients with normal diastolic function (hazard ratio 3.9).[42] The hospitalization admission rates for the treatment of heart failure were also higher (hazard ratio 6.3).[42]

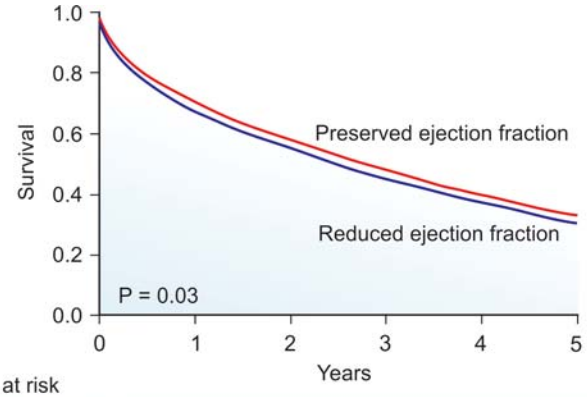
In symptomatic patients with diastolic heart failure, the prognosis has been evaluated in many observational studies and has been compared to that of patients with systolic heart failure and in general, the reported mortality of patients with diastolic heart failure was lower than that of patients with systolic heart failure (Table 8). In the Helsinki Aging study, the 4-year mortality of patients with diastolic heart failure was 43% and those with systolic heart failure 54%.[8] In the Framingham Heart Study, the annual mortality rate in patients with diastolic heart

TABLE 8

Diastolic and systolic heart failure—prognosis

	Mortality	
	DHF	*SHF*
Helsinki aging study four-year mortality	43%	54%
Framingham heart annual mortality	8.7%	18.9%
In-CHF registry one-year mortality	8.9%	35%
Adhere registry hospital mortality	3%	4%
Cardiovascular health deaths/1000 patient years	87	154

(Abbreviations: DHF: Diastolic Heart Failure; SHF: Systolic Heart Failure)



No. at risk

Reduced ejection fraction	2424	1637	1350	1049	813	604
Preserved ejection fraction	2166	1539	1270	1001	758	574

FIGURE 5: Kaplan-Meir survival curves in patients with systolic (reduced ejection fraction) and diastolic (preserved ejection fraction) are illustrated. The mortality at 5 years in both groups was approximately 40%. (*Source:* Owan et al. N Engl J Med. 2006;363:308, with permission)

failure was 8.7% and in those with systolic heart failure 18.9%.[13] In the Cardiovascular Health Study, 269 patients of 65 years of age or older with heart failure were followed to assess prognosis. In patients with diastolic heart failure, the mortality rates were 87 per 1,000 person-years and that of in systolic heart failure 154 per 1,000 person-years. The adjusted hazard ratio in systolic heart failure was 1.88, and in diastolic heart failure was 1.48 compared to patients without heart failure.[43] In the Congestive Heart Failure Registry, annual mortality rate in patients with diastolic heart failure was 8.9% and with systolic heart failure 35%.[44] In patients with decompensated heart failure the mortality is high in patients with systolic or diastolic heart failure. In a single center study of 6,076 patients, 1-year mortality of patients with diastolic heart failure was 29% and 32% in patients with systolic heart failure.[2] In a study of 413 patients hospitalized for heart failure, the risk of mortality was 13% in patients with diastolic heart failure and 21% in patients with systolic heart failure.[45] In another community-based cohort study of 2,802 patients with decompensated heart failure, 1-year mortality in diastolic heart failure was 22% and that in systolic heart failure 26%.[46] The in-hospital mortality of patients with decompensated diastolic heart failure was 3% and it was 4% in patients with decompensated systolic heart failure.[47]

In a few studies, however, it has been reported that the mortality of patients with diastolic and systolic heart failure are similar. In a community-based study in patients with heart failure 5-year mortality was approximately 40% in both diastolic and systolic heart failure (Fig. 5).[2] In this study, number of patients at risk in systolic heart failure group was 2,424, and it was 2,166 in the diastolic heart failure group. In another community-based study, the mortality after 400 days was approximately 20% in both systolic and diastolic heart failure patients (Fig. 6).[46]

It should be appreciated that the prognosis of patients with diastolic or systolic heart failure is related to the severity of heart failure. In patients with NYHA class II or III heart failure, the annual mortality rate was 3.8% in patients with diastolic and systolic heart failure in the CHARM-Preserved study.[15] In

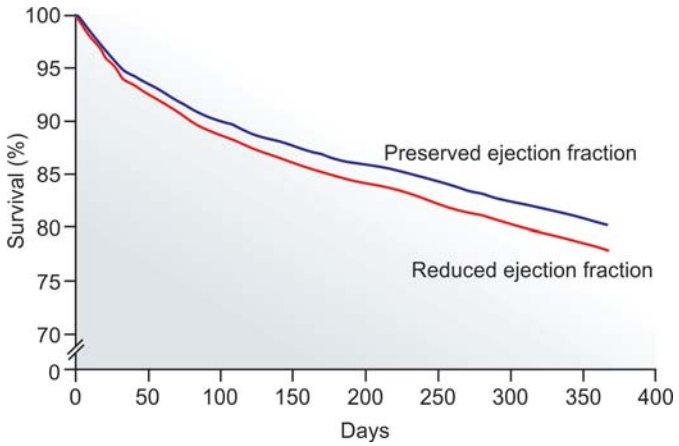


FIGURE 6: Kaplan-Meir survival curves in patients with systolic (reduced ejection fraction) and diastolic (preserved ejection fraction) are illustrated. The mortality at 400 days was approximately 20% in both groups. (*Source*: Bhatia et al. N Engl J Med. 2006;355:260, with permission)

TABLE 9

Diastolic and systolic heart failure

	Mortality and morbidity	
	DHF	*SHF*
• EF%	60	25
• Mortality %		
in hospital	2	3
2-mo	6	11
6-mo	11	16
• Readmission + mortality %	53	56

(Abbreviations: DHF: Diastolic heart failure; SHF: Systolic heart failure; EF: Ejection fraction). (*Source:* Danciu SC, et al. AJC. 2006;97:256-9)

patients with severe decompensated hospitalized patients however, the mortality and morbidity in patients with systolic or diastolic heart failure are similar (Table 9).[48] Six-month hospital mortality rate was 11% and 16% in diastolic and systolic heart failure respectively. The hospital mortality rate and hospital readmission rates at 6 months were similar in both groups.

The risk factors for worse prognosis such as age, severity of heart failure, the severity of coronary artery disease, presence of peripheral arterial disease, diabetes and renal failure are similar in both systolic and diastolic heart failure.[49-51]

The risk of sudden cardiac death appears to be higher in patients with systolic heart failure than in patients with diastolic heart failure. In systolic heart failure the risk of sudden cardiac death is more than 30%.[52] In patients in NYHA II, risk of sudden cardiac death was 64%, in NYHA III 59% and in NYHA class IV, it was 33%. In patients with diastolic heart failure, the risk of sudden cardiac death appears to be much lower. In a retrospective analysis of the Duke Data base, the risk of sudden cardiac death was assessed in 1,941 patients during follow-up between the years 1995 and 2004. In patients with diastolic heart failure the mean left ventricular EF was 58%. Sudden cardiac death occurred in 40 of 548 patients of total mortality (7.3%).[53] In the PEACE trial 8,290 patients were studied. During the follow-up of 4.8 years sudden cardiac death occurred in only 1.5% of patients with diastolic heart failure. The use of digitalis, diuretics and left ventricular EF of less than 50% were associated with increased risks of sudden cardiac death.[54]

TREATMENT STRATEGIES

Although a substantial improvement in the therapeutic interventions has been achieved in the management of systolic heart failure during last three decades; there has been very little progress in the treatment of diastolic heart failure.[55] The pharmacologic and non-pharmacologic therapies, that have been shown to improve prognosis of patients with systolic heart failure, have been found to be largely ineffective in patients with diastolic heart failure.

The principal objectives of the treatment of diastolic heart failure are to relieve symptoms, improve quality of life and decrease mortality and morbidity.[11a]

The majority of patients with diastolic heart failure present with symptoms of systemic and pulmonary venous congestion. To improve symptoms related to systemic and pulmonary venous hypertension diuretics are necessary. In the Hong Kong Diastolic Heart Failure Study, the patients were randomized to receive diuretics alone, diuretics and ramipril or diuretics and irbesartan.[56] In all three groups, hospital admission rates decreased and exercise tolerance improved. Addition of ramipril or irbesartan resulted in a decrease in NT-proBNP. This study suggests that diuretics alone are effective to ameliorate congestive symptoms. The nitrates decrease right atrial and pulmonary capillary wedge pressures and can relieve symptoms of systemic and pulmonary venous congestion. Diuretics and nitrates also decrease left ventricular end-diastolic volume (preload). In patients with diastolic heart failure, left ventricular size is normal or decreased; excessive reduction of preload during diuretic or nitrate therapy, stroke volume and cardiac output decrease. This is associated with hypotension and impaired renal function. Thus, diuretics and nitrates should be used cautiously in patients with diastolic heart failure. In clinical practice the doses of diuretics and nitrates should be adjusted monitoring the changes in jugular venous pressures. It is reasonable to maintain jugular venous pressures of 10–12 mm Hg.

The pharmacologic agents that are of proven benefit in systolic heart failure are also being used for management of diastolic heart failure. Angiotensin blockade by either angiotensin-converting enzyme inhibitors or angiotensin receptor blocking agents (ARBs) have been attempted in small and large clinical trials. The rationale for considering the use of angiotensin inhibitors is that these agents have the potential to improve diastolic function and also modify the risk factors for development of diastolic heart failure. These agents are effective for the treatment of hypertension, coronary artery disease and diabetes. Angiotensin-converting enzyme inhibitors can cause regression of left ventricular hypertrophy and improve diastolic function in patients with hypertensive heart disease.[57] In the large registries, in patients with diastolic heart failure hypertension was present in 80%, excess body weight in 80% and diabetes in 30% of patients.[58-60] Angiotensin-converting enzyme inhibitors can also decrease myocardial stiffness. Intracoronary infusion of enalaprilat, in a dose that does not reduce blood pressure, was associated with improved left ventricular diastolic compliance and relaxation in patients with left ventricular hypertrophy due to aortic stenosis.[61] The mechanism of the beneficial effect was assumed to be decreased production of myocardial angiotensin II.

The efficacy of the angiotensin-converting enzyme inhibitor perindopril in diastolic heart failure was studied in a large prospective, randomized clinical trial.[62] In this trial, 850 patients aged 70 years or older were randomized to receive perindopril or placebo. Approximately, 80% of patients had history of hypertension. The primary endpoint in this study was combined all-cause mortality and unexpected hospitalization for the treatment of heart failure. The treatment with perindopril was associated with an insignificant reduction in the primary endpoint events compared to placebo (perindopril 8.0, placebo 12.4%, hazard ratio 0.69). The beneficial effects of perindopril were entirely due to reduction of hospitalizations and there was no mortality benefit. Perindopril, however, caused significant improvement in functional class and an increase in six minutes walk distance.

The ARBs have also been studied in randomized clinical trials. The rationale for the use of ARBs is similar to that of angiotensin-converting enzyme inhibitors. Angiotensin II subtype 1 receptor blocking agents decrease left ventricular hypertrophy and improve diastolic function.[63] Losartan has been reported to decrease myocardial fibrosis and improve left ventricular compliance.[64]

The randomized clinical trials, however, have failed to demonstrate a substantial benefit of ARBs in patients with diastolic heart failure. In one trial, 382 patients with hypertension and diastolic dysfunction were randomized to receive ARB valsartan or other antihypertensive agents.[65] Reduction in blood pressure and improvement in diastolic function were similar in two groups.

In another randomized trial, 3,023 patients with symptomatic diastolic heart failure were randomized to receive candesartan or placebo.[15] The background treatments were similar in both groups. In this trial, preserved EF was defined when the left ventricular EF was greater than 40%. The primary endpoint in this study was cardiovascular death or hospitalization for heart failure. The event rates in the candesartan group was 22% and in the placebo group 24%. This difference in the primary endpoints was not statistically significant. The hazard ratio was 0.86 and the confidence interval was 0.74–1.00. This benefit was entirely due to a reduction in the rates of hospitalization and there was no mortality benefit with treatment with candesartan. In another large randomized clinical trial, 4,128 patients with symptomatic diastolic heart failure were randomized to receive either irbesartan or placebo.[16] In this trial, the patients were in NYHA class II or III. The left ventricular EF was 45% or higher. The mean EF was 59% before randomization. The background treatments in both groups were similar. The primary endpoint in this trial was death from any cause and hospitalization for a cardiovascular cause.

During a follow-up of approximately over 4 years, there was no difference in mortality or morbidity. Furthermore, angiotensin inhibition therapy may be associated with impaired renal function, and thus it should be used with caution and monitoring of renal function is necessary (Fig. 7).

The beta adrenergic antagonists are essential treatment for systolic heart failure due to their beneficial effects on ventricular remodeling and prognosis. However such beneficial effects of beta blockers have not been documented in patients with diastolic heart failure. The rational for the use of beta blockers

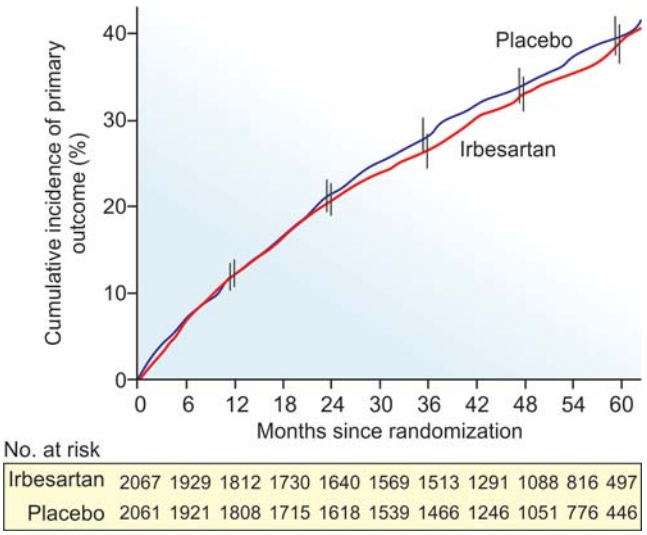


FIGURE 7: The outcome of patients with diastolic heart failure treated with angiotensin receptor blocking agent irbesartan compared to placebo is illustrated. There was no difference between placebo and irbesartan on mortality and morbidity

is to decrease heart rate which improves ventricular filling which is impaired in diastolic heart failure. Furthermore, beta-blockers have the potential to decrease myocardial ischemia which is associated with diastolic dysfunction.

The large prospective, randomized clinical trials have not been performed to assess the effects of beta-blocker therapy in diastolic heart failure. In the Swedish Doppler-echocardiographic study (SWEDIC), 113 patients with diastolic heart failure were randomized to receive carvedilol or placebo. There was a significant improvement in the E/A ratio without any changes in other indices of diastolic function.[66]

In a randomized clinical trial of 2,128 patients aged 70 years or older with heart failure, there was an indication that nebivolol, which is a beta blocker with vasodilating property, had a beneficial effect on all-cause mortality and rate of hospital admissions for heart failure.[67,68] However, in another large registry of heart failure, beta-blocker therapy was not associated with beneficial effect in diastolic heart failure, although it decreased mortality and morbidity in systolic heart failure. It should be appreciated that a marked reduction in heart rate may be associated with impaired exercise tolerance.

Aldosterone antagonists are beneficial in patients with systolic heart failure as they decrease adverse ventricular remodeling and improve prognosis. However, in patients with diastolic heart failure, such benefits have not been documented.

In a small clinical trial, patients with diastolic heart failure were randomized to receive either selective aldosterone antagonist or eplerenone or placebo. There were 20 patients in the control group and 24 patients in the treatment group. The majority of patients in both groups were receiving beta-blockers and angiotensin inhibitors. The mean age of the patients was 80 ± 7.8 years, and approximately 50% of patients were female. The primary objective of the study was to determine changes in procollagen type I and III aminoterminal peptides, MMP type-2, interleukin-6 and -8 and TNFα. Doppler-echocardiography was performed to assess diastolic function. During 12 months

of follow-up in the placebo group, there was a progressive increase in the markers of collagen turnover and inflammation and deterioration of diastolic function. With eplerenone treatment, there was no increase in type III collagen amino-terminal peptide. There was also no decrease in brain-natriuretic peptide levels. With eplerenone treatment there was only a modest improvement in diastolic function without any change in other clinical variables.[69] This study suggests that diastolic heart failure is a progressive disease.

In another small randomized study, 30 patients with hypertensive diastolic heart failure were randomized to receive 25 mg of spironolactone or placebo. After 6 months of treatment, echocardiographic indices of diastolic function improved with spironolactone.[70]

The two large randomized ongoing trials, Aldosterone Receptor Blockade in Diastolic Heart Failure (ALDO-DHF) and Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) are designed to assess the effects of aldosterone antagonists on the mortality and morbidity of patients with diastolic heart failure.[55]

In experimental animals with hypertensive heart failure, statins have been shown to decrease fibrosis and regression of hypertrophy.[71] In an observational study, retrospective analysis reported a 22% reduction in the relative risk of mortality with statins in patients with diastolic heart failure.[72]

A small randomized trial was performed to assess the clinical and hemodynamic effects of a phosphodiesterase-5 inhibitor sildenafil (50 mg three times daily) in patients with diastolic heart failure.[73] All patients had pulmonary hypertension. The etiology of diastolic heart failure was hypertensive heart disease. Twenty-two patients received sildenafil and twenty-two placebo. The hemodynamics was determined by pulmonary artery catheterization. Two dimensional echocardiography was employed to assess right and left ventricular function, volumes and ejection fraction. Evaluations were repeated at 6 and 12 months. With sildenafil treatment there was a significant reduction in pulmonary artery pressure, pulmonary vascular resistance and right atrial pressure. The reduction in pulmonary vascular resistance suggests pulmonary vasodilatation by sildenafil. There was also a reduction in pulmonary capillary wedge pressure and an increase in cardiac output. There was an improvement in pulmonary function along with a decrease in lung-water. Reduction in right atrial and pulmonary capillary wedge pressures along with an increase in cardiac output suggest an improvement in right and left ventricular function with sildenafil therapy. In the placebo treated patients, there was either no change or deterioration in hemodynamics and in right and left ventricular function (Table 10). With sildenafil therapy there was also improvement in quality of life. The mechanism of the beneficial effect of sildenafil appears to be due to increased cGMP by inhibition of phosphodiesterase-5.

In approximately 30% of patients with advanced diastolic heart failure, atrial fibrillation develops. If atrial fibrillation is paroxysmal or persistent, efforts should be made to maintain sinus rhythm. Amiodarone and dronedarone are the pharmacologic agents of choice. If atrial fibrillation is permanent adequate control of ventricular rate should be attempted with beta-blockers and heart rate regulating calcium channel blockers. Digoxin should be avoided if possible. If the ventricular rate cannot be adequately controlled pharmacologically, atrioventricular nodal ablation and pacemaker therapy should be considered. It is preferable to assess heart rate response during activity and not on resting heart rate to adjust pharmacologic therapy for rate control.

In patients with severe diastolic heart failure with low cardiac output intravenous positive inotropic drugs are rarely effective in increasing cardiac output and there is increased risk of inducing ventricular arrhythmias.

Non-pharmacologic treatments, such as chronic resynchronization therapy (CRT), have not been shown to be of any benefit in the management of patients with diastolic heart failure, although dyssynchrony is present in approximately 30% of patients. Implantable cardioverter-defibrillator treatment is indicated in the survivors of sudden cardiac death which is, however, uncommon in diastolic heart failure. In a rare patient with refractory diastolic heart failure, cardiac transplantation

TABLE 10

Effects of sildenafil in diastolic heart failure

	Placebo		*Sildenafil*	
	Baseline	*12 months*	*Baseline*	*12 months*
MRAP (mm Hg)	23.1 ± 5.5	24.1 ± 4.3	23.0 ± 4.6	9.3 ± 3.4
PASP (mm Hg)	52.1 ± 5.1	55.6 ± 5.5	54.5 ± 6.3	28.0 ± 3.7
MPAP (mm Hg)	36.8 ± 5.1	39.6 ± 4.7	39.0 ± 5.0	20.8 ± 3.3
MPCWP (mm Hg)	21.9 ± 2.0	22.2 ± 1.6	22.0 ± 2.5	17.8 ± 1.9
PVR (Wood Units)	3.27 ± 0.9	3.96 ± 1.03	3.88 ± 1.38	1.0 ± 0.56
MAP (mm Hg)	105 ± 12	107 ± 10	109 ± 11	111 ± 9
CI (l/min/m^2)	2.33 ± 0.64	2.28 ± 0.60	2.39 ± 0.59	2.51 ± 0.51
SVR (dynes.s cm-5 m^2)	2694 ± 688	2859 ± 710	2717 ± 721	3114 ± 698
LVEF (%)	60 ± 6	58 ± 7	60 ± 4	63 ± 3
LVMI (g/m^2)	168.2 ± 10.5	174.8 ± 10.4	166.4 ± 12.1	163.9 ± 11.2

(Abbreviations: MRAP: Mean right atrial pressure; PASP: Pulmonary artery systolic pressure; MPAP: Mean pulmonary artery pressure; MPCWP: Mean pulmonary capillary wedge pressure; PVR: Pulmonary vascular resistance; MAP: Mean arterial pressure; CI: Cardiac index; SVR: Systemic vascular resistance; LVEF: Left ventricular ejection fraction; LVMI: Left ventricular mass index). (*Source*: Guazzi et al. Circulation. 2011;124:164-74)

TABLE 11

Diastolic heart failure—management strategies

- Diuretics and/or nitrates to relieve congestive symptoms
- Digitalis may be effective in selected patients
- Reduction in heart rate is beneficial in diastolic heart failure
- Adequate treatment of hypertension, diabetes, obesity
- Treatments to reduce determinants of myocardial ischemia and to increase coronary blood flow
- Restoration and maintenance of sinus rhythm in patients with atrial fibrillation
- Implantable cardioverter—defibrillator in the survivors of sudden cardiac death
- Cardiac transplantation in selected patients
- Exercise training
- Counseling of the patient and the family of the disease, treatment options and prognosis
- Regular follow-up evaluation preferably by the heart failure team

can be attempted, provided there are no other contraindications for cardiac transplantation. It should be appreciated that diastolic heart failure is a disease of elderly, and thus cardiac transplantation therapy is seldom performed in such patients.

Exercise training is an important non-pharmacologic intervention in patients with diastolic heart failure. Although exercise training has not been demonstrated to be of benefit in improving outcome, it has the potential to improve overall sense of physical and emotional well-being.[74] The treatment strategies of diastolic heart failure are summarized in Table 11.

FUTURE DIRECTIONS

Diastolic heart failure is a common disease entity with poor prognosis. There have been considerable advances in the understanding of the structural and functional abnormalities in diastolic heart failure. However there has been very little or no advances in therapy. It appears that the initiating pathophysiologic mechanisms for the structural and functional abnormalities continue and progressively worsening heart failure develops. Thus, research should continue for novel therapies for management of diastolic heart failure. The new potential therapies are summarized in Table 12. Regression of left ventricular hypertrophy with phosphodiesterase-5 has been observed in animals with induced hypertrophy.[75] Restoration of protein kinase G by phosphodiesterase-5 inhibitors appears to be the mechanism of regression of hypertrophy.

TABLE 12

Diastolic heart failure

- New potential therapies:
  - — Modulation of collagen cross-links
  - — Modulation titin isoforms
  - — Modulation of MMP/TIMP
- Reduction of matrix fibrosis:
  - — Chymase antagonists
  - — TGF-beta
- Improved relaxation:
  - — Phospholamban inhibition
  - — D-ribose
  - — Levosimendan (calcium sensitizer)
  - — PDE-5 inhibitors
  - — To decrease myocardial deposition of AGEs
  - — To enhance myocardial NO

(Abbreviations: MMP/TIMP: Matrix metalloproteinase/tissue inhibitor of metalloproteinase ratio; TGF: Transforming growth factor; D-Ribose: Dextro-ribose; AGE: Acylate glycation end product; PDE: Phosphodiesterase; NO: Nitric oxide)

Protein kinase G can improve myocardial distensibility through phosphorylation of cytoskeletal protein titin.[76-81] The changes in the MMPs which cause degradation of matrix and the TIMPs are different in systolic and diastolic heart failure. The TIMPs/MMPs ratio is increased in diastolic heart failure. The therapies to decrease TIMPs or enhance MMPs can be potentially beneficial in diastolic heart failure. The myocardial deposition of advanced glycation end products (AGEs) has been shown to increase myocardial stiffness, and has been thought to be the principal mechanism of diastolic dysfunction in diabetes.[78] The AGE deposition also reduces nitric oxide (NO) availability which contributes to increased left ventricular stiffness.[79-81] Therapies to increase myocardial NO potentially can improve left ventricular diastolic function.

Chymase inhibitors and transforming growth factor-beta (TGF-beta) have the potential to decrease myocardial fibrosis. Inhibition of phospholamban enhances calcium-2, reuptake by the sarcoplasmic reticulum and can promote relaxation. The pentose d-ribose and the calcium sensitizer levosimendan can also enhance myocardial relaxation and can be potentially useful in therapy of diastolic heart failure. However it should be appreciated that without a proper clinical trial, the potential benefits of the new therapies remain speculative.

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Chapter 72

Anemia in Patients with Chronic Heart Failure
(Prevalence, Mechanism, Significance and Treatment)

James Prempeh, Barry M Massie

Chapter Outline

- Overview of the Problem
- Prevalence of Anemia in Heart Failure Patients
- Mechanisms Underlying Anemia in Heart Failure Patients
- Prognostic Significance of Anemia in Heart Failure Patients
- Should Anemia be Treated in Heart Failure Patients?
- Safety Concerns Related to ESPs in a Variety of Anemic Patients
- Treatment of Anemia in Heart Failure Patients
  - Erythropoietin Stimulating Proteins (ESPs)
  - Iron Deficiency and Iron Replacement in Heart Failure

OVERVIEW OF THE PROBLEM

In recent years, it has been recognized that anemia is common in heart failure patients and is associated with a poor prognosis compared to patients with normal hemoglobin levels. Anemia itself can cause heart failure, although it is uncommon for it to be the sole mechanism. In part this not only reflects the impact of comorbid conditions, such as chronic kidney disease, but also processes such as cytokine activation, other inflammatory processes and aging. Conversely, heart failure may itself cause anemia or increase plasma volume which may present as anemia due to low hemoglobin levels. Importantly, heart failure patients with anemia have a poor prognosis. As a result, there has been considerable interest in the correction of anemia with erythropoietin stimulating proteins (ESPs) or iron replacement.

This chapter has reviewed the current information on the prevalence, mechanisms and prognostic significance of anemia in heart failure patients. It has also discussed the potential benefits and risks of anemia correction and reviewed the data from clinical trials that have evaluated the effects of anemia correction.

PREVALENCE OF ANEMIA IN HEART FAILURE PATIENTS

Anemia is common in older population, and particularly so in patients with cardiovascular and renal disease. Using the World Health Organization definition of anemia (hemoglobin < 13.0 g/dL in men and < 12.0 g/dL in women),[1] 9% of patients in the Atherosclerosis Risk in Communities (ARIC) cohort, a well-characterized community based cohort of subjects 45-64 years of age, were found to be anemic.[2]

Within the last decade, several studies have reported high prevalences of anemia in heart failure patients in a variety of clinical settings, includig a 17% prevalence of anemia in a community based cohort of 12,065 patients with new onset heart failure,[3] and 43% in a cohort of 59,772 patients followed in a large Health Maintenance Organization.[4] Increased rates of anemia have also been seen in patients with acute decompensated heart failure,[5] and chronic heart failure with reduced[6] or preserved ejection fractions.[7] Compiling data from 15 papers in patients with low ejection fractions, Tang and Katz reported range of anemia prevalence from 4% to 61% (median 18%).[8] In patients with both acute and chronic heart failure, anemia was associated with poorer outcomes, including more frequent hospitalizations and shorter survival.

MECHANISMS UNDERLYING ANEMIA IN HEART FAILURE PATIENTS

The mechanisms underlying anemia are diverse, and multiple causes may be present in many patients. Figure 1 illustrates these factors and their interactions schematically.[9] As in the general population, in heart failure patients anemia is associated with older age and commonly chronic kidney disease, but cytokine activation, inflammation and hematinic abnormalities, including low levels of iron, vitamin B_{12} and folic acid, also play a role. The most common cause of anemia in heart failure patients is concomitant chronic kidney disease, which is present in approximately 40–50% and becomes more prevalent with advancing age. Renal disease is associated with both reduced erythropoietin production and responsiveness. Treatment with angiotensin converting-enzyme inhibitors and angiotensin receptor blockers has also been associated with decreased erythropoietin production and impaired bone marrow responsiveness.[10]

In five studies cited by Anand,[9] the prevalence of iron deficiency varied from 5% to 21%. In one study, low levels of

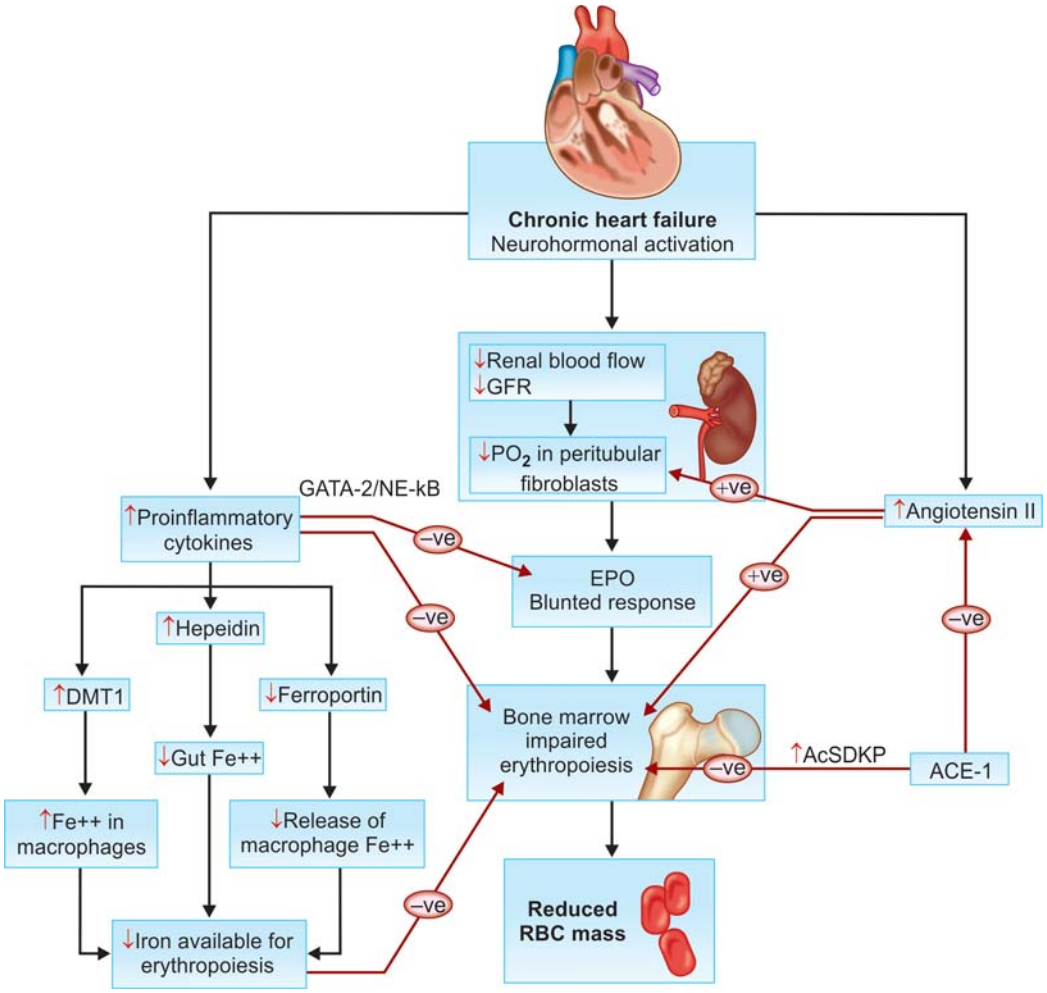


FIGURE 1: Possible mechanisms in the genesis of anemia in heart failure. (Abbreviations: ACE-1: Angiotensin-converting enzyme inhibitor; AcSDKP: N-acetylserl-aspartyl-lysyl-proline; ARB: Angiotensin receptor blocker; DMT1: Divalent mental transporter 1; EPO: Epoetin; GRF: Glomerular filtration rate; HF: Heart failure, NFkB: Nuclear factor kappa B; RBC: Red blood cell mass). (*Source*: Modified from Anand IS. Anemia and chronic heart failure: implications and treatment options. J Am Coll Cardiol. 2008;52:501-11)

serum iron or ferritin were found in 43% of patients, but only 6% presented with a characteristic microcytic anemia, suggesting that other factors may be inhibiting erythropoiesis.[11] Surprisingly, another study found depleted bone marrow iron stores in 73% of patients despite normal serum iron, ferritin and erythropoietin levels.[12] This was interpreted as a potential manifestation of inflammation and cytokine activation, evidenced by elevated levels of TNF-alpha, interleukin-6 and CRP, which suppress erythropoietin levels with diversion of iron stores from the bone marrow to less available reticuloendothelial stores.[13] Similar findings have been reported in patients with apparent anemia of chronic disease in which inflammation is thought to have a causal role mediated by impaired bone marrow response to suppressed erythropoietin production. Paradoxically, some anemic heart failure patients have elevated erythropoietin levels, and notably this finding has been associated other findings suggestive of more severe heart failure and with increased mortality risk.[14,15] Another confounding factor is hemodilution, which may present as apparent anemia in patients with severe heart failure and is associated with a particularly poor prognosis.[16]

PROGNOSTIC SIGNIFICANCE OF ANEMIA IN HEART FAILURE PATIENTS

Regardless of the underlying mechanism, the presence of anemia or its development in heart failure patients has been consistently associated with a poorer prognosis, as evidenced by increased rates of mortality and hospital admissions. This finding has emerged from cohort studies[3,4,17] and the long-term follow-up of patients enrolled in several clinical trials.[18-20] An extensive meta-analysis of 34 studies including 153,180 patients reported a consistent increase in mortality in anemic patients, with an overall odds ratio of 1.96 (95% CI 1.74, 2.21)[21] with confidence intervals that crossed 1.0 in only 3 studies due with small numbers of events. In addition, anemic heart failure patients are more likely to be hospitalized.

SHOULD ANEMIA BE TREATED IN HEART FAILURE PATIENTS?

However, the key question that remains unresolved is whether the poor outcomes of anemic heart failure patients are causally

related to anemia or whether anemia is a marker for more severe heart failure and/or associated comorbid conditions that are associated with worse outcomes. Intuitively, if the former hypothesis is correct, treating anemia with erythropoiesis stimulating proteins (ESPs) should improve patients' symptoms, activity tolerance and quality of life and potentially improve patient outcomes. On the other hand, if anemia is a consequence of more severe heart failure or comorbid conditions, the benefits of ESPs may be limited. Furthermore, as discussed in the next section, a growing body of data suggests that correction of anemia with ESPs may not produce the expected benefit and appears to have deleterious effects in a variety of conditions associated with anemia.[22]

SAFETY CONCERNS RELATED TO ESPs IN A VARIETY OF ANEMIC PATIENTS

For many years the use of ESPs to correct anemia has been assumed to be beneficial and is widespread in a variety of anemic patients. The benefit of enhancing oxygen delivery to peripheral organs and tissues seems intuitive, and is demonstrably effective in improving exercise performance when inadequate oxygen delivery is the limiting factor. Similarly, improving myocardial oxygen delivery might be expected to improve the performance of the failing heart.

These expectations led to the rapid growth of the use of ESPs in patients with chronic kidney disease with at best very limited data on either the benefits or the safety of this approach. Although the first ESP, epoetin alfa, was approved by the Food and Drug Administration in 1989 for the treatment of chronic kidney disease "to elevate or maintain the red blood cell level and decrease the need for transfusions", data regarding both benefits and safety were very limited. The first prospective randomized trial of epoetin alpha to examine outcomes in patients treated with ESPs, the Normal Hematocrit Study, evaluated the hypothesis that raising hemoglobin concentrations to normal levels (hematocrit 42 ± 3%) versus maintaining the hematocrit at 30 ± 3% in chronic kidney disease patients undergoing dialysis with either congestive heart failure or ischemic heart disease would prevent cardiovascular events.[23] Surprisingly, given the acceptance and high use of ESPs in chronic kidney disease patients, this trial was stopped early due to a strong trend toward an excess of deaths and non-fatal MIs in the group with a normal hematocrit target. The subsequent Correction of Hemoglobin and Outcomes in Renal Insufficiency Trial (CHOIR),[24] which employed the longer acting darbepoetin alfa in chronic kidney disease patients undergoing regular dialysis, was also halted prematurely due to an excess occurrence of the composite primary endpoint of death, myocardial infarction, hospitalization for congestive heart failure or stroke in the darbepoetin group.

The lack of benefit in these trials came as a shock to many physicians and patients. One explanation was that the adverse cardiac outcomes resulted from overly rapid correction of anemia. As a result, one more trial was undertaken: the Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT), which also employed darbepoetin alfa in patients with type 2 diabetes and chronic kidney disease who were not being dialyzed.[25] Again, darbepoetin treatment was associated with a numerical excess the composite of death or cardiovascular events and a statistically significant near doubling of fatal and non-fatal strokes, as well as a significant excess of venous and arterial thromboembolic events and trends toward an increase in cancer deaths.

Studies in patients with other conditions in which ESPs have been considered potentially beneficial have also not found the expected benefits. Darbepoetin was evaluated for the treatment of anemia in cancer patients who were not receiving chemotherapy or radiotherapy in a randomized, double-blind, placebo controlled study. There was no significant reduction in the use of transfusions, and patients treated with darbepoetin had a shorter survival time.[26]

Lastly, based on observations that recombinant human erythropoietin may provide neuroprotection, erythropoietin was administered in a double blind, placebo controlled trial of patients presenting within 6 hours of an acute ischemic stroke. Patients who received erythropoietin did not show greater improvement in the Barthel Index, which assesses ability to perform activities of daily living. Furthermore, the erythropoietin patients experienced a significantly higher death rate.[27]

Taken together, the results of these trials in a variety of patient groups with anemia, ranging from chronic kidney to cancer and ischemic stroke, suggest limited benefit from the anemia correction in these conditions and potential harm from thrombotic events and, possibly, exacerbation of the underlying condition.

TREATMENT OF ANEMIA IN HEART FAILURE PATIENTS

ERYTHROPOIETIN STIMULATING PROTEINS (ESPs)

At this time, data on the use of ESPs to treat anemia in heart failure patients remain limited. These are summarized in a previously cited review article and a meta-analysis.[9,28] Most studies were small (enrolling fewer than 60 patients), involved a single center, and were often conducted in an unblinded or single-blinded manner. The target hemoglobin levels were generally in the low end of the normal range. Follow-up periods ranged 3–8 months. A variety of endpoints were employed, but most studies included a measure of exercise capacity, symptom status or quality of life, and clinical endpoints (usually deaths and hospitalizations). The results of these studies varied with the rigor of the trial design. Single center studies without control groups or blinded treatment reported consistently favorable results,[29-31] including improvement in New York Heart Association (NYHA) class, quality of life measures, exercise capacity and left ventricular function. In addition, in some studies diuretic requirements declined and treated patients experienced fewer hospitalizations.

Two of the studies[32,33] were larger (319 and 575 patients respectively), conducted in a double-blind manner in multiple centers and included longer follow-up periods (27 and 53 weeks respectively). In the former study led by van Veldhuisen,[32] one measure of quality of life (the Kansas City Cardiomyopathy Questionnaire) was significantly improved, but another (the Minnesota Living with Heart Failure Questionnaire) did not

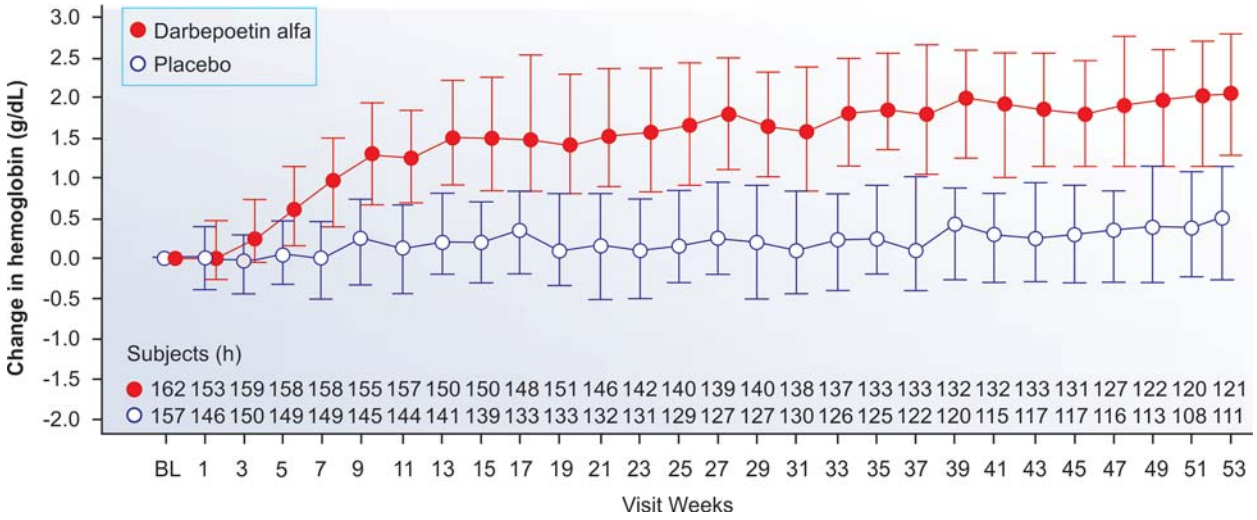


FIGURE 2A: STAMINA-heft—change in hemoglobin with darbepoetin versus placebo

show improvement. Nor was their significant improvement in the 6 minute walk distance, left ventricular ejection fraction or NYHA class. Six deaths, which were considered unrelated to treatment, occurred in the 110 darbepoetin alfa treated patients, whereas no deaths occurred in the 55 patients in the placebo group.

STAMINA-HeFT,[33] the largest (319 patients) and longest (53 weeks) completed study of an ESP in heart failure patients, also yielded mixed findings. At 27 weeks, serum hemoglobin rose by a median of 1.8 g/dL (IQ range 1.1, 2.5) compared to an increase of 0.3 g/dL (IQ range -0.2, 1.0) in the control group, with a slight further rise to 2.1 g/dL and 0.5 g/dL in the darbepoetin and placebo respectively at 53 weeks (the end of study). The primary endpoint of treadmill exercise tolerance after 27 weeks of treatment did not differ between the placebo and the darbepoetin groups (409 vs 408 seconds respectively), nor did the mean change in exercise duration (+ 46.5 in vs + 57.3 seconds) differ significantly (p = 0.459). There was no apparent relationship between the change in hemoglobin and the change in exercise tolerance in either group. The Minnesota Living with Heart Failure Questionnaire score improved similarly in both the groups.

Importantly, given the concerns raised by trials of ESPs in other clinical conditions, there have been no clear safety signals concerning the safety of ESPs in heart failure patients. Indeed, in STAMINA HeFT, the largest and longest trial in this population, there were numerically more deaths in the placebo group, 18 (11%),[33] than in the darbepoetin group, 11 (7%); and there was a trend favoring the darbepoetin for the composite endpoint of time to death or first heart failure hospitalization (HR 0.68; 95% CI 1.08) (p = 0.10) (Figs 2A and B). Other adverse events were generally equally distributed between the two treatment groups. Whether the lower rates of adverse events in these relatively small heart failure trials represent differences in the ESPs employed (epoetin vs darbepoetin), the rapidity or magnitude of anemia correction, the underlying conditions (chronic kidney disease or cancer versus chronic heart failure) or comorbid conditions, or the play of chance is uncertain. However, given the adverse prognosis associated with anemia

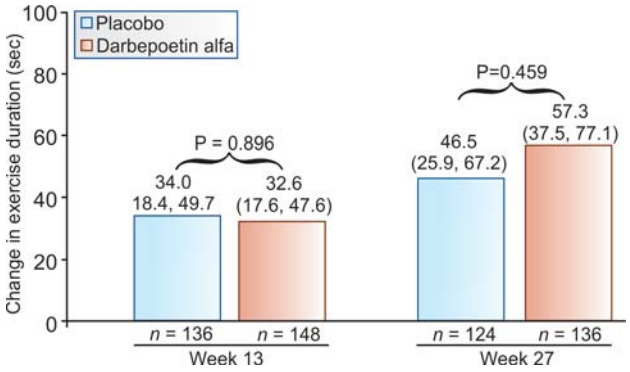


FIGURE 2B: STAMINA-heft—change in exercise time with darbopoetin vs placebo. (*Source*: Modified from Ghali JK, Anand IS, Abraham WT, et al. Randomized double-blind trial of darbepoetin alfa in patients with symptomatic heart failure and anemia. Circulation. 2008;117:526-35)

in heart failure patients, reasonable arguments have been advanced for addressing the potential benefit of ESPs (specifically darbepoetin alfa) in this population.[34-36]

Such a trial, RED-HF, is now ongoing sponsored by Amgen and is designed to enroll approximately 2,600 patients with symptomatic (NYHA class II-IV heart failure, an ejection fraction ≤ 40%, and hemoglobin levels consistently ≤ 12.0 but ≥ 9.0 g/dL). Exclusions include transferrin saturation less than 15%, heart failure due to valvular heart disease or presence of valvular disease that might lead to surgical correction within 12 months of randomization, recipients of a major organ transplant or receiving renal replacement therapy, and a serum creatinine greater than 3.0 mg/dL. Darbepoetin alpha is being dosed in a double-blind randomized manner to achieve a hemoglobin concentration of 13.0 g/dL but not to exceed 14.5 g/dL with sham adjustments of the placebo dosing. The primary endpoint is the time to first event of death from any cause or first hospital admission for worsening heart failure, with completion of the study when approximately 1,150 primary events have occurred, which would provide 80% power to detect a 20% reduction in the primary endpoint with darbepoetin treatment, assuming a 25% per year primary endpoint rate in

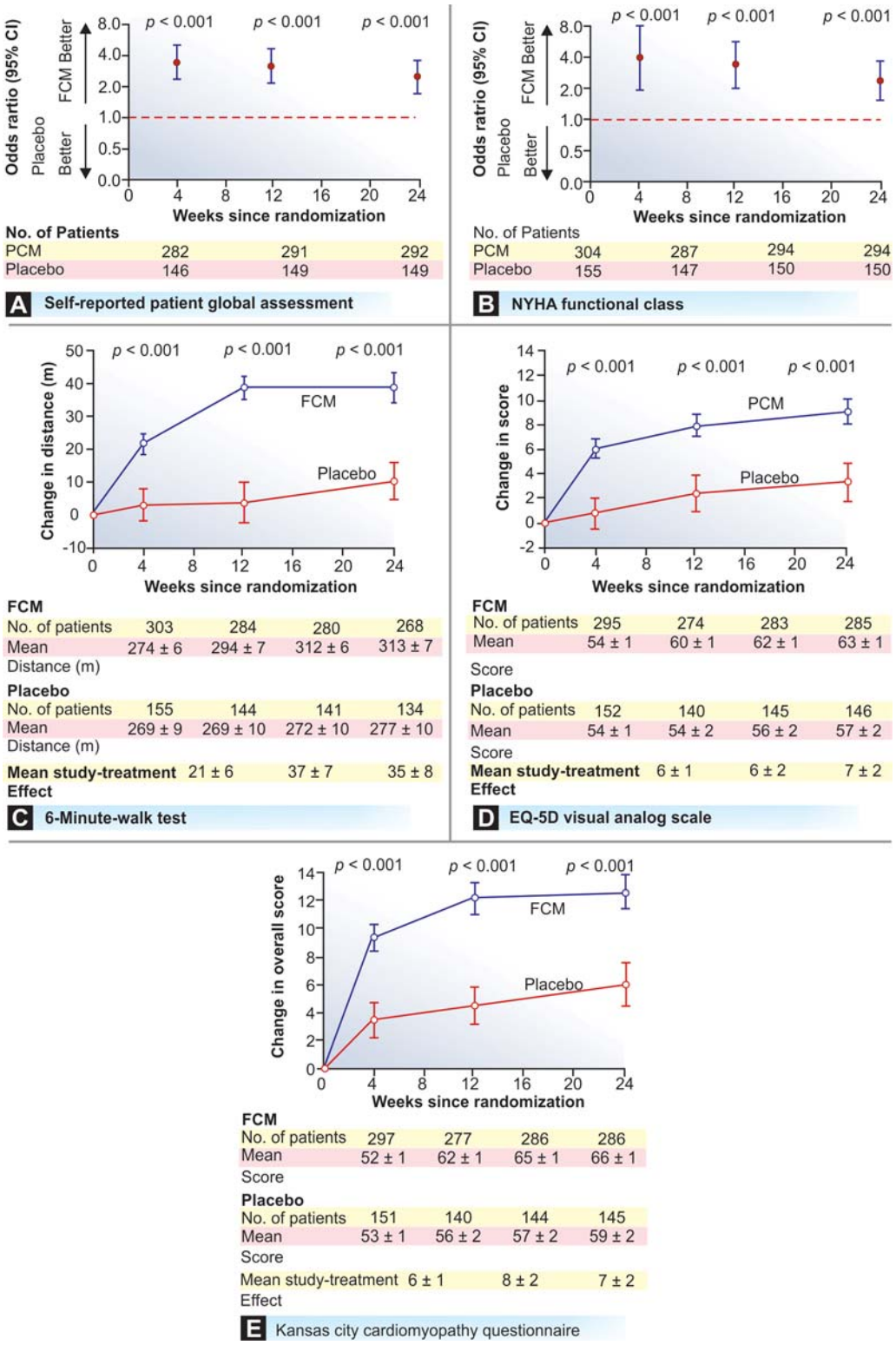


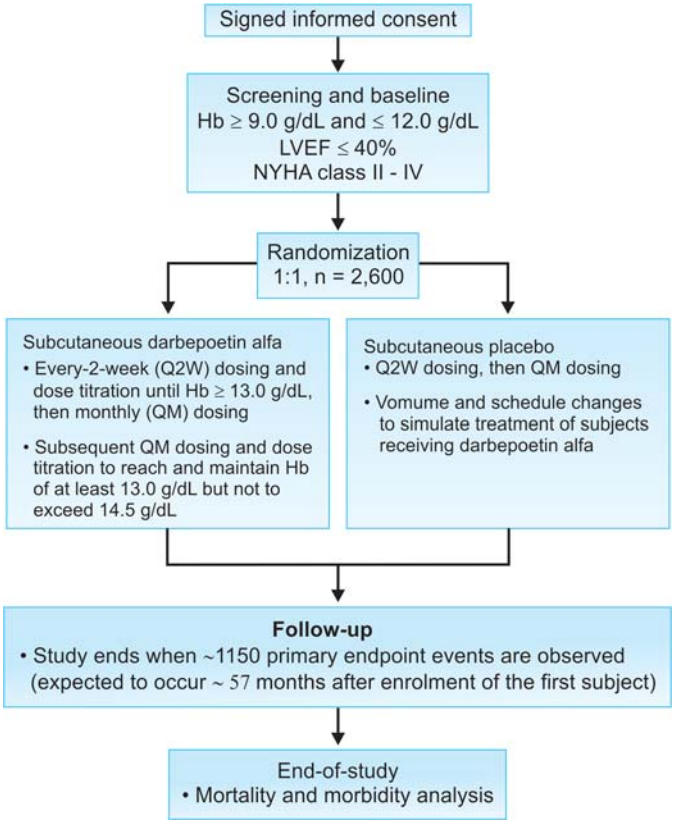
FIGURE 3: FAIR-HF—effect of intravenous iron on primary and secondary endpoints. (*Source*: Modified from Anker S et al. Ferric carboxymaltose in patients with heart failure and iron deficiency. Ferric carboxymaltose in patients with heart failure and iron deficiency. N Engl J Med. 2009;361:2436-48)

the placebo group. Secondary outcomes are effects of treatment with darbepoetin alfa on change in the Kansas City Cardiomyopathy Questionnaire (KCCQ) Overall Summary Score from baseline to Month 6, time to death from any cause; time to cardiovascular death or first hospital admission for worsening heart failure (Flow chart 1 and Fig. 3).

IRON DEFICIENCY AND IRON REPLACEMENT IN HEART FAILURE

Although most of the interest in the treatment of anemia in heart failure patients has centered on the use of ESPs, as noted earlier abnormalities of iron supply and handling are also common,

FLOW CHART 1: RED-HF study design



(Abbreviations: Hb: Hemoglobin; LVEF: Left ventricular ejection fraction; NYHA: New York Heart Association; Q2W: Once every 2 weeks; QM: Once monthly). (*Source*: Modified from McMurray JJV, Anand IS, Diaz R, et al. Design of the reduction of events with darbepoeitin alfa in heart failure (RED-HF): a Phase III, anaemia correction, morbidity-mortality trial. Eur J Heart Failure. 2009;11:795-81)

although the usual phenotype of a hypochromic microcytic anemia is frequently absent. Similarly, although serum iron levels and saturation are often maintained, bone marrow iron stores may be depleted. These findings have been attributed variously to impaired gastrointestinal iron absorption and inflammation,[12,13,37] both of which may depress erythropoiesis. Silverberg et al.[30] noted more than a decade ago that combined administration of intravenous iron with erythropoietin was more effective than erythropoietin alone, even in patients without clear evidence of iron deficiency. Other studies supported a benefit from intravenous iron, without concomitant ESP use.[38-40]

These findings led to the initiation of the Ferinject Assessment in Patients with Iron Deficiency and Chronic Heart Failure Trial (FAIR-HF), in which 4 ml of ferric carboxymaltose (equivalent to 200 mg of intravenous iron) was administered weekly in a double-blind randomized manner in a ratio of 2:1 active:placebo to 459 patients with or without anemia, who had iron deficiency defined as serum ferritin level was less than 100 µg per liter or between 100 and 299 µg per liter when the transferrin saturation was less than 20%. Weekly injections were continued until iron was repleted (usually within 8 weeks) and then at 4-weekly intervals up to 24 weeks (Table 1).[41]

The co-primary endpoints, patient-assessed global assessment and NYHA class, improved by week 4 in the active group with little change in the placebo group, and these differences widened until the end of the pre-specified 24 week treatment period ($p < 0.001$ at each assessed time point). Significant improvements were also seen in each of the pre-specified secondary endpoints (6 minute walk distance, Kansas City Cardiomyopathy Questionnaire, and EuroQual 5D quality of life assessment).

Most intriguingly, although the numbers of events were small, there were proportionally fewer deaths and hospitali-

TABLE 1

FAIR-HF safety endpoints

End point or event	*Ferric carboxymaltose (n = 305)*		*Placebo (n = 154)*		*P value*
	No. of end points or serious adverse/any adverse events	*No. of patients with end point or event (incidence/100 patient-yr at risk)*	*No. of end points or serious adverse/any adverse events*	*No. of patients with end point or event (incidence/100 patient-yr at risk)*	
Safety end point					
Death	5	5 (3.4)	4	4 (5.5)	0.47
Death due to cardiovascular causes	4	4 (2.7)	4	4 (5.5)	0.31
Death due to worsening heart failure	0	0	3	3 (4.1)	
First hospitalization	28	25 (17.7)	22	17 (24.8)	0.30
Hospitalization for any cardiovascular cause	16	15 (10.4)	18	14 (20.0)	0.08
Hospitalization for worsening heart failure	7	6 (4.1)	9	7 (9.7)	0.11
Any hospitalization or death	33	30 (21.2)	26	19 (27.7)	0.38
Hospitalization for any cardiovascular cause or death	21	20 (13.9)	22	16 (22.9)	0.14
First hospitalization for worsening heart failure or death	12	11 (7.5)	13	10 (13.9)	0.15

(*Source*: Modified from Anker S et al. Ferric carboxymaltose in patients with heart failure and iron deficiency. Ferric carboxymaltose in patients with heart failure and iron deficiency. N Engl J Med. 2009;361:2436-48)

zations attributed to heart failure or all cardiovascular causes in the intravenous iron group, although none of these reached nominal statistical significance. This study suggests that iron deficiency itself is a legitimate therapeutic target and warrants more studies in morbidity and mortality.

SUMMARY AND CONCLUSIONS

In summary, anemia is found frequently in chronic heart failure patients as well as inpatients who present with acutely decompensated heart failure. The mechanisms underlying this association are not well defined, but likely include chronic renal insufficiency, cytokine induced inflammatory responses, resulting in impaired erythropoiesis, and effects of medications.

Although it is intuitive that stimulating erythropoiesis should stimulate hemoglobin production, the evidence supporting this has been limited. Importantly, the bulk of the evidence garnered from trials in which erythropoitin was administered suggested a limited beneficial effect of this approach and potentially serious adverse outcomes, including excessive strokes and other pro-thrombotic effects.

Intriguingly, the administration of intravenous iron has resulted in greater erythropoiesis, as well as improved symptoms, exercise tolerance, and indices of quality of life. Trials of both erythropoietin simulating proteins and exogenous iron are ongoing and are awaited with considerable anticipation.

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Chapter 73

Hyponatremia and Congestive Heart Failure

Anne Mani, David J Whellan

Chapter Outline

- Mechanisms Causing Hyponatremia in Heart Failure
  - Sympathetic Nervous System
  - Renin-Angiotensin-Aldosterone System
  - Arginine Vasopressin
- Treatment of Hyponatremia
- Role of Diuretic Therapy in Hyponatremia
- Role of Vasopressin Receptor Antagonists in Hyponatremia
- Tolvaptan
- Lixivaptan
- Conivaptan

INTRODUCTION

Approximately 5 million people in the United States are affected by congestive heart failure, resulting in more than 1 million heart failure hospital admissions annually. Hyponatremia, which is variably defined, but most commonly accepted to be a serum sodium level less than 135 mEq/l, is diagnosed in approximately 20–30% of patients admitted for acute decompensated heart failure. In general, hyponatremia is classified according to the patient's volume status: hypovolemic, euvolemic or hypervolemic. Patients with heart failure tend to develop hypervolemic hyponatremia due to inappropriate retention of sodium and water, with excessive water retention leading to low serum sodium. Hyponatremia has been associated with increased short-term and long-term morbidity and mortality in the heart failure population.[1–3]

In a retrospective analysis of the Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbation of Chronic Heart Failure (OPTIME-CHF) study, which involved 949 patients with systolic dysfunction hospitalized for worsening heart failure, low serum sodium on admission was associated with a longer length of stay in the hospital as well as increased short-term mortality.[1] When patients were classified according to quartiles of serum sodium levels, patients with hyponatremia (serum sodium 132–135 mEq/l) were more likely to have more severe heart failure, as evidenced by a higher number of hospital admissions within the previous year (average of 2 admissions in the lowest quartile with serum sodium 132–135 mEq/l, compared to 1 admission in the highest quartile with serum sodium 141–144 mEq/l, $p = 0.003$). They also tended to have a lower systolic blood pressure and higher blood urea nitrogen (BUN) on admission. However, left ventricular ejection fraction and NYHA class were similar across quartiles, and medication regimens were similar. Approximately, 90% of patients were taking diuretics, 70% were on an angiotensin-converting enzyme (ACE) inhibitor, and 20–25% were on a beta blocker. Patients in the lowest serum sodium quartile had the highest number of days hospitalized for cardiovascular causes within 60 days of randomization, which was the primary endpoint in this analysis. Patients in the lowest serum sodium quartile spent an average of 8 days in the hospital, versus 6 days in the highest quartile ($p < 0.001$). In-hospital mortality was 5.9% in the lowest quartile, compared to 2.3% in the highest quartile ($p = 0.015$), and 60-day mortality was also higher in the hyponatremic quartile (15.9%) compared to the highest quartile (7%, $p = 0.002$). There was a trend toward a higher rate of death or rehospitalization at 60 days as a combined endpoint for patients in the lowest serum sodium quartile (41% vs 33.6% in the highest quartile, $p = 0.095$). Interestingly, in 38% of patients who fell in the lowest quartile of sodium levels, serum sodium increased to greater than 135 mEq/l by discharge. Compared to the other patients who remained hyponatremic at discharge, there was a trend toward improvement in 60-day mortality (10.75% vs 17.22%, $p = 0.19$). In multivariable-adjusted Cox proportional hazards analysis, serum sodium on admission remained a significant predictor of increased 60-day mortality, with a hazard ratio of 1.18 (95% CI 1.03–1.36) for every 3 mEq/dL decrease in serum sodium ($p = 0.018$) (Fig. 1).

The OPTIME-CHF analyzed a relatively homogeneous cohort of patients with systolic dysfunction but with preserved renal function, admitted to the hospital for worsening heart failure. The OPTIMIZE-HF registry, which includes a much larger, unselected population of 47,647 heart failure patients hospitalized for acute decompensated heart failure, still supports the association between hyponatremia and poorer outcomes.[2] A subset of 10% of the total patient population (5,791 patients) was followed for 60–90 days post-discharge to document clinical events. In the general registry, the mean admission serum sodium was 138 mmol/l, and 19.7% of patients met the definition of hyponatremia with serum sodium less than 135 mmol/l. Patients with hyponatremia had lower admission systolic blood pressure (135.7 mm Hg vs 144.4 mm Hg, $p < 0.0001$), but there was no significant difference in the baseline use of ACE inhibitors (38.5% vs 39.9%, $p = 0.252$) or

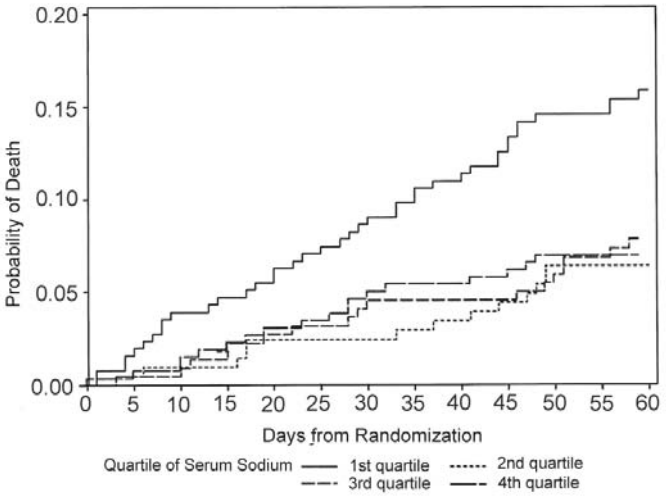


FIGURE 1: Kaplan-Meier survival curves to 60 days by serum sodium quartiles (unadjusted analysis). Probability value < 0.05 for first quartile versus each of the other quartiles from Cox proportional hazards model. (*Source:* Klein L, O'Connor C, Leimberger J, et al. Lower Serum Sodium is Associated with Increased Short-Term Mortality in Hospitalized Patients with Worsening Heart Failure: Results From the Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) Study. Circulation 2005;111:2454-60, with permission)

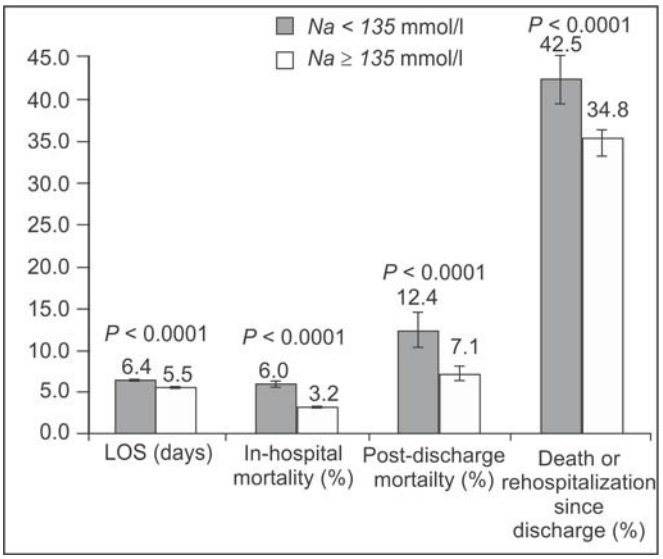


FIGURE 2: LOS and clinical outcomes by admission serum sodium groups. (*Source:* Gheorghiade M, Abraham WT, Albert NM, et al. Relationship between admission serum sodium concentration and clinical outcomes in patients hospitalized for heart failure: an analysis from the OPTIMIZE-HF registry. Eur Heart J 2007;28:980-8, with permission)

beta-blockers (52.7% vs 53.2%, $p = 0.801$). During hospital admission, however, patients in the hyponatremic group were more likely to receive intravenous inotropes (14.2% vs 7.6%), dialysis (6.1% vs 4.8%, $p < 0.0001$), LV assist devices (0.3% vs < 0.1%, $p < 0.0001$) or mechanical ventilatory support (3.8% vs 3.0%, $p < 0.0001$). Despite these differences in hospital treatment, overall diuresis as measured by mean change in weight from admission to discharge was not statistically different (2.5 kg vs 2.6 kg, $p = 0.198$). The use of aldosterone antagonists at discharge was higher in the hyponatremia group (19.5% vs 17.8%, $p = 0.0001$), but patients in this group were less likely to receive an ACE inhibitor or angiotensin receptor blocker (79.7% vs 83.2%, $p < 0.0001$) or diuretics (74.1% vs 78.1%, $p < 0.0001$) at discharge.

Rehospitalization rates during follow-up were not significantly different for patients with hyponatremia, but mean length of stay was longer (6.4 days vs 5.5 days, $p < 0.0001$). The overall in-hospital mortality rate for registry patients was 3.8%. Hyponatremic patients had higher in-hospital mortality (6.0% vs 3.2%, $p < 0.0001$) and 60–90 day mortality (12.4% vs 7.1%, $p < 0.0001$) compared to normonatremic patients. The risk of in-hospital mortality began to rise significantly when serum sodium was less than 138 mmol/l, and was more than double for patients in the range of 132–135 mmol/l. After adjusting for multiple other prognostic factors, serum sodium on admission remained a significant independent predictor of length of stay, in-hospital mortality, post-discharge mortality and 60–90 days death or rehospitalization in this analysis (Fig. 2).

The association between hyponatremia and increased mortality remains robust even in patients with heart failure and preserved LV function. In the 21,149 patients with heart failure and preserved systolic function included in the OPTIMIZE-HF study, in-hospital mortality rates were still higher in hyponatremic patients than normonatremic patients (4.2% vs 2.6%, $p < 0.0001$). However, the risk of in-hospital mortality was higher for patients with systolic dysfunction and hyponatremia (6.8%) than patients with preserved systolic function and hyponatremia (4.2%). For each 3 mmol/l decrease in serum sodium, the risk of in-hospital mortality increased by 19.5% for patients with systolic dysfunction and by 8.6% for patients with preserved systolic function. Hyponatremia appears to have an effect on long-term mortality in patients with heart failure and preserved LV function as well. In a study of 358 patients with normal LV systolic function surviving a first hospitalization for heart failure who were prospectively followed for 7 years, patients with admission hyponatremia (defined as a serum sodium < 136 mEq/l) had increased mortality compared to patients with normal serum sodium levels. Approximately, 25.4% of the total cohort met the criteria for hyponatremia on admission. In both groups, approximately 45% of patients were taking ACE inhibitors, 23% were taking beta blockers and 85% were taking loop diuretics. Patients with hyponatremia, however, had lower systolic and diastolic blood pressures. During follow-up, one-, three- and seven-year survival rates were 84%, 64% and 40% for patients with normal serum sodium levels, compared to 67% ($p < 0.001$), 42% ($p < 0.001$) and 19% ($p < 0.001$) for patients with hyponatremia. The risk of 7-year mortality increased by 6% for each 1 mEq/l decrease in serum sodium. Hyponatremia was associated with a hazard ratio of 1.98 (95% CI 1.50–2.61) for overall mortality and a hazard ratio of 1.92 (95% CI 1.36–2.73) for cardiovascular mortality.[4]

The studies thus far discussed evaluate the association between hyponatremia and outcomes in patients acutely hospitalized for worsening heart failure. However, they do not address the impact of hyponatremia on patients with chronic heart failure being treated as outpatients. A small observational prospective study of 364 patients with heart failure and systolic dysfunction enrolled in a heart failure disease management

program in Louisiana followed for 40 months did not find a significant difference in mortality for patients with hyponatremia compared to those with normal serum sodium levels.[5] Approximately 13% of the patients had hyponatremia on admission to the program, with 8 deaths in the hyponatremia group (17%) compared to 31 (9.8%) in the normonatremia group. However, this difference was not statistically significant. The adjusted odds ratio was 1.60 (95% CI 0.57–4.53, $p = 0.37$). The investigators attribute the lack of an association between hyponatremia and higher mortality in this study to a high incidence of ACE inhibitor and beta blocker use (95–100%) in their cohort, which may attenuate the effect of hyponatremia. This hypothesis is supported by data from Lee and Packer, who published one of the earliest studies of the use of ACE inhibition in heart failure in 1986, which showed that hyponatremic patients treated with ACE inhibitors had better short-term outcomes than those treated with other vasodilator drugs.[6] A larger observational study of 553 ambulatory patients in the United Kingdom with mild to moderate heart failure (UK-HEART) found that low serum sodium was predictive of 5-year mortality.[7] In this group, low serum sodium had a hazard ratio of 1.14 (CI 1.06–1.24, $p < 0.001$). However, compared to the cohort of patients in the Louisiana outpatient group who were almost all taking ACE inhibitors and beta blockers, 82% of patients in the UK group were treated with ACE inhibitors, and only 7.9% were taking atenolol. The difference in medication regimen may explain the variance in outcomes in patients with hyponatremia between these two studies. A larger registry of 1,315 Italian patients (IN-CHF) with chronic heart failure due to LV systolic dysfunction followed for at least one year found that hyponatremia was an independent predictor for one year all-cause mortality.[8] Approximately 5% of the cohort had hyponatremia. Approximately 90% were taking ACE inhibitors or ARBs, but only 15% were taking beta blockers. After adjusting for other prognostic variables, a serum sodium less than 135 mEq/l conveyed a hazard ratio of 1.468 (95% CI 1.13–1.90, $p = 0.0038$). Again, the differences in medication regimens between studies make it difficult to compare the association between serum sodium and mortality outcomes.

Hyponatremia has been found to be an important predictor of survival in several risk models developed for use in heart failure patients, which are applied to cohorts in the outpatient, inpatient, and pre-transplant settings. The heart failure survival score (HFSS) was the first predictive model developed in 1997 to assess pre-transplant mortality risk in ambulatory patients.[9] It was derived from a 268 patient cohort, which identified seven variables associated with increased risk. Ischemic heart failure was found to be the strongest predictor of mortality, with an HR of 2.00 (95% CI 1.35–2.97), while serum sodium had the weakest association (HR 0.95, 95% CI 0.92–1.00). The EFFECT model was developed to predict 30-day and 1-year mortality in heart failure patients on admission to the hospital. Again, hyponatremia on admission, which was defined as a serum sodium less than 136 mEq/l, was found to be associated with increased 30-day (HR 1.53, 95% CI 1.14–2.05) and 1-year (HR 1.46, 95% CI 1.19–1.80) mortality.[10] The most popular model, the Seattle Heart Failure Model, was derived in a cohort of 1,125 patients and validated in five additional cohorts comprising 9,942 patients.[11] Eleven predictive variables were identified, including a baseline serum sodium less than 138 mEq/l, which conveyed an HR of 1.050 (95% CI 1.005–1.097). Although the evidence overwhelmingly supports the deleterious association of hyponatremia with poorer outcomes, it is unclear whether hyponatremia directly contributes to increased morbidity and mortality in heart failure, or is simply a marker of the severe activation of the neurohormonal system known to occur with heart failure.

MECHANISMS CAUSING HYPONATREMIA IN HEART FAILURE

The pathophysiology of hyponatremia in heart failure involves multiple neurohormonal pathways, including the sympathetic nervous system, the renin-angiotensin-aldosterone system (RAAS) and arginine vasopressin (AVP). These systems are initially activated to preserve cardiac function in the failing heart, but eventually lead to progressive cardiac dysfunction and renal retention of sodium and water. As early as 1984, Lilly et al. published data showing markedly elevated levels of catecholamines, renin, angiotensin II, aldosterone and vasopressin in patients with heart failure and hyponatremia compared to normonatremic patients.[12] Also in the 1980s, Lee and Packer followed 203 patients with severe heart failure before and after the initiation of heart failure treatment and found that hyponatremic patients had a marked elevation of plasma renin, and their survival improved when treated with ACE inhibitor compared to other vasodilator drugs (median survival 232 days vs 108 days, $p = 0.003$).[6] In contrast, heart failure patients with normal sodium levels and low plasma renin did not have a significant improvement in survival with ACE inhibitors. This evidence would suggest that hyponatremia is simply a marker for neurohormonal activation, and that neurohormonal blockade with agents, such as ACE inhibitors, can attenuate the association between hyponatremia and increased mortality. However, studies such as OPTIME-CHF and OPTIMIZE-HF, in which hyponatremic subjects already on ACE inhibitors and beta blockers still had significantly increased morbidity and mortality, provide evidence that neurohormonal activation may not entirely explain the association between hyponatremia and poor outcomes.

SYMPATHETIC NERVOUS SYSTEM

Decreased effective arterial blood volume is sensed by baroreceptors in the carotid sinus, aortic arch and renal afferent arterioles, and activates the sympathetic nervous system, which manifests early in the course of heart failure. Norepinephrine levels are two to three times higher in patients with advanced heart failure compared to normal subjects, which occurs due to both increased release as well as reduced uptake of norepinephrine at the adrenergic nerve synapses. High circulating norepinephrine leads to increased heart rate, myocardial contractility and peripheral arterial vasoconstriction. The increase in peripheral arterial resistance increases afterload, which reduces cardiac output and can decrease renal blood flow. In the kidney, sympathetic stimulation causes renal arterial vasoconstriction, which also decreases renal perfusion and the glomerular filtration rate, leading to increased proximal tubule sodium and water reabsorption as well as the release of AVP.

RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM

The renin-angiotensin-aldosterone system (RAAS) is activated later in the natural course of heart failure, but is also exquisitely sensitive to low cardiac output and decreased renal perfusion. Hypotension causing arterial underfilling is the primary stimulus for activation, and normally once hypotension has been corrected, the system returns to baseline to maintain homeostasis. However, the activity of the RAAS remains elevated in most patients with heart failure. There is increased renin release from the juxtaglomerular apparatus in response to decreased sodium reaching the distal tubule of the kidneys. The renin then converts circulating angiotensinogen to angiotensin I, which is activated by ACE to angiotensin II. Angiotensin II stimulates the production of aldosterone in the zona glomerulosa of the adrenal cortex, which promotes the reabsorption of sodium in exchange for potassium in the distal tubule. Angiotensin II binds to two G-protein coupled receptors; angiotensin type 1 (AT_1) and angiotensin type 2 (AT_2) receptors. AT_1 is found mostly in the myocardium and leads to vasoconstriction, aldosterone secretion and catecholamine release, whereas AT_2 is localized to fibroblasts and the interstitium and is involved in vasodilation and natriuresis. In patients with heart failure, it is believed that AT_1 receptors are downregulated, while AT_2 receptor density remains unchanged. Angiotensin II increases resistance in the afferent arterioles of the kidneys, which reduces renal perfusion and decreases the glomerular filtration rate. Decreased renal perfusion promotes salt and water retention by upregulating proximal tubule sodium reabsorption and decreasing the amount of sodium and water delivered to the distal tubules, which are involved in dilution.

In normal subjects, high doses of aldosterone initially increase renal sodium and water retention, which leads to expansion of the extracellular fluid volume by 1.5–2 liters, as occurs in patients with primary hyperaldosteronism. However, patients with primary hyperaldosteronism and normal subjects given aldosterone adapt and become less responsive to the retentive effects of aldosterone and therefore do not develop edema. This adaptive response to aldosterone does not occur in patients with heart failure, and so they continue to retain sodium and water. The mechanisms responsible for this phenomenon have not been fully explained, although it is known that alpha-adrenergic and angiotensin-II stimulation decrease the delivery of sodium to the collecting ducts, which promotes persistent aldosterone-mediated salt and water retention, leading to hypervolemic hyponatremia (Fig. 3).

ARGININE VASOPRESSIN

The hyponatremia seen in patients with heart failure is also mediated by arginine vasopressin (AVP), which is an antidiuretic hormone that regulates water absorption and osmolality. The AVP is synthesized in the supraoptic and paraventricular nuclei of the hypothalamus and stored in the posterior lobe of the pituitary gland. Its major role in the kidneys is to increase the permeability of the cortical and medullary collecting tubules to water, promoting water reabsorption. Hyperosmolality and decreased circulating blood volume are the primary stimuli for AVP secretion, whereas hypo-osmolality inhibits secretion. In patients with heart failure, however, AVP levels are inappropriately high despite low plasma osmolality. In fact, in a baseline evaluation of the participants in the Studies of Left Ventricular Dysfunction (SOLVD) study, which assessed neuroendocrine activation in patients with LV dysfunction, plasma AVP levels increased with the severity of cardiac dysfunction, and were highest in

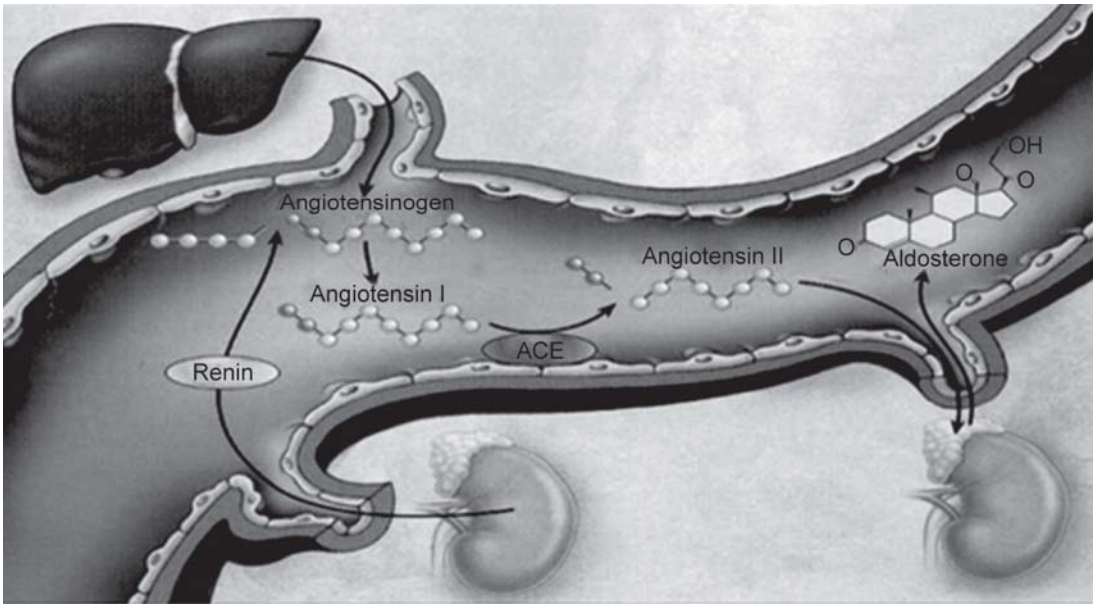


FIGURE 3: The Renin-Angiotensin-Aldosterone System. Angiotensinogen, the precursor of all angiotensin peptides, is synthesized by the liver. In the circulation it is cleaved by renin, which is secreted into the lumen of renal afferent arterioles by juxtaglomerular cells. Renin cleaves four amino acids from angiotensinogen, thereby forming angiotensin I. In turn, angiotensin I is cleaved by angiotensin-converting enzyme (ACE), an enzyme bound to the membrane of endothelial cells, to form angiotensin II. In the zona glomerulosa of the adrenal cortex, angiotensin II stimulates the production of aldosterone. Aldosterone production is also stimulated by potassium, corticotropin, catecholamines (e.g. norepinephrine), and endothelins. (*Source:* Weber KT. Aldosterone in Congestive Heart Failure. N Engl J Med 2001;345:1689-97, with permission)

TABLE 1

Vasopressin receptors

Receptors	*Location*	*Effects of AVP*
V_{1a}	Lymphocytes and monocytes	Coagulation factor release
	Platelets	Platelet aggregation
	Adrenal cortex	Glycogenolysis
	Vascular smooth muscle cells	Vasoconstriction
	Cardiac myocytes	Increased intracellular calcium, possible myocardial hypertrophy
V_{1b}	Anterior pituitary	Adrenocorticotrophic hormone and beta-endorphin release
V_2	Renal collecting duct principal cells	Free-water retention

(*Source*: Lee CR, Watkins ML, Patterson JH, et al. Vasopressin: a new target for the treatment of heart failure. Am Heart J. 2003;146:9-18, with permission)

patients with symptomatic heart failure.[13] The inappropriate increase in AVP despite hypo-osmolality may be explained by the activation of a separate baroreceptor-mediated pathway of AVP secretion.[14] Low cardiac output and arterial underfilling in heart failure patients unloads the carotid sinus and aortic arch baroreceptors, which stimulate AVP secretion in an effort to increase intravascular volume. This pathway is independent of osmolality, and therefore results in elevated AVP levels even in the setting of hypo-osmolality.

The AVP binds to three receptor subtypes, all of which are rhodopsin-like G-protein-coupled receptors. They are classified based on the second messenger system which they utilize. The V_{1a} and V_{1b} receptors are linked to the phosphoinositol signaling pathway, with intracellular calcium acting as the second messenger. The V_2 receptor is linked to the adenylate cyclase signaling pathway, with intracellular cAMP acting as the second messenger.[15] The V_{1a} receptors are found on vascular smooth muscle cells and cardiac myocytes. They play a role in blood vessel vasoconstriction, and have also been shown to increase intracellular calcium levels and possibly promote myocardial hypertrophy in cardiac myocytes.[16–19] The V_{1b} receptors are found in the pituitary gland and mediate the release of ACTH and beta-endorphins. The V_2 receptors are located in principal cells in the collecting ducts of the kidney, where they are involved in free-water reabsorption. More specifically, V_2 receptors are coupled to aquaporin-2 (AQP-2) water channels in the principal cells, and receptor binding leads to translocation of these channels to the transluminal membrane, where they facilitate water transport. The V_2 receptor binding also increases AQP-2 synthesis (Table 1).

TREATMENT OF HYPONATREMIA

Hyponatremia typically develops slowly in heart failure patients and does not cause obvious clinical symptoms until the serum sodium falls below 120 mEq/l. Signs and symptoms include nausea, vomiting, headache, irritability, confusion, lethargy, fatigue, loss of appetite and muscle spasms or cramping. With more severe or acute hyponatremia, decreased consciousness, respiratory depression, seizures or coma can occur. These neurologic symptoms are due to cerebral edema caused by fluid shifting from the hypotonic extracellular fluid into the more hypertonic cells in the brain. There is little evidence of clinical benefit for treating hyponatremic patients who are asymptomatic, and the main indications for treatment are for symptoms or for a serum sodium level below 120 mEq/l. Restricting fluid intake to 1–2 L a day, or less than the urine output, is the cornerstone of therapy in patients with chronic hypervolemic hypernatremia. Fluid restriction should decrease total body water volume and increase the ratio of sodium to water to increase the serum sodium level. However hyponatremic patients tend to have increased thirst and may be unable to be compliant with significant fluid restriction, limiting the effectiveness of this therapy. Other treatments include the use of isotonic or hypertonic saline with or without the use of loop diuretics to avoid fluid overload, but these therapies require strict monitoring of serum sodium levels so that sodium is not corrected by more than 0.5 mEq/l per hour, or a total of 12 mEq/l over 24 hours. Overly rapid correction of serum sodium can lead to the phenomenon of central pontine myelinolysis, in which fluid shifts from the more hypotonic brain cells into the relatively hypertonic extracellular fluid, leading to severe and irreversible damage of the myelin sheath of neurons in the brainstem, and possibly death. Demeclocycline, which is a tetracycline antibiotic that inhibits the action of AVP, induces a nephrogenic diabetes insipidus and promotes free-water loss to raise serum sodium levels. However, demeclocycline can be nephrotoxic, particularly in patients with cirrhosis, and can take several days to have an effect on serum sodium.

ROLE OF DIURETIC THERAPY IN HYPONATREMIA

Diuretics increase the rate of urine flow and are commonly used to treat hyponatremia, but they also increase the rate of sodium excretion and so may actually exacerbate hyponatremia.

Currently diuretics are a cornerstone of therapy for congestion in heart failure, but are known to cause electrolyte abnormalities and worsening renal function. Thiazide diuretics, which include hydrochlorothiazide, metolazone and chlorthalidone, block the Na/Cl transporter in the distal convoluted tubule and prevent the maximal dilution of urine. Thiazides do not interfere with AVP-induced water retention, which occurs in the collecting ducts. The combination of increased sodium and potassium excretion due to thiazide use and enhanced water reabsorption due to elevated AVP levels can result in the excretion of urine with a sodium plus potassium concentration higher than that of plasma. Loss of this fluid can contribute to

the development of hyponatremia independent of the degree of water intake.

Loop diuretics, which include furosemide, bumetanide and torsemide, reversibly inhibit the Na/K/2Cl transporter in the epithelial cells in the thick ascending loop of Henle, decreasing sodium retention. The inhibition of concentration of solute within the medullary interstitium also decreases the driving force for water reabsorption in the collecting duct, resulting in the production of urine that is nearly isotonic with plasma and can therefore worsen hyponatremia by promoting an isotonic diuresis with salt loss. However, loop diuretics are much less likely than thiazide diuretics to induce hyponatremia unless the diuretic therapy has resulted in volume depletion or if the oral water intake is very high.

In a review of 129 cases of severe diuretic-induced hyponatremia (serum sodium < 115 mEq/l), investigators concluded that thiazide diuretics were responsible for 94% of cases.[20] Patients were taking diuretics for hypertension (58%), heart failure (20%), or a combination of hypertension with heart failure (22%). In 97% of cases, the dose of diuretics was within the limits of pharmacologic recommendations. In 62% of patients, hyponatremia occurred within 5–14 days of initiation of treatment with diuretics. Hyponatremia with diuretics was four times more common in women than in men (79% vs 21%, $p < 0.001$), and advanced age was not found in this study to be associated with a higher tendency for hyponatremia. In the majority of patients who received thiazides, increased vasopressin activity, hypokalemia, and excess water intake appeared to contribute to the development of hyponatremia.

All diuretics can also cause the depletion of potassium and magnesium, which can lead to life-threatening cardiac arrhythmias, particularly with the concomitant use of digoxin. Vasopressin antagonists, which may increase net volume loss without causing electrolyte abnormalities or worsening renal function, are being researched as alternatives to diuretic use. These agents are in various stages of clinical development, and have differing selectivity for V_{1a} and V_2 receptors.

ROLE OF VASOPRESSIN RECEPTOR ANTAGONISTS IN HYPONATREMIA

Given the central role of AVP in hyponatremia in patients with heart failure, decreasing vasopressin activity has long been a therapeutic goal. With no current therapy available to decrease production of AVP, attention has been turned instead to minimizing its effect by blocking its binding to AVP receptors. In 1992, an orally active, nonpeptide V_2 receptor antagonist (OPC-31260) was described for the first time.[21] Since then, clinical studies of several different agents have demonstrated that V_2 receptor antagonism produces effective and sustained reductions in congestion without worsening renal function or electrolyte abnormalities, as seen with diuretics (Table 2).

TOLVAPTAN

Tolvaptan, a selective non-peptide V_2 receptor antagonist, can help achieve dose-dependent production of dilute urine.[22] It induces aquaresis by causing excretion of electrolyte-free water. It was the first of its class to be approved by the US Food and Drug Administration to treat euvolemic hyponatremia. The effects of tolvaptan, an oral agent with a half-life of 6–8 hours, were initially evaluated in 83 patients with heart failure (NYHA Class II-III) in a randomized, controlled trial in 2002.[23] Patients discontinued their baseline diuretics and were subsequently randomized to placebo ($n = 21$), monotherapy with tolvaptan 30 mg ($n = 20$), monotherapy with furosemide 80 mg ($n = 22$) or both tolvaptan and furosemide ($n = 20$) once daily for 7 days. Tolvaptan reduced body weight and lessened edema without concomitant diuretic therapy compared to placebo. In addition to its aquaretic effect, tolvaptan appears to have significant acute hemodynamic effects as well. In a study of 181 patients with advanced heart failure on standard therapy randomized to receive a single oral dose of tolvaptan of 15, 30 or 60 mg or placebo, all tolvaptan groups showed a significant reduction in pulmonary capillary wedge pressure compared to placebo, in addition to reductions in right atrial pressure and pulmonary artery pressure.[24] Tolvaptan also increased urine output by 3 hours in a dose-dependent manner ($p < 0.0001$) without affecting renal function.

The Acute and Chronic Therapeutic Impact of a Vasopressin Antagonist in Congestive Heart Failure (ACTIV in CHF) was a dose-ranging, phase 2 trial of 319 patients with left ventricular ejection fraction of less than 40% who were hospitalized for heart failure with persistent signs and symptoms of venous congestion despite standard therapy.[25] The study was conducted at 45 centers in the United States and Argentina. Patients were randomized to 30, 60 or 90 mg/day of oral tolvaptan or placebo in addition to standard therapy, which included diuretics. Abnormal baseline serum creatinine (> 1.3 mg/dL) was present in approximately 40% of patients. The study drug was continued for up to 60 days. The study had two primary endpoints, in order to assess both the acute and intermediate-term effects of the study drug: change in body weight at 24 hours after administration of the first dose of study drug, and the incidence of worsening heart failure by 60 days after randomization, as defined by hospitalization or unscheduled visit to an emergency department or outpatient clinic associated with a need for increased or new therapy for heart failure, or death. Patients in the tolvaptan groups had a significant reduction in body weight compared to placebo, although the effect was not dose dependent. The median reduction in body weight was 1.80 kg

TABLE 2

Arginine vasopressin antagonists for the treatment of hyponatremia

	Tolvaptan (OPC-41061)	*Lixivaptan (VPA-985)*	*Conivaptan (YM-087)*
Receptor subtype specificity	V_2	V_2	V_{1a}/V_2
Selectivity index in humans (K_i V_{1a}: K_i V_2)	29:1	100:1	10:1
Route of administration	Oral	Oral	Intravenous
Urine volume effects	Increased	Increased	Increased
Urine osmolality effects	Decreased	Decreased	Decreased
Sodium excretion/ 24 hours	No change	No change at low doses	No change

(*Source*: Lee CR, Watkins ML, Patterson JH, et al. Vasopressin: a new target for the treatment of heart failure. Am Heart J. 2003;146:9-18, with permission)

in the tolvaptan 30 mg group ($p = 0.002$), 2.10 kg in the 60 mg group ($p = 0.002$) and 2.05 kg in the 90 group ($p = 0.009$), compared to 0.60 kg in the placebo group. This effect on weight reduction persisted to discharge, with a median weight loss of 3.30 kg ($p = 0.006$), 2.80 kg ($p = 0.002$) and 3.20 kg ($p = 0.06$) respectively in the 30, 60, 90 mg tolvaptan groups compared to 1.90 kg in the placebo group. The reduction in body weight was attributed to the significantly higher urine volume produced by patients in the tolvaptan groups compared to placebo, which was maintained throughout the period of hospitalization. Despite the increased urine volume and decreased body weight in the tolvaptan groups, all patients reported improvement in dyspnea and peripheral edema, with no significant differences in global assessment scores between the tolvaptan groups and placebo. There was also no significant difference in median length of stay between the groups. Treatment with tolvaptan did not cause significant hypokalemia or worsening of renal function, but did slightly improve serum sodium in patients with hyponatremia, an effect which persisted throughout the follow-up period. Despite its positive acute effects, tolvaptan did not appear to have any significant intermediate-term effects in this study. There were no statistically significant differences in the incidence of worsening heart failure, 60 day mortality, or the rate of rehospitalization for heart failure between the groups. A post-hoc analysis showed possible reduced mortality with tolvaptan in the subgroups of patients with elevated BUN and severe volume overload at baseline. Approximately 22.5% of patients with BUN greater than 29 mg/dL in the placebo group died during the study compared to 10% in the tolvaptan group ($p = 0.07$). Approximately 17.8% of patients with severe congestion in the placebo group died during the study, compared to 5.6% in the tolvaptan groups ($p = 0.03$). However, the study was not prospectively designed to evaluate mortality alone and was underpowered to assess this effect.

The Efficacy of Vasopressin Antagonism in hEart failuRE Outcome Study with Tolvaptan (EVEREST) trial was a prospective, multicenter, randomized, double-blind, placebo-controlled study to assess the longer-term effects of tolvaptan.[26] The study was conducted at 359 centers in North America, South America and Europe. Approximately 4,133 patients with a left ventricular ejection fraction less than 40% and NYHA class III or IV symptoms who were hospitalized for systolic heart failure and signs of volume overload were randomized within 48 hours of admission to receive either tolvaptan 30 mg daily or placebo for a minimum of 60 days. Patients on dialysis or with a serum creatinine greater than 3.5 mg/dL were excluded, as were patients with a serum potassium level greater than 5.5 mEq/l. At baseline, the majority of patients were receiving diuretics (96.8%), ACE inhibitors or angiotensin receptor blockers (84.2%) and beta-blockers (70.2%). Median follow-up was 9.9 months. During the study, 22% of patients discontinued the study drug. There were two primary endpoints: all-cause mortality, and the composite of cardiovascular death or hospitalization for heart failure. Secondary endpoints included serum sodium, changes in dyspnea, body weight and edema. In the short-term, tolvaptan significantly affected dyspnea, with patient-assessed dyspnea scores improving in 74.3% of the tolvaptan group and 68.0% of the placebo group by day 1 ($p < 0.001$). Mean body weight at day 1 was reduced by 1.76 kg in the tolvaptan group and by 0.97 kg in the placebo group ($p < 0.001$). This effect was maintained for weeks after hospital discharge. Among patients with hyponatremia with baseline serum sodium less than 134 mEq/l, mean serum sodium concentrations increased by 5.49 mEq/l (SD 5.77 mEq/l) by day 7 with tolvaptan, compared to 1.85 mEq/l (SD 5.10 mEq/l) in the placebo group ($p < 0.001$). This effect was also maintained well after discharge, through 40 weeks of treatment. Pedal edema scores by day 7 improved in 73.8% of patients in the tolvaptan group and 70.8% of patients in the placebo group ($p = 0.003$).

In this larger study, tolvaptan again did not worsen renal function or electrolyte abnormalities. At day 7 or discharge, mean serum urea nitrogen levels had increased by 3.30 mg/dL (SD 12.16 mg/dL) in the placebo group, compared to 1.94 mg/dL (SD 11.70 mg/dL) in the tolvaptan group ($p < 0.001$). Mean serum creatinine had increased by 0.03 mg/dL (SD 0.35 mg/dL) in the placebo group and 0.08 mg/dL (0.31 mg/dL) in the tolvaptan group ($p < 0.001$). Hyperkalemia occurred in 7.8% of patients in the tolvaptan group and 6.6% of patients in the placebo group ($p = 0.15$). Thirst and dry mouth were the only adverse events that occurred significantly more frequently in the tolvaptan group.

There were no statistically significant differences in mortality, cardiovascular death or hospitalization for heart failure in the tolvaptan group compared to placebo. Approximately 25.9% of patients in the tolvaptan group and 26.3% of patients in the placebo group died during follow-up (HR 0.98, 95% CI 0.87–1.11, $p = 0.68$). Approximately 42% of patients in the tolvaptan group and 40.2% of patients in the placebo group reached the second primary endpoint of death from cardiovascular causes or hospitalization for HF (HR 1.04, 95% CI 0.95–1.14, $p = 0.55$). Other secondary long-term endpoints, such as clinical worsening of heart failure did not significantly differ between the two groups. The authors conclude that tolvaptan is a useful treatment for fluid removal and improves short-term symptoms, without causing adverse effects with long-term use. However, there appears to be no significant mortality benefit with tolvaptan, despite its promising short-term effects. Recent data also shows that tolvaptan does not appear to have a significant effect on long-term LV remodeling. In a randomized controlled trial of 240 patients with EF < 30% and class II to III NYHA functional class on standard therapy randomized to tolvaptan 30 mg daily or placebo for 1 year, there was no significant difference in LV end diastolic volumes between groups after 1 year of therapy.[27] This may not be surprising, however, given that tolvaptan is a V_2-specific receptor antagonist and would therefore primarily exert its action in the renal principal cells.

LIXIVAPTAN

Lixivaptan is an orally active, non-peptide, highly specific V_2 receptor antagonist currently in phase 3 clinical trials. Its binding affinity for V_2 receptors is approximately one hundred-fold higher than for V_{1a} receptors, and it produces little or no effect on V_{1b} receptors.[28] In a double-blind, placebo-controlled study that randomized 42 patients with a left ventricular ejection fraction less than 35% and NYHA class II–III heart failure requiring diuretics to either placebo or varying doses of

lixivaptan, a single administration of lixivaptan was found to produce a significant and dose-related increase in urine volume, solute-free water excretion and serum sodium concentration over the course of 24 hours.[29] Patients with significant renal insufficiency, defined as a glomerular filtration rate less than 40 mL/min, were excluded from participation in the study. Interestingly, if patients were already taking diuretics, ACE inhibitors, or other heart failure medications (except for digoxin), these drugs were held for several days prior to the administration of the study drug. During the first 24 hours after receiving the study drug, urine volume increased by 1.8 L in the placebo group, compared to 3.9 L in the 400 mg of lixivaptan group ($p < 0.01$). Urine osmolality decreased in all lixivaptan groups by hour 2 compared to placebo, but there were no significant differences in urinary sodium, potassium or chloride excretion. Interestingly, levels of serum AVP also significantly increased with administration of lixivaptan, particularly with the higher dosages of 150–400 mg. No serious adverse events were reported. The Treatment of Hyponatremia Based on Lixivaptan in NYHA Class III/IV Cardiac Patient Evaluation (BALANCE) trial is an ongoing large-scale multicenter study that will evaluate the impact of lixivaptan on all-cause morbidity and mortality specifically in patients with heart failure and hyponatremia.

CONIVAPTAN

Conivaptan is a non-peptide, nonspecific V_{1a}/V_2 receptor antagonist with a relatively short median half-life of 6.7 hours. Conivaptan has been developed in both oral and intravenous forms, but only the intravenous preparation has been approved by the US Food and Drug Administration for the short-term treatment of euvolemic and hypervolemic hyponatremia. The approval was based on a study of 84 hospitalized patients with hyponatremia randomized to receive IV conivaptan (given as a 20 mg loading dose followed by a 96-hour infusion of either 40 or 80 mg/day) or placebo. Both conivaptan doses increased serum sodium levels with no significant adverse events.[30] Conivaptan has also been examined in the heart failure population. In a study of 142 patients with NYHA class III–IV systolic heart failure randomized to placebo or a single IV dose of conivaptan, conivaptan significantly increased urine volume and reduced urine osmolality, without any change in plasma osmolality or serum sodium levels.[31] Patients were required to be on standard background therapy for heart failure, including at least one month of therapy with a loop diuretic and an ACE inhibitor. Exclusion criteria included a systolic blood pressure less than 90 mm Hg and a serum creatinine greater than 2.5 mg/dL or a creatinine clearance less than 30 mL/min. All patients also received a pulmonary artery catheter to monitor hemodynamics before and after administration of the study drug. Conivaptan caused a reduction in pulmonary capillary wedge pressure and right atrial pressure, without a significant effect on cardiac index, blood pressure or heart rate, despite its known effect on V_{1a} receptors. Plasma AVP levels were not significantly increased by the administration of conivaptan in this study. Conivaptan was well tolerated with no serious side effects.

To assess the longer-term effects of conivaptan in the heart failure population, a double-blind, multicenter trial of 170 patients with decompensated systolic heart failure randomized to receive conivaptan (given as a 20 mg loading dose followed by two successive 24 hour continuous infusions of 40, 80 or 120 mg daily) or placebo was performed.[32] Patients with a sustained systolic blood pressure less than 85 mm Hg were excluded, as were patients with a serum potassium concentration less than 3.5 or greater than 5.5 mmol/l, and those with serum creatinine greater than 3 mg/dL. Approximately, 80% of patients were taking ACE-inhibitors, and 80–90% were also on loop diuretics. There was no significant difference in patient or clinician assessments of global and respiratory status at 48 hours. Conivaptan again increased urine output by an average of 1.0–1.5 L in 24 hours, with a statistically significant dose-response relationship ($p = 0.003$). Mean body weight decreased from baseline in all groups at 24, 48 and 72 hours, but the difference between the conivaptan groups and placebo did not reach statistical significance. Plasma AVP levels were found to be significantly higher at 48 hours compared to placebo in all treatment groups except for those receiving conivaptan 40 mg daily, in contrast to the previous study. Serum sodium levels at 24, 48 and 72 hours were significantly higher in each of the conivaptan groups compared with the placebo group ($p < 0.036$), with the largest increases occurring in the higher dose groups. There was no significant effect on blood pressure or heart rate, as seen previously. Infusion site reactions were the most common adverse event reported.

CONCLUSION

In patients with heart failure, hyponatremia has been shown to be associated with increased morbidity and mortality, although the exact mechanism of this association is unknown. Hyponatremia appears to occur due to activation of the sympathetic nervous system, the renin-angiotensin-aldosterone system and elevation of AVP levels. However, large randomized controlled trials and registries of heart failure patients have shown that hyponatremia persists despite the majority of patients being treated with neurohormonal blockade agents, and that hyponatremia continues to be associated with poorer outcomes. Currently, treatment of hyponatremia is indicated for severe hyponatremia with a serum sodium less than 120 mEq/l, or significant symptoms. Fluid restriction, IV fluids and diuretics remain the most commonly used methods of treatment. However, research has led to the development of vasopressin receptor antagonists, which are now being studied in the heart failure population. To date, clinical trials have shown that this class of medications may improve symptoms of volume overload and correct hyponatremia by promoting aquaresis, and, in contrast to diuretics, do not appear to worsen renal function or electrolyte abnormalities. However, no significant mortality benefit has been identified, and so the place of vasopressin receptor antagonists in the treatment of heart failure is not yet certain.

Other issues that remain to be addressed include the long-term effect of V_2 receptor blockade. Studies of V_2 receptor antagonists have consistently shown that this class of agents can cause a reflexive increase in the plasma vasopressin level, which may have unexpected consequences with long-term use. With V_2 receptor antagonism and elevated AVP levels, unopposed stimulation of the V_{1a} and V_{1b} receptors may occur.

One could hypothesize that increased V_{1a} receptor binding would result in increased vasoconstriction, release of coagulation factors, platelet aggregation, and myocyte hypertrophy, which could be deleterious to patients with heart failure. The EVEREST trial, which collected safety data on patients taking tolvaptan for a median of 9.9 months, did not show any significant harmful effects of V_2 receptor antagonism with long-term use. However, longer-term studies would be required to definitively answer this issue. Conivaptan, which acts at both V_{1a} and V_2 receptors, may in theory provide better outcomes in this patient population. To date, the effect of conivaptan on morbidity and mortality has not yet been assessed, and it is clinically indicated for only short-term use. Many questions remain unanswered regarding the clinical utility of this class of medications, but the possibility of improving outcomes in the treatment of heart failure continues to drive research in this area.

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Chapter 74

Cardiorenal Syndrome: The Interplay Between Cardiac and Renal Function in Patients with Congestive Heart Failure

Nestor Mercado, J Thomas Heywood

Chapter Outline

- Epidemiology of Chronic Kidney Disease in Patients with Heart Failure
- Prognosis of Worsening Renal Function
- Definition of the Cardiorenal Syndrome
- Pathophysiology of the Cardiorenal Syndrome
- Role of Decreased Cardiac Output
- Role of Elevated Central Venous Pressure
- Role of Evidence-based Therapies in Patients with Heart Failure and the Cardiorenal Syndrome
  - Diuretics
  - ACE-I and ARB
  - Inotropes
- Role of Ultrafiltration on Diuretics Resistance and the Cardiorenal Syndrome
- Treatment of the Cardiorenal Syndrome: An Approach to the Individual Patient

INTRODUCTION

Since our invertebrates ancestors moved from the oceans to the land, the maintenance of an internal carefully balanced fluid milieu in a hostile environment was a key factor in survival. Organ systems evolved to this specific task with the heart and kidney being foremost of these. Heart failure (HF) in its most fundamental sense is a derangement of this carefully choreographed balance of fluid and electrolytes. The physiologic disturbances that are unique in the HF syndrome have appeared so recently and usually so late in life that evolution provides few mechanisms that deal effectively with a syndrome where salt and water, typically jealously preserved, are in pathologic overabundance as in the late industrial era.

In the two centuries during which pharmacologic therapy for HF has existed, the foci of these therapies have shifted between the heart and the kidneys. For most of this time extracts from the foxglove provided some succor for HF due primarily to rheumatic heart disease. In the early 20th century, mercurial diuretics allowed some excretion of excess sodium and the kidney's important role was emphasized by such luminaries as Homer Smith.

EPIDEMIOLOGY OF CHRONIC KIDNEY DISEASE IN PATIENTS WITH HEART FAILURE

Until recently renal insufficiency was not seen as a significant problem in patients with HF, largely because serum creatinine was the primary benchmark of renal function. Calculated glomerular filtration rate (GFR) is a much more precise indicator of renal disease and fortunately is now much more widely available. The prevalence of chronic kidney disease (CKD), defined as a GFR less than 60 ml/min/1.73 m^2, has ranged from 26–57% in clinical trials (Table 1) and 35–56% in observational studies that have enrolled ambulatory HF patients (Table 2). The CKD was a predictor of adverse clinical outcomes in both the randomized clinical trials and observational studies.

The prevalence of CKD in acute decompensated heart failure (ADHF) at hospital admission has been studied extensively (Table 3). The ADHF national registry (ADHERE) has been the largest study involving greater than 100,000 patients. At admission, 9.0% had normal renal function (GFR ≥ 90 ml/min/1.73 m^2), 27.4% had mild renal dysfunction (GFR 60–89 ml/min/1.73 m^2), 43.5% had moderate renal dysfunction (GFR 30–59 ml/min/1.73 m^2), 13.1% had severe renal dysfunction (GFR 15–29 ml/min/1.73 m^2) and 7.0% had kidney failure (GFR < 15 ml/min/1.73 m^2 or chronic dialysis) (Fig. 1). In-hospital mortality was correlated with CKD and increased from 1.9% for patients with normal renal function to 7.6% and 6.5% for patients with severe renal dysfunction and kidney failure, respectively.[1]

Worsening renal function (WRF), defined as an increase in creatinine or a corresponding decrease in GFR, occurs in approximately 25% of ADHF patients during hospitalization. Clinical predictors of WRF comprise a wide range of demographic and laboratory variables. The WRF was associated with increased mortality, prolonged hospital stay and a higher percentage of readmission rates (Table 4).

TABLE 1

Prevalence of renal impairment in the major ambulatory heart failure clinical trials

HF clinical trial	*EF*	*Inclusion SCr*	*% GFR < 60*	*n*	*Outcomes*
CHARM	All	< 3.0	36	2,680	Increased all-cause mortality and combined endpoint of CV death or HF hospitalization
SOLVD	≤ 35%	≤ 2.5	32	6,630	Increased all-cause mortality
HERS (women)	All	All	57	702	Increased mortality
PRIME-2	< 35%	All	50	1,906	Increased mortality
MERIT-HF	< 40%	All	37	3,965	Increased all cause mortality and hospitalization for HF
VALIANT-Echo	HF or asymptomatic LVSD	< 2.5	29.9	603	Increase in combined endpoint of all-cause mortality or HF hospitalization
DIG	< 45%	≤ 3.0	46	6,800	Increased mortality
SENIORS	All	< 2.83	42	2,112	Increased mortality of CV hospital admission

(Abbreviations: HF: Heart failure; EF: Ejection fraction; SCr: Serum creatinine; GFR: Glomerular filtration rate; CHARM: Candesartan in heart failure assessment of reduction in mortality and morbidity; SOLVD: Studies of left ventricular dysfunction; HERS: Heart and estrogen/progestin replacement study; PRIME-2: Second prospective randomized study of ibopamine on mortality and efficacy; MERIT-HF: Metoprolol CR/XL controlled randomized intervention trial in chronic HF; VALIANT-Echo: VALsartan in Acute myocardial iNfarcTion Trial-Echo; DIG: Digoxin intervention group trial; SENIOR: Study of effects of nebivolol intervention on outcomes and rehospitalization in seniors with heart failure). (*Source:* Bishu KG, Redfield MM. Epidemiology of the cardiorenal syndrome. Heywood JT, Burnett J. The Cardiorenal Syndrome: A Clinician's Guide to Pathophysiology and Management. Cardiotext Publishing, 2011)

TABLE 2

Studies of renal impairment in the community setting

Studies	*n*	*EF*	*GFR < 60*	*Factors associated with renal impairment*	*Outcomes*
GO As et al. (ANCHOR)	59,772	All	47%	Not reported	Increased mortality and HF hospitalization
Ezekowitz et al. (APPROACH)	6,427	HF Dx and CAD	32	More comorbidities, greater coronary atherosclerotic burden, and lower EF. Less likely to be prescribed ACE-I, beta-blockers, statins or aspirin	Increased one year mortality
de Silva et al	955	< 45	57	Anemia	Increased mortality
McAlister et al	754	All	50	Older, more likely to be female, had more symptomatic HF, were more likely to have CAD or hypertension, and were less likely to receive ACE-I, beta-blockers, or spironolactone	Increased one year mortality
Mullens et al	784	All	37	Not reported	Increased all-cause mortality
Maeder et al	196	LVSD	42	Increased age, loop diuretic use and tricuspid regurgitation severely associated. Less likely to be on ACE-I/ARB	Not reported

(Abbreviations: EF: Ejection fraction; GFR: Glomerular filtration rate; ANCHOR: Anemia in chronic heart failure: outcomes and resource utilization; HF: Heart failure; CAD: Coronary artery disease; APPROACH: Alberta provincial project for outcome assessment in coronary heart disease; LVSD: Left ventricular systolic dysfunction; ACE-I: Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor blocker). (*Source:* Bishu KG, Redfield MM. Epidemiology of the cardiorenal syndrome. In: Heywood JT, Burnett J (Eds). The Cardiorenal Syndrome: A Clinician's Guide to Pathophysiology and Management. Cardiotext Publishing, 2011)

PROGNOSIS OF WORSENING RENAL FUNCTION

There is consistent and powerful evidence that renal dysfunction adversely effects prognosis in congestive heart failure (CHF). Hampton and his colleagues[2] analyzed 1,906 patients in the Second Prospective Randomized Study of Ibopamine on Mortality and Efficacy by evaluating mortality in four quartiles of the study group based on the estimated GFR using the Cockroft Gault equation. Mortality in the lowest renal function quartile had a survival of less than 50% in 2 years (Fig. 2). In another outpatient study,[3] blood urea nitrogen (BUN) was the most powerful predictor of survival in a cohort of more than 800 HF patients with reduced ejection fraction (Fig. 3). Renal dysfunction also plays a significant role in patients hospitalized with HF. Gottlieb and his colleagues[4] evaluated the effects of renal function on a diverse group of 1,028 patients admitted to academic medical centers with both normal and low ejection fraction HF. The WRF was strongly associated with both mortality and increased length of stay (Fig. 4). Fonarow and his colleagues[5] using data from over 60,000 admissions created a mortality model based of classification and regression tree (CART) analysis and found that a BUN greater than 43 mg/dL

TABLE 3

Studies on prevalence of renal impairment in heart failure hospitalizations

Studies	*n*	*EF*	*GFR cut off value*	*Prevalence*	*Factors associated with renal impairment*	*Outcomes*
Heywood et al. (ADHERE)	118,465	All	< 60	64%	Hypertension, diabetes, CAD, PVD, older, female and white	Increased in-hospital mortality
Smith et al. (NHC)	53,640	All	< 60	67%	Black race, older, women, CAD, less likely to be on ACE-I	Increased mortality, more pronounced in whites
Amsalem et al.	4,102	All	< 60	57%	Not reported	Increased in-hospital mortality
O'Connor et al. (IMPACT-HF)	567	All	< 60	23.5%	Not reported	GFT did not predict outcomes
Nohria A et al. (ESCAPE)	433	< 30%	< 60	31%	Baseline RAP correlates with baseline GFR and SCr	Increased death, rehospitalizations
Akhter et al. (VMAC)	481	All	> 1.5 mg/dL	45%	Old age, male sex, diabetes, CAD, ICDs, pacemakers	Prolonged length of stay and readmission, increased 6-month morality
Mullens et al.	145	All	< 60	64%	Baseline cardiac index	Worsening renal function

(Abbreviations: EF: Ejection fraction; ADHERE: Acute decompensated heart failure national registry; CAD: Coronary artery disease; PVD: Peripheral vascular disease; NHC: National heart care project; ACE-I: Angiotensin converting enzyme inhibitors; IMPACT-HF: Initiation management pre-discharge assessment of carvedilol heart failure; ESCAPE: Evaluation study of congestive heart failure and pulmonary artery catheterization effectiveness; RAP: Right atrial pressure; SCr: Serum creatinine; VMAC: Vasodilation in the management of acute congestive heart failure; ICD: Implantable cardioverter defibrillator). (*Source:* Bishu KG, Redfield MM. Epidemiology of the cardiorenal syndrome. In: Heywood JT, Burnett J (Eds). The Cardiorenal Syndrome: A Clinician's Guide to Pathophysiology and Management. Cardiotext Publishing; 2011)

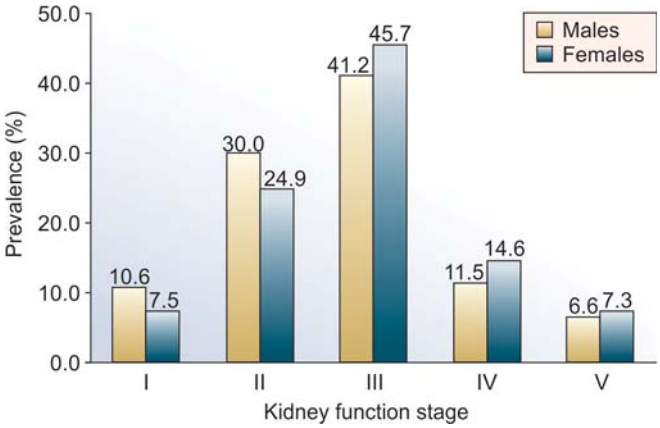


FIGURE 1: Data from the Acute Decompensated Heart Failure National Registry (ADHERE) in 118,465 patients with acute decompensated heart failure for whom the glomerular filtration rate was calculated using the modification of diet in renal disease (MDRD) formula. By this metric, more than 60% of these patients had at least moderate renal dysfunction at the time of admission. (*Source*: Modified from Heywood JT, et al. J Card Failure. 2007;13:422-30)

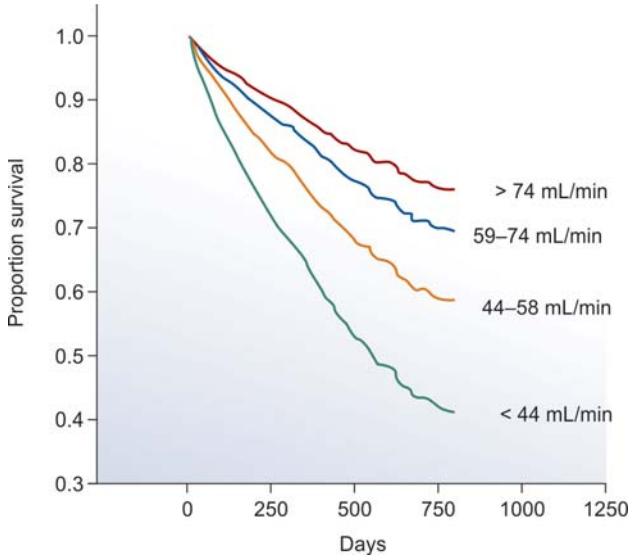


FIGURE 2: Estimated creatinine clearance, calculated for study participants using the Cockcroft-Gault equation, is a powerful predictor of survival in heart failure (*Source*: Modified from Hampton JR, et al. Lancet. 1997;349:971-7)

was the most powerful predictor of inpatient mortality, followed by low systolic blood pressure and serum creatinine (Flow chart 1).

DEFINITION OF THE CARDIORENAL SYNDROME

The definition of the cardiorenal syndrome (CRS) is described as concomitant dysfunction of the heart and kidneys in which an acute or chronic dysfunction in one organ may result in an acute or chronic dysfunction in the other organ, WRF during acute HF treatment or diuretic resistance.[6,7] Ronco and his colleagues have suggested that the CRS should be characterized according to whether the impairment of each organ is primary, secondary or whether abnormal heart and kidney functions occur simultaneously as a result of a systemic disease.[6] For example, acute HF decompensation can cause both acute renal failure (ARF) and CKD: a decreased cardiac output (CO) is associated with renal arterial underfilling and increased venous pressure which, in turn, result in a reduced GFR.[8]

The direct and indirect effects of each dysfunctional organ can initiate and perpetuate the combined disorder of the two organs through complex neurohormonal feedback mechanisms. Consequently the subdivision of CRS into five different subtypes may facilitate care of individual patients (Table 5).

TABLE 4

Studies on worsening renal function during heart failure hospitalization

Authors	*N*	*WRF definition*	*% WRF*	*Factors associated with WRF*	*Outcomes*
Owan et al	6,440	> 0.3 mg/dL	23	Higher admission creatinine, lower GFR and hemoglobin, higher prevalence of hypertension, coronary disease and diabetes	Increased 3-month and 5-year mortality
Logeart D et al	416	≥ 0.28 mg/dL	37	Old age, DM, hypertension, ACS	Increased 6-month mortality or readmission
Nohria A et al. (ESCAPE)	433	≥ 0.3 mg/dL	29.5	Hypertension and in hospital thiazide use	No increase in death/ hospitalization
Gottlieb et al	1,002	≥ 0.3 mg/dL	39	Not reported	Increased mortality and length of stay
Akhter et al. (VMAC)	480	> 0.5 mg/dL	25	Elevated baseline creatinine	Increased 6-month mortality and length of stay
Butler et al	382	> 0.3 mg/dL	NA	CCB and loop diuretic use, high baseline creatinine, uncontrolled hypertension, hx of HF and DM	Not reported
Krumholz et al. (Age > 65)	1,681	> 0.3 mg/dL	28	Male gender, hypertension, rales > basilar, HR >100, SBP > 200, admission SCr > 1.50	Increased length of stay, increased in-hospital mortality
Weinfeld et al	48	≥ 25% increase to ≥ 2 mg/dL	21	Old age, lower baseline CrCl, atrial fibrillation	Increased length of stay and mortality
Cioffi et al	79	≥ 25% increase to ≥ 2 mg/dL	20	Lower baseline CrCl and furosemide dose	Increased death and rehospitalization for HF
Forman et al	1004	> 0.3 mg/dL	27	Diabetes mellitus, baseline creatinine > 1.5, SBP > 160	Increased length of hospital stay and in-hospital mortality
Cowie et al. (POSH)	299	> 0.3 mg/dL	29	High baseline creatinine and pulmonary edema. Decreased in patients with atrial fibrillation	Increased length of stay. No effect in 6-month mortality or rehospitalization
Smith et al	412	≥ 0.3 mg/dL	45	Not reported	Increased mortality only with the stricter definition ≥ 0.4 mg/dL
Liviu Klein et al. (OPTIME-CHF)	949	BUN Increase > 25	39	Not reported	Increased 60 days mortality
Metra et al	318	≥ 0.3 mg/dL and ≥ 25% increase	32	Baseline CKD, admission furosemide, NYHA class, low LVEF	Increased death and HF hospitalization
Mullens et al	145	≥ 0.3 mg/dL	40	High admission and post-treatment CVP, baseline renal insufficiency	Not reported
Damman et al. (COACH)	1,023	≥ 0.3 mg/dL and ≥ 25%	11	Baseline GFR, age, DM and Anemia	Increased HF hospitalization and all-cause mortality

(Abbreviations: WRF: Worsening renal function; GFR: Glomerular filtration rate; ACS: Acute coronary syndrome; ESCAPE: Evaluation study of congestive heart failure and pulmonary artery catheterization effectiveness; VMAC: Vasodilation in the management of acute congestive heart failure; CCB: Calcium channel blocker; CrCl: Creatinine clearance; POSH: Prospective outcomes study in heart failure; OPTIME-CHF: Outcomes of a prospective trial of intravenous milrinone for exacerbations of chronic heart failure; COACH: Outcomes of advising and counseling in heart failure). (*Source:* Bishu KG, Redfield MM. Epidemiology of the cardiorenal syndrome. Heywood JT, Burnett J (Eds). The Cardiorenal Syndrome: A Clinician's Guide to Pathophysiology and Management. Cardiotext Publishing, 2011)

TABLE 5

Cardiorenal syndrome

Type	*Name*	*Description*
Type 1	Acute cardiorenal syndrome	Abrupt worsening of cardiac function (e.g. acute cardiogenic shock, or acutely decompensated heart failure) leading to acute kidney injury
Type 2	Chronic cardiorenal syndrome	Chronic abnormalities in cardiac function (e.g. chronic heart failure) causing progressive and potentially permanent chronic kidney disease
Type 3	Acute renocardiac syndrome	Abrupt worsening of renal function (e.g. acute kidney ischemia or glomerulonephritis) causing acute cardiac disorders (e.g. heart failure, arrhythmia, ischemia)
Type 4	Chronic renocardiac syndrome	Chronic kidney disease (e.g. chronic glomerular or interstitial disease) contributing to decreased cardiac function, cardiac hypertrophy and/or increased risk of adverse cardiovascular events
Type 5	Secondary cardiorenal syndrome	Systemic conditions (e.g. diabetes mellitus, sepsis) causing both cardiac and renal dysfunction

(*Source:* Reference 6)

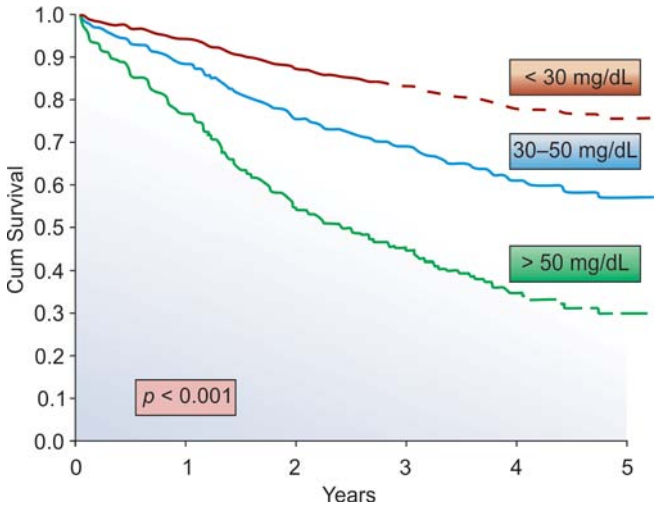


FIGURE 3: Relationship of blood urea nitrogen (BUN) to survival in 680 outpatients with left ventricular systolic dysfunction followed for five years. By multivariate analysis BUN was a better predictor of survival than serum creatinine. (*Source*: Modified from Heywood JT, et al. J Cardiovasc Pharmacol Ther. 2005;10:173-80)

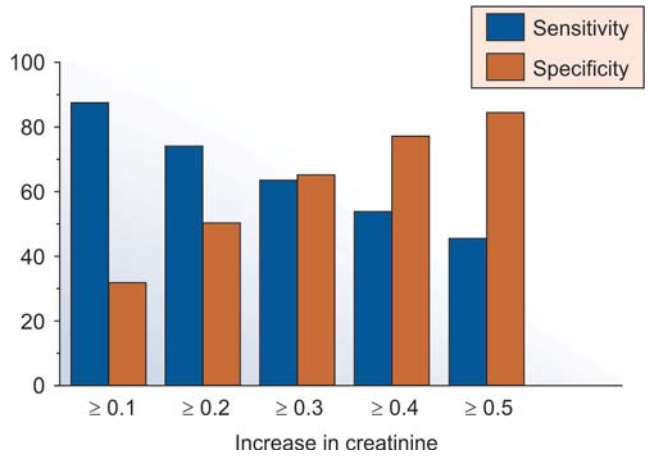
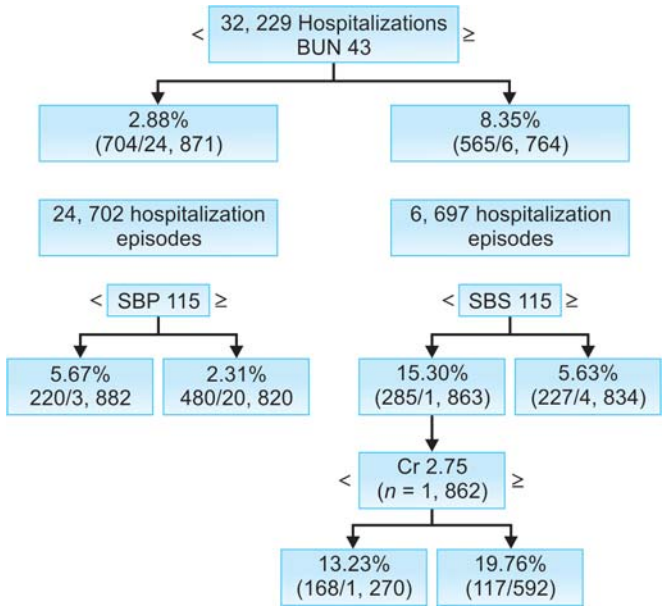


FIGURE 4: Worsening renal function is a strong predictor of increased length of stay and mortality in patients admitted with acute decompensated heart failure. A serum creatinine rise of ≥ 0.3 mg/dL provided the best sensitivity and specificity in predicting both mortality and increased length of stay. (*Source*: Modified from Gottlieb SS, et al. Journal of Cardiac Failure. 2002;8:136-41)

FLOW CHART 1: Data from the Acute Decompensated Heart Failure National Registry (ADHERE) was used to create a risk classification system for patients admitted with heart failure. Using CART analysis, 39 variables were evaluated to create a model to predict inpatient mortality. This was done first for a derivation group of 33,046 patients and then applied to a 32,229 patient validation group with very similar results. In this model a BUN of 43 mg/dL was the most powerful predictor of mortality followed by low systolic blood pressure and then serum creatinine. In the validation group shown 32,229 patients were evaluated but only 31,635 had all 3 parameters for evaluation



(*Source*: Modified from Fonarow GC, et al. JAMA. 2005;293:572-80)

Type 1 CRS (acute CRS) defines a rapid deterioration in cardiac function, which produces ARF. Pre-existent CKD is frequent and increases the risk of ARF. The severity of ARF is greater in patients with impaired than in those with preserved LV systolic function, and it occurs in more than 70% of patients with cardiogenic shock.[9] Renal dysfunction independently predicts one-year mortality in patients with ADHF, possibly due to an acute decline in renal function accelerates progression of cardiovascular (CV) disease through activation of inflammatory pathways.[10] Fundamental concerns regarding ARF are whether it represents inadequate renal perfusion due to either a low CO and/or marked increase in central venous pressure (CVP), or intravascular volume depletion from overdiuresis. Accurate diagnosis and appropriate treatment of type 1 CRS may require measurement of CO and CVP. Renal function should also be closely monitored in patients with acute myocardial infarction (AMI), and in those undergoing cardiac surgery, percutaneous coronary intervention (PCI) or radiocontrast imaging because in these settings an increase in creatinine signals the onset of ARF which, in turn, may accelerate CV injury through activation of neurohormonal, immunological and inflammatory pathways. Even a modest increase in creatinine (> 0.3 mg/dL) is an independent predictor of unfavorable CV outcomes.[4]

Type 2 CRS (chronic CRS) refers to progressive CKD occurring in approximately 25% of HF patients.[11] The presence and worsening of renal function in HF patients is associated with adverse outcomes. Chronic HF may be associated with longstanding renal hypoperfusion often aggravated by coexisting microvascular and macrovascular disease.[12] Other causes of the onset and progression of renal dysfunction in chronic HF include neurohormonal activation, resistance to natriuretic peptides, iatrogenic hypovolemia and hypotension.

Type 3 CRS (acute renocardiac syndrome) consists of a rapid worsening of kidney function due to ARF, ischemia or glomerulonephritis which leads to acute cardiac abnormalities including ischemia, arrhythmias and HF. According to the Risk, Injury, and Failure; Loss; and End-stage kidney disease (RIFLE) consensus definition, ARF can be identified in approximately 9% of ADHF patients and in more than 35% of those requiring ICU care.[13] In patients with an acute renocardiac syndrome, fluid overload can result in pulmonary edema, and hyperkalemia can cause arrhythmias and even cardiac arrest. Untreated uremia

causes accumulation of myocardial depressant factors and pericarditis.[14] Patients with bilateral renal artery stenosis (or unilateral stenosis in a solitary kidney) are prone to decompensated diastolic HF due to neurohormonally mediated arterial hypertension, sodium and water retention from renal dysfunction, and acute myocardial ischemia caused by an increased myocardial oxygen demand resulting from intense peripheral vasoconstriction.[10] Markers of myocardial ischemia (troponin), or of myocyte stress (BNP), may permit earlier diagnosis and treatment of type 3 CRS.[15] Detection of ARF can trigger reduction or even discontinuation of both diuretics and ACE-I, which exposes patients to a greater risk of ADHF and kidney injury due to hyperfiltration. If ARF is severe enough to require renal replacement therapy (RRT), continuous techniques are safer than conventional dialysis because the avoidance of rapid fluid and electrolyte shifts minimizes the risk of hypotension, arrhythmias and myocardial ischemia.

Type 4 CRS (chronic renocardiac syndrome) develops when primary CKD contributes to the aggravation of systolic and diastolic LV dysfunction, left ventricular hypertrophy (LVH) and increased risk of adverse CV events. In CRS type 4, increased levels of biomarkers, such as BNP and troponin, have also been correlated to unfavorable CV outcomes. These findings suggest a possible link between chronic inflammation, subclinical infections, accelerated atherosclerosis and adverse cardiorenal outcomes. Unfortunately, because of concerns about WRF, less than 50% of CKD patients are treated with therapies aimed at minimizing CV risk factors, including aspirin, beta-blockers, ACE-I and statins.[16]

Type 5 CRS (secondary CRS) is characterized by concomitant cardiac and renal dysfunction due to acute or chronic systemic disorders such as sepsis, hypertension, diabetes, amyloidosis and autoimmune diseases. Severe sepsis can produce AKF and myocardial depression through the upregulation of tumor necrosis factor (TNF)-α and other proinflammatory mediators.[17] While decreased CO can further impair renal function, ARF can negatively affect cardiac performance. Hypotension-induced renal ischemia can further worsen myocardial injury in a vicious cycle harmful to both organs. Therefore, early detection and interruption of this circle is important to improve cardiorenal outcomes.

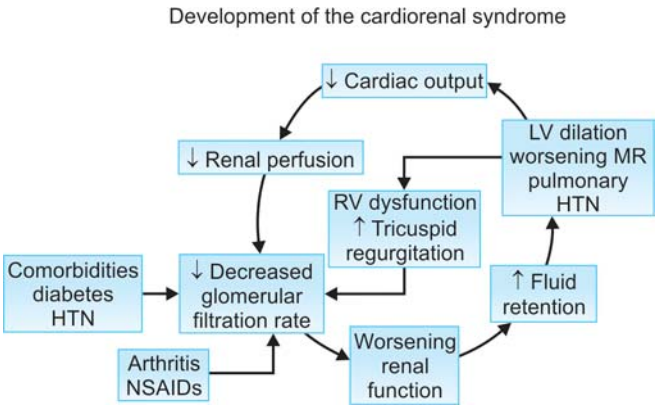
PATHOPHYSIOLOGY OF THE CARDIORENAL SYNDROME

The kidney receives 20% of CO; thus the function of the heart and kidney are closely intertwined. Changes in volume and pressure in the cardiac atria initiate atrial-renal reflexes, which alter renal function. An increase in left atrial pressure is associated with diuresis through suppression of the antidiuretic hormone, arginine vasopressin (AVP) via vagus nerve stimulation and a decrease in renal sympathetic activity, attenuating neurally mediated vasoconstriction of the kidney[18] (Flow chart 2).

ROLE OF DECREASED CARDIAC OUTPUT

The heart can also affect the kidney by activating high-pressure arterial stretch baroreceptors[19] located in the carotid sinus, aortic arch and afferent arteriole of the glomerulus. The vagal and

FLOW CHART 2: The development of the cardiorenal syndrome is complex and still poorly understood. Intrinsic renal disease and impaired renal perfusion are important physiologic components of the syndrome. Renal blood flow is not only dependent on CO, but is affected by high venous pressures as well. Patients may have worsening renal function due to multiple intrinsic and extrinsic renal factors



glossopharyngeal afferent pathways from these high-pressure receptors would normally inhibit sympathetic outflow from the central nervous system (CNS), but with a decrease in stroke volume or a decline in arterial pressure, CNS inhibition is removed and an increase in sympathetic efferent outflow as well as non-osmotic AVP release occurs with multiple effects on the kidney. When stimulated, the adrenergic and angiotensin receptors on the proximal tubule epithelium enhance proximal tubule sodium reabsorption. In addition to these direct effects on sodium balance, the resultant decreased fluid and sodium delivery to the distal nephron also has an effect on urinary sodium excretion. The sodium retaining effect of aldosterone is only temporary due to the "escape phenomenon". Normally, the expansion of extracellular fluid volume (ECVF) secondary to aldosterone increases GFR, decreases proximal tubule reabsorption and enhances sodium delivery to the distal nephron, the site of aldosterone activity. This effect, along with the rise in plasma ANP, which occurs with ECVF expansion, overrides the effect of aldosterone to enhance tubular sodium reabsorption and accounts for aldosterone escape. In contrast, the diminished distal sodium delivery, which occurs with neurohumoral activation, abolishes the normal aldosterone escape. This leads to continued aldosterone-mediated renal sodium retention. As with aldosterone, the site of action of natriuretic peptides is also in the distal nephron, namely the collecting duct. The natriuretic response of these peptides is also dependent on distal sodium delivery. Therefore, the resistance to the natriuretic response of ANP and BNP in HF appears to be secondary to the neurohumoral-mediated diminished sodium delivery to the collecting duct site of their action.

The role of decreased CO in the pathogenesis of the cardiorenal syndrome is more complex than it would first appear. A seminal study by Ljungman[20] clearly demonstrates the powerful autoregulatory ability of the kidney to maintain renal perfusion even with significant reductions in CO. However, the same study found that when the cardiac index fell below 1.5 l/min/m^2 renal perfusion was reduced with a significant fall in GFR (Fig. 5). Finally, marked cardiorenal dysfunction can be reversed in some patients when CO is restored using a left ventricular assist device.[21]

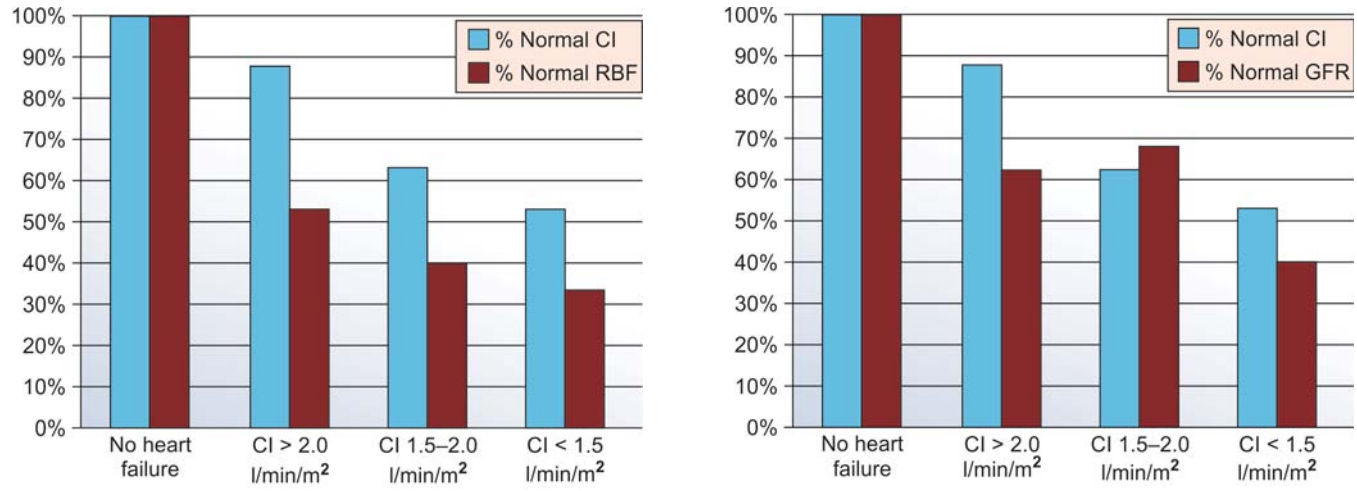


FIGURE 5: Data from Ljungman et al. evaluating the effect of CO on renal function. There was a stepwise decrease in renal blood flow as cardiac index declined with worsening heart failure. Of note, however, GFR is relatively maintained until cardiac index falls below a critical level of 1.5 l/min/m^2. (*Source*: Modified from Ljungman S, et al. Drugs. 1990;39:10-21)

The Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial did not find a significant relation between CO and WRF.[22] Similarly, Mullens[23] reported that reduced CO was not associated with declining renal function. The average entry creatinine in the ESCAPE trial was only 1.5 mg/dL[24] and investigators may not have enrolled patients who had already improved with inotrope infusions. In general, the data suggest that very low CO may impair renal function in selected patients but other factors clearly play a role.

ROLE OF ELEVATED CENTRAL VENOUS PRESSURE

Renal perfusion, as in all organs is influenced by the pressure gradient across its vascular bed. Thus maintenance of a threshold arterial pressure is required for normal renal function. Blood pressure varies from individual to individual and surprisingly low arterial pressures may be well tolerated although rarely below 70–80 mm Hg systolic. Sensitivity to low arterial pressure may also be influenced by coexisting vascular disease. Less well appreciated has been the influence of renal venous pressures on renal perfusion. This is not a new concept since it was formulated by Winton in 1931.[25] However, despite convincing animal data, this concept has been largely ignored (Fig. 6). Firth and his colleagues found that GFR declined significantly in a rodent model when venous pressure was raised above 18 mm Hg and was reversible when pressure was normalized.[26] The fact that the kidney is an encapsulated organ may augment the effects of venous hypertension. In an elegant model in the rhesus monkey, Stone[27] produced acute tubular necrosis and instrumented each kidney. The renal capsule was stripped from one organ and left in place in the other. Creatinine and urea clearance fell to a much greater extent in the encapsulated kidney (Fig. 7).

Until recently data supporting the role of elevated venous pressure in the development of renal dysfunction in HF has been lacking, but recent studies have lent support to this concept. Mullens in a study of severely ill HF patients found that CVP was the best predictor of the percentage who would go on to

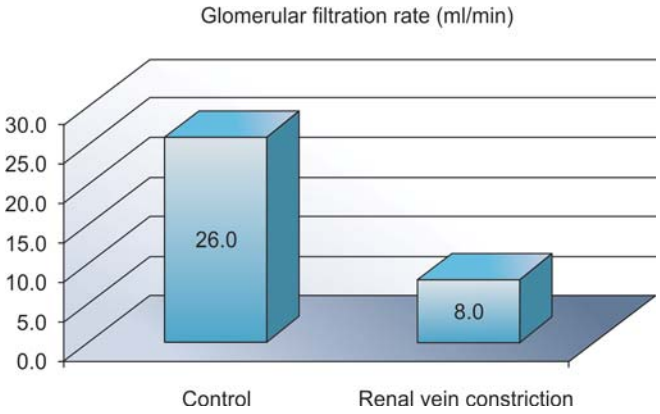


FIGURE 6: Effect of elevated renal vein pressure on renal blood flow (RBF) and glomerular filtration rate (GFR). In this swine experiment, the central venous pressure was increased to 30 mm Hg. The RBF decreased from 2.7 to 1.5 ml/min/gr and GFR was reduced to less than 30% of the baseline value. (*Source*: Modified from Doty JM, et al. J Trauma. 1999;47:1000-3)

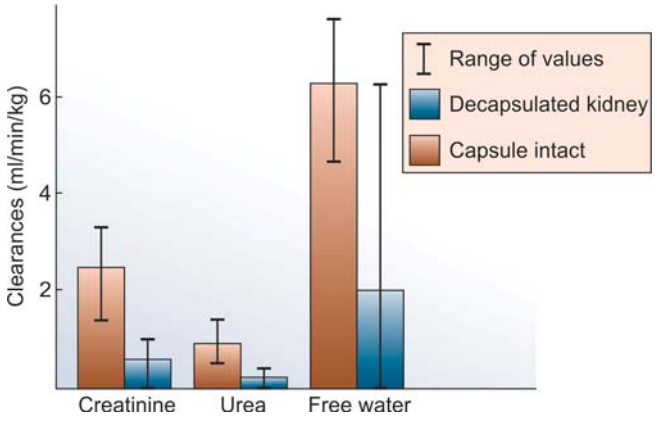


FIGURE 7: In this elegantly simple experiment, the authors induced acute tubular necrosis in rhesus monkeys via aortic clamping above the renal arteries for one hour. In each animal the renal capsule was removed prior to unclamping the aorta from one kidney and left in place in the other. Clearances of creatinine, urea and free water were calculated for each kidney. (*Source*: Modified from Stone HH, et al. Ann Surg. 1977;186:343-55)

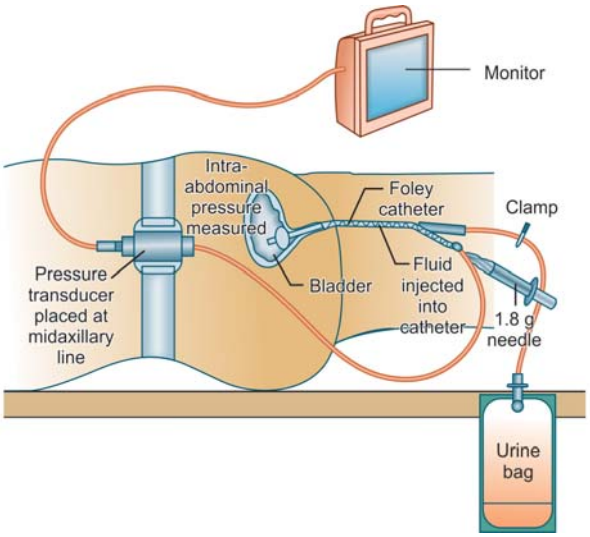


FIGURE 8: Technique for measuring intra-abdominal pressure at the bedside using a modified urinary catheter. When filled with fluid the bladder pressure is at equilibrium with the intra-abominal pressure and can be measured using a standard transducer leveled at the midaxillary (midabdominal) line. (*Source*: Modified from Mullens W, et al. J Am Coll Cardiol. 2008;51:300-6)

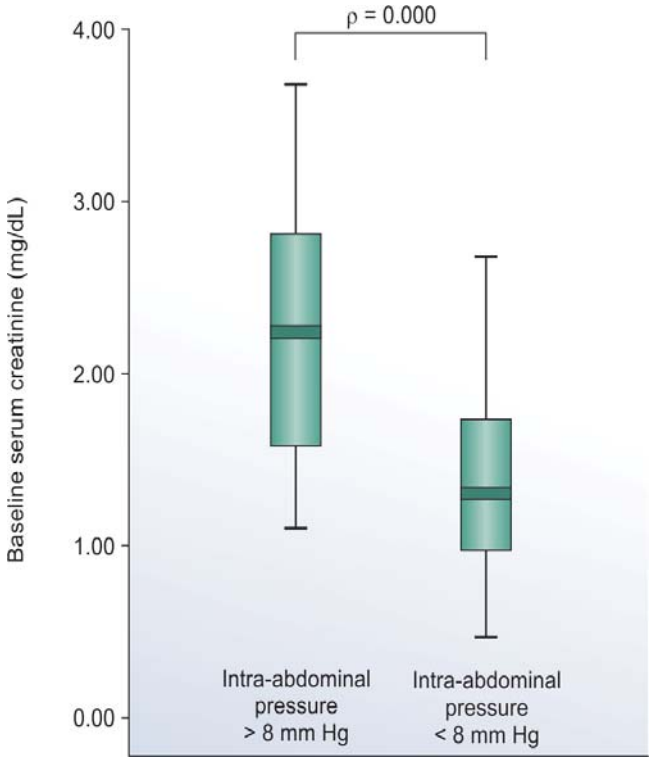


FIGURE 9: Levels of intra-abdominal pressure greater than 8 mm Hg were associated with significantly higher serum creatinine levels in patients admitted with severe decompensated heart failure. (*Source*: Modified from Mullens W, et al. J Am Coll Cardiol. 2008;51:300-6)

develop renal insufficiency.[23] The same group has advanced the concept of a related parameter, namely increased intra-abdominal pressure as risk factor for renal insufficiency[28] (Figs 8 and 9). In the Figure 8, the technique for measuring intra-abdominal pressure at the bedside with the use of a modified urinary catheter is illustrated. They also have reported that in patients admitted with decompensated HF serum creatinine levels are significantly higher when intra-abdominal pressure was greater than 8 mm Hg (Fig. 9). They also have shown that reduction of intra-abdominal pressure either by paracentesis when ascites is present or by ultrafiltration may at times result in improved renal function.[29]

ROLE OF EVIDENCE BASED THERAPIES IN PATIENTS WITH HEART FAILURE AND THE CARDIORENAL SYNDROME

DIURETICS

Diuretics form the cornerstone of therapy for patients with HF who are hospitalized for symptoms of volume overload and are also important for maintenance of euvolemia in the outpatient setting. Renal dysfunction is common in patients with HF. Since impaired clearance of sodium and water occur in both HF and CKD, patients with these comorbidities have a tendency for volume overload and effective diuretic management is essential. The basic physiology of diuretic agents when renal dysfunction is present can be categorized according to the different types of diuretics as: loop, distal convoluted tube and potassium sparing diuretics.

Loop Diuretics

Furosemide, torsemide, bumetanide and ethacrynic are amongst the most potent agents for stimulating diuresis and natriuresis through inhibition of the $Na^+/K^+/2Cl^-$ cotransporter on the luminal side of the thick ascending limb of the loop of Henle. Since 25% of the filtered load of sodium chloride is normally reabsorbed here, loop diuretics can cause profound diuresis and natriuresis. Nevertheless, loop diuretics often lower GFR via adenosine release and stimulation of the renin angiotensin aldosterone system (RAAS). Loop diuretics decrease pulmonary congestion and lower left ventricular filling pressures prior to the onset of their diuretic effects. This is probably related to increased synthesis and release of prostaglandins by the kidney in response to these agents.[30] In this way, loop diuretics can be effective in the treatment of acute pulmonary congestion and edema even in cases of advanced or end-stage renal disease.

Distal Convoluted Tubule Diuretics

Thiazide diuretics and metolazone (a thiazide-like agent) inhibit an electrically neutral sodium and chloride cotransporter in the early distal convoluted tubule. These drugs are rarely used as sole diuretic agents in HF as they are significantly less potent compared to loop diuretics. Renal clearance of thiazides is affected in CHF or other disorders with impaired renal blood flow (RBF). Compared to loop diuretics, thiazides also carry a greater risk for hyponatremia and hypokalemia.[31] Thiazide and thiazide-like agents have greatest utility in CHF when used concomitantly with loop diuretics.[32] In advanced HF the combination of decreased RBF, progressive renal dysfunction and RAAS activation may render maximal doses of loop diuretic therapy ineffective. In the setting of acute and chronic loop diuretic therapy, functional adaptation of the distal tubule with compensatory increases in sodium reabsorption (or diuretic resistance) and the effects of extracellular fluid volume depletion

have also been well described. Simultaneous use of high-dose loop diuretics and a thiazide or metolazone inhibits sodium transport in the ascending thick limb of the loop of Henle as well as the compensatory sodium reabsorption in the early distal convoluted tubule. Most thiazide drugs also directly inhibit carbonic anhydrase, which minimizes compensatory sodium reabsorption in the proximal tubule. Diuresis and natriuresis can be greatly enhanced by combination diuretic therapy, though the risk of severe hyponatremia and hypokalemia can be significant. Thus the combination may aid in diuresis when there is significant diuretic resistance in the cardiorenal syndrome with impaired natiuretic response to loop diuretics alone.

Potassium Sparing Diuretics

Spironolactone, eplerenone, triamterene and amiloride inhibit sodium reabsorption at the cortical collecting tubule. Spironolactone and eplerenone are competitive inhibitors of the intracellular mineralocorticoid receptor, decreasing translocation of active sodium transporters to the luminal membrane. Triamterene and amiloride directly inhibit these extracellular sodium channels. Since only 1–2% of the filtered load of sodium chloride is absorbed at this location, the potassium sparing diuretics have relatively low potency as diuretic and natriuretic agents. Their diuretic utility in HF is to counteract potassium wasting and hypokalemic metabolic alkalosis associated with loop and thiazide diuretic use. High doses of potassium-sparing diuretics should be avoided or used with caution in patients with CHF and renal dysfunction as development of dose-dependent hyperkalemia is common in this setting. However, in some instances of marked diuretic resistance; high dose spironolactone when used with careful monitoring has been found to augment diuresis.[33]

Effect of Diuretic Use on Morbidity and Mortality

According to the ADHERE registry, 70% of patients took a diuretic as part of their outpatient medication regimen.[34] Among patients hospitalized for HF, loop diuretic use is associated with further deterioration of renal function, and this is observed more frequently among patients receiving combination loop diuretic and metolazone therapy.[35] Furthermore, higher doses of loop diuretics are associated with higher serum creatinine and reduced survival.[36] Patients taking loop diuretics also have an increased risk of hospitalization and death related to CHF compared to those not taking these medications.[37] The observations regarding progression of CKD and HF associated with diuretic use are derived from non-randomized or retrospective studies and should be interpreted with caution. Even though multivariate analyses of retrospective studies that have adjusted for possible confounders have observed disease progression associated with diuretics, such studies cannot control for all the differences among patients, and individuals with more CKD and HF are the most likely to be on diuretics. Thus the severity of baseline disease, rather than the diuretic therapy, may be the cause of the disease progression and death. While the use of diuretics is essential for most patients with CHF, there are adverse outcomes associated with worsening renal and left ventricular function. Spironolactone and eplerenone are currently the only diuretics which have been shown to reduce mortality in HF, and this is probably not related to the agents' diuretic effect.[38,39] The largest diuretic trial to date, the diuretic optimization strategies evaluation (DOSE) in acute heart failure trial[40] brings a new perspective to the debate on dose and route of administration of diuretics in HF. In this trial, patients were randomized into four groups who received substantially different diuretic regimens. Group 1 received 2.5 times their daily furosemide dose give continuously over the next 48 hours. Group 2 was given the same dose as Group 1 but in divided doses on every 12 hours. Group 3 continued the same daily dose of furosemide but via a continuous intravenous infusion while Group 4 received the same daily dose as Group 3 but in two increments at 12 hours similarly to Group 2. The high doses of furosemide were associated with slightly higher serum creatinine levels at 48 hours but these were not statistically significant. This change was greatest at day 4 and resolved by day 60. There was a greater total urine output at 48 hours in the high dose groups. There was no statistically significant difference in the combined endpoint of death, rehospitalization or emergency department visit at 60 days between the groups. The DOSE study is perhaps our best look at different diuretic regimens and their outcomes but it has important limitations in that it was underpowered to evaluate mortality differences and perhaps the low dose regimen was too low to be effective. Nonetheless, it demonstrated that mild WRF that was seen early in hospitalization usually resolved after discharge without long-term consequences.

ACE-I AND ARB

In patients with both symptomatic and asymptomatic myocardial dysfunction, long-term administration of ACE-I reduces symptoms, morbidity and mortality from HF associated with reduced ejection fraction.[41] The beneficial effects of ACE-I and ARB treatment in patients with CKD (with or without HF) are related to their hemodynamic actions and a wide range of neurohumoral, cellular and vascular actions. The frequency with which renal function changes in HF patients treated chronically with ACE-I was reported in the studies of left ventricular dysfunction (SOLVD). Decreased renal function was defined as a rise in serum creatinine of greater than 0.5 mg/dL above baseline. More patients randomly assigned to enalapril had a decrease in renal function compared with controls (16% vs 12%). Older age, diuretic therapy and diabetes were associated with a greater likelihood of a negative renal function change, whereas beta-blocker treatment and a higher ejection fraction were renoprotective in all patients irrespective of therapy.[42] Renal function can also deteriorate suddenly when ACE-I or ARB therapy is first begun or it can acutely change in patients receiving chronic therapy. In most patients who experience ARF with ACE-I or ARB therapy, one or more of four mechanisms are typically implicated. First, ACE-I or ARB related hypotension is more common with long-acting agents, and if the mean arterial pressure falls to levels that cannot maintain renal perfusion, renal function can be expected to decline.[43] Second, ACE-I or ARBs are more likely to cause ARF in the patient with HF who becomes volume depleted from overly aggressive diuresis or intercurrent volume-depleting illness.[44] Third, ACE-I or ARB may induce ARF in patients with high-grade bilateral renal artery stenosis or stenosis of a dominant or a single kidney renal artery, or in patients with extensive atherosclerotic disease in smaller preglomerular vessels.[45] Finally, ACE-I or

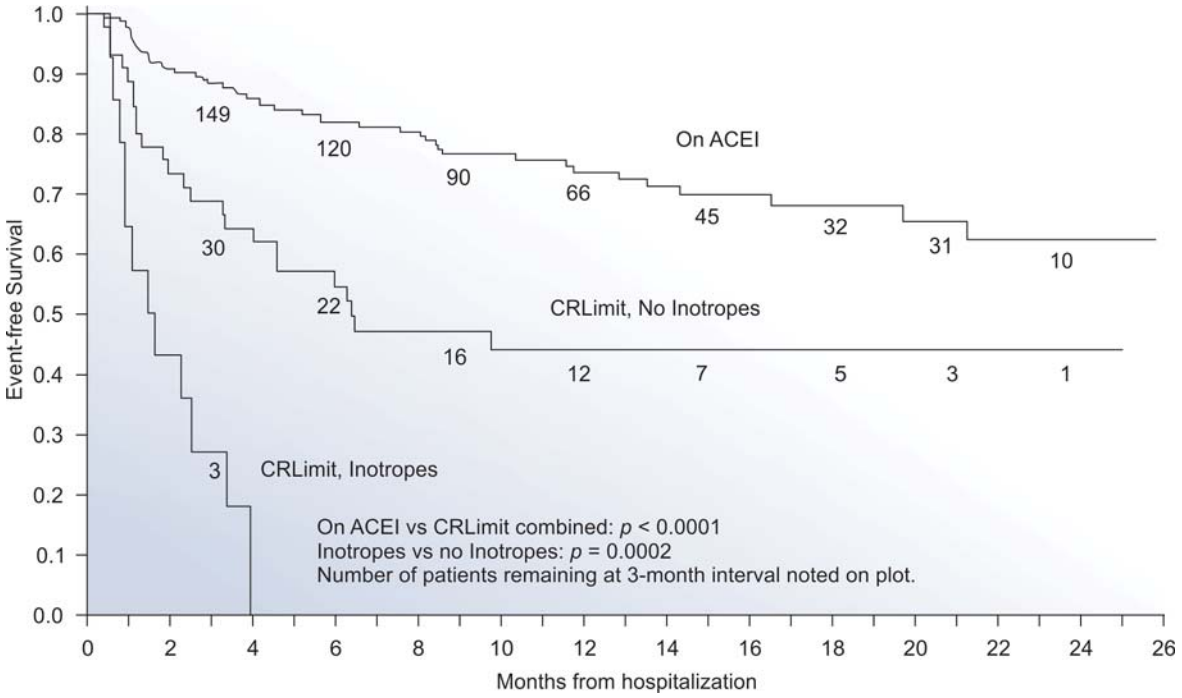


FIGURE 10: Inability to tolerate RAAS blockade is a sentinel event in heart failure patients. Transplant and left ventricular assist device free survival in 173 patients with advanced heart failure. In patients in whom angiotensin converting enzyme inhibitors (ACE-I) were withdrawn for low blood pressure or renal dysfunction survival (or need for transplant or left ventricular assist device) was only 50% at one year. The need to stop ACE-I suggests very advanced heart failure with high mortality. (*Source*: Modified from Kittleson M, et al. J Am Coll Cardiol. 2003;41:2029-35)

ARB may precipitate ARF in patients who are taking nonsteroidal anti-inflammatory agents (NSAIDs) or cyclooxygenase-2-specific inhibitors[46] (Table 6). Nonetheless, RAAS blockade should be continued when at all possible as mortality is very high when ACE-I/ARBs are stopped for renal reasons and the inability to maintain the use of these agents is a marker for very poor prognosis[47] (Fig. 10).

In HF increased angiotensin II levels cause constriction of the efferent arteriole which elevates glomerular filtration pressure and helps to preserve GFR. Reversal of these elevated pressures in the CKD patient with either ACE-I or ARB therapy will generally lead to an initial fall in GFR around 10–20%[48,49] (Fig. 11). Such small increases in serum creatinine should not prompt discontinuation of the RAAS blocking drug. The risk of ACE-I or ARB WRF is greater in patients with CKD of any cause than in those with normal renal function.

INOTROPES

Inotropes, such as dobutamine, milrinone, levosimendan and dopamine, are drugs used to increase cardiac contractility,

TABLE 6

Principles of ACE-I or ARB therapy: renal considerations

- ACE inhibitors and ARBs improve RBF and stabilize glomerular filtration rate in most patients with HF unless they adversely affect cardiac hemodynamics
- ACE inhibitor and ARB therapy is indicated in patients with diabetic nephropathy and in patients with nondiabetic nephropathies when protein excretion exceeds 1 g/d. Concurrent primary renal diseases are not uncommon in the HF patient
- A rise in serum creatinine may occur after initiation of RAAS inhibitor therapy in patients with HF. This rise usually occurs shortly after initiation of therapy, is in the 10–20% range, is not progressive and is of renal hemodynamic origin. Renal function often stabilizes and may decline thereafter
- Although there is no serum creatinine level per se that contraindicates ACE inhibitor therapy, greater increases in serum creatinine occur more frequently when ACE inhibitors are used in patients with underlying chronic kidney disease
- The occurrence of AKI should prompt a search for systemic hypotension (MAP < 65 mm Hg), ECF volume depletion or nephrotoxin administration and attempts to correct/remove these factors. Consideration should also be given to searching for high-grade bilateral renal artery stenosis or stenosis in a solitary kidney
- ACE inhibitors should be temporarily discontinued when AKI occurs and precipitating factors for AKI corrected; an ARB or a DRI is not an appropriate substitute under these conditions. Once AKI has resolved with correction of the precipitating factors, ACE inhibitor therapy can be cautiously reintroduced

(*Source:* Sica DA. The use of ACE inhibitors and angiotensin receptor blockers in patients with coexistent renal disease and heart failure. In: Heywood JT, Burnett J (Eds). The Cardiorenal Syndrome: A Clinician's Guide to Pathophysiology and Management. Cardiotext Publishing; 2011)

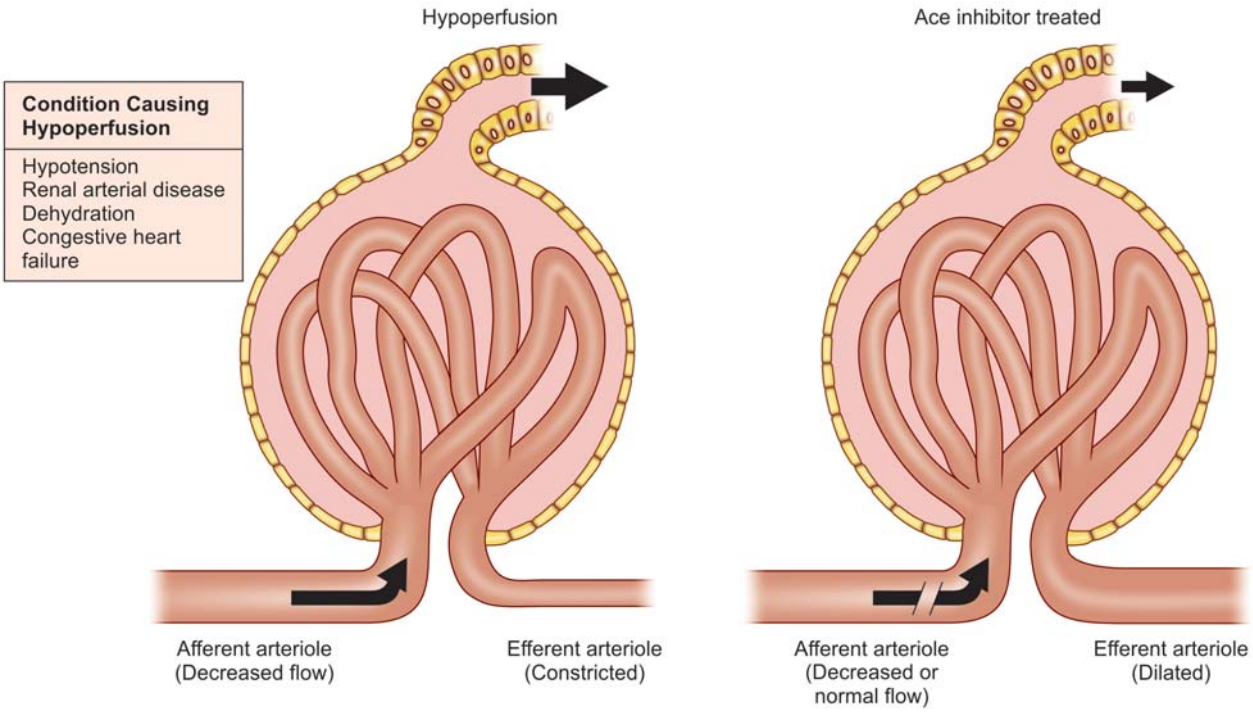


FIGURE 11: Glomerular filtration is regulated in part by changes in vascular tone in the afferent and efferent arterioles. Angiotensin II (ANG II) is a potent vascular smooth muscle constrictor and preferentially constricts the efferent arteriole leaving the glomerulus more than the afferent arteriole entering the glomerulus. Therefore higher levels of ANG II tend to preserve GFR. When ACE-I or ARB are used for heart failure ANG II is reduced or its effects are blocked at the receptor site with resulting efferent arteriolar dilation and reduced pressure in the glomerulus. This causes a physiologic and expected small decline in GFR and rise in serum creatinine. (*Source*: Modified from Schoolwerth AC, et al. Circulation. 2001;104:1985-91)

improve CO and renal function.[50] These drugs are recommended in patients with fluid overload if they respond poorly to intravenous diuretics or have diminished or WRF,[51] but the effects of these drugs on the kidney in patients with HF have not been clearly defined.

Dobutamine

A catecholamine-derived inotrope acts predominantly on beta 1- and beta 2-adrenergic receptors. Dobutamine also binds to alpha1-adrenergic receptors, but the clinical effect of vasoconstriction appears to be ameliorated by the beta 2-mediated vasodilation. Dobutamine increases RBF. This effect appears to depend on the clinical setting and most likely only occurs when renal perfusion is improved secondary to an increase in CO, although this has not been a universal finding. Despite its potential to aid renal perfusion, clinical studies suggest that dobutamine has little effect on renal vascular resistance and indices of renal function such as GFR. Clinically dobutamine may improve renal function when CO in significantly reduced.

Milrinone

Milrinone confers its positive inotropic effect through antagonism of the phosphodiesterase III (PDE) enzyme, resulting in cyclic adenosine monophosphate (cAMP) mediated increases in cardiomyocyte intracellular calcium concentrations. Milrinone also has profound vasodilatory effects, which have been demonstrated in peripheral, coronary, splanchnic, skeletal muscle and renal arteries. In an open-label study, 11 patients with severe chronic HF, NYHA functional class III or IV and LVEF less than 20%, milrinone administered as a single oral dose of 7.5 mg was associated with a significant increase in RBF compared to baseline at 90 minutes post-dose.[52] Milrinone may lower systolic blood pressure to unacceptably low levels and thus impair renal function.

Levosimendan

An inodilator approved for acutely decompensated HF in Europe. Unlike catecholamine and phosphodiesterase III inhibitors, its inotropic effects are achieved without an increase in intracellular calcium. Data on levosimendan and renal function in HF are limited to two small prospective studies[53,54] and results from the Levosimendan Infusion Versus Dobutamine (LIDO) Study.[55] The LIDO study compared the effects of levosimendan and dobutamine on hemodynamic performance and clinical outcome in patients with low-output HF and demonstrated that in patients with severe, low-output HF, levosimendan improved hemodynamic performance more effectively than dobutamine. This benefit was accompanied by lower mortality in the levosimendan group than in the dobutamine group for up to 180 days.

The mechanism(s) of renoprotection are unknown but could include an augmentation of RBF via an increase in CO or reduction on vascular renal resistance, anti-inflammatory effects and ATP-dependent potassium channel activation.

Dopamine

Known to exhibit a graded pharmacological response with a dose-dependent predominant activation of dopaminergic

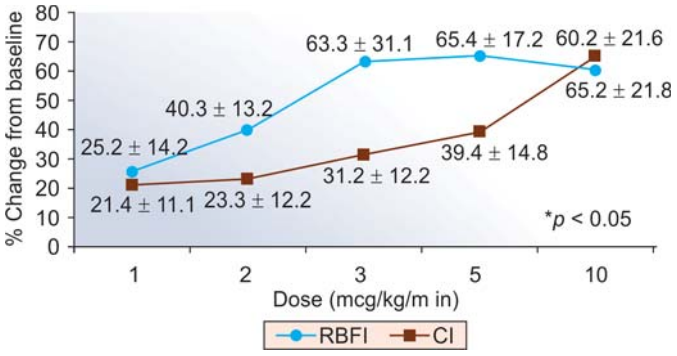


FIGURE 12: Dopamine can selectively dilate renal arteries and can therefore increase renal blood flow to a greater extent than the increase of cardiac index produced at the same infusion concentration. The greater percentage of increase in renal blood flow over cardiac index reached statistical significance at 5 mcg/kg/min. (*Source*: Modified from Elkayam U, et al. Circulation. 2008;117:200-5)

receptors, beta-receptors and alpha-receptors.[56] At doses less than 3 mcg/kg/min dopamine was found to activate dopamine A1 receptors which cause vasodilatation of the renal arteries and other vascular beds, including mesenteric, coronary and cerebral. In addition, stimulation of dopamine A2 receptors leads to inhibition of norepinephrine release from sympathetic nerve endings. Activation of dopamine A1 and A2 receptors also leads to a decline in systemic vascular resistance (SVR) and to an increase in RBF. Dopamine infused at approximately 3–5 mcg/kg/min activates β_1 and β_2 adrenergic receptors, conferring a positive inotropic effect that is responsible for an increase in CO. At a dose of greater than 5 mcg/kg/min dopamine has been reported to exert clinically relevant activation of α_1 adrenergic receptors, which may result in arterial vasoconstriction. A recent study[57] by Elkayam et al. evaluated the renal effect of dopamine at dose of 1, 2, 3, 5 and 10 mcg/kg/min in 13 patients with chronic HF. The RBF increased, whereas renal vascular resistance decreased at 2 mcg/kg/min through 10 mcg/kg/min. The CO gradually increased at doses of 5 and 10 mcg/kg/min, but the increase in RBF was much larger than the corresponding increase in CO, providing a strong support to the direct vasodilatory effect of dopamine on both large conductance and small resistance renal blood vessels (Fig. 12).

ROLE OF ULTRAFILTRATION ON DIURETIC RESISTANCE AND THE CARDIORENAL SYNDROME

Ultrafiltration, as supportive care in patients with the cardiorenal syndrome, is emerging as a useful therapeutic strategy in both elective and emergency situations.[58,59] The primary therapeutic goals for acute HF exacerbation include removal of excess fluid, reduction in ventricular filling pressures and increase in CO, myocardial protection, neurohormonal modulation and renal function preservation. Intravenous treatment with diuretics may initially facilitate fluid loss and improve symptoms, but their use is associated with increased neurohormonal activation, intravascular volume depletion, hemodynamic impairment and renal function decline. Alternative therapeutic strategies are needed to counteract development of diuretic refractoriness, particularly in those cases in which progressively increasing diuretic doses are required. Ultrafiltration, in the short term, may reverse the vicious cycle responsible for the progression of the disease in which CO reduction, neurohormonal activation and renal dysfunction negatively impact each other.[60] Reduction of extravascular lung water with ultrafiltration allows the rapid improvement of respiratory symptoms (dyspnea and orthopnea), pulmonary gas exchanges, lung mechanics and radiological signs of pulmonary vascular congestion and alveolar and interstitial edema. Removal of systemic extravascular water allows resolution of peripheral edema and, when present, ascites and pleural effusions.[58] The subtraction of extravascular pulmonary water, by reducing the intrathoracic pressure and, thus, the diastolic burden on the heart, exerts a positive influence on cardiac dynamics.[61] The hemodynamic improvement following ultrafiltration is the result of both the reduction of the extracardiac constraint and the optimization of circulating volume. Even withdrawal of several liters of fluid, over a period of a few hours, can be safely performed without detrimental hemodynamic consequences, and clinical improvement is usually maintained for a long time following a single session. The decrease in the ventricular filling pressures reflects the reduction of intrathoracic pressure and of pulmonary stiffness due to reabsorption of the excessive extravascular lung water that burdens the heart. In addition to edema removal, ultrafiltration allows for other effects that are particularly useful in patients with advanced HF and associated CKD: correction of hyponatremia, restoration of urine output and diuretic responsiveness, reduction of circulating levels of neurohormones and, possibly, removal of other cardiac-depressant mediators.[59] Recovery of diuretic responsiveness is a major clinical effect because it allows for maintenance, and even improvement in the following days and months, of the clinical benefits achieved at the end of a single session of ultrafiltration. Moreover, it permits the use of lower dosages of diuretics, with potentially fewer side effects. The UNLOAD trial (ultrafiltration versus intravenous diuretics for patients hospitalized for acute decompensated CHF) has demonstrated that early treatment with ultrafiltration in patients with acute HF safely produces greater weight and fluid loss than intravenous diuretics and is associated with a 44% reduction of rehospitalizations for HF in the following three months.[62] Further studies are needed to confirm the positive clinical impact of ultrafiltration, to better define protocols and more appropriate renal replacement modalities, to identify patients and clinical settings in which the greatest benefit can be obtained and, finally, to definitively establish the effect of ultrafiltration on hard clinical endpoints.

TREATMENT OF THE CARDIORENAL SYNDROME: AN APPROACH TO THE INDIVIDUAL PATIENT

Due to the many potential etiologies of the cardiorenal syndrome and potential treatments, which may be diametrically opposed, a systematic approach to the HF patient presenting with WRF is critical. In order to focus the evaluation, five key questions must be answered about the patient at hand.

1. What is the volume status of the patient, i.e. hypovolemic, hypervolemic or euvolemic?
2. Is there systemic hypotension (systolic BP < 80 mm Hg)?

TABLE 7

Management of the cardiorenal syndrome

Cause of the cardiorenal syndrome	*Volume status*	*Cardiac output*	*SVR*	*Treatment*
Hypovolemia	↓↓	↓	↓ or normal	Stop diuretic Volume replacement
Excess vasoconstriction	↑ or normal	↓↓	↑↑	↑ RAS blockade Nitroprusside Nesiritide Nitroglycerin
Cardiogenic shock	↑ or normal	↓↓	↑ or normal	Dobutamine Dopamine Norepinephrine LVAD
Excessive vasodilation	↑ or normal	↓ or normal	↓↓	Dopamine Norepinephrine Vasopressin LVAD
Diuretic resistance	↑↑	↓ or normal	normal	Diuretic infusion Diuretic combination Ultrafiltration Nesiritide
Intrinsic renal disease	↑↑	Normal	normal	Diuretic Infusion Ultrafiltration Hemodialysis Renal transplantation

3. Is the central venous pressure markedly elevated?
4. What is the cardiac output?
5. Is there evidence for intrinsic renal disease?

Evaluation of volume status and the early recognition of hypovolemia are important because intercurrent gastrointestinal illness and iatrogenic volume depletion are common yet rapidly correctable. A focused history and physical examination which looks for postural blood pressure changes, flat neck veins and absence of rales and a third heart sound should be adequate to identify most cases of hypovolemia. When the fluid status is in doubt, then a limited echocardiogram can often resolve the issue. Vigorous collapse of the inferior vena cava during respiration, a transmitral E wave is greater than the A wave and an E wave deceleration time is greater than 200 milliseconds strongly suggests low filling pressures in HF with WRF.[63] The recognition of hypovolemia is critical because rapid volume replacement of 500–1000 cc of normal saline can improve CO by restoring normal preload, and hence blood pressure and renal perfusion. Hemodynamic monitoring to determine volume status may be necessary in some circumstances when uncertainty remains (Table 7).

Once hypovolemia has been ruled out or corrected, then systolic hypotension should be addressed. Clearly, the lower the systolic blood pressure the more urgently this should be corrected if renal perfusion is to be restored before irreversible damage occurs. In patients with less severe hypotension, blood pressure may be restored with dobutamine if there is a history of severe LV dysfunction. Profound hypotension may require pressor support with norepinephrine and/or epinephrine. The appearance of the cardiorenal syndrome coupled with hypotension is a true medical emergency that requires rapid action but also hemodynamic data to address the underlying CV abnormality. Knowing the CO can be important for decision making for several reasons. When the cardiac index is below 1.5 l/min/m^2 then renal function is difficult to maintain. The use of dobutamine or milrinone in this instance can rapidly improve renal function and stabilize the patient. The resolution of renal dysfunction by improving CO with inotropes demonstrates adequate renal reserve and confirms a cardiac basis for the cardiorenal syndrome. Due to the problematic long-term outcomes with inotropes and poor prognosis associated with renal dysfunction, strong consideration should be given to more definitive therapy such as cardiac transplantation or LVAD placement. Use of an LVAD can restore renal function and is associated with improved prognosis[21] (Figs 13 and 14).

Knowledge of the CO and calculation of SVR can give further insight into the pathophysiology of the cardiorenal syndrome. A small minority may have hypotension without profound reduction of CO; hence calculated SVR is very low due to peripheral vasodilation, mimicking septic shock. Kanu Chatterjee has coined the phrase "pseudosepsis syndrome" to describe this syndrome in HF patients, often with renal dysfunction. The etiology of the syndrome is unclear but appears to result in renal hypoperfusion from low blood pressure and shunting of blood to the periphery. This syndrome may be seen after bypass surgery in patients with marked LV dysfunction and is often resistant to norepinephrine infusion. There is a beneficial response to vasopressin infusions in such patients with improved blood pressure and reduced requirements for norepinephrine.[64] Due to hypotension and vasodilation, ACE-I, ARB or other vasodilators should be discontinued in these patients until blood pressure stabilizes without pressor support (Fig. 15).

On the other hand, patients may present with the cardiorenal syndrome with low normal blood pressure coupled with a very elevated SVR. Although much less common in the era of

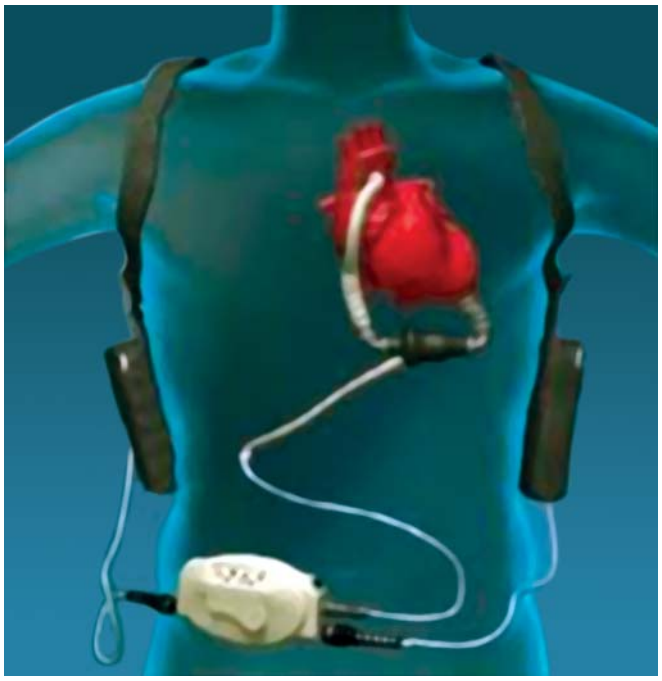


FIGURE 13: In the event of inadequate CO to support end organ function as exemplified by worsening renal function, implantation of a left ventricular assist device can restore adequate renal perfusion. The HeartMate II® has been approved for bridge to transplant and destination therapy. (*Source*: Thoratec Corporation)

ACE-I, it can be seen when ACE-I are not used out of concern for renal dysfunction or when an intercurrent gastrointestinal illness results in an abrupt withdrawal of ACE inhibition. Patients present with poor urine output, WRF and cold extremities. Vasodilators are critical here because of the profound vasoconstriction producing increased afterload and reduced CO. Intravenous vasodilators such as nitroprusside or nesiritide may be employed until the patient can be placed on ACE inhibitors. Some may require short-term inotropic support as vasodilators are added. The CO can more than double in such patients with attendant improvement in renal perfusion and function. This syndrome can also be seen in rare patients who acutely decompensate during the initiation of beta-blocker therapy.

The role of nesiritide in the management of decompensated HF is controversial. Although it lowers filling pressures and improves symptoms, two meta-analyses raised concerns that the drug increased 30-day mortality and was associated with WRF.[65,66] Due to these concerns, the Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF) trial was undertaken and recently reported. The ASCEND-HF randomized 7,141 patients in 30 countries (including 45% from North America) in double-blind fashion and within 24 hours of hospitalization and institution of acute IV therapy for ADHF to receive IV nesiritide or placebo on top of standard therapy. Nesiritide was infused at 0.01 μg/kg/min for up to seven days, sometimes preceded by a nesiritide bolus of 2 μg/kg. The results of the study showed that nesiritide did not compromise renal function or increase mortality within a month of its use in ADHF patients.[67] The NAPA trial evaluated nesiritide in 279 patients with LV dysfunction undergoing bypass and valve surgery. Compared to the placebo group, patients receiving nesiritide developed less renal dysfunction had reduced length of stay and lower long-term mortality.[68] Thus the drug may be beneficial in some patients with the cardiorenal syndrome, especially perhaps those with vasoconstriction.

An important practical consideration is the method used to measure CO. The gold standard remains invasive monitoring with a pulmonary artery catheter. Recent concerns about complications and the publication of the ESCAPE trial have led to a dramatic reduction in its use.[24] This does not mean it should never be used, and the hemodynamic information it provides can be invaluable in managing critically ill HF patients. In the patient with cardiorenal syndrome a single measurement of CO may be sufficient to determine hemodynamics and guide initial therapy.[69] In this instance a bedside echocardiographic determination of CO can be quicker, less expensive and noninvasive. The most accurate technique involves pulsed Doppler interrogation of the LV Outflow Tract and Measuring the Time-Velocity Integral (LVOT-TVI cm/sec). This number

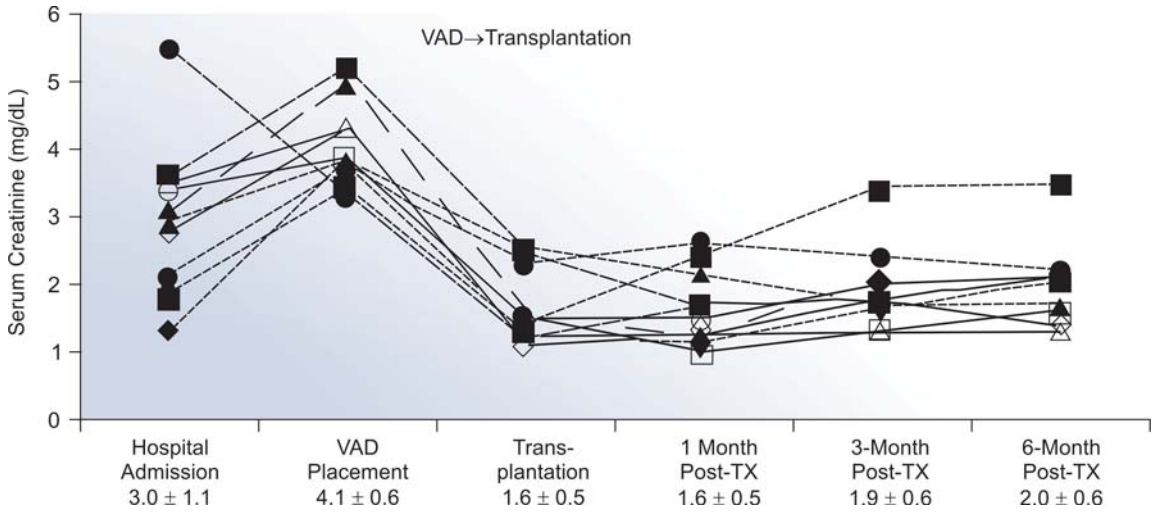


FIGURE 14: Data on ten patients with advanced heart failure complicated with significant renal dysfunction that was largely reversible with left ventricular assist implantation. (*Source*: Modified from Khot UN, et al. J Am Coll Cardiol. 2003;41:381-5)

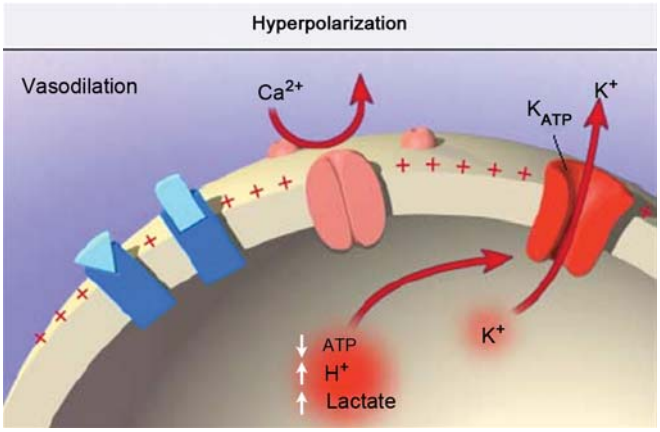
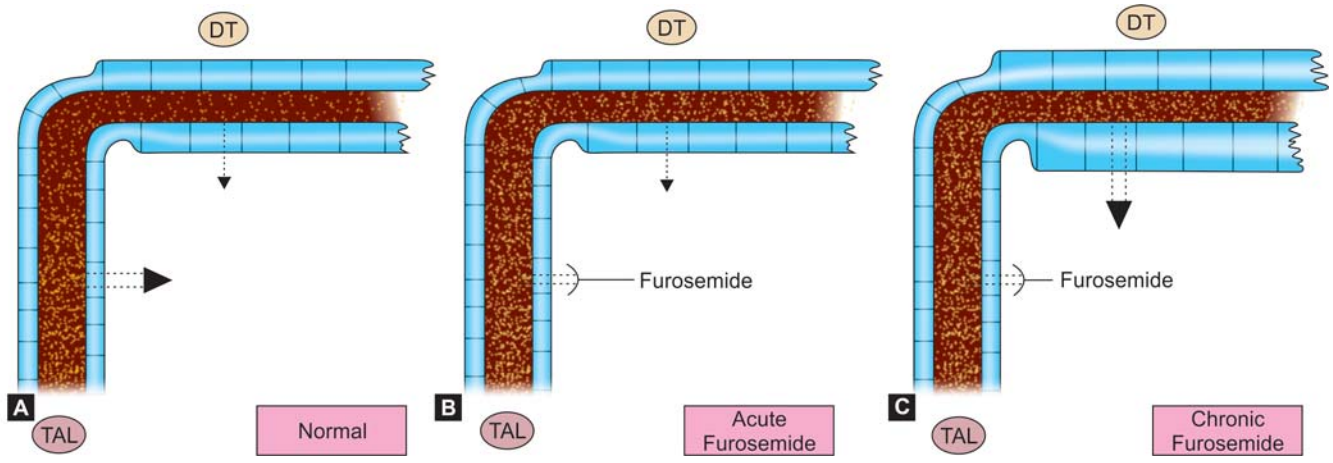


FIGURE 15: Vasodilation lactic acidosis produces vasodilatation via KATP channels. Potassium leaves smooth muscle cells via the KATP channels, resulting in plasma membrane hyperpolarization. This leads to inactivation of the voltage-gated calcium channels and prevents a rise in the cytoplasmic calcium concentration and so prevents arteriolar smooth muscle constriction. (*Source*: Modified from Landry DW, et al. N Engl J Med. 2001;345:588-95)

is then multiplied by the outflow tract area just below the aortic valve (cm^2) to determine the stroke volume, LVOT-TVI × LVOT area = stroke volume (cm^3/sec). The stroke volume is then multiplied by the heart rate to determine CO. In general, LVOT-TVI less than 10 cm/sec suggest severe reduction in CO. When hypovolemia has been ruled out and adequate renal perfusion ensured with normal blood pressure and CO, then intrinsic renal disease should be considered the cause of renal dysfunction. Indeed, given the advanced age and frequent comorbidities in the HF population it would be surprising if intrinsic renal disease was not common. A renal etiology of the cardiorenal syndrome is more likely when there is evidence for longstanding renal dysfunction. Significant proteinuria (> 1 gm/day) also strongly suggests an intrinsic renal disorder. Once the kidney has been identified as the cause of the renal dysfunction there are important implications for therapy. Diuretics can be used as long as the patient remains volume overloaded, although meticulous care should be taken to avoid overdiuresis and hypotension. In some instances bumetanide or torsemide may be more effective than furosemide and may be tried if urine output is inadequate. Another technique to deal with renal resistance is the addition of a distal tubular diuretic to block sodium reuptake in this area of the nephron. With prolonged use of loop diuretics distal tubular hyperplasia and increased reabsorption of sodium may occur with resulting diuretic resistance[70] (Fig. 16). Metolazone or hydrochlorothiazide can be used to mitigate this effect. However, the response to this therapy is unpredictable and can result in tremendous diuresis and electrolyte abnormalities. Therefore, it is best to use a single dose of these agents and then observe their effect rather than giving them daily. An intravenous form thiazide (chlorothiazide) is available for those who cannot take oral agents.

When renal dysfunction is profound then the option of dialysis is available as either a temporary or permanent therapy for the cardiorenal syndrome. Short of dialysis for patients who do not respond adequately to diuretics, ultrafiltration is an important option. In selected patients renal transplantation should be considered as the ultimate therapy for the kidney centered cardiorenal syndrome. Although many HF patients are not appropriate for renal transplant, some patients do extremely well with transplantation and may even see an improvement in cardiac function following renal transplantation.[71] This is especially true for younger individuals with nonischemic, hypertensive HF with associated renal failure. In a sense all HF is a manifestation of a cardiorenal syndrome.

The CV system evolves to maintain a balanced milieu, and HF develops when the system fails, usually because of CV disease, to regulate this balance. Present therapies can restore this balance in many patients, but not in all, especially when



FIGURES 16A TO C: (A) In normal circumstances Cl^- is reabsorbed actively with passive Na^+ reabsorption in the thick ascending limb of Henle (TAL). Sodium and chloride are also reabsorbed in the distal tubule (DT) but to lesser extent than in the TAL. (B) When furosemide is given initially, it blocks Cl^- transport from the lumen of the TAL and is reabsorbed with Na^+ into the vascular bed in the medulla. As a consequence more NaCl is delivered to the DT with more than normal reabsorption. However, net NaCl excretion is increased. (C) With chronic administration of furosemide the increased concentration of NaCl in the DT results in hypertrophy of the DT cells with enhanced Na^+ reabsorption. Therefore, net excretion of NaCl is reduced. The addition of a second diuretic acting at the DT can restore furosemide-induced NaCl excretion. (*Source*: Modified from Ellison DH. The physiologic basis of diuretic drug action and synergism. Principles of medical biology. Molecular and Cellular Pharmacology. JAI Press Inc. 1997. pp. 577-99)

the kidney, a much more complex organ than the heart, is responsible. If the progress made in HF is to be continued, the kidney should be a major focus of research, and if renal function could be restored and GFR increased reliably, then care of patients with the cardiorenal syndrome would be greatly improved.

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Chapter 75

Acute Heart Failure Syndromes

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Chapter Outline

- Definition
- Epidemiology
- Patient's Characteristics
- Classification
- Pathophysiology
  - Congestion
  - Myocardial Injury
  - Renal Impairment
  - Vascular Failure
  - Cardiac Metabolism
  - Untoward Drug Effects
  - Viability
- Acute Heart Failure Syndromes Management
  - Stabilization Phase
  - Transition to Evidence-based Phase
  - Reconstruction Phase
- Clinical Trials in Acute Heart Failure Syndromes
  - T1 Translation Phase

INTRODUCTION

Over one million hospitalizations for acute heart failure syndromes (AHFS) occur every year in the United States, an increase of more than 150% over the last several decades.[1,2] Hospitalization marks a significant event in terms of risk for patients, as up to 1 out of every 2 patients may be readmitted or dead within 90 days.[3,4] Although inpatient mortality has decreased in the last 15 years, early post-discharge event rates, namely death and rehospitalization remain high, reaching 14% and 31% respectively, within 90 days.[4,5] This contrasts sharply with chronic heart failure (HF), where 1 year mortality is approximately 5%.[6] The tremendous advances seen in chronic HF management have not been replicated in AHFS; early management has changed little over the last 40 years, despite substantial efforts.[7] Improving outcomes for AHFS patients is one of the greatest challenges facing cardiology today.

DEFINITION

Acute heart failure syndromes have been defined as new onset or gradual or rapidly worsening HF signs and symptoms requiring urgent therapy.[8,9] Regardless of the underlying etiology for HF or the precipitant for acute decompensation, patients are characterized by pulmonary and systemic congestion due to elevated ventricular filling pressures with or without low cardiac output.

EPIDEMIOLOGY

Six million people in the United States are currently diagnosed with HF, with over 670,000 new diagnoses each year.[1,2] Combined primary, secondary and tertiary discharge hospital diagnoses for HF are well over 3 million per year.[2,8] HF is the most expensive diagnosis for Medicare beneficiaries, and the number one cause of rehospitalization.[2,10-13] The overall cost of HF care is projected to be over 40 billion USD in 2011, with the majority of this cost due to hospitalization for HF.[14]

The average HF patient is over 70 years of age; when this fact is combined with the overall aging of the US population, improved survival post-myocardial infarction as well as a decrease in sudden cardiac death, the burden of AHFS will likely increase.[2,15]

PATIENT'S CHARACTERISTICS

Over the last decade, large registries and clinical trials have provided important insight regarding the AHFS population. Approximately 80% of AHFS patients have worsening chronic HF requiring hospitalization, of which only a small subset (~5%) present with advanced or end-stage HF. The remaining 20% of admissions have de novo or HF for the first time.[16,17] Of these patients, approximately 50% have a relatively preserved ejection fraction, what has been termed diastolic dysfunction, HF with normal ejection fraction, HF with preserved systolic function or heart failure with preserved ejection fraction (HFPEF).[9,18,19] For simplicity, we will use the term HFPEF.

The mean age is 75 with a nearly equal split between males and females[17,20] (Table 1). For HFPEF, patients are slightly older with a greater predominance of women.[17,19,20] Dyspnea, or breathlessness, is the most common symptom at the time of presentation, with classic HF signs, such as jugular venous distention, peripheral edema and rales, commonly seen.[17,20] Nearly 50% of patients will have systolic blood pressure of 140 mm Hg or greater at the time of presentation, with less

TABLE 1

Preserved versus reduced systolic function patient characteristics

Characteristics at admission	*Patients with LVSD (n = 20,118)*	*Patients with PSF (n = 21,149)*
Demographics:		
Mean age (years)	70.4 ± 14.3	75.1 ± 13.1
Male	62%	38%
Caucasian	71%	77%
African American	21%	15%
Medical history:		
Diabetes, insulin-treated	15%	17%
Diabetes, noninsulin-treated	24%	26%
Hypertension	66%	76%
Hyperlipidemia	34%	32%
Atrial arrhythmia	28%	33%
Vital signs on admission:		
Median body weight [kg (25th, 75th percentile)]	78.5 [65.8, 94.0]	78.9 [64.0, 97.5]
Mean heart rate (beats/min)	89 ± 22	85 ± 21
Mean SBP (mm Hg)	135 ± 31	149 ± 33
Mean DBP (mm Hg)	77 ± 19	76 ± 19
Etiology:		
Ischemic	54%	38%
Hypertensive	17%	28%
Idiopathic	18%	21%
Findings on admission:		
Acute pulmonary edema	3%	2%
Chest pain	23%	24%
Uncontrolled hypertension	9%	12%
Dyspnea at rest	44%	44%
Dyspnea on exertion	63%	62%
Rales	63%	65%
Lower extremity edema	62%	68%
Jugular venous pulsation	33%	26%
Left ventricular EF	24.3% ± 7.7%	54.7% ± 10.2%
Laboratory values:		
Mean serum sodium (mEq/l)	137.7 ± 4.6	137.9 ± 4.8
Median serum creatinine [mg/dl (25th, 75th percentile)]	1.4 [1.1, 1.9]	1.3 [1.0, 1.8]
Mean serum hemoglobin (g/dL)	12.5 ± 2.0	11.9 ± 2.0
Median BNP [pg/ml (25th, 75th percentile)]	1,170.0 [603.0, 2,280.0]	601.5 [320.0, 1,190.0]
Median troponin I [ng/ml (25th, 75th percentile)]	0.1 [0.1, 0.3]	0.1 [0.0, 0.3]
Medications on admission:		
ACE inhibitor	45%	36%
ARB	11%	13%
Amlodipine	5%	10%
Aldosterone antagonist	10%	5%
Beta-blocker	56%	52%
Loop diuretic	63%	58%
Digoxin	30%	17%
Aspirin	42%	38%
Anti-arrhythmic	13%	8%
Hydralazine	3%	3%
Nitrate	22%	21%
Statin	40%	39%

(Abbreviations: ACE: Angiotensin-converting enzyme; ARB: Angiotensin receptor blocker; BNP: B-type natriuretic peptide; DBP: Diastolic blood pressure; EF: Ejection fraction; LVSD: Left ventricular systolic dysfunction; PSF: Preserved systolic function; SBP: Systolic blood pressure; SD: Standard deviation)
Statin is being used among patients with coronary artery disease, cerebrovascular disease/transient ischemic attack, diabetes, hyperlipidemia or peripheral vascular disease.
(Adopted and reproduced from Fonarow et al. JACC 2007, with permission)

than 10% of patients hypotensive.[4] The AHFS patient has substantial cardiac and non-cardiac comorbidities. Several unique differences are noted between patients with reduced systolic function and those with HFPEF, namely a history of hypertension and atrial arrhythmias.[4,19]

Despite robust evidence for beta blockade, ACEI/ARB and aldosterone blockade for appropriate patients, a sizable number of eligible patients are not on evidence-based therapies.[21] Peterson et al. highlight what has been termed a "risk-treatment paradox" in HF, where higher risk patients receive less evidence-based therapies when compared to lower risk patients.[21]

CLASSIFICATION

No universally accepted method of classification of AHFS currently exists, reflecting both the heterogeneity of the patient population as well as our limited, albeit growing, knowledge of AHFS pathophysiology. From a clinician's perspective, a classification schema that guides therapy would be ideal. Several have been proposed based on presenting clinical profile;[22-24] whether utilization of such profiles affects outcomes is not known. In addition, patients may need to be reclassified depending on their clinical course. The European Society of Cardiology classification based on presenting profiles is shown in Figure 1.

Patients may also be divided based on the presence or absence of chronic HF. De novo HF, or HF for the first time patients, should be exhaustively assessed to determine both the precipitant, as well as any underlying functional/structural abnormalities. After stabilization, patients with worsening HF should be assessed to implement evidence-based chronic HF therapies. The EF will influence such management decisions, as the evidence-base for reduced EF patients is robust when compared to preserved EF.

Another scheme classifies patients based on the potential to restore cardiac function.[25] Patients may be broadly divided into two groups: (1) those with end-stage or advanced HF and (2) those in whom a restoration of cardiac function is possible.[26]

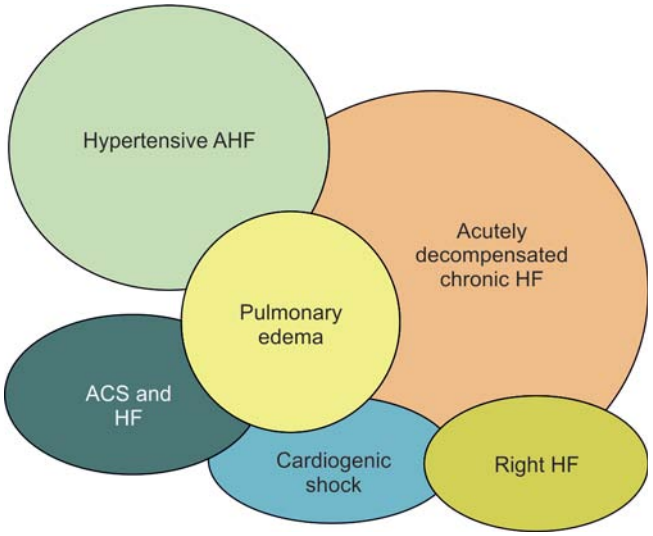


FIGURE 1: The European Society of Cardiology classification based on presenting profiles. (*Source:* Reproduced with permission from Filippatos G, Zannad F. An introduction to acute heart failure syndromes: definition and classification. Heart Fail Rev. 2007;12:87-90)

TABLE 2

Assessment of congestion

Body weight	Increase in BW predicts hospitalization[33,96] However, a reduction in BW in response to different therapies may not necessarily result in decreased hospitalization or mortality
Arrhythmias	Both bradyarrhythmias and tachyarrhythmias can contribute to congestion
Blood pressure	Either no change in BP or an increase in BP from supine to the upright position or valsalva manuever usually reflects a relatively high LV filling pressure[111]
Jugular venous pressure	Equals RA pressure. In a chronic state, the RA pressure correlates with PCWP/LVDP
Rales	Associated with increase in PCWP when present with other signs of elevated filling pressure (e.g. JVD, S3), but is non-specific by itself
Edema	Peripheral edema, only when associated with JVD, indicates right sided failure that is usually associated with left sided HF. During hospitalization, may move from dependent periphery to the sacral area
Orthopnea test	Patients often do not tolerate lying flat when there is a rapid increase in filling pressure. However, in a chronic state, this position may be tolerated in spite of a relatively high filling pressure
BNP/NT-proBNP	Marker of increased filling pressures
Chest X-ray	Pulmonary congestion (cephalization, interstitial edema, alveolar edema, pleural effusions) may be absent in spite of a very high PCWP, even in patients with severe, but chronic HF. However, when present, indicates a high PCWP

(Exercise testing to assess functional classification might aid in assessment of residual congestion) (Abbreviations: BW: Body weight; BP: Blood pressure; HF: Heart failure; PCWP: Pulmonary capillary wedge pressure; LVDP: Left ventricular diastolic pressure; BNP: B-type natriuretic peptide). (*Source:* Georghiade M, Pang PS. Acute heart failure syndromes. J Am Coll Cardiol. 2009;53:557-73, with permission)

End-stage or advanced HF patients may be defined as those with persistent, severe signs and symptoms despite maximal medical management. For the remainder of patients, identification and treatment of specific targets may result in both improved symptoms and prolonged life.

PATHOPHYSIOLOGY

Similar to the heterogeneity seen in the AHFS patient population, there is no single overarching pathophysiologic construct that encompasses all patients. Rather there are multiple overlapping pathophysiologic mechanisms, with some playing a greater role in certain patients than others. The model proposed by Gheorghiade et al. encompasses the essential pathophysiologic domains: (1) the substrate (the heart itself, including all functional and structural components); (2) initiating mechanisms (what begins the process of an AHFS episode) and (3) amplifying mechanisms (once AHFS has begun, the resulting neurohormonal and hemodynamic cascade with its subsequent downstream effects).[27]

CONGESTION

Pulmonary and systemic congestion resulting from high left ventricular (LV) diastolic filling pressures are a pathophysiologic feature common to nearly all AHFS patients[8,17,28-31] (Table 2). Congestion, or fluid overload, is the primary driver for hospitalization.[17,29] Hemodynamic congestion, resulting from an increase in left ventricular filling pressure (LVFP) commonly results in signs and symptoms of clinical congestion, namely JVD, peripheral edema and/or an increase in body weight (Table 3). Importantly, hemodynamic congestion may begin days, if not weeks, prior to overt signs of clinical congestion.[32,33] These high filling pressures lead to further activation of neurohormones, may cause subendocardial ischemia, as well as changes in LV geometry resulting in mitral insufficiency, all of which may contribute to worsening HF.[29,34-36]

TABLE 3

Hemodynamic versus clinical congestion

- *Hemodynamic congestion* refers to the state of volume overload resulting in increased left ventricular filling pressure
- *Clinical congestion* refers to the constellation of signs and symptoms that result from increased left ventricular filling pressure
- Clinical congesting can be thought to consist of cardiopulmonary congestion (respiratory distress, third heart sound, rales, interstitial/alveolar edema, chest X-ray findings) and systemic congestion (jugular venous distention, peripheral edema)
- Hemodynamic congestion precedes cardiopulmonary congestion by several days
  - In its preclinical state, hemodynamic congestion can exist without clinical manifestation
  - Intervention in preclinical hemodynamic congestion may prevent development of clinical congestion that generally requires hospitalization contributing to heart failure progression
- Resolution of clinical congestion can occur with persistent hemodynamic congestion.

(*Source:* Gheorghiade M, Filippatos G, De Luca L, et al. Congestion in acute heart failure syndromes: an essential target of evaluation and treatment. Am J Med. 2006;119:S3-10, with permission)

MYOCARDIAL INJURY

Troponin release, in the absence of clinical ACS, is a well documented phenomenon in HF and a negative prognostic marker.[11,37-39] While the exact pathophysiologic mechanisms are not fully known, troponin release likely occurs due to a supply/demand mismatch (increased myocardial oxygen demand and decreased coronary perfusion).[40] The abnormal neurohormonal and hemodynamic milieu seen in HF, as well as the potential untoward effects of therapeutic agents (e.g. inotropes) may precipitate injury. Patients with coronary artery disease (CAD) may particularly be at risk, as they often have hibernating and/or ischemic myocardium.[41] Myocardial injury in AHFS remains an area of investigation; likely new insights will emerge, given the continued development of high sensitivity troponin assays.[39]

RENAL IMPAIRMENT

Approximately 90% of AHFS patients have renal impairment at hospital admission, defined by eGFR < 90 ml/min/m.[42] Worsening renal function during hospitalization occurs in approximately 30% of patients.[43,44] Both baseline renal impairment and worsening renal function during hospitalization are associated with worse outcomes.[44-47]

The cardiorenal syndrome (CRS) has been defined as a "pathophysiologic disorder of the heart and kidneys whereby acute or chronic dysfunction of one organ may induce acute or chronic dysfunction of the other."[48] Hemodynamic abnormalities, such as low cardiac output, high venous pressure, neurohormonal disturbances, untoward drug effects (e.g. high dose loop diuretics or ACEI), may all contribute to renal impairment. In addition, patients have significant comorbid conditions, such as diabetes and hypertension, which play a role in renal impairment. The degree to which these changes, either separately or together impair renal function and are reversible versus permanent injury is an area of ongoing research.

VASCULAR FAILURE

Fluid overload is the clinical hallmark of AHFS. However, it has been suggested that total volume increase may not be the predominant pathophysiologic result for all patients; rather fluid redistribution may be a significant driver of pulmonary congestion.[49,50] Mechanisms, such as vascular stiffness and increased arterial resistance leading to increased preload and afterload, combined with abnormalities of the ventricular substrate, namely stiffness leading to decrease compliance, have been proposed as contributors to fluid redistribution.[49,51] Vasoconstriction due to activation or further activation of the renin-angiotensin-aldosterone system (RAAS) as well as inflammation have also been put forth as contributors to fluid redistribution.[49] A classic clinical example is the case of "flash" pulmonary edema.

CARDIAC METABOLISM

The improper availability, metabolism and/or utilization of substrates to fuel the energy needs of the heart has been proposed as another pathophysiologic contributor to HF.[52,53] As the heart pumps over 7,000 L of blood a day, utilizing over 6 kg of ATP, the metabolic needs of the heart are substantial.[54] Agents, such as inotropes that stimulate the heart but do not address or supply the metabolic needs of such increased activity, are an example of a mismatch in cardiac energetics. Whether supplemental nutrition to augment or replenish the fuel needs of the heart, in addition to the other benefits of nutritional supplementation, improves outcomes in AHFS is an area of ongoing research. Results in chronic HF are promising.[55,56]

UNTOWARD DRUG EFFECTS

Unlike chronic HF, there are no class-I, level-A therapeutic guideline recommendations for AHFS. Treatment remains largely empiric. Although traditional therapies improve signs and symptoms, they have also been associated with undesirable effects.

Non-potassium sparing IV loop diuretics are the most commonly used therapy to relieve congestive signs and symptoms, yet diuretics have been associated with electrolyte abnormalities, further activation of neurohormones and worsening renal function.[57,58] High-dose diuretic therapy has been associated with worse outcomes; whether this reflects a sicker patient population or a true dose-related effect of diuretics remains to be determined.[58-60] The recently published diuretics optimization strategies evaluation (DOSE) trial examined the risks and benefits of high versus low dose, bolus versus continuous infusion of IV diuretics in patients admitted with AHFS, with a co-primary endpoint of global assessment of symptoms and change in creatinine from baseline to 72 hours.[61] High dose was defined as 2.5 times the patient's total oral dose, while low dose was defined as equivalent to the patient's oral dose. No differences were seen in terms of the co-primary endpoint between high and low dose, or between bolus and continuous infusion. There was a trend towards greater symptomatic improvement in the high dose arm as well as greater volume loss. A significant transient worsening of renal function was also seen; however, no differences were seen between groups in terms of outcomes at 60 days.[61]

Commonly used inotropes, such as dobutamine and milrinone (and levosimendan in Europe), improve hemodynamics, but have been associated with worse outcomes.[46,62,63] The mechanisms of action of these inotropes have been suggested as one reason to explain their potential deleterious effects; they increase myocardial oxygen consumption in the face of inadequate reserves. In addition, these inotropes have also been commonly called inodilators; these vasodilatory effects may impair coronary and renal perfusion, initiating or amplifying injury or dysfunction.[40]

VIABILITY

Viable but dysfunctional myocardium is most commonly associated with chronic ischemia (i.e. hibernation), yet patients without CAD have also been shown to exhibit viable but dysfunctional myocardium. Excessive sympathetic stimulation (as seen in Takotsubo cardiomyopathy) or micronutrient deficiencies are two other potential mechanisms contributing to viable but dysfunctional tissue in HF patients.[54,64,65] The hemodynamic and neurohormonal stress of AHFS may further jeopardize this viable tissue.

The presence or absence of viable myocardium may serve to identify those patients in whom improved cardiac function is possible, through restoration of function to currently dysfunctional areas, as opposed to those patients in whom function cannot be restored due to the predominant presence of scar tissue. Work by Seghetol et al. and Bello et al. have demonstrated restoration of function with beta-blocker therapy in HF patients.[66,67] The role of viable but dysfunctional myocardium as a pathophysiologic target in AHFS is an area undergoing further research.

ACUTE HEART FAILURE SYNDROMES MANAGEMENT

For the vast majority of patients, hospital management begins in the emergency department (ED). As patients progress through their hospital stay, on an average around 6 days

TABLE 4

Phases of AHFS management

Phases	*Goals*	*Available tools*
Initial or emergency department phase of management	Treat life-threatening conditions	e.g. STEMI -> reperfusion therapy
	Establish the diagnosis	History, physical exam, EKG, X-ray, natriuretic peptide level
	Determine the clinical profile	BP, HR, signs (e.g. pulmonary edema), ECG, X-ray, laboratory analysis, echocardiography
	Identify and treat precipitant	History, physical exam, X-ray, ECG, laboratory analysis
	Disposition	No universally accepted risk-stratification method
In-hospital phase	Monitoring and reassessment	Signs/symptoms, HR, SBP, ECG, orthostatic changes, body weight, laboratory analysis (BUN/Cr, electrolytes), potentially BNP
	Assess right and left ventricular pressures	SBP (orthostatic changes, valsalva maneuver), echocardiography, BNP/NT-proBNP, PA catheter
	Assess and treat (in the right patient) other cardiac and non-cardiac conditions	Echo-Doppler, cardiac catheterization, electrophysiology testing
	Assess for myocardial viability	MRI, stress testing, EKG, radionuclear studies
Discharge phase	Assess functional capacity	6-minute walk test
	Re-evaluate exacerbating factors (e.g. non-adherence, infection, anemia, arrhythmias, hypertension) and treat accordingly	Examples: physical therapy, education for diet control and medication, evaluation for sleep apnea
	Optimize pharmacologic therapy	ACCF/AHA and ESC guidelines
	Establish post-discharge planning	Discharge instructions including body weight monitoring, smoking cessation, medication adherence, follow-up

(*Source:* Khan SS, Gheorghiade M, Dunn JD, et al. Managed care interventions for improving outcomes in acute heart failure syndromes. Am J Manag Care. 2008;14:S273-86; quiz S287-91, with permission)

(median = 4 days),[17,68] management goals also change. The AHFS care can broadly be divided into three main phases:

1. Stabilization
2. Evidence-based management
3. Reconstruction

The three phases of management (Table 4) addresses each of the pathophysiologic components previously mentioned:

1. The substrate
2. Initiating mechanisms
3. Amplifying mechanisms.[27]

STABILIZATION PHASE

Identification and prompt management of immediately life-threatening conditions is paramount. Definitive airway management, assessment and support of breathing, and circulatory support as needed (the A, B, C's) remain essential principles of initial assessment and resuscitation. Other life-threatening conditions, such as STEMI, papillary muscle rupture, malignant arrhythmias and hypertensive emergencies, should be promptly identified and treated. In patients who present in extremis, diagnosis and treatment occur in parallel.[25] A proposed algorithm for treatment is presented in Flow charts 1 to 4.

Diagnosis

Contrary to popular belief, patients most commonly present with signs and symptoms as opposed to an HF diagnosis. As AHFS is a clinical diagnosis, a careful history and physical exam, especially assessment volume status (e.g. jugular venous distention, edema, rales), are needed. Chest X-ray is a helpful adjunct; however, the absence of overt signs of volume overload radiographically does not rule out AHFS.[69] A completely normal electrocardiogram would be extremely unusual. Natriuretic peptides should be ordered when the diagnosis is in question. However, studies suggest that natriuretic peptide use leads to a more rapid diagnosis, earlier treatment, and more effective resource utilization.[61,70-73]

Treatment According to Clinical Profile

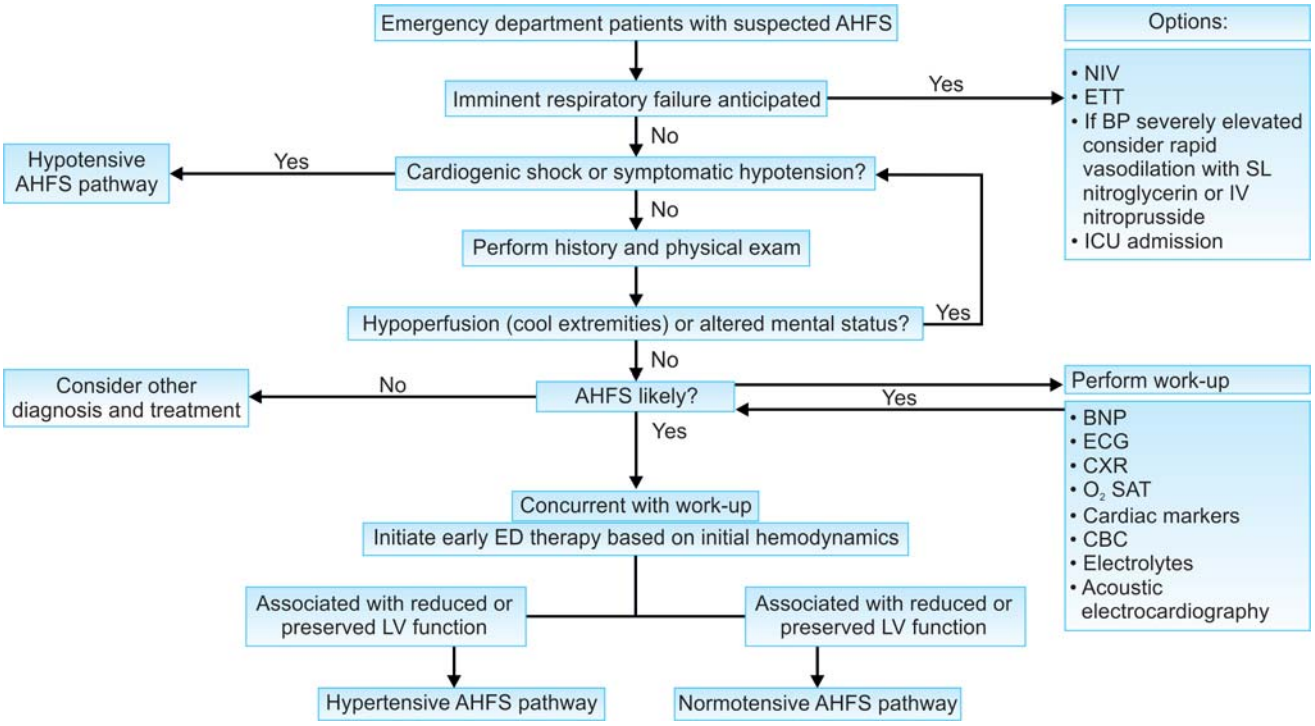
Patients' initial management should be guided by their predominant clinical profile (Fig. 1). For example, vasodilators should promptly be considered for those who present with a hypertensive profile. The goals are to improve hemodynamic and volume status, leading to symptom improvement. However prudent attention to vital signs are warranted; while hypotensive episodes, for example, may have little immediate impact; if short-lived, they may have a significant downstream effect. Improving signs and symptoms should not cause harm through a decrease in coronary or renal perfusion, tachycardia, or further neurohormonal activation.[25]

We refer readers to the chapters on cardiovascular pharmacology for in-depth discussion of therapies.

Precipitants for Admission

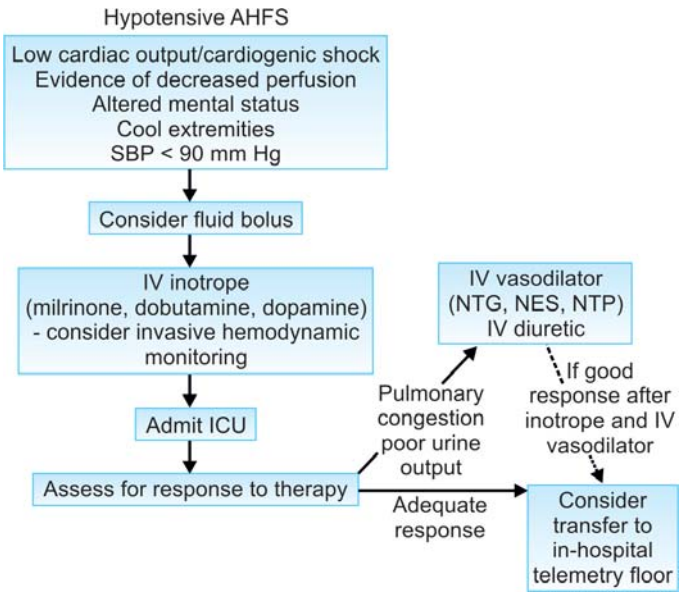
Identification and treatment of the precipitant for decompensation is essential (Table 5). In patients presenting with *de novo* HF, a significant number are diagnosed with ACS.[74]

FLOW CHART 1: Suggested initial triage in patients with suspected heart failure syndromes



(Abbreviations: AHFS: Acute heart failure syndrome; NIV: Noninvasive ventilation; ETT: Endotracheal intubation; BP: Blood pressure; SL: Sublingual; BNP: B-type natriuretic peptide; CXR: Chest X-ray; O_2 SAT: Oxygen saturation; LV: Left ventricular). (*Source:* Reproduced with permission from Collins S, Storrow AB, Kirk JD, et al. Beyond pulmonary edema: diagnostic, risk stratification, and treatment challenges of acute heart failure management in the emergency department. Ann Emerg Med. 2008;51:45-57)

FLOW CHART 2: Suggested treatment algorithm for patients with hypotensive acute heart failure syndromes



(Abbreviations: NTG: Nitroglycerin; NES: Nesiritide; NTP: Nitroprusside). (*Source:* Reproduced with permission from Collins S, Storrow AB, Kirk JD, et al. Beyond pulmonary edema: diagnostic, risk stratification, and treatment challenges of acute heart failure management in the emergency department. Ann Emerg Med. 2008;51:45-57)

Disposition

Patients at higher risk for morbid events or with high-risk clinical or laboratory features have been relatively well defined[75] (Table 6). While the unstable patient warrants intensive care admission, clear guidelines for ICU versus step-down or intermediate care versus general ward have not been well established.

Importantly, absence of high-risk features does not equal low-risk. Lee et al. conducted a population-based analysis comparing outcomes in admitted versus discharged ER patients with overlapping predicted probabilities of death and found that outcomes were worse for discharged patients (Fig. 2). At the present time, discharge decisions should be made based on the entire clinical picture, taking into account health literacy, socioeconomic status, and follow-up and transition of care to the patients' primary outpatient physicians.

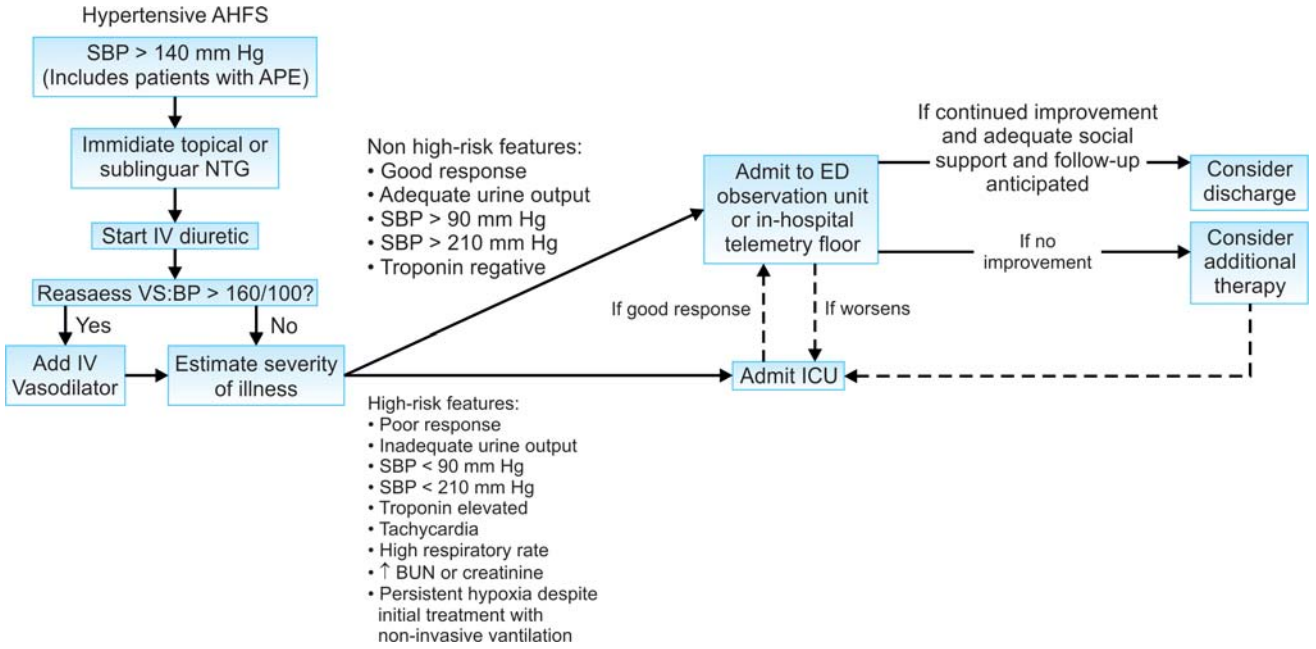
Goals of Stabilization Phase

After addressing any immediate life-threats, improving symptoms, hemodynamic and volume status, along with identification and treatment of precipitants of decompensation are the initial stabilization phase goals.

TRANSITION TO EVIDENCE-BASED PHASE

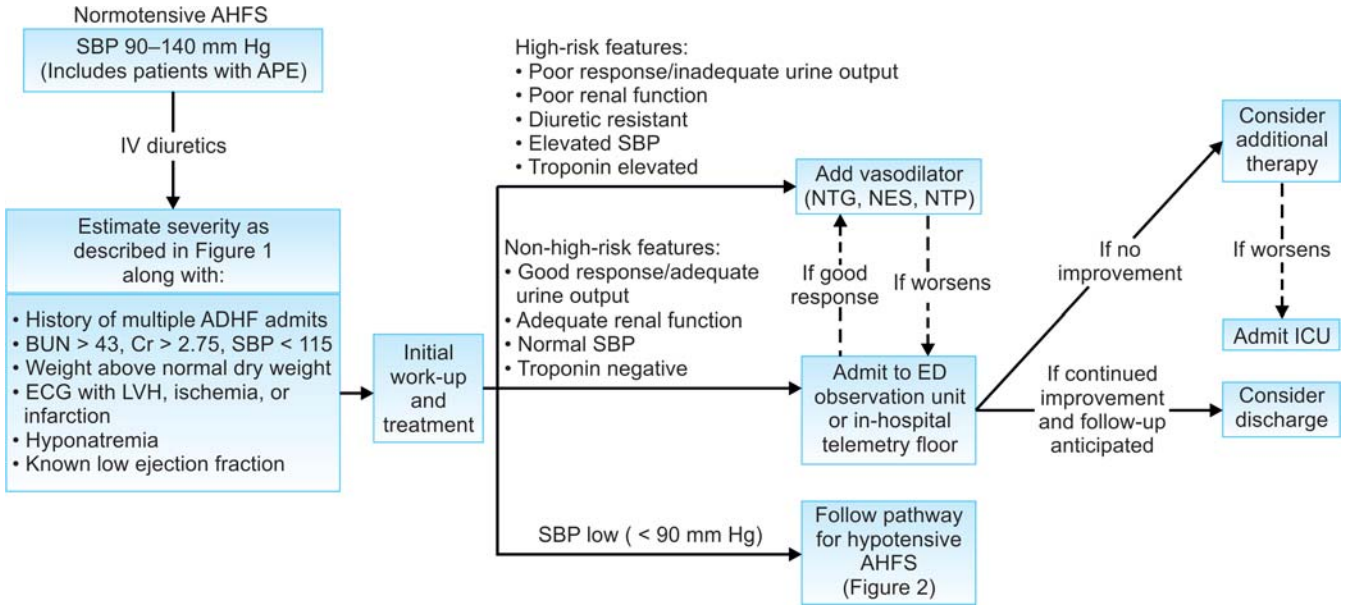
Chronic HF patients account for the vast majority of patients hospitalized with worsening HF. Once stabilized, they transition

FLOW CHART 3: Hypertensive AHFS Algorithm



(Abbreviations: SBP: Systolic blood pressure; NTG: Nitroglycerin; IV: Intravenous; VS: Vital signs; BP: Blood pressure; ED: Emergency department; ICU: Intensive care unit). (*Source:* Reproduced with permission from Collins S, Storrow AB, Kirk JD, et al. Beyond pulmonary edema: diagnostic, risk stratification, and treatment challenges of acute heart failure management in the emergency department. Ann Emerg Med. 2008;51:45-57)

FLOW CHART 4: Normotensive AHFS Algorithm



(Abbreviations: SBP: Systolic blood pressure; APE: Acute pulmonary edema; ADHF: Acute decompensated heart failure; LVH: Left ventricular hypertrophy; NTG: Nitroglycerin; NES: Nesiritide, NTP: Nitroprusside; ED: Emergency department; AHFS: Acute heart failure syndromes; ICU: Intensive care unit). (*Source:* Reproduced with permission from Collins S, Storrow AB, Kirk JD, et al. Beyond pulmonary edema: diagnostic, risk stratification, and treatment challenges of acute heart failure management in the emergency department. Ann Emerg Med. 2008;51:45-57)

back to chronic HF management, where evidence-based management is robust.[10,76-86] However, translational gaps between evidence and daily practice have been noted, with variations seen by age, race, geographic region and comorbid conditions.[8,76,86-90] Hospitalization provides an opportunity to initiate or potentially up-titrate therapies in appropriate patients according to guidelines.

When compared to guidelines for reduced EF patients, the evidence is limited for those patients with HFPEF. For HFPEF, management of comorbid conditions is strongly recommended.[91]

TABLE 5

Precipitating factors for HF hospitalization and their association with in-hospital mortality

Factor	No. of patient	Adjusted length of stay ratio	p value	In hospital mortality	
				Adjusted odds ratio (95% confidence interval)	p value
Ischemia/acute coronary syndrome	7155	0.99	.22	1.20 (1.03-1.40)	.02
Arrhythmia	6552	1.04	<.001	0.85 (0.71-1.01)	.07
Nonadherence to diet	2504	0.96	.01	0.69 (0.48-1.00)	.05
Uncontrolled hypertension	5220	.096	<.001	0.74 (0.55-0.99)	.04
Nonadherence to medications	4309	0.96	<.001	0.88 (0.67-1.17)	.39
Pneumonia/respiratory process	7426	1.08	<.001	1.60 (1.38-1.85)	<.001
Worsening renal function	3304	1.09	<.001	1.48 (1.23-1.79)	<.001
Other	6171	0.99	.23	1.15 (0.97-1.36)	.10

(*Source:* Fonarow GC, Abraham WT, Albert NM, et al. Factors identified as precipitating hospital admissions for heart failure and clinical outcomes: findings from OPTIMIZE-HF. Arch Intern Med. 2008;168:847-54, with permission)

TABLE 6

Prognostic indicators as potential targets of therapy in AHFS*

Systolic blood pressure	Admission and early post-discharge SBP inversely correlates with post-discharge mortality. The higher the BP, the lower both in-hospital and post-discharge mortality. However, the readmission rate of ~30% is independent of the SBP at time of admission[4]
Coronary artery disease	Extent and severity of CAD appears to be a predictor of poor prognosis[41]
Troponin release	Results in threefold increase in in-hospital mortality, twofold increase in post-discharge mortality and a threefold increase in the re-hospitalization rate[11,112,113]
Ventricular dyssynchrony	Increase in QRS duration occurs in ~40% of patients with reduced systolic function and is a strong predictor of early and late post-discharge mortality and re-hospitalization[114]
Renal impairment	Associated with a 2–3-fold increase in post-discharge mortality. Worsening renal function during hospitalization or soon after discharge is also associated with an increase in in-hospital and post-discharge mortality[44,47,59] (REF LBCT)
Hyponatremia	Defined as serum sodium < 135 mmol/L, occurs in ~25% of patients, and is associated with a 2–3-fold increase in post-discharge mortality[115]
Clinical congestion at the time of discharge	An important predictor of post-discharge mortality and morbidity[29,31]
Ejection fraction	Considered adverse prognostic marker. Similar post-discharge event rates and mortality between reduced and preserved EF[19]
BNP/NT-proBNP	Elevated natriuretic peptides associated with increased resource utilization and mortality[72]
Functional capacity at the time of discharge	Pre-discharge functional capacity, defined by the 6-minute walk test, is emerging as an important predictor of post-discharge outcomes[93,116]

(*Source:* Gheorghiade et al. Circulation. 2005, with permission)
*This is not an all-inclusive list

We refer readers to other chapters in this text regarding chronic HF management.

Goals of Transitional Phase

During hospitalization, attempts to resolve or either return to baseline status prior to hospitalization is an important goal. Optimization of hemodynamic status and return to euvolemia should ideally be achieved prior to discharge. A strategy of earlier discharge with mild signs and symptoms and close follow-up may also be considered; however, further research is needed. Unless clearly contraindicated and/or the cause for decompensation, outpatient chronic HF medications (such as beta-blockers) should be continued.[92] Initiation or assessment for implementation of guideline-based therapies should occur during the hospital setting. Use of biomarker guided strategies to facilitate management decisions appear promising, however further studies in the hospital setting are needed prior to universal recommendations. Finally, a clear post-discharge plan with reconciliation of all medications, comprehensive understanding from the patient's perspective and a resilient transition of care plan is needed prior to discharge.

As discussed, hemodynamic congestion may precede signs and symptoms of clinical congestion. In the same fashion, clinical improvement does not necessarily equal normalization of hemodynamic derangements. Careful measurement of JVP is a key physical exam measurement to aid in hemodynamic assessment. Although routine pulmonary artery (PA) line use is

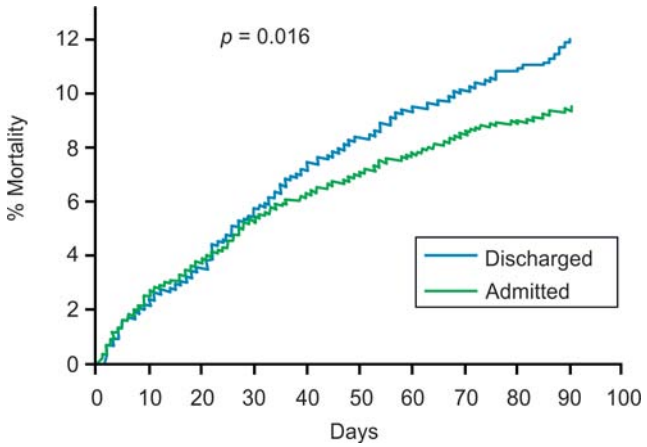


FIGURE 2: Time to death for patients discharged from the ED or admitted to the hospital with comparable predicted risks of 30 days death. Discharged patients had significantly higher rates of death (log-rank p = 0.016). (*Source:* Reproduced with permission from Lee DS, Schull MJ, Alter DA, et al. Early deaths in heart failure patients discharged from the emergency department: a population-based analysis. Circ Heart Fail. 2010)

no longer recommended, for patients who continue to worsen or fail to improve, tailored therapy guided by invasive hemodynamic monitoring may be necessary.[93]

Quality Measures

Publically reported quality measures are critical metrics for hospitals. Current HF quality measures, however, namely ACEI/ARB, anticoagulant at discharge for HF patients with AF, assessment of ejection fraction, smoking cessation and adequate discharge instructions, are not associated with improved outcomes, with the exception of initiation of ACEI/ARB.[87,94,95] As quality measures are updated or revised, ongoing debate over these process measures and whether or not to enact outcome measures continues. At the present time, it is doubtful current quality measures alone will significantly impact post-discharge outcomes, given the complex pathophysiology and heterogeneity of this patient population.

RECONSTRUCTION PHASE

The concept of cardiac reconstruction is controversial as the traditional view of HF, strongly supported by epidemiologic data, is that HF is both progressive and irreversible. Yet the vast majority of patients do not have end-stage HF, improvement or restoration of cardiac function has been observed in a sizable number of patients and, most importantly, many patients have potential targets that, if treated per guidelines, may improve cardiac performance.[25] Optimization of evidence-based therapies along with targeted interventions at other cardiac and non-cardiac conditions according to guidelines (i.e. pharmacologic, electrical, surgical) may improve the substrate sufficiently to "reconstruct" the heart, as well as mitigate morbidity from other causes. This hypothesis, however, remains to be tested.

Vulnerable Phase

The early post-discharge period may also be called a vulnerable phase, as patients demonstrate continued changes in signs and symptoms, worsening neurohormonal profile, and changes in renal function, despite evidence-based therapy.[25,96] As optimization of guideline therapies and/or implementation of other therapies that require optimal medical management (e.g. cardiac resynchronization therapy) may be difficult to achieve during a short hospital stay, comprehensive assessment and implementation of known life-saving therapies during the early post-discharge period may improve outcomes (Fig. 3). However, whom to treat (everyone or just high risk?), when to treat (one week post-discharge, repeat visits?) who should treat (PCP, cardiologist, both?) and how to implement such a thorough post-discharge assessment and implementation protocol remains to be determined.[26]

CLINICAL TRIALS IN ACUTE HEART FAILURE SYNDROMES

Attempts to improve symptoms and/or outcomes with novel therapies have largely failed.[62,63,97-103] Only one new AHFS has been approved in the last decade, nesiritide, whose primary benefit was improved dyspnea at 3 hours when compared to regular therapy excluding nitroglycerin.[102] Retrospective analyses regarding the safety of nesiritide led to the acute study of clinical effectiveness of nesiritide in decompensated heart failure (ASCEND-HF) trial, the largest AHFS clinical trial conducted to date. Although the safety of nesiritide was well established, the efficacy co-primary endpoint—death or HF rehospitalization through 30 days; or dyspnea score at 6 and 24 hours—was not achieved.[104,105] A more modest dyspnea improvement was seen as compared to vasodilation in acute congestive heart failure (VMAC), approximately 2% improvement over standard therapy, which was statistically significant but did not achieve the prespecified alpha level of 0.025.

Only one trial achieved its primary endpoint; the efficacy of vasopressin antagonism in heart failure study with tolvaptan (EVEREST) clinical status trials, which were comprised of two identical short-term trials.[97] The composite primary endpoint of global clinical status and body weight was reached; however, this was driven entirely by the body weight component. A key secondary endpoint, dyspnea reduction at day one was also seen in both trials, however, the absolute clinical benefit was modest; approximately 6–7% compared to standard therapy. Although no long-term benefit was seen, there was also no evidence of long-term harm.[106]

Given the current and growing burden of AHFS, there remains an unmet need for novel therapies. While multiple and intriguing new molecules are currently in development, we briefly discuss several new development strategies.

Novel use of existing therapies, such as aldosterone blocking agents and digoxin, has not been rigorously tested in the AHFS setting. At higher doses, aldosterone blocking agents demonstrate more potent diuretic properties that in addition to their neurohormonal benefits might be of benefit in selected patients. Early use of digoxin continued after discharge is also an intriguing hypothesis.[107]

The concept of continuing medication after discharge can be applied to other therapies. Whether short-term therapies (2–3 days during hospitalization) will significantly alter long-term outcomes remains to be seen, however, use of post-

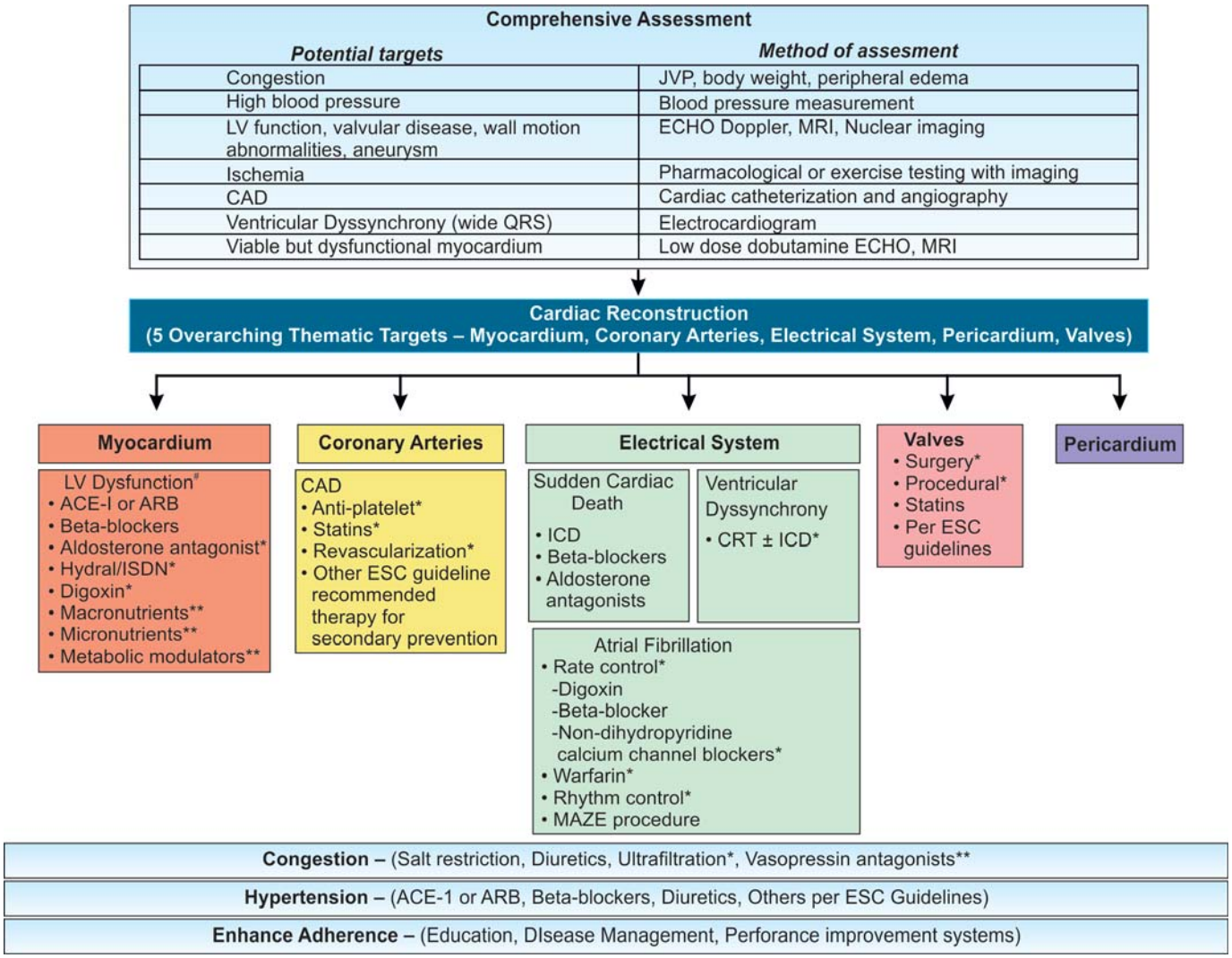


FIGURE 3: Comprehensive assessment and cardiac reconstruction. (Abbreviations: AHFS: Acute heart failure syndromes; JVP: Jugular venous pulse; LV: Left ventricle; CAD: Coronary artery disease; ACE-I: Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor blocker; ICD: Implantable cardiac defibrillator; CRT: Chronic resynchronization therapy; Hydral: Hydralazine; ISDN: Isosorbide dinitrate; CABG: Coronary artery bypass grafting; AF: Atrial fibrillation)
*Select patients
**Investigational agents
#Viable but dysfunctional myocardium
(*Source:* Modified and reproduced with permission from Gheorghiade M, Pang PS. Acute heart failure syndromes. J Am Coll Cardiol. 2009;53: 557-73

discharge infusions may provide a mechanism to continue therapies that might sufficiently alter underlying the underlying pathophysiology.

In general, past trials have had relatively broad inclusion criteria and have enrolled patients relatively late after presentation. Rather than targeting AHFS, focusing on specific subgroups, such as those with AHFS and low-blood pressure, may be a more effective way to demonstrate efficacy signals. It is possible that effective drugs for certain subgroups may not be as effective in others; when these groups are combined, both the efficacy and safety signals may be attenuated.

T1 TRANSLATIONAL PHASE

The difficulty of translating basic science discoveries into clinical practice has been well recognized.[108,109] We have adopted this terminology specifically to HF clinical development, as a more focused and rigorous approach during earlier stages of development may better identify promising novel therapies. In addition, this approach would allow for discontinuation of programs that have little chance of success[110] (Table 7).

CONCLUSION

Acute heart failure syndromes represent a significant public health burden with its high morbidity, mortality and cost. Improving outcomes is the single most important goal and challenge today. The fact that most patients improve symptomatically during hospitalization, yet continue to have a high rate of post-discharge events suggests that treatment of the outward manifestations of a failing heart is insufficient. Identification and treatment of appropriate targets are necessary if we are to improve outcomes.

TABLE 7

The translational phase 1 of development

T1 Concept
• A more thorough understanding of all a molecule's effects on the heart (effects on viable but non-contractile myocardium, coronary profusion, diastolic function, etc.) is important • Reproduce the results obtained in large animal HF models in homogeneous group of patients taking into account systolic and diastolic dysfunction, extent and severity of CAD, viable but dysfunctional myocardium, etc. • These in depth evaluations should take advantage of recent progress made in noninvasive methods of assessment of cardiac function and structure (echocardiography, MRI spectroscopy, etc.) • These studies would also expand our understanding of the pharmacokinetic and pharmacodynamic properties of novel molecules as, unlike animal models to date, patients with HF are commonly on background therapy for HF and have substantial comorbid conditions that might influence safety, efficacy and outcomes • These studies should be conducted in dedicated centers that have the patient population, technology and the expertise to conduct such technically challenging studies

(*Source:* Gheorghiade M, Pang PS, O'Connor CM, et al. Clinical development of pharmacologic agents for acute heart failure syndromes: a proposal for a mechanistic translational phase. Am Heart J. 2011;161:224-32, with permission)

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Chapter 76

Cardiopulmonary Exercise Testing and Training in Heart Failure

Ileana L Piña

Chapter Outline

- Normal Response to Exercise
- Exercise Response in Heart Failure
  - Central Factors
  - Peripheral Factors
- Cardiopulmonary Exercise Testing
  - Technical Aspects
  - Exercise Measurements by CPX
  - Conducting the Exercise Test
- Indications for CPX Testing in Heart Failure
  - Peak VO_2 and Prognosis
  - Evaluation of Dyspnea; Presence of Ventilatory Limitations
  - Extent of Deconditioning and Deriving an Exercise Prescription
- Exercise Training in Heart Failure
  - Deleterious Effects of Bed Rest
  - History of Exercise Training in Heart Failure
  - Benefits of Exercise Training in Heart Failure
  - Safety
  - Mortality and Morbidity
  - Guideline Recommendation
  - Exercise Prescription Recommendation

INTRODUCTION

Heart failure (HF) is characterized by symptoms of dyspnea on exertion leading eventually to dyspnea at rest. Patients also often complain of fatigue with activity. Therefore exercise intolerance is tightly linked to the diagnosis of HF. One would expect that resting ventricular function would be predictive of functional capacity. But in fact, there is no relation between resting ejection fraction and exercise duration or between ejection fraction and functional capacity, as expressed by oxygen uptake (VO_2).[1,2] Therefore the limitations to performing exercise must be more complex and involve more than the central circulation. In addition, recommending bed rest for patients with HF has no support in the literature rather the guidelines have specific recommendations on activity for patients with HF.[3]

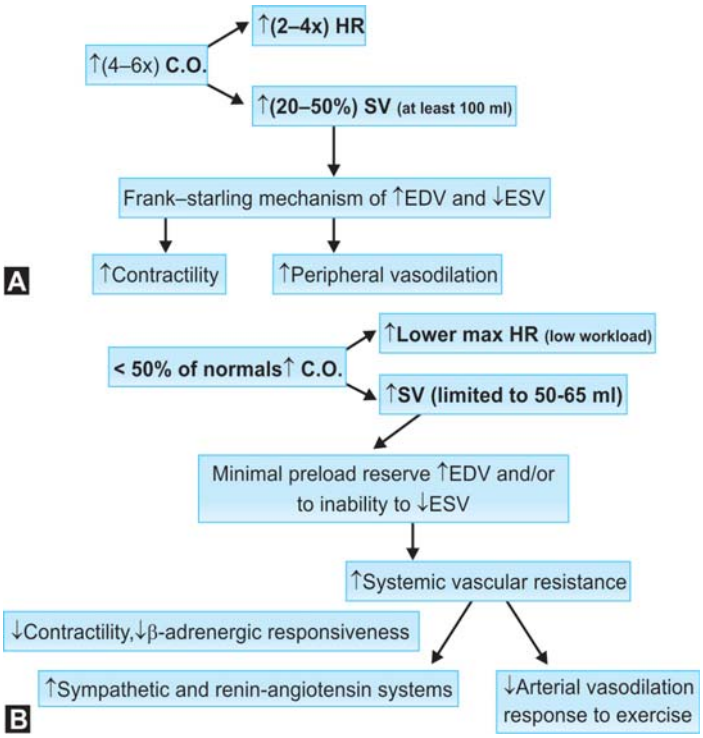
Decreased maximal exercise capacity is associated with decreased patient survival.[4-6] Therefore exercise capacity (functional capacity) in patients with HF has prognostic value, and objective testing becomes an important tool to assess patients for mortality risk. This chapter reviews the normal physiology of exercise pathologic responses to activity in patients with HF, presents the methodology used for testing and discuss the rationale for exercise training as a therapy. The terms "functional capacity" and "exercise capacity" have been used interchangeably.

NORMAL RESPONSE TO EXERCISE

Oxygen uptake is the product of the central cardiovascular system and the peripheral expressed as cardiac output x the arterio-venous difference (Flow charts 1A and B). This equation is derived from the Fick principle. Maximal oxygen uptake (VO_{2max}) is defined as the maximal amount of oxygen that the organism can "uptake" and even if workload is increased, no further increases in oxygen uptake are noted. Thus the ability to increase one's VO_2 is related to the ability of the heart to increase its cardiac output in response to the demand of muscles and the ability of muscles to extract more oxygen from the oxygenated blood. In the normal adult cardiac output can increase by 400–500% of baseline by a 2–4-fold rise in heart rate and a more modest but significant increase in stroke volume of 20–50%.[7] The Frank-Starling mechanism is responsible for the increase in end-diastolic volume and coupled with increased inotropism and a lower end-systolic volume, the stroke volume increases (Flow chart 1). Most of the blood flow during exercise is directed toward the active muscles facilitated by peripheral dilatation coupled to an increase in cardiac output. A combination of sympathetic increase in vascular tone maintains hemodynamics at high workloads which maintains blood pressure.[7,8]

The term "peak VO_2" is often used rather than "maximal VO_2" to define the last VO_2 recorded at the highest workload of exercise, leaving the definition of "maximal" to obtaining a plateau effect at high levels of work. The cardiovascular response to exercise is dependent on age, gender, level of fitness and genetic factors. The type of exercise and posture that is performed, and the number of skeletal muscles involved also affect the VO_2.[9] Therefore, exercise that involves bicycle testing will generally produce a 10-15% lower VO_2 than treadmill

FLOW CHARTS 1A AND B: Maximal oxygen uptake (VO_{2max}) = C.O. (HR × SV) × Δ(A-V)O_2. Mechanisms to augment cardiac output (C.O.) in (A) healthy persons without HF and (B) patients with HF. VO_{2max}=C.O. (HR × SV) × ▲A-V O_2. C.O. indicates cardiac output



(Abbreviations: HR: Heart rate; SV: Stroke volume; ▲A-VO_2: Arteriovenous oxygen difference; EDV: End-diastolic volume; ESV: End-systolic volume). (*Source*: See text from: Piña. Circulation. 2003;107:1210-1225)

testing where more muscles are involved in the movement. Exercise performance, specifically VO_2, decreases with increasing age. These relationships hold true in HF patients as well. Fit individuals have higher peak VO_2's related to multiple factors including enhanced oxygen extraction and higher stroke volumes.[10-12] There are several formulae that predict the VO_{2max} by age, gender and weight. Often, the VO_2 is presented as a percent of predicted maximal based on one or more of these formulae. Figure 1 illustrates the VO_2 curve as it increases with increased workload, plateaus at maximal exercise and drops in recovery. The area under the exercise curve is the oxygen consumed and that of the area under the recovery portion is the oxygen debt. Baseline VO_2 is the value at rest and often referred to as 1 MET or "metabolic equivalent". Generally, this value is approximately 3.5 ml/kg/min.

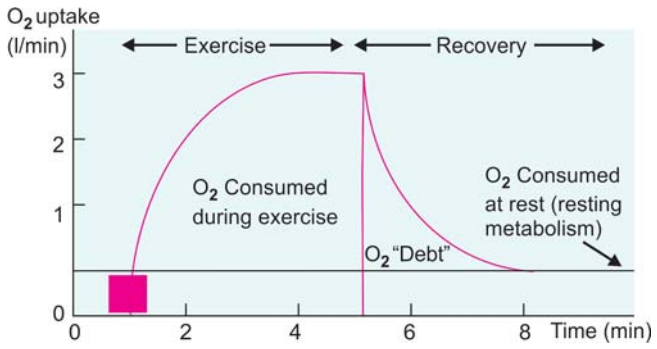


FIGURE 1: Oxygen uptake during exercise and recovery

EXERCISE RESPONSE IN HEART FAILURE

In contrast to normals described above, exercise capacity is reduced even in mild HF. The cardiac output may appear to be relatively normal at rest, but cannot increase adequately with even mild exertion.[9] The abnormal exercise response has many etiologies.[13-16] Some may predominate in certain patients, such as chronotropic incompetence but in general, the source of exercise intolerance is multifactorial.

CENTRAL FACTORS

- The heart rate and inotropic responses to circulating catecholamines are impaired, partly due to down-regulation of beta receptors due to the chronically increased circulating catecholamines that characterized chronic HF.[17-19]
- HF patients may already be within their end-diastolic volume reserve coupled to poor contractility, and be unable to further increase stroke volume via the Starling mechanism.[20] Pericardial constraint may also play a role.[21,22]
- In contrast to normals, exercise is associated with an elevation in the pulmonary wedge pressure. This can exacerbate pulmonary congestion, thereby causing dyspnea and limiting exercise capacity. The high left-sided pressure is accompanied by equalization with right atrial pressure, probably due to pericardial constraint in addition to increased blood return to the right side of the heart.[23-26]
- As ventricular dilatation worsens, mitral regurgitation may occur due to stretching of the mitral annulus and contribute to the poor forward cardiac output.[19] Vasodilators may

TABLE 1

Skeletal muscle changes in heart failure

Changes in structure	*Changes in metabolism*
Loss of Type I (slow twitch) fibers (endurance fibers)	Reduced glycogen content
Increase in Type II (fast twitch) fibers (easily fatigued)	Decreased citrate synthase (mitochondrial oxidative enzyme)
Decreased fiber size (cross-sectional area)	Increase in reactive oxygen species
Decreased capillary density	Decreased pH
Decreased mitochondrial size and number	Ergoreflex over-activity
Apoptosis	

improve peak forward cardiac output by decreasing the regurgitant jet.[27,28]

PERIPHERAL FACTORS

- Blood flow is impaired in HF due to vasoconstriction due to the neurohormonal responses (angiotensin II, endothelin) coupled with impaired cardiac output and abnormal vasodilatation due to abnormal release of vasoactive substances.[29-32] Nitric oxide secretion is also impaired as is the vasodilatory response to it.[33,34] Some studies, however, have shown that over 20% of patients with HF have normal blood flow.[35]
- Patients with HF have a lower percent of Type I oxidative skeletal muscle fibers and an increase in the more glycolytic Type IIb when compared to normal subjects. This fiber "switch" can account for peripheral muscle fatigue.[7,8,14,36] Intramuscular acidosis is due to early and increased anaerobic metabolism with exercise leading to increased lactic acid levels. Table 1 lists the skeletal muscle changes in HF.
- In general, capillary density is also lower in patients with HF when compared to normal healthy subjects.[37,38] Oxidative enzymes, such as citrate synthase, succinate dehydrogenase and others, are also decreased in patients with HF.[39-41]

CARDIOPULMONARY EXERCISE TESTING

Exercise capacity is an important prognostic indicator in patients with HF and is frequently used to gauge the severity of the patient's symptoms.[6,42] Measuring the maximal oxygen uptake in HF patients has become a common clinical practice. It provides an objective measure of the HF patient's functional status and helps in monitoring the response to treatment as well as making decisions in terms of various interventions, including referral for heart transplantation. Since improving exercise capacity has become an important clinical goal, the factors limiting VO_{2max} in HF patients have been extensively studied as noted above.

Exercise testing has been a modality used by clinicians for decades to assess both diagnosis and prognosis of patients with cardiovascular disease. Exercise testing can be administered using various modalities, e.g. treadmill or bicycle, adjusted to patient level of ability and modified with the use of imaging to improve accuracy. When oxygen uptake measurements are added, exercise testing can add much information to the ordinary exercise test. Cardiopulmonary exercise (CPX) testing with metabolic parameters has been used in fitness testing of athletes to determine true maximum function and to study exercise physiology. CPX testing is often misunderstood. While involving more equipment and expertise, CPX testing is the most accurate exercise test to determine true functional capacity and in the case of HF patients, to predict prognosis. With the advent of modern testing systems that integrate breath by breath technology, computerized systems and patient-friendly mouthpiece and tubing, CPX testing has become accessible for broader use.

Understanding the link between the pulmonary system and the cardiovascular system is necessary to fully comprehend the mechanism of cardiopulmonary testing (Fig. 2).[43] Physical exercise capability requires that the pulmonary system provide sufficient O_2 to exercising muscle and clears the carbon dioxide (CO_2) via the lungs by ventilation moving air in and out. The minute ventilation (VE) represents the increase in air movement with exercise. Diffusion and exchange of O_2 and CO_2 takes place between the lungs and the blood and these gases are transported to the tissues where the exchange of gases happens now in the tissues, i.e. from the blood and the skeletal muscles. These two exchanges of gases need the circulatory system, both central and peripheral. The minute ventilation must increase during exercise and matched by an increase in blood flow due to a higher cardiac output and more efficient extraction of O_2 at the muscle level.

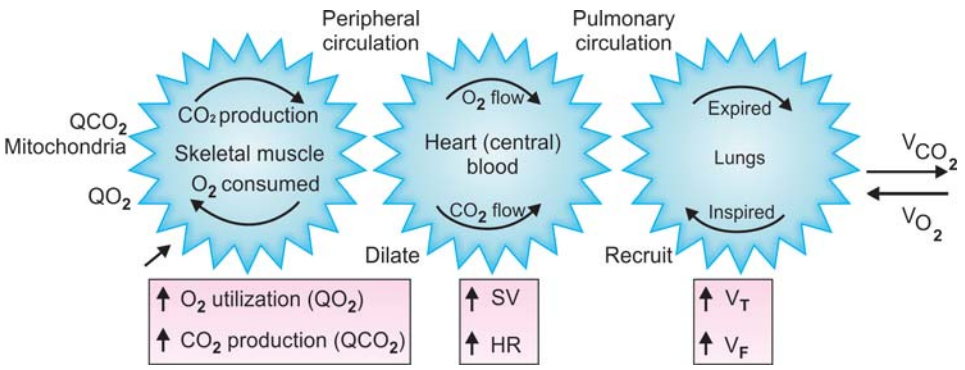


FIGURE 2: Cardiopulmonary unit

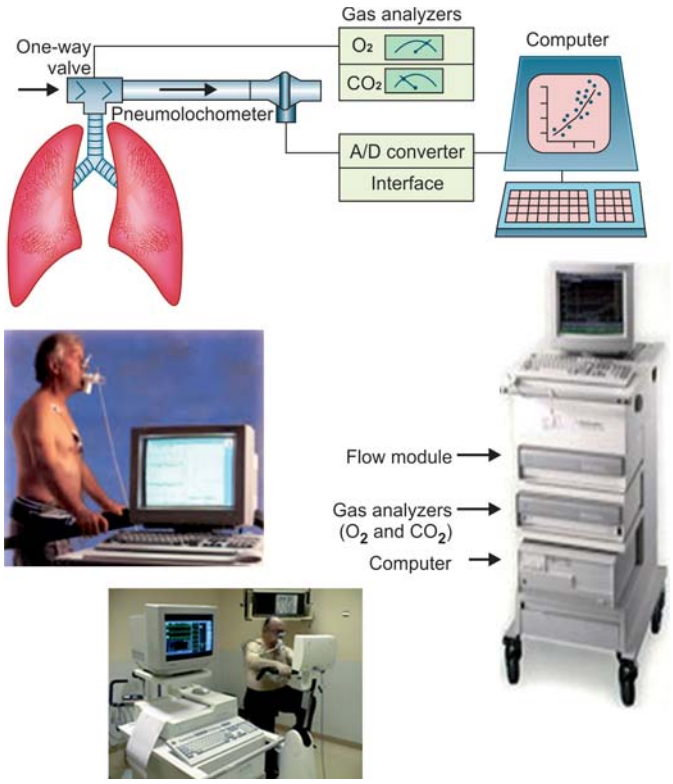


FIGURE 3: Technical components

TABLE 2

Parameters measure or derived from CPX

Parameter	*Expressed as units of measure*
Oxygen uptake	VO_2 l/min or ml/kg/min
Carbon dioxide production	CO_2 l/min or ml/kg/min
Ventilatory (anaerobic) threshold	VT or AT ml/kg/min or % peak VO_2
Respiratory exchange ratio (RER)	VCO_2/VO_2
Oxygen pulse	VO_2/heart rate
Ventilatory equivalent for O_2	VE_{O_2}
Ventilatory equivalent for CO_2	VE_{CO_2}
Minute ventilation	VE
Ventilatory efficiency	VE/VCO_2

TABLE 3

Functional impairment during incremental treadmill testing the Weber classification

Class	*Severity*	*Peak VO_2 (ml/kg/min)*	*AT*	*C.I. max (l/min/m²)*
A	Mild to none	> 20	> 14	> 8
B	Mild to moderate	16–20	11–14	6–8
C	Moderate to severe	10–16	8–11	4–6
D	Severe	6–10	5–8	2–4
E	Very severe	< 6	< 4	< 2

CPX can measure the VO_2 and the CO_2 production by quantifying gases at the mouth with the use of a pneumotachometer to measure air flow. Therefore CPX is an indirect measure of what is occurring at the tissue level by gas detection at the mouth.

TECHNICAL ASPECTS

The pneumotach measures airflow across a membrane and converts it to a digital signal for minute ventilation (VE) (Fig. 3). Current pneumotachs are pliable and more comfortable for patients. A nose clip is used to assure no loss of gas through the nares. Rapid gas analyzers include a heated zirconium for O_2 where the gradient between room air (adjusted to temperature, humidity and barometric pressure) is measured and converted to a digital signal for O_2 consumed (VO_2). The CO_2 analyzer is infrared since CO_2 absorbs infrared light and the amount is converted to a digital signal for the VCO_2 in the sample air. For more details on technical aspects and software considerations, the readers are referred to Clinician's Guide to Cardiopulmonary Exercise Testing in Adults: A Scientific Statement From the American Heart Association.[44-47]

EXERCISE MEASUREMENTS BY CPX

Some of the parameters that can be measured or derived by CPX have been listed in Table 2.

Oxygen Uptake

Exercise capacity can be quantitated clinically by measurement of oxygen uptake (VO_2), carbon dioxide production (VCO_2) and minute ventilation.[3] VO_2 is usually expressed as "peak" or "maximal" in l/min or normalized by body weight to ml/kg/min. Weber and Janicky have divided the levels of VO_2 in HF patients by class of A-D based on testing with hemodynamic parameters. Class A has the least impairment as shown in Table 3. These classes have been used extensively in the literature to quantitate the degree of impairment in HF patient. Women with HF have lower peak VO_2 than the men with a similar disease burden.[48]

Ventilatory Threshold or Anaerobic Threshold

The ventilatory threshold (VT), formerly referred to as the anaerobic threshold (AT), is another index used to estimate exercise capacity. It is defined as the point at which minute ventilation increases disproportionately relative to VO_2, a response that is generally seen at 60–70% of VO_{2max}. The VT is a reflection of the disproportionate increase in lactic acid production by working muscles. It can be used to distinguish between non-cardiac (pulmonary or musculoskeletal) and cardiac causes of exercise limitation, since patients who fatigue prior to reaching VT are likely to have a non-cardiac problem.[43] It has been suggested that the VT might be more predictive than the peak VO_2 because it is less prone to error or to patient effort. Figure 4 illustrates the VT choice using the VCO_2-VO_2 slope method.[49] Most current CPX systems have this algorithm built into the software.

Oxygen Pulse

The Peak VO_2 divided by the heart rate ($PeakVO_2$/HR) is called the oxygen pulse and is an indirect measure of stroke

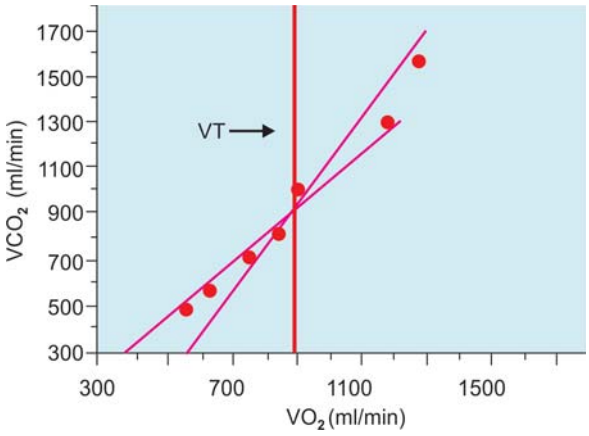


FIGURE 4: VT choice using the VCO_2-VO_2 slope method

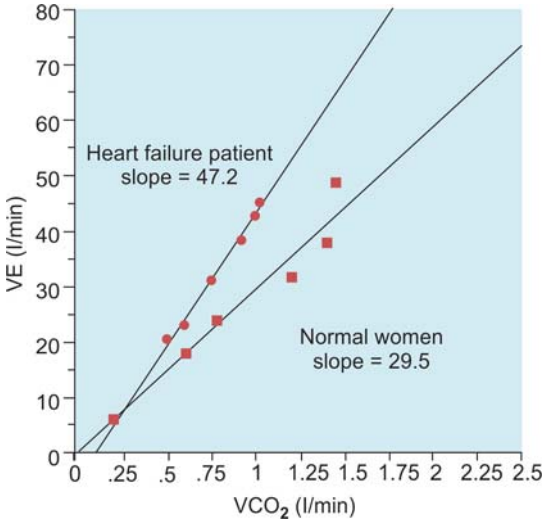


FIGURE 5: Slope of VE/VCO_2 in a normal woman and a man with heart failure

volume. The relationship between cardiac output and VO_2 also forms the basis for the Fick equation used to measure cardiac output.

Respiratory Exchange Ratio (RER)

This value is equal to the VCO_2/VO_2 and is an indirect measure of effort. As exercise progresses, and VCO_2 exceeds the rate of VO_2 increase, the RER will increase beyond 1.0. As VT approaches, the RER is usually greater than 1.1. The RER can help the professional who administers the test to gauge the level of patient effort and compare to the level of perceived exertion.

Ventilatory Efficiency

A possible alternative in HF patients who cannot achieve a true VO_{2max} is the measurement of the ventilatory efficiency, i.e. ventilation-to-CO_2 production ratio in early exercise.[50,51] During CPX a close linear relationship exists between the production of CO_2 (VCO_2) and minute ventilation (VE). The slope of the regression line relating CO_2 production and minute ventilation (VE/VCO_2) can be used to describe the ventilatory response to exercise. In patients with HF, the VE/VCO_2 slope is easier to obtain than parameters of maximal exercise capacity and may be an additional predictor of outcome.[52] In HF, the VE/VCO_2 slope is higher than in normals (Fig. 5). A VE/VCO_2 regression line slope of greater than 34 is associated with reduced cardiac output during exercise, increased pulmonary artery wedge pressures and reduced survival.[52] In one report, patients with a VE/VCO_2 slope greater than 34 had more severe disease and impaired survival. An increase in VE/VCO_2 slope is also predictive of outcome in patients with preserved exercise capacity. Among 123 patients with a VO_{2max} greater than or equal to 18 ml/kg/min, the 3-year survival was significantly lower in those with a VE/VCO_2 greater than or equal to 34 (57% vs 93% for $VE/VCO_2 \leq 34$)[53]

Ventilation

Pulmonary disease can also be evident on CPX. Limitation of ventilation, as seen in chronic lung disease, is described as an "encroachment" or reduction in the ventilatory reserve as a percent of the maximal voluntary ventilation (MVV). A patient with primarily lung disease may exhibit a low VO_2 due to ventilatory limitations which impair the exercise response prior to achieving a cardiovascular limit. It is recommended that if testing a patient with known lung disease, a full pulmonary function test be performed and these results should be evaluated in conjunction with the CPX findings (see section Evaluation of Dyspnea).

CONDUCTING THE EXERCISE TEST

The protocol most commonly used for testing of patients with HF is the modified Naughton-protocol. However, with CPX, most protocols can work well. It is important, as a good testing format, to choose a protocol that fits with the patient's ability to walk or bike. Choosing an acceptable protocol tailored to a patient can make a great difference in cooperation and feeling of comfort and trust. Since actual measurements of effort (RER) and function (VO_2) are being collected, the choice of protocol is not as salient. A warm-up period is recommended especially for patients who are fairly sedentary. This warm-up period will also allow to quality check the CPX gases for accuracy, drift and potential troubleshooting.

CPX testing is safe as demonstrated in over 4,000 patients in the recently completed HF-ACTION trial.[54] The test should be conducted as any other exercise test with blood pressure measurements at rest and during the test as well as in recovery. ECG monitoring should follow standard procedures for testing.[47] Achieving an adequate test is as essential as knowing how to interpret the findings. The report should contain information about symptoms encountered during testing, the blood pressure and heart rate response, the ECG at rest, exercise and recovery, any arrhythmias encountered, in addition to the CPX parameters. The report should also include a conclusion and recommendations for further testing or medication changes, etc.

INDICATIONS FOR CPX TESTING IN HEART FAILURE

Common indications for CPX testing in patients with HF have been listed in Table 4. Several of these have been discussed hereunder.

TABLE 4

Indications for CPX testing in heart failure

- Prognostic implications
- The presence and nature of ventilatory limitations
- The presence and nature of cardiovascular limitation with heart failure
- The extent of conditioning or deconditioning
- The maximum tolerable workload and safe levels of daily exercise to give recommendations
- The extent of disability for rehabilitation purposes
- Oxygen de-saturation and appropriate levels of supplemental oxygen therapy if lung disease is present

PEAK VO_2 AND PROGNOSIS

The peak VO_2 provides the most objective assessment of functional capacity in patients with HF. This parameter has been an important predictor of optimal timing for cardiac transplantation in eligible patients.[6] The values of peak VO_2 were illustrated in a report of 114 consecutive ambulatory patients with advanced disease referred for possible cardiac transplantation to a large academic medical center and were prospectively divided into three groups:

- Group 1: Patients who were accepted as transplant candidates (peak $VO_2 \leq 14$ ml/kg/min)
- Group 2: Patients who were considered too well for transplantation (peak $VO_2 > 14$ ml/kg/min)
- Group 3: Patients who were rejected for transplantation due to various reasons such as malignancy or age (peak $VO_2 \leq 14$ ml/kg/min)

Keeping in mind that a normal person can achieve higher than 20 ml/kg/min, these values were considered low and demonstrated impaired functional capacity.

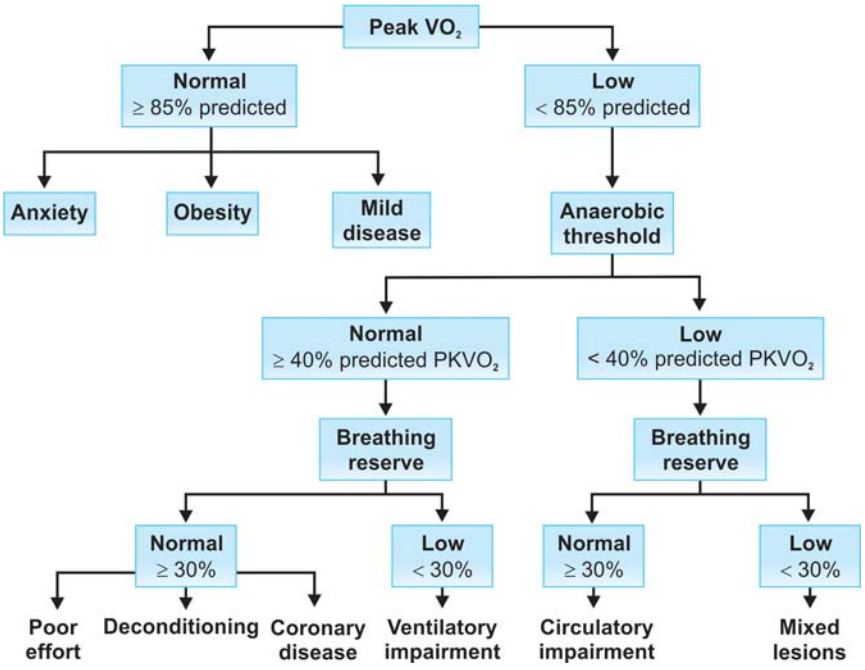
The 1-year survival of the healthier patients in group 2 was 94%, an outcome that was similar to that in transplanted patients in group 1. The prognosis was the poorest in group 3, although survival varied with the peak VO_2 in this group. Patients with a value less than or equal to 10 ml/kg/min had the lowest survival, while those between 10–14 ml/kg/min had an outcome that was only slightly worse than patients in group 1. Based on this study, many transplant centers have used 14 ml/kg/min as a cutoff point for listing patients for transplantation. However it does not take into consideration; the lower peak VO_2 that occurs with age alone without disease or gender.[42,48] This study was also performed prior to the extensive use of beta blockers in the HF population.

The HF-ACTION trial tested over 2,000 patients with NYHA Classes II and III HF, 50% ischemics and reported a mean peak VO_2 of 14.9 ml/kg/min. Therefore, the "magic number" of 14 ml/kg/min should be reconsidered in light of this new and extensive database.[55] Age may be the strongest predictor of peak VO_2.[56,57] Evaluation of the VE/VCO_2 will add prognostic significance to the testing.[51] It is still not clear whether improving peak VO_2 by other than drugs, e.g. exercise, will ultimately improve survival rates. Further analyses of the HF-ACTION database are awaited.

EVALUATION OF DYSPNEA: PRESENCE OF VENTILATORY LIMITATIONS

Dyspnea is a common symptom that can have either a pulmonary or a cardiac etiology. CPX can assist in discriminating symptoms that arise from the lungs versus cardiac disease. Flow chart 2 is an algorithm to help interpret the ventilation and the VO_2 parameters when dyspnea is a symptom. A peak VO_2 of below 85% predicted for age and gender is low and requires looking carefully at the VT. The VT should be approximately 60–70% of the peak VO_2. An early VT may indicate circulatory issues. Ventilatory impairment is usually indicated by a breathing reserve of less than 30%. If this is suspected, the CPX test could be accompanied by a pulse oximeter looking for desaturation.

FLOW CHART 2: Algorithm for the differential diagnosis of exertional dyspnea and fatigue



If the RER is less than 1.0, the patient may have exerted a poor effort or was experiencing anxiety. If a patient has a combination of lung and cardiac diseases, the more prominent abnormality in CPX may direct the clinician to the primary cause of symptoms. CPX testing can also be used in conjuction with nuclear imaging or echocardiography. A more extensive discussion of dyspnea on exertion can be found in the Clinician's Guide to Cardiopulmonary Exercise Testing in Adults: A Scientific Statement From the American Heart Association.[47]

EXTENT OF DECONDITIONING AND DERIVING AN EXERCISE PRESCRIPTION

Patients with HF may often under or overestimate their ability to perform activity. Patients often cut down activities that would cause symptoms and answer negatively to symptoms of dyspnea or fatigue. Alternatively, some patients may minimize their symptoms and mislead their care provider as to their limitations. A CPX can help to determine the true level of deconditioning versus limitation due to disease. The CPX test can help to better delineate patients for safe level of exercise training using either a heart rate or a perceived level of effort. Determination of VT can assure that training is prescribed at a level below it by encouraging RER to greater than 1.0 during the exercise test. In the era of beta blockers, a rate of perceived exertion (RPE) below the VT may serve as an adequate intensity where heart rate may be blunted during the CPX test. There are no data to prove that deriving an exercise prescription from CPX is superior to the standard methodology.

EXERCISE TRAINING IN HEART FAILURE

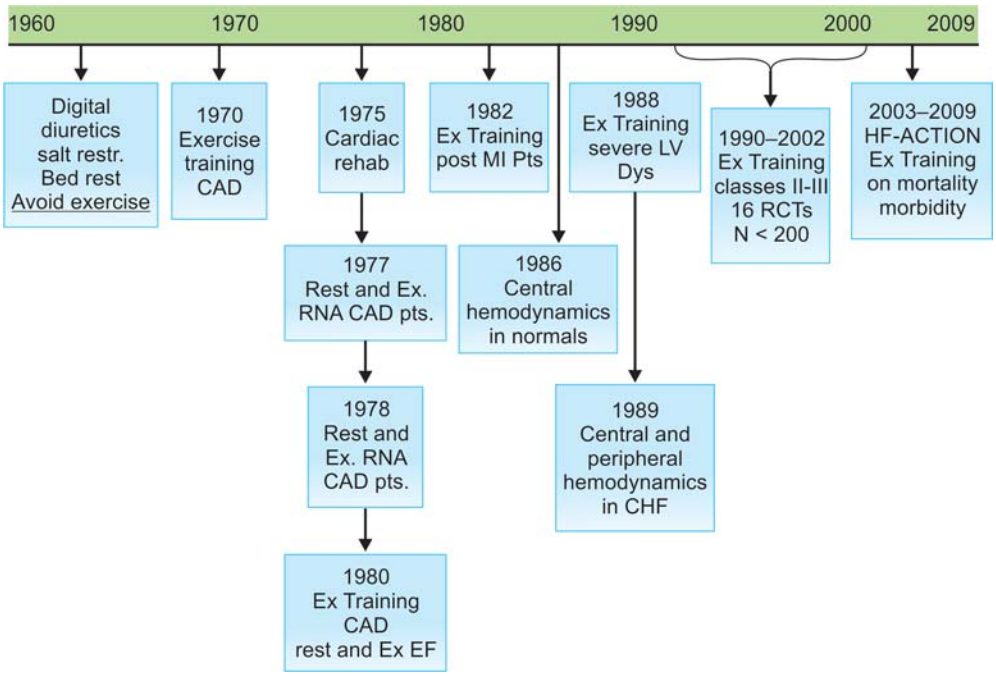
DELETERIOUS EFFECTS OF BED REST

The HF patients typically are admitted multiple times in any year and, due to their longer periods of bed rest, they will be more deconditioned and debilitated than the NYHA class II patient who remains out of the hospital. Bed rest is deleterious to normal subjects and it is certainly deleterious to patients with HF. Functional capacity can decrease by as much as 8.4% in men and 6.8% in women and total exercise tolerance decreases by 8.1% in men and 7.3% in women by 10 days.[58] Peak heart rate increases in both men and women with bed rest alone. Inactivity also increases submaximal heart rate with a decrease in vagal tone, increased sympathetic catecholamine secretion, and enhanced beta-receptor sensitivity to circulating catecholamines. Although heart rate is elevated, the functional capacity drops due to a lower stroke volume and a drop in cardiac output.[10] The patient with HF can suffer all of these consequences of bed rest in addition to the changes in muscle fibers described above. Added to this deconditioning, clinicians may recommend bed rest in an effort to not "push" the heart.

HISTORY OF EXERCISE TRAINING IN HEART FAILURE

The history of exercise training for patients with HF starting in the 1960s when exercise was contraindicated has been depicted in Flow chart 3. In the 1970s and the 1980s a series of studies, many of which were performed in the Duke University Exercise Center, demonstrated that ventricular function at rest could not predict exercise capacity and that patients with HF could indeed perform physical activity.[15,29,59-65] Other studies pointed out physiological beneficial effects of exercise training. Further investigations in the 1980s pointed out the potential benefits of exercise training in HF which included enhanced quality of life, better respiratory parameters, drop in neurohormones and improved muscle function.[66,67] In the 1990s, from several small studies (< 200 total patients), improvements in peak VO_2 varied from 10% to 30%.[68,69] In 2009, the awaited HF-ACTION trial

FLOW CHART 3: History of exercise training



published its report on 2,231 patients with NYHA Classes II-III HF randomized to a formal aerobic training program versus usual care. HF-ACTION has been discussed below. Data were needed to prospectively address outcomes since all other studies had used surrogates, and surrogates may be misleading in HF. The HF-ACTION trial showed a small but significant improvement in peak VO_2 and 6-minute walk at 3 months. The 6-minute walk benefit was not present in 1 year.[55] The health status increased in a statistically significant manner at 3 months in the exercise group and the improvement remained at 1 year. However, the overall increase in health status was lower than predicted by the trial investigators.[70]

BENEFITS OF EXERCISE TRAINING IN HEART FAILURE

Exercise training does not improve cardiac function at rest, as estimated from left ventricular ejection fraction, baseline cardiac output or wedge pressure.[71] Training, however, has been reported to affect the following:

- Increased peak VO_2, peak cardiac output and leg blood flow during exercise.[65,71]These improvements may be related to an increase in peak early diastolic filling rate of the left ventricle at rest and during exercise.[72]
- Improved muscle energetics so that oxygen utilization becomes more efficient, allowing a similar amount of work to be performed at a lower heart rate, rate-pressure product and minute ventilation (indicating improved gas exchange).[16,73,74]
- Partial reversal of the abnormalities in mitochondrial density and ultrastructure and on fiber type distribution in skeletal muscle seen with HF.[16]
- Improvement of peripheral endothelial dysfunction with restoration of endothelium-mediated flow-dependent dilation, possibly due to enhanced endothelial release of nitric oxide[75,76] This finding has also been reported in the coronary arteries by Hambrecht et al.[77]
- These benefits can result in a greater amount of work performed externally with less work internally. For patients who have concomitant angina, their exercise duration may increase prior to symptom onset. In HF-ACTION, the improvement in peak VO_2 was modest. However, the study had overall a 40% adherence that may have affected the functional capacity changes.[55]
- Potential for reduction in sympathetic tone and an increase in vagal tone at rest, thereby restoring autonomic cardiovascular control toward normal.[71]

SAFETY

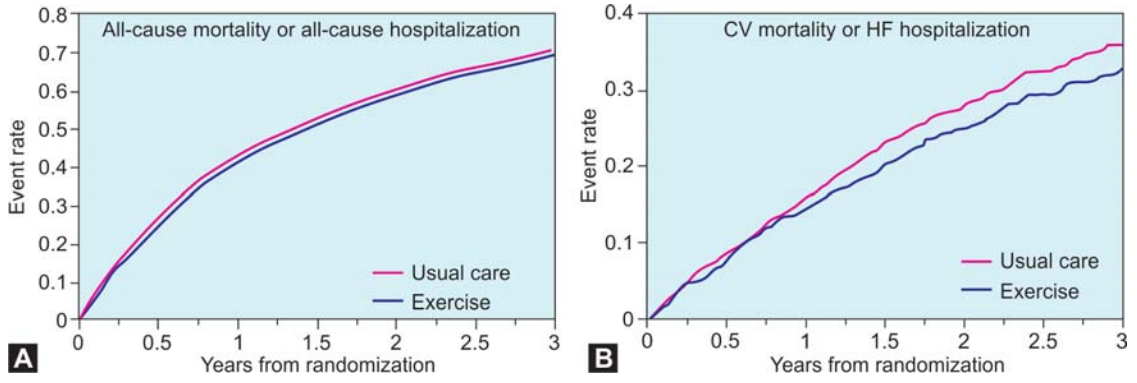
The HF-ACTION demonstrated the safety of training in this population. At the trial follow-up, 40% of the control group had suffered at least one CV event (worsening HF, myocardial infarction, unstable angina, serious arrhythmia, CVA or TIA) compared to 37% in the training group, pNS; at least one ICD firing in 23% of the control and 22% of the trained group. Hospitalizations after physical activity had been concerning but was experienced in only 3% of the trained group and 2% of the controls. The study protocol did not specify ECG monitoring during training.[55]

MORTALITY AND MORBIDITY

To date, HF-ACTION is the largest study to prospectively ask the question about benefits on exercise training in HF on mortality and morbidity. The trial showed a modest reduction in the primary endpoint of all cause mortality or all cause hospitalization, [hazard ratio (HR) 0.93, 95% (CI 0.84–1.02), *p* _0.13]. A prespecified analysis adjusted for highly predictive baseline characteristics, was also reported [HR 0.89, 95% (CI 0.81–0.99), *p*_0.03] (Figs 6A and B). Additional post-hoc analysis showed that in those who were adherent, there was a significant effect particularly on the secondary endpoint of cardiovascular mortality or HF hospitalization (manuscript in preparation). It is worth noting that the medical background therapy was excellent with 95% of patients on beta blocker therapy.[55]

GUIDELINE RECOMMENDATION

The European Society of Cardiology has added exercise training to the latest chronic HF guidelines stating that "regular, moderate daily activity is recommended for all patients with HF" and has given it a Class I, level of evidence B. The guidelines also state



(Primary) HR 0.93 (95% CI: 0.84, 1.02), *P* = 0.13
*Adjusted HR 0.89 (95% CI: 0.81, 0.99), *P* = 0.03

HR 0.87 (95% CI: 0.75, 1.00), *P* = 0.06
*Adjusted HR 0.85 (95% CI: 0.74, 0.99), *P* = 0.03

*Adjusted for key prognostic factors

FIGURES 6A AND B: Exercise training in HF on mortality and morbidity

that "exercise training is recommended, if available, to all stable chronic HF patients.[78] There is no evidence that exercise training should be limited to any particular HF patient subgroups (aetiology, NYHA class, LVEF or medication). Exercise training programs appear to have similar effects whether provided in a hospital or at home. Class of recommendation I, level of evidence A". In 2009, the AHA/ACC updated the chronic HF guidelines and stated that: "Exercise training should be considered for all stable outpatients with chronic HF who are able to participate in the protocols needed to produce physical conditioning. Exercise training should be used in conjunction with drug therapy. Exercise training is beneficial as an adjunctive approach to improve clinical status in ambulatory patients with current or prior symptoms of HF and reduced LVEF" (Class I, level of evidence: B).[3,79]

In spite of the recommendation, evidence of safety and benefit added to guideline advice, few patients with HF report engaging in exercise.[79] In the HF-ACTION trial, with barriers removed, such as coverage, access to an exercise treadmill or bike, frequent phone calls, adherence to the exercise regimen was difficult to maintain. As the duration of the trial increased, recommended adherence decreased to 40%.[55]

EXERCISE PRESCRIPTION RECOMMENDATION

No universal prescription for a particular exercise regimen has been established for patients with HF. In HF-ACTION, predicting a high use of beta-blockers, 70% of heart rate reserve served as the intensity recommendation. A patient who is much debilitated can start at a lower heart rate reserve and progress toward 70%. All training in HF-ACTION was aerobic and included a warm-up and cool-down period three times/week, while supervised for 6–8 weeks and 5 days/week for home training with duration of 30–35 minutes in a center and up to 40 minutes at home. This regimen was found to be safe and can easily be incorporated into an outpatient program.[55] Although not a requisite, a baseline exercise test is strongly recommended to accurately and safely assign an exercise prescription. Although CPX test is optimal, a regular exercise test taken to a RPE of 17 will provide sufficient effort to derive a heart rate reserve. Another alternative is to recommend training to an RPE of 13–15 which will probably include a VT. Importantly, however, is to build in a progression recommendation that an exercise center can follow and give the patients targets to attain. Involvement in recreational activities will enhance the activity experience and should be encouraged. Patients should be instructed on an appropriate warm-up period prior to exercise and cool down post exercise. Warm-up should be at least 10–15 minutes prior to an exercise period of 20–30 minutes at a variable intensity depending on the patient. Walking or even stretching can serve as a warm-up. Cool down is equally important to dissipate body heat and redistribute blood from exercising muscles to the rest of the circulatory tree. Other advice includes avoidance of extreme of temperatures and not exercising immediately after meals. Patients with HF may feel more rested in the morning hours and may choose to exercise at those times.

SUMMARY

In clinical practice, many physicians follow the symptoms and signs of patients with HF as a guide to their course and prognosis. Serial exercise tests may not be necessary as long as the patient remains stable. However CPX testing can be an invaluable tool to evaluate changes in clinical symptoms and signs, discrimination of dyspnea symptoms, assessing a safe and direct functional status and assigning an objectively derived exercise prescription. In addition, peak VO_2 measurement remains one of the most powerful predictors of prognosis and one that cannot be deduced from resting ventricular function. Exercise training for HF patients has now been shown to be safe, with modest reduction of outcomes and improvements in health status and should be recommended concomitant to optimal medical and device therapy. Noting that behavior modification underlies the barriers to initiating and continuing increased physical activity, clinicians need to add these recommendations to their care plan and work with their patients and exercise training groups to improve the lives of their patients.

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Chapter 77

Hibernating Myocardium

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Chapter Outline

- Historical Perspective
- Definition
- Pathophysiology
- Hibernation and Stunning: Clinical Prevalence
- Detection of Hibernating Myocardium
  - Rationale
  - Techniques
- Revascularization of Hibernating Myocardium and Changes in Ventricular Function
- Revascularization of Hibernating Myocardium and Changes in Prognosis

INTRODUCTION

Systolic heart failure also termed "heart failure with reduced ejection fraction" (HFREF) is one of the two common clinical subsets of chronic heart failure. The other subset is diastolic heart failure which is also called "Heart failure with preserved ejection fraction" (HFPEF). During the last three decades, there have been considerable advances in the management of systolic heart failure. A substantial improvement in the prognosis of patients with systolic heart failure is expected with the implementation of these interventions. With modern pharmacotherapy, annualized mortality rate has decreased from 18–21% to 8–12%.[1] With introduction of chronic resynchronization treatment and implantable defibrillators the mortality of patients with systolic heart failure has further decreased. However the prognosis of patients refractory to these therapies remains very poor. The 1-year mortality is approximately 45%.[2,3] It has been estimated that 5–10% of patients develop refractory heart failure.[4] Cardiac transplantation which improves prognosis and quality of life is the only effective treatment for patients with end-stage refractory heart failure. In the United States of America, there are approximately 80,000 patients with end-stage heart failure who are potential candidates for cardiac transplantation. However only about 2,500 patients can receive cardiac transplantation. Many patients are not considered suitable candidates for cardiac transplantation due to their age and comorbidities. Thus, the potential role of other surgical therapies, including revascularization, is being explored for the treatment of refractory heart failure. As revascularization is likely to be of benefit when viable, ischemic hibernating myocardium is reperfused, it is logical to assess the presence and extent of hibernating myocardium. However controversy exists regarding the necessity of detection of hibernating myocardium before revascularization therapy is undertaken. In this chapter, the potential mechanisms of hibernation, its detection and clinical relevance have been discussed.

HISTORICAL PERSPECTIVE

In the studies of experimental animals, in 1978, Diamond GA et al. first reported that "ischemic non-infarcted myocardium can exist in a state of 'hibernation'".[5] They demonstrated that "sometimes dramatic improvement in segmental ventricular function can occur after coronary bypass surgery". Rahimtoola SH, however, first demonstrated the importance of "hibernation" in patients with chronic ischemic heart disease and popularized the concept of hibernating myocardium.[6] In 1984, the term "hibernating myocardium" was adopted during a National Heart, Lung, and Blood Institute workshop on the treatment of coronary artery disease.[7]

DEFINITION

Myocardial hibernation is defined as a condition of chronic systolic and diastolic dysfunction in patients with obstructive coronary artery disease which is reversible after successful revascularization.

Myocardial stunning, a related but a different pathophysiologic condition, is defined when there is a delayed recovery of myocardial function after reperfusion of the ischemic myocardium is established.[8,9] Myocardial stunning can be mechanical, metabolic or electrical. In mechanical stunning there is delayed recovery of mechanical function after reperfusion of ischemic myocardium. Metabolic stunning is defined when there is delayed recovery of metabolic function after perfusion of ischemic myocardium has been established. This phenomenon can be observed in some patients with ischemic heart disease undergoing exercise test. After cessation of exercise and after resolution of manifestations of myocardial ischemia, such as ischemic ECG changes, metabolic dysfunction may persist for several hours. In electrical stunning, there is delayed recovery of electrical function after reperfusion of ischemic myocardium is established. In some patients with ST segment elevation

myocardial infarction with Q waves reappearance of R waves may be delayed even after recovery of regional myocardial mechanical function.

PATHOPHYSIOLOGY

Although the existence of myocardial hibernation has been documented, the pathophysiologic mechanisms still remain controversial. One of the proposed mechanisms is "that there is a prolonged subacute or chronic stage of myocardial ischemia that is frequently not accompanied by pain and in which myocardial contractility and metabolism and ventricular function are reduced to match the reduced blood supply".[10,11] This mechanism has been termed "perfusion-contraction matching hypothesis".[12] It is speculated that the ischemic myocardial segments decrease the energy requirement by reducing its contractility. There is, however, residual contractile and metabolic function and, after revascularization, the function recovers.[13,14] This proposed mechanism for "hibernation" has been termed "Smart heart hypothesis".[10] There is, however, considerable controversy about whether the resting coronary blood flow is reduced in the hibernating myocardial segments. In a study of 27 patients with one- or two-vessel atherosclerotic obstructive coronary artery disease, first-pass cardiovascular magnetic resonance perfusion imaging was performed for quantitative measurement of myocardial blood flow. Cine myocardial resonance imaging was used to assess regional and global left ventricular function. Delayed enhancement magnetic resonance imaging (MRI) technique was employed to determine myocardial viability. In this study, coronary blood flow was measured before and after percutaneous coronary intervention (PCI). Before coronary intervention, resting coronary blood flow in the hibernating myocardial segments was reduced and, after successful intervention, it normalized. In the reperfused myocardial segments, the systolic and end diastolic wall thickness increased.[15] However other studies have demonstrated that the resting myocardial perfusion is similar before and after revascularization of the hibernating myocardial segments, suggesting that the resting myocardial blood flow is not reduced in the hibernating myocardium.[16]

In the experimental animal studies, an impaired excitation-contraction coupling has been observed.[17] In the myocytes from the hibernating myocardial segments, a reduction in the myofibrillar protein content has been reported.[17-19] In a study of 11 patients with chronic stable angina, the changes in oxidative metabolism and myocardial perfusion were studied by single photon emission computed tomography (SPECT) imaging with a free fatty acid analog, I-123-beta-methyl iodophenylpentadecanoic acid and thallium-201, before and after successful percutaneous intervention of the coronary artery, providing blood flow to the hibernating myocardial segments.[20] This study reported that the free fatty acid metabolism is impaired in hibernating myocardium, indicating impaired oxidative metabolism which improves after reperfusion.[20] In a study of 12 patients with hibernating myocardium, transmural biopsy specimens obtained during coronary artery bypass surgery were analyzed for Sarcoplasmic-calcium ATPase (SERCA2a), phospholamban and sodium-calcium exchanger concentrations.[21] A decreased SERCA2a was observed.

Other proposed mechanism of "hibernation" is that there is repetitive "stunning" of the myocardium (repetitive stunning hypothesis).[8-11] Myocardial stunning is defined when there is a delayed recovery of myocardial mechanical and metabolic function after reperfusion of the ischemic myocardium is established. The determinants of the time course of recovery of function are the duration of ischemia before reperfusion and the amount of baseline myocardial fibrosis.[22] The clinical studies indicate that recovery of function occurs earlier in stunned myocardium than in hibernating myocardium.[23] The experimental studies suggest that "stunning" is associated with upregulation of anti-apoptotic survival proteins and down regulation of anti-survival signaling pathways.[14] According to the stunning hypothesis, the myocardium is subjected to repeated episodes of ischemia followed by reperfusion, which maintains myocardial viability and preserve metabolic and mechanical function. The myocardial ischemia occurs due to an imbalance between myocardial oxygen demand and oxygen supply. When there is increased oxygen demand as during exercise ischemia is precipitated because of limited coronary flow reserve due to coronary artery stenosis. With the cessation of increased demand, perfusion becomes adequate, producing "myocardial stunning". This repeated episodes of stunning produce sustained chronic reduction of myocardial contractile function. The myocardium, however, remains viable and the function recovers after reperfusion.

Irrespective of the initial mechanisms, it appears that in the "hibernating" myocardium the cell survival pathways are triggered and there is activation of survival proteins and concurrently there is suppression of "cell death pathways".[14] The cellular, biochemical and genetic changes in the myocytes in hibernating myocardium have been investigated. Biopsy studies during coronary artery bypass surgery have reported that the myocytes in the hibernating myocardial segments can be dedifferentiated with loss of myofilaments and glycogen accumulation.[24] However other studies have reported that there is no dedifferentiation of myocardial proteins and there is no necrosis, but apoptosis of the myocytes in the hibernating myocardial segments.[25] Apoptotic loss of myocytes result in reduced numbers of functional myocytes and is associated with hypertrophy of the remaining functional myocytes.[25] Myocyte remodeling has been observed in experimental models of hibernating myocardium induced by coronary artery stenosis. In the hibernating myocardial segments, the myocytes are hypertrophied and the action potential duration is prolonged. The L-type calcium (2+) currents and calcium release are also decreased.[26] In human hibernating myocardium, it has been reported that the sarcoplasmic reticulum Ca (2+)-ATPase activity is impaired due to reduced phosphorylation of phospholamban, contributing to reduced contractile function.[21] The gene profile has been studied in human hibernating myocardium in the tissue samples obtained during coronary artery bypass surgery. An upregulation of the inhibitor of apoptosis gene, cytoprotective heat-shock proteins, the hypoxia-inducible factor-1a, vascular endothelial growth factor and the stress-responsive glucose transporter gene has been reported.[14] An upregulation of beta-adrenergic receptor kinase-1 and fas-activated serine/threonine kinase and reduced expression of desmoplakin has been observed.[26] An increased expression of B-type natriuretic peptide has also been reported.[27]

TABLE 1

A few proposed mechanisms of myocardial hibernation and stunning

- Prolonged subacute or chronic stage of ischemia
- Decrease in metabolic and mechanical function to match the reduced coronary blood flow (smart hypothesis)
- Repetitive stunning (stunning hypothesis)
- Activation of "Survival pathways"
- Suppression of "Cell death pathways"
- Apoptotic loss of myocytes
- Myocytes hypertrophy
  - Prolonged action potential duration
  - Decreased L-type Ca^{2+} currents and Ca^{2+} release
  - Decreased SERCA Ca^{2+}-ATP
- Stunning
  - Upregulation of the antiapoptotic and other survival pathways
  - Downregulation of antisurvival pathways

An increase in alpha-adrenergic receptor density and an increased ratio of alpha to beta-receptor density in the hibernating myocardium in patients undergoing coronary artery bypass surgery has been observed.[28] However the cellular mechanism by which the altered adrenergic receptor activity induces hibernation and/or stunning remains unclear.

Increased levels of tumor necrosis factor-alpha (TNF-α) and inducible nitric oxide synthase (iNOS) have been detected in the human hibernating myocardial segments in tissue samples obtained during coronary artery bypass surgery. TNF-α has been thought to be a contributing molecular mechanism for depressed contractile function.[29] The levels of TNF-α and iNOS are much higher in the irreversibly damaged myocardial segments compared to hibernating myocardium.[29] The proposed mechanisms of hibernation and stunning are summarized in Table 1.

HIBERNATION AND STUNNING: CLINICAL PREVALENCE

In several clinical subsets of coronary artery disease, the phenomenon of myocardial stunning is observed. In patients with ST segment elevation myocardial infarction, recovery of regional and global left ventricular function is often delayed even after successful myocardial reperfusion. In some studies, at 90 days after reperfusion, there was only 22% complete recovery and in 36% partial recovery of mechanical function following successful recanalization of the infarct related artery.[30,31] In patients with stable angina, stunning phenomenon also occurs. During exercise or dobutamine stress myocardial ischemia is induced due to mismatch between oxygen demand and supply. The coronary blood flow becomes inadequate for the increase in myocardial oxygen demand during induced stress. With cessation of stress, coronary blood flow to the ischemic myocardium becomes adequate for the oxygen demand. However there is a delayed recovery of left ventricular mechanical and metabolic function.[32]

The coronary flow reserve which is the ratio of blood flow during the maximal reduction of coronary vascular resistance to resting blood flow is reduced in the presence of coronary artery stenosis. The more severe the coronary artery stenosis greater is the reduction of coronary flow reserve. In patients with markedly reduced coronary flow reserve, mild to modest increase in myocardial oxygen demand induces ischemia of the myocardium supplied by the stenosed coronary artery. Even after return of baseline oxygen demand and coronary blood flow, there is a delay in recovery in function due to stunning phenomenon.[33,34]

In chronic ischemic heart disease, presence of hibernating myocardium has been documented. In one study in 59 of 81 hypokinetic or akinetic myocardial segments, mechanical function improved after revascularization, confirming presence of hibernating myocardium.[35] Hibernating myocardial segments are present in patients with acute coronary syndromes as well.[36] The frequency of presence of hibernating myocardium appears to be higher in patients with unstable, than in patients with chronic stable angina (75% vs 28%), probably reflecting shorter duration and more severe ischemia in patients with unstable angina.[37] Hibernating myocardium may be present in patients with left ventricular dysfunction with or without symptoms of congestive heart failure and without angina.[38]

In patients with systolic heart failure, due to ischemic cardiomyopathy, the prevalence of hibernating myocardium has been investigated. In the analysis of 24 myocardial viability studies in 3,088 patients with systolic heart failure, with average left ventricular ejection fraction of 32%, the prevalence of hibernating myocardium was 42%.[38] Several studies have reported that approximately 10% of patients with ischemic systolic heart failure referred for cardiac transplantation had some viable ischemic myocardium.[39-41] In patients with "anomalous left coronary artery from the pulmonary artery" (ALPACA), almost complete recovery of left ventricular function occurs after appropriate corrective surgery, probably due to the presence of hibernating myocardium.[42]

DETECTION OF HIBERNATING MYOCARDIUM

RATIONALE

It has been suggested that the detection of presence and magnitude of hibernating ischemic myocardium is desirable before revascularization treatment is undertaken in patients with systolic heart failure.[28,34] The rationale is that it is more likely the regional and global myocardial function will recover following revascularization of hibernating myocardium than of nonviable fibrotic myocardium. When the myocardium with predominantly scar tissue is revascularized, functional recovery and improvement in prognosis is unlikely to occur.[35-39] In contrast, revascularization of ischemic viable myocardium is likely to be associated with not only of amelioration of symptoms but also with an improvement of function and prognosis.[39]

TECHNIQUES

Initially, contrast ventriculography, before and after administration of nitroglycerin or positive inotropic agents, was employed for detection of viable ischemic myocardium.[43-45] Nitroglycerin reduced myocardial ischemia primarily by decreasing myocardial oxygen demand, but it also dilated epicardial coronary arteries. With decrease in myocardial ischemia, there is improvement in mechanical function of the hibernating myocardium. The rationale for the use of positive inotropic agents is that the mechanical function is likely to improve in response to inotropic stimulation if viable hypofunctioning

TABLE 2

A few of the noninvasive imaging techniques that have been employed for detection of hibernating myocardium

- Dobutamine echocardiography
- Thallium-201 stress imaging
- Use of Technetium labeled agents for nuclear myocardial imaging
- FDG-PET
- MRI
- MRI with contrast delayed enhancement
- Contrast echocardiography
- Strain rate echocardiography with or without use of dobutamine
- Magnetic resonance spectroscopy
- Metabolic imaging with beta-methyl-p-[^{123}I]-iodophenyl-pentadecanoic acid (BMIPP)
- Molecular imaging

myocardium is present. Post-extrasystolic potentiation and exercise can also be used instead of positive inotropic agents for detection of presence of viable ischemic hibernating myocardium.[46] Amrinone, a relatively cardiac-specific phosphodiesterase inhibitor has also been used instead of dobutamine to detect hibernating myocardium.[47]

Noninvasive tests should be considered before invasive tests are performed. The conventional electrocardiogram frequently provides information about the extent of myocardial damage in patients with coronary artery disease. The presence of widespread "Q waves" and/or loss of "R waves" usually indicate extensive loss of functional myocardium and irreversible myocardial damage. However positron emission tomography (PET) studies have documented that the presence of Q waves correlate poorly with the presence and extent of viable ischemic myocardium.[48] Thus, for detection of presence and magnitude of hibernating myocardium, it is necessary to use other imaging methods. Several noninvasive techniques are available for detection of hibernating myocardium (Table 2).[48-52]

Dobutamine echocardiography, thallium-201 myocardial perfusion imaging, imaging with use of technetium-99 m labeled agents, and F18-fluorodeoxyglucose positron emission tomography (FDG-PET) can be employed. Cardiac MRI, contrast echocardiography, strain rate analysis by dobutamine echocardiography,[53-55] molecular imaging and fatty acid imaging have also been introduced for the diagnosis of hibernating myocardium.

The sensitivity, specificity and predictive values of commonly used techniques for detection of hibernating myocardium are summarized in Tables 3 and 4. In these studies, patients with systolic heart failure with a wide range of ejection fraction have been studied. Most of these studies are not prospective or randomized. The number of patients in these studies is also relatively small. Thus, it is difficult to estimate the potential impact of these studies in clinical practice. Nevertheless, the results of these studies may have some practical application.

In clinical practice, dobutamine stress echocardiography is most frequently used due to the wide spread availability and easy to perform and interpret the results (Fig. 1). During dobutamine stress echocardiography, after obtaining resting images in different views, images are obtained during moderate and peak dose of dobutamine infusion. If there is increased left

TABLE 3

Detection of hibernating myocardium—a few techniques used in clinical practice

Modality	*Sens (%)*	*Spec (%)*	*+PV (%)*	*–PV (%)*
DSE	80	78	75	83
TH-201	87	54	67	79
SPECT	83	65	74	87
MRI-WT	95	41	56	92
DE	74	82	78	78
MRI-CE	84	63	72	78

(Abbreviations: Sens: Sensitivity; Spec: Specificity; +PV: Positive predictive value; –PV: Negative predictive value; DSE: Dobutamine stress echocardiography; TH-201: Thallium-201 myocardial scintigraphy; SPECT: Single photon emission computed tomography using Technetium-99 m labeled agents; FDG-PET: Fluorodeoxyglucose positron emission tomography; MRI-WT: Magnetic resonance imaging-wall thickness; DE: Delayed enhancement; MRI-CE: Magnetic resonance imaging-contrast enhancement)

TABLE 4

Detection of hibernating myocardium in deciding revascularization in systolic heart failure

Modality	*Sens (%)*	*Spec (%)*	*+PV (%)*	*–PV (%)*
MRI-DE	99	94	99	94
MRI-WMS	88	90	98	56
MRI-WT	96	35	90	57
SPECT	86	68	94	44

(Abbreviations: Sens: Sensitivity; Spec: Specificity; +PV: Positive predictive value; –PV: Negative predictive value; MRI-DE: Magnetic resonance imaging-dobutamine echocardiography; MRI-WMS: Magnetic resonance imaging-wall motion study; MRI-WT: Magnetic resonance imaging-wall thickness; SPECT: Single photon emission computed tomography using Technetium-99 m labeled agents)

ventricular regional wall motion and wall thickening during infusion of moderate dose and paradoxical motion and thinning of the same myocardial segments during the infusion of peak dose of dobutamine presence of hibernating myocardium can be diagnosed with high degree of certainty. It should be appreciated that some expertise is necessary for detection of presence and extent of hibernating myocardium by dobutamine stress echocardiography. In many institutions FDG-PET is used for detection of the presence and extent of hibernating myocardium. Radionuclide PET method is used. In this technique, the resting myocardial perfusion images are obtained with the use of radioactive tracer such as rubidium-82. Perfusion defects suggest presence of scar and nonviable tissue. The perfused segments indicate viability. The metabolic activity of the myocardium is studied with the use of radioactive tracer fluorodeoxyglucose (FDG). The FDG uptake indicates metabolically active myocardium. Hibernating myocardium is diagnosed when perfused and metabolically active myocardium is present (Fig. 2). Thallium-201 imaging along with imaging for wall motion can be used for the diagnosis of hibernating myocardium. Thallium-201 imaging is a technique in which perfusion images are obtained at rest and after exercise or pharmacologic stress. The reversible perfusion defects indicate

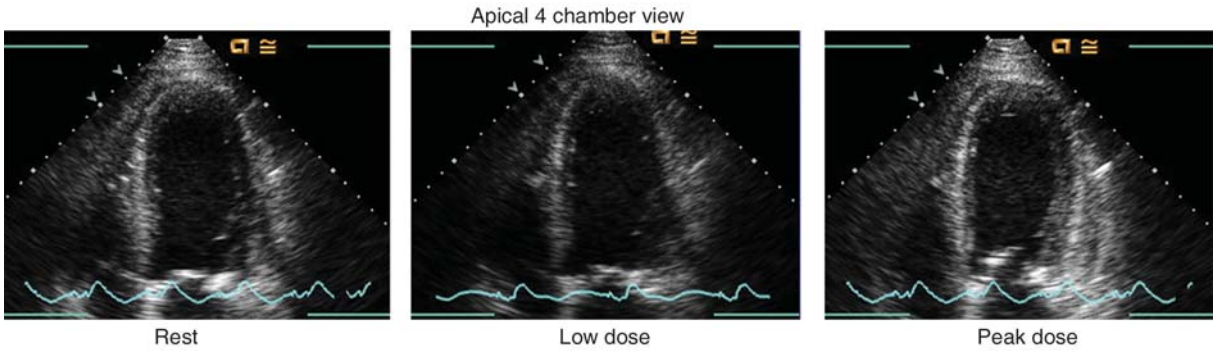


FIGURE 1: Apical four chamber view during dobutamine stress echocardiography is illustrated. During lower dose of dobutamine infusion, there was increased wall motion of the anteroapical segment of the left ventricle. During peak dose the same segments had paradoxical motion

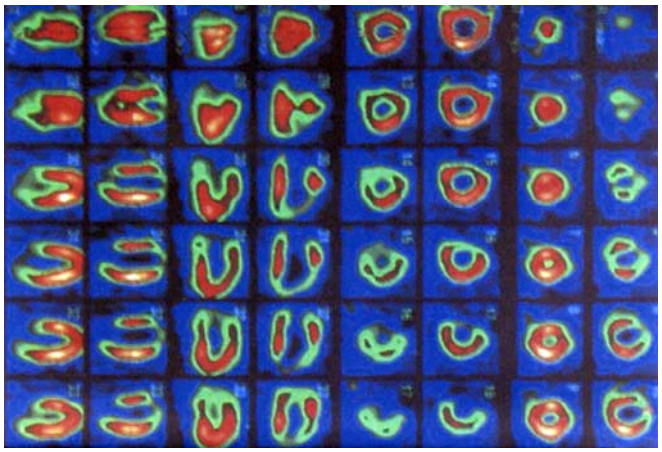


FIGURE 2: Radionuclide (scintigraphic) detection of hibernating myocardium by positron emission tomography (PET) is illustrated. Short axis slices (rows 1–4), vertical long axis slices (rows 5 and 6) and horizontal long axis slices (rows 7 and 8) are shown. The resting perfusion images with rubidium-82 (rows 1, 3, 5 and 7) show a large lateral wall perfusion defect which indicates nonviable myocardium. The other areas show uptake of rubidium-82 indicating that these segments are viable. The myocardial metabolic activity was assessed with the use of radioactive fluorodeoxyglucose (FDG). The FDG uptake (rows 2, 4, 6 and 8) indicates active myocardial metabolism and viability

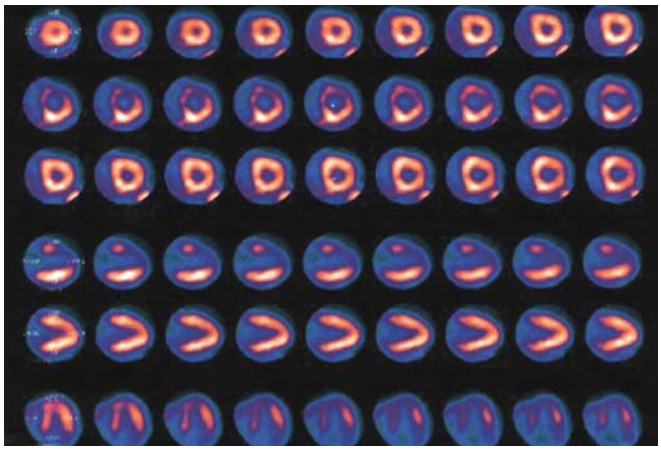


FIGURE 3: Gated perfusion single photon emission computed tomography dual isotope imaging using thallium-201(rest even rows), technitium-99 m sestamibi (stress related, odd rows) to detect presence and extent of ischemic myocardium is illustrated. The first four rows from the top show short axis slices from apex (left) and to base (right). Rows 5 and 6 show vertical long axis slices from septum (left) to lateral wall (right) and rows 7 and 8 show short long axis slices from inferior wall (left) to anterior wall (right). A large reversible perfusion defect in the anterolateral wall of the left ventricle demonstrates ischemia

presence of myocardial ischemia (Fig. 3). Hibernating myocardium is diagnosed abnormality of the same segments if there is also wall motion abnormality of the same segments.

Cardiac MRI is a noninvasive technique which can be used to determine left ventricular volumes, ejection fraction, wall motion abnormalities and wall thickening. Thus, MRI can be used for detection of hibernating myocardium. Cardiac MRI with delayed contrast enhancement is being increasingly used to assess the magnitude and distribution of fibrosis[35,37,38,50,51] (Fig. 4). The magnitude of fibrosis correlates with functional, hemodynamic, and short-term and long-term improvements in prognosis of patients with Stage C systolic heart failure undergoing revascularization treatments. Even in patients with nonischemic dilated cardiomyopathy, mid-wall fibrosis is associated with increased all cause mortality, cardiac hospitalization and increased risk of sudden cardiac death and ventricular tachycardia.[53-55] The NOGA electroanatomic endocardial mapping has been used to distinguish between fibrosis and viable myocardium. Very low endocardial unipolar voltages indicate fibrosis, whereas presence of viable myocardium is associated with larger voltages.[56] However, the electroanatomic endocardial mapping is an invasive technique and rarely required in clinical practice. Metabolic SPECT imaging with beta-methyl-p-[^{123}I]-iodophenyl-pentadecanoic

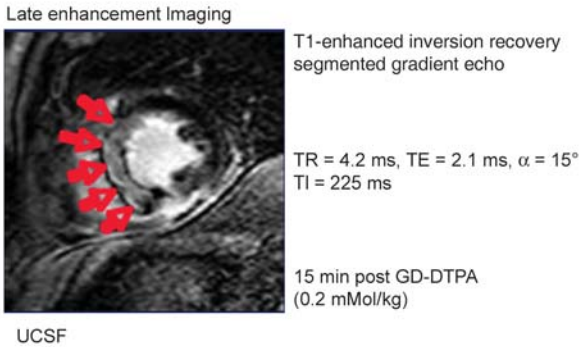


FIGURE 4: Cardiac magnetic resonance imaging with late delayed gadolinium enhancement demonstrating presence of areas of myocardial fibrosis (arrows)

acid (BMIPP) has been used to assess presence of ischemic myocardium.[57] BMIPP is a fatty acid analog. Fatty acid metabolism is suppressed during ischemia, such as during exercise, and induced myocardial ischemia, and there is delayed recovery of metabolic function after reperfusion (metabolic stunning, ischemic memory). However the role of these newer techniques for detecting hibernating myocardium in clinical practice has not been established.

REVASCULARIZATION OF HIBERNATING MYOCARDIUM AND CHANGES IN VENTRICULAR FUNCTION

That revascularization of ischemic myocardium by coronary artery bypass surgery improves left ventricular regional and global mechanical and metabolic function has been reported many years before the importance of detection of hibernating myocardium was realized.[58-60a] There was a reduction of end diastolic and end systolic volumes along with an increase in ejection fraction. There is also an improvement in myocardial metabolic function as evident from conversion from lactate production to lactate extraction (Fig. 5). The improvement of function was observed both in patients with acute ischemic syndrome and chronic ischemic heart disease. In patients with "preinfarction angina" with reduced ejection fraction, revascularization of ischemic myocardium by coronary artery bypass graft surgery (CABG) was associated with increased ejection fraction, and improved regional wall motion.[58,59] In patients with chronic ischemic heart disease, CABG also improves regional wall motion and ejection fraction. Improvement in wall motion was not observed in the areas of previous myocardial infarction detected by the presence of Q waves presumably because these areas contain predominantly scar tissue. However, when these studies were performed, the advanced imaging techniques, such as MRI or FDG-PET, were not available. The improvement in left ventricular ejection fraction following CABG has been reported in other studies.[6,7,38] In a meta-analysis of 24 studies of 3,088 patients with left ventricular ejection fraction of 0.32 ± 0.08%, ejection fraction increased after an average follow-up of 25 ± 10 months. The various imaging techniques have been used to predict the likelihood of improvement of regional and global left ventricular function. For the prediction of improvement of regional function FDG-PET had the highest sensitivity. Dobutamine stress echocardiography had relatively low sensitivity but high specificity. The assessment of end diastolic wall thickness by MRI is very sensitive but not specific for prediction of improvement of regional function after revascularization. It should be appreciated that even after successful revascularization of the hibernating myocardium, functional improvement does not occur in all revascularized segments. The extensive cellular damage, presence of widespread fibrosis and already severely remodeled left ventricle may preclude improvement in regional left ventricular function. The duration of ischemia before revascularization, incomplete revascularization and extensive myocyte loss either due to necrosis or apoptosis are also contributing factors for lack of improvement of ventricular function.

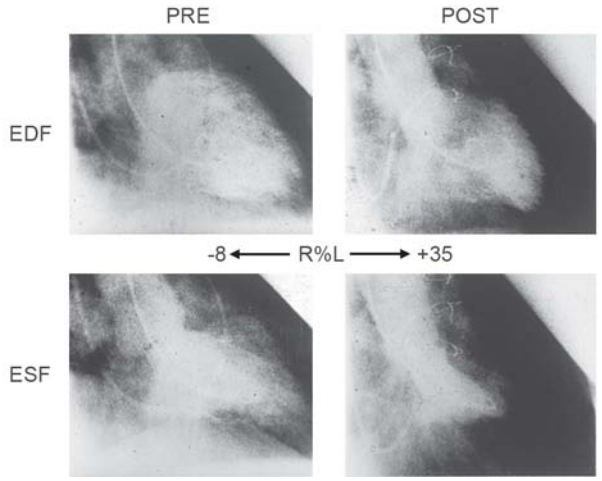


FIGURE 5: Effects of successful bypass grafting of occluded left anterior descending coronary artery on regional mechanical and metabolic function. Preoperative and postoperative contrast ventriculograms and left ventricular anterior wall myocardial lactate extractions are illustrated. Preoperative end diastolic (EDF) and end systolic (ESF) frames show severe hypokinesis of the left ventricular anterior wall. Postoperative EDF and ESF show normal anterior wall motion. Global ejection fraction also improved. Preoperatively there was lactate production from the left ventricular anterior wall (–8%) which normalized after bypass surgery

Reverse remodeling is inversely related to the number of viable myocardial segments present before revascularization. A significant reverse remodeling with improvement of left ventricular function is expected if the number of viable myocardial segments are 4 or greater.[55] Reverse left ventricular remodeling is associated with a decrease in left ventricular end diastolic and end systolic volumes and an increase in ejection fraction.[61] In patients with systolic heart failure with ventricular remodeling mechanical dyssynchrony with or without electrical dyssynchrony are relatively common.[62] Revascularization of hibernating myocardium has the potential to establish synchrony and improve regional and global systolic and diastolic function.[62] For prediction of improvement in global left ventricular function defined as an increase in ejection fraction by 5% or more, nuclear imaging techniques such as Thallium-201 scintigraphy has a relatively high sensitivity whereas dobutamine stress echocardiography has a higher specificity.

Many contemporary studies have also demonstrated that reperfusion treatment either by CABG or PCI improves left ventricular function.[30,31] Successful revascularization has the potential to produce beneficial effects on left ventricular remodeling.[30,31,61] Reverse left ventricular remodeling is associated with a decrease in end diastolic and end systolic volumes and often with increased ejection fraction.[58-61]

REVASCULARIZATION OF HIBERNATING MYOCARDIUM AND CHANGES IN PROGNOSIS

In the coronary artery surgery study (CASS) registry, 651 patients with ejection fraction of less than 35% were included.[63] The 5-year survival in patients who had CABG was 68% as compared to 54% in the medical therapy group. The survival benefit of CABG was greater in patients with ejection fraction of less than 26% (surgical: 63%, medical: 43%). It should be appreciated that this was not a randomized trial.

That revascularization of hibernating myocardium improves prognosis compared to medical therapy has been observed in

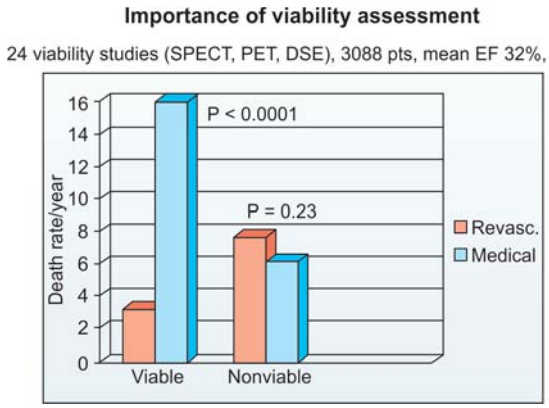


FIGURE 6: The influence of presence of myocardial viability on mortality in patients with systolic heart failure (mean ejection fraction 32%). A meta-analysis was performed of 24 viability studies consisting of 3,088 patients. The viability studies were done by SPECT, or PET or dobutamine stress echocardiography. In patients with viable myocardium, revascularization therapy was associated with a significantly lower mortality compared with medical therapy. In patients without viable myocardium, there was no difference in mortality between medical therapy and revascularization therapy. The duration of follow-up (f/u) was 2 years. (*Source:* Published with permission from Allman KC et al)[38]

other studies.[38] In this study reported by Allman KC et al., 24 viability studies were analyzed. There were 3,088 patients with mean left ventricular ejection fraction of 32%. During 2 years of follow-up, in patients with viable myocardium, the annualized mortality was 16% with medical therapy and 3.2% following revascularization. Thus there was an 80% reduction in mortality with revascularization treatment compared to medical therapy. In patients with nonviable myocardium there was no difference in mortality with medical or revascularization treatment (Fig. 6).

The results of coronary bypass surgery with or without surgical ventricular reconstruction (STICH) trial suggest that CABG with or without ventricular reconstruction can be performed with a low operative mortality.[64] In this prospective, randomized trial, the stable patients with ejection fraction of 35% or less were randomized. The average ejection fraction was 28%. The median follow-up was 48 months. The operative mortality was 2–4%. The death from any cause or hospitalization for cardiac causes was 59% (approximately 15% annually). Thus, this study demonstrated that revascularization can be performed with low operative mortality in patients with severe systolic heart failure. In this study detection of hibernating myocardium was not essential and also there was no medically treated group.

In another non-randomized study, it was reported that the operative mortality for surgical anterior ventricular restoration and coronary artery bypass surgery was between 4% and 9%.[65] There was an increase in left ventricular ejection fraction early after surgery with reduction in end diastolic and end systolic volumes. The long-term survival was 63% at 120 months. In this study, also there was no medically treated group.

In a contemporary study, the influence of off-pump coronary artery bypass surgery (OPCAB) was compared to that of conventional on pump technique (CCAB) in patients with low left ventricular ejection fraction.[66] In OPCAB group, the average ejection fraction was 27.5% and in CCAB group, 30.1%. The

TABLE 5

Mortality and morbidity of patients with severe systolic heart failure following coronary artery bypass surgery

	Results	
Variables	*OPCAB*	*CCAB*
EF	27.5%	30.1%
Urgent	33.3%	32.1%
UA	60.6%	41.7%
Euros	12.96	8.47
Mortality	6.1%	10.7% NS
Morbidity	19.7%	35.7%

(Abbreviations: CCAB: Conventional on pump coronary artery bypass; EF: Ejection fraction; UA: Unstable angina; OPCAB: Off pump coronary artery bypass surgery; Euros: Euro score). (*Source:* Darwazah et al. Myocardial revascularization in patients with low ejection fraction < 35%: effect of pump technique on early morbidity and mortality. J Card Surg. 2006;21:22)

percentage of patients who required surgery urgently was similar in both groups (OPCAB 33.3% and CCAB 32.1%); however, the percentage of patients with unstable angina was higher in the OPCAB group (OPCAB 60.6% and CCAB 41.7%). The mortality was similar in both groups (OPCAB 6.1% and CCAB 10.7%, p = NS). This study suggests that even in patients with urgent indication of CABG, as in some patients with acute coronary syndrome, the operative mortality is relatively low (Table 5).

The traditional view has been that only patients who present with angina are likely to improve after revascularization and patients with symptoms of heart failure are unlikely to benefit.[67] In a prospective study,[67] 97 patients with angina only and 83 patients with only symptoms of heart failure were evaluated. All patients had low ejection fraction (28 ± 9%) and were in NYHA class III or IV. The number of patients undergoing CABG or PCI in the angina group was 59/38 and in patients with only symptoms of heart failure were 54/29. In hospital mortality was 5% in the angina group and 7% in the heart failure group. Thallium-201 scintigraphy was employed to detect viable myocardium and scar tissue.

At 6 months, the heart failure symptoms improved in patients with viable myocardium. In patients with viable myocardium, the 3-year survival in the angina group was 89% and in the heart failure group, 87%. The results of this study suggest that, if significant viable myocardium is present, revascularization improves long-term survival in patients with systolic heart failure irrespective of the presenting symptoms of angina or of heart failure (Table 6).

Earlier uncontrolled single center study compared long-term survival of patients undergoing CABG to that of cardiac transplantation.[68,68a] The operative mortality for CABG was 7.2% and that of cardiac transplantation 18.2%. In this study, 2-, 4- and 6-year survival in patients with CABG were 90.3%, 87.6% and 78.9%, and after cardiac transplantation 74.9%, 73.2% and 68.9%. It should be emphasized that the results of cardiac transplantation have improved considerably in recent years. The transplant operative mortality is approximately 5%. Ten-year survival is about 50%, despite much sicker patients being transplanted.[69]

TABLE 6

Results of revascularization on mortality and morbidity in patients with severe systolic heart failure with or without viable myocardium patients with mainly angina and patients with only heart failure were studied

Variables	*Angina*	*Only heart failure*
Patients	97	83
CABG/PCI	59/38	54/29
Mean VMS	8.5	8.4
In hospital mortality	5%	7%
WMSI		
with VM	Decreased	Decreased
without VM	Unchanged	Unchanged
3 years		
Survival	84%	78%
with VM	89%	87%

(Abbreviations: WMSI: Wall motion segment index; CABG/PCI: Coronary bypass graft/Percutaneous coronary intervention; VMS: Viable myocardial segments; WMSI: Wall motion segment index; VM: Viable myocardium). (*Source:* Gimelli A, et al. Beneficial effects of coronary revascularization in patients with ischemic left ventricular dysfunction with and without anginal symptoms. Interactive Cardiovascular and Thoracic Surgery. 2002;1:9)

In a prospective randomized unblinded clinical trail, role of CABG was assessed in the era of advanced medical therapy. A total of 1,212 patients with left ventricular ejection fraction of 35% or less were enrolled. There were 602 patients who received medical therapy alone and 610 patients who received CABG and medical therapy.[70] The median duration of follow-up was 56 months. The death from any cause was 41% in the medical therapy alone group compared to 36% in the CABG and medical therapy group. This difference in the all cause mortality between the two groups was not statistically significant. However the cardiovascular mortality was 28% in the CABG group compared to 33% in the medical group and this difference was statistically significant. Death from any cause or hospitalization for cardiovascular causes occurred in 58% in the CABG group and in 68% in the medical therapy group (Table 7). The results of this study suggest that revascularization and optimal medical therapy has the potential to improve long-term prognosis of patients with systolic heart failure.

It has been postulated that the improvement in prognosis of patients with severe systolic heart failure after revascularization either by PCI or by CABG is related to the presence and extent of hibernating myocardium.[71] If the extent of hibernating myocardium is less than 25%, the prognosis remains poor despite successful revascularization. It has also been suggested that it is desirable to assess the presence, magnitude and distribution of myocardial fibrosis before revascularization is contemplated.

The relation between presence of viable myocardium and prognosis with medical or revascularization treatment in patients with systolic heart failure has been investigated in many uncontrolled studies.[38,72-79] In general, in patients with viable myocardium, surgical revascularization was superior to medical therapy. However these studies were uncontrolled and retrospective and mostly single center experience. Furthermore the techniques used to assess viability were variable in different studies.

The influence of revascularization by CABG in patients with severe systolic heart failure in presence or absence of viable myocardium has been investigated in a randomized unblinded prospective clinical trial.[80] The assessment of myocardial viability was performed in 601 patients. Either SPECT or dobutamine echocardiography or both was used to assess viability. The patients were randomized to receive medical therapy alone (303 patients) or to receive CABG and medical therapy (298 patients). The medical therapy consisted of angiotensin inhibitors (92%), beta-blocker (89%), statin (85%) and aspirin (85%). Eight percent of patients had a previous myocardial infarction. The average left ventricular ejection fraction was 26.7 ± 8.6%. The majority of patients were in NYHA functional class II or III. Only 14% of patients were in functional class IV. The median follow-up period was 5.1 years.

There was no difference in mortality in the medical therapy alone group compared to patients who received CABG and medical therapy. In patients without myocardial viability the mortality was 55.8% in the medical group and 41.5% in the CABG group. This difference was not statistically significant. In patients with viable myocardium, the mortality in the medical group was 35.4% and 31.2% in the CABG group (p = 0.53).

The overall mortality tended to be higher in patients without myocardial viability (51%) than in patients with myocardial viability (37%) (Fig. 7). However, following multivariate analysis, no significant difference was found between the two groups (p = 0.21) (Figs 8A and B).Thus assessment of

TABLE 7

The differences in outcome in patients with severe systolic heart failure with left ventricular ejection fraction of 35% or less treated medical therapy alone or CABG and medical therapy

	Medical therapy (N = 602)	*CABG HR with CABG (N = 610)*	*(95% CI)*	*P*
Death from any cause	41%	36%	0.86	0.12
Death from CV cause	33%	28%	0.81	0.05
Death from any cause or hospitalization for heart failure	54%	48%	0.84	0.03
Death from any cause or hospitalization for CV cause	68%	58%	0.74	< 0.001
Death from any cause or hospitalization for any cause	73%	65%	0.81	0.003
Death from any cause or PCI or CABG	55%	39%	0.60	< 0.001

(Abbreviations: CV: Cardiovascular; PCI: Percutaneous coronary intervention; CABG: Coronary artery bypass graft surgery; N: Number; CI: Confidence interval). (*Source:* Published with permission from Velazquez EJ, et al)[70]

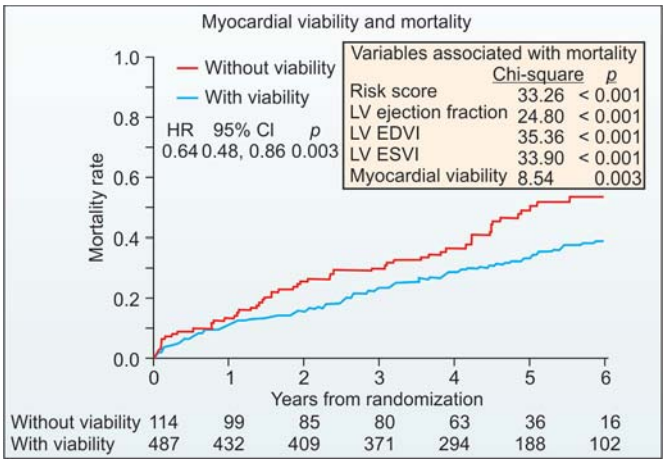
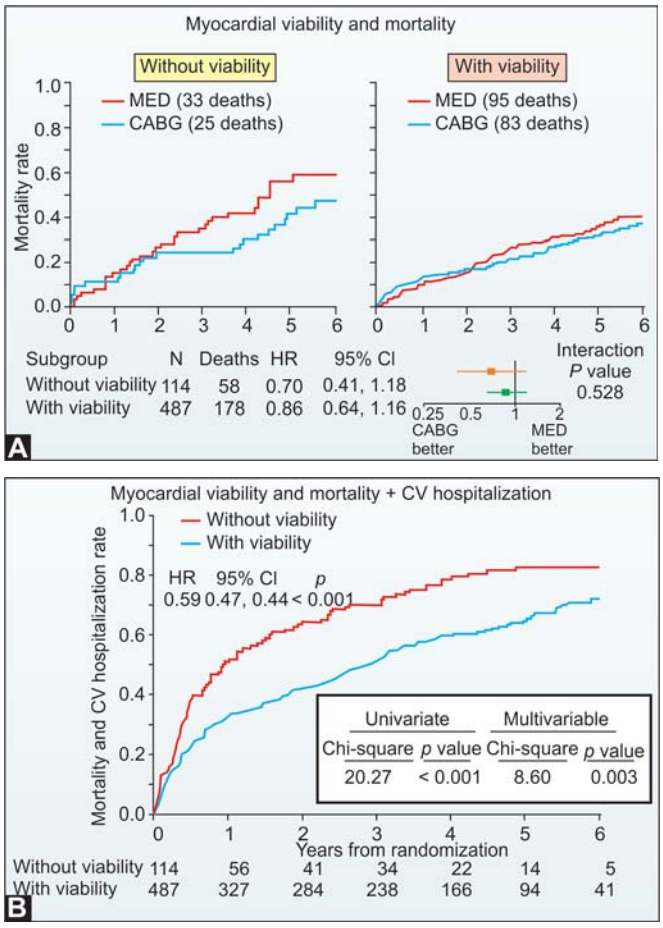


FIGURE 7: Kaplan-Meier analysis of probability of mortality in patients with ischemic cardiomyopathy is illustrated. In patients with viability the mortality tended to be lower. The other variables analyzed were: ejection fraction, end diastolic volume index (EDVI); end systolic volume index (ESVI) and surgical risk score. (*Source:* Modified from Bonow RO, et al)[80]



FIGURES 8A AND B: Kaplan-Meier analysis of the probability of mortality according to the myocardial viability status and medical or surgical treatment. There was no significant difference in mortality with CABG or medical therapy and the myocardial viability status. (*Source:* Modified from Bonow RO, et al)[80]

myocardial viability did not influence the long-term prognosis of patients with obstructive coronary artery disease and severe systolic heart failure whether they received CABG or medical therapy. In this study, there was no significant interaction between myocardial viability and medical or CABG treatment in respect to all cause mortality, cardiovascular mortality and rate of hospitalization.[80]

It should be appreciated that there has been considerable improvement in both medical and surgical therapy of systolic heart failure.[80,81] The annual mortality with current medical therapy is about 7%[80] which is lower than (approximately 15%) reported in previous studies.[72-79] In the randomized clinical trials, the patients with severe angina and left main coronary artery disease are excluded and in these patients revascularization treatments should be considered. It should be appreciated that in this trials, the viability study was optional and was at the discretion of the physician. Furthermore the number of patients randomized was relatively small. The number of events both in medical therapy alone and CABG and medical therapy groups was also low. Nonetheless, the results of these studies suggest that determination of myocardial viability may not be always necessary before CABG is considered. These studies also suggest that the patients with overt severe systolic heart failure with low left ventricular ejection fraction should be adequately treated that medical therapy that has been documented to improve prognosis. Revascularization therapy either by PCI or by CABG should be considered only in patients refractory to medical therapy.

SUMMARY

Hibernating myocardium is frequently encountered in patients with systolic heart failure. Various imaging techniques can be employed to detect the presence and the extent of hibernating myocardium. Revascularization has the potential to improve ventricular function. However there is paucity of data to support that routine revascularization improves prognosis of such patients. Currently available aggressive medical therapy should be initially employed even when hibernating viable myocardium is present. Revascularization treatment should be considered in patients refractory to medical therapy.

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Chapter 78

Advanced Cardiac Therapies for End Stage Heart Failure: Cardiac Transplantation and Mechanical Circulatory Support

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Chapter Outline

- Identifying Candidates for Advanced Cardiac Therapies
  - — Recognition of Advanced Heart Failure with Poor Prognosis
  - — Prognostic Determinants and Risk Scores in Heart Failure
  - — Prognostic Scores
  - — Functional Assessment
  - — A Perspective on Optimal Medical Management
  - — Evaluation of Patient Referred for Advanced Cardiac Therapies
  - — General Approach to Preoperative Assessment of Advanced Cardiac Therapies
- Heart Transplantation
  - — Indications and Contraindications for Cardiac Transplantation
  - — Donor Selection and Perioperative Period
  - — Survival with Cardiac Transplantation
- Mechanical Circulatory Support
  - — Selection of a Ventricular Assist Device Patient
  - — Indications and Contraindications for Mechanical Circulatory Support
  - — Design of Ventricular Assist Device and Impact on Post-implant Physiology
  - — Caring for the Mechanical Circulatory Support Device Recipient
  - — Postoperative Patient and Device Management
  - — Survival with Mechanical Circulatory Support
  - — Myocardial Recovery with Device Explanation
  - — Future Directions

INTRODUCTION

Heart failure afflicting, otherwise healthy people, is a tragic circumstance. The desire to fully rehabilitate people with isolated organ failure has driven the fields of organ transplantation and artificial organ replacement since its inception, and continues to do so today. First reported in 1963 with the use of implantable artificial ventricle in a human, major boost to development of mechanical circulatory support (MCS) and assist devices came with National Institutes of Health establishing the of the artificial heart program in 1964 and National Heart Lung Blood Institute in 1970.[1,2] Concurrent development of techniques of heart transplantation in 1970s and advances in immunosuppression in the 1980s and 1990s have made transplantation most desirable therapy in end stage heart failure patients. However shortage of donors and development of safer, durable assist devices have led to an expansion of treatment options.

Treatment of end stage heart failure now exploits both organ transplant and circulatory pump strategies with good results, even if the goal of full rehabilitation remains elusive for most. Heart transplantation and left ventricular assist device (LVAD) implantation have well-established benefit over medical therapy for palliation of advanced heart failure in well-selected individuals.[3,4] Survival with heart transplantation is about 88% in the first year and 50% at the end of 10 years (Fig. 1). Likewise, with improved durable LVADs, the survival is remarkable at 66% at the end of 2 years (Fig. 2). These therapies offer almost an absolute survival improvement of 150% at the end of 1 year in appropriately selected heart failure patients when compared to conventional medical management.[4] This kind of therapeutic paradigm is quite unmatched in the modern era of medicine.

The major challenge in treating people with end stage heart failure today is the appropriate application of these therapies to a burgeoning number of afflicted individuals, many of whom have serious comorbidities involving other organ systems.

Centers offering advanced cardiac therapies are highly regulated, which is appropriate since heart transplantation and mechanical circulatory device implantation are resource intensive treatments that require highly trained multidisciplinary teams in

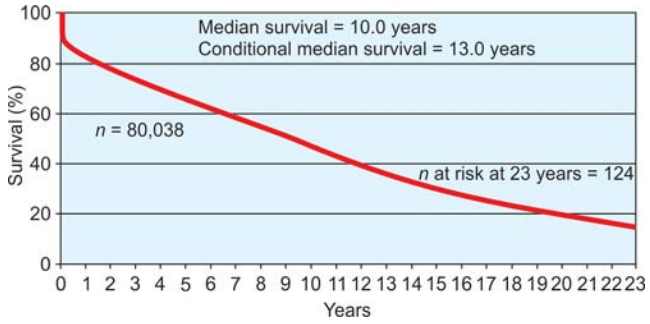


FIGURE 1: Long-term survival of patients undergoing heart transplantation. (*Source:* Modified from ISHLT registry)

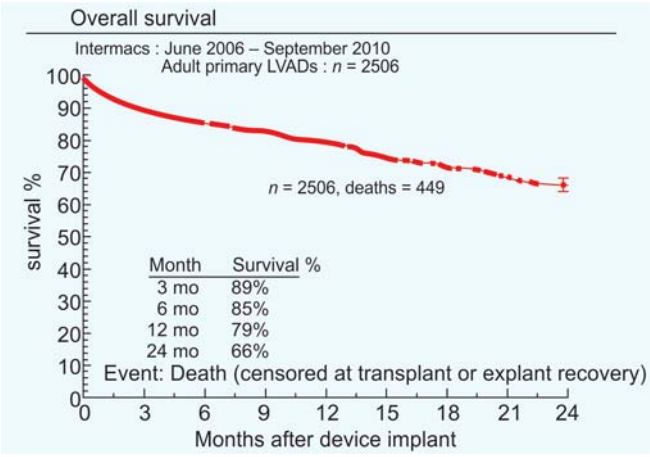


FIGURE 2: Medium-term survival after LVAD implantation. (*Source:* Modified from INTERMACS registry)

order to succeed. In the United States, certifications by the United Network of Organ Sharing (UNOS) and The Joint Commission indicate compliance with consensus standards for the evaluation, treatment and aftercare of these patients. Center-specific heart transplant volumes and outcomes must be reported through the Surgical Registry of Transplant Recipients and are available to the public through the UNOS website.[5] Ventricular assist device programs providing long-term support as an alternative to transplantation, a strategy called "Destination Therapy" is certified by The Joint Commission. Certified LVAD centers are required to participate in a unique national registry designed to continually assess the efficacy and cost effectiveness of MCS. The registry is the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS),[6] which is a collaborative effort of the US National Institutes of Health, Food and Drug Administration (FDA) and the Center for Medicare Services (CMS) with data coordination support from a contracted academic center (currently, the University of Alabama at Birmingham). Quarterly outcome reports are available to the public on the web.[5,6] Unlike UNOS transplant outcome reports, INTERMACS does not report the outcomes of individual centers. Overall, regulatory processes assure high quality care with a high degree of public transparency at the expense of treatment accessibility outside of major tertiary referral centers.

Worldwide trends in the use of heart transplant and MCS have shifted markedly in the last decade, and more dramatic changes are expected in the foreseeable future. While heart transplant remains the best treatment for end stage heart failure, number of heart transplants performed in the United States and worldwide is declining, while the number of mechanical circulatory device implants is increasing.[7] This is primarily a function of the growing heart failure population and improvements in circulatory device design and availability.

Advanced surgical therapies for the palliation of end stage heart failure will be increasingly available to patients, primarily due to technological improvements in MCS devices and increasing experience in the medical and surgical management of patients receiving the devices.

IDENTIFYING CANDIDATES FOR ADVANCED CARDIAC THERAPIES

RECOGNITION OF ADVANCED HEART FAILURE WITH POOR PROGNOSIS

Prognosis of heart failure has dramatically changed in the past two decades following introduction of angiotensin converting enzyme inhibitors, beta-blockers and implantable cardioverter and defibrillators (ICD). However for patients with end stage prognosis remains guarded without advanced cardiac therapies. Recognition of patients in this category is important for the general internist, family practitioner and general cardiologist to triage patients into appropriate care strategies.

Nature of prognostication in daily practice vastly remains subjective with terms such as "reduced life expectancy", "impaired quality of life" and comparison of heart failure with a malignant process. A reasonable assessment of prognosis influence several treatment decisions in heart failure patients. For example, if anticipated survival is less than 25% in 1 year's time, a frank patient-physician discussion should include referral for advanced cardiac therapies or hospice as options depending on patient preferences. Likewise, estimation of patient's risk of sudden cardiac death and survival is important in consideration for device therapies such as implantable defibrillators and biventricular pacemakers.

Determination of prognosis in heart failure has evolved from recognizing different patient characteristics, which are associated with poor prognosis to prospectively validated risk scores that are able to predict short-term and long-term survival, and morbidity better. It is however, important to note that these characteristics themselves are not etiologically related to heart failure or its worsening.

PROGNOSTIC DETERMINANTS AND RISK SCORES IN HEART FAILURE

Many individual patient characteristics, which are determinants of the prognosis in heart failure, have been identified (Table 1).[8] Of all these individual characteristics New York Heart Association (NYHA) classification, serum sodium and creatinine have been long recognized as important indicators of severity of heart failure. Increased age and other comorbidities, such as anemia, diabetes mellitus and ischemia, have been known to be associated with worse prognosis, but individual prognostic determinants have limited scope in terms of predicting 1-year or 5-year survival.

TABLE 1

Poor prognostic indicators in patients with heart failure

Demographic/Patient indicators
• Advancing age
• Female gender
• Diabetes mellitus
• Presence of coronary artery disease
• Worsening NYHA class
• Increasing heart rate
Laboratory/Electrocardiogram/Echocardiogram indicators
• Rising serum creatinine
• Anemia
• Prolonged QT interval
• NT Pro BNP
• LV mass
• LV ejection fraction

(Abbreviations: LV: Left ventricular; NYHA: New York Heart Association; NT Pro BNP: N-terminal prohormone brain natriuretic peptide)

PROGNOSTIC SCORES

Development of prognostic scores in the last decade has improved our ability to predict survival and also risk of sudden cardiac death. This information is important in deciding two important therapeutic decisions: (1) referral for transplantation and (2) implantation of cardioverter-defibrillator.

Heart failure survival score (HFSS) was one of first scores developed to predict survival of patients on the transplant list.[9] Subsequently, Seattle heart failure model (SHFM) and MUerte Subita en Insuficiencia Cardiaca (MUSIC) score have been developed as prognostic tools.[10,11] These three major prognostic systems have been validated in populations receiving optimal medical therapy and have been compared in Table 2.

A prognostic risk model has been developed to predict the probability of sudden cardiac death. The model consists of increased cardiothoracic ratio, QRS dispersion, QTc dispersion and nonsustained ventricular tachycardia as independent predictors of sudden death, and these have been combined in a score. Such a risk score is especially important in resource poor societies to decide on expensive therapies such as implantable cardioverter defibrillators and biventricular pacemaker.[12]

Another important prognostic indicator, which is not included in the risk scores, is repeated hospitalizations. In a study of 14,374 patients with repeated heart failure hospitalizations, mortality increased with repeated heart failure hospitalizations. The incremental increase in mortality in this study suggests that a patient with third hospitalization in a year has 50% mortality in the following year.[13] It is important to remember when interpreting the risk scores and the individual determinants that these act as a guide to decision-making and not the sole criteria in deciding selection of patients for advanced cardiac therapies. These often help the patients to understand the gravity of their disease process and start a frank discussion about goals of the patient and treatment options.

FUNCTIONAL ASSESSMENT

New York Heart association classification of heart failure is the most widely used tool for evaluation of functional status. It has been shown to have prognostic value, and class IV (patients with symptoms at rest) heart failure is associated with mortality of greater than 50% in 1 year.[14] Patients with heart failure often have coexisting illnesses and associated deconditioning make it hard to assess the contribution of heart failure to these symptoms. Cardiopulmonary exercise testing not only helps in discerning the cause of poor functional status but also provides valuable prognostic information.

During cardiopulmonary exercise testing oxygen consumption (VO_2), carbon dioxide elimination (VCO_2) and minute ventilation (VE) are measured. Peak VO_2 can be used as a surrogate for cardiac output and is a powerful prognostic indicator in patients with heart failure. Patients with peak VO_2 of greater than 14 ml/kg/min have a 1-year life expectancy of 94%, which is greater than 1-year survival with transplantation, thus providing a valuable cutoff point for patient selection.[15] American College of Cardiology/American Heart Association has recommended cardiopulmonary exercise testing as a class I indication for use in transplant patient selection. Use of different variables of cardiopulmonary exercise testing in patient selection is listed in Table 3.[15]

A PERSPECTIVE ON OPTIMAL MEDICAL MANAGEMENT

American College of Cardiology/American Heart Association has put forth guidelines for the management of heart failure. This includes recommendations for clinicians regarding both medical and device therapy.

However there is a definite variation in the applications of these guidelines in real practice. These could be due to differences in training, unfamiliarity with guidelines and lack of appropriate human and material resources to ensure that guidelines are implemented. There have been multiple studies documenting the benefit of multidisciplinary approach to care of patients with heart failure. These exist usually in the form of "heart failure clinics" or "heart failure management programs".

Dedicated heart failure clinics are usually comprised of a heart failure cardiologist, heart failure nurse practitioner, specialist nurses, dietician and a social worker. Most of them also have some form of tele or home monitoring system incorporated within them.

The goals of these clinics are very variable, and most of them aim to improve clinical outcomes, quality of life and decrease cost of care by identifying worsening health status to prevent hospitalization, aggressively delivering medical management to achieve clinical stability, improving patient heart failure knowledge and self-care maintenance and management.

EVALUATION OF PATIENT REFERRED FOR ADVANCED CARDIAC THERAPIES

Patients with advanced heart failure often are already being managed by heart failure programs or have been referred to them by general cardiologist or internists for optimal medical management. These patients usually have been on some form of medical and/or device therapy to optimize heart failure. However it is incumbent upon the heart failure specialist to identify the candidates who would benefit the most, and in whom other interventions would postpone the need for orthotopic heart transplantation (OHT). This process includes

TABLE 2

Comparison of heart failure prognostic risk scores

Risk scoring system	*Variables included*	*Advantages*	*Disadvantages*
Heart failure survival score	• Ischemic cardiomyopathy • Resting heart rate • LVEF • Mean BP • Inter-ventricular conduction delay (IVCD) • Peak VO_2 • Serum sodium	• Extensively validated in the current era • Useful in low-risk and high-risk group	• For moderate-risk group patients other factors need to be considered before deciding on transplant listing • Validated in patients waiting for transplant • Lack of validation in patients in racial groups in whom isosorbide dinitrate and hydralazine combination has been shown to be beneficial
Seattle heart failure model	*Demographics* • Age • Gender • Body mass index • NYHA class • Ejection fraction < 30% • Ischemic etiology of heart failure • Systolic blood Pressure < 160 mm Hg • Diuretic dose (mg/kg per day) • Allopurinol use *Laboratory* • Serum sodium • Serum creatinine • Serum cholesterol • WBC count • Hemoglobin (g/dL) • Percentage of lymphocytes • Uric acid (mg/dL) *Medications* • ACE inhibitor use • Beta-blocker use • ARB use • Potassium sparing diuretic • Statin use *Device use* • ICD implantation • Bi ventricular pacemaker implantation • VAD implantation	• Well validated in all populations with optimal medical therapy and device therapy	• Not validated in populations in whom isosorbide dinitrate and hydralazine have been beneficial • Developed using clinical trial database • May not be completely relevant to clinical practice
MUSIC score	• Previous atherosclerotic event • Left atrial enlargement • LVEF < 35% • Atrial fibrillation • Left bundle branch block or IVCD • NSVT or frequent PVCs • eGFR < 60 ml/min/1.73 m^2 • Sodium < 138 mEq/l • NT-proBNP < 1.0 ng/l • Positive troponin	• Developed in ambulatory heart failure population • Validated for both causes of mortality-pump failure and sudden cardiac death	• Data regarding post-transplant outcomes is not available • Population was not racially diverse

(Abbreviations: ACE: Angiotensin converting enzymes; ARB: Angiotensin receptor blockers; BP: Blood pressure; eGFR: Estimated glomerular filtration rate; ICD: Implantable cardioverter defibrillator; LVEF: Left ventricular ejection fraction; MUSIC: MUerte Subita en Insuficiencia Cardiaca; NSVT: Nonsustained ventricular tachycardia; NYHA: New York Heart Association; PVCs: Premature ventricular contractions; VAD: Ventricular assist device; WBC: White blood cell)

identification of eligible candidates (expected annual mortality > 25%) after optimal medical therapy, assess patient goals of therapy and determine the rehabilitation potential of the candidate.

Patients in cardiogenic shock or prolonged inotropic support usually require an expedited evaluation for OHT. On the other hand, patients referred with NYHA class IIIb–IV symptoms on oral medications initially require an evaluation of reversible causes of worsening heart failure. These include discontinuation of alcohol or drugs use, optimization of medical therapy, interventional or device-based treatment of coexisting arrhythmias such as atrial fibrillation or dyssynchrony and surgical treatment of any correctable valvular lesions before considered for advanced cardiac therapies. This period of 6–8 weeks often gives the heart failure physicians an opportunity to assess patient goals, the social support structure, psychological

TABLE 3

Cardiopulmonary stress testing and indications for transplantation

Use of cardiopulmonary stress testing and indications for cardiac transplantation	*Class of recommendation (level of evidence)*
1. In patients not on or intolerant to beta-blocker, peak VO_2 < 14 ml/kg/min	Class I (B)
2. In patients on beta-blockers, peak VO_2 < 12 ml/kg/min	Class I (B)
3. In patients younger than 50 years and women, percent of predicted (< 50%) peak VO_2 should be used in conjunction with absolute VO_2 max	Class II a (B)
4. In the presence of a submaximal CPX test (RER < 1.05), use of ventilation equivalent of carbon dioxide (VE/VCO_2) slope of > 35 as a determinant in listing for transplantation	Class II b (C)
5. In obese (body mass index > 30 kg/m^2) patients, lean body mass adjusted peak VO_2 < 19 ml/kg/min can be used to guide pretransplant prognosis	Class II b (B)

(Abbreviations: CPX: Cardiopulmonary exercise; RER: Respiratory exchange ratio; VE/VCO_2: Minute ventilation/carbon dioxide elimination; VO_2: Oxygen consumption)

issues and patient's compliance to medical treatment, which are all an important requirement for improved survival and quality of life after advanced cardiac therapies.

However, the key to decision in assessing the patient for advanced cardiac therapies is the concept of "survival benefit margin".[16] This concept encompasses evaluation of the perceived survival benefit of the patient at a given point in time with and without any of the advanced cardiac therapies, and its bearing on physician decision-making. These decisions include evaluating the right time for transplantation listing, selecting the right donor organ and time for MCS. The risk scores discussed above play an important role in providing some objectivity to these decisions.

GENERAL APPROACH TO PREOPERATIVE ASSESSMENT OF ADVANCED CARDIAC THERAPIES

Published consensus documents exist to guide patient selection for heart transplantation.[15] Individual center criteria for patient selection are available to regulatory agencies and third party payers. This encourages uniform practices in the application of this scarce resource. No consensus guidelines exist for optimizing the use of MCS as life-saving ridge to cardiac transplant. INTERMACS registry data suggests that implant prior to the development of cardiogenic shock leads to better post-implant survival.

A CMS coverage decision and published expert opinion documents exists to guide patient selection for MCS as an alternative to transplantation or "destination therapy".[17] The current CMS coverage decision is based on data from a single multicenter randomized trial of MCS against optimal medical therapy (REMATCH).[18] This trial tested a single LVAD device. The more recent guidelines, compiled from expert opinion, are based primarily on the use of another LVAD implanted as DT therapy compared to historical controls.[19]

HEART TRANSPLANTATION

INDICATIONS AND CONTRAINDICATIONS FOR CARDIAC TRANSPLANTATION

Patients who have persistent symptoms after optimization of medical and device therapy should undergo evaluation to further prognosticate their condition. This usually involved a cardiopulmonary stress testing and calculation of risk scores. Patients demonstrating poor prognostic signs such as VO_2 max less than 12 ml/kg/min (on beta-blockers) and less than 14 ml/kg/min, SHFM survival less than 80% in 1 year and high risk patients per HFSS should be evaluated for transplant listing.

Transplant evaluation begins with thorough search for coexisting conditions, which would increase early and long-term mortality. The absolute and relative contraindications are institution specific but most of them follow the broad guidelines set in the International Society of Heart and Lung Transplantation (ISHLT) guidelines for transplant candidate selection[15] (Table 4).

Patients who are in cardiogenic shock and inotrope dependent are sometimes too sick to be transplanted or get a durable device implant as a bridge to transplant. These patients who are INTERMACS class 1 may need to be bridged with an implantable or percutaneous device as a bridge to decision.[20] This can often stabilize the patient and reverse end-organ dysfunction so that post-transplant prognosis improves.

TABLE 4

Commonly accepted absolute and relative contraindications to transplantation

Age
- Greater than 70 years

Malignancy
- Current active malignant conditions
- Pre-existing malignancies which have high rates of recurrence

Obesity
- Body mass index > 35 kg/m^2

Insulin-dependent diabetes mellitus
- Uncontrolled diabetes mellitus with hemoglobin A1c > 7.5
- Presence of end-organ damage

Vascular disease
- Severe symptomatic peripheral vascular disease not amenable to intervention
- Symptomatic cerebrovascular disease not amenable to revascularization

Substance abuse
- Active tobacco, alcohol and drug use

Psychosocial issues
- No demonstrated ability to comply with medical regimen

TABLE 5

United Network of Organ Sharing (UNOS) status and criteria

UNOS status	*Inclusion criteria*	*Patients receiving transplantation (%) (UNOS report 2008–2009)*
1A	1. Mechanical circulatory support for acute hemodynamic decompensation that includes at least one of the following: a. Left and/or right ventricular assist device implanted (includes patients discharged with total artificial heart)* b. Hospital admitted patients with: • Total artificial heart† • Intra-aortic balloon pump† • Extracorporeal membrane oxygenator† 2. Mechanical circulatory support with objective medical evidence of significant device-related complications like device infection, thromboembolism, pump failure and/or life-threatening ventricular arrhythmias† 3. Continuous mechanical ventilation† 4. Continuous infusion of a single high-dose intravenous inotrope (dobutamine ≥ 7.5 mcg/kg/min, or milrinone ≥ 0.50 mcg/kg/min), or multiple intravenous inotropes, in addition to continuous hemodynamic monitoring of with a pulmonary artery catheter‡	50
1B	1. Left and/or right ventricular assist device implanted 2. Continuous infusion of intravenous inotropes	41
2	A candidate who does not meet the criteria for status 1A or 1B	9
7	A candidate listed as status 7 is considered temporarily unsuitable to receive a thoracic organ transplant	

*Candidates may be listed for 30 days at any point after being implanted as status 1A once the treating physician determines that they are clinically stable. Admittance to the listing transplant center hospital is not required.
†Status valid for 14 days and must be recertified by an attending physician every 14 days extend the status 1A listing.
‡Status valid for 7 days and may be renewed for an additional 7 days for each occurrence of a status 1A listing under this criterion for the same candidate.

Management of Patients on the Transplant List

Transplantation requires an elaborate set-up of support structure to ensure timely identification and management of donor, expeditious procurement, and transplantation. In the United States, UNOS is a private not-for-profit agency, which manages transplant system. The selection of recipients is based on the UNOS criteria, which are listed in Table 5.[5]

Patients listed for transplantation have to be meticulously managed so that they are well optimized when the donor heart becomes available. Outpatients on the list have to been evaluated periodically, and the transplant center has to be informed for the change in their health status. The preoperative care of these patients falls into the following categories:

Optimization of heart failure: Patients have to be continually evaluated for changes in their functional status and additional use of devices or inotropes to keep their pulmonary vascular resistance and filling pressures as low as possible.

Preventing infections: Patients requiring inotropic support and outpatients with ventricular assist devices (VADs) are at higher risk of catheter related and driveline infections respectively. Appropriate skin care and early recognition of skin infection can minimize the risk of life-threatening blood stream infection which will necessitate the patient to be inactivated (status 7) on the transplant list. Age and season specific vaccinations have to be administered to prevent infections.

Prevention of allosensitization: Patients on the transplant list should not be exposed to newer human antigens, which could increase their chances of forming antibody thus decreasing the donor pool from whom an organ can be accepted. So in the pretransplant period blood product transfusions should be avoided, if feasible.

DONOR SELECTION AND PERIOPERATIVE PERIOD

Appropriate donor recipient match is essential for short-term and long-term organ function and patient survival in all organ transplantation. Cardiac transplantation unlike other organ transplantation differs in that harvesting beating hearts require the patients to be brain dead. The process of brain death leads to certain physiologic responses, which can damage the heart. Preoperative management of the heart not only involves meticulous search of contraindications but also the optimization of the organ with pre-explant donor management and post-explant organ preservation.

Donors have to be screened for various characteristics, which have been commonly agreed upon to have a deleterious effect on post-transplant outcome[21] (Table 6). Certain donor hearts considered suboptimal can be used for patients on the extended criteria list as noted before.

Donor Management[21]

Brain death imposes several physiological responses, which can have a deleterious effect on the heart. These include an initial Cushing's response (coronary vasospasm due to release of catecholamines) and Anrep effect (maintenance of coronary circulation despite increased afterload) followed by loss of vasomotor tone and hypotension. These physiological states require appropriate management with vasodilators and

TABLE 6

Criteria for donor heart selection

Donor heart screening (Mostly accepted contraindications)	*Class of recommendation (level of evidence)*
Age	Class II a (B)
• Greater than 55 years	
Donor infection	Class II a (C)
• HIV, Hepatitis B and Hepatitis C, HTLV-1	
• Bacterial infection	
— Donor infection is community acquired and death occurs before 96 hours	
— Repeat blood cultures are positive	
— Pathogen specific antibiotic not administered	Class II a (C)
— Endocarditis	
Potential drug use	
• Intravenous cocaine use	Class I (B)
• Chronic alcohol use	
• Carbon monoxide poisoning	
Evaluation of cardiac function	
• LV ejection fraction < 40%	
• Discrete wall motion abnormalities	
• Excessive use of inotropes	Class II a (C)
• Intractable ventricular arrhythmias	
Evaluation of cardiac structure	
• Electrocardiograph evidence of LV hypertrophy or echocardiography evidence of wall thickness > 1.4 cm	Class I (C)
• Coronary artery disease involving major coronary artery	Class I (C)
Donor-recipient size matching	
• Donors whose body weight is > 30% below that of the recipient	
Projected ischemic time	
• Greater than 4 hours	

(Abbreviations: HIV: Human immunodeficiency virus; HTLV-1: Human T-lymphotropic virus type I; LV: Left ventricular)

vasopressors as required. Myocardial depression in the setting of increased catecholamines may require brief inotropic support. Prolonged high doses of inotropes indicate myocardial injury, which would be a contraindication.

Organ Explantation and Preservation

The donor heart explantation procedure begins with decompression of left ventricle and the right ventricle with an incision of the left atrium and inferior vena cava respectively. Subsequently, the aorta is cross-clamped and the preservation solution is infused along with topical cooling. The superior vena cava and main pulmonary artery are subsequently transected to completely excise the heart. The heart is then bagged with preservation solution and ice. The preservation solution contains ice slush, potassium, magnesium, lactiobionate, raffinose and free radical scavengers.[21]

Donor Heart Implantation

Traditionally biatrial technique was used for implantation, which involved anastomoses of the donor and recipient atria. Due to increased incidence of atrial tachyarrhythmias, sinus node dysfunction and tricuspid regurgitation, this technique is being abandoned for the bicaval technique. Bicaval technique involves performance of left atrial anastomoses initially followed by inferior vena cava, superior vena cava and aortic anastomoses.[16]

Immediate Post-transplant Physiology and Management

Important goals of immediate postoperative management are hemodynamic stabilization and prevention of rejection.

Hemodynamic Stabilization

Left ventricular systolic function in immediate post-transplant period is usually preserved or hyperdynamic in nature. Left ventricular (LV) dysfunction in the immediate postoperative period points either to hyperacute/acute rejection or primary graft failure (defined as systolic dysfunction of either LV, right ventricular (RV) or both not due to obvious anatomic or immunologic cause). Diastolic dysfunction is common in the early postoperative period due to ischemic and preservation-related injury to the allograft.

Primary graft failure often manifests as RV dysfunction and is related to poor organ preservation, elevated pulmonary venous resistance or injury to right ventricle during implantation. RV failure is recognized by the elevation of right atrial pressure (above 15 mm Hg) in the presence of decreased cardiac output with increased or normal pulmonary artery pressures. Management of primary graft failure broadly falls into following categories:

Afterload reduction: The use of pulmonary vasodilators such as inhalational nitric oxide, prostanoids or sildenafil.

Inotropic and vasopressor support: Predominantly isoproterenol, dobutamine and milrinone and vasopressors (epinephrine, norepinephrine or vasopressin) if there is hypotension despite use of inotropes.

Preload reduction: Diuretics are often needed in higher doses especially in patients with preoperative diuretic resistance to unload the right ventricle. Ultrafiltration or continuous veno-venous hemofiltration can be used in case of postoperative oliguric renal failure.

Mechanical circulatory support: Intra-aortic balloon pump or temporary assist devices such as Extracorporeal Membrane Oxygenation(ECMO) or Tandem Heart or Levitronix Centrimag device can be used as a bridge to recovery or retransplantation in case of persistent graft failure with end-organ dysfunction.

Rhythm management: Postoperatively between 14% and 60% of the patients have bradyarrhythmias predominantly due to sinus node dysfunction needing chronotropic support with agents such as isoproterenol and dobutamine or temporary pacing. Need for temporary pacing has decreased from since the widespread adoption of the bicaval technique to 18–27% from about 37% with biatrial technique.[22]

Early Immunosuppressive and Antimicrobial Management

Hyperacute rejection in the immediate postoperative period can lead to graft dysfunction and decreased post-transplant survival. This can be prevented with careful prevention of allosensitization in the preoperative period as described earlier and prospective HLA matching in the postoperative period.

Induction therapy usually begins intraoperatively during the removal of the cross clamp and continues as soon as the patient is moved to the ICU. Successful prevention of rejection and infections in the immediate postoperative period is the key to decreasing early morbidity and mortality. Immunosuppressant and regimens with their adverse effects are listed in Table 7.[23-25] Commonly used antimicrobial regimen is also listed in Table 8.

Long-term Management of Transplant Patients

Heart transplantation has been shown to improve quality of life and most patients lead a near normal life and go back to their previous level of functioning as early as 1-year post-transplantation. This requires meticulous management of their immunosuppression and long-term management of the sequelae of transplantation.

The sequelae can be broadly divided into:

Graft related: This includes acute rejection and coronary allograft vasculopathy (CAV), which some believe to be primarily a manifestation of chronic rejection. These two problems lead to chronic allograft dysfunction, which can

TABLE 7

Commonly used immunosuppressants with their mechanism of action and common side effects

Immunosuppressant class	*Mechanism of action*	*Indications for use*	*Major adverse effect*
Antilymphocyte preparations			
• Polyclonal antilymphocyte preparation (ATGAM or thymoglobulin)	• T and B lymphocyte depletion due to complement dependent opsonization	• Steroid resistant acute rejection	• Urticaria • Cytokine release syndrome: fever, chills and rash
• Monoclonal antilymphocyte antibodies (muromonab or OKT3)	• Binds to CD3 molecule of T cell causing depletion due to opsonization	• Steroid resistant rejection	• Cytomegalovirus infections • Cytokine release syndrome
Anti-interleukin (IL)-2 receptor antibodies			
• Basiliximab and Daclizumab	• Blocks IL-2 receptor alpha chain and inhibits proliferation of T lymphocytes	• Induction therapy	• Hypersensitivity
Corticosteroids			
• Prednisone, Prednisolone and Methylprednisolone	• Increased death, decreased proliferation and function of leukocytes including T and B lymphocytes, macrophages, and monocytes	• Induction and maintenance therapy	• Hypertension • Hyperglycemia, diabetes mellitus and weight gain • Osteoporosis and proximal myopathy • Gastric ulcer
Antiproliferative agents			
• Azathioprine • Mycophenolate mofetil	• Decreases proliferation of T and B lymphocytes by inhibiting purine synthesis	• Maintenance therapy	• Myelosuppression • Pancreatitis and hepatitis
	• Inhibits lymphocyte proliferation by blocking purine synthesis	• Induction and maintenance therapy	• Nausea, vomiting and diarrhea
Calcineurin inhibitors			
• Cyclosporine and Tacrolimus	• Reduces function of T lymphocytes by calcineurin dependent transcription particularly by preventing production of IL-2	• Induction and maintenance therapy	• Nephrotoxicity • Hypertension, dyslipidemia and diabetes mellitus • Neurological toxicity
Mammalian target of rapamycin (mTOR) inhibitors			
• Sirolimus	• Inhibits growth and proliferation of T and B lymphocytes by inhibiting IL-2 and IL-6	• Maintenance therapy in place of CI, in patients with CNI related renal dysfunction	• Dyslipidemia • Pancytopenia • Wound healing impairment

(Abbreviation: CNI: Calcineurin inhibitors)

TABLE 8

Post-transplant infection prophylaxis

Organisms and common antimicrobial agent	*Indications*	*Adverse effects and interactions*
Pneumocystis jirovecii (*carinii*)		
• Trimethoprim-sulfamethoxazole	• Induction therapy • Acute and chronic rejection • Use of antilymphocyte agents	• Rash • Renal insufficiency • Hyperkalemia • Bone marrow suppression
Aspergillus sp and *Candida sp*		
• Nystatin	• Induction therapy	• Not significant
Cytomegalovirus		
• Ganciclovir or valganciclovir	• Induction therapy	• Bone marrow suppression

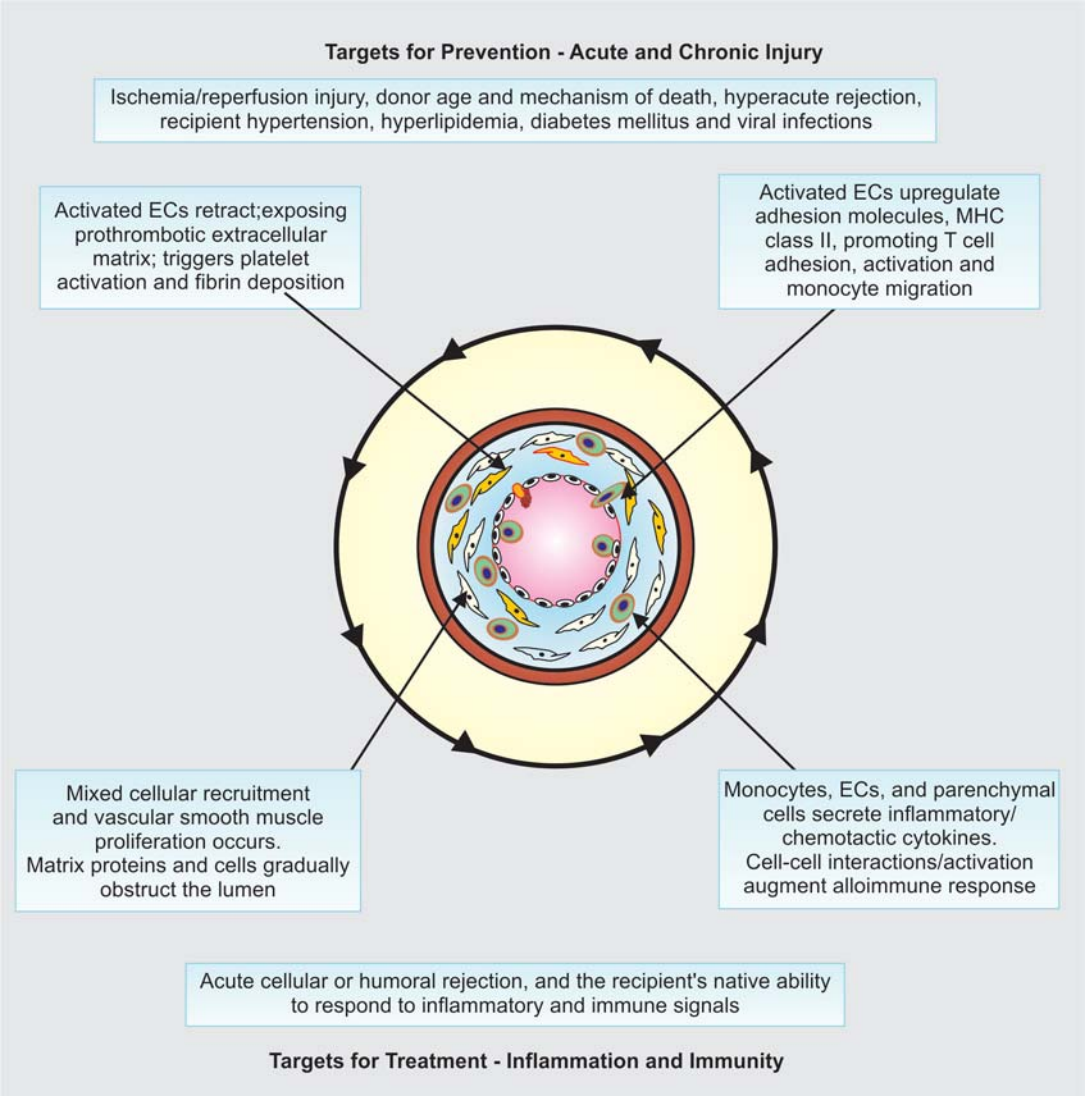


FIGURE 3: Pathogenesis of transplant vasculopathy (Abbreviation: EC: Endothelial cell)

eventually lead to death if retransplantation is not an option. Detailed discussion of rejection and transplant vasculopathy along with its management is listed in Table 9 and Figures 3 and 4.[23,26-28]

Immunosuppression related organ dysfunction: Chronic immunosuppression affects all organ systems in myriad ways. These contribute to post-transplant morbidity and mortality. Minimizing adverse effects, while maintaining adequate immunosuppression to prevent rejection, are one of the main challenges of long-term post-transplant management. Common problems associated with transplant in the long term are described in Table 10.

TABLE 9

Types of rejection

Type of rejection	*Pathophysiology and diagnostic modalities*	*Management medications and principles*
Acute cellular rejection • Classified based on histopathology • Grade 1R (mild rejection) • Grade 2R (moderate rejection) • Grade 3R (severe rejection)	• T lymphocyte mediated damage to the myocardium • Diagnosed by endomyocardial biopsy and staining with hemotoxylin/eosin • Gene expression profiling (GEP) tests evaluating the lymphocyte activation can be used to screen for rejection	• High dose corticosteroids and polyclonal/monoclonal antithymocyte antibody are mainstay of treatment • All grades of rejection are treated in symptomatic patients and in the presence of allograft dysfunction • Asymptomatic patients with moderate to severe grades of rejection have to be treated • Treatment of resistant or recurrent rejection include methotrexate, photopheresis or total body irradiation • Surveillance with periodic endomyocardial biopsies and/or GEP tests
Antibody mediated rejection • Hyperacute (occurs within minutes to hours of implantation of the heart) • Acute (occurs anytime post-transplant)	• Complement mediated destruction due to production of recipient antibodies against the allograft • Hyperacute rejection often involves preformed antibodies to donor HLA or endothelial antigens • Diagnosed by endomyocardial biopsy with immunofluorescence staining against complement fragments in the tissue	• Management of hyperacute rejection includes use of IV immunoglobulin (IVIg), plasmapheresis, high dose steroids and cytolytic therapy • Management of acute rejection includes high dose IV corticosteroids, plasmapheresis, IVIg and rituximab • Screening of donor anti-HLA antibodies to prevent antibody mediated rejection

(Abbreviations: HLA: Human leukocyte antigen; IV: Intravenous)

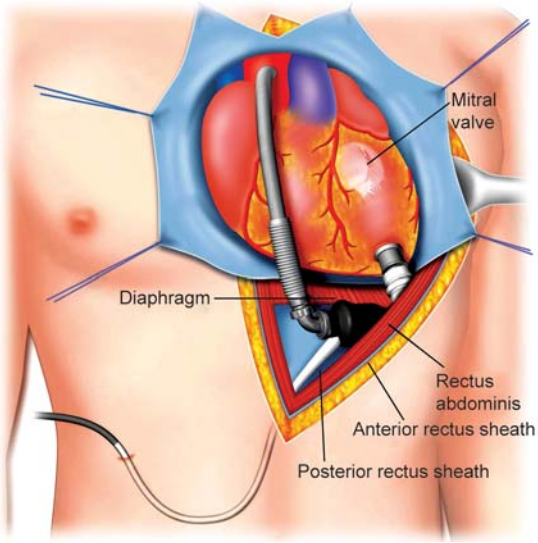


FIGURE 4: Position of thoratec HeartMate II LVAD

Cardiac Retransplantation

Cardiac retransplantation is a controversial issue. The paucity of organs coupled with death of many patients who have not received any transplantation and higher mortality with retransplantation contributes to the ethical dilemma of transplant physicians. Cardiac retransplantation is common in the pediatric and young adult patients who have received their first hearts as children. CAV, early graft failure (within 6 months of first transplantation) and acute rejection are common indications of retransplantation. The survival rates with retransplantation are lower with 1-year survival of about 54% compared to 84% with first transplant.[29] The rates of retransplantation are about 3% and coming years may see an increase in retransplantation rates due to the improvement in survival of patients with heart failure on MCS, making retransplantation less of an ethical issue.

SURVIVAL WITH CARDIAC TRANSPLANTATION

Survival with cardiac transplantation has improved over years and, as per the latest UNOS report, the 1-year survival is about 88% and 10-year survival is about 50%.[5] Median survival of patients who survive up to 1 year is about 13 years. The mortality risk is highest in the first six months after transplant and drops off subsequently to 3–4% per year, which is still high compared to the general population.

Risk factors for 1-year mortality are long-term circulatory support dependence (RR = 1.3; 1.02-1.7; p = 0.03), ischemic cardiomyopathy (RR = 1.2; 1.02-1.3; p = 0.02) and congenital cause of heart failure (RR = 2.27; 2.02–3.68; p < 0.0001). Other comorbidities at the time of transplantation including temporary circulatory support (RR = 2.7; 2.0-3.7; p < 0.001), dialysis dependence (RR = 1.65; 1.30–2.09; p < 0.0001), ventilator dependence (RR = 1.61; 1.24–2.09; p < 0.0004) and infections (RR = 1.16;1.02–1.33; p < 0.02) portend a higher risk as well.[3] Risk factors for mid- to long-term mortality include being female recipient, male recipient receiving female allografts, recipient history of stroke, age at both extremes and lack of treatment with mycophenolate, azathioprine or rapamycin at the end of one year.

MECHANICAL CIRCULATORY SUPPORT

Development of intra-aortic counterpulsation and cardiopulmonary bypass in the 1960s heralded the era of mechanical support. The development of VADs has gone through distinctive phases. Initial phase from 1990s to early 2000 was the era of stronger

TABLE 10

Long-term problems associated with heart transplantation[24,25]

Problems	*Post-transplant incidence and prevalence*	*Pathophysiology and risk factors*	*Management*
Coronary allograft (Transplant) *Vasculopathy*	• Prevalence of 42% at 5 years (moderate-severe CAV of 15%)	• Endothelial injury which begins time of procurement with further insults from prolonged ischemic time, acute rejection, immunosuppressants and post-transplant metabolic syndrome	1. Periodic monitoring with coronary intravascular ultrasonography (IVUS), coronary angiography or CT angiography 2. Choice of Immunosuppressant: preferred use of sirolimus 3. Vitamin C and vitamin E supplementation 4. Choice of statin: pravastatin better than other statins 5. Choice of antihypertensive: calcium channel blocker or ACE inhibitor better 6. Percutaneous coronary intervention in patients with obstructive CAV 7. Retransplantation in patients with established CAV and allograft dysfunction
Opportunistic infections • CMV, *Pneumocystis jirovecii*, *Aspergillus sp*, *Candida sp*	• Incidence and prevalence vary for different organisms during different post-transplantation periods	• Decreased T lymphocyte function • Main risk factor included induction therapy with cytolytic agents	1. Periodic screening for CMV especially during first year in recipients who were CMV seropositive or received hearts from seropositive donor 2. Antimicrobial prophylaxis 3. Season and age appropriate vaccinations
Metabolic syndrome • Diabetes mellitus	• 5-year cumulative incidence of 32%	• Steroid and calcineurin inhibitor induced	1. Frequent screening with hemoglobin A1c and fasting glucose 2. Early weaning of steroids in diabetes prone individuals
• Hypertension	• 5-year prevalence of 95%	• Steroid and calcineurin inhibitor related	1. Use of calcium channel blocker or ACE-I depending on comorbidities 2. Lifestyle modifications
• Dyslipidemia	• Lifetime prevalence of 60-80%	• Immunosuppressants, loop diuretics	1. HMG-CoA inhibitors (pravastatin preferred)
Osteoporosis	• 1-year incidence of fractures of 21–36%	• Steroid and calcineurin inhibitor induced • Hypogonadism can contribute	1. Early weaning of steroids 2. Limiting calcineurin inhibitors 3. Screening and treating hypogonadism in men
Chronic kidney disease	• 5-year prevalence of 10.9%	• Calcineurin inhibitor use • Pre-existing renal dysfunction, old age and female gender are risk factors	1. Minimizing CNI use. Sirolimus (Rapamycin) can be used instead 2. Management of risk factors including hypertension and diabetes mellitus 3. Use calcium channel blockers as a preferred antihypertensive agent
Malignancy (in the order of frequency)	• 20-year cumulative • Incidence 14.4% (all malignancies)		
• Skin (50%) • Lymphomas (10%) or post-transplant lymphoproliferative disorder (PTLD) • Other solid malignancies including lung, breast and prostate (40%)	• 5-year cumulative prevalence 15.1% • 10-year cumulative prevalence of 31.9%	• Decreased activity of NK lymphocytes due to chronic immunosuppression • Epstein Barr virus (EBV) is implicated in the development of lymphoma or PTLD	1. Decrease use of cytolytic therapy especially if antiviral prophylaxis 2. Use of antiproliferative agents (specifically MMF) 3. Yearly skin screening and risk reduction by modification of patient behavior 4. Age appropriate screening for colon, breast and genitourinary cancers

(Abbreviations: ACE: Angiotensin converting enzyme; CAV: Coronary allograft vasculopathy; CNI: Calcineurin inhibitor; CT: Computed tomography; MMF: Mycophenolate mofetil; NK: Natural killer)

more physiologic pulsatile pumps, which had a problem of easy wear and tear. The earlier trials, which included REMATCH, demonstrated significant improvement in survival using these pulsatile pumps. This led to the approval of VADs as destination device in patients who were not transplant candidates in 2002.

The current generation of devices has rotary pumps with non-physiologic continuous flow but offer durability. Successful results from the Thoratec HeartMate II trial as a bridge to transplantation has led to transition from pulsatile devices (HeartMate XVE) to continuous flow devices as the foremost

TABLE 11

Classification of ventricular assist devices

Classification of VADs	*What they mean*	*Examples*
Position		
• Extracorporeal	• Pumping system outside the patient	• Levitronix CentriMag
• Paracorporeal	• Pumping system on the body of the patient	• Thoratec PVAD
• Intracorporeal	• Pumping system inside the body of the patient	• Thoratec HeartMate II
Ventricle supported/replaced		
• Left ventricular assist device (LVAD)	• Supports the LV	• Thoratec HeartMate II
• Right ventricular assist device (RVAD)	• Supports the RV	• Levitronix CentriMag
• Biventricular assist device (BiVAD)	• Supports both LV and RV	• Thoratec PVADS
• Orthotopic replacement of heart	• Replaces the heart	• Total artificial heart
Pumping principle/flow mechanics		
• Displacement pumps or pulsatile pumps	• Similar to native heart; Work by displacement of blood from a filling chamber	• Thoratec HeartMate XVE • Thoratec PVAD
• Rotary pumps or continuous flow pumps (two types): — Axial flow — Centrifugal flow	• Has an impeller, which spins at high speed to propel blood forward continuously • Inflow and outflow are parallel to the rotational axis • Inflow is parallel but outflow is orthogonal to rotational axis	• Thoratec HeartMate II • HeartWare VAD
Purpose of use		
• Bridge to decision — Reversal of end-organ dysfunction — Ascertain transplant candidacy	• Temporary mechanical support in patients who present with cardiogenic shock and their transplant candidacy is uncertain	• Levotronix CentriMag • TandemHeart
• Bridge to transplantation — Reversal of end-organ (especially renal dysfunction) — Decreasing PVR	• Durable mechanical support to help patients survive till transplantation	• Thoratec HeartMate II • HeartWare VAD
• Destination Therapy	• Durable mechanical support as a palliative support till end of life	• Thoratec HeartMate II

(Abbreviations: LV: Left ventricular; NYHA: New York Heart Association; PVAD: Paracorporeal ventricular assist device; PVR: Pulmonary vascular resistance; RV: Right ventricular; VAD: Ventricular assist device)

choice in bridge to transplantation. Currently, about 25–30% of patients undergoing heart transplantation undergo assist device implantation prior to transplantation. The VADs have been classified in several different ways though most common ones are based on indication of use and ventricle being assisted (Table 11).

SELECTION OF A VENTRICULAR ASSIST DEVICE PATIENT

Patients with end stage heart failure, who are being considered for advanced cardiac therapies, should undergo evaluation for transplant eligibility. The patients considered suitable transplant candidates undergo listing and are meticulously followed for deterioration. Listed patients who have worsening pulmonary artery pressures, repeated hospitalization, poor nutrition and quality of life due to heart failure are often considered for VAD implantation as a bridge to transplantation. The key issue with selection is identifying the patients with heart failure early enough that their benefits of undergoing implantation outweigh the risks of surgery. However, unlike guidelines for patient listing for transplantation, consensus guidelines for implantation do not exist. In 2005, INTERMACS has put forth a classification consisting seven categories based on the severity of heart failure to aid in patient selection[30] (Table 12).

INDICATIONS AND CONTRAINDICATIONS FOR MECHANICAL CIRCULATORY SUPPORT

Evaluation for VAD implantation begins with thorough search for conditions, which would:

- Limit survival
- Prevent therapeutic anticoagulation
- Cause intraoperative mortality
- Impair ability to follow complex medical regimens

The indications and contraindications (Table 13) are institution specific but most of them follow the broad guidelines set in the CMS approved indications for durable mechanical support[17] (Table 14).

INTERMACS category 1 constitutes a category of patients with acute cardiogenic shock refractory to inotropes, vasopressors and often intra-aortic balloon support. This category of patients constituted the vast majority of patients being implanted in the earlier era of pulsatile VADs. These patients often have severe end-organ dysfunction or uncertainty about their neurological recovery to perform a durable VAD implantation. In a study from the INTERMACS registry, it was seen that patient belonging to this class undergoing durable assist device implantation had higher mortality compared with less sicker patients. Paucity of time and poor outcomes in the setting of multiorgan dysfunction obviates transplantation as an option.

TABLE 12

INTERMACS classification of advanced heart failure patients

Class	*Description*	*Time to mechanical circulatory support*	*National percentage of patients receiving VAD implantation (%)*
1	"*Crashing and Burning*"; critical cardiogenic shock	Emergent intervention within hours	27
2	"*Sliding on Inotropes*"; deteriorating end-organ function on inotropes	Urgent or semi-elective intervention within days	41.4
3	"*Dependent Stability*"; stable blood pressure and organ function on inotrope	Elective intervention within days to weeks	15.7
4	"*Resting Symptoms*"; daily rest symptoms of volume overload with intensive diuretic dose management	Elective intervention within days to weeks	9.5
5	"*Exertion Intolerant*"; comfortable at rest but homebound due to exertional symptoms often needing extensive symptomatic management	Dependent on progression of symptoms and deterioration of organ function	2.3
6	"*Exertion Limited/Walking Wounded*"; comfortable at rest and minor activities. Fatigability and SOB with minor activity	Dependent on progression of symptoms and deterioration of organ function	2.1
7	*NYHA Class III*; living comfortably with activity limited to mild exertion	Advanced cardiac therapies not currently indicated	1.8

(Abbreviations: INTERMACS: Interagency Registry for Mechanically Assisted Circulatory Support; NYHA: New York Heart Association; VAD: Ventricular assist device)

TABLE 13

Contraindications to ventricular assist device implantation

- Recent stroke or stroke in evolution
- Neurological or psychiatric illness impairing the ability to manage device
- Metastatic cancer deemed incurable
- Advanced cirrhosis
- Dialysis dependent renal failure
- Abdominal aortic aneurysm > 5 cm
- Peripheral arterial disease
- Active systemic infection or major chronic risk for infection such as diabetic neuropathy/stasis ulcers
- Severe pulmonary dysfunction (FEV1 < 1 liter)
- Inability to tolerate anticoagulation
- Lack of social support and inability to comply with medical instructions

(Abbreviation: FEV1: Forced expiratory volume in 1 second)

TABLE 14

Center for Medicare services approved indications for ventricular assist device implantation

1. Postcardiotomy cardiogenic shock
2. Bridge to transplantation
   - Listed for transplantation at a Medicare approved transplantation site
3. Destination therapy
   - Severely decreased LVEF (< 25%)
   - NYHA class IV heart failure for at least 90 days
   - Failure to respond to medical management in 60 of 90 days
   - Not a transplant candidate
   - Life expectancy < 2 years
   - Peak oxygen consumption < 12 ml/kg/min
   - Continuous need for intravenous inotropic support limited by symptomatic hypotension, renal failure or pulmonary congestion

(Abbreviations: LVEF: Left ventricular ejection fraction; NYHA: New York Heart Association)

Such patients are often considered for a "bridge to decision" device that allows physicians to assess cardiogenic shock patients for 24–72 hours before transitioning to a "more durable" MCS device and consideration for transplant listing. The patients who have transitioned to a durable pump are often implanted as "bridge to candidacy". This gives the transplant physician time to assess end-organ function improvement, social support structure, medication compliance and other comorbidities related to transplantation. Minority of these patients who have cardiogenic shock due to myocarditis or post-cardiopulmonary bypass myocardial dysfunction, there is functional recovery leading to explantation of the pump.

The essential characteristics of such devices include easy implantability and removal, reliable and sufficient cardiac support, and easy transportability. Some of the most common devices used today are summarized in Table 11.

Patients belonging to INTERMACS categories 1, 2 and 3 are often the most implanted patients (84%). They constitute patients who are stable or declining functionally on inotropic support. Timing of implantation is the key to postoperative survival and rehabilitation.

Patients in INTERMACS categories 4–6 have heart failure but not severe enough for immediate implantation. The risk-benefit ratio of implanting these patients is unknown. Data from the recently initiated MEDAMACS registry, which has patients with advanced heart failure on medical therapy, is awaited.

Important consideration in deciding the type of assist device also depends on the right ventricular function. If the patient has

severe preoperative RV failure or has a high-risk of developing RV failure postoperatively, such patients may need biventricular support. In the different trials of LVADs, the incidence of RV failure is 10–20%, and 6–17% have needed right ventricular assist device (RVAD) implantation.[4]

Postoperative RV failure is particularly difficult problem to deal with and is associated with decrease postoperative survival and increased length of stay. Inotropic support with a pulmonary vasodilators is often needed postoperatively but suboptimal cardiac output with chronically elevated venous pressure can often result in end-organ dysfunction.

There are several preoperative predictors of postoperative RV failure. Predominantly low RV stroke work index (< 600 mm Hg ml/m^2), increased bilirubin (> 2.0 g/dL), increased creatinine and increased liver enzymes.[31] Though patients with higher risk of RV failure can undergo LVAD placement, postoperative vigilance is necessary for early detection and prompt management with inotropes and pulmonary vasodilators.

DESIGN OF VENTRICULAR ASSIST DEVICE AND IMPACT ON POST-IMPLANT PHYSIOLOGY

Design of a Ventricular Assist Device

A VAD consists of a pump to circulate blood. The pump could be external or housed within the body. The pump has an inflow cannula, which drains the chamber of the heart that is being supported into the pump (Figs 5 and 6). The outflow cannula is another conduit, which connects the pump to the outflow tract of the chamber being supported. All pumps need power, which is usually supplied by an external power source through an electrical lead.

The inflow cannula can be connected to either the atria or the ventricles to unload the right or the left side. Occasionally it can be in the inferior vena cava or the pulmonary veins. The most common place for at the inflow cannula to be anastomosed is the apex. The outflow cannula is anastomosed to the aorta

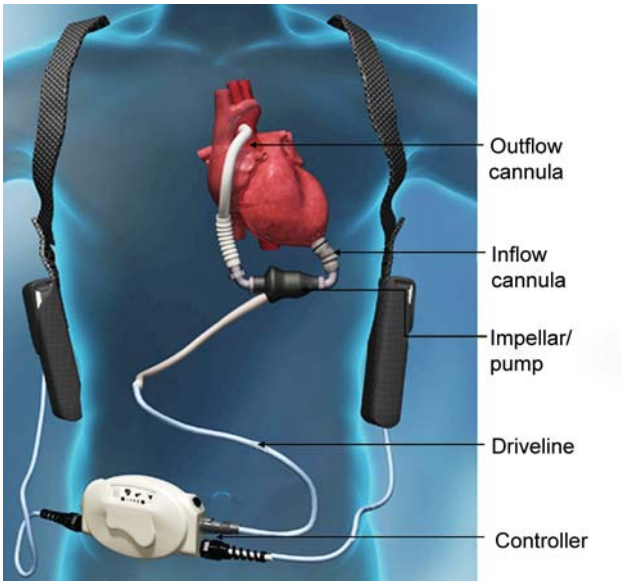


FIGURE 5: Parts of an LVAD (HeartMate II as a prototype)

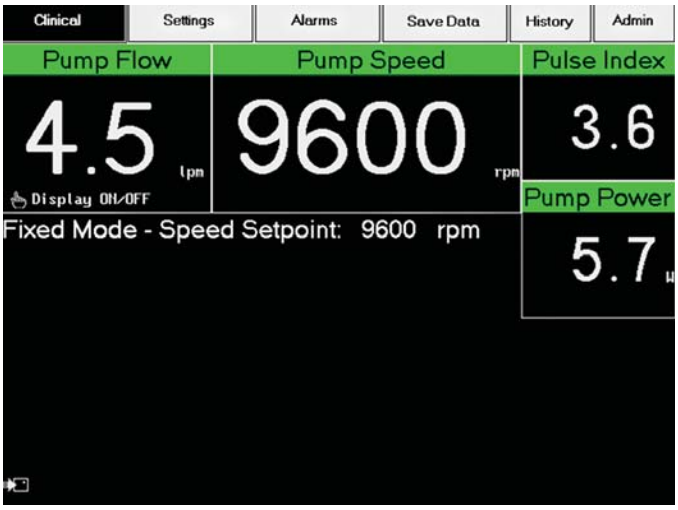


FIGURE 6: Display clinical screen of Thoratec HeartMate II VAD

for the left and the pulmonary artery for the right. The cannula is made of woven Dacron or expanded PTFE. The inner lining of the pump as well as the cannula are lined with titanium microspheres in an attempt to form a textured surface on which biofilm forms soon after implantation. This results in lesser activation of platelet and clotting cascade resulting in lesser thromboembolic events.

Physiology of Ventricular Assist Devices

Insertion of VAD into the circulatory system establishes two systems, which are parallel and competing for flow. The blood from the left atrium has two conduits that it can go to aortic or the inflow cannula of the pump. So the flow through the VAD is mostly preload dependent. The cardiac output becomes heart rate dependent for a given preload per cardiac cycle. Since both the LV and the pump face the same systemic vascular resistance (SVR), the work done (power consumed) by the pump will increase with increasing SVR. For the most part if the pump is functioning optimally, the LV will act as a passive conduit. Most continuous flow devices work in a synchronous mode with maximum flow through the device occurring during native systole.

In contrast, the pulsatile pumps, especially BiVADs, have the capability of functioning in asynchronous mode with the no dependence on native rhythm for functioning. Most of such devices are displacement/pulsatile pumps. In these pumps the rate of pumping can be altered on the pump to deliver the required cardiac output; however, the preload dependence is similar to the continuous flow devices.[31]

Structural and Molecular Effects of Mechanical Unloading

Mechanical unloading leads to remodeling of the ventricle, which includes a reduction in LV end diastolic and end systolic dimension with reduction of size primarily seen in the radial dimension. In most cases, there is an improvement in LV and RV ejection fraction. The QRS duration and QT duration shortening suggestive of electrical remodeling has been observed as well.

At the molecular level, improvements are seen in myocardial filament structure, metabolic gene expression and function and calcium handling by myocytes.

Myocardial structure: Mechanical unloading has been shown to cause regression of LV hypertrophy. There is increased myocardial fibrosis due to increased angiotensin activity.

Neurohormonal Milieu: Myocardial rennin and aldosterone levels decrease after VAD implantation but angiotensin I and II levels increase. This leads to increase in myocardial norepinephrine levels leading to more fibrosis.

Microvascular structure and function: There is an increase in microvascular density and increased endothelial activation after VAD placement.

Beta-adrenergic pathways and signaling: There is reversal of beta-adrenergic remodeling seen in chronic heart failure with improved myocardial contractile response to norepinephrine. Beta-adrenergic receptor density increases as well.

CARING FOR THE MECHANICAL CIRCULATORY SUPPORT DEVICE RECIPIENT

Preoperative Management

Several factors influence poor outcomes after VAD implantation. Prominent patient factors include decreased glomerular filtration rate, decreased platelets, right heart failure, low serum albumin, elevated mean pulmonary artery pressure (> 25 mm Hg), intravenous inotrope therapy and low hematocrit. These variables have been prospectively validated in the form of a risk score in determining patients with higher risk for VAD implantation. Consequently, optimization of patients prior to surgery primarily involves optimization of end-organ function and improving nutritional status.

Intraoperative Management

Certain intraoperative considerations are extremely important in determining optimal functioning of the pump and in turn affect the survival and quality of life post implantation.

Concomitant valvular lesions: Moderate-severe aortic regurgitation and mitral stenosis offer particular challenges due to recycling of ejected blood and decreased preload respectively. Aortic insufficiency should be repaired. In patients with pre-existing RV dysfunction tricuspid repair to reduce moderate to severe tricuspid regurgitation may be beneficial in the postoperative period to prevent RV failure.

Position of the inflow cannula: Inflow cannula should be positioned facing the mitral valve and away from facing the septum or the LV free wall to prevent suction during diastole.

Position of the percutaneous lead: Appropriate positioning of the percutaneous lead is important to prevent infections and percutaneous lead damage in the postoperative period.

POSTOPERATIVE PATIENT AND DEVICE MANAGEMENT

Hemodynamic Stabilization

In the immediate postoperative period, the LV unloading has favorable effects of kidney and respiratory function. In patients with LVAD, reloading an unsupported right ventricle with increased volume may be counterproductive with total cardiac output decrease, as well as worsening hepatic and renal function from an increase in central venous pressure.

Hemodynamic instability in LVAD patients is usually due to RV dysfunction the postoperative period. Pre-existing RV dysfunction and perioperative fluid shifts and transfusions can affect this. Often higher pump speed can result in greater return of blood to the right compared to preoperative state resulting in RV failure.

Management of RV failure is similar to that in post-transplant patients and consists of afterload reduction (with inhalational nitric oxide, prostanoids or sildenafil), inotropic support and preload reduction with diuresis or ultrafiltration. Failure to resolve end-organ dysfunction and hypotension with conservative management should be managed with an insertion of an RVAD.

Hemodynamic instability in BiVAD patients often occur due to an increased incidence of postoperative bleeding in these patients. Volume shifts in these patients need to be managed well to prevent decrease in preload.

Anticoagulation

Thromboembolic events are one of the most common and important adverse event immediately after VAD implantation. Due to continuous flow of blood through a foreign conduit, these patients are at higher risk of activation of procoagulant factors and platelets resulting in thromboembolic events. Therapeutic anticoagulation with warfarin and aspirin is required. The international normalized ratio (INR) goal varies depending on the type of VAD being implanted and other patient comorbidities. The goal INR for Thoratec HeartMate II device is between 1.5 and 2.5. This is often achieved by starting warfarin postoperatively without a heparin bridge to prevent bleeding complications.

Pump Management

Monitoring a ventricular assist device: The display modules of VADs show data regarding the electromechanical functioning and flow characteristics (Fig. 7).

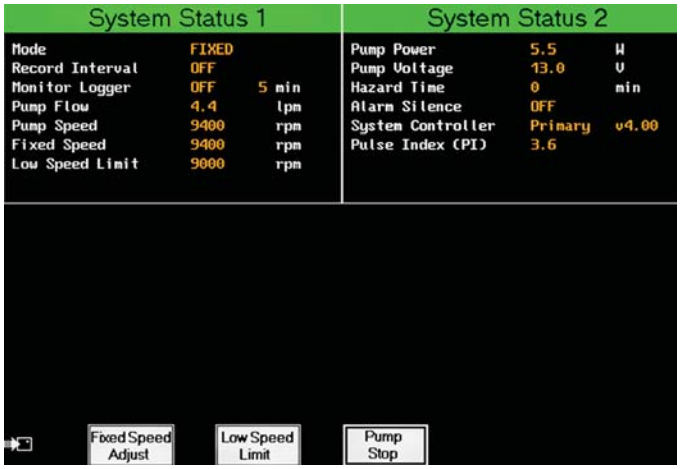


FIGURE 7: Display of setting screen of Thoratec HeartMate II VAD

Electrical and mechanical data: Continuous flow device modules display the speed of the rotor and the power consumed by the rotor to generate the given flow through the device.

Displacement pumps often display the rate of the pump along with the time spent in filling and emptying. Pulsatile pumps often display the pressure being applied to suction and displace the blood.

Flow characteristics: Both pulsatile and continuous flow pumps either display a measured flow (measured by a flow meter) or calculated flow (calculated based on a normogram of power consumption for a given flow). In addition, continuous flow devices also display pulsatility index, which is a measure of flow variation during cardiac cycle.

Both these parameters can be used to make therapeutic decisions to alter preload and afterload to maximize pump performance.

Pump optimization: Optimal pump management in the postoperative period is geared toward the following two goals:
1. Delivering optimal cardiac output
2. Preventing failure of unsupported RV

Cardiac output optimization is a function of preload and afterload management. Adequate preload will also prevent suctioning of the wall or septum by the inflow cannula and reduce thromboembolic events. This can be achieved by anticipating the postoperative fluid shifts and maintaining adequate filling pressures on the right side.

Measuring afterload (blood pressure) can be challenging in continuous flow devices due to lack of pulsatility. Use of a Doppler ultrasound is required to detect flow after the sphygmomanometer cuff is inflated. In these devices, "opening pressure" which is very similar to mean arterial pressure is used to guide therapy. Ideal range of 70–90 mm Hg is recommended. Higher pressures can not only reduce cardiac output but also increase risk of intracranial hemorrhage.

In patients with BiVAD, matching the flows in RVAD and LVAD with appropriate speed changes are important. In patients with LVAD, pump speeds can be reduced to prevent the amount of return to the RV, hence decreasing the chances of postoperative RV failure.

Long-term Management of Ventricular Assist Device Patients

Patients with VAD implantation require meticulous outpatient management. Successful management can be grouped into three categories:[32]
1. *Antiplatelet and thrombosis management*: Long-term antiplatelet and thrombotic management in VAD patients is particularly challenging due to presence of acquired Von Willebrand's disease in few patients, which predisposes them to increased bleeding. Individualization of INR goals is essential to balance these risks. Optimization of pump speed and preload to avoid suction events also decreases thrombotic risks.
2. *Infection prevention*: Stabilization of percutaneous lead to prevent local trauma and sterile cleaning or dressing techniques is key to preventing percutaneous lead infections. These infections can often spread to the pump pocket and systemically. Sepsis is one of the life-threatening complications of VAD implantation. Also repeated infections in bridge to transplant patients can have deleterious effect on immediate post-transplant outcomes.
3. *Heart failure management*: Resumption of optimal medical therapy of heart failure is essential to prevent neurohormonal excitation, which exists despite mechanical unloading. Angiotensin converting enzymes inhibitors are usually well tolerated. Beta-blockers may be harder to use in the presence of RV failure but has an additional benefit of suppressing post-VAD implant arrhythmias. Some of the common complications and their prevention strategies are listed in Table 15.

SURVIVAL WITH MECHANICAL CIRCULATORY SUPPORT

Survival of patients with MCS is definitely influenced by the indication for implantation, whether it is bridge to transplantation, decision, candidacy or a destination device. It is also influenced by the number of ventricles supported—LVAD versus BiVADs. Newer generation continuous flow devices clearly have better survival compared to the pulsatile devices. In a randomized control trial of 200 patients, 68% and 58% of continuous flow device patients survived till the end of 1st and 2nd year respectively when compared to 54% and 24% pulsatile device patients ($p < 0.0008$).[19]

Survival data from INTERMACs registry reveals a 1-year survival of 74% for patients undergoing LVAD implantation. Actuarial survival is better in bridge to transplantation (84%) and bridge to candidacy (72%) patients when compared to destination therapy patients (64%; $p < 0.0001$). LVAD patients fared better with 74% 1-year survival compared to BiVAD patients with a 50% 1-years survival ($p < 0.001$). Primary cause of early death being cardiac (30%) and infection is the primary late cause of death (20%). Patients are at risk for CNS events, which are the next common cause of death throughout their VAD implanted period (14%).[4] Old age, RV failure and cardiogenic shock are three important predictors of postimplantation mortality.

MYOCARDIAL RECOVERY WITH DEVICE EXPLANTATION

Small percentages of patients with VAD implantation undergo explantation successfully and have recurrence-free survival with good quality of life. Most of the explant experience comes from a few centers across the world with greatest success reported from Harefield Hospital, London, UK.[33] This group has used a recovery protocol, which involves aggressive neurohormonal blockade along with mechanical unloading. Patients who have an improvement of ejection fraction undergo echocardiography, cardiopulmonary exercise testing at a lower support speed of the VAD to evaluate LV function on minimal support. In addition, selected patients who are deemed candidates for explantation are treated with clenbuterol to cause myocardial hypertrophy. In two prospective studies, one involving pulsatile device and recently with a continuous flow device, this group has shown up 60% explants rates in carefully selected patients,

TABLE 15

Long-term complications in patients with ventricular assist device support

Complications	*Incidence with newer generation LVADs (per 100 patient months)*	*Pathogenesis and risk factors*	*Clinical presentation*	*Management*
Hardware related complications • Pump stops • Percutaneous lead fracture • Motor failure	0.82	• Due to device/hardware malfunction or loss of electrical power	• Syncope • Heart failure symptoms • Decrease in arterial blood pressure with increase in pulse pressure	• Pump replacement • Replacement of controller if it is damaged
Device related Infection • Driveline site infection • Pump pocket infection	11.8	• Improper stabilization of driveline • Obesity • Improper exit site dressing techniques	• Redness and discharge at the exit site • Abdominal pain and fever with sepsis	• Intravenous antibiotics • Chronic infection may require suppressive oral antibiotics • Pump replacement for resistant and recurrent infections
Right heart failure	2.23	• Pump being run at high speeds • Inadequate diuresis • Preoperative right ventricular dysfunction • Unrepaired severe tricuspid insufficiency	• Heart failure symptoms • Diuretic resistance • Intermittent inflow cannula obstruction	• Pulmonary artery vasodilators • Intravenous inotrope infusions • Exchange LVAD for a BiVAD
Major bleeding • Hemorrhagic stroke • Gastrointestinal bleeding-epistaxis	17.41	• Over anticoagulation • Acquired Von Willebrand's (VW) disease due to shearing of platelets and loss of VW multimers	• Syncope and hypotension • Other symptoms dependent on type of bleed	• Avoid over anticoagulation • Avoid hypertension (Keep MAP range between 70–90 mm Hg)
Thromboembolic complications • Pump thrombus • Arterial thrombosis • Venous thrombosis	1.84	• Subtherapeutic anticoagulation • Inadequate antiplatelet therapy	• Heart failure symptoms • Hemolysis • Systemic embolization	• CT angiography or echocardiography to confirm presence of thrombus • Thrombolysis can be tried along with heparin • Pump replacement is definitive treatment
Cannula obstruction • Inflow cannula • Outflow cannula		• Malpositioning during surgery • Remodeling of LV leading to suctioning of septum/LV lateral wall during part of cardiac cycle	• Heart failure symptoms • Hemolysis	• Chest X-ray, echocardiography or CT angiography to evaluate cannula position • Hydration to improve LV end-diastolic volume • Decreasing pump speed • Surgical repositioning

(Abbreviations: CT: Computed tomography; LV: Left ventricular; LVAD: Left ventricular assist device; MAP: Mean arterial pressure; VAD: Ventricular assist device)

out of which 80–90% of patients stay successfully explanted. Most of these patients are young and have nonischemic cardiomyopathy for a short duration (< 3–4 years).

FUTURE DIRECTIONS

Organ re-engineering with stem cells is an exciting new development in the field of heart transplantation. Three-dimensional biologic scaffold is built from decellularization of organs from allogeneic or xenogenic donors. Subsequently, these are populated with progenitor cells. In animal models, this has resulted in formation of organs, which have worked in vivo the short-term (few hours). Vascular regeneration and scar formation during organ growth are some of the challenges, which still have to overcome prior to medium term in vivo experiments.

MCS has entered its third generation with newer devices having magnetically levitated rotor to prevent friction and decrease energy loss. Development of transcutaneous energy transfer system (TETS) would obviate the need for a percutaneous lead decreasing infection rate. Ideal VAD would be one which could be completely implantable within the thoracic cage powered by TETS with enhanced durability.

CONCLUSION

Both heart transplantation and MCS provide effective palliation of advanced heart failure symptoms and prolong life. Currently, medium-term and long-term outcomes with heart transplant are superior to those of MCS. This may be due to differences in the patient populations and overall maturity of the field.

Heart transplantation will be limited by donor availability for the foreseeable future.

MCS use is expected to increase, given the good 18 month published survival rates. Innovations leading to improved outcomes and wider applicability are expected if there is adequate research support and a favorable economic environment for translation of these innovations.

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Chapter 79

Palliative Medicine and End of Life Care in Heart Failure

KellyAnn Light-McGroary

Chapter Outline

- Epidemiology of Heart Failure
- Economic Impact of Heart Failure
- History of Palliative Care/Definitions
- Feasibility of the Use of Palliative Care in Heart Failure
- Issues of Prognostication
- Communication and Patient's Understanding of their Disease
- Suffering in End Stage Heart Failure
- Symptom Management in Heart Failure
  - Dyspnea
  - Pain: Anginal and Non-anginal
  - Edema
  - Fatigue
  - Anorexia/Cachexia
  - Depression
- Management of Implantable Cardiac Devices

INTRODUCTION

End stage heart disease has become an increasingly common affliction. Despite multiple advancements in the treatment of the disease, it remains incurable and contributes to the death of hundreds of thousands of patients annually. Due to improvements in the treatment of acute coronary syndromes, acute decompensated heart failure (HF), myocardial infarction and arrhythmias, chronic and progressive HF has become a more common ailment.

Establishing goals of care and using palliative care/hospice services are frequently not a part of the dialogue between the provider, the family and the patient with advanced heart disease. Even those most experienced and adept at caring for the most gravely ill patients often do not possess a proficiency in dealing with this topic. Research has shown that providers are reticent to have advanced directive conversations in HF patients. Issues cited by providers include the unpredictability of disease trajectory and difficulty responding to patients and families shocked by the difficult news about a life limiting illness.[1] These conversations are often relegated to those times of dire illness and extreme distress. Unfortunately when patients are profoundly ill, they are less likely to be able to participate in these discussions. Frequently the moment has "snuck up" on families and providers, often leaving them unprepared for these challenges.

As clinicians provide advanced and aggressive therapies for heart disease, palliation should be acknowledged for the critical role it plays in the treatment of these patients. In many cases it may be as important as life saving medications, transplantation and mechanical circulatory support. The goals of this chapter are to review the physical, psychosocial and economic impacts of HF, to define palliative care and its utility in this disease process and to operationalize these concepts in a comprehensive and integrated plan for HF care.

EPIDEMIOLOGY OF HEART FAILURE

Based on the most current data from the American Heart Association,[2] HF affects 5,800,000 Americans who are 20 years of age or older; in 2006, there were 670,000 cases of newly diagnosed HF in individuals greater than or equal to 45 years of age. It was responsible for 282,754 deaths in the United States for the same period of time. To put this into perspective, annual HF deaths alone exceed the estimated 255,000 deaths annually from breast cancer, lung cancer and colorectal cancer combined,[3] and the National Institutes of Health reported that there were 87,812 deaths in 2007 for patients on renal replacement therapy for end stage renal disease.[4] End stage HF causes a significant amount of morbidity and mortality. As shown in Figure 1, the mortality statistics for HF portend a prognosis worse than many types of cancer. These graphs do not reflect the substantial morbidity of this disease, which is a tremendous drain on the physical, emotional and financial resources of patients and their families.

ECONOMIC IMPACT OF HEART FAILURE

Heart failure is a major economic burden on the health care system, requiring a substantial investment of funds from the annual health care budget. The 2008 national health expenditure was $2.3 trillion dollars, accounting for 16.2% of the Gross Domestic Product (GDP) in the United States. The health share of the GDP is projected to have reached 17.3% in 2009 and

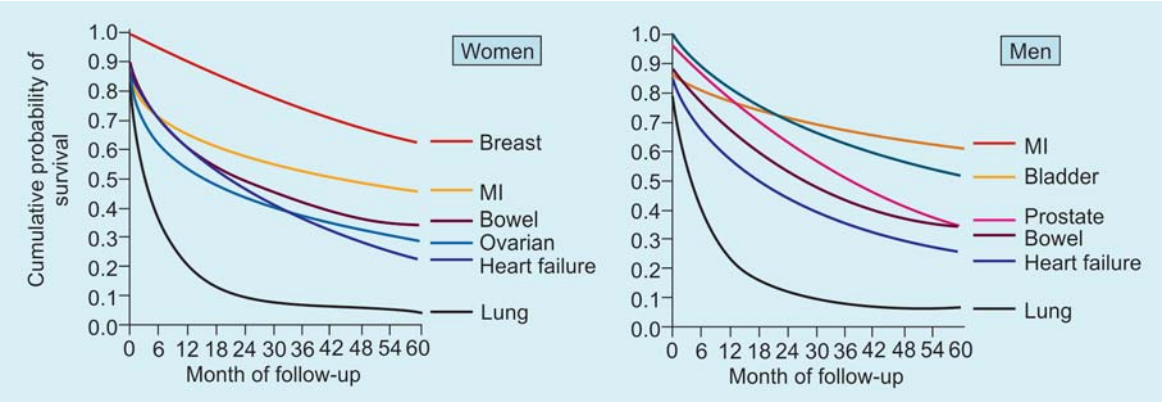


FIGURE 1: Five-year survival following a first admission to any Scottish hospital in 1991 for heart failure, myocardial infarction and the four most common sites of cancer specific to men and women. (*Source:* Modified from Stewart S et al. More 'malignant' than cancer? Five-year survival following a first admission for heart failure. Eur J Heart Fail. 2001;3:315-22)

19.3% by 2019.[5,6] As the population continues to age, advanced heart disease will be associated with a rising share of the national health expenditure, especially as there is an increase in utilization of advanced therapies including destination ventricular assist devices.

In 2006, there were well over a million hospital discharges for the diagnosis of HF; in 2010, the estimated cost to treat HF will exceed $39.2 billion dollars.[2] A review of a large database of hospital admissions identified that more than a third of HF hospitalizations had a length of stay (LOS) greater than or equal to 5 days with an average LOS of almost 6 days. Almost 50% of admissions associated with a HF diagnostic related group (DRG) had costs associated with it that well exceed the national average DRG reimbursement for HF. When only the top 5% most costly admissions were considered, the mean total cost was greater than $53,000 per admission.[7] As the US healthcare system undergoes reform, these rapidly escalating health costs will need to be addressed. Health care providers will continue to be held responsible for justifying the use of limited resources and for ensuring that treatments which carry significant financial, physical and psychosocial burdens are employed appropriately.

There is some research on resource utilization in advanced HF and the impact of palliative medicine services on costs of health care delivery. In the Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial, investigators evaluated the costs of treating patients with advanced HF in the final two years of life. It was estimated that the mean total cost of medical therapy per patient was $156,168, largely in part to frequent and long hospitalizations and ICU utilization. As the disease intensifies and death approaches, the costs go up significantly; the REMATCH data shows that more than half of the total costs, or $78,880, was accrued in the last six months of life.[8] Palliative care services were underutilized by patients in this study.

Historically, fewer than 5% of HF patients have advanced directives and a limited number of patients with HF are enrolled in hospice at their time of death. In 2006, according to CDC statistics, heart disease was responsible for 26% of all deaths in the United States[9] and yet, according to the National Hospice and Palliative Care Organization (NHPCO), in 2007 and 2008,

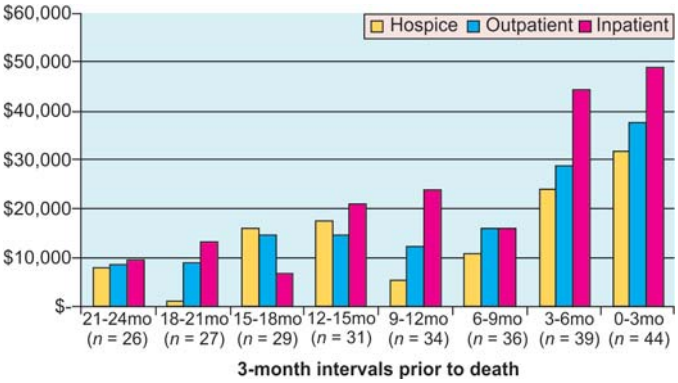


FIGURE 2: Total cost by location of death in the final 2 years of life. (*Source:* Modified from Russo MJ, Gelijms AC, Stevenson LW, et al. The cost of medical management in advanced heart failure during the final two years of life. J Card Fail. 2008;14:651-8)

less than 12% of patients who died in hospice had heart disease as the primary diagnosis.[10]

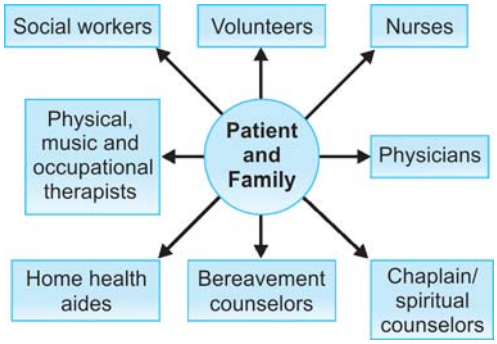
Some research has been done investigating the economic impact of hospice/palliative care on HF financial expenditures. Studies from Duke University have demonstrated an average Medicare cost savings of $2,309 per patient enrolled in hospice while delivering quality care to terminal patients.[11] The REMATCH data shows a trend toward reduced costs at multiple time points (Fig. 2) for HF patients receiving hospice services.

This reduction in cost is not due to shortened survival. In fact, HF patients experience an increased length of survival in hospice when compared to their non-hospice counterparts. The NHPCO data also shows that patients admitted to hospice with HF often have an increase in survival from an average of 321 days to 402 days. This gain in duration of survival is most profound in advanced HF patients, although cancer patients do have an increase in days of survival.[10] To summarize, palliative medicine offers quality, comprehensive end of life care while concurrently conserving precious financial resources and overall extending survival in HF patients.

HISTORY OF PALLIATIVE CARE/DEFINITIONS

The hospice movement began in the 1970s as a means to provide services for terminally ill oncology patients within their homes.

FLOW CHART 1: Multidisciplinary approach to palliative care



(*Source:* Reprinted from Lemond L, Allen LA. Palliative care and hospice in advanced heart failure. Prog Cardiovasc Dis. 2011;54:167-78, with permission from Elsevier)

In 1982, Medicare began to compensate for hospice services and at present most private insurers offer coverage for similar services. While hospice has become an insurance program for the end of life circumscribed by a 6-month prognosis, the field of palliative medicine covers pain and symptom management, shared decision making and grief support at the time of a life limiting illness.

A careful review of the WHO definition of palliative care demonstrates that advanced HF is in fact quite amenable to the framework of palliative care given that it is a progressive and life limiting disease with significant amounts of morbidity and suffering. The World Health Organization defines the aim of palliative care as working to prevent and alleviate suffering and to focus on promoting quality of life for patients and their caregivers.[12] Palliative care attempts to provide an organized structure, or anticipatory guidance, to address physical, psychological and spiritual aspects of care of the patient with a life limiting illness. It focuses on a holistic team approach that offers support not only to those struggling with HF but also their families providing a source of respite and emotional support from initial referral through the bereavement period. The Heart Failure Association of the European Society of Cardiology published in 2009 its position statement on palliative care in HF and most aptly and succinctly states "Palliative care provides care in the relief of pain and other distressing symptoms; affirms life, and regards dying as a normal process; intends neither to hasten nor postpone death and offers a support system to help patients live as actively as possible until they die". An example of the components of a comprehensive, multidisciplinary palliative care program has been given in Flow chart 1.

Given its development within the world of cancer treatment, palliation is quite often not a service that many cardiovascular professionals feel comfortable with or knowledgeable about. Difficulties with prognostication in HF are often an additional barrier to timely referrals for palliative care services. There are many providers who lack the understanding of the difference between non-hospice and hospice palliative care and may be unaware that non-hospice palliative medicine may augment the care of their patients by providing services that are often beyond the scope of a busy cardiology practice.

Palliative medicine can begin during the phase of treatment that still focuses on life sustaining therapies by offering a multidisciplinary approach to symptom management as well as guidance in establishing goals of care and advanced directives. Hospice falls under the auspices of palliative medicine. Hospice focuses on the terminal phase of an illness, usually identified when a physician certifies that a patient has a life expectancy of less than six months and generally all treatments transition from life prolonging to those which focus on promoting quality of life. It is a misnomer to consider this the end of "aggressive therapies" as hospice care can be fierce in its approach to symptom modification as well as psychosocial and spiritual support. It can allow patients increased autonomy and control and give them a framework for dealing with complex issues surrounding illness, loss of identity and life as well as complex social and family dynamics.

FEASIBILITY OF THE USE OF PALLIATIVE CARE IN HEART FAILURE

As stated earlier, palliative care is not limited to the terminal phase of life as is hospice care. Rather it addresses the spectrum of health care delivery once an individual has been diagnosed with a progressive and life limiting disease process. It is ideal for working to improve quality of life for patients and families dealing with complicated chronic illness in which prognosis is unclear and the struggle may last years. For most patients this is the very experience of congestive HF. It is a disease with multiple etiologies and therefore has many different treatment combinations. Comorbid conditions accompanying HF such as coronary artery disease, diabetes, hypertension and renal dysfunction compound the complexity of the care of these patients as well as the prognostic estimations. Furthermore, HF can often be significantly debilitating leading to difficulties participating in activities of daily living, monitoring and participating in health care and for many isolating them from many opportunities for support.

When considering the needs of this patient population, it is clear that involvement of palliative care services is quite appropriate in that it meets several essential criteria: there are symptoms which can be managed, there is a significant and rapidly increasing prevalence of HF in the population, and the overall prognosis is poor. Furthermore the traditional treatment options for patients with advanced heart disease almost uniformly are aimed at reduction in symptom burden; prolonging life is less often the main goal.

Discussions regarding goals of care and an understanding of HF as a life limiting disease should be a part of care from the very beginning so that providers, patients and families can have open and honest conversations. By including this early in care it normalizes the conversation and often may facilitate the harder discussions when the disease progresses and symptoms worsen. This can be done by individual primary care providers or primary cardiologists. As heart disease advances the specialist palliative care service can be involved in order to assist with symptom management, facilitate communication and identify services, including hospice, which may be beneficial to patients and their families.

The National Hospice and Palliative Care Organization generated guidelines for admission for advanced heart disease in 1996. In general, a patient may be "considered to have 6 months or less to live if he/she has: (1) Rest symptoms of HF, meaning NYHA Class IV symptoms and (2) optimization of

HF regimen as tolerated (although symptoms/side effects may limit) including angiotensin-converting enzyme inhibitors, beta blockers, aldosterone antagonists, diuretics, vasodilators, angiotensin receptor blockers and device therapy. There is a recommendation that the left ventricular ejection be less than or equal to 20% although this is not a requirement. A patient can also be admitted to hospice for "Decline in clinical status", when the guidelines for the specific diagnosis of HF are not met. The Decline in clinical status guidelines include increasing hospitalizations, increasing oxygen requirements, declining albumin, nausea, ascites, edema and pericardial/pleural effusions. An early referral to the community hospice for an "informational" visit would dispel the myths that patients might have about hospice. Consideration is also given to comorbid conditions that may affect survival when determining hospice eligibility.[13] In addition a physician must certify that the patient has an estimated survival of less than 6 months if the disease were to follow its usual course. Each patient is reviewed by the hospice at 90-day intervals for the first 6 months and at every 2 months thereafter. If the patient stabilizes, he/she may be discharged from hospice, but can be readmitted if a clinical decline recurs. In certain chronic non-malignant conditions (HF, COPD, dementia), it is not unusual for a patient to be admitted and discharged two-three times.

ISSUES OF PROGNOSTICATION

For many practitioners, the greatest challenge in the care of HF patients is the difficulty in providing accurate prognostication on disease progression and likelihood of death. Figure 3 illustrates that as opposed to other life limiting disease processes such as malignancy, patients have a much more varied course.

For most patients dying of cancer they experience a relatively long period of relatively high functional status until they advance and enter a more acute dying period, generally characterized by a rapid and steady decline with a fairly predictable clinical course. For patients who are dying from organ failure, such as advanced HF, the process tends to be quite different. For most they enter the end of life with some functional compromise but they go on to experience acute decompensations from which they can be rescued with treatment, for example, intravenous diuretics and vasodilators for volume overload or percutaneous coronary interventions for progressive coronary disease. Their course is a slow decline punctuated by decompensations with a degree of recovery; however, functional status declines over time because they never truly return to their previous baseline. The greatest challenge is determining when a decompensation will lead to an individual's death.

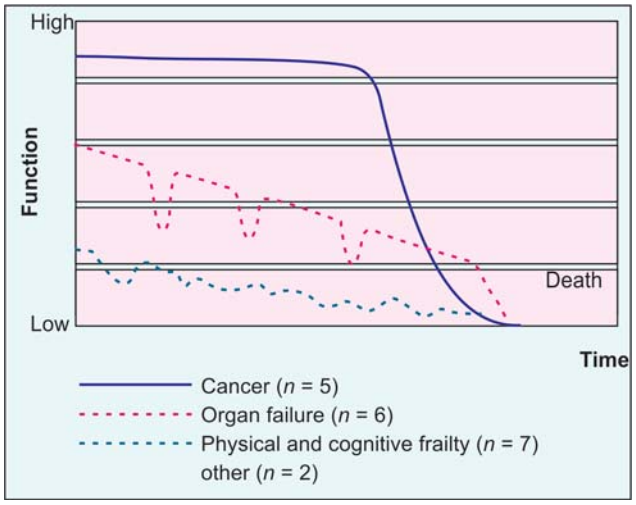


FIGURE 3: The three main trajectories of decline at the end of life. (*Source:* Modified from Murray SA et al. Palliative care beyond cancer: care for all at the end of life. BMJ. 2008;336:958-9)

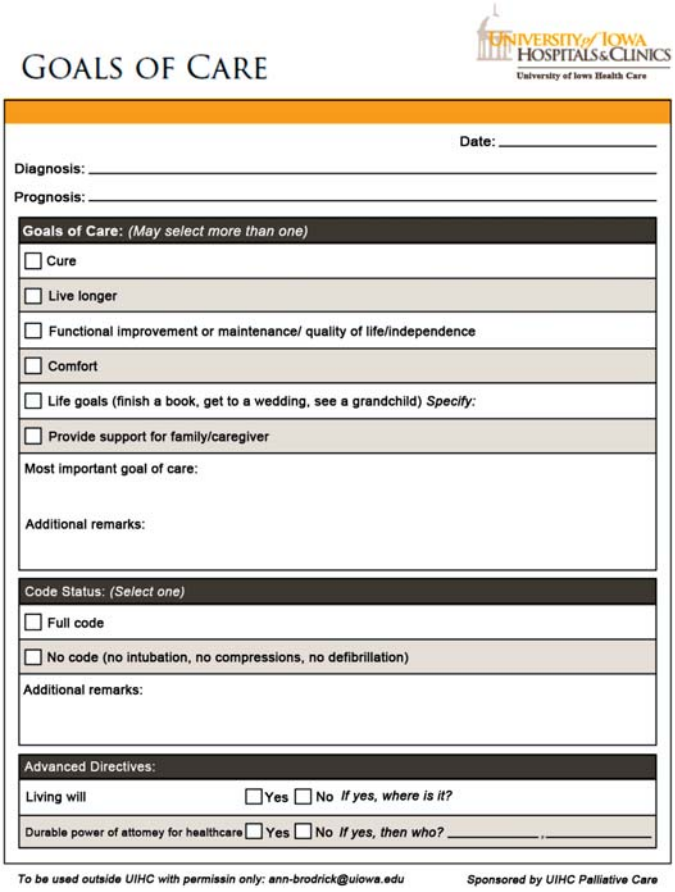
There are a number of biochemical and functional predictors that have been used to estimate mortality including the brain natriuretic peptide (BNP), renal function and peak VO2 consumption.[14-16] Additionally there are several multivariate models that predict mortality in HF patients. Examples of these include the Heart Failure Survival Score, a model designed to evaluate patients for transplantation eligibility, and the Seattle Heart Failure Score (SHFS), which is available as an online calculator through the University of Washington.[17] The SHFS model uses clinical, pharmacological, device and laboratory data to predict 1 year, 2 year and 3 year survival with HF. There are several other validated models but at present none include BNP in the algorithm. While all these markers can contribute to survival estimates, the combination of this data and good clinical judgment should be the main trigger for discussions of goals of care.

Practitioners can begin to identify the terminal phase of advanced HF with worsening of renal function and evidence of diuretic resistance, the development intolerance to neurohormonal modifying medication, and progressive weight decline with loss of lean muscle. Hospitalizations for decompensated HF despite maximal medication, inotrope dependence, dysrhythmia and NYHA class IV symptoms are reliable indicators of advanced disease. When patients reach this crucial point the conversations need to move past simply reassessing goals of care and to focus energy on identifying symptom-modifying interventions and preparing for severe life limitations and death. Very often this is best done with the assistance of a palliative medicine consultation to facilitate access to support for patients and families. Early discussions addressing HF as a life limiting illness facilitates this transition in care as patients, families and practitioners have all had the opportunity to discuss previously these issues at less critical times.

COMMUNICATION AND PATIENT'S UNDERSTANDING OF THEIR DISEASE

Communication lies at the forefront of an effective provider-patient-family relationship, although there is evidence from multiple studies that there is often significant discordance between what providers are trying to relate and what patients actually hear.[18] Effectively conveying a difficult and uncertain prognosis is essential and must start with a discussion early in the provider-patient relationship. Using a communication tool can facilitate discussions and allow ongoing assessments during the course of treatment. Figure 4 is an example of a tool that can be used with inpatients and outpatients to provide a starting point for these conversations.

A number of issues contribute to ineffective communication between patients and their physicians. This includes issues such



GOALS OF CARE

UNIVERSITY of IOWA HOSPITALS & CLINICS
University of Iowa Health Care

Date: _____

Diagnosis: _____

Prognosis: _____

Goals of Care: *(May select more than one)*

- ☐ Cure
- ☐ Live longer
- ☐ Functional improvement or maintenance/ quality of life/independence
- ☐ Comfort
- ☐ Life goals (finish a book, get to a wedding, see a grandchild) *Specify:*
- ☐ Provide support for family/caregiver

Most important goal of care:

Additional remarks:

Code Status: *(Select one)*

- ☐ Full code
- ☐ No code (no intubation, no compressions, no defibrillation)

Additional remarks:

Advanced Directives:

Living will ☐ Yes ☐ No *If yes, where is it?*

Durable power of attorney for healthcare ☐ Yes ☐ No *If yes, then who?* _____, _____

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FIGURE 4: UIHC goals of care tool. (*Source:* Modified from The Palliative Care Consultation Service, University of Iowa Hospitals and Clinics)

as difficulty with prognostication as previously discussed, variability in the trajectory of the illness, interpersonal issues within the family and the dynamics between the family and the health care team. Additionally there is often a lack of continuity of care and poor communication between inpatient and community health care providers which often lead to the perfunctory conversation regarding code status at the time of urgent hospitalization for decompensated symptoms. In a study by Kaldjian et al., 96% of patients stated that they were comfortable with a Goals of Care discussion in an inpatient General Medicine setting. Only 30% of patients could identify the meaning and the three components of cardiopulmonary resuscitation and even fewer could estimate the probability of success of inhospitial CPR leading to discharge to home.[19] Early goals of care discussions will obviate the need for patients or their families to make decisions when the patient is most ill, potentially anxious and impaired cognitively due to poor perfusion state.

Even when circumstances are not dire, health care providers often do not know how to approach the discussion, especially with uncertainty over prognosis complicating the issue. Goodlin presents suggestions for the elements needed for effective communication when discussing HF prognosis with patients and families as detailed in Table 1. This can provide a framework of approaching these difficult meetings.

In a qualitative study by Harding et al., the communication and information needs of chronic HF patients were assessed.[20] Researchers inverviewed 20 HF patients in the UK and then went on to speak to family carers, cardiologists and palliative care staff. A resounding issue that comes through is that information is often not presented in understandable lay terminology. Frequently patients lack a solid understanding of the causes and management of their HF symptoms and medications, that they did not comprehend what to expect with regard to progression of disease and what the future held for them. Multiple patients described significant anxiety as a result of being uninformed about their disease and its impact on their quality and quantity of life. From their work they were able to create an integrated map of needs, barriers and recommendations for the care of individuals with end stage heart disease (Table 2).

TABLE 1

Elements of communication about prognosis with heart failure patients and families

"Bad news" conversation	Plan the delivery of sad or unexpected information, and warn the patient that you have bad news: follow the points below:
Ask-Tell-Ask	Ask what the patient understands (before you talk). Correct misunderstanding and Tell your information Ask what questions they have, clarify information.
Simple, honest language Simple statistics	Define medical terms. Speak plainly and avoid euphemisms and relative statistics or percentages. Use numbers ("1 out of 5 people....")
Ground data in more than 1 way	Describe both chance of death and chance of life.
Hope for best, plan for the worst "Both-And"	Ask what the patient hopes for, and identify what you can also hope for. Plan for death or other bad outcomes "if things do not go as we hope." Create a dichotomy and address both issues.
Normalize uncertainty	Acknowledge that we can't know for sure, "like many things in life."
Partner and plan	Tell the patient you (or your team) will work with them to meet specific goals.
Deliver length of life in broad range	Provide a broad range "months to years," and allow for error on either end.
Empathize	Name your emotions ("I feel sad"), and identify emotions the patient expresses or might reasonably have ("you look surprised," "many would feel angry").
Follow-up	Summarize the plan and set an appointment to follow-up on plans and their status.

(*Source:* Reprinted from Goodlin SJ. Palliative care in congestive heart failure. JACC. 2009;54:386-95, with permission from Elsevier)

TABLE 2

Integration of communication needs, barriers and recommendations

Patient and carer needs and expereience	Barriers to effective information provision	Recommendations for cardiology and palliative care clinicians
1 CHF symptoms and management ■ Poor understanding of disease ■ Expectations of symptom control efficacy 2 Disease progression and future care ■ Absence of discussion with staff ■ No choices offered for managing future exacerbations ■ Confusion regarding implications of diagnosis 3 Living with inadequate information ■ Uncertainty causes anxiety ■ Significant psychological morbidity ■ Inability to plan appropriately ■ Unrealistic expectations	1 Disease-specific ■ Difficulty of prognostication 2 Patient-specific ■ Cummunication difficulties of older population ■ High rate of co-morbidity ■ Patients feel disempowered to ask questions 3 Specialism-specific ■ Curative focus ■ Lack of confidence and skills in discussing end of life ■ Fear of taking away hope ■ Confusion and misapprehension re: palliative care ■ Lack of knowledge of when to refer to palliative care 4 Staff time and resources ■ Inadequate time for communication ■ Lack of contact with families	1 Methods of providing information ■ Honesty and sensitivity to reduce anxiety ■ Improve comprehensibility ■ Reduce burden throguh family conferences ■ Provide a support group or telephone line 2 Mutual education and joint working ■ Cardiologists require generalist palliative care training, including communication skills ■ Palliative care staff require CHF management skills ■ Establish co-management systems that respect each speciality ■ Cardiologists are best placed to continue care 3 Referral criteria and care pathways ■ Clarification of when to refer and of specialist roles ■ Facilitates information provision

(*Source:* Reprinted from Harding R, Selfman L, Beynon T, et al. Meeting the communication and information needs of chronic heart failure patients. Jl of Pain and Symptom Management. 2008;36:149-55, with permission from Elsevier)

SUFFERING IN END STAGE HEART FAILURE

There is a significant burden of suffering for many individuals in the last stages of living with HF. Many health care providers are able to recognize and treat physical symptoms such as breathlessness, edema and pain. They are tangible and frequently the easier issues to address. What is often not fully assessed is the psychological sources of suffering in these patients include anxiety and depression. Nearly 20% of HF patients experience a clinically significant depressive episode.[21] Depression reduces survival in HF patients.[22] Spiritual conflicts can be a major component of suffering as part of the experience of dying with HF. It is often this type of care and support that health care providers fail to address, often thinking that religious and spiritual issues are quite personal and not an important part of the provider-patient relationship. Additionally there is a perception that there is limited time for such intimate and deep conversations. Spiritual concerns can have a profound impact on quality of life. Qualitative studies have described that HF can lead to a compromised sense of self, grief over the loss of a "normal" life and many significant changes in their socialization due to physical limitations. The holistic approach of palliative care medicine addresses these issues and concerns.

Traditional HF treatment in many cases allows people to live longer while relieving many of their symptoms. Many of the pharmacologic and mechanical interventions employed in the aggressive treatment of HF continue to have a role when an individual's goal of care has shifted to focusing primarily on improving quality of life rather than disease cure or prolonging life. These interventions may be covered by the hospice, or can be paid for separately (in non-Medicare patients), allowing clinicians and patients to continue to reap the benefits of these agents and devices. Depending on its philanthropic base or the insurance policy of the patient, a hospice might be able to cover expensive interventions such as intravenous agents if the medication is directed toward the improvement of symptoms. It is critical to develop an ongoing relationship with the hospice so that you are knowledgeable about the resources available to your patient and guarding the resources for the community as a whole. Offering to provide educational opportunities for both HF and palliative care/hospice teams would provide effective collaboration and a common perspective for the treatment of HF and pulmonary hypertension patients.

SYMPTOM MANAGEMENT IN HEART FAILURE

There are a number of symptoms that bear discussion in the treatment of advanced HF, including but not limited to dyspnea, angina, non-anginal pain, edema, depression, cachexia and fatigue. There are strategies that can be employed to minimize the intensity and frequency of these issues. The cornerstone of treatment of HF symptoms is frequent and comprehensive assessment of symptoms and function, and, most importantly, early intervention to obtain optimal improvement. The multi-disciplinary approach of palliative care, employing the services of nursing, nutrition, physical therapy and psychosocial support allows for early identification and treatment. It is also important to recognize the impact of psychological and existential suffering on the experience of many physical symptoms. This is well exemplified in the symptom of dyspnea and an appreciation of the multifactorial origins of dyspnea may guide how this is treated.

DYSPNEA

The factors leading to dyspnea are not well understood in part due to the multifactorial nature of the symptom. For many

TABLE 3

Summary of factors responsible for dyspnea in HF

Factor	*Impact*
Respiratory	Increased lung stiffness Increased dead space due to tachypnea Increased physiological dead space due to diminished apical ventilation Ventilation perfusion mismatch Impairment of ventilation, through diaphragmatic splinting, due to hepatic congestion and ascites Increased work of breathing J receptors are nerve endings of C-fibers located on the alveolar wall
Central chemo-receptors	Chemoreceptors respond to changes in carbon dioxide and arterial pH
Muscle changes	Skeletal muscle wasting
Psychological and social	Fear and anxiety Compliance and adherence
Myocardial	Ischemia

(*Source:* Beattie J, Goodlin SJ (Eds). Supportive Care in Heart Failure, 1st edition. Oxford: Oxford University Press; 2008. p. 162)

patients with advanced HF there are both pulmonary and cardiovascular causes. Fluid overload, while often perceived as the main driving force in the development of dyspnea, is not the only factor. Often these patients will develop symptoms at rest: discussing the sensations surrounding the experience can help a clinician identify the source and a possible therapeutic approach. In Table 3, there is a summary of some of the factors leading to dyspnea.

The assessment of dyspnea should include medication assessment including non prescription and herbal formulations, daily weight measurements, evidence of sleep disordered breathing or ischemia on history, edema, jugular venous distention, cardiac exam, chest auscultation and breath sounds, and evidence of ascites/hepatic congestion. Also included should be an evaluation of the level of anxiety and depression as well as assessing the capacity for self care and compliance with current treatments.

With the diversity of the underlying influences on this symptom in mind, an approach to treatment of dyspnea can be formulated. For most HF patients, attention should be placed on maximizing pharmaceuticals aimed at modulation of the neurohormonal activation that occurs with HF including angiotensin converting enzyme inhibitors, angiotensin receptor blockers, beta blockers and aldosterone antagonists. In addition, if volume overload is a significant issue than addition or uptitration of diuretics is an important intervention which should be paired with reinforcement of fluid and sodium restrictions. Again, given the significant contribution of these medications to symptom relief they are quite consistent with the palliative approach to advanced HF and withdrawal should only be considered if they are causing significant side effects such as profound hypotension leading to dizziness and syncope. Once these issues have been addressed consideration may be given for supplemental oxygen. If a patient is not receiving hospice services hypoxemia is generally required to obtain insurance coverage for home oxygen therapy; if a patient is on hospice oxygen therapy can be obtained if it improves air hunger or the symptom of dyspnea.

Using opioids and/or benzodiazepines can be considered, especially if there is significant anxiety contributing to the development of dyspnea or if the patient develops anxiety in response to the breathlessness. The data regarding the use of opioids in the palliation of dyspnea in chronic HF is fairly limited. There are two randomized trials utilizing opioids in HF; one tested the effect of diamorphine (boluses of 1–2 mg) on exercise tolerance. It was well tolerated without evidence of respiratory suppression; a much dreaded side effect which often prevents clinicians from administering opioids.[23] Another randomized trial used low dose morphine to treat breathlessness in ten patients with Class III/IV HF. Patients receiving morphine had a significant improvement in breathlessness in the first day of treatment, which improved over the next 24 hours and persisted. Sedation did increase over the first 3 days with mild improvement by Day 4. Six of the ten patients felt morphine had improved breathlessness; however, two discontinued use due to sedation. At one year, four of the six were still receiving benefit from morphine use. Of note, the respiratory rate and blood pressure did not decrease at doses of 2.5–5 mg of morphine.[24] While larger studies are needed to further evaluate opioids it would appear that low doses of opioids titrated to breathlessness generally do not lead to compromise of respiratory function. Attention should be paid to sedation, constipation and nausea to minimize unwanted side effects.

PAIN: ANGINAL AND NON-ANGINAL

Pain is a very common complaint of patients with end stage HF. This is not limited to anginal symptoms from ischemic heart disease. It can include pain from chronic conditions such as arthritis, gout, osteoporosis and fractures and neuropathy. In this patient population treatment of pain may be a challenge as the use of non-steroidal anti-inflammatory medications and corticosteroids is not generally advisable for HF patients. In addition, adjuvant medications, especially the tricyclic antidepressants (TCAs) and even gabapentin, need to be used with caution in this patient population given drug interactions and side effects such as fluid retention. Even with these limitations, pain needs to be routinely and methodically addressed with the goal of using non-pharmacological techniques and lifestyle modifications to prevent acute pain (such as a gouty attack) and improve chronic pain. If these measures are inadequate, then approaching pain with opioids and adjuvant medications in a “start low; go slow” fashion would be advisable.

Augmenting anti-ischemic/anti-anginal medications may be crucial to modulating anginal pain. This includes nitrates, oxygen and beta blockers. In addition, in patients with ischemic cardiomyopathy, volume overload may provoke ischemia and increase anginal episodes. Other potential approaches may be the use of enhanced external counterpulsation (EECP) which has been FDA approved for the treatment of angina and has been shown to decrease anginal episodes and delay the time to onset of exercise induced angina, although the mechanisms are not clearly understood.[25]

EDEMA

Edema may be a consequence of volume overload in the setting of decompensated HF in which case the use of diuretics would

likely be of benefit. Additionally, sodium and fluid restrictions may be helpful in controlling this symptom. Venous insufficiency may also be a contributing factor and thus compression stockings and elevation of the lower extremities may also be helpful. Ascites is also a frequent complication of chronic HF. Palliation with therapeutic paracentesis may be considered as a comfort measure. For many patients significant ascites may compromise renal function and nutritional status making paracentesis a reasonable approach.

FATIGUE

This is a common complaint of advanced HF patients and can have multiple etiologies including anemia, infection, hormonal imbalances, sleep disordered breathing and depression. Often addressing the underlying issue will help to improve fatigue. When that has not been successful, consideration of stimulants, such as methylphenidate, can be considered. There is limited literature examining the use of methylphenidate to treat fatigue and depression in medically and terminally ill patients. There are no studies focused on patients with end stage HF A meta-analysis of studies in terminally and chronically ill patients, which included patients with heart disease, did not demonstrate worsening of heart disease.[26] Tachycardia and hypertension are possible and this does have the potential of worsening HF. Methylphenidate use should be approached cautiously. Its use in the treatment of depression at the end of life has been discussed in further detail below.

ANOREXIA/CACHEXIA

Cachexia in HF is defined as a non-edematous weight loss of greater than 6% over 6 months and portends a poor prognosis in advanced HF patients. The underlying mechanisms leading to cardiac cachexia are diverse and complex. At the core of cachexia and the overall pathology of HF are the abnormal neurohormonal milieus that exist and the chronic activation of the sympathetic nervous system leading to increased levels of circulating catecholamines that serve to increasing the resting energy expenditure of the body. Various catecholamines and stress hormones are elevated in cachectic patients whereas non-cachectic HF patients have relatively normal levels. In addition, aberrations in inflammatory system activation and evidence of growth hormone resistance are other possible contributors to cachexia.

Optimizing neurohormonal modulation with the standard HF medication regimen is at the center of the approach to treatment. Trials of agents directed against cytokines and the inflammatory system have demonstrated a lack of benefit and actually have shown an increase in mortality.[27] While there are other inflammatory substances and hormones which play a role in catabolic/anabolic imbalances that may be future targets of therapy, few have been investigated or found to have benefit in advanced HF.

Nutritional support to limit malnutrition is important in the treatment of elderly patients with chronic systemic illnesses. While there is an abundance of the prognostic significance of cachexia in HF, there is limited data regarding the impact of nutritional support in this population. Parenteral nutrition is not recommended. There has been one clinical trial using enteral nutrition in advanced HF. It demonstrated improvement in lean body mass and exercise capacity; however, it was a small series of 34 patients and statistical information was not completely available.[28]

DEPRESSION

Depression and heart disease have been linked in the literature extensively over the last 15–20 years. The incidence in association with HF has been evaluated in the inpatient and outpatient settings with estimates of prevalence ranging from 20% to 75%. In a meta-analysis by Rutledge et al., data was reviewed from 27 studies and an aggregated estimate of 21.5% was determined for the prevalence of clinically significant depression. Five of the studies reviewed also evaluated the prevalence based on the severity of NYHA functional class and found that as functional class worsened there was an associated increase in the prevalence of depression. Data demonstrated a pattern of increased need for health care services in HF patients with depression. Eight of the studies evaluated the effect of depression on mortality and cardiac events and the aggregated risk estimate suggests a greater than twofold risk of death and cardiac events in HF patients with evidence of a depressive disorder.[29]

Screening for depression is essential in the HF population. Psychotherapy may play a role in treating depression although there are no clinical trials demonstrating efficacy; however, it is a reasonable approach, especially given that adding pharmacologic agents may be difficult to manage especially if there is associated renal or hepatic compromise. Serontonin receptor inhibitors (SSRIs) are a mainstay in the treatment of depression due to effectiveness and a relatively good side effect profile. SADHART-HF, a randomized trial of the safety and efficacy of sertraline in the treatment of depression and HF, did not demonstrate a significant survival benefit, although it also did not show any increase in adverse events. It demonstrated a trend toward decreased hospitalizations but was underpowered to answer this question.[30] The MOOD-HF trial is currently underway to evaluate the effect of escitalopram on morbidity, mortality and mood in patients with depression and HF. This study will hopefully lend more support to the use of SSRIs in this patient population. The TCAs should be used with great caution given the issues with QT prolongation, anticholinergic effects, and orthostatic hypotension. Nortriptyline and desipramine have less significant anticholinergic effects and may be better tolerated.

Finally, although there is no data specifically looking at methylphenidate in advanced HF patients, it has had success in treating depression in patients with other chronic medical conditions. Its effects are seen relatively quickly; in patients with a short time to live waiting 4–6 weeks for SSRIs and TCAs to work may not be practical. There may be an increased risk of tachyarrhythmias with methylphenidate and thus, if started, it would be advisable to start at a low dose with slow uptitration to find the lowest effective dose. Discontinuation may be considered once the effects of SSRIs and TCAs can be achieved.

MANAGEMENT OF IMPLANTABLE CARDIAC DEVICES

There has been a significant increase in the placement of implantable cardiac devices over the last decade, especially implantable cardioverter-defibrillators (ICDs). ICDs have been demonstrated in multiple trials to confer survival benefit on patients with HF and impaired left ventricular systolic function.[31,32] While they do provide mortality benefit they do not in and of themselves provide a treatment for the underlying HF or an improvement in symptoms. It is essential to discuss this in detail with patients prior to implantation of the ICD to ensure they understand the purpose of the device and that in end stages of HF they may prolong life by treating malignant arrhythmias. Further, patients should be aware that with worsening of HF, ICDs may discharge with increasing frequency and that they can be deactivated if that is in line with the patient's identified goals of care. As heart function continues to deteriorate in the end stages of HF, patients' may experience increased anxiety over fears of device discharges, especially if they have been shocked in the past.

Biventricular devices (with or without ICDs) have been shown in patients with advanced HF and intraventricular dysynchrony as evidenced by QRS prolongation on the electrocardiogram, to provide improvement in symptoms, quality of life and exercise tolerance. There was also evidence for reduction in all-cause mortality with these devices.[33,34] Prior to undergoing an invasive procedure to initiate cardiac resynchronization therapy (CRT), patients should be optimized medically and still have significant symptoms and cardiac dysfunction. There is some added complexity when dealing with deactivation of these devices at the end of life when compared to ICDs as discontinuation of therapy can lead to decompensation of HF and clinical worsening, compromising quality of life and symptom management. Thus, this needs to be disclosed to the patient and family in order to allow them to make informed decisions about continuation of therapy.

Ventricular assist devices and total artificial hearts have been implanted with increasing frequency in the treatment of advanced HF. In some cases they are implanted as a bridge to a more durable therapy, specifically heart transplantation which is recognized as being potentially curative for end stage HF. There is a 50% average survival of 10 years post transplant and this time period carries an increased risk of infection, graft rejection, neoplasia and other symptoms. There are fewer than 3,500 heart transplants annually worldwide, a number which has remained fairly stable, making this option available only for a small and highly selected group of patients.[35] The use of mechanical circulatory support as a destination therapy was a result of the findings of the REMATCH trial which demonstrated improvement not only in survival but in quality of life parameters as well.[36] The Heart Mate 2 VAD (Thoratec Corporation, Pleasonton, CA) received FDA approval in early 2010 as the first continuous flow device approved for destination therapy,

TABLE 4

Communicating with patients and families about goals of care relating to CIEDs

Steps	*Sample phrases to use to begin conversation at each step*
1. Determine what patients/families know about their illness.	"What do you understand about your health and what is occurring in terms of your illness?"
2. Determine what patients/families know about the role the device plays in their health both now and in the future.	"What do you understand the role of the (cardiac device) to be in your health now?"
3. Determine what additional information patients/families want to know about their illness	"What else would be helpful for you to know about your illness or the role the (cardiac device) plays within it?'
4. Correct or clarify any misunderstandings about the current illness and possible outcomes, including the role of the device.	"I think you have a pretty good understanding of what is happening in terms of your health, but there are a few things I would like to clarify with you."
5. Determine the patient/family's overall goals of care and desired outcomes.	"Given what we have discussed about your health and the potential likely outcomes of your illness, tell me what you want from your health care at this point." For patients or families needing more guidance: "At this point some patients tell me they want to live as long as possible, regardless of the outcome whereas other patients tell me that the goal is to be as comfortable as long as possible while also being able to interact with their family. Do you have a sense of what you want at this point?"
6. Using the stated goals as a guide, work to tailor treatments, and in this case, management of the cardiac device to those goals.	Phrases to used here depend on the goals as set by the patient and family. 1. For a patient who states that his/her desired goal is to live as comfortably as possible for whatever remaining time she has left: "Given what you have said about assuring that you are as comfortable as possible it might make sense to deactivate the shocking function of your ICD. What do you think about that?" OR 2. For a patient who states she/he wants all life-sustaining treatments to be continued, an appropriate response might be, "In that case, perhaps leaving the anti-arrhythmia function of the device active would best be in line with your goals. However, you should understand that this may cause you and your family discomfort at the end of life. We can make a decision at a future point in time about turning the device off. Tell me your thoughts about this."

(*Source:* Reprinted from Lampert R, Hayes DL, Annas GJ, et al. HRS expert consensus statement on the management of cardiovascular implantable electronic devices (CIEDs) in patients nearing end of life or requesting withdrawal therapy. Heart Rhythm. 2010;7:1008-26, with permission from Elsevier)

TABLE 5

Steps for your conversation

Timing of conversation	*Points to be covered*	*Helpful phases to consider*
Prior to implantation	• Clear discussion of the benefits and burdens of the device • Brief discussion of potential future limitations or burdensome aspects of device therapy • Encourage patients to have some form of advance directive • Inform of option to deactivate in the future	"It seems clear at this point that this device is in your best interest, but you should know at some point if you become very ill from your heart disease or another process you develop in the future, the burden of this device may outweigh its benefit. While that point is hopefully a long way off, you should know that turning off your defibrillator is an option."
After an episode of increased or repeated firing from an ICD	• Discussion of possible alternatives, including adjusting medications, adjusting device settings, and cardiac procedures to reduce future shocks in context of goals of care	"I know that your device caused you some recent discomfort and that you were quite distressed. Lets see if we can find a correctable reason why this may be happening, and discuss options to decrease the number of firing."
Progression of cardiac disease, including repeated hospitalizations for heart failure and/or arrhythmias	• Re-evaluation of benefits and burdens of device • Assessment of functional status, quality of life, and symptoms • Referral to palliative and supportive care services	"It appears as though your heart disease is worsening. We should really talk about your thoughts and questions about your illness at this point and see if your goals have changed at all."
When patient/surrogate chooses a Do Not Resuscitate Order	• Re-evaluation of benefits and burdens of device • Exploration of patient's understanding of device and how she/he conceptualizes it with regards to external • Defibrillation • Referral to palliative care or supporting services	"Now that we have established that you would not want resuscitation in the event your heart was to go into an abnormal pattern of beating, we should reconsider the role of your device. In many ways it is also a form of resuscitation. Tell me your understanding of the device and let's talk about how it fits into the larger goals for your medical care at this point."
Patients at End of Life	• Re-Evaluation of benefits and burdens of device • Discussion of option of deactivation addressed with all patients, though deactivation not required	"I think at this point we need to re-evaluate what your (device) is doing for you, positively and negatively. Given how advanced your disease is we need to discuss whether it makes sense to keep it active. I know this may be upsetting to talk about, but can you tell me your thoughts at this point?"

(*Source:* Reprinted from Lampert R, Hayes DL, Annas GJ, et al. HRS expert consensus statement on the management of cardiovascular implantable electronic devices (CIEDs) in patients nearing end of life or requesting withdrawal therapy. Heart Rhythm. 2010;7:1008-26, with permission from Elsevier)

and an increase in the implantation of the mechanical circulatory support devices is expected. With this comes potential benefits for HF patients but at the same time there are risks and burdens of relying on a support device. Patients have potential for increased thromboembolic events and a higher rate of infection. For many, the challenges of managing this device are outweighed by the benefit of an increase in life expectancy. Given the complexity of the decision and the impact on quality of life it is essential to have goals of care and palliative care discussions prior to device implantation to ensure that VADs are placed in appropriate patients who have made informed choices. Additionally, patients and families must have an understanding of what occurs with device failure and device deactivation as well as its impact on the dying process. Advanced directives and Goals of Care documentation should be in place to help practitioners and families understand what patients would want if they are unable to participate in a future discussion. Palliative care consults prior to device implantation and/or as part of the work up for all advanced therapies may be useful to clarify and to assist with documenting advanced directives and goals of care.

Recently, through collaboration with international cardiology associations and palliative care associations, the Heart Rhythm Society (HRS) released a consensus statement detailing recommendations for the management of implantable cardiac devices as patients approach end of life or make decisions to withdraw life sustaining therapies.[37] While it was aimed at addressing pacemaker, ICD and CRT, the principles can be extended to mechanical circulatory support devices. It details the ethical and legal underpinnings and techniques involved in the process of device deactivation. Perhaps one of the most important messages from this paper is that it is critical to have ongoing conversations with patients and families to review devices and their implications at the end of life. These conversations should happen prior to implantation and multiple times during the course of their care. Documentation of these conversations is crucial to ensure that all providers are aware of patients' wishes so that they can be honored. In Table 4, from the HRS consensus statement, suggestions are provided to guide goals of care discussions related to implantable devices. A second reference from that publication gives a general road map as to the appropriate timing for having these discussions with patients and families (Table 5).

CONCLUSION

Heart failure remains a progressive life limiting disease and despite improvements in interventional, pharmacological and mechanical treatments for HF, the prevalence continues to rise. It, perhaps more so than almost any other cardiovascular

TABLE 6

Comprehensive heart failure program

	Phase 1	*Phase 2*	*Phase 3*	*Phase 4*	*Phase 5*
	Initial symptoms of HF develop and HF treatment is initiated	*Plateau of variable length reached with initial medical management or following mechanical support or heart transplant*	*Functional status declines with variable slope, intermittent exacerbations of HF that respond to rescue efforts*	*State D HF, with refractory symptoms and limited function*	*End of life*
NYHA functional classification	II-III	II-IV	III[a]	IV	IV
HF care and interventions	• Identify etiology of HF • Eliminate precipitating factors and causative conditions • Diuretics → euvolemia • ACE inhibitor • Beta-blocker • Evaluate for coexistent conditions[1]	• Spironolactone if NYHA functional class III-IV • Digoxin if NYHA functional class III-IV and LVEF < 35% • Hydralazine/nitrates? • Evaluate and treat for sleep-disordered breathing • ICD if EF < 35% and defibrillation desired for SCD • CRT or CRT/D?	• Re-evaluate medication and compliance • Re-evaluate for precipitating factors and coexistent conditions • Diuretics → euvolemia	• Evaluate for heart transplant • Evaluate for destination LVAD • Meticulous fluid management • Inotrope trial if hypotensive and volume-overloaded (LVSD) • Intravenous nitrates/ hydralazine?	• Discontinue medications not impacting symptoms • Continue ACE inhibitor or ARB, titrate beta-blocker dose, or stop if hypotensive • Diuretics → euvolemia • Inotrope trial if hypotensive and volume-overloaded
Decision-making	• Preferences for CPR/ defibrillator • Durable power of attorney for health care or proxy	• Defibrillator for primary prevention of SCD? • Durable power of attorney for health care or proxy decision-maker • General goals for care, preferences for unacceptable health states	• Urgent care decisions using doctor's best judgment or clear patient preferences • Are advanced or invasive therapies indicated? • Are advanced therapies consistent with patient preferences?	• Candidate for transplant or destination VAD? • Is palliative care appropriate? • Does patient benefit from inotrope infusion? • Review preferences for CPR/ defibrillator	• Clarify goals of care • Site of care (hospital, home, other) • Health care delivery (hospice, other provider) • How to manage death (review CPR decision, review ICD and other devices, if appropriate, plan deactivation)
Supportive care					
A. Communication	• Understand patient concerns and fears • Identify life-limiting nature of HF • Elicit preferences for care in emergencies or sudden death and for information and role in decision-making • Elicit symptoms and assess QOL	• Elicit symptoms and assess QOL • Re-evaluate resuscitation preferences for care in emergencies • Set goals for care • Identify coping strategies • Re-educate about sodium, weight, and volume status	• Elicit symptoms and QOL • Elicit values and re-evaluate preferences • Identify present status and likely course(s) • Re-evaluate goals of care • Re-educate about sodium, weight and volume status, medication compliance	• Elicit symptoms • Acknowledge present status • Elicit preferences and reset goals for care • Identify worries • Review appropriate care options and likely course with each • Explore suitability and preferences about surgery or devices	• Elicit desired symptom relief and identify medication for symptom goals • Assistance with delivery of care • Preferences for end-of-life care, family needs, and capabilities • Plan after death (care of the body, notifications, memorials, burial)
B. Education	• Patient and family self-management (sodium, weight and volume) • Diet, exercise • HF course including sudden death and options for management	• What to do in an emergency • Review self-management	• Review self-management • Review what to do in an emergency • Symptom management • Eliminate NSAIDs	• Optimal management for given care approach • Interventions for deterioation in status • What to do in an emergency?	• Likely course and plans for management of events • Symptom management • What to do for worsened or change in status • What to do when death is near and at the time of death

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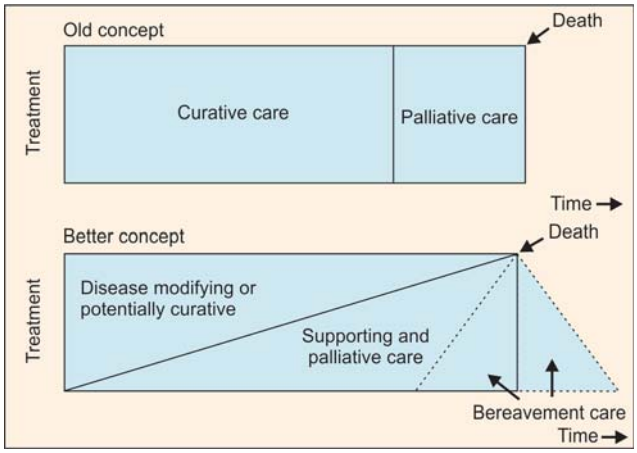
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	Phase 1	*Phase 2*	*Phase 3*	*Phase 4*	*Phase 5*
	Initial symptoms of HF develop and HF treatment is initiated	*Plateau of variable length reached with initial medical management or following mechanical support or heart transplant*	*Functional status declines with variable slope, intermittent exacerbations of HF that respond to rescue efforts*	*State D HF, with refractory symptoms and limited function*	*End of life*
C. Psychosocial and spiritual issues	• Coping with illness • Insurance and financial resources • Insurance and financial resources regarding medications and loss of income • Emotional and spiritual support	• Roles and coping for patient and family • Emotional support • Spiritual support • Social interaction • Evaluate both patient and family anxiety, distress, depression, impaired cognition	• Family stresses and resources • Re-evaluate patient and family needs • Caregiver education and assistance with care • Evaluate cognition and initiate compensation	• Insurance coverage • Re-evaluate stresses, needs, and support patient and family • Address spiritual and existential needs • Support coping with dying	For both patient and family • Address anxiety, distress, depression • Address spiritual and existential needs, concerns regarding dying • Anticipatory grief support • Assist in care provision • Post-death bereavement
D. Symptom management	• HF medications for dyspnea • Exercise/endurance training for fatigue • Antidepressant for depression (check Na^+ with SSRIs) • Local treatment and/or opioids for pain	• Identify new or worsened symptoms • CPAP/O^2 for sleep-disordered breathing • Exercise program (lower extremity strengthening) • Local treatment and/or opioids for pain • SSRI or tricyclic or stimulant for depression	• Oxygen for dyspnea; consider opioids for acute relief of dyspnea • Lower extremity strengthening for dyspnea/fatigue CPAP/O_2 for sleep-disordered breathing • Local treatment and/or opioids for pain • SSRI or tricyclic or stimulant for depression	• Oxygen for dyspnea • Opioids for dyspnea • Lower extremity and inspiratory strengthening • CPAP/O_2 for sleep-disordered breathing • Local treatment and/or opioids for pain • Benzodiazepines/counseling for anxiety • Stimulant for depression	• Opioids for dyspnea and pain • Oxygen for dyspnea • Stimulants for fatigue • Benzodiazopines/counseling for anxiety • Lower extremity strengthening for fatigue and dyspnea CPAP/O_2 for sleep-disordered breathing • Stimulant for depression

•Coexistent conditions atrial fibrillation with uncontrolled rate, sleep-disordered breathing, anemia, physical frallty, coexistent pulmonary disease.

(Abbreviations: ACE: Angiotensin-converting enzyme; ARB: Angiotensin-receptor blocker; CPAP: Continuous positive airway pressure; CPR: Cardiopulmonary resuscitation; CRT/D: Cardiac resynchronization therapy defibrillator; EF: Ejection fraction; HF: Heart failure; ICD: Implantable cardiovascular defibrillator; LVAD: Left ventricular assist device; LVEF: Left ventricular ejection fraction; LVSD: Left ventricular systolic dysfunction; NSAID: Nonsteroidal anti-inflammatory drug; NYHA: New York Heart Association; QOL: Quality of life; SCD: Sudden cardiac death; SSRI: Selective serotonin reuptake inhibitor; VAD: Ventricular assist device. (*Source:* Reprinted from Goodlin SJ. Palliative care in congestive heart failure. JACC. 2009;54:386-95, with permission from Elsevier)

FLOW CHART 2: Appropriate care near the end of life



(*Source:* Modified from Murray SA et al. Illness trajectories and palliative care. BMJ. 2005;330:1007-11)

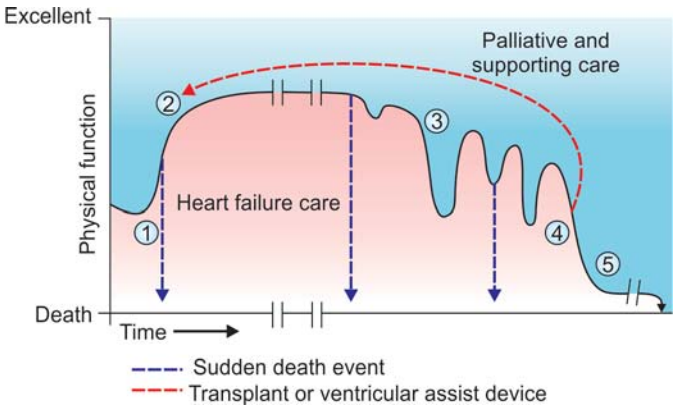


FIGURE 5: Phases in the progression of heart failure. (*Source:* Reprinted from Goodlin SJ. Palliative care in congestive heart failure. JACC. 2009;54:386-95, with permission from Elsevier)

diagnosis, is well suited for incorporation of the principles and practices of palliative care as many of these treatments focus as much on symptom management as they do on prolonging life. In the past palliative care has only been entertained when all curative measures have been employed. Below is a schematic of how palliative and supportive measures can be better incorporated throughout the health care experience (Flow chart 2).

Most clinicians develop a long lasting relationship with their HF patients. Although this may make it personally more of a challenge as they come to the end of their lives it puts providers in a unique and valuable position. By taking advantage of the multiple opportunities to walk patients and families through the process of establishing and revising goals of care, practitioners can help to ensure that advanced directives are in place that honor the belief systems and wishes of their patients. Early conversations focused on understanding these wishes and establishing a trusting relationship can prove to be invaluable in the latter stages of disease. Figure 5 and Table 6, from Goodlin (2009), are the excellent demonstrations of the comprehensive and multidisciplinary approach of palliative care effectively being incorporated into the care of HF patients at all spectrums of disease severity. The phases in the progression of HF seen in Figure 5 are linked to detailed descriptions of multifaceted care plans for each stage of the disease process.

As technology continues to advance there will be increasingly more diverse and challenging end of life issues. The complexity of these decisions can be minimized by effective communication and a patient centered approach to long-term care of individuals with advanced HF. By developing and implementing an HF program that incorporates the advances in pharmacological and surgical treatment of HF with the holistic and multidisciplinary approach of palliative medicine to quality of life and symptom control, the care of this patient population has the potential to be a more rewarding experience for patients, clinicians and families. Truly, managing advanced HF patients through cutting edge treatments and complex symptom management epitomizes the art as well as the science of medicine.

ACKNOWLEDGMENT

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Section 9

MYOCARDIAL AND PERICARDIAL DISEASES

Chapter 80

Hypertrophic Cardiomyopathy

M Fuad Jan, A Jamil Tajik

Chapter Outline

- Definition
- Epidemiology and Genetic Considerations
- Pathology
- Pathophysiology
  - Left Ventricular Outflow Tract Obstruction
  - Diastolic Dysfunction
  - Systolic Dysfunction
  - Myocardial Ischemia
  - Mitral Regurgitation and Mitral Valve Abnormalities
  - Arrythmogenic Substrate and Sudden Death
  - Myocardial Fibrosis
  - Autonomic Dysfunction
- Clinical Presentation
  - Symptoms
  - Physical Examination
- Diagnosis
  - Electrocardiogram
  - Holter Monitoring
  - Chest X-ray
  - Echocardiography
  - Doppler Inflections
  - Cardiac Magnetic Resonance Imaging
  - Cardiac Catheterization
  - Stress Test
- Natural History
- Management
  - Genotyping, Genetic Counselling and Family Screening
  - Assessment, Risk Stratification and Prevention of Sudden Death
  - Athletes with Hypertrophic Cardiomyopathy
  - Medical Therapy
  - Septal Myectomy
  - Percutaneous Alcohol Septal Ablation
  - Dual-Chamber Pacemaker
- Additional Points of Interest
  - Atrial Fibrillation
  - Obstructive Sleep Apnea and HCM Symptoms
  - End-stage Hypertrophic Cardiomyopathy (Burnt-out or Dilated Stage)
  - Pregnancy and Hypertrophic Cardiomyopathy
  - Infective Endocarditis

DEFINITION

Hypertrophic cardiomyopathy (HCM) is a clinically heterogenous, autosomal dominant heart muscle disorder due, primarily to mutations in the genes encoding the cardiac sarcomere myofilament proteins (Fig. 1). This culminates in the protein's altered structure and function with myofibrillar disarray, marked ventricular hypertrophy (frequently asymmetric), diastolic dysfunction and, in some patients, sudden cardiac death as its most devastating outcome.

Since the first modern descriptions of HCM by Brock[1] in 1957, Teare[2] in 1958 and Braunwald (who called it the "Brady heart"—attributed at that time to a family trait)[3] in 1959, thousands of reports describing the various elements of the disease have been published.[3-19] Based on this wealth of published knowledge, we now recognize HCM to be the most common inherited heart disease (autosomal dominant with incomplete penetrance), characterized by extraordinary heterogeneity in genetic substrate, phenotypic expression, clinical presentation and natural history, as well as management and specific therapy. Formerly known by several names (each of which is dependent on the presence of obstruction), viz. idiopathic hypertrophic subaortic stenosis in the United States, muscular subaortic stenosis in Canada and hypertrophic obstructive cardiomyopathy in the United Kingdom,[20] the name HCM now, predominates the current literature as the formal name for this disease to describe the unique process of primary muscle hypertrophy, which may exist with or without a dynamic left ventricular (LV) outflow tract gradient,[21,22] since, this term is inclusive and allows for both the obstructive and nonobstructive forms of the disease.[23]

EPIDEMIOLOGY AND GENETIC CONSIDERATIONS

Hypertrophic cardiomyopathy is the most prevalent, monogenic heritable cardiovascular disease (Fig. 2), affecting approximately 1 in 500 people (0.2% of the population) and is the most common cause of sudden cardiac death in young people, including competitive athletes.[5,6,8,24-29]

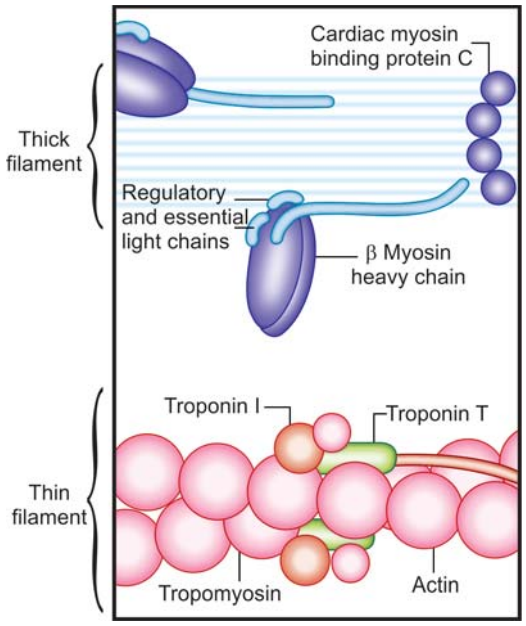


FIGURE 1: The cardiac sarcomere comprises the contractile proteins of the thick and thin filaments. Mutations in genes encoding each of the proteins labeled in this figure can cause hypertrophic cardiomyopathy (HCM); thus, the disorder can result from abnormalities of proteins that have diverse structural, enzymatic and regulatory functions. (*Source:* Modified from Ashrafian et al. Hypertrophic cardiomyopathy: a paradigm for myocardial energy depletion. Trends Genet. 2003;19:263-8, with permission)

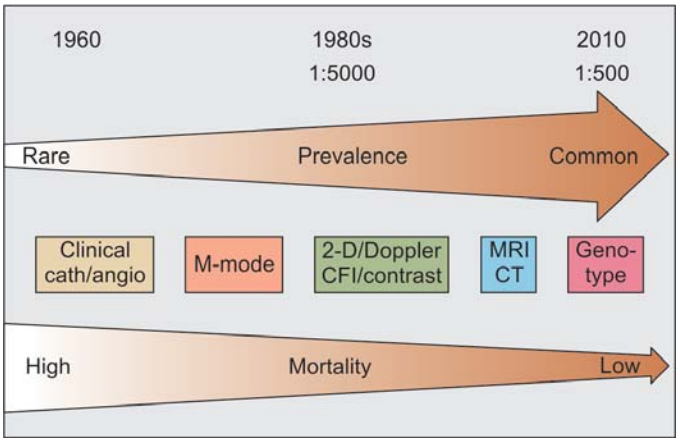


FIGURE 2: Evolution of the epidemiological data on hypertrophic cardiomyopathy (HCM) over the last five decades. Major diagnostic modalities that evolved over time are shown in the boxes. Note that recognition of this genetic disease has dramatically improved. Once considered a rare disease, HCM is now recognized as the most common heritable cardiac disorder. Also shown is the dramatic improvement in clinical outcome (bottom arrow) in contemporary practice with many patients surviving to near-normal age. (Abbreviations: CFI: Contrast flow index; CT: Computed tomography; MRI: Magnetic resonance imaging)

HCM is global and found with equal frequency in males and females as well as across all populations, including non-Hispanic whites, Hispanic whites, blacks and Asians (Chinese included). Genetic penetrance of HCM is incomplete and age-related, therefore HCM can be present at any age and may be detected in infancy, childhood, adolescence[30-32] or as a coincidental finding at autopsy in the elderly.[32] HCM is caused by mutations (inherited in an autosomal dominant pattern) in genes that encode sarcomeric proteins.[16,33] Genetic diagnosis can identify pathogenic sarcomere mutations in persons at any age, including mutation carriers with overt HCM and mutation carriers without hypertrophy who are at high risk for development of disease. Over the past 20 years, several hundred mutations, scattered among at least 27 putative HCM susceptibility genes encoding various sarcomeric, calcium-handling and mitochondrial proteins have been identified.[34]

The spectrum of HCM-associated genes currently involves not only the myofilaments of the sarcomere, "sarcomeric HCM," but also additional subgroups (nonsarcomeric proteins), tentatively classified as "Z-disc HCM" and "calcium-binding HCM" (Table 1). The mutant proteins cause diverse structural and functional defects in the cardiac muscle sarcomere, but converge into a common final pathway characterized by impaired myocyte function and increased myocyte stress accompanied by activation of stress-responsive intracellular signaling kinases, which activate the myocyte transcriptional machinery producing compensatory hypertrophy, myocardial disarray and fibrosis.[35-39]

TABLE 1

Summary of hypertrophic cardiomyopathy susceptibility genes

Gene	*Locus*	*Protein*	*Frequency (%)*
Myofilament HCM			
TTN	2q24.3	Titin	< 1
MYH7	14q11.2-q12	Beta-myosin heavy chain	15–25
MYH6	14q11.2-q12	Alpha-myosin heavy chain	< 1
MYL2	12q23-q24.3	Ventricular regulatory myosin light chain	< 2
MYL3	3p21.2-p21.3	Ventricular essential myosin light chain	< 1
MYBPC3	11p11.2	Cardiac myosin-binding protein C	15–25
TNNT2	1q32	Cardiac troponin T	< 5
TNNI3	19p13.4	Cardiac troponin I	< 5
TPM1	15q22.1	Alpha-tropomyosin	< 5
ACTC	15q14	Alpha-cardiac actin	< 1
TNNC1	3p21.3-p14.3	Cardiac troponin C	< 1
Z-disc HCM			
LBD3	10q22.2-q23.3	LIM binding domain 3 (alias: ZASP)	1–5
CSRP3	11p15.1	Muscle LIM protein	< 1
TCAP	17q12-q21.1	Telethonin	< 1
VCL	10q22.1-q23	Vinculin/metavinculin	< 1
ACTN2	1q42-q43	Alpha-actinin 2	< 1
MYOZ2	4q26-q27	Myozenin 2	< 1
Calcium-handling HCM			
JPH2	20q12	Juntophilin-2	< 1
PLN	6q22.1	Phospholamban	< 1

Genes in italics are available as commercial genetic tests. (*Source:* Bos et al. Diagnostic, prognostic, and therapeutic implications of genetic testing for hypertrophic cardiomyopathy. J Am Coll Cardiol. 2009;54:201-11, with permission).

TABLE 2

Hypertrophic cardiomyopathy phenocopies

Gene	*Locus*	*Protein*	*Syndrome*
Myofilament HCM			
TAZ	Xq28	Tafazzin (G4.5)	Barth syndrome/LVNC
DTNA	18q12	Alpha-dystrobrevin	Barth syndrome/LVNC
PRKAG2	7q35-q36.36	AMP-activated protein kinase	WPW/HCM
LAMP2	Xq24	Lysosome-associated membrane protein 2	Danon syndrome/WPW
GAA	17q25.2-25.3	Alpha-1,4-glucosidase deficiency	Pompe's disease
GLA	Xq22	Alpha-galactosidase A	Fabry's disease
AGL	1p21	Amylo-1,6-glucosidase	Forbes disease
FXN	9q13	Frataxin	Friedrich's ataxia
PTPN11	12q24.1	Protein tyrosine phosphatase nonreceptor type 11, SHP-2	Noonan syndrome, LEOPARD syndrome
RAF1	3p25	V-RAF-1 murine leukemia viral oncogene homolog 1	Noonan syndrome, LEOPARD syndrome
KRAS	12p12.1	v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog	Noonan syndrome
SOS1	2p22-p21	Son of sevenless homolog 1	Noonan syndrome

Genes in italics are available as commercial genetic tests. (*Source:* Bos et al. Diagnostic, prognostic, and therapeutic implications of genetic testing for hypertrophic cardiomyopathy. J Am Coll Cardiol. 2009;54:201-11, with permission). (Abbreviations: AMP: Adenosine monophosphate; HCM: Hypertrophic cardiomyopathy; LEOPARD: Mnemonic for syndrome with clinical characteristics of lentigines, electrocardiographic conduction abnormalities, ocular hypertelorism, pulmonary hypertension, abnormal genitalia, retarded growth, deafness; LVNC: Left ventricular noncompaction; WPW: Wolff-Parkinson-White syndrome)

Genetic studies in HCM patients with specific myofilament mutations have revealed that the phenotype of HCM may not always express itself as a severely thick ventricle, as evidenced by patients with an identified genetic mutation and only mild LV thickness (~15–18 mm), normal wall thickness, or absence of left ventricular hypertrophy (LVH) until middle age when the full-fledged phenotype of the thick ventricle may appear.[40-44] This probably can be explained by the variability in the degree and age of penetrance.

There is a subset of diseases (Table 2) that mimic the HCM phenotype by presenting with unexplained LVH or increased wall thickness. These rare variants are referred to as phenocopies of HCM and pose a dilemma for the clinician. If the phenotype does not look like typical HCM and other symptoms like ventricular pre excitation or muscle weakness are present, presence of an underlying multisystem disease should be suspected and additional evaluation performed. On the other hand, if myofilament genetic testing does not reveal an HCM-associated mutation, testing for mutations in the metabolic genes can reveal that the increased wall thickness is the primary presentation of a multisystem disease process.

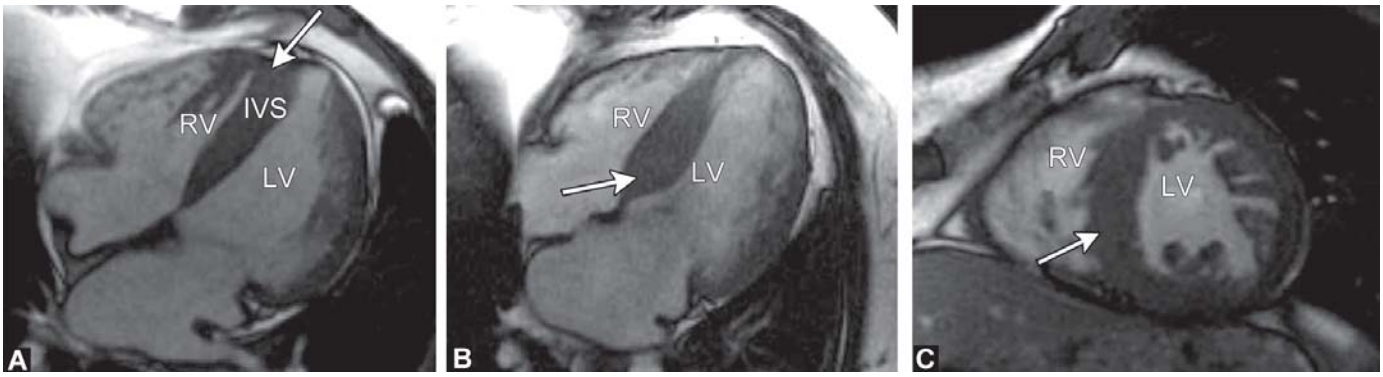
Left ventricular noncompaction (LVNC), a primary genetic cardiomyopathy characterized by a thickened two-layered myocardium, prominent trabeculations and deep intertrabecular recesses,[45,46] can present with seemingly unexplained increased wall thickness and mimic HCM. Mutations in the TAZ (G4.5)-encoded tafazzin—also associated with Barth syndrome—DTNA-encoded alpha-dystrobrevin, and LDB3 gene have been implicated in the pathogenesis of LVNC.[47-49] Recently,[50] mutations in the myofilament encoding genes have been found in unrelated patients with LVNC, suggesting that there might be a shared etiology for the myofilament forms of the common allelic cardiomyopathies of HCM, dilated cardiomyopathy (DCM) and LVNC.

PATHOLOGY

HCM is characterized by a thick ventricle (symmetrical or asymmetrical) and hypertrophy (increased LV mass) involving particularly substantial portions of the LV wall (Fig. 3, Table 3).[4-8,15,51-57]



FIGURE 3: Autopsy specimen of the heart of a young patient with hypertrophic cardiomyopathy who had sudden death. Massive asymmetric hypertrophy of the myocardium can be recognized, which dwarfs the cavity size of the left ventricle in comparison. Also observe the grossly visible area of necrosis toward the apical septum. (*Source:* WD Edwards, MD, Rochester, MN)



FIGURES 4A TO C: Cardiac magnetic resonance (CMR) images from patients with different morphologic variants of hypertrophic cardiomyopathy. (A) A CMR four-chamber view of a patient with asymmetric septal hypertrophy (ASH) showing the relatively increased thickness of the interventricular septum (IVS) (arrow) compared with the left ventricular (LV) lateral wall. Notice the increased thickness of the IVS toward the middle and apical area. (B) A CMR four-chamber view of another patient with ASH involving primarily the basal and middle portion of the septum (arrow). (C) A CMR short-axis view of a patient with ASH demonstrating marked increase in the septal thickness involving primarily the inferior septum (arrow) compared to the anterior septum. Note the prominent hypertrophic trabeculae along the lateral wall of the LV. (Abbreviation: RV: Right ventricle)

TABLE 3

Gross anatomic and microscopic features of HCM

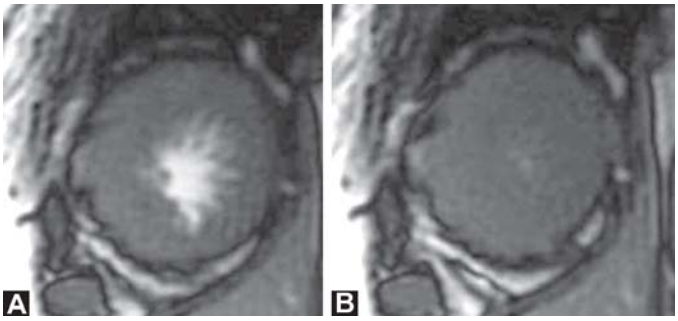
Gross examination:

1. Asymmetrically or symmetrically thick ventricle
2. Basal septal bulge or sigmoid septum
3. Endocardial fibrosis
4. "Septal callus" or subaortic mitral impact friction lesion (plaque on the interventricular septum where mitral-septal contact has repeatedly occurred)[#]
5. Elongated and/or thickened chordae tendineae
6. Increased anterior leaflet length of the mitral valve
7. Increased number of posterior leaflet scallops
8. Abnormal attachments of mitral valve chordal apparatus to septum
9. Hypertrophied papillary muscles with or without anterior displacement
10. Abnormal attachment of papillary muscle heads directly into the mitral leaflets
11. Dilated atria

Microscopy (characterized by disorganization or "whorling" of muscle fibers):

1. Myocardial disarray characterized by severely hypertrophied myocytes aligned perpendicularly or obliquely to each other around central cores of collagen in a pinwheel configuration or herringbone pattern
2. Fibrosis (pericellular, patchy or extensive)
3. Degenerating muscle fibers
4. Intimal and medial smooth muscle hyperplasia of intramural coronary arteries and capillaries (small-vessel disease)
5. Reduced arteriolar density
6. Microscopic evidence of subacute/acute myocardial necrosis

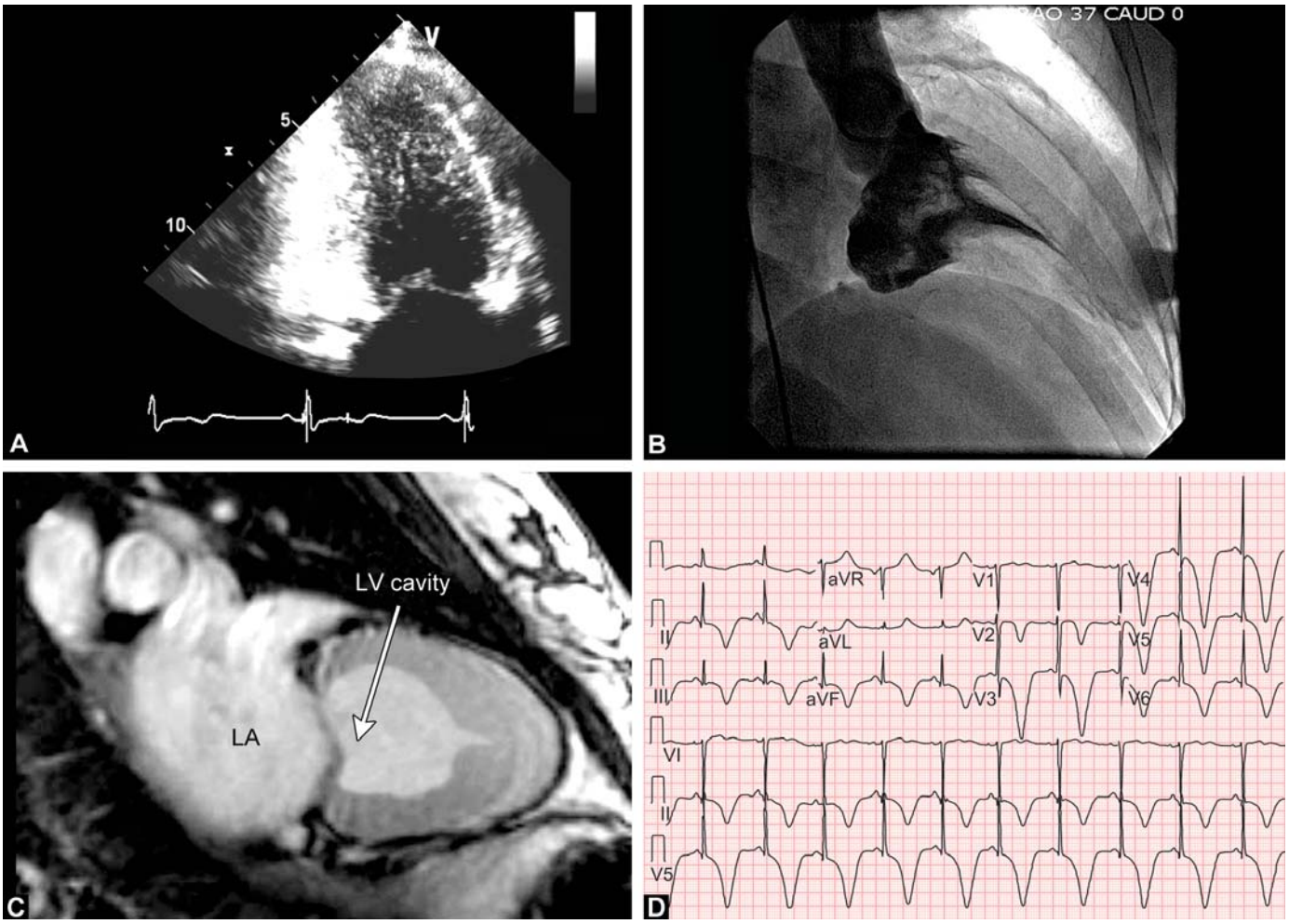
[#]This lesion is an exact mirror image of the anterior cusp of the mitral valve and chordae and is characterized by a sharper lower edge, corresponding to the lower border of the valve cusp.



FIGURES 5A AND B: Steady-state free precession (bright blood) cardiac magnetic resonance (CMR) images from a cine loop oriented in short axis in the mid-ventricle in a patient with hypertrophic cardiomyopathy (HCM). These images demonstrate the abnormal wall thickening associated with diffuse HCM at end-diastole (A) and the obliteration of the ventricular cavity at end-systole (B)

Asymmetrical hypertrophy is confirmed by comparing the width of the septum with the LV free wall and is characterized by a septal-to-free wall thickness ratio greater than 1.3.[55,58] The classic anatomic form of HCM described by Teare in 1958 involved thickening of the basal anterior septum, which bulges beneath the aortic valve and causes narrowing of the left ventricular outflow tract (LVOT).[2] Contemporary studies demonstrate a spectrum of patterns of LV wall thickening that constitute the phenotypic expression of HCM. Asymmetric involvement of the interventricular septum (IVS) (also referred to as asymmetric septal hypertrophy, or ASH) (Figs 4A to C) is the most common form of the disease, although other phenotypes include symmetric (Figs 5A and B), apical (Figs 6A to D) and mass-like LVH as well as an end-stage form, known as the "burned-out phase," that is characterized by progressive wall thinning and systolic dysfunction. Right ventricular involvement occurs in approximately 17.6% of all cases of HCM, most commonly involving the middle to apical portion of the right ventricle (RV).[51,59]

Histology (Table 3) remains the cornerstone for the diagnosis of HCM. At the microscopic level, pathological hallmarks of HCM include myocyte hypertrophy (maximal in the subendocardial region) and disarray (with bizarre enlarged nuclei, hyperchromasia and pleomorphism) together with expansion of the interstitial collagen compartment (Fig. 7).[60-62] The histologic criteria for the diagnosis of HCM require disarray of at least 5–10% of the myocytes within the IVS.[51] Myocyte disarray, however, is not specific to HCM and is seen in other cardiovascular disorders (congenital heart disease, for one, and even in the normal heart where it is, usually, found at the points at which the RV interdigitates with the IVS). In these locations, the normal disarray is accompanied by increased interstitial adiposity.[13,51]



FIGURES 6A TO D: Multimodal images demonstrating isolated apical hypertrophic cardiomyopathy (HCM), a form more common in Asian populations (25% in the Japanese and only 1–2% in non-Japanese). (A) An apical two-chamber view of the left ventricle (LV) demonstrating hypertrophy of the apex in "ace of spades" configuration. (B) Right anterior oblique view showing vigorous contraction with near total obliteration of the ventricular cavity at end-systole. (C) Cardiac magnetic resonance imaging demonstrating severe apical hypertrophy. (D) A 12-lead surface electrocardiogram revealing left ventricular hypertrophy and giant negative T-waves in the precordial leads, a pattern very suggestive of apical HCM. Although large negative T-waves in the midprecordial leads are characteristic of this form of HCM, these may "wax and wane" with time and transition from normal T-waves to negative T-waves can occur acutely or take several years. (Abbreviation: LA: Left atrium)



FIGURE 7: Microscopic sections of the myocardium from a young patient with hypertrophic cardiomyopathy who had sudden death. There is myocardial disarray characterized by hypertrophied myocytes aligned perpendicularly to each other around central cores of collagen. Also note the pericellular patchy fibrosis. (*Source:* WD Edwards, MD, Rochester, MN)

PATHOPHYSIOLOGY

The morphologic and functional changes associated with HCM result in complex and multiple interrelated changes in cardiac physiology, including diastolic dysfunction, LVOT obstruction, mitral regurgitation (MR), myocardial ischemia, arrythmias and, in a minority of patients over time, overt systolic dysfunction (Table 4).

Based on functional studies of mutant contractile proteins, energy deficiency or depletion has been cited as a unifying dysfunction in HCM (Fig. 8). This is related to increased energy demand owing to inefficient sarcomeric adenosine triphosphate (ATP) utilization. The increased demand compromises the capacity of cardiomyocytes to maintain energy levels in subcellular compartments responsible for contraction and critical homeostatic functions such as calcium reuptake.[63] The ensuing myocyte dysfunction results in hypertrophy. Sarcomeric mutations are a potent source of energy deficiency through inefficient or profligate energy use (e.g. troponin T mutations).[63,64] This hypothesis has been supported by various clinical studies,[65,66] extending the "disease of the sarcomere"

TABLE 4

Pathophysiologic hallmarks of hypertrophic cardiomyopathy

Diastolic Dysfunction
Multifunctional etiology:
1. Molecular function (e.g. mutations, calcium economy and sensitivity)
2. Myocardial tissue function (e.g. hypertrophy, fibrosis and disarray)
3. Global function (e.g. geometry and ischemia)

LVOT Obstruction
Multifunctional etiology:
1. Septal hypertrophy and configuration
2. Systolic anterior motion and SAM-septal contact
3. Elongated, redundant and often anteriorly positioned mitral apparatus
4. Altered ventricular loading conditions
5. Reduced ventricular chamber volume

Midventricular obstruction:
1. Mid-septal hypertrophy
2. Hypertrophic papillary muscles
3. Anomalous papillary muscle insertion

Arrhythmogenic Substrate
Tachyarrhythmias:
1. Myocardial disarray
2. Interstitial fibrosis
3. Small-vessel disease:
   a. Structurally abnormal intramural arterioles with thickened media and narrowed lumina
   b. Silent myocardial ischemic with replacement fibrosis/scarring (perivascular fibrosis)
4. Apical pouch
5. Dilated left atrium (diastolic dysfunction ± mitral regurgitation)

Bradyarrhythmias:
1. Conduction system disease
2. Chronotropic incompetence
3. Left bundle branch block; uncommonly, right bundle branch block
4. Spontaneous complete heart block (rare)

Dilated Hypokinetic Phase (burnt-out stage)

(Abbreviations: LVOT: Left ventricular outflow tract; SAM: Systolic anterior motion)

TABLE 5

Left ventricular outflow tract obstruction

Hemodynamic groups:
1. LVOT obstruction at rest (obstructive HCM: LVOT gradient ≥ 30 mm Hg); 25–30% of HCM patients
2. LVOT obstruction with provocation only (latent obstruction); 60–70% of HCM patients
3. No LVOT obstruction either at rest or provocation (nonobstructive HCM); 5–10% of HCM patients

Mechanism:
1. Venturi effect
2. Drag forces
3. Alterations in chamber geometry and morphology*

Consequences:
1. Increased wall stress
2. Chronic elevation of left ventricular intracavitary pressure
3. Myocardial ischemia
4. Cellular death and replacement fibrosis

Outcome:
1. Increased risk for progression to NYHA class III and IV symptoms
2. Increased risk for progression to cardiovascular death
3. Increased risk for sudden death
4. Increased risk for death due to heart failure or stroke

*LVOT cross-sectional area can be reduced in HCM due to a combination of septal hypertrophy and anterior displacement of the mitral valve apparatus and papillary muscles. (Abbreviations: HCM: Hypertrophic cardiomyopathy; LVOT: Left ventricular outflow tract; NYHA: New York Heart Association)

concept to one of energy deficiency. Recently, it has also been recognized that even the missense mutations in muscle LIM protein (MLP), which are only distantly, related to sarcomeric function, can be integrated into this energy-deficiency concept. It is believed that a failure of energy transfer from its source of generation (mitochondria) to its site of use (sarcomeres) results in subcellular energy deficiency, contributing to energetic and contractile dysfunction.[67] A central role for abnormal energetics in HCM can be helpful in explaining delayed clinical onset and asymmetrical hypertrophy in HCM, and has potential implications for therapy for HCM. Thus, for example, Coenzyme Q_{10} (CoQ_{10}) is believed to improve cellular ATP production in cardiomyocytes and may bring about an improvement in the active process of diastolic function with secondary clinical improvement.[68]

LEFT VENTRICULAR OUTFLOW TRACT OBSTRUCTION

The defining pathophysiological abnormality—and one that has been the subject of heated debates[23] in cardiology—is the increased intraventricular systolic pressure component of the complex ejection dynamics that occur in HCM. Several noninvasive imaging studies[69-78] have provided unequivocal and overwhelming evidence for true obstruction and significant LV pressure overload in HCM. The mechanism of LVOT obstruction (Table 5) in HCM is complex and multifactorial. Systolic anterior motion (SAM) (Figs 9A to D) of the mitral leaflets sucked toward the septum by a high-velocity outflow jet (the Venturi effect) is the primary event in LVOT obstruction, although most recent studies[69,73,79,80] emphasize the "flow drag" phenomenon (or the pushing force of flow) as the dominant hemodynamic mechanism underlying SAM. It is believed that during ventricular systole, flow against the abnormally positioned mitral valve apparatus results in a drag force on a portion of the mitral valve leaflets and actually "pushes" the leaflets into the outflow tract, creating a self-amplifying loop where longer durations of SAM-septal contact lead to further increases in obstruction. The LV is not devoid of blood in mid-to-late systole after an early rapid systolic ejection phase, but conversely, a large and highly variable proportion of stroke volume (about 50%) remains to be ejected when the gradient is present and is mechanically impeded in its egress by SAM-septal contact; the earlier and more prolonged the septal contact, the greater the obstructed flow. Furthermore, forward flow persists throughout systole (to aortic valve closure), with ejection time prolonged and related to the magnitude of the gradient. Biphasic aortic flow patterns and midsystolic drop in LV ejection velocities are also consistent with the "spike and dome" arterial pulse and midsystolic aortic valve closure or "peak and dome" configuration on M-mode echocardiography of the aortic valve (Fig. 10). Obstruction can also be present in the midcavitary region due to hypertrophied papillary muscles.

Although LVOT obstruction occurs at rest in approximately 30% of patients with HCM, the obstruction to LVOT is

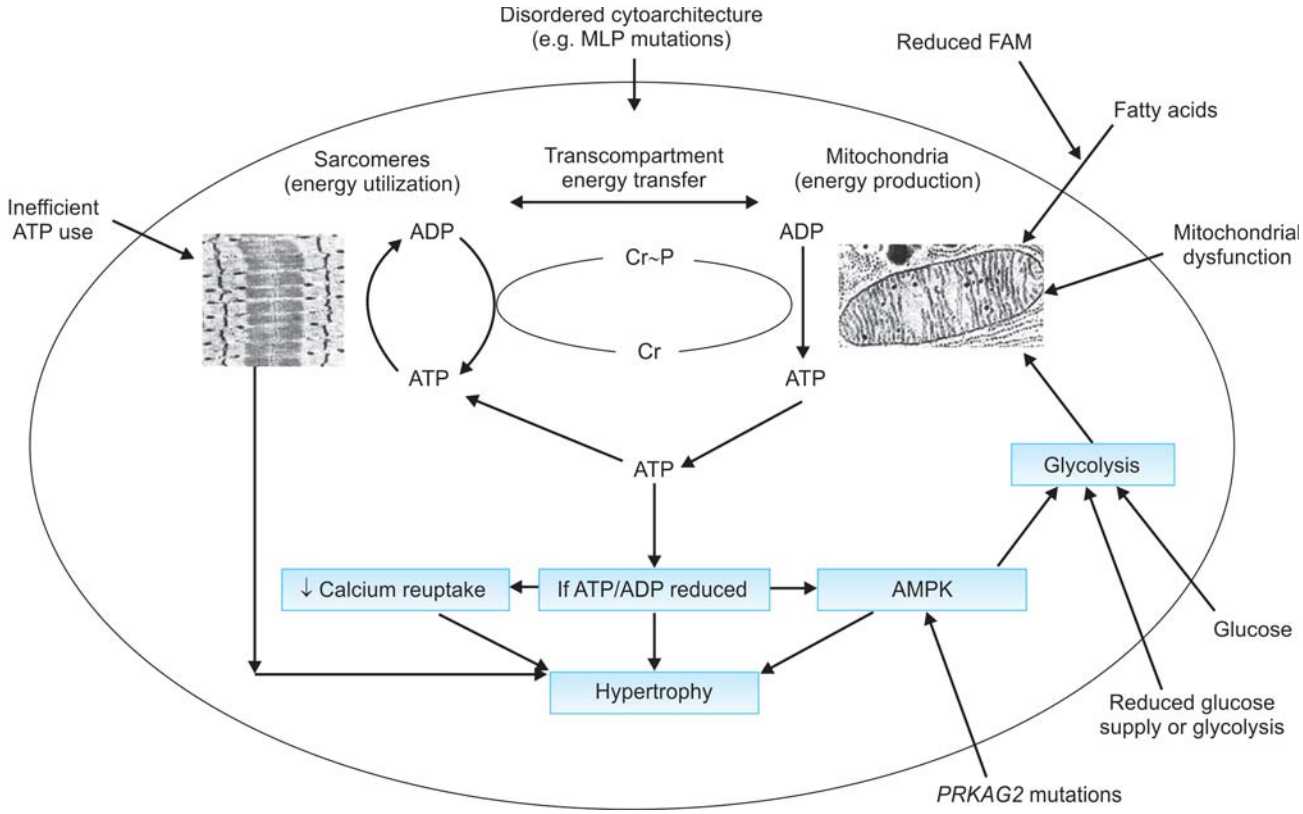
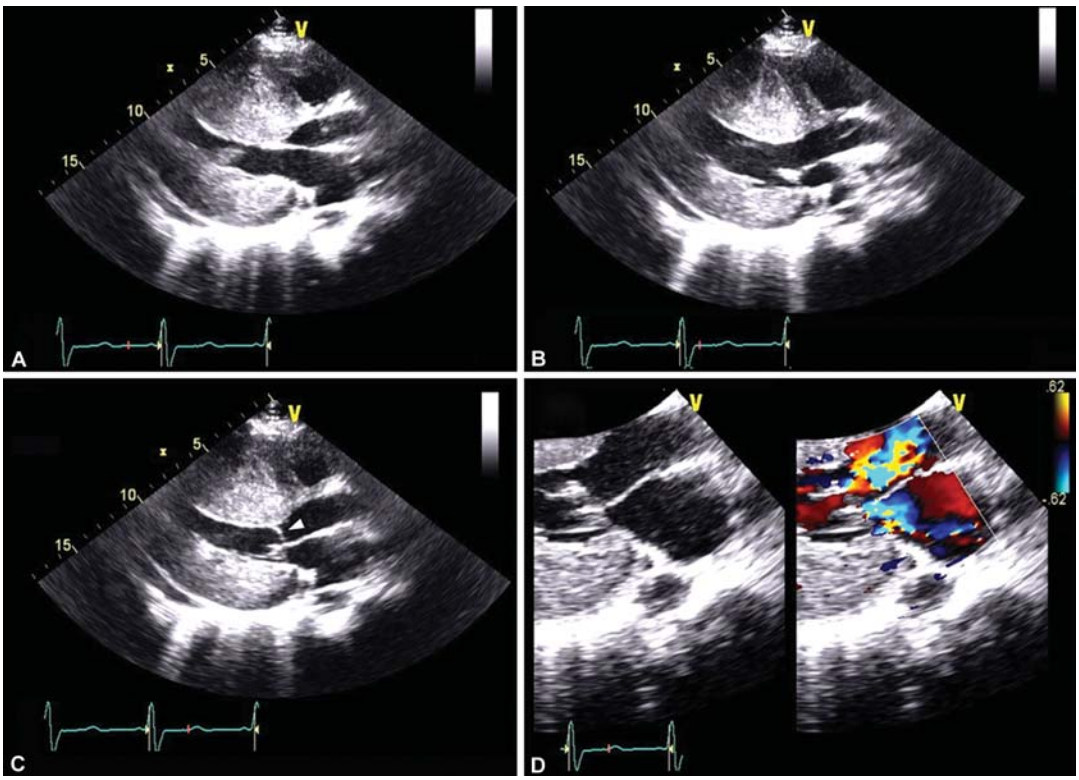


FIGURE 8: As indicated in red, the phenotype of hypertrophic cardiomyopathy (HCM) can arise from: (1) excessive energy use (e.g. by aberrant sarcomeres); (2) inadequate energy production (e.g. from poorly functioning mitochondria), inadequate metabolic substrates, or a failure to transfer energy across cellular compartments owing to cytoarchitectural defects as exemplified by muscle LIM protein (MLP) mutations or (3) aberrant signaling of energy deficiency [e.g. with AMP-activated protein kinase (AMPK) mutations]. The final common path for these diverse defects is energy deficiency and ensuing hypertrophy. (*Source:* Modified from Ashrafian et al. Reviews of translational medicine and genomics in cardiovascular disease: new disease taxonomy and therapeutic implications. Cardiomyopathies: therapeutics based on molecular phenotype. J Am Coll Cardiol. 2007;49:1251-64, with permission). (Abbreviations: ADP: Adenosine diphosphate; AMP: Adenosine monophosphate; ATP: Adenosine triphospate; Cr: Creatine; FAM: Fatty acid metabolism)



FIGURES 9A TO D: Illustrated in this figure are successive long-axis parasternal 2D echocardiographic views in a patient with obstructive hypertrophic cardiomyopathy. Massive asymmetric hypertrophied septum with small left ventricle (LV) cavity and abnormal texture of the myocardium is noted. (A) An end-diastolic frame where mitral valves are open and the LV is filling. (B) Shows the LV in early systole as the LV wall begins to thicken. (C) Demonstrates the beginning of systolic anterior motion of the mitral valve (arrowhead) with left ventricular outflow tract (LVOT) obstruction. (D) Shows progression of the systolic anterior motion with development of significant LVOT obstruction. Note the simultaneous anterior motion causing a narrowed LVOT and associated mitral regurgitation

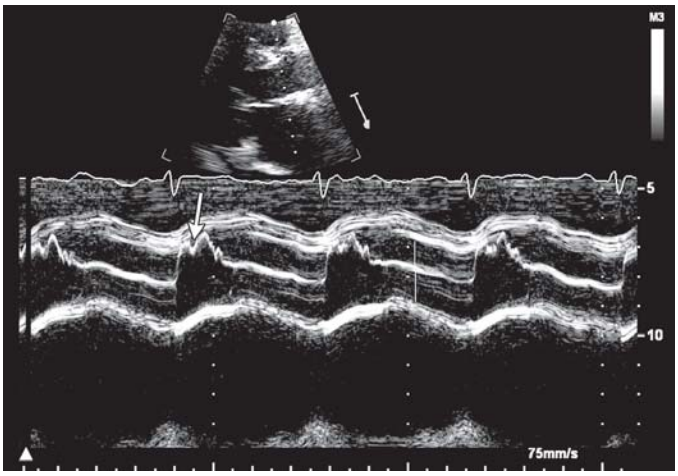


FIGURE 10: M-mode echocardiogram recorded in a patient with hypertrophic cardiomyopathy demonstrating systolic notching of the aortic valve—the "peak and dome" phenomenon

TABLE 6

Maneuvers used in clinical practice to provoke LVOT gradients*

1. Standing from supine position
2. Valsalva maneuver
3. Amyl nitrite inhalation
4. Dobutamine infusion
5. Isoproterenol infusion
6. Exercise:
   a. Treadmill exercise
   b. Upright cycle ergometry
   c. Supine cycle ergometry

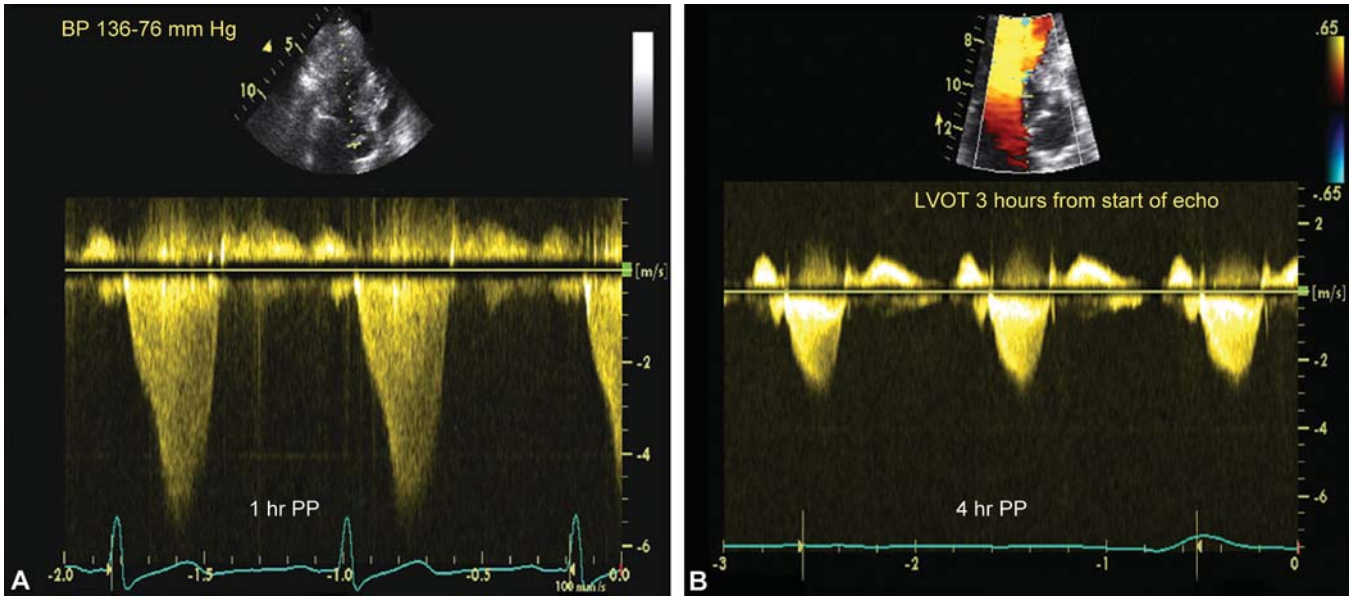
*Note that in contemporary clinical practice, the use of provocative maneuvers is not standardized. With the exception of exercise, these maneuvers are considered nonphysiologic and unable to perfectly reproduce the conditions under which obstruction occurs in routine daily life. Also note, that the ACC[5] does not recommend the use of dobutamine as a maneuver for provoking LVOT gradients (Abbreviations: LVOT: Left ventricular outflow tract)

dynamic[4,81] and varies with loading conditions and contractility of the ventricle. These include interventions or maneuvers (Table 6) that decrease ventricular size/volume, thus increasing SAM-septal contact, e.g. decreasing preload or increasing contractility (standing position, dehydration, inotropic agents, isoproterenol, digoxin). A decrease in afterload will also have a similar effect, e.g. vasodilation (amyl nitrite inhalation). Patients with HCM may have little or no LVOT obstruction at rest but can generate large LVOT gradients under conditions such as exercise, the strain phase of the Valsalva maneuver, pharmacologic provocation or even after a meal (Figs 11A and B).

The LVOT obstruction is a highly visible feature of HCM, contributing to both debilitating symptoms of the disease and outcome (independent predictor of mortality). The presence of LVOT obstruction predicts adverse outcomes, and patients with obstruction (resting outflow tract gradient > 30 mm Hg) are nearly 5 times more likely to progress to severe symptoms of heart failure (HF) and HF-related death.[82]

DIASTOLIC DYSFUNCTION

Diastolic dysfunction is a major pathophysiologic phenomenon of HCM. It is multifactorial (Table 3) and central to several clinical symptoms like dyspnea, exercise intolerance and pulmonary congestion, as well as pathophysiologic changes of impaired early diastolic filling, increased filling pressures and left atrial enlargement. These abnormalities stem from a multitude of factors affecting contraction and relaxation loads: nonuniformity of ventricular contraction, myocardial calcium handling and LV chamber stiffness.[7,15,83,84] Severe hypertrophy, increased myocardial mass and myocardial fibrosis culminate in increased myocardial stiffness. Diffuse myocardial ischemia, further affects both relaxation and chamber stiffness. Echocardiographic indices of diastolic function identify patterns consistent with impaired relaxation or restrictive filling[85,86] and



FIGURES 11A AND B: Continuous Doppler-wave recordings in a patient with hypertrophic cardiomyopathy (HCM). Depicted is the left ventricular outflow tract (LVOT) gradient of about 120 mm Hg seen in the patient after one hour of having consumed a meal. Also shown is the significant decrease in the LVOT gradient (36 mm Hg) in the same patient several hours later. Patients with HCM can experience exacerbation of exertional symptoms after a meal. The hemodynamic effects of a meal relate to production of arterial vasodilation with afterload reduction and a compensatory increase in heart rate. These changes, directly and indirectly, lead to worsening of LVOT obstruction and elevation of diastolic filling pressures

can assist in characterizing diastolic function and guiding treatment in patients with HCM. In close association with these alterations is a compensatory increase in the contribution of late-diastolic filling during atrial systole. Exercise or any other type of catecholamine stimulation decreases the diastolic filling period and increases myocardial ischemia, leading to severe abnormalities in diastolic filling of the heart, with an increase in pulmonary venous pressure causing symptoms of dyspnea.

Diastolic filling parameters, however, have not reliably predicted resting filling pressures or exercise capacity in patients with HCM. No relationship between transmitral indices of diastolic function and LV end-diastolic pressure have been identified in patients studied simultaneously with cardiac catheterization and echocardiography.[84,87,88] Furthermore, no consistent correlation with transmitral Doppler flow patterns and the extent of LVH, presence or absence of LVOT obstruction, symptoms or exercise capacity have been identified.[88,89]

SYSTOLIC DYSFUNCTION

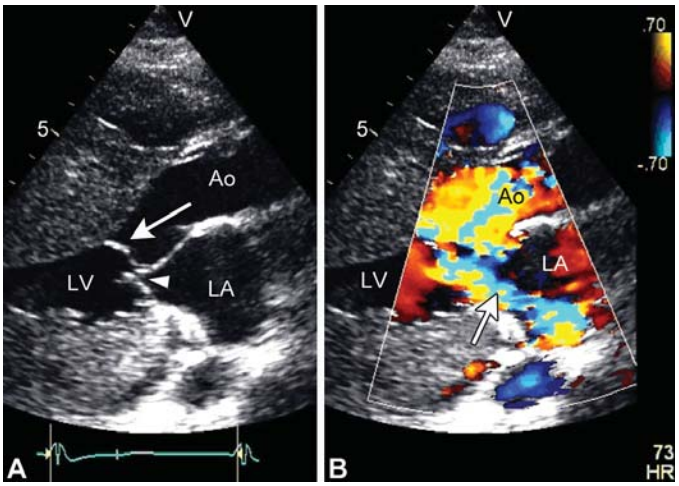
In spite of a preserved or hyperdynamic LV ejection fraction (LVEF), the traditional metric of systolic function, more advanced and sophisticated measures of contractile function (e.g. LV strain and strain rate, twist and untwist mechanics) have shown evidence of diminished systolic function in HCM, which can possibly be explained by regional differences in contractile function not recognized by global measures such as LVEF. Both cardiac magnetic resonance (CMR) and echocardiographic strain imaging demonstrate abnormal contractility in HCM, particularly in hypertrophied segments and the IVS.[86,90,91]

MYOCARDIAL ISCHEMIA

Small-vessel disease in which intramural coronary vessels are narrowed by medial hypertrophy[92-94] is a common feature of HCM and contributes to the development of myocardial ischemia.[95,96] Severe myocardial ischemia and even infarction can occur in HCM,[95,97,98] frequently in the absence of epicardial atherosclerotic disease (due primarily to a supply-demand mismatch). Patients with HCM, not only have an oxygen supply-demand mismatch due to the increased muscle mass and adverse loading conditions, but also a compromised LV coronary blood flow due to the abnormally small and partially obliterated intramural coronary arteries. Microvascular ischemia can be detected and quantified by single-photon emission computed tomography (SPECT), positron emission tomography (PET) and CMR imaging as a blunted increase in myocardial flow after exercise (SPECT) or administration of a coronary vasodilator such as dipyridamole (PET, SPECT or CMR). Differentiation of microvascular abnormalities from epicardial stenosis may be facilitated by identifying nonanatomic perfusion abnormalities, which do not follow typical coronary artery distribution, and CMR may be more useful in this regard given its superior spatial resolution.

MITRAL REGURGITATION AND MITRAL VALVE ABNORMALITIES

Mitral regurgitation (MR) is frequent in patients who have HCM with LVOT obstruction and may play a central role in symptomatology.[7,15,99] From a pathophysiological standpoint, MR is a secondary phenomenon owing its origin to the "eject-obstruct-leak" mechanism.[7,15,99] The mitral valve apparatus gets distorted from the SAM of the anterior mitral leaflet secondary to the LVOT obstruction. The SAM of the mitral valve leads to a diminished systolic coaptation of the mitral leaflets and creates an "interleaflet gap" resulting in MR. Classically, the MR jet is eccentric and directed laterally and posteriorly (as the anterior leaflet is selectively pulled into the LVOT), with maximum regurgitation occurring in mid and late systole (Figs 12A and B) and the severity of MR defined, essentially by the severity of the LVOT obstruction. However, ventricular loading conditions and contractility affect the severity of outflow tract obstruction and, therefore, the severity of MR.



FIGURES 12A AND B: Expanded parasternal long-axis view of the left ventricle (LV) in a patient with hypertrophic cardiomyopathy. Systolic anterior motion (white arrow, left panel) of the mitral valve with diminished mitral leaflet coaptation—"the interleaflet gap" (white arrowhead, left panel)—is seen in the non-color image. The corresponding color picture demonstrates the eccentric jet of mitral regurgitation directed laterally and posteriorly (white arrow, right panel) in late systole. (Abbreviations: Ao: Aorta; LA: Left atrium)

However, it needs to be emphasized that a number of anatomic and functional abnormalities of the mitral valve accompany the primary cardiomyopathy disease in HCM. These may include: (1) increased mitral leaflet area (Fig. 13) and (2) abnormal origin and insertion of the papillary muscles (papillary muscle insertion directly into the anterior leaflet without intervening chordae tendineae in more than 10% of patients with obstruction),[100,101] characteristically seen on two-dimensional (2D) echocardiography. Recognition often requires nontraditional transthoracic windows (slightly rotated, parasternal long-axis view of the LV), which are critical since these findings may influence subsequent treatment decisions.[102] In patients who undergo myectomy, the surgical approach may have to be adapted and include creating a deeper myectomy trough and partial resection of papillary attachments to ensure adequate postoperative relief of obstruction.[103]

Several patients with HCM and SAM are also recognized to have abnormally elongated posterior mitral valve leaflets and even overt prolapse. In such cases, the direction of the regurgitant jet is the key to the differentiation of primary mitral valve disease from MR secondary to SAM. A centrally or anteriorly

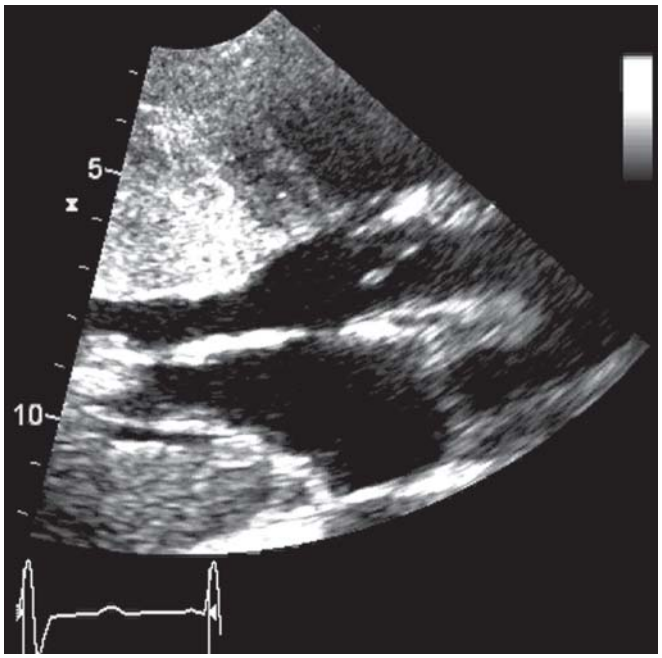


FIGURE 13: Expanded parasternal long-axis view of the mitral valve demonstrating elongated leaflets and increased mitral valve leaflet area

directed MR jet, strongly suggests that the MR may not resolve with amelioration of obstruction and SAM (i.e. intrinsic mitral valve disease). Moreover, patients with long-standing SAM can develop traumatic fibrosis of the anterior mitral leaflet due to recurrent septal contact (with the septum itself developing a friction lesion—the so-called "septal callus"), which may subsequently become a determinant of MR independent of LVOT obstruction.[7] Ruptured chordae may also be seen.

ARRYTHMOGENIC SUBSTRATE AND SUDDEN DEATH

The shadow of sudden death (SD) looms large in patients with HCM diagnosis (Fig. 14). Although the most visible complication of HCM,[5,8,27,104,105] SD occurs in only a small minority of patients and is less common than other adverse consequences including atrial fibrillation (AF) and progressive HF.[5,25,106] The HCM-related SD events are caused by sustained ventricular tachycardia (VT) and/or ventricular fibrillation (VF),[104,105,107] and although the trigger for these potentially lethal rhythms is poorly understood, sinus tachycardia is identified as an initiating rhythm in some cases, suggesting that high sympathetic drive can be proarrhythmic,[108] providing a possible clue to the mechanisms of SD in athletes with HCM.[29] The architectural disorganization and scarring (and possibly the expanded interstitial matrix),[61] in addition to microvascular dysfunction and ischemia, are believed to represent the unstable electrophysiological substrate that creates susceptibility to reentry arrhythmias.

An important feature of the life-threatening ventricular tachyarrhythmias associated with HCM is the unpredictable nature of their occurrence with varying periods of dormancy.[104,105,109-111] Years may pass before an event recurs,[109,110] and long-term survival (up to 30 years) after VT/VF without recurrence of life-threatening arrhythmias has been reported.[112]

The introduction of implantable cardioverter-defibrillators (ICD)[104,105,113] has created an effective strategy for SD prevention and, at the same time, an enhanced focus on risk stratification and need for reliable identification of high-risk patients.[24-28,105,113]

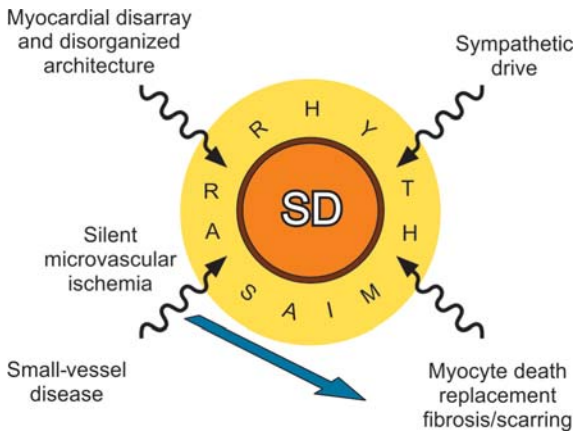


FIGURE 14: Pathogenesis of sudden death (SD) in hypertrophic cardiomyopathy (HCM). Note the interplay of multiple factors involved in HCM-related SD. Eventually, the architectural disorganization and scarring (and possibly the expanded interstitial matrix), with contribution from small-vessel disease and sympathetic tone, leads to an unstable electrophysiological substrate, which creates susceptibility to reentry arrhythmias. Data assembled from stored electrograms document that SD events in HCM are caused by sustained ventricular tachyarrhythmias (i.e. rapid ventricular tachycardia and/or ventricular fibrillation)

MYOCARDIAL FIBROSIS

Interstitial fibrosis (Fig. 15) affects the heart at several levels in HCM. Increased cardiac collagen occurs prominently at sites of prior ischemic injury (replacement fibrosis), myocyte disarray and near the IVS junction.[114] Interstitial fibrosis is detected clinically by visualizing delayed gadolinium (extracellular tracer) enhancement (DE) with CMR imaging (Fig. 16). Increased fibrosis is believed to play a role in the pathogenesis of ventricular arrhythmias and SD and can be clinically useful (by visualizing DE) in risk stratification for SD.[115,116] Thus, DE is linked to the underlying electrical substrate by recognition that ventricular tachyarrhythmias

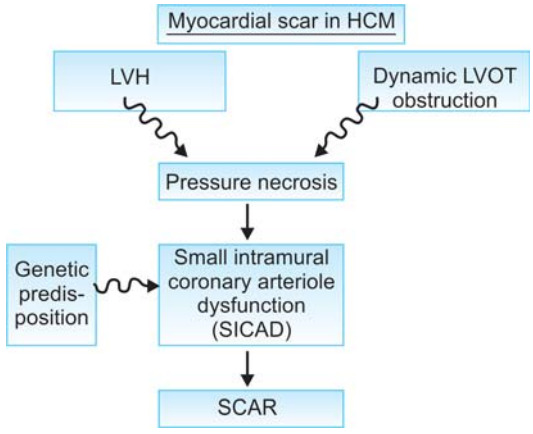


FIGURE 15: Complex interaction of pressure necrosis and genetic predisposition leading to small intramural coronary arteriole dysfunction that ultimately leads to formation of myocardial scar. The latter is an arrythmogenic substrate that predisposes patients with hypertrophic cardiomyopathy (HCM) to sudden death. (Abbreviations: LVOT: Left ventricular outflow tract; LVH: Left ventricular hypertrophy)

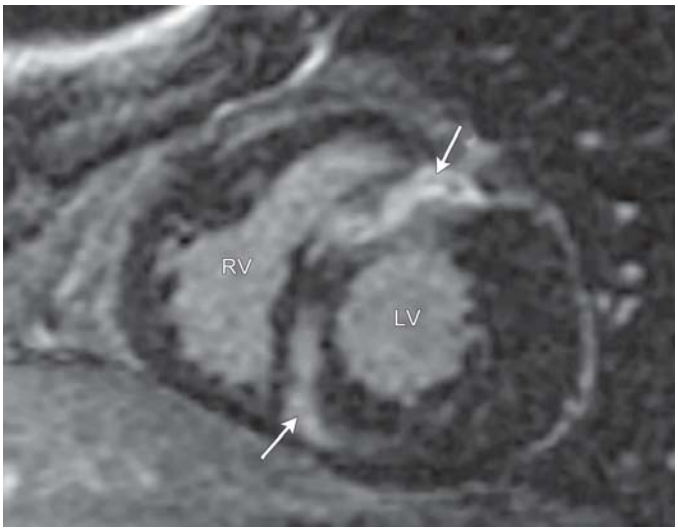


FIGURE 16: Short-axis inversion recovery gradient echo image (delayed cardiac magnetic resonance) obtained during systole, 15 minutes following the intravenous administration of gadolinium contrast (gadobenate dimeglumine). The normal myocardium has low signal. The patchy areas of bright signal, in the anterior and posterior septal walls (white arrows) and at the insertion points of the right ventricular free wall, correspond to area of fibrosis (late gadolinium enhancement) seen in this patient with concentric hypertrophic cardiomyopathy. (Abbreviations: LV: Left ventricle; RV: Right ventricular)

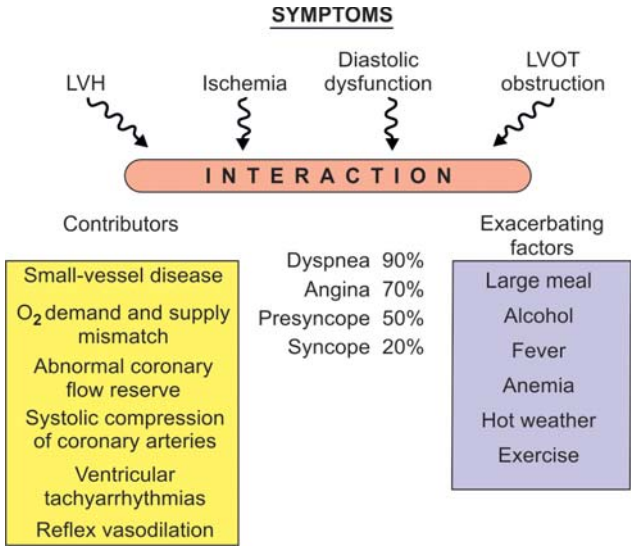


FIGURE 17: The symptoms of hypertrophic cardiomyopathy (HCM) arise from a close interaction of left ventricular outflow tract (LVOT) obstruction, diastolic dysfunction, small-vessel ischemia and left ventricular hypertrophy (LVH). These symptoms are often exacerbated (purple box) by factors that can increase LVOT obstruction, either by decreasing preload or afterload or increasing left ventricular contractility. Several other factors (yellow box) may also interact to contribute to the symptom complex of HCM

(including nonsustained VT), as noted on ambulatory Holter electrocardiogram (ECG), are most common in patients with DE.[117]

AUTONOMIC DYSFUNCTION

Autonomic impairment is associated with HCM and may be associated with both VT and syncope.[118] The myocardial disarray/disorganization and interstitial fibrosis seen in HCM may damage afferent autonomic nerves (indicating decreased cardiac parasympathetic activity) in the heart. This is expressed as reduced heart rate (HR) variability with deep breathing and reduced HR variation with the Valsalva maneuver.[119] An abnormal blood pressure response during exercise, defined by either a failure of systolic blood pressure to increase greater than 20 mm Hg or a decrease in systolic blood pressure, is noted in approximately 25% of HCM patients,[120,121] and its presence is associated with poorer prognosis.[121,122] The failure of systolic blood pressure to rise may be due to systemic vasodilation during exercise and a high degree of abnormal autonomic tone in HCM with some probable contribution from exercise-induced augmentation of outflow-tract obstruction. A hypotensive or attenuated blood pressure response to exercise is, in fact, one of the conventional primary prevention risk factors for HCM in patients less than 50 years old.

CLINICAL PRESENTATION

SYMPTOMS

HCM is unique by virtue of its potential for clinical presentation during any phase of life (from infancy to 90 years of age).[2,4,6,7,10,12,14,15,25,123-132] The remarkable diversity in the severity of symptoms associated with the disease remains a defining feature of HCM. On one end of the spectrum are asymptomatic patients who are diagnosed serendipitously by a screening ECG, a murmur detected in a routine office visit, or an echocardiogram for an entirely different indication. At the other end of the spectrum is diagnosis via autopsy in patients whose presentation is SD. Older literature on HCM has persistently defined this disease in an ominous light, citing annual mortality rates of 4–6%.[126,133] However, these figures are based largely on skewed tertiary-center experience, contributing to the misguided perception of HCM as equating to SD. A much more favorable light is cast by reports throughout the past 15 years from less-selective regional- or community-based HCM cohorts, which have cited annual mortality rates of about 1%.[8,129,134,135] Such data provide a more balanced view, with HCM being associated with important symptoms and premature death, but, more frequently, with no or relatively mild disability and normal life expectancy.[123,129,131,132,136,137]

In HCM, there are at least four interacting pathophysiological mechanisms (Fig. 17) that may be responsible for symptoms: (1) LVH, (2) diastolic dysfunction, (3) LVOT obstruction and subsequent MR and (4) myocardial ischemia. A characteristic pattern of day-to-day variation in the activity needed to cause symptoms is also unique to HCM.

Dyspnea occurs in the vast majority of patients, either at rest or with exertion, and is primarily due to elevated LV diastolic filling pressures caused by impaired LV filling. Angina pectoris is also a frequent symptom, occurring in the absence of epicardial coronary disease and primarily related to small-vessel disease and oxygen supply-demand mismatch. Patients with HCM may also be present with presyncope and syncope due to either a rhythm or hemodynamic alteration. The latter is due to a state of low cardiac output induced by a sudden increase

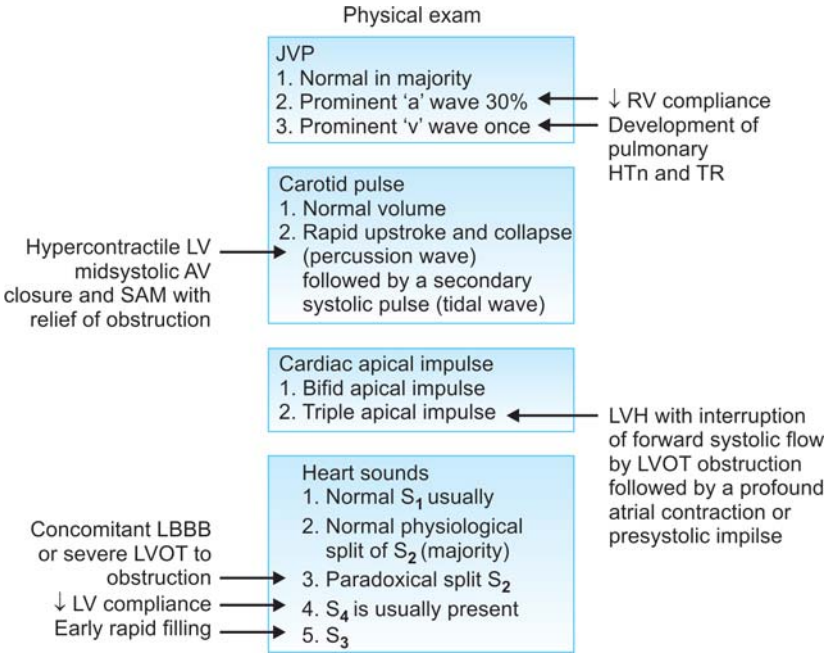


FIGURE 18: Common findings on physical exam in patients with hypertrophic cardiomyopathy. Potential pathophysiological mechanisms are shown by arrows. (Abbreviations: AV: Atrioventricular; JVP: Jugular venous pressure; HTn: Hypertension; LBBB: Left bundle branch block; LV: Left ventricle; LVH: Left ventricular hypertrophy; LVOT: Left ventricular outflow tract; RV: Right ventricle; SAM: Systolic anterior motion; TR: Tricuspid regurgitation)

in HR in the presence of a low LV filling volume, especially when assuming an upright posture or with exercise. Activation of LV baroreceptors with subsequent reflex vasodilation plays a role in this response, a mechanism worsened by a dynamic LVOT gradient. Alterations in both preload and afterload (fluid loss, vasodilation) can occur in hot humid weather and can exacerbate the symptoms of HCM as can a large meal[138-140] or alcohol.[141] The hemodynamic effects of a meal and/or alcohol are related to arterial vasodilation (with afterload reduction and a compensatory increase in HR), changes that—directly and indirectly—lead to worsened LVOT obstruction and elevation of diastolic filling pressures. Other, less commonly reported symptoms include palpitations, paroxysmal nocturnal dyspnea, dizziness and symptoms of HF.

PHYSICAL EXAMINATION

Classic physical examination findings in HCM (Fig. 18) relate to the obstructive variant, with minimal findings (save the presence of an LV lift or a palpable or audible fourth heart sound) in the nonobstructive or apical form. However, variants of HCM may all develop LVOT obstruction at various times, and these physical signs refer to HCM with LVOT obstruction.

Jugular Venous Pressure

Generally, the jugular venous pressure (JVP) is normal in HCM patients, although a prominent "a" wave may occur, reflecting decreased RV compliance (RV hypertrophy and hypertrophied IVS).

Carotid Pulse

A rapid or brisk upstroke (spike), followed by a collapse, followed still later by a secondary systolic wave (dome), is the classic physical examination finding in HCM with LVOT obstruction. The spike and dome configuration results in what is often referred to as pulsus bisferiens (bifid pulse).

Cardiac Apical Impulse

As in other pressure overload situations, a heaving apex (sustained apical impulse) is often palpated. Commonly, a bifid apical impulse is palpated due to a prominent atrial kick. Close attention may reveal the classic triple apical impulse (triple ripple) —a singular physical examination finding in HCM with LVOT obstruction. A systolic thrill may also be palpable at the mitral area due to severe MR or at the lower left sternal border (LLSB) from outflow tract obstruction.

Murmurs and Other Heart Sounds

The auscultatory hallmark of HCM is a harsh, crescendo/decrescendo systolic ejection murmur, best heard at the LLSB or the cardiac apex starting just after first heart sound (a clear interval between the S1 and the murmur is often appreciated), radiating to the axilla or the base of the heart (not the neck) and ending before the second heart sound. Listening to the patient during various maneuvers and changes in position (dynamic auscultation, Table 7) may be necessary to help differentiate the murmur of HCM from other systolic murmurs. These

TABLE 7

Auscultatory responses to commonly performed maneuvers

Maneuver	*Response*	*Mechanism*
Handgrip	Decreased murmur	Increased afterload
Amyl nitrite	Increased murmur	Decreased afterload
Dobutamine or isoproterenol infusion	Increased murmur	Increased contractility
Exercise	Increased murmur	Increased heart rate, increased contractility and vasodilation

TABLE 8

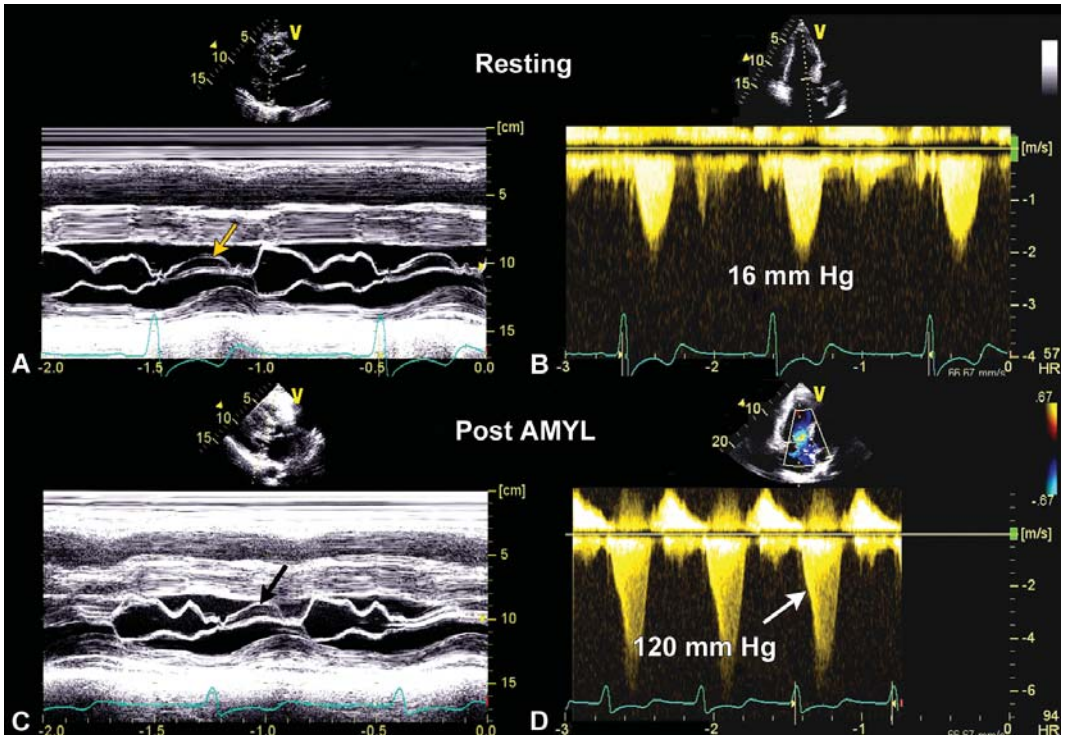
Dynamic auscultation maneuvers in hypertrophic cardiomyopathy

Maneuver	*Venous return*	*Response*	*Sensitivity*	*Specificity*	*Positive LR*	*Negative LR*
Straining phase of Valsalva	Decreased	Louder	70%	95%	14.0	0.3
Squatting to standing	Decreased[#]	Louder	95%	84%	6.0	0.1
Passive leg elevation	Increased	Softer	90%	90%	9.0	0.1
Standing to squatting	Increased	Softer	88–95%	84–97%	7.6	0.1

[#]A progressive increase in intensity of the murmur continues for the next 4–5 beats as preload to the left side is reduced.
(Abbreviation: LR: Likelihood ratio)

maneuvers are classified into: (1) respiratory maneuvers, (2) maneuvers that primarily change systemic vascular resistance (isometric hand grip, transient arterial occlusion and inhalation of amyl nitrite) and (3) maneuvers that change venous return (Valsalva maneuver, squatting to standing, standing to squatting, passive leg elevation). The most frequently performed maneuvers in general clinical practice are Valsalva and squatting.

Unlike most other systolic murmurs, the murmur of HCM increases in intensity with decreased venous return and becomes softer with increased venous return. This paradoxical response relates to increased SAM-septal contact (and, therefore, more LVOT obstruction) due to decreased venous return and vice versa when venous return increases. All four venous return maneuvers (Table 8) help in differentiating HCM (where obstruction is preload-dependent), the most compelling being the strain phase of Valsalva maneuver (likelihood ratio = 14),[142,143] though this classic response does not occur in all patients with HCM. Afterload-changing maneuvers are most useful for differentiating murmurs over the aortic valve (stenosis/regurgitation) from left-sided regurgitant lesions (MR/ventricular septal defect). The inhalation of amyl nitrite is commonly used in the echocardiography laboratory (rarely at the bedside) to help unmask hitherto undefined LVOT obstruction and, consequently, can intensify the murmur of HCM (Figs 19A to D). Manipulating the afterload at the bedside by isometric handgrip and transient arterial occlusion (both increase afterload and thereby decrease LVOT obstruction) will decrease the intensity of the murmur of HCM. Simple exercise, such as ambulation or climbing stairs, can also be used to assess for augmentation of the murmur as well.



FIGURES 19A TO D: Simultaneous depiction of M-mode echocardiograms of the mitral valve and continuous-wave (CW) Doppler tracings across the left ventricular outflow tract (LVOT) in a patient with obstructive hypertrophic cardiomyopathy. (A) Demonstrates only mild systolic anterior motion (SAM) with lack of apposition of the mitral valve (yellow arrow) with the septum. Obstruction of the LVOT (B) (16 mm Hg) with this pattern is expected to be mild compared to (C) where, after inhalation of amyl nitrite (AMYL), systolic anterior motion (black arrow) increases for a greater part of the systole and LVOT obstruction (D) (120 mm Hg) intensifies significantly. Note the close approximation of the mitral valve with the septum for an extended period of time in (C) compared to the mitral valve in (A) (yellow arrow vs black arrow). The CW Doppler at rest shows a gradient of 16 mm Hg, which increases to 120 mm Hg after the amyl nitrite inhalation (B vs D)

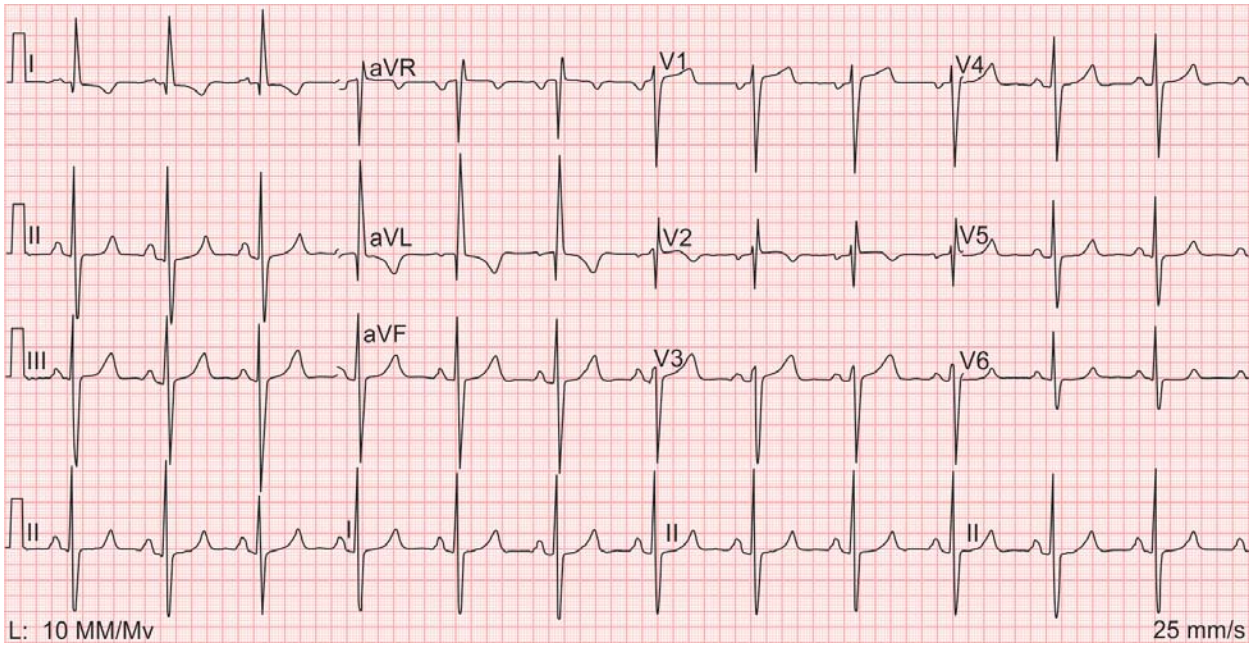


FIGURE 20: A 12-lead surface electrocardiogram from a patient with hypertrophic cardiomyopathy revealing left ventricular hypertrophy (LVH). Note the nonspecific ST-T segment changes and T-wave inversions in the lateral leads, which can be part and parcel of LVH

Although change in cycle length is sometimes used to differentiate various systolic murmurs, including that of HCM, the murmur of HCM may respond unpredictably to changing cycle lengths; the long pause may make the murmur louder, softer or not change it at all.[144]

Uncommonly, a low-pitched mid-diastolic murmur is also heard in HCM, due to the abnormal diastolic filling of a noncompliant LV with the hypertrophied IVS encroaching on the mitral inflow. MR may be a separate murmur audible at the apex and is more holosystolic in nature.

DIAGNOSIS

ELECTROCARDIOGRAM

The vast majority of patients with HCM have an abnormal ECG manifest either as left-axis deviation, LVH or abnormal Q-waves simulating myocardial infarction (representative of massive septal hypertrophy and/or fibrosis) (Table 9). ST-segment changes with T-wave abnormalities are common (due primarily to LVH) (Fig. 20). ECG changes may be the initial manifestation of childhood HCM, appearing even before LVH is detected by echocardiography. The ECG in apical HCM may show repolarization changes in the anterolateral leads and, sometimes, giant negative T-waves (Fig. 6D). Of note, a normal ECG can be observed in 5–10% of patients with echocardiographic evidence of HCM. Such patients have been seen to have a more benign phenotypic expression of HCM as evidenced by lower wall thickness, LVOT gradient, symptom progression, complication rates and cardiac-related mortality compared to HCM patients with abnormal ECGs.[145]

HOLTER MONITORING

Ambulatory 24-hour (Holter) ECG is an important part of the armamentarium used in primary risk stratification for SD in HCM. Holter monitoring demonstrates the basic rhythm in most patients to be normal sinus, but will occasionally demonstrate a high incidence of supraventricular tachycardia (46%), premature ventricular contractions (43%) and nonsustained VT (26%).[146-148] AF is also commonly seen in patients with HCM, with a reported prevalence of approximately 22% and an annual incidence of up to 2% per year.[106]

TABLE 9

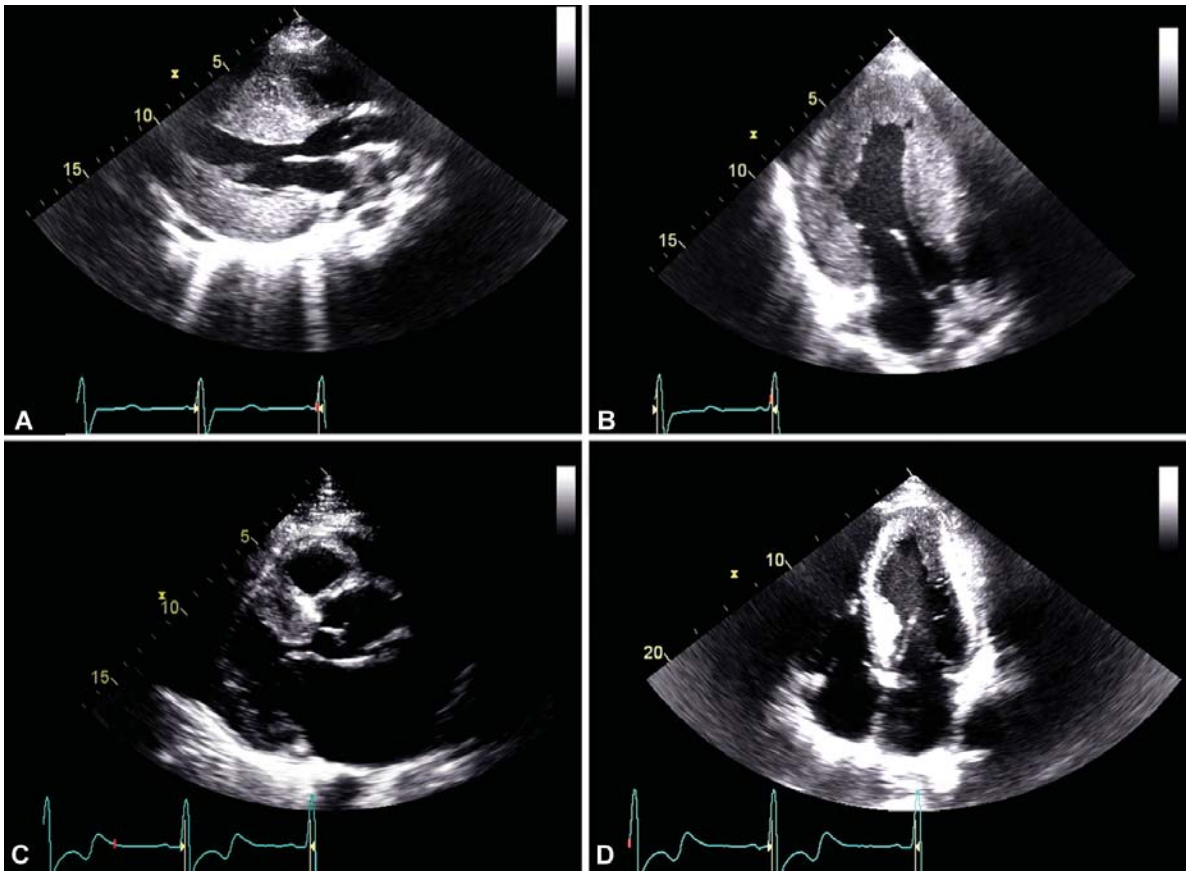
Electrocardiographic features of HCM

1. Normal axis 60–70%
2. Left axis 30%
3. LVH 70–80% (tallest QRS complexes in mid-precordial leads)
4. Abnormal Q-waves 25% (pseudoinfarct pattern)
5. Grant diffuse symmetric T-wave inversions (apical HCM)
6. Left anterior hemiblock
7. First-degree atrioventricular block
8. Complete left bundle branch block
9. Left atrial abnormality
10. Prominent delta wave of ventricular preexcitation may also be seen
11. Biventricular hypertrophy when RV involvement (mostly in children)
12. Normal electrocardiogram (5–10%)

(Abbreviations: HCM: Hypertrophy cardiomyopathy; LVH: Left ventricular hypertrophy; RV: Right ventricular)

CHEST X-RAY

A normal chest X-ray (CXR) is common in HCM patients, although it may show an enlarged cardiac silhouette. Evidence of elevated LV filling pressures may be evident in the form of increased pulmonary interstitial markings, and left atrial enlargement may also be noted, particularly when accompanied by MR or AF. An important differentiation on the CXR from patients with aortic stenosis may be the absence of aortic root dilation and aortic valve calcification.



FIGURES 21A TO D: (A) Parasternal long-axis view recorded in diastole in a patient with hypertrophic cardiomyopathy (HCM) and massive hypertrophy of the ventricular septum. In this instance, the anterior septum measures approximately > 30 mm in thickness. Noted also is a thickened posterior wall, albeit, less so compared to the septum. (B) Apical two-chamber view recorded in a patient with HCM depicting diffuse hypertrophy of the ventricular walls extending to the apex. A spectrum of hypertrophy of the left ventricle is noted, with maximum hypertrophy in the proximal septum. (C) Parasternal long-axis view recorded in early diastole in a patient with classic HCM. Note the marked thickening of the interventricular septum and the normal thickness of the posterior wall. Also note the marked hypertrophy of the proximal septum that narrows the left ventricular outflow tract. (D) Four-chamber view recorded in a 48-year-old patient with milder HCM. Note the relative hypertrophy of the proximal ventricular septum

ECHOCARDIOGRAPHY

Two-dimensional and Doppler echocardiographies are the essential parts of the evaluation of all patients with suspected HCM and are the current gold standard for diagnosis. Echocardiographic evaluation of HCM involves assessment of: (1) presence, magnitude and distribution of LVH, (2) LVOT obstruction, (3) MR, (4) diastolic dysfunction and (5) identification of HCM variants and screening of all first-degree relatives for occult HCM.

Left Ventricular Hypertrophy and the Thick Ventricle

The presence of a localized or generalized thick ventricle (> 13 mm; average = 20–22 mm) in the absence of hypertension or other factors, likely to cause pressure overload or an infiltrative state is the initial clue to the presence of HCM. As a general rule, LV mass is increased (LVH).

The increased LV thickness on echocardiography can be recognized in many patterns (Figs 21A to D, Table 10),[52,53,56] with the most common pattern consisting of maximal involvement of the anterior septum, intermediate involvement of the lateral wall and inferior septum, and substantially, less involvement of the posterior wall. The pattern of septal hypertrophy may vary by age,[130] with more diffuse hypertrophy of the entire septum (convex septal contour or reverse-curve HCM, Fig. 22) in the younger population compared to older HCM patients in whom hypertrophy may be localized to the basal and middle septum ("sigmoid" septum) while the remaining septum is concave in contour (normal shape). These various septal morphologies may have an underlying genetic basis (Fig. 23, Table 11) as suggested by a large genotype-phenotype

TABLE 10

Spectrum of HCM phenotype by echocardiography

1. Isolated septal hypertrophy (predominant)	
2. Concentric LVH	
3. Hypertrophy confined to inferior wall, posterior wall, lateral free wall	
4. Isolated mid-septal involvement	
5. Primary right ventricular involvement	
6. Sigmoid septal HCM (40-50%)	Septal morphologies
7. Reverse curve HCM (30–40%)	
8. Apical HCM (~ 10%)	
9. Neutral HCM (~10%)	

(Abbreviations: HCM: Hypertrophic cardiomyopathy; LVH: Left ventricular hypertrophy)

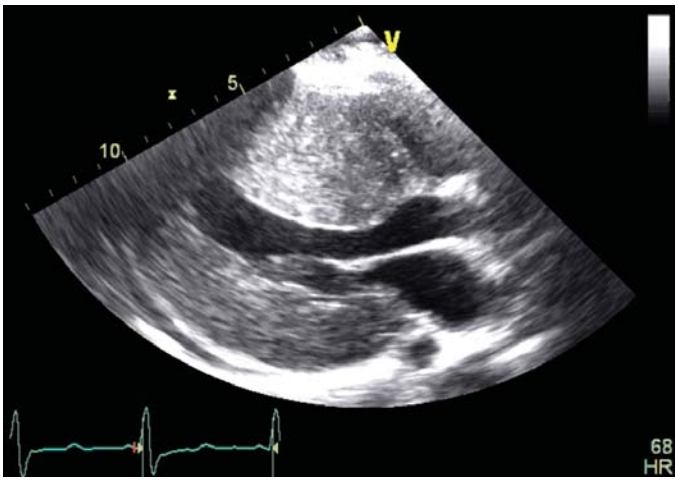


FIGURE 22: Expanded parasternal long-axis view of the interventricular septum at end-diastole in a young patient with hypertrophic cardiomyopathy (HCM). Note the "reverse curve" morphology of the septum, defined as a predominant midseptal convexity toward the left ventricular cavity, with the cavity itself having an overall crescent shape. When classified by the morphology of interventricular septum, 79% of patients with "reverse curve" HCM test positive, while only 8% of patients with a sigmoidal-shaped septum ("sigmoidal-HCM") have an HCM-causing mutation

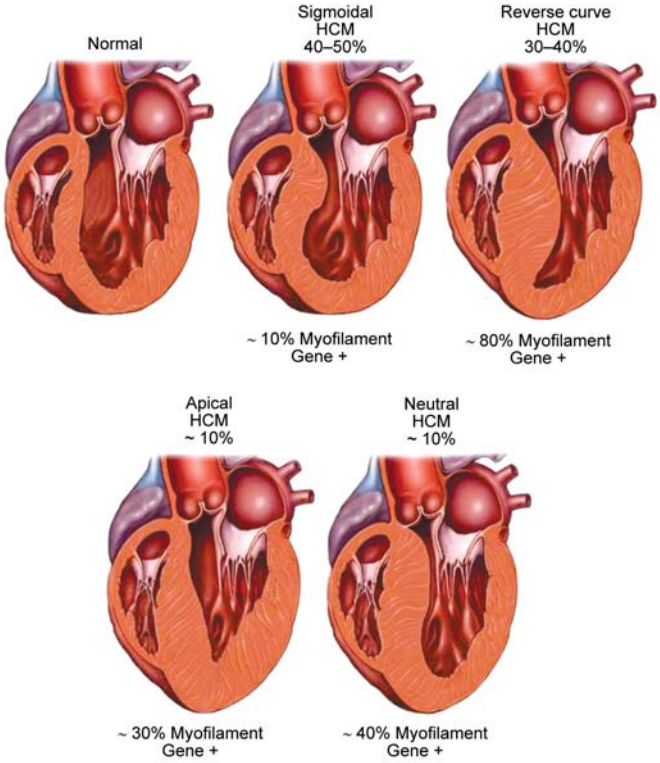


FIGURE 23: Hypertrophic cardiomyopathy (HCM) septal morphological subtypes based on standard echocardiography long-axis views taken at end-diastole. The normal heart is shown for comparison. Sigmoid septal morphological subtype is defined as a generally ovoid left ventricular (LV) cavity with the septum being concave toward the LV with a pronounced basal-septal bulge. Reverse curvature septal morphological subtype is defined as a predominant midseptal convexity toward the LV cavity, with the cavity itself having an overall crescent shape. Apical variant HCM is defined as a predominant apical distribution of hypertrophy. Neutral septal contour is defined by an overall straight or variable convexity that is neither predominantly convex nor concave toward the LV cavity. (Abbreviation: Gene+: Presence of myofilament mutation). (*Source:* Modified from Bos et al. Diagnostic, prognostic, and therapeutic implications of genetic testing for hypertrophic cardiomyopathy. J Am Coll Cardiol. 2009;54:201-11, with permission)

TABLE 11

Frequency of genetic mutations in HCM by septal contour

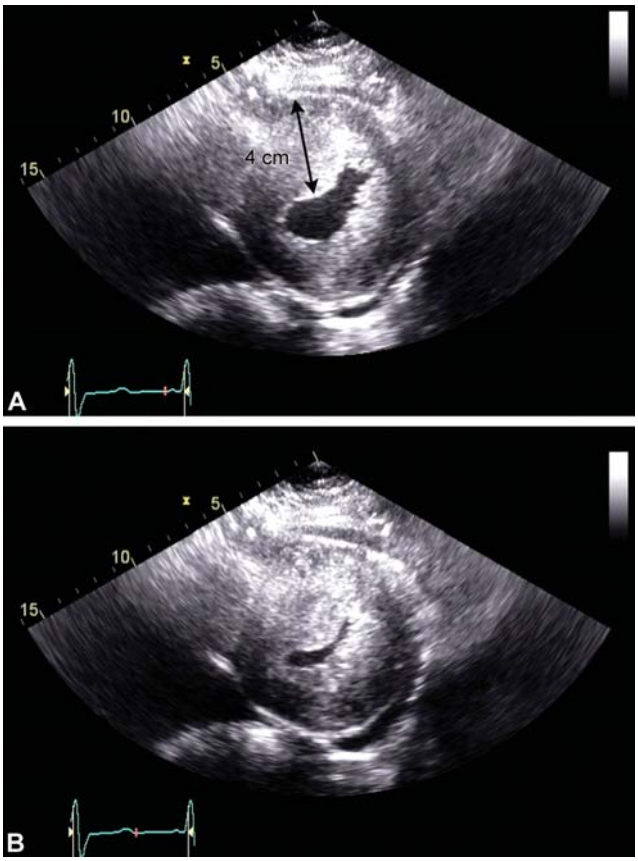
Characteristics	*Reverse*	*Sigmoid*	*Neutral*	*Apical*
Genotype positive (%)	79	8	41	30
Family history of HCM (%)	45	21	34	22
Family history of SCD (%)	19	10	16	11
Type of mutation				
None (%)	21	92	59	68
MYBPC3 (%)	34	5	19	14
MYH7 (%)	29	2	13	14
MYL2 (%)	4	0	3	3
TNNT2 (%)	3	1	0	3
TNNI3 (%)	2	1	3	0
TPM1 (%)	2	0	0	0
ACTC (%)	1	0	0	0
Multiple mutations (%)	5	0	3	0

(Abbreviations: ACTC: Actin; HCM: Hypertrophic cardiomyopathy; MYBPC3: Myosin binding protein C; MYH7: Myosin heavy chain; MYL2: Myosin light chain; SCD: Sudden cardiac death; TNNI3: Troponin I; TNNT2: Troponin T; TPM1: α-tropomyosin). (*Source:* Syed IS et al. Hypertrophic cardiomyopathy: identification of morphological subtypes by echocardiography and cardiac magnetic resonance imaging. JACC: Cardiovasc Imaging. 2008;1:377-9, with permission)

analysis correlating the septal morphology with the underlying genotype.[149] Thus, sigmoidal HCM and reverse-curve HCM represent the two most prevalent anatomical subtypes of HCM and are associated with myofilament HCM (8 genes) in 10% and 80%, respectively, with septal contour being the strongest predictor of a positive HCM genetic test regardless of age (odds ratio: 21, $P < 0.0001$).[149]

A thick ventricle on echocardiography (Figs 24A and B) should not necessarily be identified with HCM, and a differential diagnosis should always be considered (Table 12). Common clinical entities like systemic hypertension or valvular aortic stenosis may cause an increase in the LV wall thickness, while chronic kidney disease patients (especially dialysis-dependent ones) may also present with increased wall thickness on echocardiography. The echocardiographic and electrocardiographic correlation may be important at times, since a relatively low voltage on the 12-lead ECG in the presence of increased wall thickness may arouse the suspicion of an infiltrative disorder like amyloidosis.

Special mention needs to be made of the athlete's heart in which a physiological adaptive process to regular exercise can induce symmetric LVH with the extreme forms of increased LV wall thickness noted in elite athletes (rowing, cycling). In such cases, LV wall thickness rarely exceeds 15 mm and global indices of both systolic and diastolic function are preserved. In such hearts, peak myocardial systolic velocity and strain rate are also normal or supranormal.[150] Mild forms of HCM may be difficult to differentiate from the athlete's heart, and this can have substantial implications, since SD from HCM in an athlete



FIGURES 24A AND B: Parasternal short-axis view in late diastole (A) and late systole (B). Note the diffuse hypertrophy of the left ventricle (LV), with maximal thickness of the septum measuring ~4 cm. The hypertrophy can be distributed throughout the myocardium in any pattern but commonly involves the entire ventricular septum. No phenotypic expression is "classic" or particularly typical of this disease. The average maximal LV wall thickness in a population of HCM patients is usually 20–22 mm; however, 5–10% of patients will have maximal wall thickness that exceeds 30 mm

is preventable. However, a reduction in wall thickness after cessation of training for approximately 6–12 weeks may provide a clue to proper diagnosis of the athletic heart.[151,152] Doppler tissue imaging (DTI), myocardial strain and CMR imaging can also provide insights into this difficult diagnostic challenge of differentiating milder forms of HCM from the athlete's heart.[153,154]

Systolic Anterior Motion of the Mitral Valve

Initially, detected by M-mode echocardiography as SAM of the mitral valve and abrupt partial closure of the aortic valve (peak and dome pattern) in systole (Fig. 10), SAM is also a dramatic event on 2D echocardiography (Fig. 9) and is the primary event that defines the presence of LVOT obstruction.[155] SAM of the mitral valve commonly involves the anterior leaflet, although SAM with posterior leaflets is also seen.[156] The severity of LVOT obstruction can be estimated from the M-mode image by analysis of the severity of SAM (Fig. 25);[157] the greater the degree and duration of SAM, the larger the outflow tract obstruction.

Two-dimensional echocardiography is helpful in defining the exact site of the obstruction as determined by visualizing

TABLE 12

Thick ventricle on echocardiography (HCM phenocopies)

1. HCM (sarcomeric)
2. Systemic hypertension
3. Aortic stenosis
4. Syndromic HCM:
   a. Noonan syndrome
   b. Friedreich's ataxia
   c. Beckwith-Wiedemann syndrome
   d. LEOPARD syndrome
   e. Swyer's syndrome (pure gonadal dysgenesis)
5. Infiltrative cardiomyopathy (storage disorders):
   a. Anderson-Fabry disease
   b. Pompe's disease
   c. Danon's disease
   d. Forbe's disease
6. Athlete's heart
7. Metabolic disease:
   a. Hurler syndrome and Hunter syndrome (mucopolysaccharidosis)
   b. Carnitine deficiency
   c. Mannosidosis
   d. Fucosidosis
   e. Mitochondrial cytopathy (MELAS, LHON, MERRF)
8. Miscellaneous:
   a. Obesity
   b. Chronic kidney disease
   c. Phaechromocytoma
   d. Muscle LIM protein
   e. Phospholamban promoter

(Abbreviations: HCM: Hypertrophy cardiomyopathy; LHON: Leber's hereditary optic neuropathy; MELAS: Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes; MERRF: Myoclonic epilepsy with ragged red fibers)

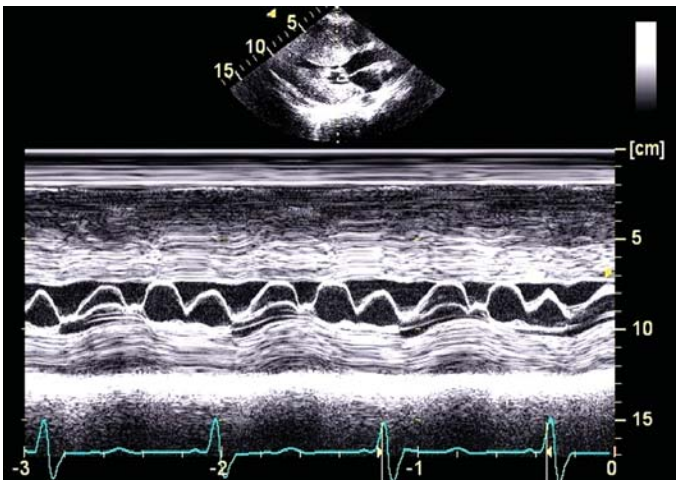


FIGURE 25: M-mode echocardiogram recorded in a patient with hypertrophic cardiomyopathy (HCM) demonstrating disproportionate septal hypertrophy and systolic anterior motion (SAM) of the mitral valve. The dramatic systolic anterior motion is indicative of significant left ventricular outflow tract (LVOT) obstruction. The severity of LVOT obstruction can be estimated from the M-mode image by analysis of the severity of SAM. The greater the degree and duration of SAM, the larger the LVOT obstruction. SAM is graded as follows: 0 = absent; 1+ = present, with a minimum distance between the mitral valve and the ventricular septum during systole > 10 mm; 2+ = without mitral-septal contact, but with a distance of < 10 mm between the mitral valve and the septum; 3+ = brief mitral-septal contact (< 30% of echocardiographic systole); 4+ = prolonged apposition of the mitral valve leaflet with the septum (> 30% of echocardiographic systole). The SAM depicted in this figure can be graded as 4+

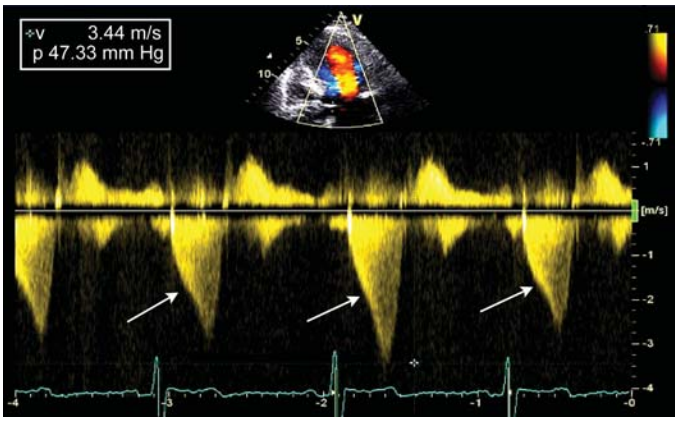


FIGURE 26: Patients with hypertrophic cardiomyopathy have a typical shape (Dagger sign) on continuous-wave (CW) Doppler tracings through the orifice in the outflow tract and left ventricular (LV) body. In the rising portion of the CW Doppler velocity tracing, an inflection point (arrows) occurs early in systole where the tracing changes from convex-to-the-left to concave-to-the-left, generally between a velocity of 1 and 2.5 m/s, correlating temporally with the time of mitral-septal contact and beginning of the pressure gradient across the LV outflow tract

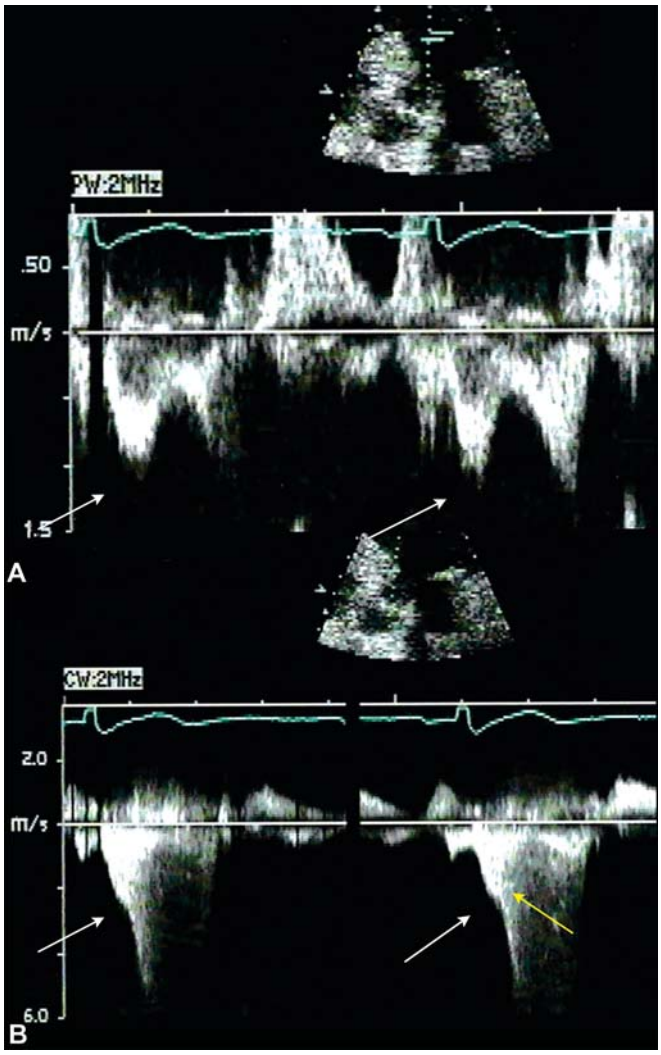
the area of the SAM-septal contact.[158] Although LVOT obstruction in classic HCM is known to occur at the most basal portion of the septum, the obstruction may also extend into the LV from SAM of the chordal apparatus (chordal SAM). Midventricular obstruction in which a hypertrophied papillary muscle abuts against the IVS can also be identified.[159]

DOPPLER INFLECTIONS

The HCM patients with SAM and mitral-septal contact have a typical shape on continuous-wave (CW) Doppler tracings, through the orifice in the outflow tract and LV body (Fig. 26). The Doppler tracing reveals an inflection point early in systole where the tracing changes from convex-to-the-left to concave-to-the-left (a point that generally occurs between a velocity of 1 and 2.5 m/s) and continues until peak velocity, the so-called "dagger-shaped" profile. This early systolic inflection point correlates temporally with the time of mitral-septal contact and beginning of the pressure gradient across the LV outflow tract.[71,160-162]

The concave-to-the-left pattern (dagger sign) (Fig. 26) is a demonstration of increasing acceleration in HCM, i.e. acceleration increases due to the progressive decrease in the size of the orifice formed as the mitral valve is pushed by the rising pressure gradient into the septum.[73,162-164] In obstructive HCM with gradients greater than 60 mm Hg, another inflection point can be seen on CW Doppler tracing, occurring simultaneously, but apical of the mitral valve in the body of the LV cavity. At the entrance of the LVOT, an abrupt midsystolic drop in LV ejection velocities and flow may occur due to the obstruction. This is called the "lobster claw abnormality" (Figs 27A and B) because of its characteristic appearance.[71,161,162] The abrupt drop in velocity averages 60% from its peak. The midsystolic drop in velocity and flow is caused by premature and abrupt termination of LV longitudinal shortening.[70,161]

In midventricular hypertrophy with midcavity obstruction, blood may become trapped in the apex, leading to its own unique



FIGURES 27A AND B: Doppler echocardiographic tracings in a patient with systolic anterior motion of the mitral valve, mitral-septal contact and a left ventricular outflow tract (LVOT) gradient of more than 100 mm Hg. (A) Pulsed-wave tracing with the cursor at the entrance of the LVOT, upstream from the mitral valve. The midsystolic drop in left ventricular ejection velocities begins at the inflection point (arrows). It is caused by afterload mismatch. The left ventricle is unable to maintain instantaneous ejection against the sudden rise in afterload. (B) Continuous-wave tracing through *both* the orifice and also through the LVOT entrance that is apical of the mitral valve. After the inflection point (left white arrow), the contour of the *jet* velocity becomes concave-to-the-left. The *superimposed* midsystolic drop that occurs at the entrance of the LVOT is shown with the yellow arrow. The midsystolic drop also begins at the same point (middle arrow). (*Source:* Sherrid et al. Reflections of inflections in hypertrophic cardiomyopathy. J Am Coll Cardiol. 2009;54:212-9, with permission)

Doppler characteristics (Fig. 28). Blood trapped by a narrowed neck may not emerge until the onset of diastole, beginning with the isovolumic relaxation phase, when it flows into the body of the LV. Such flow is termed "paradoxic" because it courses toward the mitral valve in diastole and is a sign of a concealed apical chamber.[165-168]

It is important to demonstrate the 2D features of dynamic obstruction in HCM. Thus, in patients with low outflow tract velocities (< 3 m/s), provocation with the Valsalva maneuver, inhalation of amyl nitrite, or exercise can unmask labile or latent obstruction (Figs 29A to D).

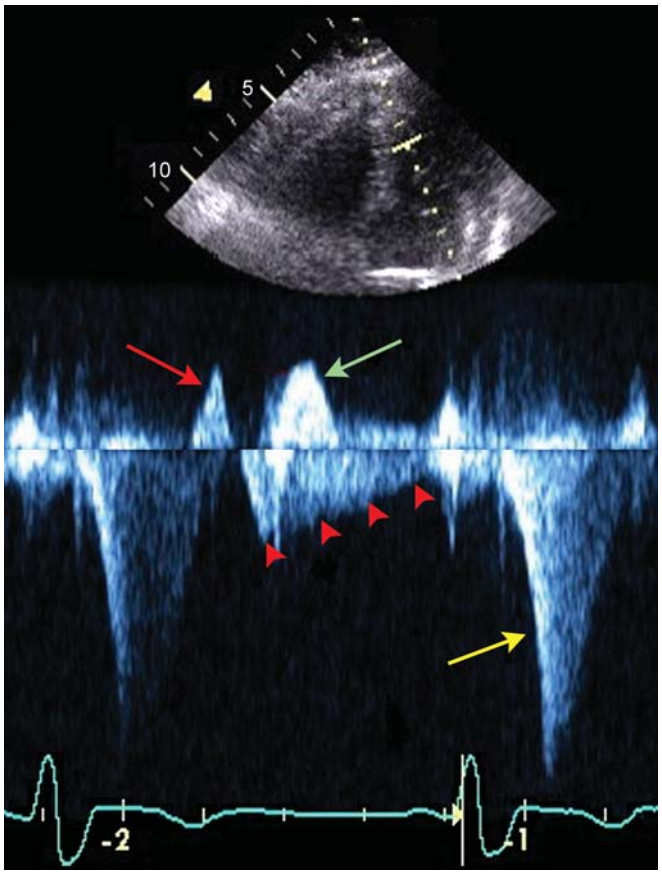


FIGURE 28: Continuous-wave Doppler recording in a patient with apical hypertrophic cardiomyopathy and also midventricular obstruction. The red arrow highlights blood flow toward the apex in isovolumic relaxation time (IVRT), demonstrating a pressure gradient within the left ventricle during this period, a phenomenon counterintuitive to classic physiologic teaching. The green arrow points toward the mitral inflow during diastole. The red arrowheads define blood flow from the apex toward the mid-ventricle (diastolic signal), starting with the IVRT and extending through the filling phase of the diastole. The yellow arrow is the inflection signal of left ventricular outflow tract obstruction and, in this patient, calculated as 3 m/s

Mitral Regurgitation

Color Doppler imaging can be used to visualize the presence and severity of MR in HCM, the severity of which can range from mild to severe. MR is due to the dynamic malcoaptation that occurs during SAM and mitral-septal contact ("eject-obstruct-leak" phenomenon), occurring predominantly in mid-to-late systole. The MR jet is typically eccentric (directed posterolaterally) into the left atrium. Occasionally, the late peaking MR jet is mistakenly interrogated for the outflow tract gradient. However, longer duration of the MR signal as well as peak velocities in the supraphysiologic range help differentiation between MR and LVOT flow (Figs 30A to C).

Diastolic Dysfunction

Diastolic dysfunction is the quintessential abnormality in HCM. Diastolic echocardiographic indices can identify HCM patients with impaired relaxation or restrictive filling[85] and can assist in characterizing diastolic function. However, direct clinical application and accurate assessment of diastolic function in this disease have been challenging. Although the mitral velocity inflow pattern may suggest diastolic dysfunction, the transmitral velocity curves themselves cannot be used due to the complex interplay of relaxation and compliance abnormalities that are present in HCM.[87] A combination of pulmonary vein flows, DTI and mitral inflow velocity curves can improve the accuracy of quantifying LV filling pressures.[169,170]

Evaluation of longitudinal contraction of the myocardium by DTI of the mitral annular motion may reveal abnormally low annular velocities despite normal or supranormal ejection fraction (Figs 31A and B). This may be helpful in detecting subclinical disease in those who carry an HCM-associated genetic abnormality, but have not yet developed the phenotypic expression of increased wall thickness (genotype-positive and phenotype-negative individuals).[171-173] Evaluation of longitudinal LV contraction by DTI may also help differentiate HCM from athlete's heart, in which annular velocities are preserved or supranormal.[154] Table 13 summarizes the classic echocardiographic features of HCM.

TABLE 13

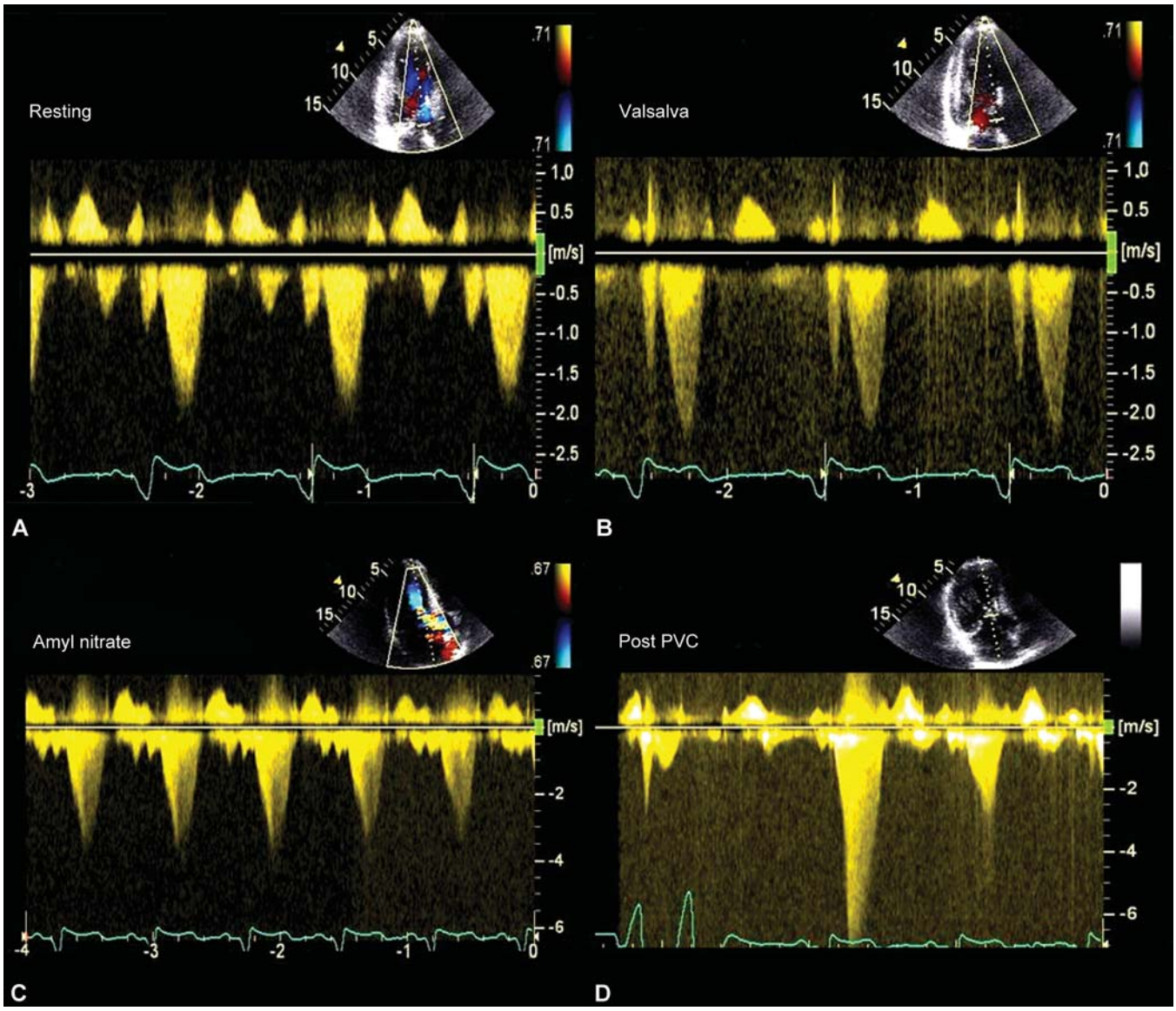
Classic echocardiographic features of HCM

1. Thick LV (≥ 13 mm)[#]
2. Increase in LV mass (HCM is the leading cause of the heaviest hearts)[§]
3. Small LV end-diastolic volume
4. Increase in left atrial volume index
5. E/A reversal, prolonged DT and prolonged IVRT
6. Restrictive filling dynamics (increased E/A ratio, short DT and short IVRT)
7. Decrease in tissue early diastolic velocity (E') and increased E/E' ratio
8. Pulmonary hypertension as measured by tricuspid regurgitation jet
9. Increase in circumferential strain and strain rate
10. Decrease in longitudinal strain and strain rate
11. Clockwise mid-LV rotation (opposite to normal)
12. Time to peak systolic twist shorter
13. Time from peak to trough twist (untwist) longer (obstructive HCM > nonobstructive HCM)

[#]A septal-to-posterior wall thickness ratio of 1.3:1 is evidence of asymmetric septal hypertrophy. However, pulmonary hypertension with right ventricular hypertrophy and inferior wall infarction in the presence of left ventricular hypertrophy also can cause such septal-to-posterior wall thickness ratio.
[§]LV mass = 1.04 [(LV end-diastolic diameter in diastole + posterior wall thickness in diastole + interventricular septal thickness in diastole)^3—LV end-diastolic diameter in diastole^3] × 0.8 + 0.6.
(Abbreviations: DT: Deceleration time; HCM: Hypertrophy cardiomyopathy; IVRT: Isovolumetric relaxation time; LV: Left ventricle)

CARDIAC MAGNETIC RESONANCE IMAGING

In contemporary clinical practice, CMR has become a useful complementary imaging tool for the diagnosis of HCM and follow-up of patients after either surgical myectomy or septal ablation therapy. In addition, CMR imaging can help discriminate HCM from closely related morphological cardiomyopathies and cardiac disorders, e.g. amyloidosis, Fabry's disease, athlete's heart and isolated apical hypertrophy. CMR provides



FIGURES 29A TO D: Continuous-wave (CW) Doppler profile recordings through the left ventricular outflow tract (LVOT) in a patient with hypertrophic cardiomyopathy. (A) A recording at rest depicting a relatively normal profile with LVOT gradient of ~13 mm Hg. (B) A recording during the Valsalva maneuver in which the gradient is seen to increase to ~20 mm Hg with the development of a hint of inflection on the LVOT tracing. (C) From the same patient during amyl nitrite inhalation, the gradient increases to ~50 mm Hg. (D) Recording of the CW Doppler profile after a spontaneous premature ventricular contraction (PVC) in which the LVOT recording demonstrates markedly increased gradient to well above 140 mm Hg. In both (C) and (D), the characteristic "dagger sign" makes its appearance

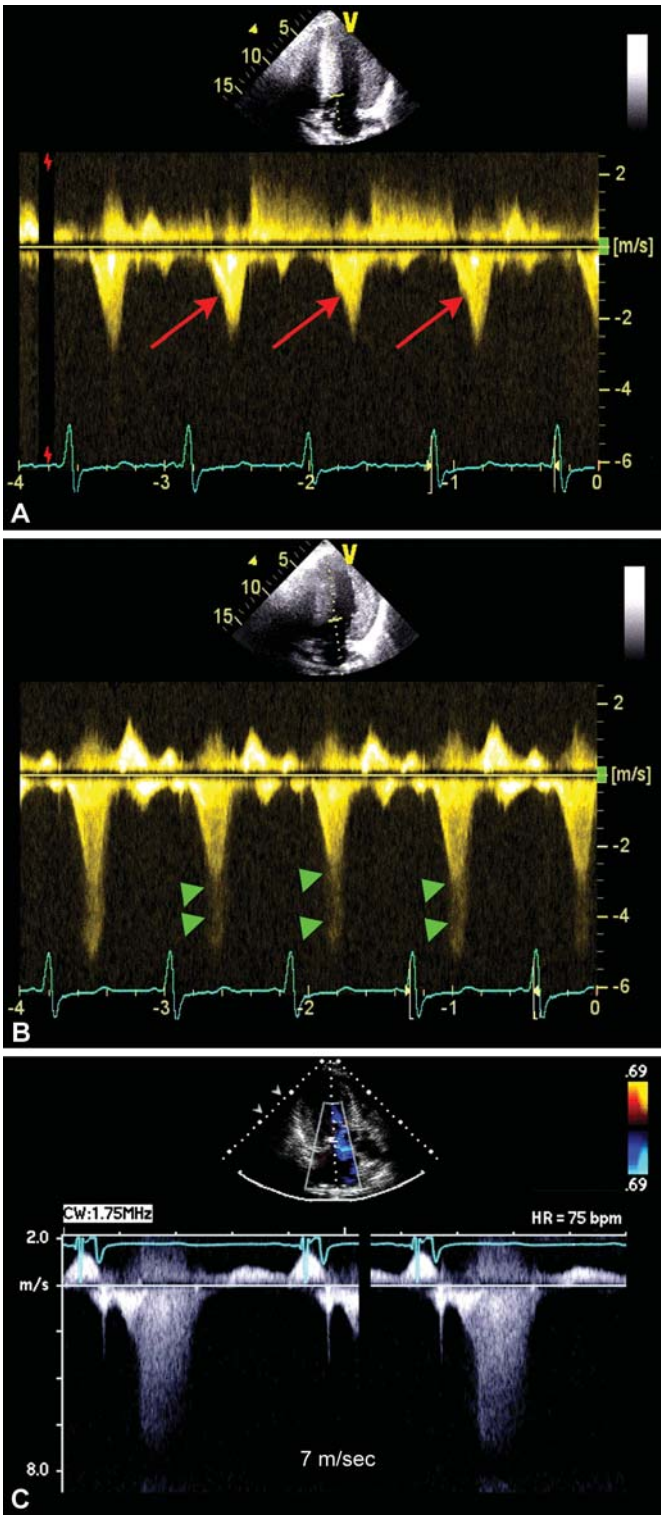
high-resolution moving images of the myocardium accurately determining the site (e.g. segmental hypertrophy) and extent of hypertrophy (Figs 32A to E). The strengths of CMR imaging include its ability to identify macroscopic areas of abnormal myocardium with delayed gadolinium-enhanced imaging.

Currently, increasing interest in CMR imaging for HCM has evolved due to delayed hyperenhancement magnetic resonance imaging (DHE-MRI), which makes it possible to accurately detect areas of myocardial fibrosis/scarring *in vivo* with a high degree of sensitivity.[174-176] In the past, this was possible only in histopathologic specimens. Areas of DHE on CMR have been shown to correlate with, histologically proven myocardial scar[175-177] as well as with wall thickness,[115,178,179] regional function[179] and ventricular tachyarrhythmias.[117,180,181]

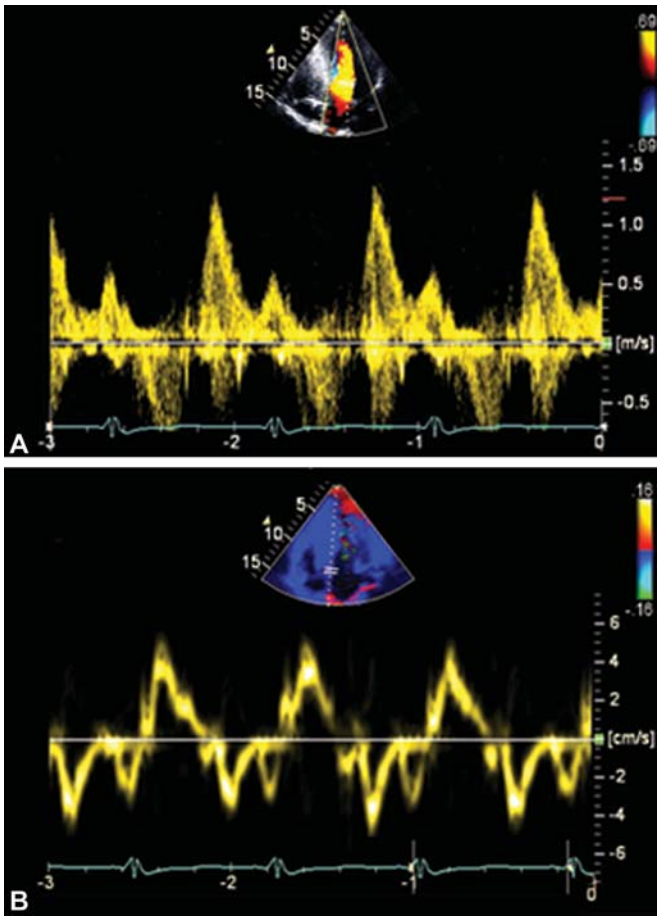
Recognizing that ventricular tachyarrhythmias (including nonsustained VT) on ambulatory Holter ECG are most common in patients with DHE-MRI,[117] delayed enhancement with MRI provides another clue into the arrythmogenic substrate in HCM patients and adds to risk stratification strategies for SD. However, presently, DE is not regarded as a bona fide risk marker for SD in HCM, as adequately powered studies in large populations with sufficient numbers of events accrued over many years are lacking.

CARDIAC CATHETERIZATION

Because 2D and Doppler echocardiographic assessment with or without CMR usually establishes the diagnosis of HCM in



FIGURES 30A TO C: Comparison of the continuous-wave (CW) Doppler recordings of dynamic left ventricular outflow tract (LVOT) obstruction and mitral regurgitation (MR). On the basis of the interrogation line, it is sometimes difficult to determine the etiology of a signal. (A) Demonstrates the "inflection point" (red arrows) on the CW Doppler tracing in a patient with hypertrophic cardiomyopathy (HCM). As the probe is positioned in a sector between the LVOT and the mitral inflow, the spectral display changes, velocity increases (> 5 cm/sec) and the late-peaking dagger profile merges with the MR signal (B, green arrowheads) until the display demonstrates a peak velocity in the supraphysiologic range (C). This comparison of the spectral display shows that the CW Doppler signals of LVOT and MR can, at times, be confused in a patient with HCM and MR and late-peaking velocity of > 6 cm/sec. A clue to the etiology of the signal is the prolonged nature of the MR signal, which extends into the isovolumetric relaxation period

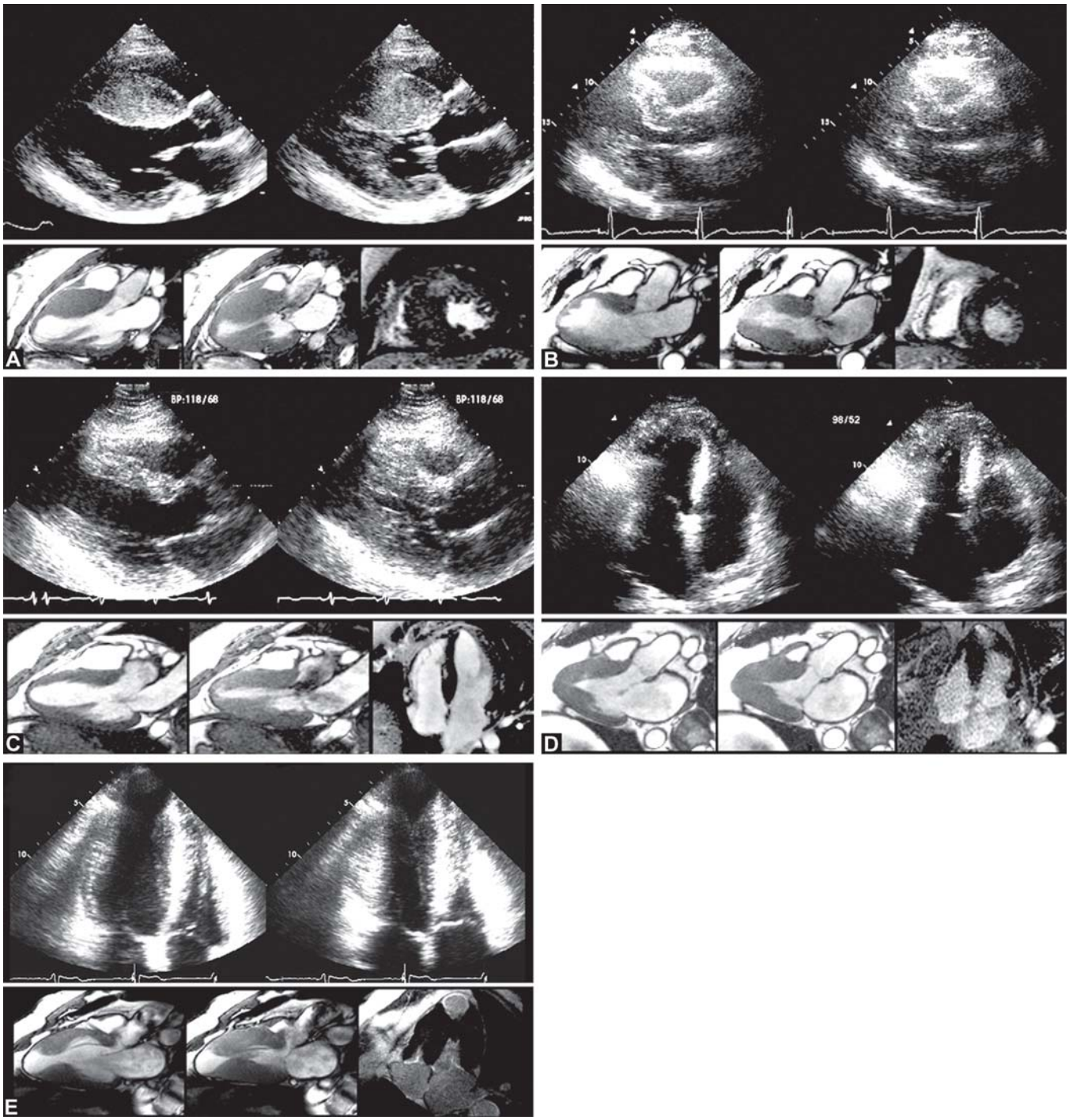


FIGURES 31A AND B: Mitral inflow and tissue Doppler recording of the medial mitral annular velocity in a patient with hypertrophic cardiomyopathy. The early-diastolic mitral annular velocity (E2) is markedly decreased, averaging 4.0 cm/s, indicating advanced diastolic dysfunction and restrictive filling pattern. Also note the ratio of transmitral E velocity to E2 velocity, the E/E2 ratio, of around 24, indicating markedly elevated left ventricular filling pressures

a given clinical situation, cardiac catheterization is seldom necessary in the vast majority of cases. However, in cases of inadequate or difficult echocardiographic imaging (suboptimal), cardiac catheterization may be of benefit in demonstrating the presence and severity of an LVOT obstruction.

Typically, the left ventriculogram (Fig. 33) may show the presence of a thickened IVS bulging into the LVOT with associated MR. More importantly, cardiac catheterization can be used to study LVOT obstruction using the "pull-back" pressure tracing, in which an end-hole catheter (commonly a pigtail catheter) is placed at the LV apex and slowly pulled back to the base of the heart and then into the aorta. In contemporary clinical practice, a double lumen pigtail catheter is used for simultaneous detection of pressure gradients between the LV cavity (apex, midventricle or base) and the aorta. Transseptal puncture to obtain accurate LV pressure measurement is seldom carried out in contemporary practice.

In cases of minimal resting obstruction and/or gradient, provocative maneuvers (Valsalva, amyl nitrite inhalation or infusion of isoproterenol) are performed in the catheterization laboratory to unmask LVOT obstruction. Ventricular premature beats can also be induced in the catheterization laboratory and



FIGURES 32A TO E: Hypertrophic cardiomyopathy (HCM) morphologic subtypes are demonstrated by echocardiography in end-diastolic (left) and end-systolic (right) images of the heart. The HCM subtypes are also demonstrated by magnetic resonance imaging in the same patients. Left and middle columns show steady-state free precession images of the heart in a three-chamber orientation in end-diastole and end-systole, respectively. Right column shows myocardial delayed-enhancement (MDE) images using an inversion-recovery gradient-recalled echo technique. (A) Reverse-curvature septum HCM shows a predominant midseptal convexity toward the left ventricular (LV) cavity with the cavity itself often having an overall crescent shape. Dynamic subaortic obstruction is present in this example with systolic anterior motion (SAM) of the mitral leaflets and turbulent flow in the outflow tract. Prominent foci of MDE that indicate myocardial fibrosis are present in the anteroseptum and inferoseptum. (B) Sigmoid septum HCM shows a generally ovoid LV cavity with the septum being concave to the LV cavity and a prominent basal-septal bulge. Subaortic obstruction is present in this example with SAM of the mitral leaflets and a posteriorly directed jet of mitral regurgitation. A small amount of MDE is seen in the septum. (C) Neutral septum HCM shows an overall straight septum that is neither predominantly convex nor concave toward the LV cavity. Subaortic obstruction is present in this example. A small focus of MDE is seen in the septum. (D) Apical HCM shows a predominant apical distribution of hypertrophy. Myocardial delayed enhancement is seen in the LV apex at the site of maximal hypertrophy in this example. (E) Midventricular HCM shows predominant hypertrophy at the midventricular level. In this example, a thinned and dyskinetic apical pouch is also present. Obstruction is at the level of the papillary muscles, where turbulence was identified. No mitral SAM. MDE is seen in the dyskinetic apical pouch. (*Source:* Syed et al. Hypertrophic cardiomyopathy: identification of morphological subtypes by echocardiography and cardiac magnetic resonance imaging. J Am Coll Cardiol Img. 2008;1:377-9, with permission)

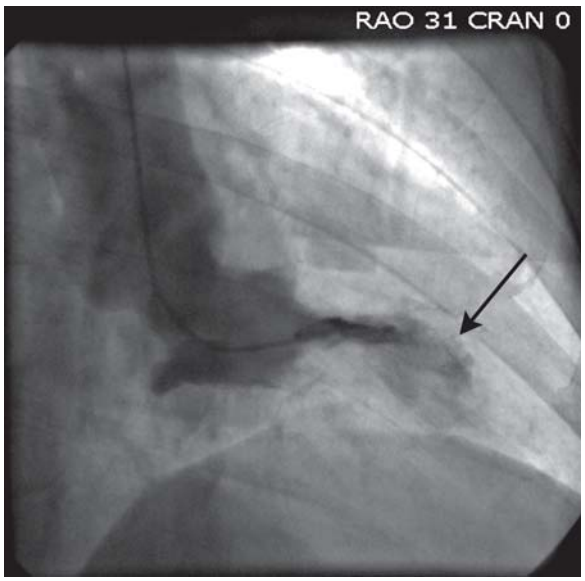
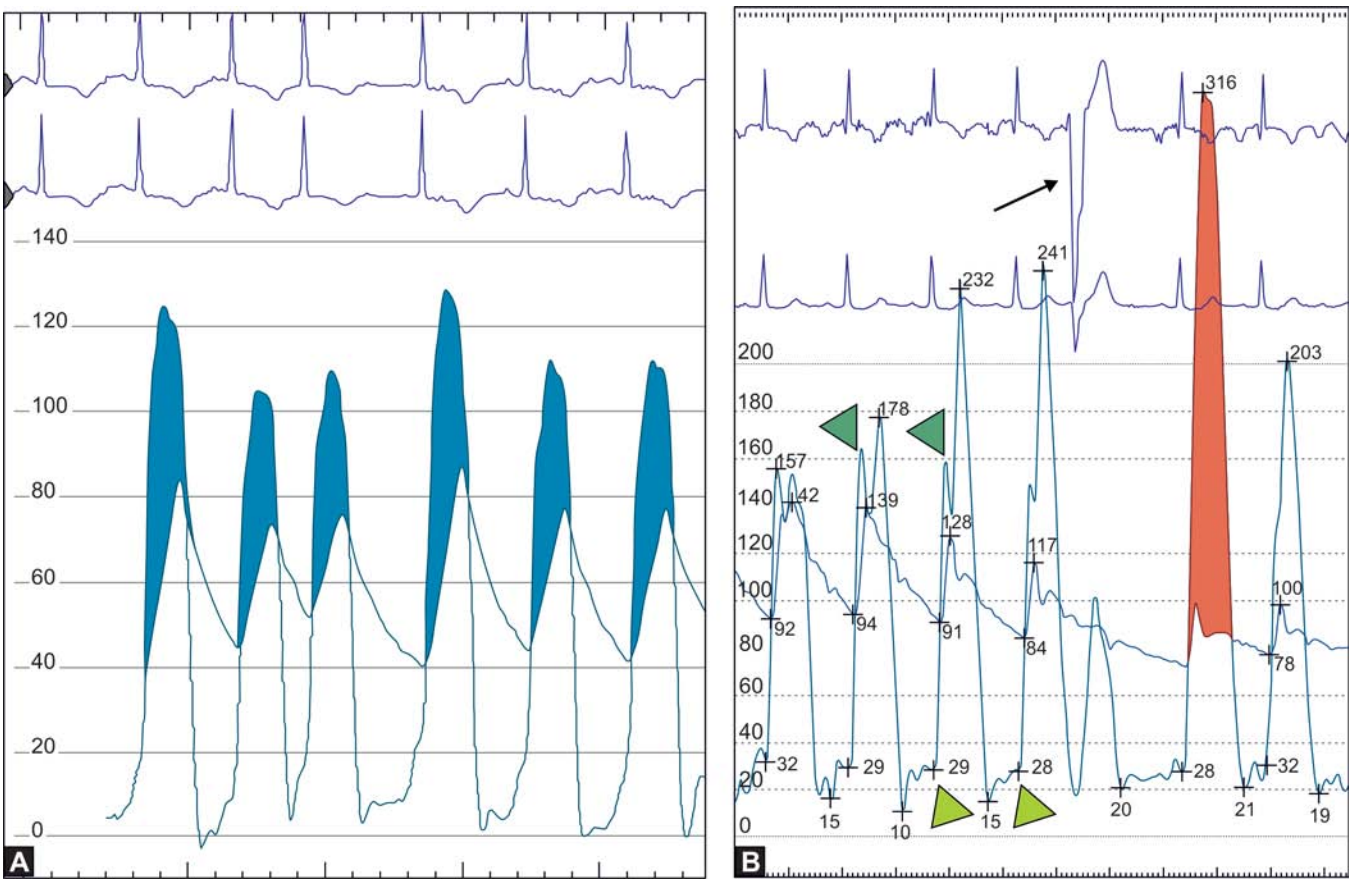


FIGURE 33: Left ventriculogram in the right anterior oblique projection demonstrating hyperdynamic left ventricular (LV) function with near total obliteration of the midventricular cavity in a patient with obstructive hypertrophic cardiomyopathy. Note the "apical pouch" (black arrow) formation and the "ballerina-slipper" deformity consequent to the vigorous LV contractility

postextrasystolic pressure gradients measured (Figs 34A and B). After an extrasystole, an increase in gradient and a decrease in the aortic pulse pressure is noted, the Braunwald-Brockenbrough phenomenon. The pressure decrease is based on the Frank Starling law, according to which, within certain limits, the LV stroke volume is directly proportional to the end-diastolic volume (myocardial stretch). At the end of a prolonged diastole, such as that seen in beats immediately after a premature beat ("compensatory pause"), the LV has a higher end-diastolic volume and increased contractility, which results in a marked increase in the degree of dynamic obstruction and pressure gradient and decrease in the aortic pulse pressure. This contrasts to a fixed obstruction, such as aortic stenosis, in which there will be an increase in gradient from the increase in stroke volume and an increase in aortic pulse pressure.

In patients where angina is out of proportion to the degree of LVOT obstruction or other symptoms of ischemia are a concern, coronary angiography is performed. Epicardial coronary obstructive disease may be present in up to 25% of older patients[182] with HCM. In such patients (coexistent coronary disease and HCM), significant angina may occur and may alter final clinical outcome.[183,184]



FIGURES 34A AND B: Simultaneous recordings of the electrocardiogram (ECG) and left ventricular (LV) and aortic pressures during cardiac catheterization in a patient with hypertrophic cardiomyopathy. (A) Demonstrates measurements at rest, indicating the presence of a resting gradient (approximately 30 mm Hg) across the LV outflow tract in this patient (shaded area). Note the rise of the aortic pressure curve is relatively rapid, distinguishing this from the valvular form of aortic stenosis. (B) A recording made during mechanically induced premature ventricular contraction (PVC) (black arrow); note the systolic pressure gradient between the LV and the aorta is dramatically accentuated (approximately 200 mm Hg – shown in the red shaded area) in the beat following the PVC due to the postextrasystolic potentiation of ventricular contractility. This is termed the Braunwald-Brockenbrough phenomenon after the authors who first described it. Also note the characteristic "peak and dome" configuration of the LV pressure tracing (dark green arrowheads) and the elevated left ventricular end-diastolic pressure averaging 28–32 mm Hg (light green arrowheads)

Stress testing in HCM for the diagnosis of obstructive coronary artery disease (CAD) is of limited value because the combination of the supply-demand mismatch and the small coronary arteriolar disease can result in findings of myocardial ischemia on ECG and nuclear imaging, even in the absence of obstructive epicardial coronary disease. However, under careful ECG and hemodynamic monitoring, exercise can be used as a physiological provocation maneuver to attempt to detect latent LVOT obstruction.[185] Besides, exercise in a patient with HCM can be used to obtain substantial information on: (1) exercise hemodynamics and MR, diastolic dysfunction and pulmonary artery pressures; (2) blood pressure response; (3) chronotropic incompetence; (4) exercise tolerance and (5) arrhythmic potential.

Stress testing can be used to obtain important prognostic information in HCM patients. Up to 25% of patients with HCM have an abnormal blood pressure response during upright exercise—systolic blood pressure fails to rise by more than 20–25 mm Hg from baseline values or falls.[121,122,186] This abnormal exercise response is believed to be related to: (1) abnormal vasodilation in nonexercising muscles, triggered by inappropriate firing of LV baroreceptors,[187] and (2) impaired cardiac output from LVOT obstruction.[188] A decrease in blood pressure with exercise and/or the appearance of ventricular arrhythmias[120,189] is an adverse prognostic sign in HCM patients.

NATURAL HISTORY

HCM is a unique disease that may present during any phase of life from infancy to old age[5] with a variable clinical course. Although patients with HCM may remain stable over long periods of time and achieve normal longevity (≥ 75 years),[8,129,131,190,191] many patients have their natural course punctuated by SD, embolic stroke and development of HF.[8,14,129,186,192] In general, the natural history of HCM follows one of several profiles (Table 14).

Early literature on HCM described a poor prognosis for patients with this disease, suggesting a high incidence of SD and overall high mortality rates (3–6% per year).[133,148,193,194] This most likely represented a selection bias, since much of the published clinical data emanated from a few select tertiary centers in North America and Europe. This subset of patients was disproportionately comprised of patients referred due to their high-risk status or severe symptoms; the data also underrepresented clinically stable, asymptomatic and elderly patients. However, more recent reports from unselected regional populations show lower mortality rates of ~1% per year,[8,25,129,134,137,195-197] and HCM in the elderly has been shown to have mortality similar to control populations.[131,194] These recent reports from nontertiary centers with fewer regional and community-based cohorts not subject to tertiary center referral bias are probably more representative of the overall disease state, with the survival of patients not dissimilar to that of the general adult U.S. population.[8,129,190] Nevertheless, subgroups of patients[6,8,14,193,198-200] within the broad HCM spectrum that are clearly at high risk for death (including SD) and in whom annual mortality exceeds 1% do exist (Table 15).

Several recent clinical studies performed in large HCM patient populations have consistently identified a relationship between LVOT gradients at rest and HF symptoms and cardiovascular events (even if patients with obstruction are mildly symptomatic).[82,201-206] For example, a 2003 long-term follow-up of a large HCM cohort of 1,101 consecutive patients established highly significant linkage between peak instantaneous LV outflow obstruction (gradient ≥ 30 mm Hg at rest) and death (relative risk 2.0; P = 0.001), risk of progression to New York Heart Association (NYHA) class III or IV or death specifically from HF or stroke (relative risk 4.4; P < 0.001), particularly among patients greater than or equal to 40 years (Figs 35A to E).[82]

Cardiac sarcomere gene mutations (most commonly MYH7 and MYBPC3) encoding for myofilament contractile proteins represent the most common genetic subtype of HCM, with a prevalence of 30–65% in cohort studies.[207-211] Recently, it has been shown that multiple sarcomere defects might be

TABLE 14

Spectrum of natural history of hypertrophic cardiomyopathy

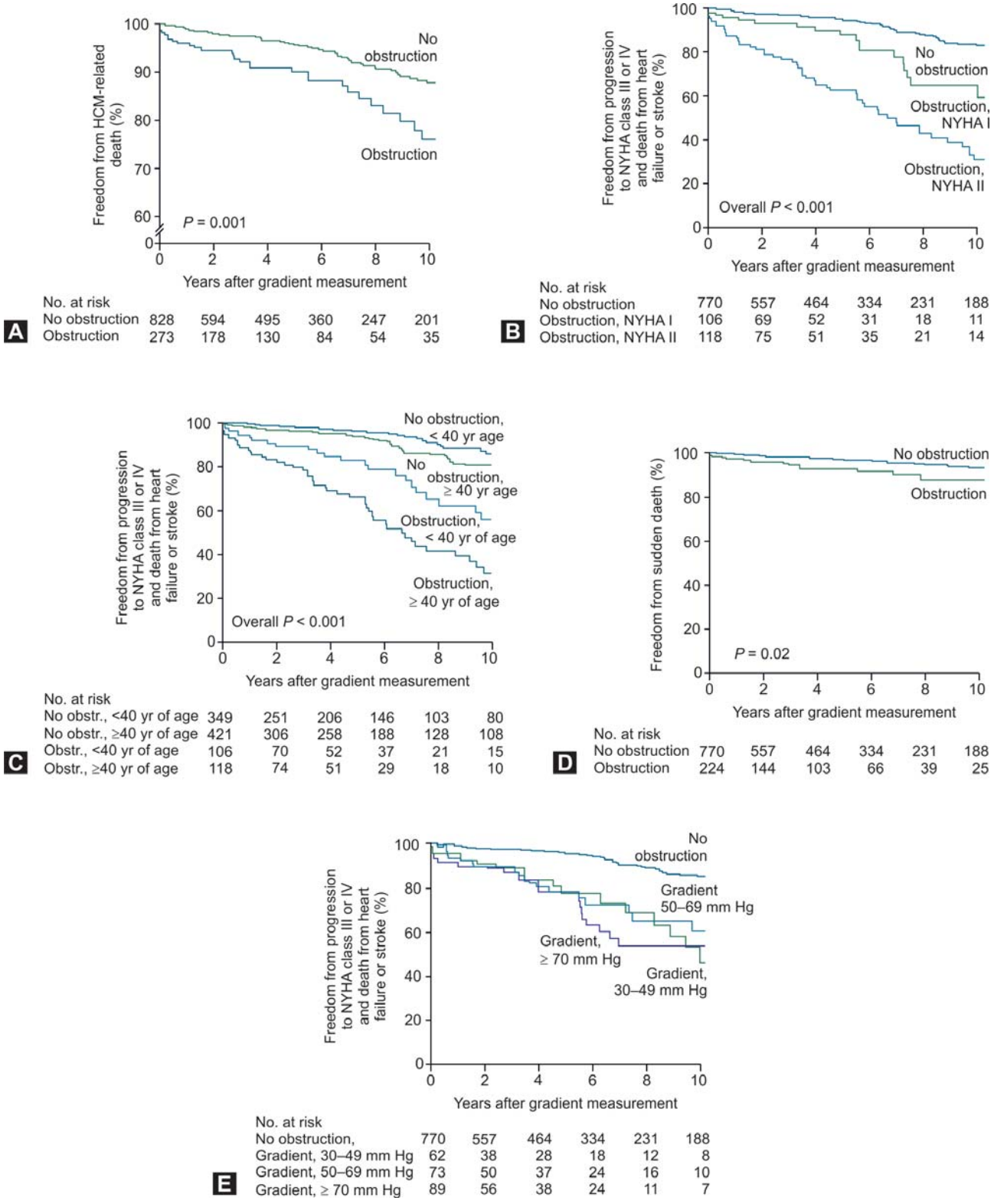
1. Stable benign course with normal longevity
2. Premature sudden death
3. Progressive symptomatic deterioration
   Exertional dyspnea
   Chest pain (either typical of angina or atypical in nature)
   Syncope, near-syncope or presyncope (i.e. dizziness/lightheadedness)
4. Progression to advanced diastolic heart failure or so-called "end-stage phase" or "burnt-out" phase with left ventricular remodeling and systolic dysfunction
5. Complications attributable to atrial fibrillation, including embolic stroke

TABLE 15

High-risk cohort for sudden death in HCM

1. Prior cardiac arrest or sustained ventricular tachycardia
2. Family history of premature SD due to HCM in a first-degree relative
3. Repetitive nonsustained ventricular tachycardia
4. Massive ventricular hypertrophy (wall thickness ≥ 30 mm)
5. Hypotensive response to exercise
6. Unexplained syncope
7. Atrial fibrillation
8. Systemic embolism
9. Vigorous physical activity and/or competitive sports
10. Development of end-stage HCM
11. Marked outflow gradient
12. Abnormal aortic stiffness as measured by increased pulse-wave velocity with VENC-MRI
13. Myocardial fibrosis as demonstrated by late gadolinium enhancement on CMR
14. Genotypic expression
    a. MYH7-R403Q mutation
    b. Multiple sarcomeric defects or "gene-dosage effect" (double, triple or compound hetezygosity)
    c. TNNT2 (troponin T)-HCM genotype

(Abbreviations: CMR: Cardiac magnetic resonance imaging; HCM: Hypertrophy cardiomyopathy; SD: Sudden death; VENC-MRI: Velocity-encoded magnetic resonance imaging)



FIGURES 35A TO E: (A) Probability of hypertrophic cardiomyopathy (HCM)-related death among 273 patients with a left ventricular outflow gradient of at least 30 mm Hg under basal conditions and 828 patients without obstruction at entry. (B) Probability of progression to severe heart failure (NYHA Class III or IV) or death from heart failure or stroke among 224 patients with left ventricular outflow tract (LVOT) obstruction and 770 patients without obstruction. (C) Effect of age and the presence or absence of LVOT obstruction of at least 30 mm Hg on the probability of progression to severe heart failure (NYHA Class III or IV) or death from heart failure or stroke. (D) Probability of sudden death among 224 patients with an LVOT gradient of at least 30 mm Hg and 770 patients without obstruction. (E) Relation of the magnitude of LVOT gradient or the absence of a gradient to the probability of progression to severe heart failure (NYHA Class III or IV) or death from heart failure or stroke. P < 0.001 for the comparison of the group without obstruction with each subgroup with obstruction; P > 0.30 for each comparison among the subgroups with obstruction. Patients who were already in NYHA class III or IV at entry were excluded from the analyses shown in (B) through (E). (*Source:* Modified from Maron et al. Effect of left ventricular outflow tract obstruction on clinical outcome in hype. N Engl J Med. 2003;348:295-303, with permission)

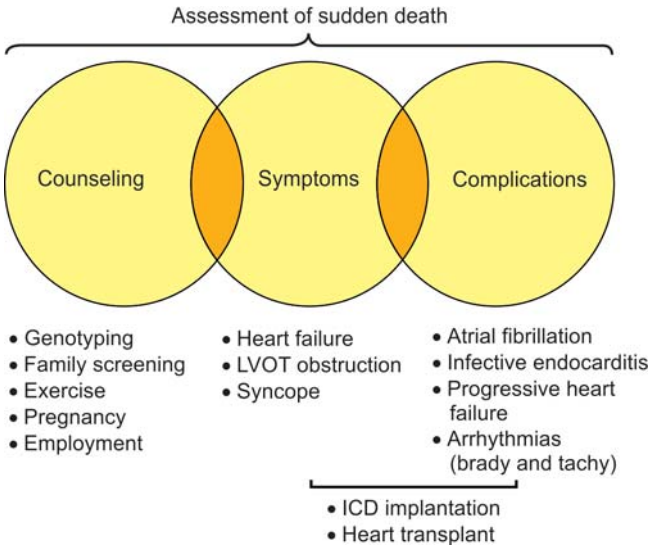


FIGURE 36: Illustrated is the complicated and formidable management plan in a given patient with hypertrophic cardiomyopathy. The physician needs to incorporate multiple facets of patient care, including the medical, social and family aspects of disease management. Not only does the physician have to be vigilant about the symptoms and complications of the disease process (an ongoing management issue) but also manage issues related to family counseling and employment. (Abbreviations: ICD: Implantable cardioverter-defibrillator; LVOT: Left ventricle outflow tract)

associated with the more severe clinical phenotype and disabling symptoms in the natural history of the disease.[212-218] In general, a positive HCM genetic test portends greater risk for disease progression, particularly relating to systolic and diastolic dysfunction and propensity to develop symptoms. Therefore, it is suggested that clinical genetic testing may aid in determining prognosis.[34]

MANAGEMENT

The management of HCM is complex and challenging (Fig. 36) and can change over a period of time. It involves not only management of the symptomatic HCM patient with pharmacological interventions, but also considerable personal commitment by the treating physician toward both patient and family counselling as well as due consideration and introduction of life-changing interventions such as exercise restrictions, ICD and/or pacemaker implantation and, sometimes, heart transplant. Since, the specter of SD is intertwined with the diagnosis of HCM, and SD continues to be the most devastating complication of HCM, an enhanced focus on risk stratification and reliable identification of high-risk patients is imperative.

GENOTYPING, GENETIC COUNSELLING AND FAMILY SCREENING

Currently, four U.S. laboratories (Harvard Partners, Correlagen, PGxHealth and GeneDX) offer testing for the eight most common myofilament-associated HCM genes. As pointed out previously, echocardiography may help to guide genetic testing by providing anticipatory guidance and a pretest probability of a positive genetic test result. Knowledge of the genetic background in HCM has significant diagnostic implications and knowledge of disease-causing mutations in an index case may enable rapid genetic testing and diagnosis of potentially at-risk relatives, thereby providing improved and informed follow-up and treatment decisions for such family members.[34] The information gained can define risk status and, in subjects with negative genetic screening, may require less follow-up and testing over time and more psychological freedom.

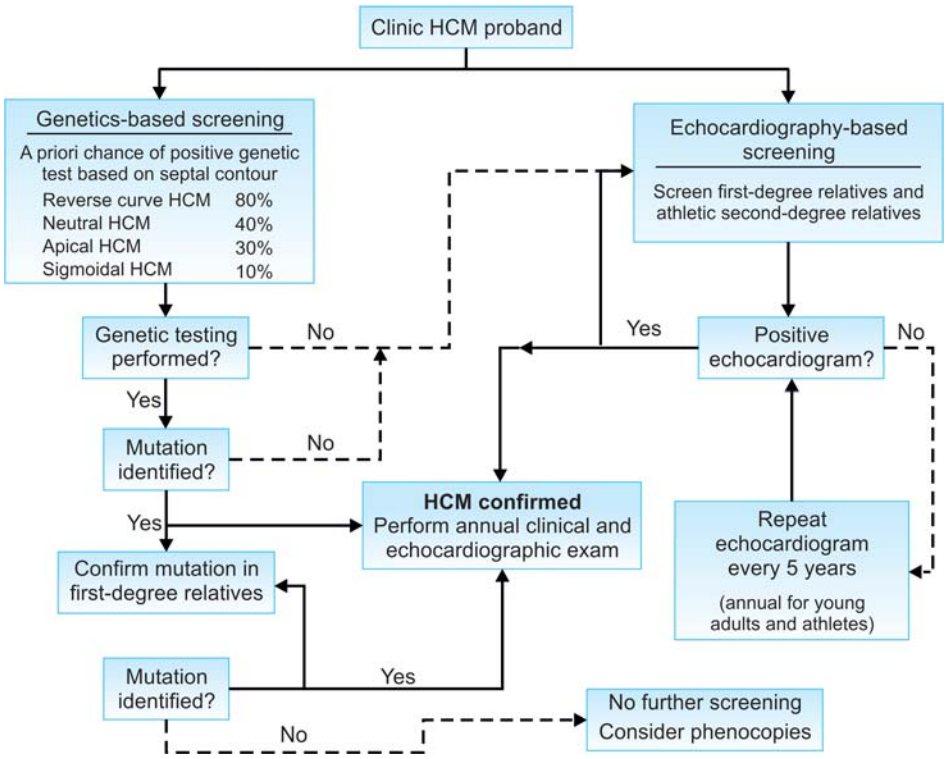
Flow chart 1 describes the two diagnostic pathways possible when an index case (HCM proband) is identified, allowing clues to be picked up to expose other causes of unexplained LVH—aortic stenosis, hypertension or the presence of a phenocopy—as being responsible for the patient's symptoms. If the phenotype is HCM, echocardiography may inform genetic counselling by providing an *a priori* probability for a positive genetic test and advice on how to proceed with further evaluation and family screening (left arm of algorithm). If genetic testing of the major genes remains negative, the presence of a phenocopy with pure cardiac involvement should be considered.

In contemporary clinical practice, genetic testing of the index case has the potential of providing the diagnostic gold standard for his/her offspring, siblings, parents and more distant relatives. A positive genetic test enables scrutiny of the index case's relatives to separate "those at risk" from "those not at risk" (positive vs negative test).[34] In other words, the genetic testing of the index case risk stratifies the family, enabling two very different courses to be charted: (1) close surveillance of the genotype-positive, preclinical individual and (2) standard observation or dismissal of the genotype-negative/phenotype-negative relative and his/her future progeny.

In summary, irrespective of genetic testing, once a clinical diagnosis of HCM is made, all first-degree relatives and probably "athletic" second-degree relatives to the index case should be screened by an ECG and echocardiogram. Annual screenings are recommended for adolescents, young adults (age 12–25) and athletes, and every 3–5 years thereafter. If an HCM-causing mutation is established for the index case, first-degree relatives should have confirmatory genetic testing performed for that particular HCM-causing mutation and depending on the established familial versus sporadic pattern, confirmatory genetic testing should proceed in concentric circles of relatedness. A decision to cease surveillance for HCM in a relative hinges critically on the certainty of the identified gene/mutation and its causative link as well as the complete absence of any traditional evidence used to clinically diagnose HCM (i.e. asymptomatic and normal echocardiogram).

It might be important to identify patients without frank phenotypic HCM due to potential beneficial effects that have been suggested for 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins) and inhibitors of the renin-agiotensin-aldosterone system (RAAS), e.g. losartan and spironolactone.[219-222] Statins may prevent the evolving phenotype in HCM by blockade of geranylgeranylation of RhoA and Rac1, which are essential mediators of cardiac hypertrophic response. However, the current yield of genetic testing and the expense involved may prevent application of this testing on a generalized basis.

FLOW CHART 1: A possible decision tree to follow in genetic- and echocardiography-based screening for hypertrophic cardiomyopathy (HCM). Noted is the *a priori* probability for a positive genetic test result based on the echocardiography-scored septal contour, as well as the steps to follow if a patient chooses not to pursue genetic testing



(*Source:* Modified from Bos et al. Diagnostic, prognostic, and therapeutic implications of genetic testing for hypertrophic cardiomyopathy. J Am Coll Cardiol. 2009;54:201-11, with permission)

ASSESSMENT, RISK STRATIFICATION AND PREVENTION OF SUDDEN DEATH

Sudden death is unpredictable in HCM and is the most frequent mode of premature death. Typically, SD in patients with HCM occurs without warning in asymptomatic or mildly symptomatic young patients (predominantly < 25 years)[4,5,8,24-29] with risk decreasing toward midlife and beyond, although a measure of longevity does not confer immunity to SD. The SD occurs most commonly during mild exertion or sedentary activities (or during sleep), but may be triggered by vigorous physical exertion.[223-225]

Precise risk stratification in HCM remains a challenge due to its clinical heterogeneity of presentation and expression, its relatively low prevalence in general cardiology practice, and the complexity of potential pathophysiologic mechanisms.[8,52,197,198,226,227] Nevertheless, it is possible to identify most high-risk patients by noninvasive clinical markers,[24,26,228] and only a small minority of those HCM patients who die suddenly (about 3%) are without any of the currently acknowledged risk markers (Fig. 37).[26]

HCM patients (particularly those < 60 years old) should undergo comprehensive clinical assessments on an annual basis for risk stratification and evolution of symptoms, including: (1) careful personal and family history, (2) noninvasive testing with 2D echocardiography (primarily for assessment of magnitude of LVH and outflow obstruction), (3) a 24- or 48-hour ambulatory (Holter) ECG recording for VT, and (4) blood pressure response during maximal upright exercise (treadmill or bicycle).[5] Subsequent risk analysis should be performed periodically and when there is a perceived change in clinical status.

No convincing evidence exist, that laboratory electrophysiological testing (i.e. programmed ventricular stimulation)[229,230] has an important routine role in identifying HCM patients at high risk for SD due to life-threatening arrhythmias. Both polymorphic VT and VF (the most commonly provoked arrhythmias) are generally regarded as nonspecific electrophysiological testing responses to multiple ventricular extrastimuli.[6,14] For example, stimulation with three ventricular premature depolarizations rarely triggers monomorphic VT in HCM (in contrast to CAD), but frequently induces polymorphic VT or VF, even in some patients at low risk for SD. Thus, risk stratification involving laboratory induction of ventricular arrhythmias is neither desirable in HCM patients on a routine basis nor, per se, to justify aggressive intervention.[6,8,14] However, electrophysiology studies with or without programmed ventricular stimulation may have some value in select patients such as those with otherwise unexplained syncope.

Although most clinical markers of SD risk in HCM patients have low positive predictive values (due to low event rates),[6,26,129,147,231,232] their negative predictive value is high (at least 90%), suggesting that the absence of these markers and certain other clinical features can be used to profile HCM patients into a low-likelihood cohort for SD or other adverse events (Table 16).[6] Patients with such features apparently have

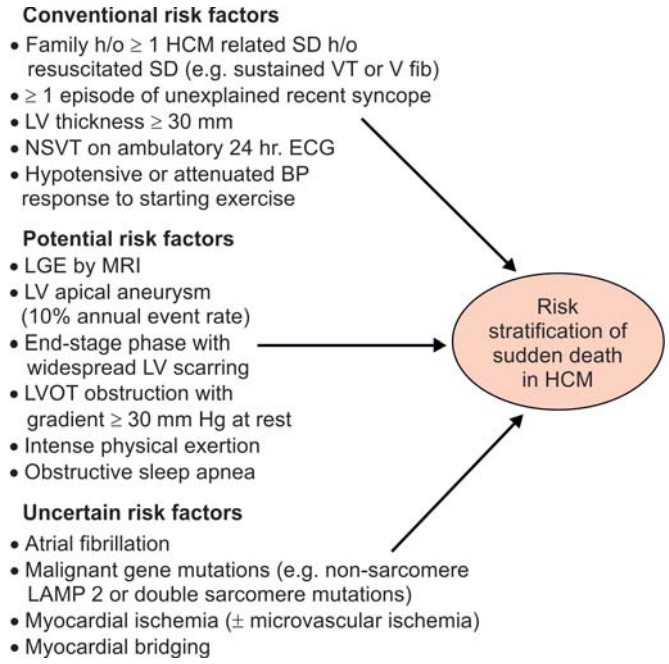


FIGURE 37: Sudden death (SD) risk stratification in hypertrophic cardiomyopathy (HCM). Top arrow identifies a clinical profile currently used to identify those patients at highest risk for SD who are potential candidates for implantable cardioverter-defibrillators (ICD). The middle and bottom arrows identify a number of disease features that can be regarded as arbitrators when the level of risk based on conventional markers is ambiguous. These may be useful in resolving otherwise uncertain ICD decisions on a case-by-case basis. Also note that sustained ventricular tachyarrhythmias have been reported in a significant minority of patients (~10%) over the short term after alcohol septal ablation. A direct relation exists between magnitude of left ventricular (LV) hypertrophy (maximum wall thickness by echocardiography) and SD risk. Mild hypertrophy conveys generally lower risk; extreme hypertrophy (wall thickness = 30 mm) conveys the highest risk as a marker for SD. (Abbreviations: BP: Blood pressure; ECG: Electrocardiogram; LGE: Late gadolinium enhancement; MRI: Magnetic resonance imaging; NSVT: Nonsustained ventricular tachycardia; V Fib: Ventricular fibrillation, VT: Ventricular tachycardia, LVOT: Left ventricular outflow tract)

a favorable prognosis and constitute an important proportion of the overall HCM population. Most such patients probably will not require aggressive major medical treatment and generally deserve a measure of reassurance regarding their prognoses. Little or no restriction is necessary with regard to recreational activities and employment, although exclusion from intense competitive sports is advised.[5]

With the availability of ICDs, prevention of SD by administration of drugs such as beta-adrenergic blocking agents (beta blockers), verapamil and type 1A antiarrhythmic agents (i.e. quinidine, procainamide) is of historical interest now. In contemporary clinical practice, ICD is the most effective and reliable treatment option available, harboring the potential for absolute protection and altering the natural history of this disease in some patients.[27,104,107,233] Evidence over the past decade, clearly demonstrates that appropriate ICD interventions are not uncommon in HCM and that they are highly effective in terminating potentially lethal ventricular tachyarrhythmias.[5,104,105,107,113,234,235] The most robust evidence for ICDs comes from an international multicenter registry of 506 HCM patients from 42 centers with ICDs implanted on the clinical

TABLE 16

Low-risk cohort for sudden death in HCM

1. Asymptomatic patients
2. Mild symptomatic class (NYHA I and II)
3. No family history of sudden death
4. No syncope (HCM-related)
5. No episodes of NSVT on ambulatory ECG monitoring
6. LVOT gradient at rest less than 30 mm Hg
7. Normal or mildly increased left atrial size (< 45 mm)
8. Normal blood pressure response to upright exercise
9. Left ventricle wall thickness < 20 mm
10. Absence of delayed hyperenhancement on CMR imaging
11. Absence of obstructive sleep apnea

(Abbreviations: CMR: Cardiac magnetic resonance; ECG: Electrocardiogram; HCM: Hypertrophy cardiomyopathy; LVOT: Left ventricular outflow tract; NSVT: Nonsustained ventricular tachycardia; NYHA: New York Heart Association)

judgment of the managing cardiologist.[105,113] This registry has twice the number of participants in the Multicenter Automatic Defibrillator Implantation Trial I (MADIT I)[236] and is larger than many randomized ICD trials.[236-240]

Data from this registry demonstrates that over an average follow-up of 3.7 years:

a. 20% of patients experienced appropriate device therapy for VT/VF, equivalent to five ICDs implanted per intervention.
b. Discharge rates were 5.5%/year overall, 11%/year for secondary prevention (after cardiac arrest or sustained VT), and 4%/year for primary prevention (more than one risk factor).

ICD therapy was most common in young patients (mean, 40 years of age), with the highest rates in children and adolescents (11% per year), which is consistent with the predilection of SD in young HCM patients.[2,5,6,8,15,24-28]

Based on current evidence, there is universal agreement that an ICD is indicated in HCM patients for secondary prevention after cardiac arrest or sustained episodes of VT,[238,239] including the American College of Cardiology/European Society of Cardiology 2003 consensus HCM panel.[5] However, ICD selection in patients for primary prevention can be a contentious issue based on available clinical evidence (risk stratification) in a particular patient scenario, the level of risk acceptable to the patient and family, and the potential complications largely related to lead systems and inappropriate device discharges. It is also worth noting that physician and patient attitudes toward ICDs (and the access to such devices within the respective health care system) can vary considerably among countries and cultures, and thereby have an important impact on clinical decision-making and threshold for implant to treat HCM.[241] Nevertheless, considerable evidence exists that a single, strong, established marker of increased risk (particularly within the context of a family history of SD in young family members) within the clinical profile of an individual patient is sufficient for both physician and patient to recognize SD risk as unacceptably high, resulting in the proposal for a primary-prevention ICD.[5,8,24,25,105,231,242-244] However, not all patients with one risk factor are at the same magnitude of risk, and

universal device implantation in this patient subgroup is not recommended.[105,113] On the other hand, although patients with multiple risk factors are at increased risk for SD,[11,24,26,28,105,113] it is unresolved whether such clinical profiles consistently convey excessive risk compared to many patients with one risk factor. For example, in the aforementioned ICD in HCM registry,[105,113] a significant proportion of appropriate ICD interventions for VT/VF occurred in patients implanted for only one risk factor (35%), and device therapy was as common in patients with one risk marker as in those with two or more markers. Thus, assessing SD risk level in HCM based on the numeric sum of risk markers in individual patients may represent an artificial strategy.[11,24,26,28] This is where the art and science of medicine blend intricately, and individual and institutional experience benefit patient selection.

In summary, decision-making dilemmas for primary prevention in HCM are inevitable because many patients fall into an ambiguous gray zone where risk stratification cannot be assessed with precision, and individual clinical judgement and experience are necessary for making judgements about ICDs. In such cases, complete transparency, full disclosure and informed consent, linked with autonomous input from the well-informed patient, is vital for resolving decisions in which there are gaps in knowledge or an absence of data, and when sufficient clarity cannot be achieved solely with the conventional risk factor algorithm.[245]

ATHLETES WITH HYPERTROPHIC CARDIOMYOPATHY

To reduce SD risk in athletes with HCM, the generally accepted recommendation of Bethesda Conference 36[246] is withdrawal from intense training and competition associated with most competitive sports due to the linkage between SD and intense exertion in trained athletes with underlying cardiovascular disease (including HCM)[225,247] and in athletes with HCM even in the absence of conventional markers.[29] However, stringent lifestyle or employment modifications for other HCM patients (who are not participants in organized athletics) do not seem justified or practical, although intense physical activity involving burst exertion (e.g. sprinting) or systematic isometric exercise (e.g. heavy lifting) should always be discouraged.[5] In genetically affected but phenotypically normal family members, and in the absence of cardiac symptoms, family history of SD or a mutant gene regarded as malignant, activity restrictions are not mandated, although such subjects may undergo periodic (usually annual) noninvasive clinical evaluation directed toward risk assessment.[5]

Healthy-appearing competitive athletes may harbor unsuspected cardiovascular disease (e.g. HCM) with the potential to cause SD. This fact raises issues of physician responsibility in preparticipation screening and eligibility disqualification decisions. A subset of medical legal cases now represents a framework for screening and eligibility decision-making in high school and college athletes (Table 17).[248] Physicians screening competitive athletes should adhere to recommendations from the Bethesda Conference 36.[246] By virtue of the court decision in Larkin vs Archdiocese of Cincinnati, high school students have no compelling right to participate in interscholastic sports without medical clearance. In Knapp vs Northwestern University, the appellate court ruled that college athletes can be medically disqualified from sports and supported the use of national association guidelines by team physicians in terminating medical eligibility/disqualification decisions.

MEDICAL THERAPY

Medical therapy is the initial therapeutic approach in HCM patients. The fundamental goal of therapy is to alleviate symptoms of obstruction. Patient response to drug therapy is highly variable in terms of magnitude and duration of benefit, and the selection of medications has not achieved standardization and has been dependent, in part, on the experiences of individual practitioners, investigators and centers.

Beta-blockers are the initial drugs of choice.[10,12,194,198,249-251] Beta-blockers are advantageous in that their use is associated with: (1) decreased HR response to exercise, (2) decreased outflow tract gradient with exercise, (3) relief of angina by a decrease in myocardial oxygen demand, and (4) improvement in diastolic filling. Also, patients (60–80%) usually report an improvement in angina, exercise tolerance and syncope. However, sustained symptomatic benefit is seen in only about 40% of patients.[249-252] Propranolol was the first drug used in the medical management of HCM, and, in current clinical practice, atenolol, metoprolol or nadolol are employed more commonly. Although standard dosages of these drugs mitigate disabling symptoms and limit the latent outflow gradient provoked during exercise when sympathetic tone is high and HF symptoms occur, there is little evidence that these agents consistently reduce outflow obstruction under resting conditions.[5] Consequently, beta-blockers are a preferred drug treatment strategy for symptomatic patients with outflow gradients present only with exertion. The dosage of a beta-blocker is, usually titrated to symptom relief or to obtain a resting HR of less than 60 beats/min, requiring up to 400 mg equivalent of metoprolol.

Initially introduced in 1979, the calcium channel blockers (CCBs) verapamil and, later, diltiazem have also been used in HCM[83,253-258] in both the nonobstructive and obstructive forms, with a reported benefit for many patients including those with a component of chest pain.[255,259,260] The CCBs are believed to work by preventing calcium influx, thereby decreasing LV contractility, HR and also improving abnormal diastolic relaxation.[83,256-258] Of the two CCBs, verapamil is used more frequently due to its minimal effect on afterload, and it is believed to improve exercise tolerance by 20–30% in short-term follow-up.[83] As with beta-blockers, verapamil results in sustained symptomatic improvement in less than 50% of patients. Again, dosage of verapamil is titrated to obtain a resting HR of less than 60 beats/min and may require up to 480 mg/day.

Although verapamil is usually safe, it is important to remember that a subset of patients with resting outflow obstruction and severe limiting symptoms may deteriorate clinically. Death has been reported in a few HCM patients with severe disabling symptoms (orthopnea and paroxysmal nocturnal dyspnea), and markedly elevated pulmonary arterial pressure in combination with marked outflow obstruction[15]

TABLE 17

Medical-legal framework relevant to competitive athletes with cardiovascular disease

Case	*Year of filing*	*Age (yrs)**	*Disease/Cause of death*	*Sport*	*Level*	*Allegation*	*Resolution*	*Legal precedent*	*Clinical message*
Ramirez vs Muroc Joint United School District et al.	2004	17	HCM	Football	High School	Failure to screen	Settlement	No	Screening mandatory before formal training
Izidor vs Knight	2003	19	HCM	Basketball	College	Screening inadequate	Settlement	No	Official clearance should not be signed before evaluation completed
Knapp vs Northwestern University	1996	19	HCM†	Basketball	College	Unfair, discriminatory restriction from sport based on medical disability	Appellate decision upheld NU's decision to disqualify	Yes	Establishes precedent for Bethesda Conference disqualification criteria; team physician can disqualify based on medical grounds
Gardner vs Holifield	1994	20	Marfan syndrome; aortic dissection	Basketball	College	Failure to screen and interpret tests adequately and disqualify athlete	Dismissed	No	Withdraw athlete from sport until diagnosis resolved
Harris-Lewis vs Mudge	1993	28	Myocarditis	Basketball	Professional	Failure to diagnose/ disqualify athlete	No negligence at trial	No	Withdraw athlete with established cardiovascular disease; appreciate powerful effort of athlete to remain in sport
Lillard vs State of Oregon	1993	20	Myocarditis	Basketball	Professional	Failure to diagnose/ disqualify athlete	No negligence at trial	No	Withdraw athlete with established cardiovascular disease; appreciate powerful effort of athlete to remain in sport
Ivey vs Providence Hospital	1993	19	Asthma	Football	College	Screening inadequate	Settlement	No	Adhere to AHA guidelines; avoid off-campus screening of athletes
Larkin v Archdiocese of Cincinnati	1990	17	HCM	Football	High School	Unnecessary restriction from sport	Dismissed	Yes	Sports in high school are optional, extracurricular activities inconsistent with cardiovascular disease
Gathers vs Loyola-Marymount	1990	23	Myocarditis	Basketball	College	Failure to disqualify athlete	Settlement	No	Withdraw athlete with established cardiovascular disease; appreciate potential for contaminated medical decision-making with elite athletes
Penny vs Sands	1989	23	HCM	Basketball	College/ Professional	Unnecessary restriction from sport	Dismissed	No	Appropriate decision to disqualify for cardiovascular disease may also trigger lawsuit

*All athletes were male.†Indicates patient-athlete survived. (*Source:* Paterick TE et al. Medical and legal issues in the cardiovascular evaluation of competitive athletes. JAMA. 2005;294:3011-8, with permission)
(Abbreviations: AHA: American Heart Association; HCM: Hypertrophic cardiomyopathy)

treated with verapamil. These adverse hemodynamic effects of verapamil presumably result from the vasodilating properties predominating over negative inotropic effects, resulting in augmented outflow obstruction, pulmonary edema and cardiogenic shock. Due to these concerns, caution should be exercised in administering verapamil to patients with resting outflow obstruction and severe limiting symptoms.[5] In fact, some investigators discourage the use of CCBs in the management of obstructive HCM and instead favor disopyramide (often with a beta-blocker) for such patients with severe symptoms.[15,261] The dihydropyridine class of CCBs (e.g. amlodipine) should be avoided in HCM, since they are pure vasodilators and will increase the severity of the outflow tract by reducing afterload.

Introduced in 1982 as a therapeutic agent for obstructive HCM, the negative inotropic and type 1A antiarrhythmic agent disopyramide has been shown to produce symptomatic benefit (at 300–600 mg/day with a dose-response effect) in severely limited patients with resting obstruction, because it decreases SAM, outflow obstruction and mitral regurgitant volume.[164,261-264] Since disopyramide can be proarrhythmic, an area of some concern in HCM with an arrhythmogenic LV substrate, it is advised to monitor the QT interval while administering the drug. Also, because it may cause accelerated atrioventricular (AV) nodal conduction and, thus, increase ventricular rate during AF, supplemental therapy with beta-blockers in low doses to achieve normal resting HR has been advised. Furthermore, disopyramide administration may be deleterious in nonobstructive HCM, causing decreased cardiac output, an effect that may limit its use to patients with outflow obstruction who have not responded to beta-blockers or verapamil.

In summary, the accepted standard clinical practice in patients with symptomatic obstructive HCM is to start beta-blockade as the initial therapy and increase the dose to optimal range. Should beta-blocker not be tolerated due to adverse effects, a CCB, usually verapamil, should be substituted. In case of severe LVOT obstruction and symptoms, it is advisable to start the CCB under monitored conditions in the hospital. If patients with obstructive HCM tolerate large doses of either a beta-blocker or CCB and continue to have severe symptoms, disopyramide may be added to either. Currently, no existing data support the combination of beta-blocker and CCBs as being better than one drug alone. When patients continue to be symptomatic and medical therapy is ineffective; septal myectomy, septal ablation or dual-chamber pacing are then considered.

SEPTAL MYECTOMY

Based on the experience of a number of centers throughout the world, the ventricular septal myectomy operation (also known as the Morrow procedure)[265] is regarded as the gold standard therapeutic option for adults and children with obstructive HCM and drug-refractory symptoms.[15,19,266-281] Transaortic septal myectomy (Table 18) involves the resection of a carefully defined, relatively small amount of myocardium from the proximal septum (about 5–10 g), extending from near the base of the aortic valve to beyond the distal margins of mitral leaflets (about 3–4 cm), thereby enlarging the LV outflow tract.[77] In the vast majority of patients, septal myectomy:

TABLE 18

Transaortic septal myectomy

Indications:
1. Marked outflow gradients (usually ≥ 50 mm Hg) at rest or with provocation
2. Severe limiting symptoms (NYHA classes III and IV) despite optimal medical therapy

Types:
1. Standard isolated myectomy (resection of 3–4 cm of ventricular septal muscle)
2. Extended myectomy (resection of 7–8 cm of ventricular septal muscle)
3. Extended distal myectomy
4. Apical myectomy (for apical HCM with or without apical pouch)
5. Combination procedure:
   a. myectomy + repositioning of anterolateral papillary muscle
   b. myectomy + mitral valve repair/replacement
   c. myectomy + mitral valvuloplasty (plication)

Operative Mortality = < 1%

High-risk patients:
1. Elderly
2. Associated severe pulmonary hypertension
3. Prior myectomy
4. Combined procedures (e.g. aortic or mitral valve replacement or CABG)

Complications (< 1%):
1. Complete heart block requiring permanent pacemaker
2. Ventricular septal perforation
3. Partial or complete left bundle branch block (100% of patients)
4. Aortic regurgitation

Advantages:
1. Marked improvement in symptoms
2. Abolition or marked decrease in LVOT gradient
3. Increase in peak oxygen consumption with exercise
4. Decreased frequency of syncope
5. Decrease in left atrial size
6. Decreased likelihood of atrial fibrillation
7. Decreased long-term mortality
8. Decreased sudden death
9. Improved quality of life

(Abbreviations: CABG: Coronary artery bypass graft; HCM: Hypertrophic cardiomyopathy; LVOT: Left ventricular outflow tract; NYHA: New York Heart Association)

1. relieves the LVOT gradient,
2. abolishes any significant mechanical impedance to ejection and mitral valve SAM,
3. normalizes LV systolic pressures,
4. abolishes MR and, ultimately,
5. reduces LV end-diastolic pressures.

In some cases, a more extensive myectomy procedure is employed, with the septal resection widened and extended far more toward the mid-ventricle than in the classic Morrow procedure (i.e. 7–8 cm from the aortic valve to below the level of papillary muscles).[103,282] In addition, the anterolateral papillary muscle may be dissected partially free from its attachment with the lateral LV free wall to enhance papillary muscle mobility and reduce anterior tethering of the mitral apparatus.[103] In situations where severe MR due to intrinsic valve abnormality (such as myxomatous mitral valve with or without ruptured chordae or prior damage from endocarditis) is identified, mitral valve replacement or repair is undertaken.[283]

Additionally, in patients with particularly deformed or elongated mitral leaflets, mitral valvuloplasty (plication) in combination with myectomy is sometimes performed.[284] Furthermore, those patients who are identified to have muscular midcavity obstruction due to an anomalous papillary muscle require an extended distal septal myectomy[103] or, rarely, mitral valve replacement.[101]

The results of ventricular septal myectomy are dependent not only on surgical expertise, but also on the use of intraoperative transesophageal echocardiography (TEE).[285-287] Intraoperative guidance with TEE is standard clinical practice and useful in assessing the site and extent of the proposed myectomy, structural features of the mitral valve, and the effect of muscular resection on SAM and MR. In contemporary surgical practice, operative mortality for isolated septal myectomy is approximately less than 1%.[203,204] Operative risk is higher in the elderly, particularly in those who require other concomitant cardiac procedures, viz. aortic or mitral valve replacement, mitral valve repair or coronary artery bypass grafting. Complications (complete heart block, ventricular septal perforation and aortic regurgitation) of the surgery are rare and occur in less than 1% of patients. Partial or complete left bundle branch block (LBBB) is an inevitable consequence of the muscular resection and is not associated with adverse sequelae.[103,271,275,277-279,288-290]

Ventricular septal myectomy affords many patients excellent symptomatic relief, near-normal exercise capacity and a return to a normal lifestyle with improved quality of life that is maintained over decades, as demonstrated by several long-term follow-up studies of patients with partial septal myectomy.[203,204,272,276,278,281,282,291-293] Although definitive evidence is lacking, a few retrospective nonrandomized studies suggest that septal myectomy in severely symptomatic patients may reduce long-term mortality and possibly SD.[133,272,275] A recent large-cohort study also showed that survival rate following myectomy is equivalent to age- and sex-matched expected survival rates in the general population and superior to that observed in a contemporary cohort of patients with outflow obstruction who did not undergo myectomy (Figs 38A to D).[203]

In the apical hypertrophic cardiomyopathy (ApHCM) morphologic variant, treatment options for symptomatic patients are limited, and clinical experience has shown that response to medical therapy is poorer than that for patients with obstructive HCM. In such patients, a novel surgical approach involving the removal of hypertrophied muscle in the apical and middle regions of the LV creates a larger chamber size in diastole. Although there might be mild hypokinesis in the region of the apical incision, overall contractility of the LV is preserved, with a resultant increase in the effective operative compliance of the LV that allows a larger filling volume without an increase in end-diastolic pressure. Recently, the Mayo Clinic published the first report[294] describing outcomes for patients with ApHCM treated with apical myectomy. They found that apical myectomy improves functional status by decreasing LV end-diastolic pressure, improving operative compliance and increasing stroke volume.

PERCUTANEOUS ALCOHOL SEPTAL ABLATION

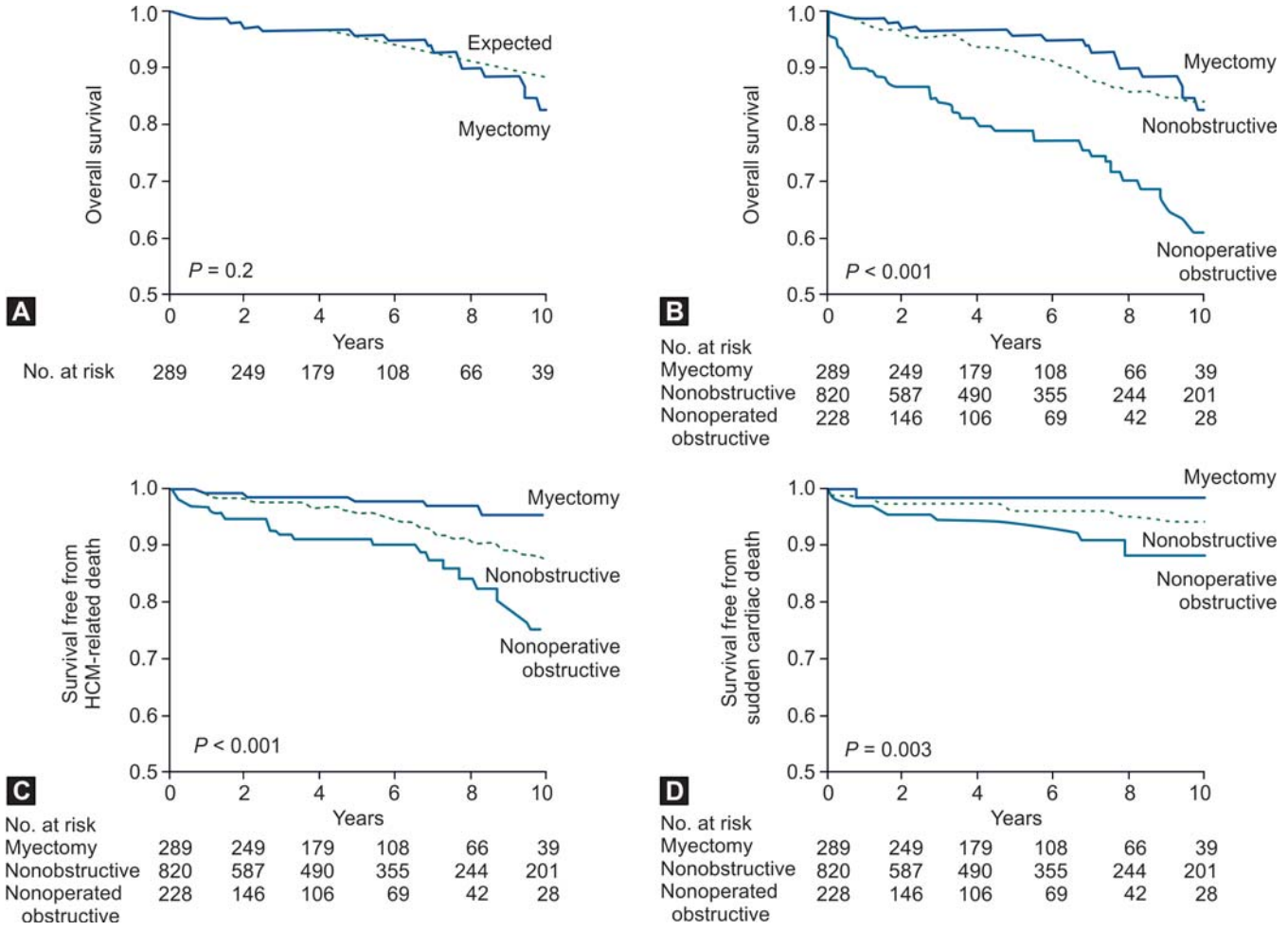
Introduced in 1995 by Sigwart,[295] catheter-based nonsurgical reduction therapy of the IVS by infusion of small amounts of pure alcohol into the first or second septal branch of the left anterior descending coronary artery (Figs 39A to E and 40 and Table 19) has gained great popularity in the past few years, and this treatment has rapidly expanded in European countries.[296] The number of septal ablations (SA) performed worldwide, since 1995, reached more than 5,000 in 2008,[5,297] surpassing the number of septal myectomies (SM) performed over the last 45 years. It is estimated that SA procedures are 15–20 times more common than SM for HCM,[297] and at some centers the frequency of SM has been reduced by more than 90% in favor of performing SA as the definitive treatment strategy.[5] Alcohol septal ablation produces a controlled myocardial infarction of the proximal septum,[298-312] which produces shrinkage and scarring of the septal wall, resulting in a widening of the LVOT, thereby lessening the SAM of the mitral valve (thereby reducing/eliminating LVOT obstruction) and MR (Table 17).[298,301,302,304,305,313]

Although some centers use a pressure-angiographic and fluoroscopy-guided technique[302,310,314] to identify the septal perforator and area for infarction (by an immediate fall in outflow gradient following balloon occlusion), many centers will use myocardial contrast echocardiography guidance (with injection of echocardiography contrast or radio-opaque medium) in selecting the appropriate septal perforator branch(es). This latter technique is useful for determining the precise area of septum targeted for alcohol and infarction and whether the selected septal perforator also perfuses other distant and unwanted areas of LV or RV myocardium or papillary muscles.[299,315] A temporary pacing catheter is universally positioned in the RV apex in the event that high-grade AV block occurs.

Following septal ablation, a progressive decrease in the LVOT gradient usually occurs up to 6–12 months from progressive remodeling of the septum without significant impairment in global LV ejection,[301,305,307,314-318] although a rapid reduction in resting LVOT gradient may also be seen in the catheterization laboratory (Fig. 39). A relatively large proportion of patients have been reported to demonstrate improvement in limiting symptoms and in quality of life along with improved exercise performance (in terms of total treadmill exercise time and peak oxygen consumption) after alcohol septal ablation.[298,301,304,305,307,318-320]

Major complications associated with alcohol septal ablation include high-grade AV block[301,304,319,321] requiring permanent pacemaker, right bundle branch block (RBBB)[301,313] and coronary no-flow[322] secondary to backward extravasation of alcohol and resultant anteroseptal myocardial infarction. Ventricular septal defects, myocardial perforations and intractable VF during the time of the procedure have also been reported, although the true incidence of these complications is unknown. Procedure-related mortality is reported to be from 1% to 2%, but is probably reduced in more recent cases.[5]

Proper selection of patients for alcohol septal ablation is a crucial issue,[321] and all patients should have outflow gradients documented to be due to SAM and proximal mitral valve-septal contact,[323] exclusive of congenital abnormalities of the mitral apparatus such as anomalous papillary muscle insertion into mitral valve, which produces more distal muscular obstruction in the mid-cavity.[101,103]

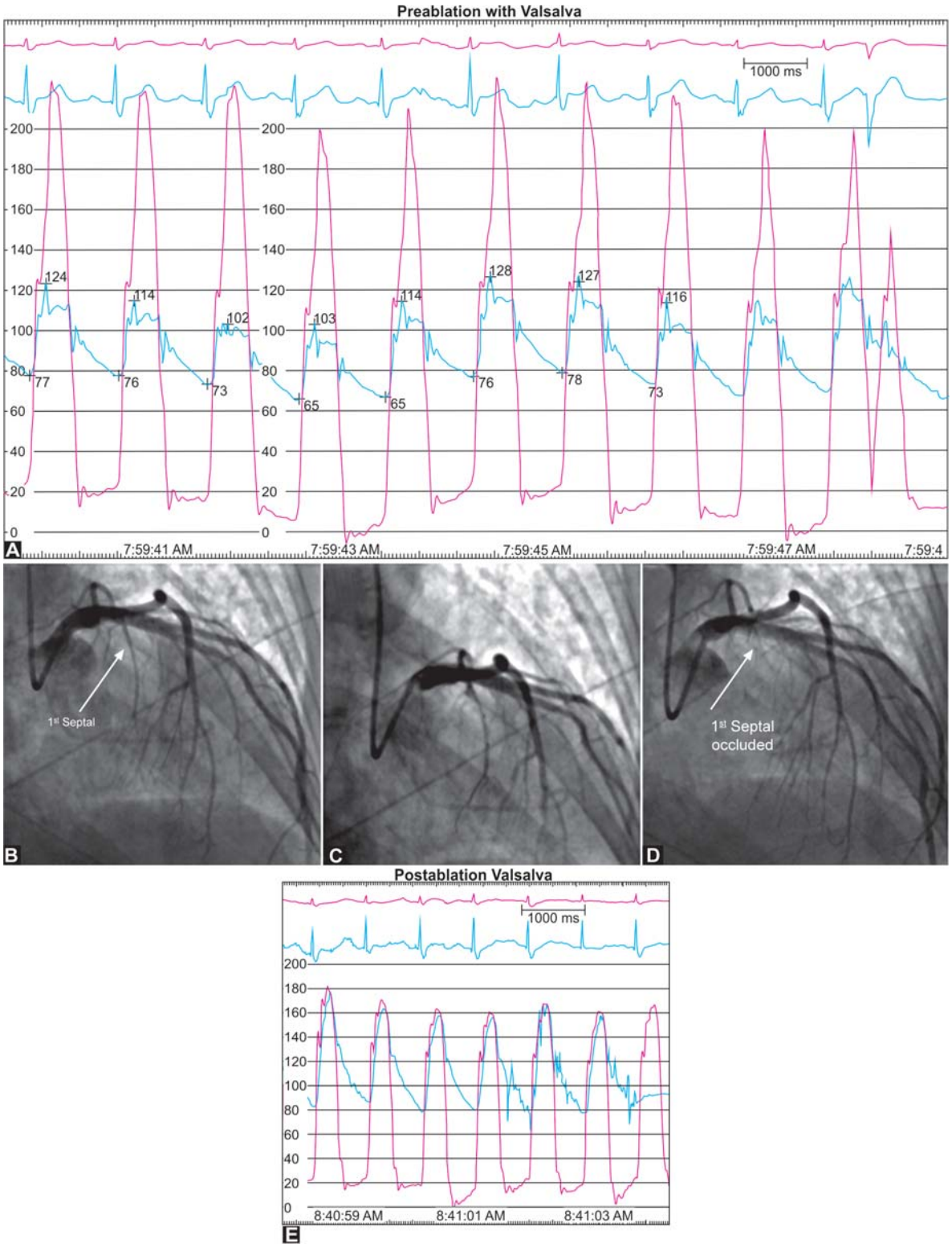


FIGURES 38A TO D: (A) Survival free from all-cause mortality after surgical myectomy for obstructive hypertrophic cardiomyopathy (n = 289) compared with the age- and gender-matched general U.S. white population. Log-rank, p = 0.2. (B) Survival free from all-cause mortality in three hypertrophic cardiomyopathy (HCM) patient subgroups: surgical myectomy (n = 289), nonoperated with obstruction (n = 228), and nonobstructive (n = 820). Overall log-rank, p < 0.001; myectomy versus nonoperated obstructive HCM, p < 0.001; myectomy versus nonobstructive HCM, p = 0.8. (C) Survival free from HCM-related death among patients in three HCM subgroups: surgical myectomy (n = 289), nonoperated with obstruction (n = 228) and nonobstructive (n = 820). Overall log-rank, p < 0.001; myectomy versus nonoperated obstructive HCM, p < 0.001; myectomy versus nonobstructive HCM, p = 0.01. (D) Survival free from sudden cardiac death among patients in three HCM subgroups: surgical myectomy (n = 289), nonoperated with obstruction (n = 228), and nonobstructive (n = 820). Overall log-rank, p = 0.003; myectomy versus nonoperated obstructive HCM, p = 0.003; myectomy versus nonobstructive HCM, p = 0.3. (*Source:* Modified from Ommen et al. Long-term effects of surgical septal myectomy on survival in patients with obstructive HCM. J Am Coll Cardiol. 2005;46;470-6, with permission)

Alcohol septal ablation is believed to potentially create a permanent arrhythmogenic substrate in the form of a healed septal scar that could increase the risk of lethal reentrant arrhythmias.[310] Single-center experiences report two-fold to six-fold increases in the rate of sustained arrhythmias after ablation.[324] Although this concern exists, no definitive evidence is yet available that alcohol septal ablation scar itself increases (or does not increase) the long-term risk for SD in absolute terms, and resolution of this issue requires extended follow-up studies in large patient cohorts.[325] However, there is a documented risk for potentially life-threatening sustained ventricular tachyarrhythmias over the short term[113,324,326-332] with reported postprocedural annual event rates of 3–5%,[327,330] presumably resulting from electrical instability potentiated by the scar in certain susceptible patients. In fact, on the basis of this consideration and a measure of concern that alcohol-imposed infarcts could compound preexisting and underlying myocardial electric instability,[113,326,328,332,333] some centers consider alcohol septal ablation a risk arbitrator[245] and implant ICDs in select patients with commonly accepted risk markers after the ablation procedure.[328]

Since the issue of arrhythmia-related events and SD as a consequence of the healed intramyocardial scar produced by alcohol septal ablation is, particularly relevant for young patients (in whom even a modest annual increase in the risk of SD would have the likelihood of shortening life considerably), very careful selection of patients is advisable (largely confining the procedure to older adults), particularly when the option of surgical myectomy is feasible.[5] Thus, there does not appear to be a primary role for alcohol ablation in children, and such procedures are not advised.[5]

Other limitations for septal ablation are related to the morphologic heterogeneity of HCM patients, and thus not all HCM patients with obstruction are ideal candidates for septal



FIGURES 39A TO E: Cardiac catheterization hemodynamic study in a 74-year-old woman with symptomatic obstructive hypertrophic cardiomyopathy (HCM). The patient was on metoprolol XL 50 mg oral twice daily and disopyramide 100 mg oral twice daily in addition to verapamil 240 mg oral twice daily and continued to have NYHA class III symptoms. (A) Demonstrates her outflow tract gradient (120 mm Hg) with Valsalva. The patient was scheduled for an alcohol septal ablation due to continuing symptoms. (B) A left anterior oblique view during a coronary angiogram of the same patient to identify the target septal perforator branch of the left anterior descending coronary artery for the purpose of producing a myocardial infarction within the proximal ventricular septum. (C) Shows the presence of a flexible coronary guidewire in the target septal perforator. (D) The arteriogram showing the occluded target septal perforator after the coronary balloon is inflated, to verify that the balloon is located in the desired anatomic position and to ensure that leakage of alcohol into the left anterior descending coronary artery or coronary venous system does not occur. In this particular patient, 2.5 ml of absolute alcohol was injected over 12 minutes to produce a controlled myocardial infarction. (E) Demonstrates a successful alcohol septal ablation result in the patient as shown by a rapid reduction in resting outflow gradient (0 mm Hg) evident in the catheterization laboratory. Postprocedure peak creatine phosphokinase (CPK) was 1,253. Three years after the procedure, the patient is on 50 mg of metoprolol XL without any inducible gradient and in NYHA Class I. (*Source:* Suhail Allaqaband, MD, Milwaukee, WI)

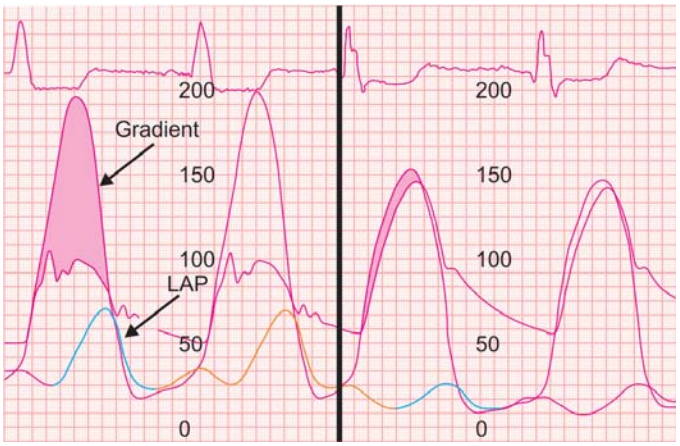


FIGURE 40: Simultaneous electrocardiographic aortic pressure, left ventricular pressure and pulmonary capillary catheter recordings in a patient undergoing alcohol septal ablation for severe unrelenting symptoms of hypertrophic cardiomyopathy after maximal medical therapy. On the left is shown the preablation gradient of approximately 100 mm Hg (pink shaded area), which disappears immediately after the procedure in the catheterization laboratory. Also demonstrated is the near complete disappearance of the associated mitral regurgitation (as depicted by the "v wave" in blue) after the procedure. (*Source:* Rick A Nishimura, MD, Rochester, MN) (Abbreviation: LAP: Left atrial pressure)

TABLE 19

Percutaneous alcohol septal ablation

Indications:
1. Severe heart failure symptoms NYHA classes III and IV refractory to all medication (same as for surgical myectomy)
2. LVOT gradient ≥ 50 mm Hg (same as for surgical myectomy)

Procedure:
1. Introduction of absolute alcohol into a target septal perforator branch
2. An average of 1.5–2 cc of 95% ethanol is infused slowly to achieve an area of necrosis 3–10% of the LV mass or 20% of the IVS
3. Classically, a biphasic response is seen with an acute decrease in LVOT gradient (stunned myocardium) followed by a rise of about 50% of preprocedure level the next day and reducing greatly over the next several weeks/months

Favorable effects:
1. Markedly reduced LVOT gradient
2. Normalization of LV pressures
3. Reduced systolic overload
4. Regression of LVH beyond the alcohol target area
5. Improvement in disease-limiting symptoms
6. Improved exercise performance
7. Improved peak oxygen consumption
8. Improved quality of life

Undesirable effects:
1. Procedure-related mortality 1–3%
2. High-grade AV block (5–30%) requiring permanent pacemaker
3. Right bundle branch block
4. Coronary artery dissection
5. Retrograde extravasation of alcohol with occlusion or abrupt coronary no-flow phenomenon and a large anteroseptal myocardial infarction
6. Ventricular septal defect and myocardial perforation
7. Healed intramyocardial scar with potential added arrhythmogenic substrate

(Abbreviations: AV: Atrioventricular; IVS: Interventricular septum; LVH: Left ventricular hypertrophy; LVOT: Left ventricular outflow tract; NYHA: New York Heart Association)

ablation.[5] Septal ablation relies on the fixed anatomic distribution and size of the septal perforator artery, thus, it cannot make adjustments for variability in the distribution and size of these arterial vessels in relation to the distribution of septal hypertrophy, or for other complexities of LVOT morphology, such as greatly elongated mitral leaflets, anomalous papillary muscle or other associated abnormalities of the mitral valve apparatus, which are best dealt with surgically. The "learning curve" for alcohol septal ablation technique is also steep (due, in part, to the relatively small number of eligible HCM patients), particularly regarding selection of the optimal septal perforator branch. Therefore, ablation should not be regarded as a routine technique to be employed by any expert interventional cardiologist.[5] As with surgical myectomy, it is advisable that alcohol ablation be largely confined to centers having substantial and specific experience with HCM in order to assure proper patient selection, lowest possible rates of morbidity and mortality, and the greatest likelihood of achieving benefits.

A recent systematic review and meta-analysis[334] of available evidence comparing outcomes after SA and SM showed no significant differences between short-term (risk difference [RD]: 0.01; 95% confidence interval [CI]: 0.01–0.03) and long-term mortality (RD: 0.02; 95% CI: 0.05–0.09). In addition, no significant differences in terms of postintervention functional status as well as improvement in NYHA functional class, ventricular arrhythmia occurrence, reinterventions performed and postprocedure MR were noted. However, SA was found to increase the risk of RBBB (pooled OR: 56.3; 95% CI: 11.6–273.9) along with need for permanent pacemaker implantation postprocedure (pooled OR: 2.6; 95% CI: 1.7–3.9). Although the efficacy of both SA and SM in LVOT gradient reduction was comparable, a small yet significantly higher residual LVOT gradient amongst SA patients compared with the SM patients, was found.

While SA represents an option available to HCM patients and a selective alternative to surgery, current guidelines do not recommend SA as the standard and primary therapeutic strategy for all severely symptomatic patients refractory to medical management with marked obstruction to LV outflow (Table 20). In real-world practice, the choice of SA versus SM for the treatment of HCM is guided by several considerations (Table 21)[334] and, although SM continues to be the gold-standard treatment for refractory HCM, SA has emerged as an attractive alternative.

DUAL-CHAMBER PACEMAKER

In patients with HCM, pacing the RV apex and apical septum can decrease the outflow tract gradient by altering the ventricular contraction sequence with a decrease in systolic projection of the basal septum into the LVOT (Fig. 41). A chronic remodeling effect[335] during continuous pacing with enlargement of the LV cavity may further decrease LVOT obstruction. In patients with HCM, pacing or sensing the atrium, in addition to pacing the ventricle, is also important to maintain the hemodynamic contribution of atrial contraction. It has been shown that there is an optimal AV delay for optimal hemodynamic performance.[336,337] Too short, an AV interval increases left atrial pressure and reduces preload, while too long, an AV delay results in

TABLE 20

Comparison of septal myectomy and percutaneous alcohol septal ablation*

Parameter	*Myectomy*	*Ablation*
Operative mortality	1–2%	1–2%
Gradient reduction (at rest)	to < 10 mm Hg	to < 25 mm Hg
Symptoms (subjective)	Decreased	Decreased
Symptoms (objective)	Decreased	Decreased
Effectiveness despite anatomic variability	Usually	Uncertain
Pacemaker (high-grade AV block)	1–2%	5–10%
Procedure frequency	X	15–20x
Sudden death risk (long-term)	Very low	Uncertain
Available follow-up	> 40 years	About 10 years
Procedure-related intramyocardial scar	Absent	Present

*Data represents best estimates based on the assimilation of published data, and with emphasis placed on the most recent clinical experience. (Abbreviation: AV: Atrioventricular). (*Source:* Maron BJ, et al. American College of Cardiology/European Society of Cardiology Clinical Expert Consensus Document on Hypertrophic Cardiomyopathy. A report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents and the European Society of Cardiology Committee for Practice Guidelines. J Am Coll Cardiol. 2003;42:1687-713, with permission)

TABLE 21

Considerations to decide choice of procedures for the treatment of HOCM

Feasibility of each approach:
1. Institutional expertise
2. Patient characteristics
3. Anatomy (septum, papillary muscles, septal perforator, mitral valve, midventricular or apical variants)

Different mechanism:
1. Size and location of septal reduction

Heterogeneous disease:
1. SAM-independent
2. SAM-related
   a. Anterior coaptation
   b. Positive angle between the LVOT and the leaflets
3. Chordal slack

Informed decision after detailed discussion about both therapies

(Abbreviations: HOCM: Hypertrophic obstructive cardiomyopathy; LVOT: Left ventricular outflow tract; SAM: Systolic anterior motion). (*Source:* Agarwal S, et al. Updated meta-analysis of septal alcohol ablation versus myectomy for hypertrophic cardiomyopathy. J Am Coll Cardiol. 2010;55:823-34, with permission)

incomplete preexcitation of the RV with suboptimal reduction in gradient. Therefore, it is necessary to place the pacemaker tip in the apex of the RV to achieve the greatest reduction in gradient. Programming of the pacemaker AV interval to ensure complete ventricular capture may require slowing intrinsic AV nodal conduction with a beta-blocker or verapamil, or ablating the AV node in select cases (thereby rendering the patient pacemaker-dependent).[5]

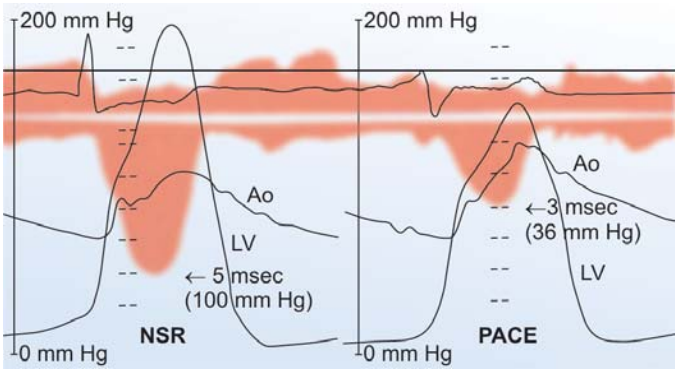


FIGURE 41: Cardiac catheterization study before and after implantation of a dual-chamber pacemaker in a patient with obstructive hypertrophic cardiomyopathy (HCM). Note the substantial decrease in the resting gradient in this patient after DDD pacer implant. Implantation of a dual-chamber pacemaker is a therapeutic modality for treatment of symptomatic HCM patients, whereby pacing the right ventricular apex can decrease the outflow tract gradient, presumably due to alteration of ventricular contraction with a decrease in systolic projection of the basal septum into the left ventricular (LV) outflow tract, although a chronic remodeling effect on LV cavity size is also suggested as a possible mechanism. (Abbreviation: Ao: Aorta)

Initial observational and uncontrolled studies[335,338,339] reported dual-chamber pacing to be associated with a substantial decrease in outflow gradient and amelioration of symptoms in most patients with HCM. Subsequent randomized trials where patients received 2–3 months of pacing and backup AAI mode (no pacing) as a control did not, however, demonstrate this consistently.[340-343] In fact, the subjective symptomatic improvement assessed by quality-of-life score was not different during pacing and without pacing (AAI-backup), and neither was any objective measure of exercise capacity (e.g. treadmill exercise time and maximum oxygen consumption).[340,342] Taken together, the available data does not support dual-chamber pacing as a "primary treatment" for most severely symptomatic patients with obstructive HCM. Nevertheless, evidence does support a trial of dual-chamber pacing in select patient subgroups (e.g. age > 65 years) in terms of gradient relief, improvement in symptoms (40% of patients)[344,345] and exercise tolerance.[340] However, currently no known parameters exist that can identify the patients who would uniformly benefit from dual-chamber pacing. Thus, the role of dual-chamber pacing is limited in contemporary practice to patients who are at high risk for other therapeutic modalities, e.g. SA and SM. Candidates for dual-chamber pacing may include: (1) patients who have significant bradycardia in which pacing may allow an increased dosage of medication and (2) patients who are receiving an ICD for high-risk status and in whom obstruction to LV outflow is also present.

ADDITIONAL POINTS OF INTEREST

ATRIAL FIBRILLATION

Atrial fibrillation is the most common sustained arrhythmia in HCM (20–25% of HCM patients)[106,129,134,192,346,347] and is independently associated with HF-related death, occurrence of fatal and nonfatal stroke, long-term disease progression with HF symptoms and severe functional disability.[106,192,346,348,349]

Both paroxysmal (PAF) and chronic AF occur in patients with HCM. Although linked to left atrial enlargement and an increasing incidence with age,[106] the mechanism is not completely understood. More recently, sleep-disordered breathing (SDB), particularly obstructive sleep apnea (OSA) has been strongly associated with increased incidence and prevalence of AF in patients with HCM. Severity of SDB may influence left atrial volume index and the prevalence of AF in this population.[350] Although AF is reasonably well tolerated by about one-third of patients and is not a primary independent determinant of SD,[106] it may be a trigger for life-threatening ventricular arrhythmias in some patients.[351,352] Risk for complications of AF is enhanced when the arrhythmia becomes chronic, onset is before age 50 and outflow obstruction is present.[106] Furthermore, episodes of PAF can result in acute clinical deterioration accompanied with syncope or HF due to reduced diastolic filling and cardiac output in a hypertrophied LV with preexisting severe diastolic dysfunction.[106,346,347]

In general, AF in HCM is managed in accordance with ACC/AHA/ESC guidelines.[353] It is believed that a more aggressive strategy for maintaining sinus rhythm may be important in HCM patients due to the association of AF with progressive HF, mortality and stroke.[192] Amiodarone is generally regarded as the most effective antiarrhythmic agent for preventing recurrences of AF.[353-355] At times, electrical cardioversion is undertaken in those patients presenting within 48 hours of onset when the presence of atrial thrombi has been excluded with a reasonable degree of certainty.

For rate control in chronic AF, beta-blockers and verapamil are effective, although AV node ablation and permanent ventricular pacing is occasionally necessary. Because even one or two episodes of PAF have been associated with increased risk for systemic thromboembolization in HCM, the threshold for anticoagulation with warfarin therapy should be low and considered in patients even after one AF paroxysm.[8,106,192]

OBSTRUCTIVE SLEEP APNEA AND HCM SYMPTOMS

Obstructive sleep apnea is a common disorder[356] in which repetitive apneas expose the cardiovascular system to cycles of hypoxia, exaggerated negative intrathoracic pressure and arousals. Such noxious stimuli, in turn, depress myocardial contractility, activate the sympathetic nervous system, raise blood pressure, HR and myocardial wall stress, depress parasympathetic activity, provoke oxidative stress and systemic inflammation, activate platelets and impair vascular endothelial function. There is a higher prevalence of AF and greater degree of left atrial enlargement in patients with OSA and HCM.[350] It also has been proposed recently[357] that the presence of OSA in patients with HCM could be an important contributor to drug-refractory symptoms and worsening LVOT obstruction as a result of heightened sympathetic activity. The hypoxemia and carbon dioxide retention that result from apnea primarily excite peripheral and central chemoreceptors, which increase sympathetic vasoconstrictor activity.[358] The repetitive nocturnal stress of hypoxemia, combined with strenuous inspiratory effort (due to occluded upper airway) and arousal from sleep, elicits a breadth of neural, humoral, vascular, inflammatory and metabolic responses that are evident even when the individual is awake. It has been suggested that elevated catecholamine levels in OSA could influence the pathophysiology of HCM by increasing hypertrophy and LV filling pressures, decreasing cardiac output, and initiating or worsening LVOT obstruction, dyspnea and dizziness and MR.[357] This early evidence of a relation between OSA and HCM should alert the clinician to the possibility that OSA may be the underlying culprit for symptoms that persist despite optimum pharmacotherapy in HCM and could contribute to a raised LVOT gradient in some patients with HCM. Treatment of OSA with continuous positive airway pressure (CPAP) is known to reduce blood pressure, sympathetic activity and systemic inflammation[359] as well as stimulate regression of LV hypertrophy.[360] Thus, it is reasonable to screen HCM patients for OSA, and those at high risk may be considered for oximetry, polysomnography or both.

END-STAGE HYPERTROPHIC CARDIOMYOPATHY (BURNT-OUT OR DILATED STAGE)

For lack of a better name, end-stage hypertrophic cardiomyopathy (ESHCM) refers to progressive systolic HF coupled with ventricular dilatation, with a reported prevalence of 2.4–15% in different series[361] and incidence of 1–2% of HCM patients per year.[361,362] Approximately, 50% or more of ESHCM cases demonstrate progressive systolic dysfunction, LV cavity dilation (remodeling), and ventricular wall thinning in addition to preexisting diastolic dysfunction, whereas others continue to have thick ventricles and normal cavity dimensions accompanied by severe diastolic dysfunction and relatively preserved systolic function at the time of cardiac transplant or death.[363] There is some evidence to suggest that genetics and molecular, biochemical, biophysical, cellular and physiological processes may be involved in the evolution of ESHCM.[362,364-367]

Development of systolic dysfunction in patients with HCM has serious clinical implications, since it is associated with higher rates of HF-related mortality and SD.[363] The average mortality of end-stage HCM is 10% per year,[361] increasing to 50% per year in advanced cases with ventricular dilation and severe systolic dysfunction (ejection fraction < 20%). In such cases, ICD coupled with aggressive medical therapy for HF is indicated. Although there are no data at present concerning the role of biventricular pacing in HCM patients[5] with severe heart disease, it has been used advantageously in isolated cases.

PREGNANCY AND HYPERTROPHIC CARDIOMYOPATHY

Most HCM patients tolerate pregnancy well (and undergo normal vaginal delivery) due, in part, to the increase in blood volume and are not at increased risk of SD. Absolute maternal mortality is very low (although possibly higher in patients with HCM than in the general population) and appears to be confined principally to women with high-risk clinical profiles.[368] Such patients are best served in highly specialized preventive obstetrical care, and labor and delivery should preferably be undertaken in an experienced center with meticulous attention to hemodynamic parameters. It is also advisable that all HCM patients who wish to become pregnant

should be offered prenatal counselling about the risk of transmission of disease to their offspring (autosomal dominant inheritance pattern with 50% risk of transmission to each child) and be followed at a tertiary care center with "expertise in pregnancy with heart disease". Additionally, if patients are on treatment with beta-blockers or calcium blockers, these drugs should be continued throughout pregnancy. Occasionally, low-dose diuretics may be required should pulmonary congestion occur.

INFECTIVE ENDOCARDITIS

Patients with HCM are at risk for bacterial endocarditis. This risk is usually confined to those patients with LVOT obstruction or intrinsic mitral valve disease.[369] Vegetations usually occur at the site of the thickened anterior mitral leaflet, although cases have been reported with lesions on the outflow tract endocardial contact plaque (at the point of mitral-septal contact) or on the aortic valve.[369,370] Therefore, prophylaxis against infective endocarditis in patients who have HCM and a latent or resting obstruction is recommended at the time of dental or selected surgical procedures.[371]

CONCLUSION

Hypertrophic cardiomyopathy is an intriguing, complex, genetic, predominantly obstructive heart muscle disease that is highly heterogeneous in its clinical and pathologic character. Its clinical course is extremely variable (the first patient diagnosed with this disease—52 years ago—has survived, to date, in good health with an active and productive lifestyle), ranging from an asymptomatic lifelong course to dyspnea and/or angina refractory to pharmacotherapy to SD as the sentinel event. Contemporary echocardiography has provided clarity to the morphology of HCM (spectrum and hemodynamic assessment) that characterizes the disease phenotype. More recent genetic studies have raised both awareness and important questions about HCM's diagnosis and prognosis. The bench-to-bedside evolution in this disease has provided an exciting opportunity to extend laboratory results of animal models to human therapy and, perhaps, the ability in the future to manipulate the abnormal genome. However, the genetic, pathological and clinical heterogeneity of HCM continues to make the diagnosis and management of HCM patients a major challenge. Referral to an HCM clinic with expertise in disease management should be strongly considered and is highly recommended in the context of contemporary clinical practice. Importantly, all patients with HCM should undergo an evaluation in which their risk of SD is assessed. Patient advocacy and support for this disorder exists in the form of the HCM Association—an internet-based organization (www.4HCM.org) dedicated to the accurate transmission of information about HCM to patients, families, the medical community and the public.

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Chapter 81

Dilated Cardiomyopathy

Jalal K Ghali

Chapter Outline

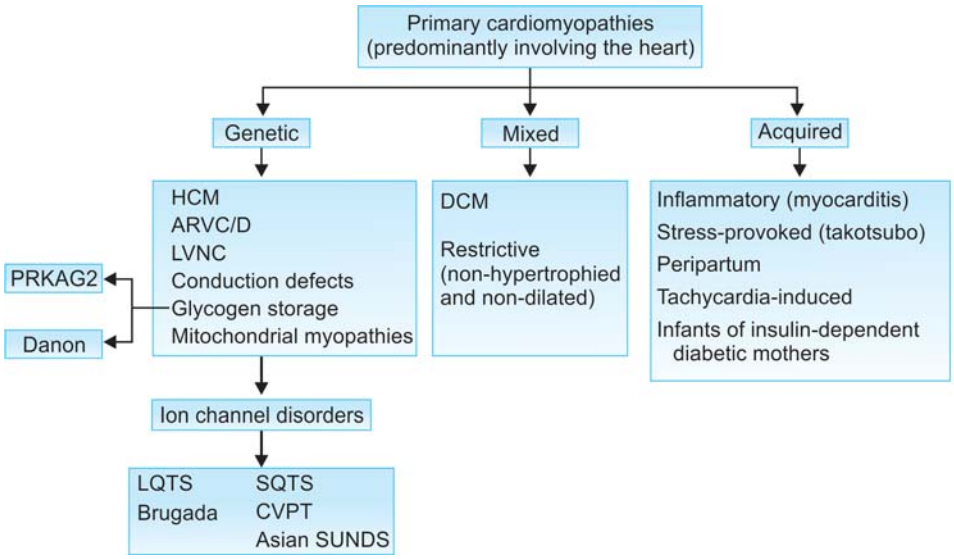
- Epidemiology
- Pathology
  - Postmortem Examination
  - Histological Examination
- Etiology
  - Ischemic versus Nonischemic Etiology
  - Myocarditis
  - Familial Dilated Cardiomyopathy
  - Tachycardia-induced Cardiomyopathy
  - Stress-induced Cardiomyopathy
  - Dilated Hypokinetic Evolution of Hypertrophic Cardiomyopathy
  - Hemodialysis and End-stage Renal Failure
  - Cirrhosis
  - Nutritional Deficiency
- Prognosis
- Predictors of Mortality

DEFINITION

Despite the frequent use of the term "cardiomyopathy" in daily clinical practice, there has been an interesting evolution in reaching a consensus on how cardiomyopathies should be defined.

The original restrictive definition,[1] suggested by the World Health Organization (WHO) in 1980[1] as "heart muscle disease of unknown cause", was changed in 1995 by the WHO International Society and Federation of Cardiology Task Force on the definition and classification of cardiomyopathies[2] to the following "diseases of the myocardium associated with cardiac dysfunction". This newer definition introduced the term "specific cardiomyopathies" under which various etiologies, such as ischemic, hypertensive and valvular, were defined. A more recent definition and classification of the cardiomyopathies[3] was proposed in a scientific statement published by the American Heart Association (AHA) (Flow chart 1) in which cardiomyopathies were defined as "a heterogeneous group of diseases of the myocardium associated with mechanical and/or electrical dysfunction that usually (but not invariably) exhibit inappropriate ventricular hypertrophy or dilatation and are due to a variety of causes that frequently are genetic. Cardiomyopathies either are confined to the heart or are part of

FLOW CHART 1: Classification of cardiomyopathies



(Abbreviations: HCM: Hypertrophic cardiomyopathy; DCM: Dilated cardiomyopathy; ARVC/D: Arrhythmic right ventricular cardiomyopathy/dysplasia; LVNC: Left ventricular non-compaction; LQTS: Long QT syndrome; SQTS: Short QT syndrome; CVPT: Catecholaminergic polymorphic ventricular tachycardia; SUNDS: Sudden unexpected nocturnal death syndrome)

generalized systemic disorders, often leading to cardiovascular death or progressive heart failure-related disability."

The AHA definition represented a departure from prior effort by adopting a genomic and molecular basis for the classification. It specifically excluded ventricular dysfunction that is secondary to other cardiovascular abnormalities such as hypertension, valvular and ischemic. This later approach was supported by the European Society of Cardiology's working group on myocardial and pericardial disease in 2007 by defining cardiomyopathy as "a myocardial disorder in which the heart muscle is structurally and functionally abnormal in the absence of coronary artery disease, hypertension, valvular disease and congenital heart disease sufficient to explain the observed myocardial abnormality".[4]

EPIDEMIOLOGY

The determination of the true incidence and prevalence of idiopathic dilated cardiomyopathy (IDC) is hampered by the lack of unified definition, the difficulty in establishing the absence of coronary artery disease and other causes of dilated cardiomyopathy (DCM), and the under recognition of asymptomatic cases.

The reported incidence varies between 2.5 and 8.3 cases per 100,000 of the population.[5-10] The risk of IDC is 2.5 fold higher in African Americans even after adjusting for socioeconomic factors.[11,12] It should be mentioned that a higher heart failure (HF) incidence in blacks compared to whites has been reported in several population studies.[13-15] Furthermore, among young population (mean age 25 years) of 2,477 white and 2,636 blacks in the coronary artery risk development in young adults (CARDIA) study, HF developed over 20 years of follow-up in 27 participants, all but one were black with a cumulative incidence before age 50 of 1.1% in black women, 0.9% in black men and 0.08% in white women.[16] These findings lend support to the earlier studies documenting higher incidence of IDC in blacks.[11,12]

PATHOLOGY

POSTMORTEM EXAMINATION

The major morphologic feature of IDC is dilation of both ventricular cavities with the left ventricle typically more severely affected than the right; in addition, both atria are usually dilated. The large end systolic ventricular volume coupled with poor contractility contributes to the relative stasis of blood and the formation of intracavitary thrombi. Likewise, dilation of atria along with the poor atrial emptying leads to the formation of thrombi in atrial appendages. Thrombi are found most frequently in the left ventricle followed by the right ventricles, right atrial and left atrial appendages.[17]

The weight of the heart is always increased (mean 615 gm in men and 551 gm in women) due to massive dilation. Although the ventricular wall thickness may be increased, the degree of hypertrophy is less than expected given the severe dilatation, and the development of hypertrophy presumably plays a beneficial role by reducing wall stress and limiting further dilation.

The leaflets of cardiac values are normal; the margins of the leaflets of the mitral and tricuspid valves may be focally thickened by fibrous tissue, and annular dilatation is usually the cause of mitral and tricuspid regurgitation.

The coronary arteries are normal and although atherosclerotic plaques may be present, no narrowing of any of the epicardial coronary arteries more than 75% in cross-sectional area is present.[17]

HISTOLOGICAL EXAMINATION

Microscopic examination reveals marked variation in myocyte size with extensive areas of interstitial and perivascular fibrosis involving mainly the left ventricular (LV) subendocardium.[18]

Ultrastructural studies demonstrate nonspecific changes including cellular edema, increased number of lipid chaplets, lipofuscin granules and lysosomes, dilatation of the tubules of the T system and sarcoplasmic reticulum, myofibrillar damage, increased size and irregularity of contour of the nuclei, increased ribosomes, enlargement of the Golgi zone and mitochondrial alterations.[18]

ETIOLOGY

ISCHEMIC VERSUS NONISCHEMIC ETIOLOGY

The consensus across the Atlantic[3,4] in discouraging the use of the term "ischemic cardiomyopathy" has done little to change its popularity, frequent use by authors and acceptance by medical journals. The general perception is that for a similar impairment of LV systolic function, the management is likely to be similar regardless of etiology with the exception of the role of revascularization when epicardial coronary artery disease is present. Identifying differences between ischemic and nonischemic systolic HF is a challenging task because the definition is often made based on clinical presentation and even when coronary arteriogram is performed, the consensus, on how nonischemic cardiomyopathy should be defined, is lacking. It is unlikely that the presence of more than or equal to 75% stenosis in the right coronary artery, for example, provides a satisfactory explanation for severe impairment of LV systolic function. Likewise, the presence of non-obstructive coronary artery disease could have been associated with prior infarction. A proposed definition of assigning an ischemic etiology to the impairment of ventricular systolic function requires the presence of more than or equal to 75% stenosis of left main or proximal left anterior descending or the presence of more than or equal to 75% stenosis of two or more epicardial vessels.[19] However, coronary microvascular and endothelial dysfunction have been well documented in patients with DCM.[20] It should be noted that the presence or absence of regional wall motion abnormalities alone does not establish the presence or absence of an ischemic etiology.[21,22]

Cardiac magnetic resonance imaging (CMRI) can help in differentiating ischemic from nonischemic etiology of LV dilatation using two criteria: regional wall motion abnormalities with reduction in wall thickness combined with hyperenhancement extending from the subendocardium up to the epicardium confined to the perfusion territories of the coronary arteries.[23]

Clinical Course

The clinical presentation may be similar in ischemic and nonischemic HF but symptoms appear at a younger age in patients

with DCM.[24,25] Chest pain, including typical angina, may be present in 40% of patients with DCM and should not be used as a determinant of etiology.[24,25] It may indicate, however, a more limited coronary vascular reserve;[26] otherwise, patients may present with the usual symptoms and signs of HF including arrhythmias and sudden death. One notable difference in the clinical course is the consistent finding of worse prognosis in patients with ischemic etiology of systolic HF[27-31] that may be secondary to recurrence of ischemic events leading to more impairment in ventricular systolic function and/or potentially more arrhythmic events. Severe impairment of myocardial blood flow has been correlated with poor prognosis in patients with IDC.[31]

Response to Treatment

Earlier reports suggesting a differential response to various medications based on etiology (ischemic vs nonischemic) were based on studies that lacked either statistical power or rigorous definition of ischemic versus non-ischemic etiology.[32] Contemporary trials with angiotensin-converting enzyme inhibitors,[33] angiotensin-receptor blockers,[34] beta-blockers,[35] aldosterone antagonists[36] and biventricular pacers[37,38] demonstrated an overall similar effect on outcome regardless of the etiology of ventricular dysfunction. Notable differences, however, appear to be present with the use of synchronization, cardioverter defibrillation (ICD) and the inodilator milrinone.

The benefits of ICD were clearly established in patients with systolic HF of ischemic etiology.[39,40] Individual trials[41-43] in patients with non-ischemic etiology, however, failed to show significant reduction in total mortality, although a meta-analysis of five trials[44] demonstrated 31% mortality reduction. Considering the limitations of meta-analysis; however, the evidence favors the existence of a more favorable response to ICD in patients with ischemic etiology.

There is a strong evidence from two randomized trials, the multicenter InSync randomized clinical evaluation (MIRACLE)[45] and the cardiac resynchronization-heart failure (CARE-HF)[46] that sustained reverse remodeling occurs to a much larger extent in patients with nonischemic etiology. It is interesting to note that the differential effect on remodeling was not associated by any differences on mortality suggesting that the mechanism for survival benefit was not related to improvement in LV function but perhaps to favorable effect on substrates for arrhythmias.[46]

A retrospective analysis[47] of the outcomes of a prospective trial of intravenous milrinone for exacerbations of chronic heart failure (OPTIME-CHF) in which 949 patients with decompensated systolic HF were randomized to milrinone versus placebo demonstrated that milrinone infusion was associated with an increase (42%) versus placebo (36%), in the composite of death or rehospitalization, while the opposite was noted in the non-ischemic patients. Thus, a differential effect for milrinone appears to be present based on etiology and the speculated mechanism is acceleration of HF progression in hibernating myocardium.[48]

MYOCARDITIS

Myocarditis is defined as an inflammation of the myocardium and a broad array of conditions have been associated and implicated as the cause of myocarditis (Table 1).[49]

TABLE 1

Causes of myocarditis

Viral agents and disorders
Adenovirus
Arbovirus
Coxsackievirus B
Cytomegalovirus
Dengue virus
Echovirus
Epstein-Barr virus
Hepatitis C
Herpes virus
Human immunodeficiency virus
Influenza virus
Mumps
Parvovirus B19
Poliomyelitis
Rabies
Rubella
Varicella
Variola
Yellow fever
Bacterial agents and disorders
Brucella
Chlamydia
Cholera
Clostridia
Diphtheria
Haemophilus
Legionella
Meningococcus
Mycoplasma
Neisseria gonorrhoeae
Psittacosis
Salmonella
Staphylococcus
Streptococcus
Tetanus
Tuberculosis
Tularemia
Spirochetal disorders
Leptospirosis
Lyme disease
Relapsing fever
Syphilis
Mycotic agents and disorders
Actinomyces
Aspergillus
Blastomyces
Candida
Coccidioidomycosis
Cryptococcosis
Histoplasma
Mucormycosis
Nocardia
Sporotrichosis
Rickettsial diseases
Q fever
Rocky mountain spotted fever
Typhus
Protozoal diseases
African sleeping sickness
Amebiasis
Chagas disease
Leishmaniasis
Malaria
Toxoplasmosis
Helminthic agents and diseases
Ascariasis
Echinococcosis
Filariasis
Paragonimiasis
Schistosomiasis
Strongyloides
Trichinosis
Cardiotoxins
Alcohol
Anthracyclines
Arsenic
Carbon monoxide
Catecholamines
Cocaine
Heavy metals
Causes of hypersensitivity reactions
Antibiotics
Clozapine
Diuretics
Insect bites
Lithium
Snake bites
Tetanus toxoid
Mesalamine
Systemic disorders
Celiac disease
Connective tissue disorders
Hypereosinophilia
Kawasaki disease
Sarcoidosis
Thyrotoxicosis
Wegener granulomatosis

The Dallas histopathological criteria were proposed in 1986, requiring the presence of inflammatory infiltrate with (definite) or without (borderline) associated myocyte necrosis.[50] Evidence for substantial interobserver variability[51] and sampling errors[52] has prompted the consideration of newer techniques such as cell-specific immunoperoxidase stains for surface antigens and anti-human leukocyte antigen for the diagnosis.[53-56] It is likely that the majority of cases of myocarditis result from viral infection.[57,58] Parvovirus B19, coxsackievirus, human herpesvirus-6 (HHV-6) type B and adenovirus have been detected in 37%, 33%, 11% and 8% of endomyocardial biopsies, from young adults histologically proven to have acute myocarditis.[58] There has been a change in the viruses detected in the heart from enterovirus in the 1980s to adenovirus in the 1990s and parvovirus at the present time.[59,60]

Hepatitis C virus and human immunodeficiency virus have also been found after heart transplantation, herpesviruses such as Epstein-Barr virus and cytomegalovirus have been associated with myocarditis.[59,60]

Studying murine models has led to the understanding that myocarditis is a continuum of three distinct disease processes.[61] The first phase is viral infection, during which viruses enter into the host through the gut (enteroviruses) or the respiratory tract (enteroviruses and adenoviruses) and reside in the immune cells of the lymphatic system, before being transported to the heart where they proliferate. This phase concludes with the activation of the host immune system. However, if host immune activation continues despite elimination of the virus, it leads to autoimmune disease initiating the second phase characterized by T cells and cytokine activation.[61] The T cells destroy virus infected cells by either cytokine production or perforin-mediated cell cytolysis. A major mediator of immune activation and its maintenance is activation of cytokines including tumor necrosis factor-α (TNF-α) and interleukin (IL)-1 and IL-6.[62]

T-cell and cytokines mediated myocyte damage leads to impairment of contractile function and the third phase, which is DCM. There is evidence to implicate viruses as directly contributing to myocyte apoptosis, as the presence of viral persistence has been associated with much worsening ventricular function. This finding, however, was observed in some[63,64] but not all[65,66] studies.

There is mounting evidence that supports the contribution of autoimmunity to the development of IDC[67] including a higher prevalence of the major histocompatibility complex class II proteins HLA-DR4 and HLA-DQ 4/6 subtypes that interact with CD4+ T-helper cells leading to the activation of B-lymphocytes. In addition, several autoantibodies have been identified, such as myosin autoantibodies, which have been reported to be present in 23–66% of patients with IDC and were correlated with worsening LV systolic function and increased diastolic stiffness. The B1 adrenoreceptor antibodies have been found in 26–46% of patients with IDC and were associated with increased all cause mortality and sudden death.[67] Interestingly, they have been found to induce a dose-dependent increase in cardiomyocytes apoptosis.

The clinical manifestations of myocarditis are highly variable and range from asymptomatic nonspecific electrocardiographic abnormalities to cardiogenic shock or sudden death.[60,68] A history of viral prodrome is variable and has been reported in 10–80% of patients with documented myocarditis,[68] dyspnea and chest pain[69] occur in 72% and 32% respectively.

Giant cell myocarditis should be considered in patients with acute DCM associated with thymoma, autoimmune disorders, ventricular tachycardia or high-grade heart block.[70]

There are no specific biomarkers or features in the electrocardiogram or echocardiogram that establish the diagnosis of myocarditis. The CMRI has been used to localize biopsy sites or as an alternative noninvasive method for diagnosing myocarditis.[71] Using delayed contrast-enhancement imaging, hyperenhancement can be found in 85% of patients with acute myocarditis within 2 weeks of the onset of symptoms[72] and is considered by some as the noninvasive gold standard for diagnosing myocarditis.

At the present time, histopathological confirmation is required[73] and myocardial biopsy should be performed in patients with unexplained, new onset HF of less than 2 weeks' duration with hemodynamic compromise and in patients with unexplained, new onset HF of 2 weeks' to 3 months' duration in the presence of dilated left ventricle and new ventricular arrhythmia or advanced atrioventricular (AV) block and in patients with suspected giant cell myocarditis if they do not show a response to usual care within 1–2 weeks.[73]

The treatment of myocarditis is primarily supportive including the occasional need for ventricular assist devices or heart transplantation. Antiviral therapy is unlikely to be of value considering the difficulty in establishing the diagnosis in the acute viral phase. The role of immunosuppression therapy has been evaluated in several randomized controlled trials and has not been found to be of significant benefit in the acute phase.[74,75] On the other hand, there appears to be a better response in patients with chronic DCM following the acute phase with significant improvement in LV function with immunosuppression (prednisone and azathioprine)[76,77] and interferon beta.[63] The data on the benefit of intravenous gamma globulin are insufficient to recommend their routine use for acute myocarditis.[78]

For giant cell myocarditis, prolongation of transplant-free survival was clearly documented with a combination of cyclosporine and steroids.[70]

FAMILIAL DILATED CARDIOMYOPATHY

The diagnosis of familial dilated cardiomyopathy (FDC) is made when IDC is diagnosed in two closely related family members. Careful screening of first degree relatives indicates that IDC may be familial in 20–48%[79-82] of cases. Rescreening of initially healthy family members demonstrates the development of disease in some[82,83] and the current practice guidelines recommends screening, every 3–5 years, beginning in childhood, and every 1–3 years in adults if a mutation is present[84] (Table 2).

The FDC is predominantly a genetic disease and more than 30 genes causing IDC have been identified (Table 3).

The frequency of which was delineated in a study involving 281 patients with FDC;[85] autosomal dominant (56%), autosomal recessive (16%), x-linked (10%) with different mutations of the dystrophin gene, autosomal dominant with subclinical muscle disease (7.7%), autosomal dominant with conduction disease (2.6%) and rare unclassifiable (7.7%).

TABLE 2

Clinical screening of disease

It is recommended that clinical screening consists of:
• History (with special attention to heart failure symptoms, arrhythmias, presyncope and syncope)
• Physical examination (with special attention to the cardiac and skeletal muscle systems)
• Electrocardiogram
• Echocardiogram
• CK-MM (at initial evaluation only)
• Signal-averaged electrocardiogram (SAECG) in ARVD only
• Holter monitoring in HCM, ARVD
• Exercise treadmill testing in HCM
• Magnetic resonance imaging in ARVD
(Level of Evidence = B) (Abbreviations: CK-MM: Creatine kinase, muscle; HCM: Hypertrophic cardiomyopathy; ARVD: Arrhythmic right ventricular dysplasia)

TABLE 3

Genetic causes of dilated cardiomyopathy

Gene	*Protein*	*OMIM*	*Frequency familial*	*Frequency, sporadic*	*Comments*	*References*
Autosomal Dominant FDC Dilated Cardiomyopathy Phenotype						
ACTC	Cardiac actin	102540	Rare	Rare		
DES	Desmin	125660	?	?		
LMNA	Lamin A/C	150330	7.3%	3.0%	5.5% overall (41/748,6 studies, see text)	
SGCD	δ-sarcoglycan	601411	Rare	Rare		
MYH7	β-myosin heavy chain	160760	6.3%	3.2%	4.8% overall (22/455,3 studies)	
TNNT2	Cardiac troponin T	191045	2.9%	1.6%	2.3% overall (15/644,3 studies)	
TPM1	α-tropomyosin	191010	Rare	Rare		
TTN	Titin	188840	?	?		
VCL	Metavinculin	193065	Rare	Rare		
MYBPC3	Myosin-binding protein	600958	?	?		
CSRP3	Muscle LIM protein	600824	Rare	Rare		
ACTN2	α-actinin-2	102573	?	?		
PLN	Phospholamban	172405	Rare	Rare		
ZASP/LDB3	Cypher/LIM binding domain 3	605906	?	?		
MYH6	α-myosin heavy chain	160710	?	?		
ABCC9	SUR2A	601439				
TNNC1	Cardiac troponin C	191040	?	?		
TCAP	Titin-cap or telethonin	604488	Rare	Rare		
SCN5A	Sodium channel	600163	?	?	2.3% overall (11/469,2 studies)	
EYA4	Eyes-absent 4	603550	?	?		
TMPO	Thymopoietin	188380	?	?		
PSEN1	Presenilin 1 / 2	104311	?	?		
PSEN2		600759				
X-linked Familial Dilated Cardiomyopathy						
DMD	Dystrophin	300377				
TAZ/G4.5	Tafazzin	300394				
Autosomal Recessive Familial Dilated Cardiomyopathy						
TNNI3	Cardiac troponin I	191044	?	?		

Genetic testing should be considered for the person most clearly affected in a family to facilitate screening and management, because it increases the likelihood of detecting a relevant mutation.[84,86] The main reason to perform a genetic testing is to more accurately predict the risk of developing DCM in a family member with no clinical evidence of having the disease. The finding of a specific mutation does not in itself guide therapy but may influence the frequency and stringency of presymptomatic screening;[84,86] several gene tests are currently available (Table 4).

TABLE 4

Presymptomatic screening for different genes

Cardiomyopathy phenotype	*Gene tests available*	*Yield of positive results*
DCM	LMNA, MYH7, TNNT2, SCN5A, DES, MYBPC3, TNNI3, TPMI, ACTC,PLN, LDB3, and TAZ.	5.5%, 4.2% 2.9% for LMNA, MYH7, and TNNT2, respectively. All data are from research cohorts

The presence of sinus/AV node dysfunction including first, second and third degree heart block, with or without atrial flutter, fibrillation, tachy-brady syndrome is an indication for genetic testing. Mutations in LMNA gene can cause DCM with conduction disease and portends high risk of sudden death.[87]

Other causes of DC associated with conduction disease and arrhythmias should be kept in mind including cardiac sarcoidosis,[88] giant cell myocarditis,[70] Chaga's disease,[89] arrhythmogenic RV cardiomyopathy[90] and end-stage hypertrophic cardiomyopathy (HCM).[91]

TACHYCARDIA-INDUCED CARDIOMYOPATHY

This is a reversible form of DC that is caused by any rhythm disturbance associated with rapid ventricular rate and is either completely or partially reversible after the normalization of heart rate.

As early as 1913, this entity was recognized initially in a patient with atrial fibrillation and in the past three decades it has been described virtually with all forms of tachycardia. In 1962, experimental tachycardia-induced DC was described.

The time course in animals is well defined with the reduction of cardiac output and systemic arterial pressure after 24 hours of rapid pacing, followed by increased filling and pulmonary artery pressure within a week. Continued hemodynamic deterioration occurs with the development of end-stage HF in 3–5 weeks. The recovery is likewise dramatic with close to normalization of cardiac index and systemic vascular resistance, and significant improvement of left ventricular ejection fraction (LVEF) within 48 hours. Normalization of ejection fraction (EF) occurs in 1–2 weeks. The LV volumes, however, remain elevated 12 weeks after termination of pacing consistent with extensive remodeling.[92]

Postulated mechanisms include depletion of myocardial energy stores, abnormal calcium handling, oxidative stress, angiotensin converting enzyme gene polymorphism and myocardial ischemia.[93]

The management is primarily restoration of a normal heart rate by either pharmacological or interventional approach. In a recent study of symptomatic systolic HF patients with drug refractory atrial fibrillation, pulmonic vein isolation was superior to A–V nodal ablation with biventricular pacing in improving LVEF, 6-minute walk distance and Minnesota Living with HF scores. The LVEF improved in 76% versus 25% of patients respectively.[94]

STRESS-INDUCED CARDIOMYOPATHY

This is a relatively new entity also called takotsubo cardiomyopathy, transient apical ballooning syndrome and broken heart syndrome. It accounts for 2% of ST-segment elevation infarcts and primarily occurs in postmenopausal women (90% of reported cases) who may present with chest pain (68%) or dyspnea (18%); ST-elevation occurs in 82%, T-wave abnormalities in 64% and Q-waves in 32%. The onset of symptoms may often be preceded by emotional (27%) or physical (38%) stress. Despite a marked impairment of LVEF, all patients experience a dramatic improvement with full recovery of most patients. In-hospital mortality is 1.1% and 3.5% experience recurrence.[95]

DILATED HYPOKINETIC EVOLUTION OF HYPERTROPHIC CARDIOMYOPATHY

Hypertrophic cardiomyopathy (HCM) progresses in a small minority of patients to dilated hypokinetic forms.[96,97] The estimated incidence and prevalence is 5–3 per 1,000 patients per year and 4.9%, respectively.[97] A higher association was noted with a younger age of presentation, a family history of HCM or sudden death and greater wall thickness. It is a risk factor for sudden death and warrant placement of cardioverter and it is the most frequent indication for heart transplantation among patients with HCM.[97]

HEMODIALYSIS AND END-STAGE RENAL FAILURE

Impairment of LV systolic function has been identified in one-third of new dialysis patients.[98] In addition to the traditional risk factors for HF, the uremic milieu itself contributes to the development and progression of HF. Biopsies from patients with dilated left ventricles on dialysis demonstrate more severe hypertrophy and disarray compared to patients with comparable degree of LV systolic dysfunction not on dialysis,[99] and the ultrafiltrate and serum of uremic patients have been shown to have negative inotropic effects.[100] Furthermore, renal transplantation results in significant improvement in LV systolic function and HF functional status.[101]

CIRRHOSIS

In a significant number of cirrhotic patients and up to 50% of those undergoing liver transplantation, there is an evidence of cardiovascular dysfunction that include systolic and diastolic dysfunction, inotropic and chronotropic incompetence, peripheral and splanchnic vasodilation and prolonged QT interval.[102,103] The systolic dysfunction has been observed in patients with nonalcoholic causes of cirrhosis and liver transplantation has been reported to normalize exercise capacity and systolic response to stress. The decreased vascular tone, including peripheral and splanchnic vasodilatation, is thought to be related to overproduction of nitric oxide.

Although, the recommended management is to follow the standard guidelines, the value of digitalis beta blockers and angiotensin-aldosterone inhibitors in improving clinical picture and outcome has not been proven.

NUTRITIONAL DEFICIENCY

Several factors contribute to nutritional deficiency in HF including loss of appetite, dietary restriction, social isolation, malabsorption and increased metabolic rate. Selective deficiency of several micronutrients has been associated with impaired systolic function and HF; however, our knowledge of this subject is very limited.[104-106]

Selenium Deficiency

Selenium is an essential trace element (must be supplied by daily diet and its blood and tissue concentrations are extremely low) that is a key component of the antioxidant glutathione peroxidases enzymes.[107] The first reported cases of DC linked to selenium deficiency were reported in northeast China and was attributed to low selenium content in the soil (termed Keshan disease).[108] Subsequently, this form of DCM was described in malabsorption or long-term selenium deficient parenteral nutrition.[109] The main mechanism is thought to be increased oxidative stress.[107] Other possible mechanisms include the role of selenium in thyroid hormone metabolism and in protection against organic and inorganic mercury.[107]

Vitamin D and Calcium

Vitamin D insufficiency could result from inadequate oral intake (exogenous source) or insufficient skin synthesis (endogenous source).The latter requires exposure to UV-B radiation contained in sunlight, and accounts for 80–90% of vitamin D supply. Vitamin D is metabolized in the liver into 25-hydroxyvitamin D and in the kidney into the vitamin D hormone 1,25 dihydroxy-vitamin D (calcitriol). The later step is regulated by parathyroid hormone (PTH).[110] Calcitriol is a primary regulator of intracellular metabolism of calcium which plays a vital role in myocardial contractility and relaxation.[111,112] Also, calcitriol is a regulator of cellular cytokine secretion.[112]

Several lines of evidence support a role for vitamin D insufficiency in the development of HF.[113] In vitro studies have demonstrated several protective effects of calcitriol that counteract the harmful effect of activation of the renin-angiotensin-aldosterone systems, proinflammatory cytokines, hypertrophy and interstitial fibrosis.[114-116]

In vivo studies have confirmed the beneficial effect of calcitriol with the reduction of plasma renin and angiotensin II levels,[117] lowering of blood pressure,[117,118] regression of LV hypertrophy[119] and suppression of proinflammatory cytokines.[120]

There have been several case reports detailing the clinical presentation of systolic HF due to hypocalcemia with subsequent resolution of symptoms as well as restoration of systolic LV function with calcium replacement.[121-125] A double-blind randomized, placebo-controlled trial was conducted in 123 patients with stable systolic HF.[126] Patients were randomized to calcium and vitamin D versus calcium alone. A significant increase in the concentration of the anti-inflammatory cytokines IL-10 was noted in vitamin D group and an improvement in systolic LV function parameters was noted equally in both groups suggesting that vitamin D may exert beneficial effect independent of its effect on calcium.

In another randomized, double blind, placebo-controlled trials in 105 elderly patients with vitamin D insufficiency with a mean age of 79 years, vitamin D did not improve physical function or quality of life despite lowering of B-type natriuretic peptide. It is not clear whether a higher dose than what was given (200,000 at baseline and 10 weeks) could have provided different results.[127]

Vitamin B

Thiamin (vitamin B_1) functions as a coenzyme for macronutrient oxidation and the production of adenosine triphosphate.[128] riboflavin (vitamin B_2) and pyridoxine (vitamin B_6) are also essential cofactors in cellular energy production.[128]

Thiamin deficiency manifests as wet beriberi with DC characterized by vasodilatation and high cardiac output.[129] It is noteworthy that deficiency of vitamin B_1,[130] B_2 and B_6[131] has been reported in one-third of patients with HF. Correction of thiamine deficiency has been associated with improvement in LVEF.[132] The postulated mechanism is inhibition of 16-pyruvate dehydrogenase complex leading to impairment of adenosine triphosphate production, increased cellular acidosis and free fatty acid levels.[129]

Carnitine Deficiency

The normal heart obtains 60% of its energy production from fatty acid oxidation and L-Carnitine is an essential component in the transport of long chain fatty acids into mitochondria.[133] Deficiencies of carnitine are classified as either primary that arise from genetic disorder that cause defective absorption of carnitine, its synthesis, renal handling, or excessive degradation or alteration in its transport to tissues.[133]

Secondary forms are much more common and are caused by genetic diseases that are associated with defects in acyl-CoA metabolism. In patients with acyl-CoA dehydrogenase deficiency, carnitine levels are reduced by 25–50% and are associated with impairment in cardiac contractility.[133]

The results of five randomized double-blind placebo-controlled studies with dosages ranging from 1.5 gm to 6 gm a day have been mixed.[134-138] In one study of 80 patients with DCM, an improvement in exercise, hemodynamics and 3-year survival was noted.

Trace Element Accumulation

In a study of 13 patients with IDC, a substantial increase in mercury, antimony, and lesser increase in gold, chromium and cobalt was identified in LV biopsy specimens when compared to patients with similar systolic impairment of valvular and ischemic etiology as well as to normal subjects.[139] It has been speculated that a preceding viral infection might have been the cause as coxsackie viral infection has been documented to increase accumulation of nickel, cadmium and mercury in the myocardium.[140] The postulated mechanism is interference of heavy metal with cellular activities and the formation of free radicals.[141]

Identification and correction of nutritional deficiency in HF is likely to play a greater role as our understanding of the crucial role that nutritional deficiency may exert on the pathophysiology and development of HF improves. The potential existence of deficiency of several elements should be kept in mind as it may complicate the search for therapeutic intervention. It is interesting to note that a small double-blind randomized trial of 30 patients with systolic HF showed that 9-month administration of a combination of high-dose micronutrients (calcium, magnesium, zinc, copper, selenium, vitamin A, B_1, B_6, B_{12}, C, D, E, folate and coenzyme Q10) has resulted a significant improvement in LVEF and quality of life.[142]

PROGNOSIS

Despite the recent evidence that the prognosis of HF has been improving, it remains a lethal disease. The one year mortality rate for patients with moderate systolic HF selected in clinical trials has declined from 17% to 7%.[143-145] Community HF patients, however, due to their older age and comorbidities have higher mortality rates.[146,147]

In mild-to-moderate HF, sudden death is the most common mode of death; while in advanced HF, pump failure becomes the predominant mode of death.[144] Both, the presence[148] as well as the absence[149] of diurnal variation with morning peak, have been described with sudden death in HF.

The mortality rate in patients with HF increases with the age,[150,151] most likely due to the cumulative exposure to comorbidities as well as the higher prevalence of comorbidities. Women have better[31,152-155] prognosis than men regardless of etiology[154,155] and the more favorable outcome may be related to sex hormones.[156] Mortality rates after hospitalization for HF are lower in blacks as compared to whites.[157]

PREDICTORS OF MORTALITY

Several variables have been associated with increased mortality (Table 5). Identifying these variables help in constructing models for estimating the risk of dying that may facilitate an open discussion with patients and family members about prognosis and their expectations, and potentially influence further management by more appropriate selection of therapies.

TABLE 5

Variables related to prognosis

Demographics
- Age[150, 151]
- Sex[152-155]
- Race/Ethnicity[157]
- Etiology
- Ischemia[27-30]

Comorbidities
- Anemia[164]
- Blood Pressure[166-168]
- Cancer[170,171]
- Cerebrovascular disease[168,170,171]
- Cirrhosis[168,170]
- COPD[168,170,171,176]
- Dementia[170,171]
- Depression[176,180,181]
- Diabetes[184,185]
- Mobility[171]
- Renal Impairment[188,189]
- Sleep Apnea[191]
- Smoking[192]
- Weight loss[194]

Clinical Presentations
- Body mass index[197]
- Decreased systolic pressure[166-169,170]
- Dry cough[181]
- Duration of symptoms[200,201]
- Edema[181]
- Fatigue[204]
- Increased JVP[181,206]
- NYHA[208]
- Pulse pressure[211,212]
- Rales[181,214]
- RR[170,216]
- Syncope[218]
- Tachycardia[168,170,221]
- Temperature[224]
- Third heart sound[206]

Chest X-ray
- Cardiothoracic ratio[229]

Electrocardiographic
- Atrial fibrillation[232]
- Decreased HR variability[234,235]
- QRS width[237]
- T-wave alternans[239]
- Tachycardia[242]
- Ventricular arrhythmia[245,246]

Imaging
- Cardiac Magnetic Resonance

Echocardiographic
- LA size[251,252]
- LA volume[254]
- LVEDD[256]
- LVEDVI[258]
- LVEF[252]
- LVESD[252]
- LVESDI[182]
- LV mass[252]
- Mitral acceleration time[264]
- Mitral annulus velocity[266]
- Mitral deceleration time[182]
- Mitral E/Ea[269,270]
- Pulmonary artery pressure[182,272]
- RA volume index[274]
- RVEDD[235]
- RVEF[182]
- Vena contracta width[258]

Hemodynamics
- CO[281,282]
- LVEDV[283]
- LVEF[285]
- LVESV[285]
- LVSWI[288]
- PAD[158]
- PAS[159]
- PCWP[160]
- Right atrial pressure[161]
- Impaired coronary blood flow[31]

Exercise Testing
- Blood pressure response[162]
- Delayed increase in VO_2[163]
- End-tidal carbon dioxide at rest[165]
- End-tidal carbon dioxide during exercise[169]
- Heart rate recovery[172,173]
- Oscillatory ventilation[174]
- Oxygen uptake slope[175]
- Peak exercise cardiac power output[177]
- Peak VO_2[178,179]
- Recovery ventricular ectopy[182,183]
- 6 minute walk[186]
- VE/VCO_2[187]
- VO_2 Kinetics[190]

Biomarkers
- Adenopectin[193]
- Adrenaline[195]
- *Albumin*[196]
- Albuminuria[198]
- Aldosterone[199]
- Angiotensin II[195]
- ANP[202]
- Asparate transaminase[203]
- Big endothelin[205]
- Bilirubin[207]
- BNP[209,210]
- BUN[213]
- Carbohydrate Antigen (CA) 125[215]
- Cholesterol[217]
- Copeptin[219,220]
- Cortisol[222,223]
- CRP[225]
- Cystatin C[226,227]
- Dehydroepiandrosterone (DHEAS)[228]
- Endothelin[230]
- Erythrole Sedimentation Rate[231]
- Estradiol[233]
- Galectin-3[236]
- Growth differentiation factor – 15[238]
- Heart-type fatty acid binding protein[240,241]
- HS – Troponin T[243,244]
- ICAM-1[247]
- IL-2[248]
- IL-6[249]
- IL-10[250]
- Impaired insulin sensitivity[253]
- Insulin-like-growth factor-1 (IGF-1)[255]
- Magnesium[257]
- Matrix metalloproteinases-2 (MMPs)[259]
- Matrix metalloproteinases-3 (MMPs)[260]
- Mid-regional pro-adrenomedullin (MR-proADM)[261]
- Mid regional pro ANP[262]
- Myosin light-chain-1[243,263]
- Norepinephrine[265]
- Osteoprotegerin[267]
- P III NPi amnioterminal propeptide of type III collagen[268]
- Pentraxin[271]
- Pro BNP[273]
- P-Selectin[275]
- Red cell distribution width (RCDW)[276,277]
- Renin[278]
- Resistin[279]
- Sodium[280]
- ST_2[278]
- Telomere length[284]
- Tenascin-C[286]
- Tissue inhibitor of metalloproteinases[287]
- TNF- α[289]
- Total testosterone[228]
- Troponin I[290]
- Troponin T[291]
- Unocortin - I[292]
- Uric Acid[293]
- Urinary kidney injury molecule-1 (KIM-1)[294]
- Von Willebrand factor[295]
- Emotional Support[296]
- Lower Socioeconomic Status[297]

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Chapter 82

Restrictive and Obliterative Cardiomyopathies

G Vijayaraghavan, S Sivasankaran

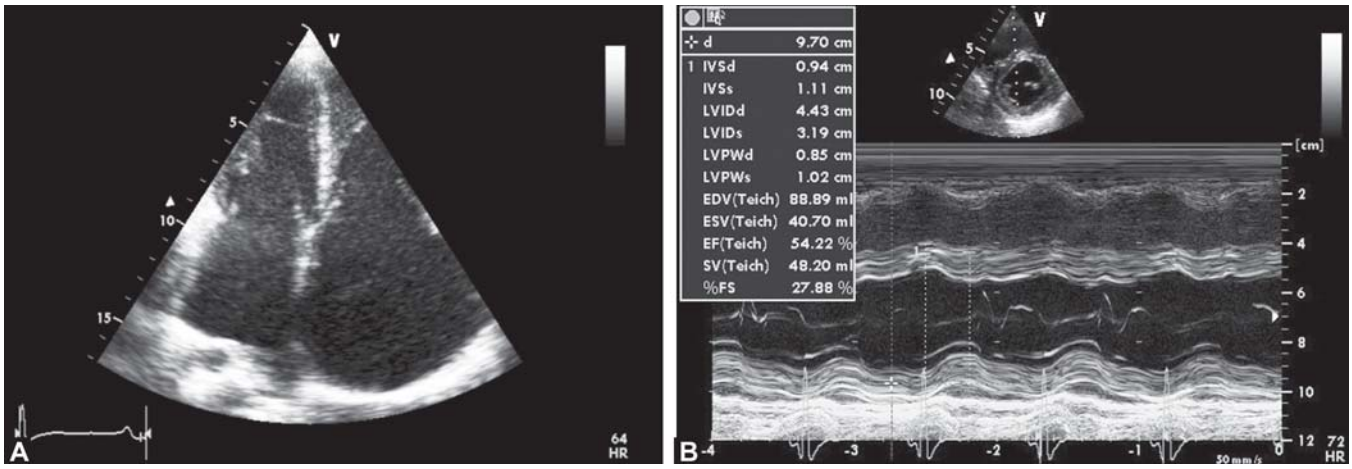
Chapter Outline

- Restrictive Cardiomyopathies
- Tropical Endomyocardial Fibrosis (Davie's Disease)
  - Definition
  - Epidemiology
  - Natural History
  - Clinical Features
- Right Ventricular Endomyocardial Fibrosis
  - Hemodynamics
- Left Ventricular Endomyocardial Fibrosis
  - Hemodynamics at Cardiac Catheterization
  - Angiographic Diagnosis of EMF
- Loeffler's Endocarditis
- Hemochromatosis
- Idiopathic Restrictive Cardiomyopathy
- Other Forms of Cardiomyopathies

INTRODUCTION

Cardiomyopathies with systolic or diastolic heart failure contribute significantly to cardiovascular morbidity and mortality. Restrictive and obliterative cardiomyopathies are characterized by impaired ventricular filling with normal ventricular wall thickness and systolic function.[1,2] They are the best examples of the syndrome of 'heart failure with normal ejection fraction' (HFNEF)[3] and can be recognized by near normal ventricular size and ejection fraction with abnormal diastolic function and dilated atrial chambers (Figs 1A and B). Unlike dilated and hypertrophic cardiomyopathies, where the definition is morphological, the definition of restrictive cardiomyopathy is based on the hemodynamic abnormality. Left ventricular (LV) involvement produces pulmonary venous congestion and dyspnea, while the right sided disease presents with signs of systemic venous congestion like jugular venous distension, tender hepatomegaly and pedal edema. Over a period of time, atrial fibrillation with thromboembolic episodes leads to a rapid downhill course. Prognoses of individuals diagnosed with primary restrictive cardiomyopathies are worse than the more common variety of diastolic heart failure, unless they receive a cardiac transplant.[4,5] By and large, a majority of the restrictive cardiomyopathies are secondary to systemic disorders like amyloidosis, scleroderma, sarcoidosis, hemochromatosis, eosinophilic heart disease or following irradiation treatment.

Myocardial relaxation abnormalities, coupled with interstitial fibrosis and calcification, form the fundamental abnormality of restrictive cardiomyopathies. The pressure volume loop of restrictive physiology is essentially shifted upward and to the left.[3,6,7] Compliance of the ventricle reflects the distensibility or increase in volume per unit increase in distending pressure.



FIGURES 1A AND B: Two dimensional (A) and M-mode (B) echocardiogram from a patient with restrictive cardiomyopathy who presented with congestive heart failure. Note the normal ventricular dimension, wall thickness and function, dilated atrial chambers and near normal looking atrioventricular valves, normal systolic function

More the restriction, lesser is the compliance and higher the pressure required for ventricular filling. This abnormality of restrictive filling reflects as a higher diastolic pressure for a given ventricular volume. This leads to passive venous congestion. The myocardium, which can no longer benefit from the Frank-Starling mechanism, heavily depends on the atrial booster function and also on the rate and rhythm to improve the cardiac output.[7] The ventricle fills rapidly in the early filling phase, which is halted abruptly in mid-to-late diastole so that the ventricular stroke volume is almost fixed. Cardiac output can be increased by an increase in heart rate but becomes counterproductive due to shortened filling period. Chronically decreased cardiac output leads to cardiac anasarca. Symptoms of any associated systemic disorder may also be present.[8,9]

RESTRICTIVE CARDIOMYOPATHIES

Restrictive cardiomyopathies are classified as 'primary' when the heart alone is affected and 'secondary' when it forms part of a systemic disorder or due to a known cause or association. In this discussion, we limit ourselves to three typical syndromes of restrictive or obliterative cardiomyopathies, namely (1) endomyocardial fibrosis (EMF), (2) eosinophilic heart disease and (3) idiopathic restrictive cardiomyopathy. The other common disorders presenting as diastolic heart failure are disorders of the pericardium, infiltrative or storage diseases like amyloidosis and sarcoidosis and post-radiation syndrome. These individual disorders are discussed in the respective chapters. Table 1 shows the recent modification of classification of cardiomyopathies, as applicable to restrictive heart diseases.[10,11]

Restrictive cardiomyopathies form 5% of the pediatric cardiomyopathies and there is an increase in its prevalence as the age advances.[12,13] Children and adults usually present with episodes of breathlessness due to pulmonary venous congestion, which gets mistaken as reactive airway disease. This soon progresses to pulmonary arterial hypertension and congestive cardiac failure. Tachycardia and atrial fibrillation are poorly tolerated and the individual gets admitted with pulmonary edema, worsening heart failure or thromboembolic episodes. Development of atrioventricular valve regurgitation by involvement of the valve apparatus worsens the symptoms and abbreviates the natural history. The late stage of the disease is dominated by the development of ventricular systolic dysfunction, complex ventricular arrhythmias and heart blocks leading to sudden cardiac death, which occasionally could be the first manifestation.

TABLE 1

Restrictive cardiac disorders

- Primary/Idiopathic restrictive cardiomyopathy
- Secondary restrictive disorders:
  - Infiltrative disorders: Amyloidosis
  - Endomyocardial: EMF and Loeffler's endocarditis (hypereosinophilic syndromes)
  - Inflammatory: Sarcoidosis, post-irradiation syndromes
  - Storage diseases: Hemochromatosis, Fabry's disease, glycogen storage diseases
  - Neuromuscular diseases
  - Connective tissue diseases and disorders (scleroderma, pseudoxanthoma elasticum)

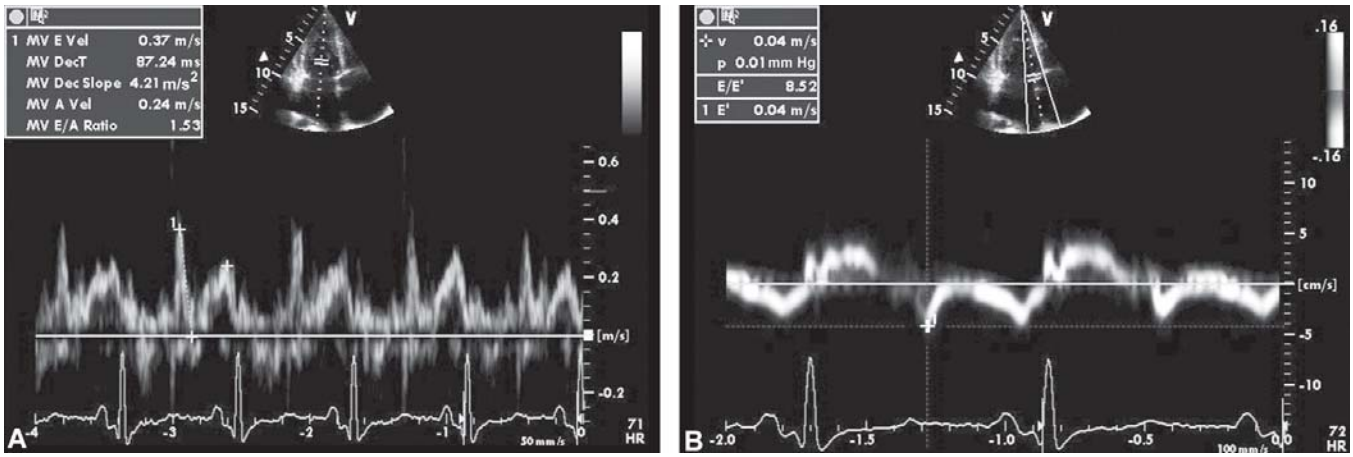
Physical examination reveals features of pulmonary hypertension and congestive cardiac failure with mild cardiomegaly or near normal heart size. Third heart sound in gallop rhythm is the most common physical finding followed by accentuated pulmonary component of the second heart sound. Systolic murmurs of atrioventricular valve regurgitation are a common finding.[12] Chest X-ray shows signs of pulmonary venous and arterial hypertension with atrial dilatation. Myocardial calcification is characteristic of EMF. Electrocardiogram may show biatrial enlargement and non-specific ST-T changes. Two dimensional echocardiography and Doppler recordings help to document the normal ventricular dimensions, systolic function, absence of myocardial hypertrophy and atrial dilatation and features of systemic venous congestion (Figs 1A and B).[6] Complications, like pericardial effusion and sluggish circulation in the cardiac chambers, presenting as smoke with thrombus formation can be documented in the late stages. Some clues to the etiology of the disease may be recognized like the granular sparkling appearance of the myocardium and atrial septal thickening in amyloidosis, endocardial thickening and thrombus formation in eosinophilic endocardial disease, and EMF. Real time three dimensional echocardiography and radionuclide studies can precisely measure the volume of the chambers. Color Doppler echocardiography helps to quantitate the atrioventricular valve regurgitation and color M-mode echocardiography demonstrates the restrictive inflow filling pattern as reduction of flow propagation velocity of less than 40 cm/sec.

The four important Doppler features of restrictive filling are:[6]

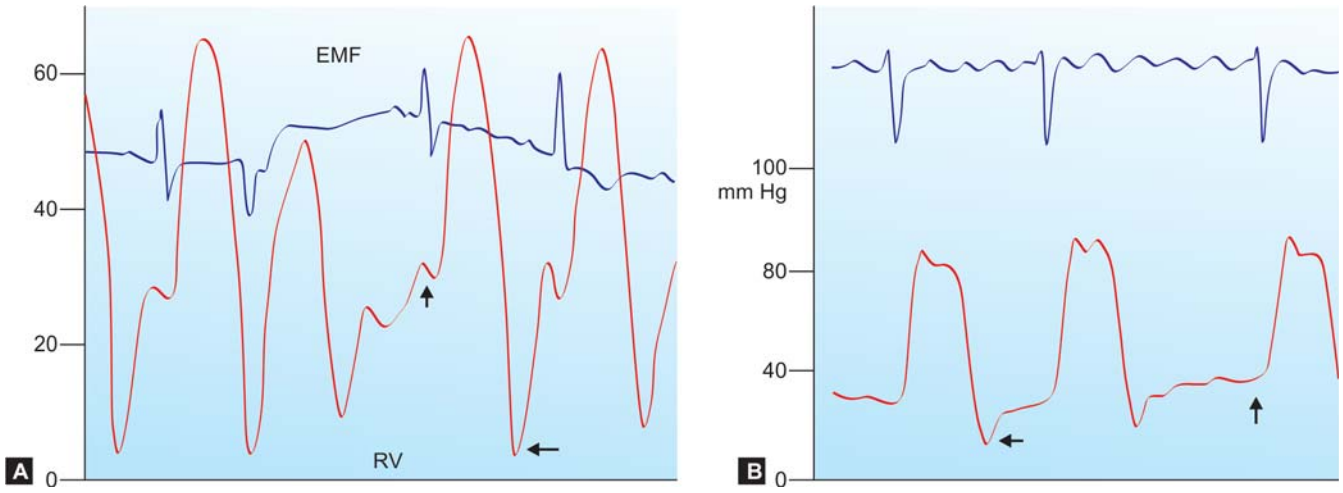
1. Large early filling wave with E/A ratio more than two (Fig. 2).
2. Short isovolumic relaxation time less than 60 milliseconds.
3. Short deceleration time less than 150 milliseconds (Figs 2A and B).
4. Pulmonary venous flow showing large atrial flow reversal and systolic to diastolic wave ratio less than 0.5.

The typical hemodynamic signature of restrictive physiology is the square root sign seen in the ventricular pressure tracings[8] (Figs 3A and B). The rapid short early diastolic filling is followed by the steep elevation of diastolic pressures. An inability to fill further is reflected as the square root sign of the pressure tracing in ventricular diastole. Atrial systole further elevates the end-diastolic pressures, at times opening the pulmonary valve during late diastole (Figs 4A and B). Restrictive cardiomyopathies affecting the left side are characterized by elevated pulmonary artery pressures of more than 50 mm of systolic pressure. The upward shift of the pressure volume curve elevates the dip diastolic pressures. However, right ventricular (RV) end-diastolic pressure will remain less than one-third of the systolic pressures.[8]

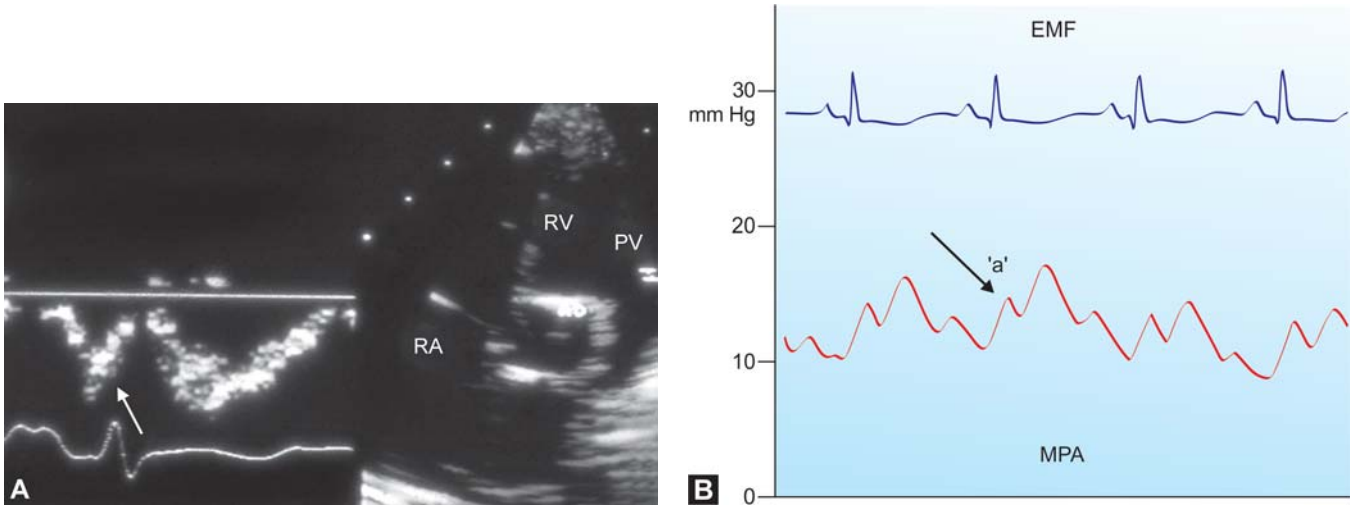
The common differential diagnosis of restrictive cardiomyopathy is the pericardial disorder of constriction, where the ventricular function is restricted from outside and the hemodynamic outcome of restricted cardiac output dominates the clinical picture.[8] Nevertheless, the pericardial restraint usually involves the whole heart, except in rare situations of localized constriction. The rigid pericardial chamber no longer transmits intrathoracic pressure changes of respiration to the cardiac chambers. The marked fall in the inspiratory filling of



FIGURES 2A AND B: Typical Doppler filling patterns in restrictive cardiomyopathy. (A) Note the tall mitral early filling wave (E) and short deceleration time—87.24 msec. (B) Shows the tissue Doppler velocity of the medial mitral annulus showing small S waves



FIGURES 3A AND B: Typical hemodynamic patterns of right and left ventricular pressure tracings in EMF with dip and plateau pattern, elevated dip diastolic pressures (side arrows) and end diastolic pressures (upward facing arrows). Right ventricular pressure tracing shows absence of post-ectopic potentiation, and the left ventricular pressure tracing shows no 'a' wave impression because of atrial fibrillation



FIGURES 4A AND B: (A) Pulse Doppler across the pulmonary valve and (B) pulmonary artery pressure tracing showing presystolic forward flow because of atrial systole (arrow)

the left ventricle leads to pulsus paradoxus, which refers to the weak arterial pulse during inspiration when the jugular venous pressure appears to increase. The intracardiac pressure studies show equalization of diastolic pressures of various cardiac chambers as well as the pulmonary artery. In restrictive cardiomyopathy, these pressures can show variation of more than 5 mm Hg. Mitral flow propagation velocity (color M-mode echocardiography) of more than 100 cm/sec and mitral annular early diastolic velocity of more than 10 cm/sec and normal S waves are characteristic of constrictive pericarditis. Electron beam computed tomography and various modalities of magnetic resonance imaging (MRI) are also useful to differentiate constrictive pericarditis from restrictive cardiomyopathy and to identify the cause for myocardial restriction.[14] But, at times, the extensive involvement of visceral pericardium can result in restrictive features and rarely both disorders can coexist.[15]

The natural history of restrictive cardiomyopathy follows that of the underlying disorder.[13] The younger the patient worse is the New York Heart Association (NYHA) class and worse is the outcome.[16,17] Development of atrioventricular valve regurgitation and atrial fibrillation portends a downhill course. The treatment of restrictive cardiomyopathy is largely symptomatic with diuretics and aldosterone antagonists. The rhythm abnormalities are treated on their own merits with pacemakers, rate control measures and adequate anticoagulation.[18] Intractable cardiac failure is an indication for cardiac transplantation.[4] The systemic causes, like amyloidosis and eosinophilia, when adequately treated in the early stages can cause reversal of the restrictive physiology.[19,20] Significant atrioventricular valve regurgitation requires valve replacement or repair with endocardectomy.[21]

TROPICAL ENDOMYOCARDIAL FIBROSIS (DAVIE'S DISEASE)

Tropical EMF is a form of restrictive cardiomyopathy commonly found in some parts of the tropics and sporadically in other parts of the world.[22-24] Arthur Williams in 1938, while working in Uganda, published an account of two cases of mitral incompetence and cardiac failure with necropsy findings of large patches of fibrosis affecting the ventricular walls. In 1946, at a meeting of the British Cardiac Society, Bedford and Konstam, reviewed necropsy findings in West African soldiers who died of heart failure.[25] They demonstrated extensive subendocardial fibrosis without appreciable signs of inflammation. It was Davies and his coworkers, Donald Ball and Arthur Williams, who attempted clinico-pathological association toward strong suspicion of the diagnosis during life and named it EMF.[26] They correlated mitral incompetence with left sided lesions, and tricuspid incompetence with right sided lesions. During the 1960s similar reports appeared in the literature from many parts of South India especially the state of Kerala and also from Bahia in Brazil.[27] It was interesting to note that all these regions were close to the equator and the disease was concentrated among the poor people. The EMF occurs primarily in the subtropical regions of Africa but is also encountered in tropical and subtropical regions elsewhere in the world, including areas in India and South America that are within 15° of the equator (Fig. 5). In equatorial African nations, such as Nigeria, EMF is the fourth most common cause of heart disease among adults, and accounts for 22% of incidence of heart failure in Nigerian children. The EMF is the most common type of restrictive cardiomyopathy in tropical countries.

DEFINITION

The EMF is an obliterative cardiomyopathy characterized by fibrotic thickening and obliteration of either right ventricular endomyocardial fibrosis (RVEMF), left ventricular endomyocardial fibrosis (LVEMF) or both ventricles endomyocardial fibrosis (BVEMF) with a predilection to selectively involve the ventricular apices and inflow region and sparing the outflow tract.[24] The fibrotic process does not involve the valve leaflets, the atria, or the great vessels, and extra cardiac involvement is



FIGURE 5: Map of the world showing the geographic distribution of places which have reported endemic cases of endomyocardial fibrosis

not known. The involvement of the subvalvar apparatus in the fibrotic process plasters and hinders the leaflet mobility leading to progressive regurgitation.[22,28]

EPIDEMIOLOGY

One of the recent reviews summarizes the epidemiology of 2,400 cases reported in literature over the last 60 years.[24] The disease in Uganda has bimodal peak at 10 and 30 years. Childhood disease affects both boys and girls equally. Adult onset disease affects women twice as common whereas it is the reverse in Nigeria. The state of Kerala has one of the largest reported series of cases from India.[28] Infiltrative and genetic varieties of restrictive cardiomyopathies are also encountered at these referral hospitals.[29,30] However, EMF formed the vast majority in these studies and in about a third no definite reason could be attributed and hence has been classified as idiopathic restrictive cardiomyopathy. Idiopathic restrictive cardiomyopathy can be recognized in utero and at birth, but no case of EMF is identified at that age; youngest reported being two years old.[22] The peculiar geographical distribution of EMF in India is well illustrated in the paper by Kutty et al.[31] There are reports of naturally occurring EMF in cats and animal models have been produced in laboratory settings.[32,33] The number of new cases diagnosed in the registry in Kerala, India, has declined to 10 new cases per year in the last decade from 20 cases as seen in the decade prior.[28] The mean age at presentation has also shifted by a decade from 25 to 33, suggesting the late recognition of asymptomatic cases and possible decline in the incidence of new cases. In the current era, EMF patients have relatively stable symptomatic course on follow-up with mortality of around 10% on 3-year follow-up. The changing trend has paralleled the nutrition transition and has similarity to the disappearance of rheumatic fever in the developed world and, therefore, socioeconomic development is suggested as a factor in the control of this enigmatic disorder.[22]

NATURAL HISTORY

The disease often starts as an acute febrile illness in young children or middle aged individuals, like acute rheumatic carditis.[34,35] There is pancarditis with peripheral blood eosinophilia in some reported series.[36] Patients develop pericarditis and/or thrombotic endocarditis complicated by cerebral embolism. The sudden and early development of cardiac failure in some, speaks in favor of acute myocarditis as the more predominant form.[17,37-39] Mitral regurgitation, often mild, with gallops completes the clinical picture. The endomyocardial biopsy at this phase of the disease shows presence of mild myocarditis. The peripheral blood eosinophilia is associated with degranulated eosinophils and intracytoplasmic vacuolations (Fig. 6). This may indicate a causal relationship with myocarditis.[40] Immunosuppressive treatment with prednisolone was effective in lowering the eosinophil count but did not avoid the development of endocardial fibrotic disease.

The earliest changes of EMF are not well described because most patients do not present with symptoms until relatively late in the clinical course.[28] Three phases of EMF could be identified from history and pathological features. The first phase involves eosinophilic infiltration of the myocardium with necrosis of the

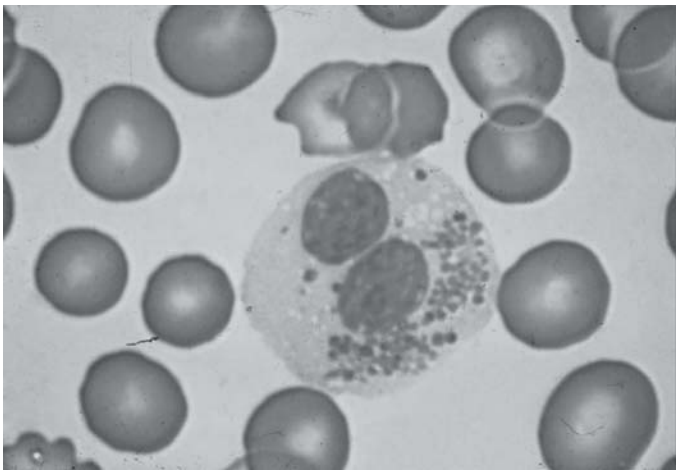
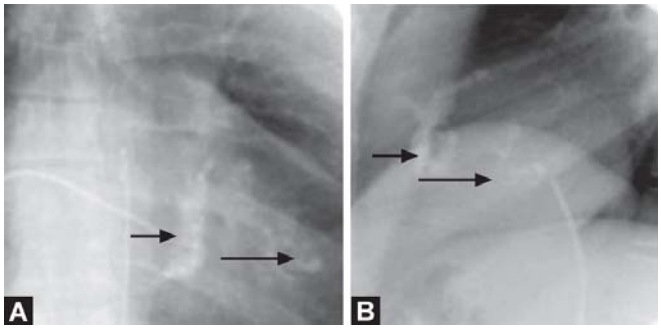


FIGURE 6: Peripheral blood smear from a patient with early phase of endomyocardial fibrosis. Eosinophils show intracytoplasmic vacuolations and degranulation

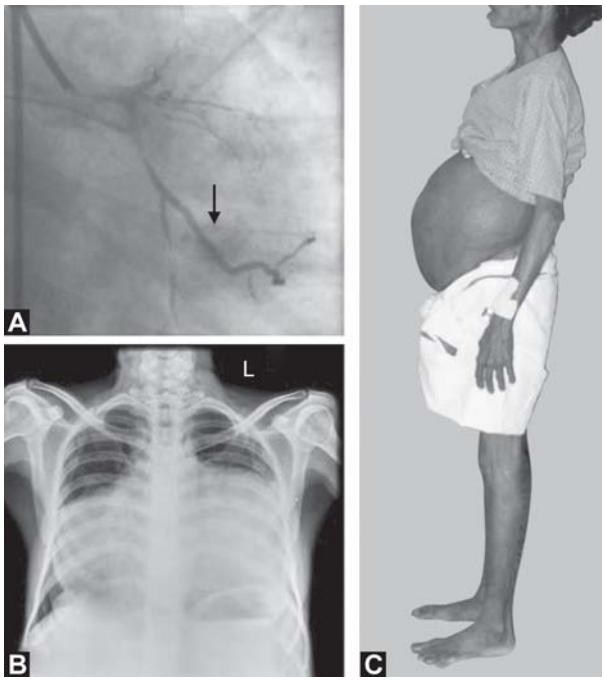
subendocardium and a pathologic picture consistent with acute myocarditis. This is reportedly present in the first 5 weeks of the illness. The second stage, typically observed after 10 months, is associated with thrombus formation over the initial lesions, with a decrement in the amount of inflammatory activity present. Ultimately, after several years of disease activity, the fibrotic phase is reached, when the endocardium is replaced by collagenous fibrosis. Fibrosis involves the inflow tract of both ventricles and the outflow tracts are spared. The involvement of the mitral and tricuspid subvalvar apparatus results in varying degrees of valve regurgitation. Calcification in areas of extensive fibrosis marks the late stage of the disease.[41] Echocardiography and angiocardiography are useful in identifying the disorder in asymptomatic subjects.[22,42,43]

Although rare, endocardial calcification (Figs 7A and B) is one of the pathognomonic features of EMF.[41] The simultaneous occurrence of endocardial fibrosis, myohypertrophy and calcification, highlights the role of inflammatory cytokines in the pathogenesis of this enigmatic disorder.[22]

In a study of the natural history of 200 EMF patients from Kerala in the 1990s, 10 years survival rate was only 37%. The presence of ascites, NYHA class III symptoms and atrial fibrillation were indicators for poor prognosis.[17] The isolated filling abnormality usually does not affect the prognosis in burnt out cases. The A-V valve regurgitation is progressive and mitral valve replacement significantly improves the natural history.



FIGURES 7A AND B: Frontal (A) and Lateral (B) plane fluoroscopic images of the thorax showing endocardial calcification. Short arrows identify right ventricular and long arrows identify the left ventricular endocardial calcium



FIGURES 8A TO C: (A) Incidentally detected endocardial calcification in a 50-year-old male evaluated for coronary artery disease. The EMF was confirmed at catheterization and angiography. (B) Massive cardiomegaly and pericardial effusion noted in the lady shown in the adjacent clinical picture. (C) Cardiac cachexia in a 30-year-old lady suffering from right ventricular EMF. Note the massive ascites and minimal pedal edema and dilated neck veins

The actuarial survival of patients who underwent surgery was 55% at 17 years, which was much better than medical management for LVEMF. In the present era, burnt out cases have a better prognosis with mortality of around 10% at 3 years.[28]

CLINICAL FEATURES

The disease comes to clinical attention in the late burnt out stage. Those individuals with minimal involvement may remain asymptomatic and will be detected only during incidental cardiac investigations (Figs 8A to C). The clinical picture in symptomatic patients depends on the predominant involvement of right or left ventricle or both, the presence and degree of atrioventricular valve regurgitation, associated cardiac arrhythmias or thromboembolic phenomena.[22]

RIGHT VENTRICULAR ENDOMYOCARDIAL FIBROSIS

The RVEMF, the most common form of the disease in many published reports, is readily diagnosed at the bedside in countries where it is commonly seen. The autopsy-proven cases had similar incidence of RV, LV and biventricular involvement. When either of the ventricles are involved, long-term follow-up have not shown further extension of the disease to the other ventricle. Isolated cases of RV inflow or outflow tract obstruction by fibrosis can occur, but are rare events.[22] Dominant or isolated RVEMF presents in an emaciated adolescent with cachexia, massive pericardial effusion and gross ascites. This type of early onset disease with aggressive clinical course is currently not seen in India but are reported elsewhere in the world.[17,28] An occasional patient can have cyanosis with digital clubbing because of stretched open foramen ovale. This type of presentation needs to be differentiated from Ebstein's anomaly to the former from constrictive pericarditis.[44,45] Development of ascites is out of proportion to the degree of pedal edema, as seen in Figure 8C, which could be inflammatory, suggestive of a systemic disorder.[22]

In an initial report of EMF from Kerala, RV involvement was seen in 60% of patients; LV and biventricular involvement in 20% each.[46] There was slight female preponderance, and 50% of patients were in the second decade of life. Stunting of growth was prominent when the age group was below 20 years. The onset was insidious with facial puffiness and abdominal distention, and half of the patients had leg edema. The classical clinical triad of RVEMF, viz. distended jugular veins, hepatomegaly and ascites, were present in all the symptomatic subjects. Dependent edema when present did not bear any relation to the degree of ascites. The hepatomegaly was smooth, firm and non-pulsatile. The upper level of the distended neck veins could not be made out in many, and prominent 'a' waves were present in sinus rhythm. Cardiomegaly was massive extending from one mid-clavicular line to the other in 15% of the subjects. The RV third sound and systolic murmur of tricuspid regurgitation were the auscultatory features.

The electrocardiogram showed atrial fibrillation in half of those studied. The specific pattern of low voltage complexes with qR pattern in lead V_1 could be demonstrated in a majority of them (Fig. 9). Radiologic features were that of massive cardiomegaly, due to aneurysmal right atrium, and prominence of the RV outflow on the left heart border (Fig. 8B). Hyperdynamic outflow pulsations and RV calcification could be demonstrated by fluoroscopy (Figs 7A and B).

The two dimensional echocardiographic findings are dominated by the aneurysmal right atrium. The RV apex will be filled by a dense fibrous mass, which encroaches on to the inflow tract involving the chordopapillary structures of the tricuspid valve. The RV cavity is shrunken with an apical notch to the right of interventricular groove due to the apical fibrosis, pulling the RV apex inward. The RV endocardial calcification is diagnostic. Fibrosis does not involve the outflow tract, which becomes dilated and hyperdynamic. The late stages of the disease will show a common right atrial and ventricular cavity with low pressure tricuspid regurgitation as in Ebstein's anomaly. Slowing of the circulation with dynamic intracavitary echoes and right atrial thrombi are not rare (Figs 10A to D). The inferior vena cava is markedly dilated and non-pulsatile. The M-mode of pulmonary valve and the Doppler flow signals may show atrial systolic opening of the pulmonary valve (Figs 4A and B). The Doppler reveals low pressure tricuspid regurgitation, which is often difficult to quantify. An echocardiographic classification was proposed on the basis of involvement of ventricular cavity obliteration and plastering of AV valves.

- Grade 1: RV involvement confined to apex; apical dimpling or minimal apical obliteration
- Grade 2: Obliteration of RV apex up to mid cavity
- Grade 3: RV cavity obliteration, distortion and outflow dilatation.

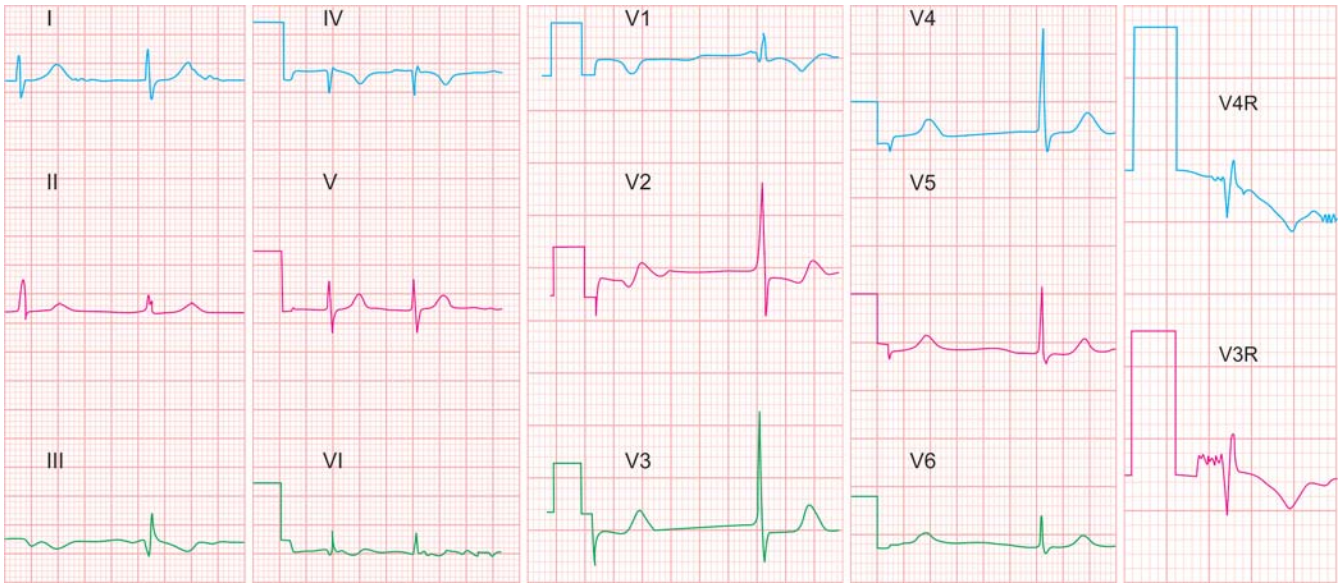
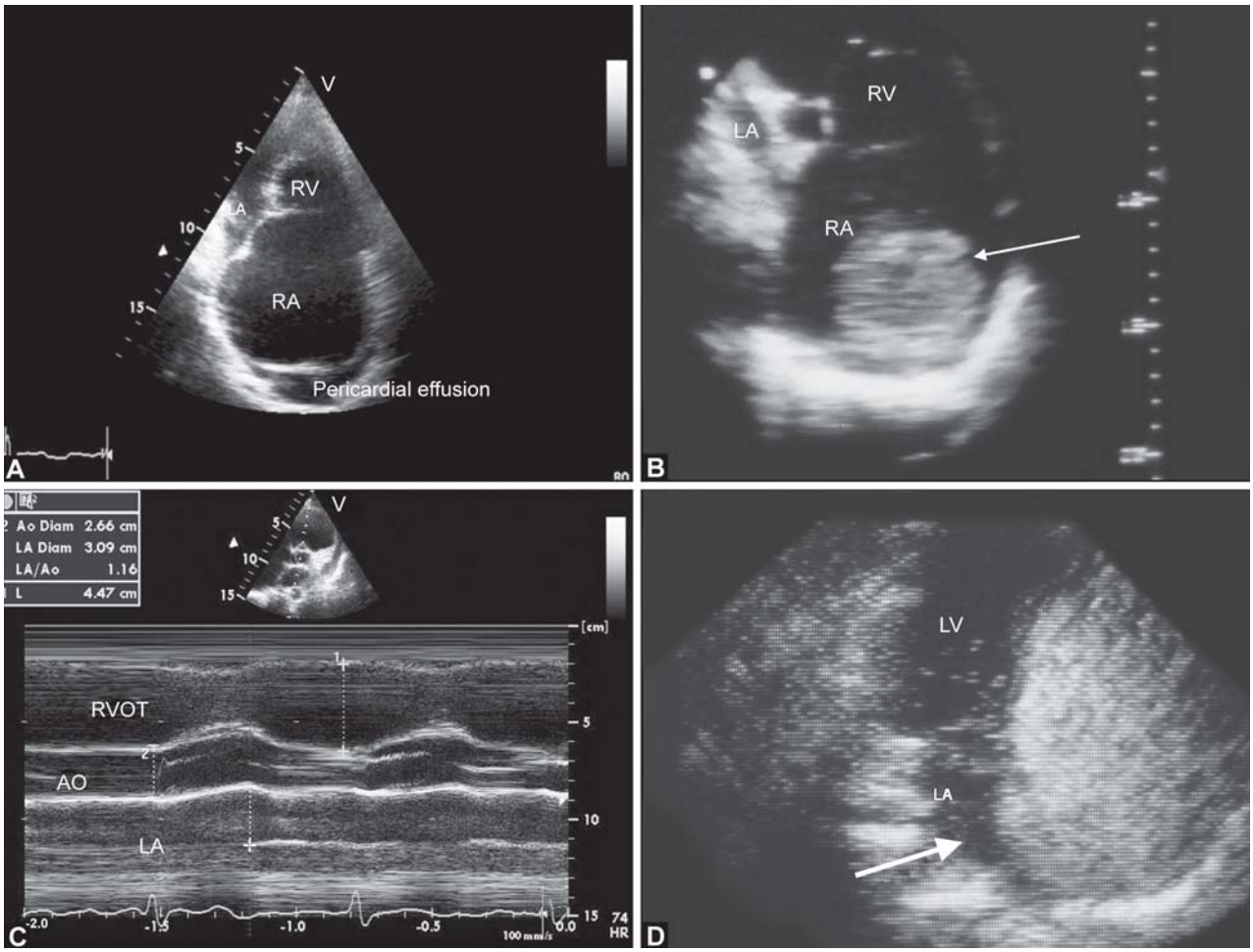
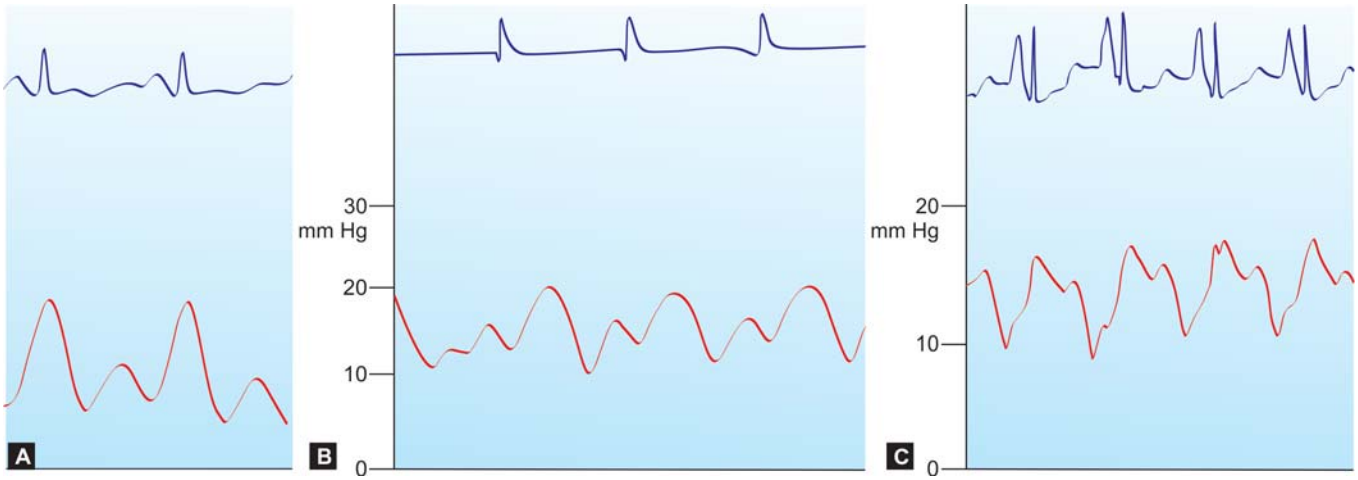


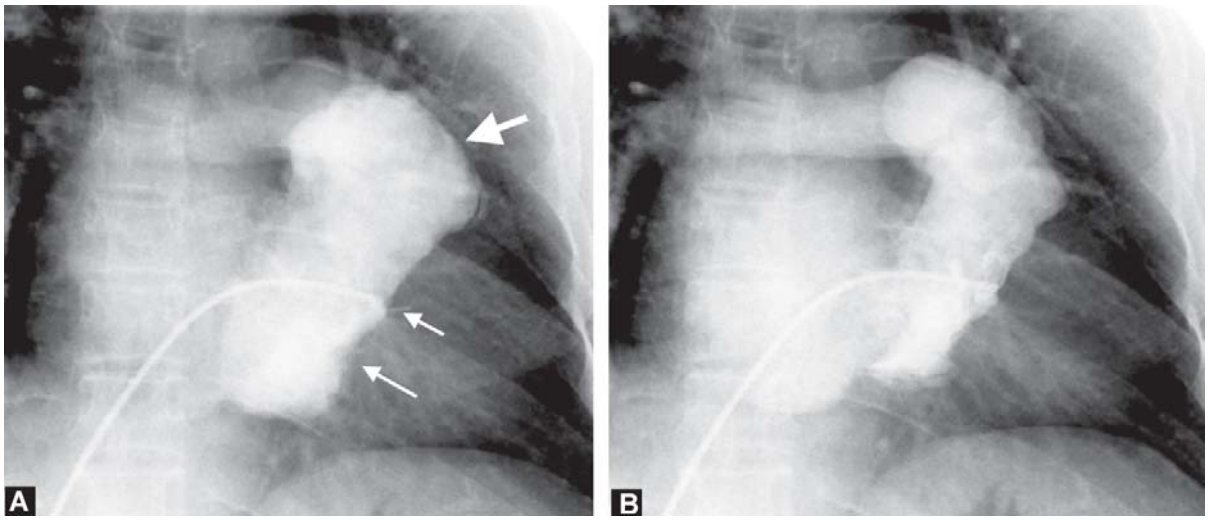
FIGURE 9: Illustrative electrocardiogram in isolated RVEMF shows atrial fibrillation, normal axis, QR morphology in right precordial leads



FIGURES 10A TO D: Echocardiographic features of RVEMF. (A) Note the aneurysmal right atrium (RA); distorted right ventricle (RV) and the small pericardial effusion. (B) Thin white arrow shows a large right atrial thrombus. (C) Dilated hyperdynamic right ventricular outflow tract (RVOT). (D) Contrast filled large right atrium with stretched open foramen ovale with small right to left shunt



FIGURES 11A TO C: Right atrial pressure tracing showing the three stages of changing hemodynamics of right ventricular disease. Initial phase has prominent 'a' waves (A), second phase has prominent 'v' waves due to tricuspid regurgitation (B) and the late phase is characterized by the ventricularization of the atrial pressure curve (C)



FIGURES 12A AND B: Right ventricular angiogram in RVEMF, diastolic frame on the left and systolic frame on the right. Note the obliteration of the RV apex and body (thin arrows), RVOT dilatation (thick arrow) and tricuspid valve regurgitation, with contrast opacifying right atrium

HEMODYNAMICS

The cardiac output is consistently low. The right atrial pressure is elevated. During the early stages of the disease, 'a' waves dominate the tracings. The large 'a' waves will be reflected not only in the right ventricle but also in the pulmonary artery tracings as the powerful 'a' waves open the pulmonary valve during late diastole (Figs 4A and B). With increasing tricuspid regurgitation, tracings show large 'v' waves finally showing ventricularization of the atrial pressure curve. Dip diastolic pressures of the ventricles are elevated except in the early stages of the disease.[47] The diastolic pressure tracings show dip and plateau pattern, reflecting restrictive filling pattern of the ventricles. End diastolic pressure is further elevated by the atrial emptying into a noncompliant ventricle (Figs 11A to C). End diastolic pressure may rise to nearly one-third of the systolic pressures in the right ventricle.

Angiography is seldom used now. The right ventriculogram will show small RV inflow tract with dilated hyperdynamic RV outflow tract. The tricuspid regurgitation will opacify the aneurysmal right atrium (Figs 12A and B). The tricuspid valve is in the normal position. The angiocardiographic studies were done to differentiate this disease from Ebstein's anomaly of the tricuspid valve.[44]

Degree of cavity obliteration in RV chamber is graded as follows:[48]

- Grade 1: Minimal RV involvement confined to trabecular alterations at apex and along septal border; normal contour of RV
- Grade 2: Obliteration of RV apex and adjacent body up to mid cavity, but sparing tricuspid annulus (saucer shaped RV)
- Grade 3: RV cavity obliteration, including area near annulus, and outflow dilatation
- Grade 4: RV body as well as RV outflow narrowed

LEFT VENTRICULAR ENDOMYOCARDIAL FIBROSIS

Isolated LVEMF often presents as mitral regurgitation or severe pulmonary hypertension.[22] Moderate cardiomegaly, well felt apex beat, left para-sternal heave, loud pulmonary component

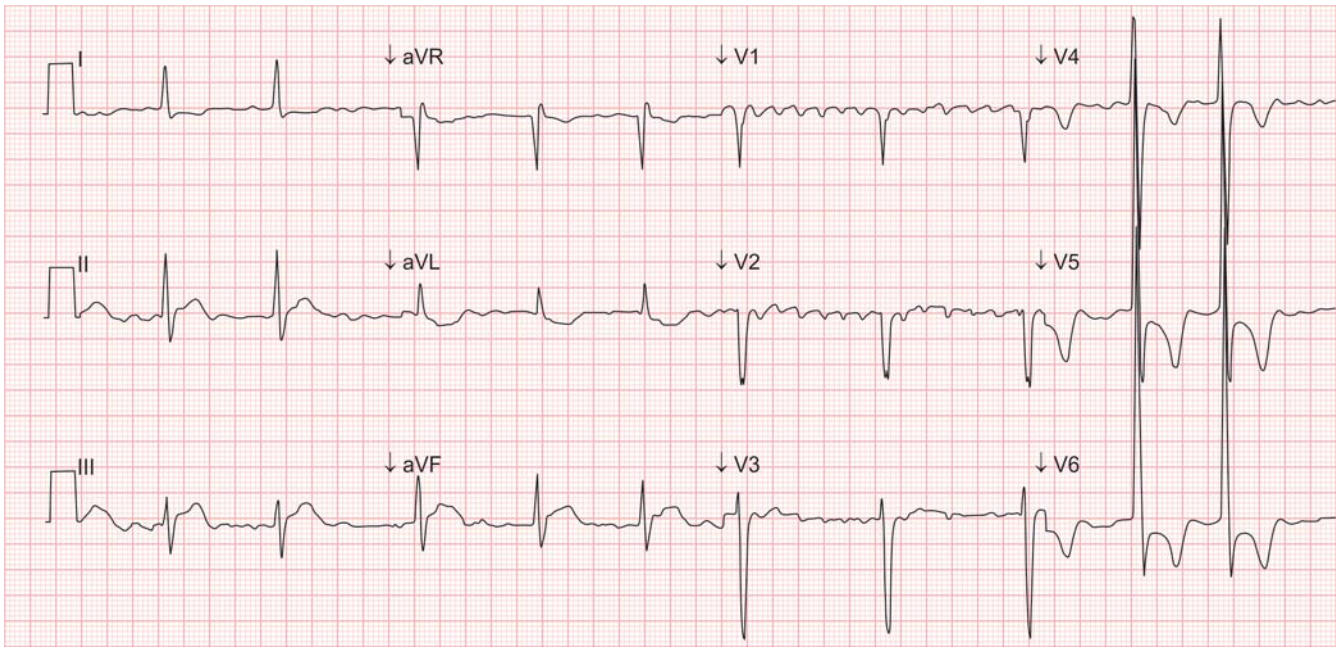


FIGURE 13: Electrocardiogram from a patient with LVEMF and endocardial calcification. Note the atrial fibrillation, left ventricular hypertrophy with marked ST depression and T inversion

of the second heart sound, loud LV third heart sound and varying degrees of mitral regurgitation are the salient clinical features. The onset of the atrial fibrillation heralds profound clinical deterioration. The left atrial P waves and the LV hypertrophy with strain are often seen in the electrocardiogram (Fig. 13). Plain X-ray film closely resembles that of patients with rheumatic mitral valve disease. The LV calcification when present is diagnostic (Figs 7A and B). Biventricular EMF can be recognized in an equal subset of patients with EMF but their signs and symptoms overlap and, at times, is dominated by the dominant chamber involvement.

Many patients presenting with atypical chest pain and palpitations, with electrocardiographic abnormalities are often referred for coronary angiogram, when in fact they have LVEMF detected by 2D echo study.[28] Endocardial fibrosis either involves the entire inflow tract or be patchy involving the papillary muscles and chordae. The apical fibrotic thickening of endocardium may be mistaken apical hypertrophic cardiomyopathy. Endocardial calcification is specific for EMF and is easily recognized by 2D echo (Figs 14A to D).[41] Fibrotic process spares the outflow tract and a distinct ridge is seen at the junction of the inflow and the outflow tracts. Posterior mitral leaflet is often plastered on the posterior LV wall as the papillary muscle is entangled in the fibrotic process. The anterior mitral leaflet appears normal. The mitral valve pathology and incompetence can be accurately quantified to plan surgical intervention. Significant left atrial dilatation is common. Color-coding of regional echo amplitude can reveal high intensity echoes at areas of early fibrosis.[42] Doppler studies reveal mitral regurgitation and restrictive LV filling pattern (Figs 10A to D). Tissue Doppler imaging can be used to assess diastolic LV function.

An echocardiographic classification was proposed on the basis of involvement of ventricular cavity obliteration and plastering of AV valves.[42]

- Grade 1: Involvement at apex or only papillary muscles
- Grade 2: Apex blunted, with disease extending to cavity
- Grade 3: Obliteration involving up to mid cavity, transverse diameter more than longitudinal, PML plastering

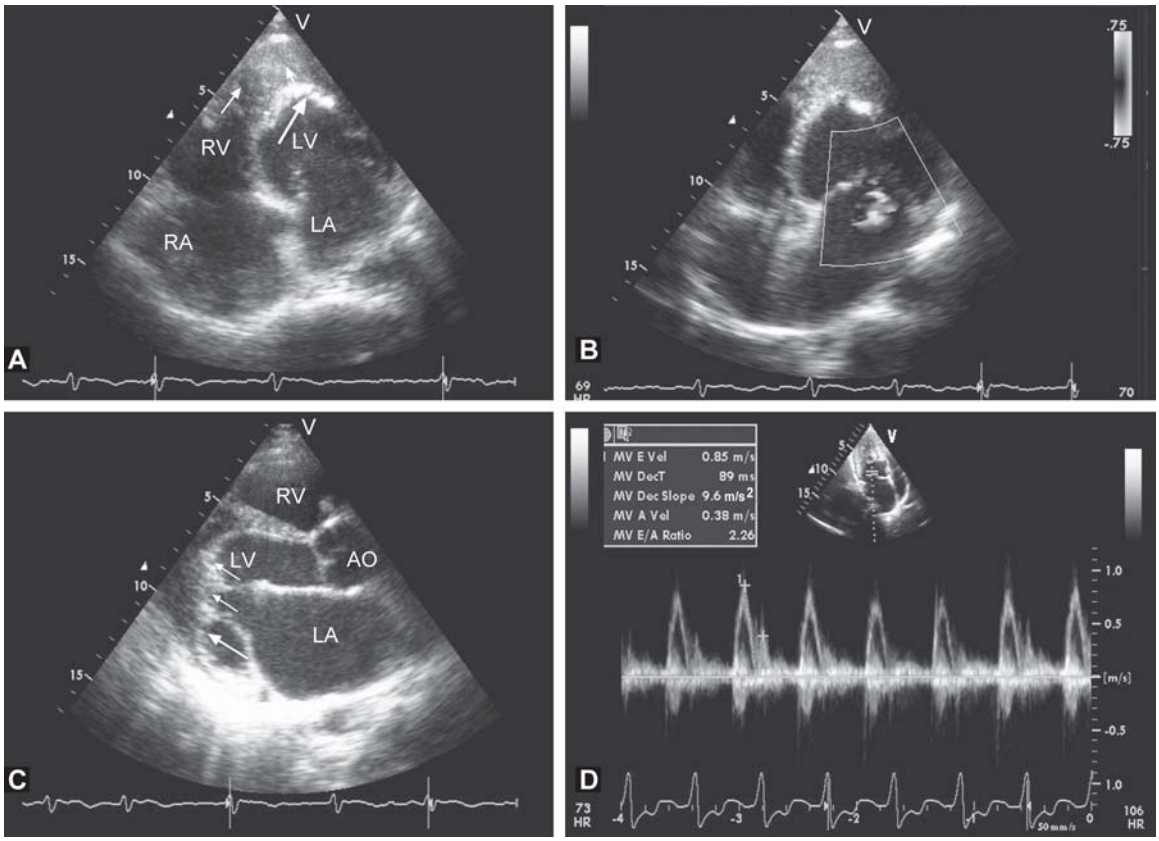
M-mode echocardiography may show abrupt posterior motion of the LV posterior wall with a notch in the opposite direction in the interventricular septum consistent with the rapid early filling. The posterior wall motion is subsequently flat, reflecting the dip and plateau phase of the pressure tracings. The mitral valve movements will look normal with a fast EF slope (Fig. 15).

HEMODYNAMICS AT CARDIAC CATHETERIZATION

Since most of the diagnostic features can be ascertained by non-invasive methods, hemodynamic studies are indicated either to differentiate the disease from constrictive pericarditis, to assess the degree of atrioventricular valve regurgitation, to document the pulmonary artery pressures or for research purposes. The simultaneous right and left heart pressures will not show any pressure equalization and a typical dip, and plateau pattern can be seen in the diastolic pressure tracings (Fig. 3).

ANGIOGRAPHIC DIAGNOSIS OF EMF

Angiography was the most reliable method of confirming EMF, especially the milder forms.[48] The LVEMF can be recognized angiographically as smoothening of the LV cavity due to loss of fine trabeculae (earliest change), irregular outline, filling defects, cervices and out-pouching (Figs 16A and B). Crevices and out-pouching are filling defects within ventricular chamber extending beyond contrast filled cavity. Varying degree of mitral regurgitation is common. Left atrium is seldom markedly enlarged. Coronary angiography reveals normal vascular pattern, although asymptomatic burned out cases may present with acquired coronary artery disease (Fig. 8A).



FIGURES 14A TO D: Echo Doppler features of LVEMF. (A) Apical four chamber view showing apical fibrosis (short arrows) and endocardial calcification (long arrow). (B and C) Mitral valve leaflets are only minimally involved with mild regurgitation. (D) Restrictive filling pattern with e/a ratio greater than 2 and mitral deceleration time of 89 msec (Abbreviations: RA: Right atrium; LA: Left atrium; RV: Right ventricle; LV: Left ventricle)

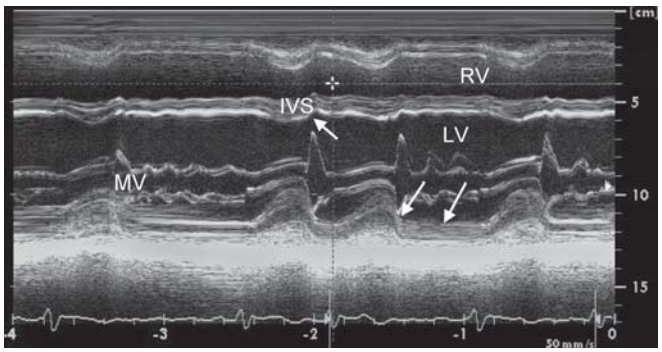
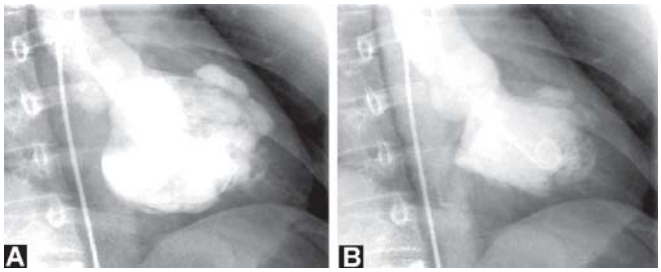


FIGURE 15: M-mode echocardiographic pattern in LVEMF. The upward directed arrow shows the early abrupt septal movement. The downward directed arrows show the early abrupt motion followed by the plateauing of the LV posterior wall (Abbreviations: RV: Right ventricle; LV: Left ventricle; IVS: Interventricular septum; MV: Mitral valve)



FIGURES 16A AND B: Left ventricle (LV) angiogram from a patient with LVEMF, diastolic frame on the left and systolic frame on the right. Note the obliteration of the left ventricular apex, transverse diameter more than the longitudinal diameter and absence of mitral regurgitation

Involvement of LV is graded as follows:[48]

- Grade 1: Generalized smoothening of LV, with small irregular filling defects at apex
- Grade 2: Apex obliterated, with smooth border and irregular filling defects
- Grade 3: Obliteration involving half or more of LV cavity (LV cavity transverse diameter is more than long axis diameter).

Pathology

The endomyocardial biopsy is useful to confirm the diagnosis even though the focal disease is often missed. The biopsy is invaluable to exclude infiltrative diseases.[49] Fibrotic replacement of the ventricular endomyocardium, affecting the apices and the inflow tract could be easily demonstrated.[50] The fibrosis can be focal or diffuse, patchy or continuous, obliterating the trabecular morphology of the endocardium. The fibrotic process can also extend into the subendocardium. The extensions of the fibrosis into the papillary muscles lead to functional deterioration and regurgitation of the atrioventricular valve.[23] The microvascular

involvement, endocardial damage and prothrombotic state can result in the formation of organized thrombi at the surface. Unaffected myocardium shows hypertrophy and dilatation. The pericardium is usually thin and contains varying amounts of transudate depending on the extent of cardiac failure.

Etiology

The etiopathogenesis of this disorder continues to be elusive.[24] In order to explain the peculiar geographic distribution, malnutrition and infections were initially implied as the cause.[23,24,51] The clinical similarity to burnt out stage of Loeffler's endocarditis initiated lot of studies on eosinophilia, eosinophil toxins and endocardial fibrosis.[20] Lymphatic obstruction due to filariasis and altered immunologic response to streptococcal infection in hosts whose immune status was altered by parasitic infections were also investigated. Isolated RV involvement was a phenomena observed in certain disorders, like carcinoid syndrome, where the lungs detoxify the toxic metabolites protecting the left side of the heart. Similar clinical features were found in EMF generated research on dietary toxic factors like excess of serotonin present in banana, the cyanogenic glycosides and vitamin D present in Cassava.[23] The peculiar geographical distribution of the disease in India co-related with the abundance of thorium and cerium in the soil. Tissue samples from affected individuals reflected the elemental excess, which turns out to be pathogenic in the setting of magnesium deficiency.[23] Diarrheal disorders common in the tropics were postulated as to cause relative magnesium deficiency. This generated a lot of basic research in understanding the role of these elements and enzymes in the endocardium and adjacent interstitium.

Treatment

Management of cardiac failure is the mainstay in the treatment of EMF. Atrial fibrillation will require use of antiarrhythmic drugs and oral anticoagulants. The patients with RVEMF may require repeated abdominal paracentesis, and rarely pericardiocentesis.[22] In 1971, Dubost introduced surgical treatment of EMF by endocardial decortication and atrio-ventricular valve replacement.[52] A plane of cleavage is easily developed and all of the yellow-white thickened endocardium removed. Other options are LV endocardectomy with mitral valve repair or replacement, exclusion of fibrotic right ventricle in RVEMF by a bidirectional Glenn connection.[53,54] Although several patients had mitral and tricuspid valve replacement during 1980–1991 for EMF, this is now rarely offered because of the poor long-term outcome for mechanical prosthetic valves placed in the tricuspid position.[28,55] Bidirectional Glenn's shunt is offered only to patients with isolated RVEMF, without mitral incompetence, LV diastolic dysfunction or pulmonary hypertension. Surgical treatment has always been contemplated only for NYHA classes III and IV patients. A detailed 2D echo Doppler evaluation can identify the ideal surgical candidates of EMF with a fair amount of certainty.

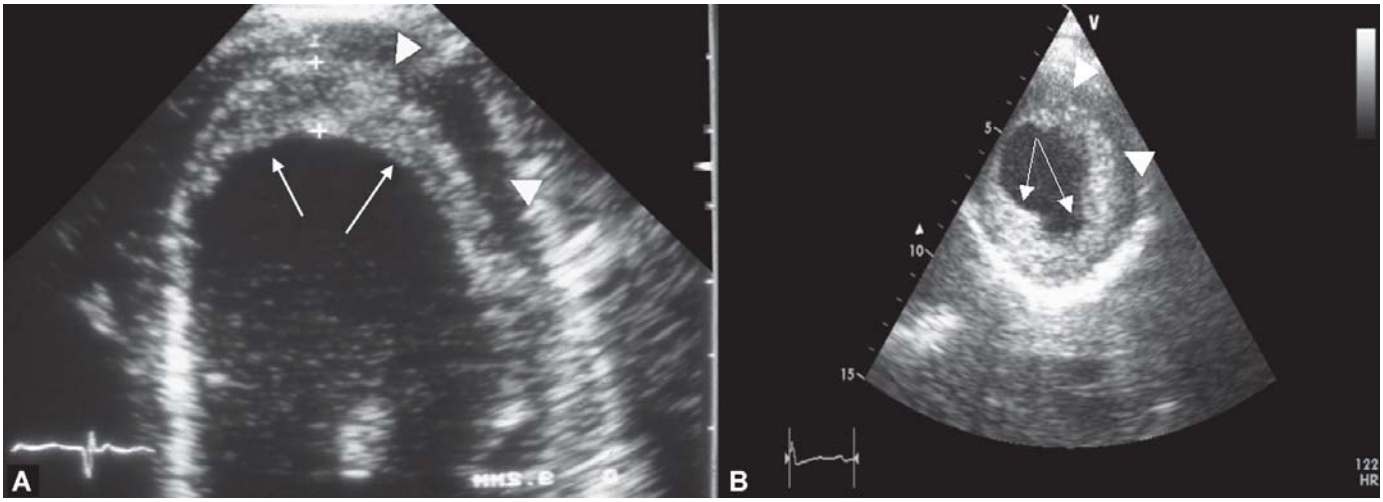
LOEFFLER'S ENDOCARDITIS

Loeffler's endocarditis is a form of eosinophilic endomyocardial disease, which manifests as restrictive cardiomyopathy and resembles EMF in the burnt out phase.[56] Both the disorders are considered to represent different spectrum of damage to the heart by activated eosinophils.[57,58] Activated eosinophils generate a spectrum of myocardial damage ranging from acute coronary syndrome, intracardiac thrombus formation, thromboembolic phenomena and sudden cardiac death to congestive cardiac failure.[20,59,60]

Loeffler, in 1936, described the syndrome of eosinophilia with multiorgan involvement, wherein the cardiac involvement was characterized by congestive heart failure and thrombo-embolism.[20] The disease is now considered to represent the specific form of endomyocardial involvement in hyper-eosinophilic syndromes (HESs). Hypereosinophilia is defined as the persistent elevation of eosinophil count of greater than 1.5 X 10^9/liter, persisting for more than 6 months without any identifiable cause. Eosinophilia in HES is an abnormal reaction to cytokines released by T cells of clonal origin with at least five identified specific gene fusion products. Cationic protein release by eosinophils, lead to myonecrosis and troponin elevation. The release of von-Willebrand factor and tissue factor, led to intracardiac thrombus formation. The plastering of the subvalvar apparatus by the endocardial inflammation makes the valve regurgitant as in EMF. The acute phase of HES is a prothrombotic state. The eosinophils are morphologically and functionally abnormal in this condition and eosinophil derived proteins can be detected in circulation. The myocardial biopsy in the early stages shows eosinophil infiltration and presence of eosinophilic granular proteins. Later studies deciphered the myocardial toxicity of eosinophils, and three stages of the disease can be clinically identified. In the initial necrotic phase, there is intense eosinophilic myocarditis and arteritis. These changes recede to a thrombotic stage characterized by endocardial thickening, mural thrombi and thromboembolic phenomena. A late fibrotic stage follows in which marked endocardial thickening and non-specific intimal thickening of intramyocardial arteries are observed.[23] It is postulated that endomyocardial disease is the outcome when the activated eosinophils act on the endocardium facilitated by secondary pathogens, and HES leads to endothelial localization and eosinophilic myocardial disease.[58]

Clinical features are rather diverse from asymptomatic incidental detection to multi-organ dysfunction.[61] The incidence of HES peaks in the fourth decade, and there is a male preponderance of 9:1. Half the patients with HES have cardiac involvement, which adversely affects the prognosis. A majority of the patients with cardiac involvement also have other organ involvement. The signs and symptoms of cardiac involvement could manifest as myocardial ischemia, pericarditis, arrhythmia, cardiac failure and thromboembolic phenomena. Mitral regurgitation is the commonest valve lesion but aortic valve lesions are also reported.[62] Specific features of HES are the elevation of blood eosinophils, elevated serum B_{12} levels and serum tryptase levels. Bone marrow aspiration with genetic studies and cell typing will characterize the myeloproliferative disorder. It is extremely important to subtype this, since specific treatment with chemotherapeutic agents and monoclonal antibodies induce prolonged remission with favorable outcome.[56]

One-third of the individuals with Loeffler's endocarditis have electrocardiographic abnormalities, and echocardiogram



FIGURES 17A AND B: Loeffler's endocarditis, two dimensional echocardiographic features, zoomed apical two chamber view of left ventricle on the left panel and cross section on the right panel. Note the layering of the left ventricular apex by thrombus (thin arrows). Thick arrow heads show the normal myocardium

typically shows the fibro-thrombotic obliteration of ventricular apices (Figs 17A and B) with atrial dilatation and atrioventricular valve regurgitation. If initial echocardiogram is normal, a repeat echocardiogram is advocated every 6 months and in case of difficult echo windows, transesophageal echocardiogram could be useful.[61] Cardiac MRI is superior to identify layered thrombus and tissue characterization, and is superior to echocardiography for early detection of eosinophilic endocardial disease.[20,63] Myocardial biopsy is diagnostic but needs to be deferred as thromboembolic complications are anticipated.

The identical pathologic features of EMF and the late stages of Loeffler's endomyocardial disease prompted Olsen and Spry to propose that both the diseases are different ends of the spectrum of disorders caused by eosinophils.[40] But eosinophilic endomyocardial disease is more common in the temperate zones affecting middle-aged people who are neither poor nor malnourished. In contrast, EMF is typically a disease of the tropics affecting younger subjects who are poor and malnourished. Eosinophilia is usually due to parasitic diseases, and eosinophil count does not reach the level that is usually seen in eosinophilic endomyocardial disease. An acute event with multisystem involvement is seldom seen.[23] Constrictive pericarditis should be considered in the differential diagnosis for all restrictive cardiomyopathies, since the diagnosis gives an option of surgical correction.

The treatment option in eosinophilic endomyocardial disease could be symptomatic or specific. The management of cardiac failure, anticoagulation to prevent thromboembolism, antiarrhythmics for the variety of arrhythmias and vasodilators for the atrioventricular valve regurgitation are suggested. Once hypereosinophilia is confirmed, specific treatment with corticosteroids, chemotherapeutic agents and monoclonal antibodies impart a favorable outcome, especially in the early stages. The development of thromboembolism is associated with 5–10% mortality. Organized fibrotic lesions can be treated with selective endocardectomy and mitral valve replacement. Cardiac transplant is an option, but the disease can recur in the transplanted heart.[20]

HEMOCHROMATOSIS

Hemochromatosis is a rare disorder characterized by cirrhosis, diabetes and skin pigmentation, endocrine disorders, heart failure and arthropathy.[2] It is inherited as a polygenic disorder affecting at least four iron metabolism genes, one of which is modulated by metabolic syndrome as well.[64] The deregulated iron absorption leads to total body iron overload, and the tissue damage is secondary. Erythropoiesis remains normal, but progressive parenchymal iron deposition leads to organ damage. The disorders requiring repeated transfusions also can lead to transfusion siderosis, where iron overload is more rapid and the overflow is from the reticuloendothelial stores. Excess of cellular iron is toxic leading to cell death and fibrosis.[65] The clinical features and the biochemical findings supplemented by genetic studies can establish the diagnosis. Unlike the endomyocardial diseases, the involved myocardium shows features of hypertrophy. The electrocardiogram will show large voltages with short PR interval. An important challenge is the non-invasive assessment of cardiac iron overload. Recent developments in cardiovascular magnetic resonance (CMR) have made it a valuable method for monitoring chelation therapy in patients at risk of transfusional iron overload, using magnetic resonance measurements. Transverse relaxation,[66] most importantly the ''T2-star'' (T2*) technique.[67] T2* is a unique, quantifiable CMR parameter (measured in milliseconds) which is shortened in proportion to the level of particulate iron (in the form of hemosiderin) within myocardial cells. Although there are minor effects from deoxygenated blood and fibrosis, these are minimal in comparison with the effect of the iron at clinically relevant levels of myocardial iron overload. Low T2* values are associated with decreasing LV ejection fraction and an increased risk of developing heart failure as a result of cardiac iron overload. Iron chelation forms the specific therapy which prevents end organ damage. Typically, storage disorders are autosomal recessive in inheritance and have multisystem manifestation.[1]

IDIOPATHIC RESTRICTIVE CARDIOMYOPATHY

Idiopathic restrictive cardiomyopathy is a rare disease primarily affecting the heart, and no other systemic disorders are apparent at the time of diagnosis.[1] One of the largest series of this disease was published recently from the Mayo clinic.[13] The last two decades of research have delineated a lot of new knowledge regarding the sarcomeric protein abnormalities responsible for the development of idiopathic restrictive cardiomyopathy.[68] Hence, family screening and collection of blood samples for genetic studies are key elements in the diagnosis. It is interesting to note that all varieties of cardiomyopathies can be identified in the same family outlining the phenotypic variation of the same genetic disease.[69]

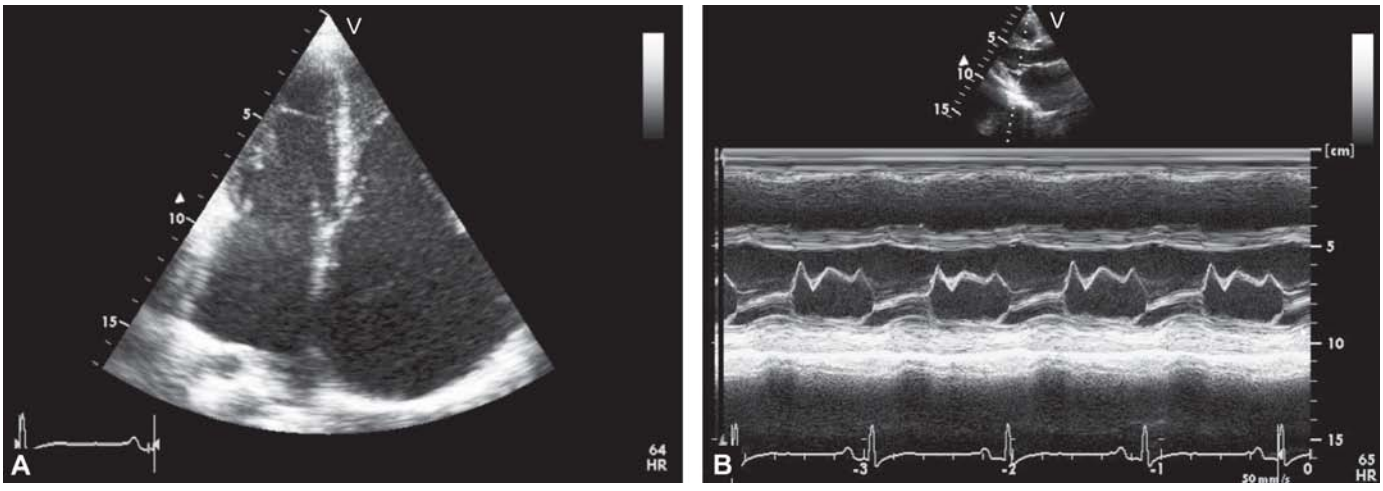
The majority of the patients are above the age of 40 years with a slight female preponderance. Dyspnea is the most common presenting feature, followed by edema. Ventricular third heart sound, systolic murmurs, jugular venous distension, pulmonary rales, ascites and edema are the common clinical features. More than 40% of the subjects are referred to rule out constrictive pericarditis, which necessitates computerized tomographic evaluation. Rarely, thoracotomy is required to make the diagnosis.

The electrocardiographic features are non-specific with three-fourth patients have atrial fibrillation or non-specific ST-T changes. Cardiomegaly is common in chest skiagram and 20% of the subjects presenting with restrictive cardiomyopathy have normal cardiothoracic ratio. Endocardial calcification is not observed in this disease. The echocardiogram is diagnostic in the majority with atrial dilatation, and ventricles with normal dimensions and wall thickness (Figs 18A and B). In the Mayo clinic series, ejection fraction was more than 50% in 65% and 20% showed minimal pericardial effusion. The mitral valve was regurgitant in 84% and tricuspid valve in 70% with a mitral early filling deceleration time of less than 140 milliseconds consistent with a restrictive filling pattern. Cardiac catheterization revealed elevated end diastolic pressures. The ejection fraction was impaired in a minority of patients.

Histological evaluation was possible in one-third of the study subjects and was diagnostic in 80%. The histological features were pericellular interstitial fibrosis with mild-to-moderate myocardial hypertrophy. Myocyte attenuation, degeneration and perivascular fibrosis were present in less than one-third of the biopsy specimens. Endocardial fibrosis could be identified in 45% of the specimens. None of the specimens had amyloid or iron deposition or inflammatory infiltrations.

Ammash et al.[13] followed up 94 subjects with restrictive cardiomyopathy for a mean period of 68 months when 50% were no more. Two-thirds died of cardiac causes of which half were due to worsening cardiac failure. On multivariate analysis hazard ratios were double for males aged above 70 years, left atrial dimension of more than 6 cm and worsening by every class of NYHA. Restrictive cardiomyopathies in children, although uncommon, carry a worse prognosis and oblique ST-T segment changes could be a marker of the restrictive physiology.[16,70]

The term idiopathic restrictive cardiomyopathy was coined when no clinically identifiable cause could be ascertained in an individual with primary myocardial disease with restrictive physiology.[68] Linkage associations studied in large multi-generational pedigrees by various laboratories specializing in various loci, and sharing of the DNA data in the last two decades, have revealed more of the genomics of these rare disorders. At least 14 genetic causes for restrictive cardiomyopathy are now known. The genes affected present varying phenotypic and pathologic severity in the same family. At least two main genetic determinants are involved in the pathogenesis. Those who are homozygous or heterozygous for two or more mutations, often show severe phenotypes. Protein-protein interaction and genetic modifiers also modify the phenotype from lifelong symptomless form to major health problems like heart failure, thrombo-embolism and wide spectrum of arrhythmias.[71] Nine mutations involving cardiac troponin I and three mutations involving cardiac troponin T and two involving beta myosin heavy chain result in restrictive cardiomyopathy. Of these, latter two mutations are recognized in at least three different cardio-myopathies like isolated ventricular non-compaction, dilated and hypertrophic cardiomyopathies with individuals in same family showing different phenotypes.[72] The clinical expression, once the genetic abnormality is identified, is considered to be benign



FIGURES 18A AND B: (A) Apical four chamber view and (B) M-mode of the mitral valve from a patient with idiopathic restrictive cardiomyopathy. Note the normal ventricular dimensions and dilated atria. Mitral valve echo shows prominent B hump

or mild if the affected individual is asymptomatic or mildly affected with no major clinical events. All other individuals who have clinically manifest disease are considered to have moderate or malignant phenotype. One-third of such patients are dead or received a transplant on 5 years follow-up, and younger the age of onset, worse the prognosis.[16]

OTHER FORMS OF CARDIOMYOPATHIES

Sarcoidosis is a systemic non-caseating granulomatous disorder, and cardiac involvement occurs in one-quarter of the patients.[2] The myocardium gets affected by patchy granulomas which lead to arrhythmia and conduction disturbances. Presence of hilar lymphadenopathy, systemic features, like fever, weight loss, erythema nodosum, eye and skin signs, are helpful in the diagnosis. Tuberculous anergy and elevated serum angiotensin converting enzyme levels are the other diagnostic pointers. Tissue diagnosis on lymph node biopsy is confirmatory and the disease is very well responsive to steroids.[2]

Irradiation and connective tissue diseases, like scleroderma, can lead to heart failure with restrictive physiology. Prior chemotherapy, mediastinal irradiation, lymphomatous disorders are the risk factors for developing radiation induced restrictive cardiomyopathy. Development of restrictive cardiomyopathy after successful treatment of a neoplastic disorder is a devastating event in the natural history.[1]

Amyloidosis is by far the commonest cause for restrictive cardiomyopathy and is a multisystem disorder involving all the four cardiac chambers and coronary vessels. The electrocardiogram shows low voltage complexes and conduction disturbances. The echocardiogram shows restrictive features in addition to the thick walls due to infiltration and, at times, features of ventricular dilatation and dysfunction.[73] It is dealt with in detail elsewhere in this book.

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Chapter 83

Amyloid Heart Disease

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Chapter Outline

- History of Amyloid
- Amyloidogenesis
- Overview of Cardiac Amyloidosis
- Classification of Amyloidosis
- Cardiac Amyloidosis
  - Light Chain (AL) Amyloidosis
  - Senile Systemic Amyloidosis
  - Familial (Hereditary) Systemic Amyloidosis (ATTR and Others)
  - Secondary Amyloidosis
  - Isolated Atrial Natriuretic Factor
- Clinical Features of Cardiac Amyloidosis
  - History and Physical Examination
  - Diagnostic Tests
  - Tissue Diagnosis
  - Radiologic Findings
  - Electrocardiography
  - Echocardiographic Findings
  - Laboratory Findings
  - Cardiac Magnetic Resonance Imaging
  - Cardiac Catheterization Hemodynamics
  - Serum Amyloid P Component Scintigraphy
  - Prognosis
- Treatment of Amyloid Cardiomyopathy
  - Heart Failure Medical Management
  - Device Therapies
  - Treatment of the Underlying Amyloid Disease
  - Heart Transplantation

INTRODUCTION

The amyloidoses are a large group of hereditary or acquired diseases characterized by the deposition of extracellular proteinaceous material known as amyloid. Amyloid is a homogenous material composed of specific highly insoluble fibrillar proteins that accumulate primarily in the extracellular spaces in certain tissues and organs, leading to architectural disruption and organ dysfunction. Although the histochemical properties and morphology of all amyloid deposits are similar, the underlying amyloid precursor proteins (APP) are highly variable. To date, 27 human and 9 animal amyloidogenic proteins have been identified, and they are listed together in Table 1 as per the current nomenclature system of amyloid fibril proteins.[1] The propensity for cardiac involvement depends on the specific APP type. Cardiac amyloidosis has a wide spectrum of clinical manifestations but the most frequent presentation is heart failure related to restrictive cardiomyopathy (CMP) due to the deposition of amyloid fibrils within the myocardial interstitium. A combination of clinical, electrocardiographic, imaging and invasive methods is commonly used to diagnose this disease and distinguish it from other forms of heart failure, including other restrictive CMPs. Treatment options for cardiac amyloidosis are very limited, and the prognosis is generally poor; however, in highly selected patients with advanced heart failure related to certain types of amyloid CMP, cardiac transplantation has significantly improved survival, especially when combined with treatment to reduce amyloid generation.[2-11] This chapter reviews amyloid and amyloidogenesis in addition to the pathophysiology, diagnosis and treatment of cardiac amyloidosis.

HISTORY OF AMYLOID

The history of amyloidosis is a convoluted story. Although autopsy reports dating back to 1639 described what were probably the first reported cases of amyloidosis involving organs such as the spleen and liver, credit for the first description of this condition is usually given to Carl Rokitansky who, in 1842, stated that infiltration by grayish "lardaceous-gelatinous" material occurred in cases of scrofula (tuberculosis), syphilis and mercury poisoning.[12] This "lardaceous", "waxy" or "albuminous substance was described subsequently by others in the setting of chronic inflammatory conditions, and likely represented what we now consider to be AA amyloidosis. In 1838, German botanist Matthias Schleiden first coined the term "amyloid" to describe the waxy constituent of plants. However it was Rudolph Virchow, in 1854, who introduced and popularized the term "amyloid" to describe tissue deposits of extracellular material seen in liver and brain autopsies, which stained in a similar manner to starch or cellulose when exposed to iodine.[12] For a period, the scientific community debated whether amyloid deposits were of albuminous or carbohydrate origin, and therefore whether the name of the condition should be recognized as "lardaceous disease" as suggested by Samuel

Wilks in 1865 or "amyloid" as indicated by Virchow. In 1871, the Committee on Lardaceous Diseases concluded that the term *lardaceous* should be adopted by the society because of its resemblance to albumin. However the term *amyloidosis* prevailed for unclear reasons, perhaps due to Virchow's prominent standing as a pathologist and to the common use of the crude iodine staining technique to identify starch.[13]

AMYLOIDOGENESIS

Amyloidosis is a disorder of protein folding, in which normally soluble proteins undergo a series of conformational changes leading to the extracellular deposition of insoluble fibrillar protein aggregates under certain circumstances.[14] Proteins that form amyloid fibrils differ in size, function, amino acid sequence and native structure, but all become insoluble aggregates that have similar properties. All amyloid deposits exhibit common staining, ultrastructural and physicochemical properties. Amyloid is an amorphous, homogenous extracellular substance, which stains pink with hematoxylin and eosin (Fig. 1) and exhibits characteristic apple-green birefringence when viewed under polarized light after Congo red staining (Fig. 2). Likewise, when viewed with electron microscopy, all types of amyloid demonstrate rigid, non-branching fibrils with a consistent diameter of 7.5–10 nm (Fig. 3).[15]

A variety of mechanisms have been identified that promote these conformational changes and lead to amyloid fibrillogenesis, including: (1) intrinsic tendency of a protein to assume a pathologic conformation that becomes evident with aging [e.g. normal transthyretin in patients with senile systemic amyloidosis (SSA)]; (2) a point mutation of a single amino acid in the protein, as occurs in hereditary/familial amyloidosis (most commonly a mutation in the transthyretin gene);[16] (3) the proteolytic cleavage of a protein that generates a precursor, such as the β-amyloid precursor protein in Alzheimer disease or (4) persistently elevated concentrations of APP in the serum (e.g. immunoglobulin light chains related to a plasma cell dyscrasia, serum amyloid A (SAA) in chronic inflammatory conditions and β_2 microglobulin in patients undergoing long-term hemodialysis, etc.).[17] The conformational change in these APP leads them to assume an antiparallel cross-beta (beta-pleated sheet) structure to form protein filaments, also called protofibrils. Two to six of these protofibrils twist around each other in a shallow helix to form rigid, non-branching amyloid fibrils 7–10 nm in diameter of indeterminate length, which can be viewed with electron microscopy (Fig. 3). Together with cofactors that are common to all forms of amyloid, including serum amyloid P (SAP—a member of the pentraxin family that includes C reactive protein), glycosaminoglycans (GAG), basement membrane heparin sulphate proteoglycan and, in some cases, apolipoproteins, they bind and form insoluble amyloid fibers within the extracellular spaces of tissues and organs. The ultrastructure of the amyloid fibrils allows the regular intercalation of Congo red dye,

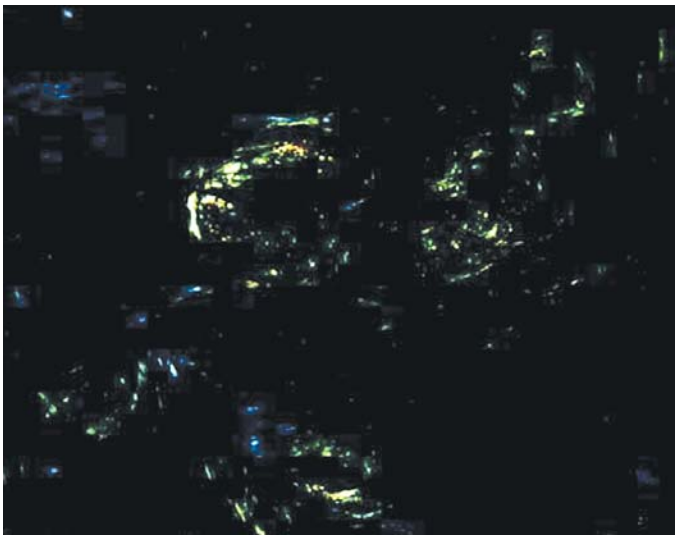


FIGURE 2: The amyloid deposits seen in this kidney biopsy under polarized light microscopy are stained with Congo red. Under polarized light, they take on an "apple-green" birefringence characteristic of amyloid; as one of the polarizing films is rotated, the green color turns into yellow and the yellow into green

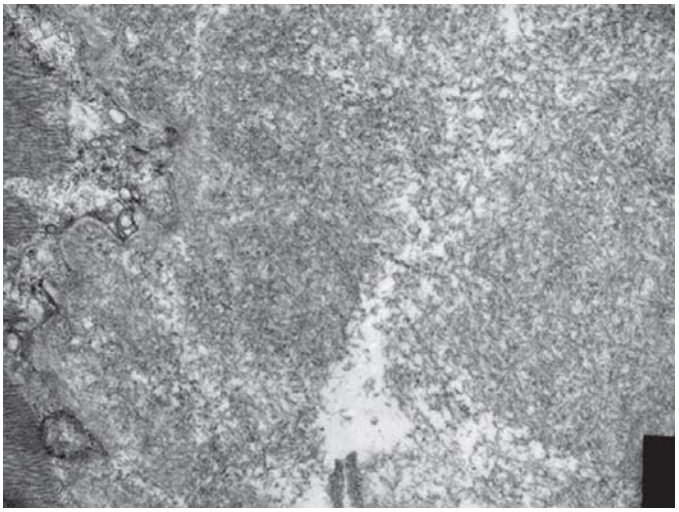


FIGURE 3: Electron microscopy of amyloid protein (high magnification) shows characteristic non-branching fibrils measuring 7.5–10 nm in diameter and indefinite length (calibration bar = 0.2 microns)

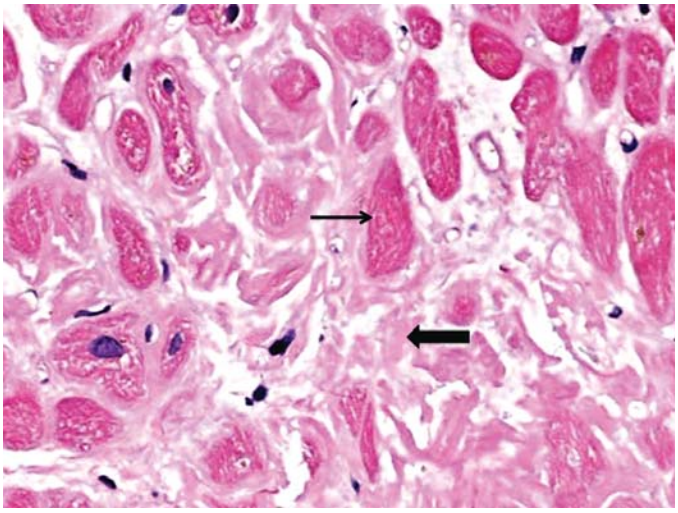


FIGURE 1: Endomyocardial biopsy specimen of a patient with cardiac amyloid, stained with hematoxylin and eosin. Note the prominent extracellular pink hyaline material (thick arrow), which is scattered throughout the interstitium. The myocardial cells, which appear dark pink-red (thin arrow), are of various sizes reflecting hypertrophy or degeneration

conferring the diagnostic optical property of apple-green birefringence to amyloid when viewed with polarized light microscopy.

Amyloidosis tends to be a relentless, progressive disease that infiltrates organs and causes their dysfunction by mechanical disruption related to bulky extracellular deposition and/or because of direct cellular toxicity from circulating APP or protein aggregates.[18-20] For example, amyloidogenic light chains appear to directly impair cardiomyocyte function in humans through an increase in cellular oxidant stress, cellular dysfunction and apoptosis, and infusion of light chains from patients with cardiac amyloidosis causes diastolic dysfunction in isolated mouse hearts.[18,19,21] With some exceptions, amyloidosis is usually a systemic process that involves more than one organ system. The four most common organs involved in amyloid disease include: (1) kidney; (2) liver; (3) heart and (4) peripheral nerves. The various types of systemic amyloidoses tend to progress at different rates; however, in all cases it is the presence and severity of cardiac involvement that drives the prognosis.

OVERVIEW OF CARDIAC AMYLOIDOSIS

Amyloid CMP is a progressive infiltrative disease, typically with distinct features seen on the macroscopic anatomy, histology, echocardiography and cardiac magnetic resonance (CMR) imaging. Until relatively recently, systemic amyloidosis was most frequently diagnosed at autopsy. However improved awareness of the disease and detection methods, including the availability of endomyocardial biopsy, currently allows for earlier diagnosis. The heart infiltrated with amyloid appears tan and waxy with a firm, rubbery consistency and increased thickness of all four-chamber walls. In addition, the valves are typically thickened with a shiny, waxy appearance (Fig. 4). The extracellular deposition of amyloid within the myocardium leads to increased ventricular wall stiffness and diastolic dysfunction of increasing severity as the disease progresses. In its advanced state, amyloidosis classically leads to restrictive physiology. Indeed, according to the two main international classifications of myocardial diseases,[22,23] amyloid CMP is a restrictive CMP that is characterized by steep rises in ventricular pressure in association with small increases in volume. At a later stage, amyloid CMP may present as a dilated CMP with predominant systolic dysfunction. The increased diastolic filling pressures lead to marked dilation of both atria. Amyloid infiltration of the left atrial wall can lead to reduced atrial contractility and mechanical atrial failure, which is best identified by pulsed wave Doppler echocardiography as a markedly reduced or absent left ventricular filling wave during atrial contraction (A wave) in the presence of sinus rhythm on the echocardiogram (EKG). In such cases, the risk for atrial thrombus formation and thromboembolism is very high. Atrial arrhythmias and conduction defects, such as atrial fibrillation, atrial flutter, atrial tachycardia and sinus node dysfunction with sinoatrial exit block, more commonly occur in later stages of the disease. Amyloid deposits frequently infiltrate the intramyocardial vessels, and these vascular deposits can lead to the development of myocardial ischemia and angina pectoris without epicardial coronary stenosis. Very rarely, amyloid deposits have been reported to cause epicardial coronary artery obstruction that is indistinguishable from cholesterol-laden plaques.[24] Amyloid can also infiltrate the pulmonary vasculature, causing pulmonary hypertension, and patients can present with symptoms and signs of cor pulmonale.[25] Pericardial and pleural effusions may be present when heart failure is present, but they may also be due to amyloid deposits in pericardium or pleura respectively. Ventricular dysrhythmias, such as ventricular tachycardia, have been reported very rarely, probably because the initial event frequently leads to cardiac arrest that is nonresuscitatable in the setting of advanced disease. The most common mode of death in patients with amyloid CMP is cardiac arrest related to electromechanical disassociation (pulseless electrical activity).

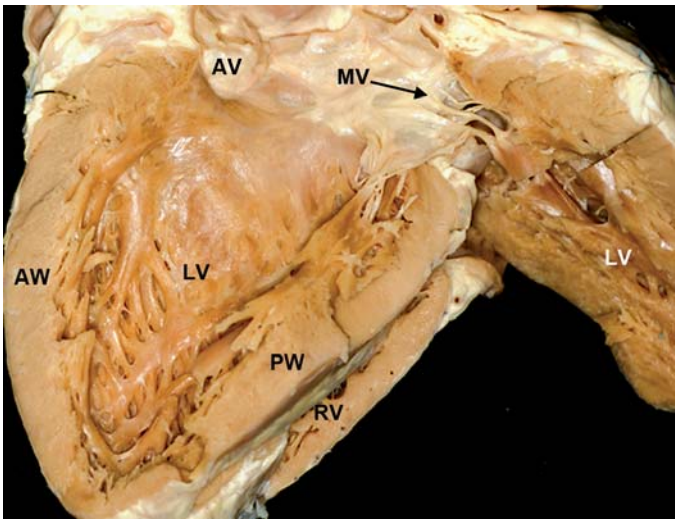


FIGURE 4: Macroscopic view of heart with amyloidosis obtained from a patient who underwent heart transplantation for advanced amyloid cardiomyopathy. Right and left ventricular walls are thick, and the formalin-fixed myocardium is pale and unusually glistening. (Abbreviations: LV: Left ventricle; RV: Right ventricular wall; AW: Anterior wall of the left ventricle; PW: Posterior wall of the left ventricle; MV: Mitral valve; AV: Aortic valve)

CLASSIFICATION OF AMYLOIDOSIS

In the past, the amyloidoses were classified mainly according to the clinical phenotype when the amyloid disease processes were poorly understood. However, the current system classifies amyloid based upon the chemical structure of the major fibrillar APP, which makes for a more logical nomenclature as the understanding of the chemical diversity of amyloid fibril proteins has increased.[26] In the current system of nomenclature, the amyloid fibril type is designated as the capital letter A followed by a suffix that is an abbreviated form of the precursor protein name. For example, when amyloid fibrils are derived from immunoglobulin light chains, the amyloid fibril is AL (A for "amyloid" and L for "light") and the disease is AL amyloidosis. Table 1 lists the classification of amyloid fibril proteins and their precursors in humans. The amyloid types in *italic face* represent those that are known to cause cardiac amyloidosis.

CARDIAC AMYLOIDOSIS

Among the 27 known amyloid fibril proteins in humans, only four proteins have been associated with 5 different cardiac amyloid phenotypes. In decreasing order of frequency, the APP

TABLE 1

Classification of amyloid fibril proteins

Amyloid protein	*Precursor*	*Systemic (S) or localized, organ restricted (L)*	*Phenotypic syndrome or involved tissues*
AL	**Immunoglobulin light chain**	**S, L**	**Primary myeloma-associated**
AH	Immunoglobulin heavy chain	S, L	Primary myeloma-associated
$A\beta_2M$	β_2-microglobulin	SL?	Hemodialysis-associated joints
ATTR	**Transthyretin***	**S**	**Familial senile systemic**
AA	**Serum amyloid A**	**S**	**Secondary, reactive**
AApoAI	Apolipoprotein AI	S, L	Familial aorta, meniscus
AApoAII	Apolipoprotein AII	S	Familial
AApoAIV	Apolipoprotein AIV	S	Sporadic, associated with aging
AGel	Gelsolin	S	Familial
ALys	Lysozyme	S	Familial
AFib	Fibrinogen α-chain	S	Familial
ACys	Cystatin C	S	Familial
ABri	ABriPP	S	Familial dementia, British
ALect2	Leukocyte chemotactic factor 2	S	Mainly kidney
ADan†	ADanPP	L	Familial dementia, danish
Aβ	Aβ protein precursor (AβPP)	L	Alzheimer's disease, aging
APrP	Prion protein	L	Spongioform encephalopathies
ACal	(Pro) calcitonin	L	C-cell thyroid tumors
AIAPP	Islet amyloid polypeptide‡	L	Islets of langerhans
AANF	**Atrial natriuretic factor**	**L**	**Cardiac atria**
APro	Prolactin	L	Aging pituitary prolactinomas
AIns	Insulin	L	Iatrogenic
AMed	Lactadherin	L	Senile aortic, media
Aker	Kerato-epithelin	L	Cornea, familial
ALac	Lactoferrin	L	Cornea
AOaap	Odontogenic ameloblast-associated protein	L	Odontogenic tumors
ASemI	Semenogelin I	L	Vesicula seminalis

Note: Proteins are listed, when possible, according to relationship. Thus, apolipoproteins are grouped together, as are polypeptide hormones. Proteins in **bold face** have been identified in cardiac tissue.
*Previously called prealbumin
†ADan comes from the same gene as ABri
‡Also called "amylin"

leading to cardiac amyloidosis are: (1) AL amyloid (phenotypically referred to as primary amyloidosis) originates from clonal populations of immunoglobulin light chains, and it is the most common type in developed countries; (2) ATTR amyloid, phenotypically responsible for both SSA (due to amyloidogenic wild-type transthyretin protein deposition) and familial/hereditary amyloidosis (originates from transthyretin gene mutations); (3) AA amyloid, also described as secondary amyloidosis, is due to serum amyloid A (SAA) protein deposition in the setting of chronic infections or untreated inflammatory conditions and (4) isolated atrial natriuretic factor (AANF) amyloid, which causes isolated atrial amyloidosis (IAA), a common autopsy finding in elderly patients with unclear clinical significance but it may be associated with atrial fibrillation. The major APP in this case is atrial natriuretic peptide.

LIGHT CHAIN (AL) AMYLOIDOSIS

Light chain (AL) amyloidosis or primary amyloidosis is a disease that results from tissue deposition of immunoglobulin light chain fragments. It is the most common form of systemic amyloidosis, accounting for 85% of all new cases of amyloidosis and 2,000–2,500 new cases annually in the United States.[27] The disease is found with a slight male predominance, and it usually presents after age 50 years. This type of amyloidosis results from the excess production of amyloidogenic kappa (κ) or lambda (λ) light chains (more commonly λ) via the monoclonal expansion of plasma cells. The plasma cell dyscrasia is usually distinct from multiple myeloma; however, myeloma coexists in 10–15% of cases, and it carries a worse prognosis.[28] More rarely, Waldenström's macroglobulinemia is associated with AL amyloidosis.[29] The plasma cell number, degree of clonality,

quantity of light chains and the light chain isotype are related to survival.[30] Very rarely, a patient with a plasma cell dyscrasia may develop restrictive CMP due to the deposition of light chains in a non-amyloid manner.[31] The so-called light chain deposition disease is similar pathogenetically to AL amyloidosis, but the light chain fragments do not have the necessary biochemical characteristics to form amyloid fibrils. The natural history and therapies for light chain deposition disease may be different with AL amyloidosis.

Amyloid deposition in AL amyloidosis is usually widespread, affecting multiple organs and the prognosis is generally poor. Cardiac involvement is common, occurring in 60–90% of patients, and heart failure related to amyloid CMP is the most common cause of death in these patients. Direct toxic effects asserted by light chains on cardiomyocytes probably account for the worse survival in AL cardiomyopathy (AL-CMP) patients. Other organs involved in AL include the kidneys (74%), liver (27%), peripheral nervous system (22%) and autonomic nervous system (18%). Carpal tunnel syndrome (20%) may precede other manifestations of the disease.[27] Isolated cardiac involvement is rare, occurring in less than 5% of cases.[32] AL amyloid also frequently infiltrates the blood vessels, particularly small vessels within the myocardium, and patients may present with symptoms of exertional angina.

Cardiac involvement in AL amyloidosis often leads to significant rapidly progressive cardiac dysfunction and death. Indeed, the median survival in untreated patients with AL amyloidosis is only 4–6 months, which is worse than patients with amyloid CMP due to familial or senile ATTR amyloidosis. The clinical presentation of AL amyloid CMP is usually dominated by right-sided heart failure including peripheral edema and hepatomegaly. However, nephrotic syndrome may contribute to the edema, and amyloid infiltration of the liver can contribute to hepatomegaly. Presyncope and syncope are not uncommon in these patients, and exertional syncope in particular is an ominous sign.[33] Exertional syncope is typically a marker of severe restrictive CMP with low stroke volume and cardiac output. It occurs because stroke volume and cardiac output do not increase appropriately in the face of peripheral vasodilation during exercise in order to provide sufficient cerebral perfusion, and it is associated with a high mortality (often sudden cardiac death) within three months of the initial event. Other factors that can contribute to syncope in these patients include postural hypotension from excessive diuresis or autonomic neuropathy (most common cause), conduction system disease with atrioventricular block (rare) and, very rarely, cardiac tamponade related to pericardial effusion from pericardial amyloid deposits. Ventricular arrhythmias infrequently cause syncope, probably because the hypoperfusion that results from tachyarrhythmias is poorly tolerated and are more likely to result in death. Occasionally, patients with AL amyloidosis may present with stroke, often cardioembolic in origin. As previously discussed, intracardiac thrombi are not uncommon in cardiac amyloidosis even in sinus rhythm, particularly in AL amyloidosis. Rarely, patients with AL amyloid CMP may present with asymmetric ventricular septal wall thickening and a dynamic outflow tract gradient that mimics hypertrophic CMP.[34] This entity may be more common in patients with senile ATTR rather than AL amyloidosis.[35,36]

SENILE SYSTEMIC AMYLOIDOSIS

Senile systemic amyloidosis (ATTR), better known as SSA, generally affects elderly men, and its incidence is increasing as the population ages. In a Finnish population-based study, the prevalence of SSA was 25% in individuals over aged 85 years.[37] Although SSA is more common in men,[38] and typically presents in after age 70 years, it can present in younger individuals.[39,40] In SSA, the amyloid fibril protein is derived from normal (non-mutant, wild-type).[38,41-43] In elderly patients, wild-type transthyretin (TTR) may become structurally unstable, resulting in the development of misfolded intermediates that ultimately aggregate and precipitate as amyloid. Recently, mutations in the genes for alpha2M and tau were found in some patients with SSA. In contrast to the rapid progression of heart failure in AL amyloidosis, SSA results in slow, relentless progression of heart failure, and the survival is better with AL amyloid. In a study by Ng et al., despite patients with SSA having greater ventricular wall thickness than those with AL amyloidosis, the median survival of patients with SSA was 75 months (6.25 years), which compared favorably to patients with AL cardiac amyloid (11 months; p 0.003).[44] Except for the frequent coexistence of carpal tunnel syndrome,[45,46] senile ATTR is often clinically limited to the heart. However autopsy reports, in cases of SSA, have found that the amyloid deposits in multiple different organs, thus its designation as a systemic disease.[16,38,44] SSA should be suspected in an elderly male with heart failure with preserved ejection fraction and unexplained ventricular wall thickening noted on echocardiography. EKG voltage may be low or normal, atrial fibrillation or flutter and right or bundle branch block may be present.[47] Sometimes permanent pacemaker implantation is required.[48-50]

FAMILIAL (HEREDITARY) SYSTEMIC AMYLOIDOSIS (ATTR AND OTHERS)

The number of identified hereditary/familial amyloidogenic proteins that can lead to amyloid deposition in the heart is growing. It is estimated that familial amyloidosis accounts for approximately 10% of cardiac amyloid cases.[51] Familial amyloidoses are inherited in an autosomal dominant manner and clinically present as any combination of neuropathy, nephropathy and/or CMP, sometimes with gastrointestinal involvement.[52-55] Occasionally, ATTR amyloidosis presents with isolated amyloid CMP.[56] A family history of neurologic disease, heart failure or early death suggests the diagnosis, but spontaneous cases are frequent and the disease may have been missed in earlier generations[57,58] (Hellman, 2008).

By far, the most frequent type of hereditary amyloidosis is transthyretin amyloidosis (ATTR). More than hundred point mutations in the transthyretin gene leading to amyloidosis have been identified to date. Plasma transthyretin is synthesized by the liver and is a carrier of the thyroid hormone thyroxine and retinol. This is how transthyretin gained its name, transports *thyroxine* and *retinol*. TTR was originally called prealbumin because it was immunologically similar to prealbumin.[59] The main clinical manifestation observed in patients with ATTR is a progressive sensory peripheral neuropathy. Hence, the disorder was formerly better known as familial amyloid polyneuropathy. Patterns of disease penetrance, clinical presentation and organs

involved are variable and roughly determined by the TTR point mutation.[52-54] The most common TTR variant is in one in which methionine replaces valine at position 30 (ATTR Val30Met),[54] which is associated with cardiac involvement typically in the form of sinus node dysfunction, bundle branch block or atrioventricular block.

Another TTR variant, which is seen almost exclusively in older black American patients, involves a substitution of isoleucine for valine at position 122 (ATTR V122I). Approximately 3–4% of black American males are heterozygous for this mutation.[60,61] The clinical presentation is often similar to senile systemic ATTR amyloidosis in that it usually presents in older males with isolated cardiac involvement, sometimes also with a history of carpal tunnel syndrome; however, in a study of 156 self-identified African Americans referred to a referral center for the diagnosis of amyloidosis, ATTR V122I and AL were equally prevalent as the cause of CMP.[62] The frequency of this heritable form of amyloid CMP in this population underscores the importance of considering the diagnosis of ATTR V122I amyloidosis in black American males presenting with late onset heart failure with features of cardiac amyloidosis.

Several less common forms of familial amyloidosis are also rarely associated with cardiac disease, including variants of fibrinogen (AFib),[63,64] apolipoprotein A1 (AApo-A1)[65-68] and apolipoprotein AII (AApo-AII)[69] that are also produced in the liver. In addition, mutant or native AApo-A1 has been reported to co-localize with wild-type ATTR in amyloid deposits in the hearts of some patients with systemic amyloidosis.[70] Although patients with AFib, AApo-AI and AApo-AII present with predominantly renal amyloidosis, cardiac involvement in the form of both restrictive and dilated CMPs have been described. In addition, coronary and systemic arterial amyloid atheromatous diseases are not uncommon, and are often predate the development of proteinuria or renal failure by several years. Cardiac parasympathetic neuropathy[71] and bradycardia requiring pacemaker insertion, and systemic autonomic neuropathy have also been described. In addition, genetic mutations in the plasma protein gelsolin (AGel) lead to systemic familial amyloidosis with predominantly cranial and peripheral neuropathies, skin involvement (cutis laxa), kidney involvement and lattice corneal dystrophy.[72] Cardiac involvement has been reported with AGel amyloidosis and is usually restricted to the conduction system, sometimes requiring a permanent pacemaker.[49,50,73,74]

SECONDARY AMYLOIDOSIS

The term secondary amyloidosis,[75] also known as reactive systemic amyloidosis, was used to describe the disease that results from excess production of a non-immunoglobulin protein, known as SAA protein. Worldwide, AA amyloidosis is one of the most common types of systemic amyloidosis. The amyloid fibrils are derived from chronic systemic infectious or inflammatory processes with high expression of the acute-phase reactant protein SAA, which is mainly expressed by the liver under regulation by several cytokines. Clinically, AA amyloidosis is associated with conditions such as chronic lung disease, inflammatory bowel disease, rheumatoid arthritis and chronic infections such as tuberculosis. The kidney is the main organ involved, and, although amyloid deposits are frequently present upon endomyocardial biopsy, clinically significant cardiac amyloidosis is rare, occurring in only about 2% of cases. The prognosis with AA is generally much better than in cases of AL amyloid.[76] However, among patients with systemic AA amyloidosis, the presence of cardiac involvement confers a worse prognosis.[75,77,78] In one series, the 5-year survival rate for patient with cardiac involvement was 31% versus 63% in those without cardiac involvement.[75]

ISOLATED ATRIAL NATRIURETIC FACTOR

Isolated atrial amyloidosis is a localized variant of cardiac amyloid that appears to have a high prevalence among older patients. The major protein subunit of the amyloid fibril in IAA is atrial natriuretic peptide (hence, its official description as AANF for amyloid atrial natriuretic factor), which is synthesized and deposited locally in the cardiac atria. The clinical significance is not certain, although it is associated with atrial tachyarrhythmias.[79] AANF first appears in the fourth decade, and its prevalence increases by 15–20% per decade, reaching up to 90% incidence in an unselected octogenarian population.[80] In contrast to senile systemic ATTR amyloidosis, which is more common in men, AANF disease is more prevalent in women. Despite its high incidence, the pathogenesis and clinical consequences of IAA are poorly defined; however, it may be important in the development of atrial fibrillation and atrial conduction abnormalities.[79] Diseases affecting the heart, such as mitral valve disease, may influence the progression of AANF. A high prevalence of IAA has been described among patients undergoing cardiac surgery[81] and in a patient with chronic heart disease, including rheumatic disease.[82,83] Mitral valve disease may cause significant dilation and hypertrophy of the left atrium, which in turn may stimulate synthesis and secretion of ANP, contributing to the deposition of AANF. Simultaneous deposition of AANF and senile ATTR amyloidosis has been described.[84] The diagnosis of AANF can only be made by tissue biopsy, often at autopsy, as there are no specific noninvasive features.

CLINICAL FEATURES OF CARDIAC AMYLOIDOSIS

HISTORY AND PHYSICAL EXAMINATION

The symptoms of amyloid CMP are often vague (fatigue, edema, weight loss), and this often leads to a delay in the diagnosis. Indeed, early diagnosis of the disease remains a major challenge in clinical cardiology. Awareness and clinical suspicion are paramount for making the correct diagnosis. Patients often present with dyspnea and symptoms predominantly of right-sided heart failure, such as ankle edema and increased abdominal girth. Although the reasons are poorly understood, ascites is often more marked than peripheral edema much like it is with other causes of restrictive CMP and constrictive pericarditis. In contrast to overt signs of right-sided congestion, symptoms of left-sided heart failure, such as paroxysmal nocturnal dyspnea and orthopnea, are often absent despite marked fluid retention. Occasionally, patients may present with palpitations due to atrial or ventricular arrhythmias. Orthostatic hypotension may occur from volume depletion related to diuretics or due to autonomic

neuropathy from amyloid infiltration. Amyloid may also infiltrate multiple different tissues leading to diverse manifestations of the disease such as skin and soft tissue thickening, vocal cord infiltration and hoarseness, adrenal gland or thyroid infiltration with resultant hypoadrenalism or hypothyroidism, lymphadenopathy, pulmonary infiltrates, factor X inhibition with bleeding diathesis and mesenteric infiltration with diarrhea.

The physical findings of systemic amyloidosis include enlargement of the tongue (macroglossia) and periorbital purpura (raccoon or panda eyes). Although very specific for the diagnosis, these signs are seen in less than 20% of patients with AL and may be easily overlooked. More frequent are recurrent petechial lesions of the eyelids, which may occur after coughing or rubbing the eye area, and result from vascular fragility. The cardiac exam reveals evidence of restrictive filling of the right ventricle with elevated jugular venous pressure, which may paradoxically increase with inspiration (Kussmaul's sign), hepatomegaly and ascites, and peripheral edema. There may also be signs of low cardiac output with cool extremities and delayed nail bed capillary refill. Auscultation often reveals a third heart sound (S3); however, a fourth heart sound (S4) is often absent because amyloid infiltration of the atria markedly impairs atrial contraction. Systolic regurgitant murmurs may be present due to mitral or tricuspid valve insufficiency; however, they are not usually severe. The blood pressure is often normal or reduced with a narrow pulse pressure consistent with low cardiac output state.

DIAGNOSTIC TESTS

The diagnosis of amyloidosis requires the histopathologic demonstration of amyloid within tissue and immunohistochemical identification of the specific amyloid fibril type. There is no single noninvasive diagnostic test for cardiac amyloidosis; however, in cases of known systemic amyloidosis, the diagnosis of amyloid CMP can be reasonably certain based upon noninvasive findings that are consistent with the diagnosis. For instance, cardiac involvement in AL amyloidosis has been defined by a consensus expert opinion as either a positive heart biopsy and/or increased left ventricular wall thickness (interventricular septal thickness > 12 mm) in the absence of hypertension or other potential cause of true left ventricular hypertrophy.[35] Additionally, elevations of the serum cardiac biomarkers appear to be even more sensitive markers of cardiac involvement in AL amyloidosis than other noninvasive modalities.[85,86] Serum BNP may also help to identify cardiac involvement in cases of hereditary ATTR amyloidosis.[87]

TISSUE DIAGNOSIS

As mentioned, the diagnosis of amyloidosis requires tissue confirmation of its presence and identification of the responsible APP. Amyloid is an amorphous extracellular material, which stains pink with hematoxylin and eosin (Fig. 1), and its presence is confirmed with Congo red staining followed by the demonstration of characteristic apple-green birefringence under polarized light (Fig. 2). Although not required for the diagnosis of amyloid, when viewed with electron microscopy, all types of amyloid demonstrate rigid, non-branching fibrils with a consistent diameter of 7.5–10 nm (Fig. 3). Antibodies are now available to identify most known amyloid fibril proteins using immunohistochemical staining techniques. DNA analysis is used to detect established mutations of the TTR gene and confirm the diagnosis of familial ATTR amyloidosis, when immunohistochemical staining detects TTR as the amyloid fibril type on biopsy. Senile TTR amyloidosis is a diagnosis of exclusion in a sense, in that this diagnosis is typically made in cases where there is TTR amyloid identified on biopsy yet genetic testing fails to detect a mutation in the transthyretin gene. DNA sequencing is the method used to identify novel and established APP gene mutations associated with hereditary amyloidosis.

In cases of suspected cardiac amyloidosis based upon the clinical history, examination and/or echocardiographic findings, a tissue biopsy should be obtained, preferably from an easily accessible site. Although the sensitivity of detecting amyloidosis within the heart via endomyocardial biopsy is virtually 100% due to widespread deposition within the myocardium,[88] it is associated with a risk for myocardial perforation and life-threatening cardiac tamponade. Less invasive tissue sampling methods are available for diagnosing systemic amyloid disease. Abdominal fat aspiration can be easily performed without serious complications and has sensitivity for detecting systemic amyloidosis in 57–88% of cases.[89-94] It is the preferred initial biopsy site in cases of suspected amyloidosis. Although rectal submucosa was previously the traditional biopsy site, it can be complicated by bleeding or perforation and the sensitivity for detecting systemic amyloidosis does not appear to be better than with abdominal fat pad biopsy. Other potential biopsy sites include the gingiva, bone marrow, liver or kidney when clinical suspicion for the respective organ involvement exists. Endomyocardial biopsy specimens should be obtained and analyzed if less invasive methods fail to enable diagnosis of suspected cardiac amyloidosis. Histologically, myocardial cells are separated and distorted by amyloid deposition and the intramyocardial vessels are frequently infiltrated by amyloid.[95]

RADIOLOGIC FINDINGS

The chest X-ray is often unremarkable, but there may be cardiomegaly, which is usually due to biatrial dilatation. Pulmonary edema and pleural effusions may be present, particularly when heart failure is present. However pleural based amyloid deposits may rarely cause pleural effusions and they should be suspected in cases when the effusions persist in a patient with compensated heart failure after adequate diuresis.[96]

ELECTROCARDIOGRAPHY

Patients with cardiac amyloidosis frequently have EKG abnormalities (Fig. 5). The amyloid deposits seen in this kidney biopsy under polarized light microcopy are stained with Congo red. Under polarized light, they take on an "apple-green" birefringence characteristic of amyloid; as one of the polarizing films is rotated, the green color turns into yellow and the yellow into green. The presence of low voltage QRS complexes in the limb and/or precordial leads, particularly in the presence of increased left ventricular mass on echocardiography, is highly suggestive amyloid CMP.[97-100] In true left ventricular hypertrophy, the EKG shows increased or normal QRS voltage, whereas infiltration from amyloidosis often results in low

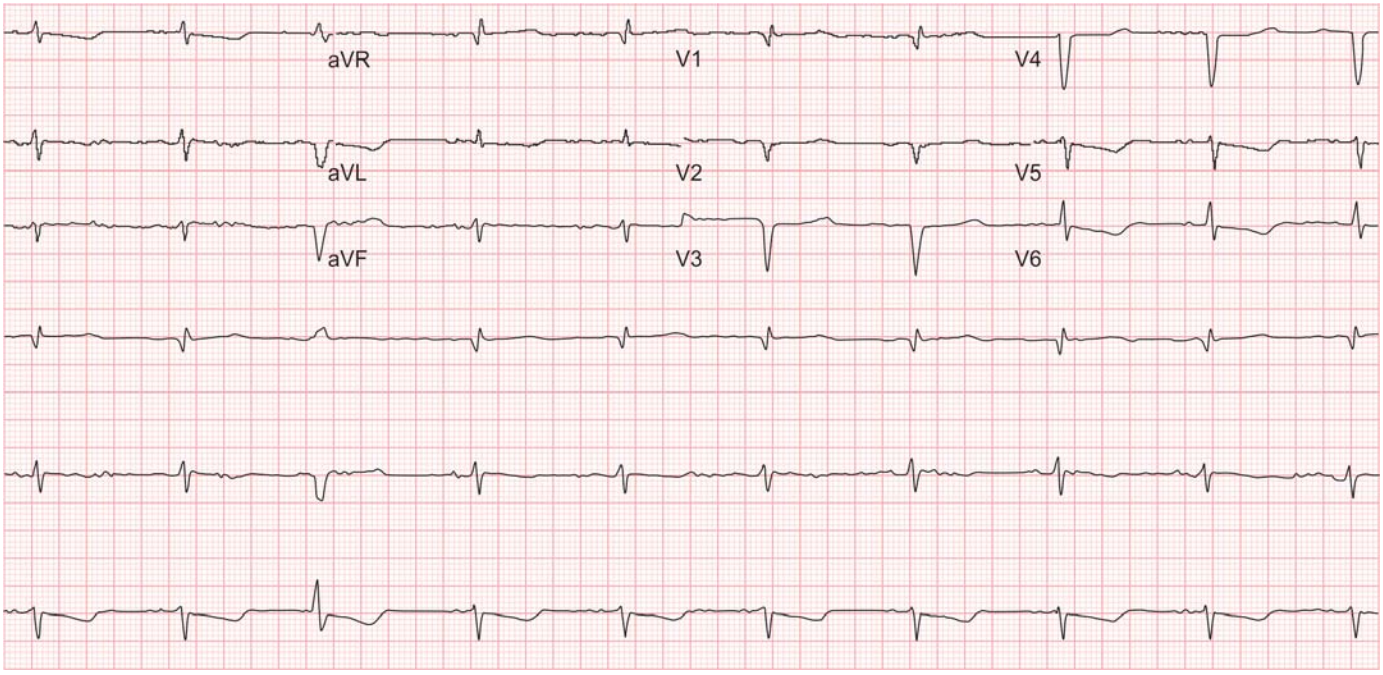
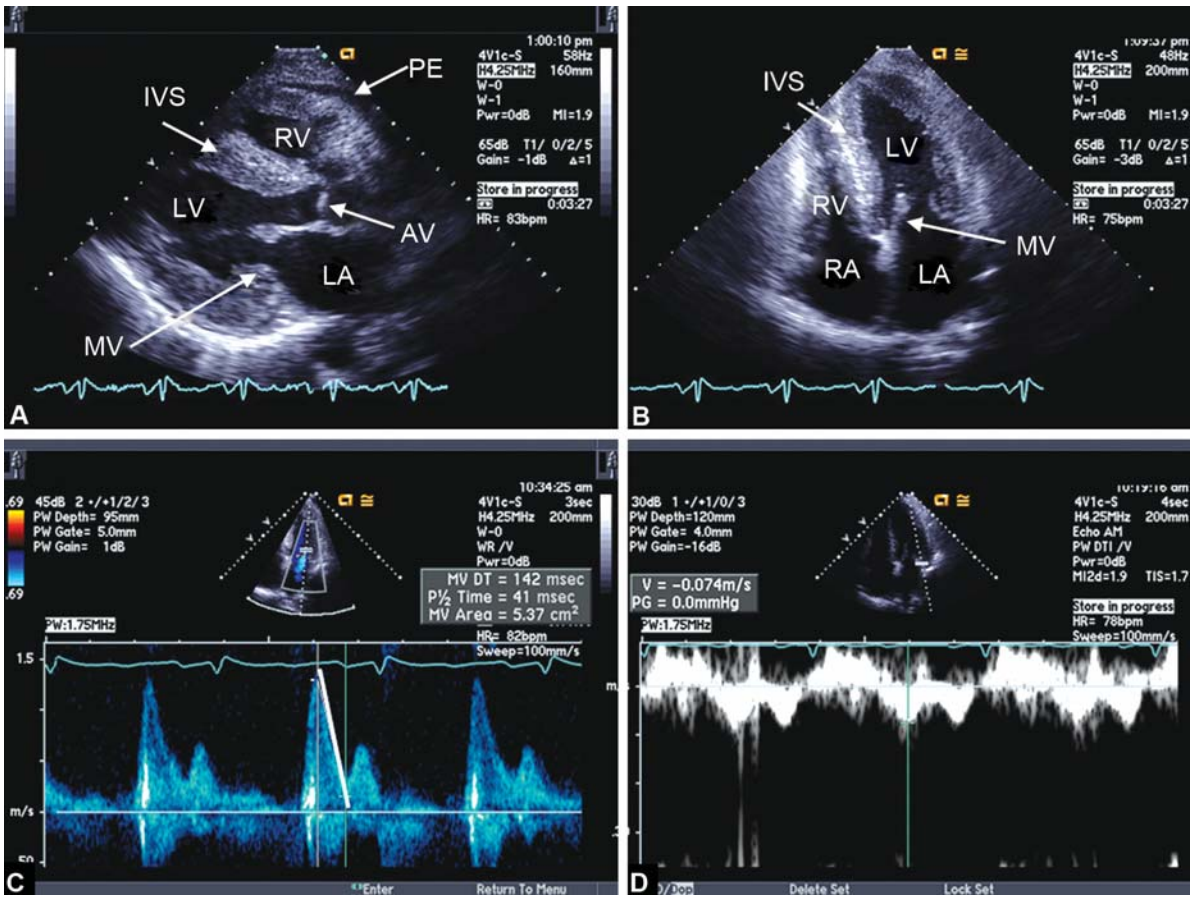


FIGURE 5: Electrocardiogram of a woman with dyspnea shows QS waves in precordial leads V1–V4, suggesting anterior wall myocardial infarction. Note low QRS voltages in limb leads. Echocardiography showed typical features of cardiac amyloidosis that was later confirmed with a biopsy specimen

voltage.[32] A "pseudoinfarction pattern" characterized by small or absent R waves (Q waves) in the right precordial or inferior leads may simulate an old myocardial infarction.[101] Patients may be incorrectly diagnosed as having had a prior silent ischemic event. Sinus node dysfunction and prolongation of the PR interval is also common.[50] Atrial dilatation from restrictive CMP or amyloid infiltration may predispose to atrial fibrillation. Bundle branch block or extreme right or left axis deviation in the absence of hypertrophy may also be present.[101] Atrioventricular conduction defects are not uncommon, particularly in familial amyloidosis with polyneuropathy where it is associated with worse prognosis. However, high-grade block is uncommon. Electrophysiological testing is usually necessary to detect significant infra-Hisian block. Prolonged HV interval appears to be frequent in AL amyloidosis and may be missed on the surface EKG with a narrow QRS complex. It appears to be an independent predictor of sudden death. The association of HV prolongation and sudden death is likely multifactorial and represents either a marker of severe myocardial infiltration with an increased propensity for lethal ventricular arrhythmias or electromechanical dissociation, or indicate severe conduction system disease eventually leading to complete atrioventricular block and bradycardic death.[102]

ECHOCARDIOGRAPHIC FINDINGS

Two-dimensional and Doppler echocardiography is extremely helpful in the diagnosis of amyloid CMP. It should be noted that it is not possible to distinguish between the different types of amyloidosis by echocardiography. Typical findings include increased right and left ventricular wall thickness with normal or small ventricular chamber size, thickened interatrial septum and biatrial enlargement (Figs 6A to D). In some cases, the ventricular wall thickening may be regional. Amyloid infiltration characteristically produces a speckled or granular appearance to the myocardium on echocardiography.[103] Although this is a nonspecific finding that can also be seen in patients with ventricular hypertrophy from hypertrophic CMP, hypertensive heart disease or other infiltrative diseases, such as Fabry's disease, this finding should prompt the consideration of amyloidosis in the differential diagnosis. Diffuse valvular leaflet thickening without significant valve dysfunction is also characteristic of the disease. Left ventricular systolic function as determined by the ejection fraction is normal in the early course of the disease. However, as amyloid infiltration within the myocardium progresses, ventricular systolic dysfunction deteriorates, and the ventricle may even dilate in the later stages of disease. In approximately 5% of patients with cardiac amyloidosis, left ventricular infiltration may mimic hypertrophic CMP on the EKG, sometimes with dynamic left ventricular outflow tract obstruction.[34,36,104-106] These patients often have normal or even mildly hyperdynamic left ventricular function with normal voltage on the EKG. Small to moderate pericardial effusions may be present but only rarely lead to cardiac tamponade.[107-109] Doppler echocardiography is used to evaluate ventricular diastolic function. Varying degrees of left ventricular diastolic dysfunction are often present, depending on the disease stage.[110] A restrictive pattern consistent with advanced left ventricular diastolic dysfunction with an increased E wave velocity, short deceleration time, and low A wave velocity (Fig. 6C) is characteristic of advanced amyloid CMP; however, early in the course of the disease, mild (grade I) left ventricular diastolic dysfunction may be present.[110,111] A Doppler index combining systolic and diastolic myocardial performance has been shown to be predictive of survival in patients with cardiac amyloidosis.[112] Tissue Doppler velocities of the mitral annulus



FIGURES 6A TO D: Echocardiographic images demonstrating typical, but nonspecific findings of restrictive cardiomyopathy from amyloidosis. (A) Parasternal long-axis view showing severely thickened left and right ventricular walls, mitral valve thickening. A trace pericardial effusion is also present. (B) Apical four-chamber view showing normal ventricular chamber volumes, severely thickened left ventricular, right ventricular and interventricular septal walls. The left and right atria are both markedly dilated, typical of restrictive cardiomyopathy. (C) Pulsed wave Doppler of mitral inflow showing a short mitral E wave deceleration time (white line) of 142 msec and peak E/A ratio of greater than 2:1, typical of restrictive physiology. (D) Tissue Doppler velocity of mitral annular early diastolic filling (E') measuring 0.074 m/sec, which is markedly reduced, consistent with left ventricular diastolic dysfunction. (Abbreviations: AV: Aortic valve; IVS: Interventricular septal; LA: Left atrium; LV: Left ventricular; MV: Mitral valve; PE: Pericardial effusion; RA: Right atrium; RV: Right ventricular)

during early diastolic filling of the left ventricle (E' velocity) are markedly reduced in advanced stages of ventricular diastolic dysfunction (Fig. 6D) from cardiac amyloid.[113] Atrial amyloid infiltration may lead to atrial standstill, as evidenced by the absence of a transmitral atrial filling wave (A wave) despite sinus rhythm on the EKG, and this finding is associated with thrombus[114] formation and high risk for thromboemboli.[115,116] However, intracardiac thrombi may be present within any chamber. Although generally still considered to be an investigational tool, tissue Doppler interrogation of left ventricular long axis systolic function, using tissue velocity, strain and strain rate imaging, is a newer technique that may be able to detect early impairment of systolic function in cardiac amyloidosis before traditional echocardiographic measures of systolic function, which could eventually lead to earlier detection of cardiac amyloidosis and treatment[117,118] (Sallach, 2004). In addition, the finding of increased twisting and untwisting motions using spectal tracking may be a sign of early cardiac involvement in AL amyloidosis patients.[119]

LABORATORY FINDINGS

Patients with amyloid CMP, as with other causes of heart failure, may develop raised serum creatinine due to inadequate renal perfusion and the cardiorenal syndrome. However systemic amyloidosis should be considered in the differential diagnosis of a patient with unexplained heart failure and heavy proteinuria, especially if in the nephrotic range. Amyloidosis accounts for 13% of adult patients with nephrotic syndrome.[120] In patients suspected of having cardiac amyloidosis, the initial investigation should include serum and urine analysis for the presence of a monoclonal immunoglobulin light chains, in addition to standard blood tests such as blood count, urea, electrolytes, liver function tests, clotting screen, glucose and thyroid function tests. Standard serum protein electrophoresis may not be able to detect a monoclonal band if the amount of circulating paraprotein or its fragments is small.[121] Immunofixation techniques have a reported sensitivity for detecting AL amyloidosis of 69% (serum) and 83% (urine), whereas the serum free light chain (FLC) assay, which measures the circulating levels of serum κ

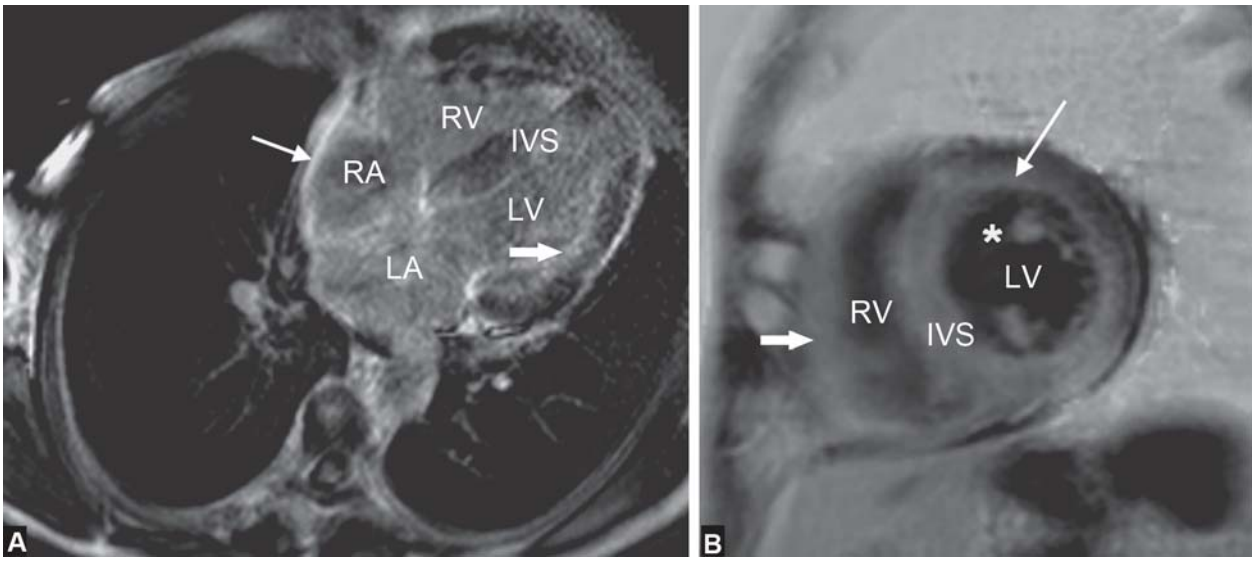
and λ light chains and their ratio, is more sensitive and detects 91–98% of cases.[122,123] However, the sensitivity of the combination of all three test approaches 100% and is recommended for all patients suspected of having amyloid CMP.[35,123,124] The serum FLC assay has become an established standard in the diagnosis, prognosis and response to therapy in patients with AL amyloidosis.[35,122-128] Once the diagnosis of AL amyloid is suspected based on serologic testing and/or clinical presentation, a bone marrow biopsy is necessary to confirm the diagnosis of a plasma cell dyscrasia, exclude coexistent multiple myeloma and evaluate for bone marrow amyloid infiltration. If the laboratory testing and bone marrow biopsy do not suggest AL, a search for other forms of amyloidosis should be pursued. In the past several years, serum cardiac biomarkers have been introduced as adjunctive markers for the presence and severity of cardiac amyloidosis, especially in AL amyloidosis. Elevated levels of cardiac troponin T (cTnT) or cardiac troponin I (cTnI) and/or serum brain-type natriuretic peptide (BNP) or N-terminal pro-brain natriuretic peptide (NT pro-BNP) levels can diagnosis the presence of cardiac involvement in AL amyloidosis with greater sensitivity than all other noninvasive diagnostic modalities.[85,86,129] Using cutoff values of NT-pro-BNP less than 332 ng/l and either cTnT less than 0.035 µg/l or cTnI less than 0.1 µg/l, Dispenzieri et al. classified AL amyloid patients into three stages of disease, which have strong prognostic significance: Stage I, both biomarkers are normal (33% incidence); Stage III, both values are high (30% incidence); or Stage II, only one marker is high (37% incidence). The median survivals for stages I, II, and III were 26.4, 10.5 and 3.5 months respectively.[129] In contrast to AL-CMP, the cardiac biomarkers are less sensitive for the detection of CMP in other types of amyloidosis; however, serum BNP elevations can be suggestive of cardiac involvement in ATTR.[87]

CARDIAC MAGNETIC RESONANCE IMAGING

Cardiac magnetic resonance imaging has been shown to detect cardiac amyloidosis with a high sensitivity.[130] In patients undergoing endomyocardial biopsy, the diagnostic accuracy of CMR is as follows: sensitivity 88%, specificity 90%, positive predictive value 88% and negative predictive value 90%.[131] CMR imaging of amyloid CMP shows a characteristic pattern of subendocardial delayed hyper-enhancement (DHE) and rapid clearance of gadolinium from the blood pool leaving it colored black (Figs 7A and B). In addition, other findings supportive of the diagnosis of amyloidosis include diffuse thickening of all cardiac walls and late gadolinium enhancement the walls of the atria. CMR is probably most useful as a noninvasive test to detect amyloidosis when noncardiac tissue stains have been negative for amyloid, but the diagnosis of cardiac amyloid is suspected. CMR may also have prognostic value in patients with AL-CMP.[132] In one study, the finding of DHE on CMR provided incremental diagnostic[121] utility and was a stronger predictor of 1-year mortality in patients with suspected amyloid CMP as compared with other noninvasive parameters.[131]

CARDIAC CATHETERIZATION HEMODYNAMICS

Hemodynamic assessment by cardiac catheterization has limited utility beyond noninvasive tests to assess suspected amyloid heart disease. However it is used to perform an endomyocardial biopsy and confirm the diagnosis amyloidosis, assess the hemodynamics for signs of restrictive physiology and evaluate coronary artery anatomy when clinically indicated.[121] In advanced amyloid CMP, right heart catheterization typically reveals restrictive physiology, which is characterized by elevated biventricular filling pressures and a prominent early diastolic dip followed by mid-to-late diastolic plateau. This finding, also



FIGURES 7A AND B: Cardiac magnetic resonance imaging with gadolinium. (A) Four-chamber view showing the characteristic pattern of subendocardial delayed hyperenhancement (thick arrow). Other notable features of cardiac amyloidosis are marked left and right ventricular wall thickening. Delayed hyperenhancement of the right atrial wall is also present (thin arrow). (B) Cross-sectional view showing the unique characteristic of cardiac amyloidosis to rapidly clear gadolinium from the blood pool leaving it colored black (marked by asterisk). These findings are highly suggestive of cardiac amyloidosis. Other notable features suggesting cardiac amyloidosis are thickening and delayed hyperenhancement of the right ventricular free wall (thick white arrow) and subendocardial delayed hyperenhancement of the left ventricle, interventricular septum. (Abbreviations: IVS: Interventricular septal; LA: Left atrium; LV: Left ventricular; RA: Right atrium; RV: Right ventricular)

known as the square root sign, is characteristically noted in both ventricular pressure curves. Simultaneous right and left heart catheterization, although not often needed in patients with suspected cardiac amyloidosis, may demonstrate concordance of ventricular pressures during respiration that is typical of a restrictive CMP. In addition, depending on the extent and severity of amyloid infiltration and restrictive CMP, the cardiac output may be low and varying degrees of passive or mixed precapillary and postcapillary pulmonary hypertension may be present. It should be noted that amyloid infiltration of pulmonary vessels can also lead directly to pulmonary hypertension from pulmonary vascular disease.[25]

SERUM AMYLOID P COMPONENT SCINTIGRAPHY

Serum amyloid P (SAP) is a cofactor which presents all of the amyloidoses. SAP scintigraphy imaging with ^{123}I-labeled human SAP is useful for locating and monitoring the extent of systemic amyloidosis, because the P component is present in all types of amyloid. It allows the quantification of amyloid burden in systemic amyloidosis; however, it is not useful for the identification of amyloid in the heart because uptake by the heart may be obscured by the high blood flow and the slow passage of the tracer across myocardial capillary endothelia.[133,134]

PROGNOSIS

Across the entire spectrum of systemic amyloidoses, patients with AL-CMP have the worst prognosis, especially patients with coexistent multiple myeloma. Median survival among patients with AL-CMP treated with oral chemotherapy is less than 6 months.[135] When stem cell transplantation (SCT) was introduced, the prognosis of patients with AL amyloidosis significantly improved with median survival rates increasing from 12–18 months to 4.6 years.[136,137] However patients with advanced AL-CMP are ineligible for this therapy because of high treatment-related mortality, and among patients with AL-CMP, who are eligible and undergo SCT, the survival is often less than 2 years.[136] Recently it has been established that not only is the presence of amyoid within the heart associated with generally poorer prognosis but also the extent of cardiac involvent, as evidenced by cardiac biomarker levels, at presentation and with therapy has even greater prognostic value.[85,86,138] As stated previously, a staging system for AL amyloidosis was developed and validated based on cardiac biomarker levels. This staging system is being routinely used to evaluate treatment outcomes in patients with AL and to identify which patients may not benefit from therapy.[129,139] Among patients treated with high-dose melphalan (HDM)/SCT, the median survivals for stages I, II, and II were 26.4, 10.5 and 3.5 months respectively.[129] Other multivariate predictors of survival in AL-CMP include New York Heart Association class III or IV, presence of pleural effusion, brain natriuretic peptide level more than 493 pg/ml, ejection time less than 273 ms, and peak longitudinal systolic basal anteroseptal strain less negative than or equal to –7.5%.[140] A recent report of 434 patients, who underwent risk-adapted HDM/SCT treatment of AL amyloidosis showed that approximately 50% had AL-CMP, and although survival in this subgroup was not reported, the most important determinant of survival among all patients was the stage of disease according to cardiac biomarker levels. Among the 213 patients who were staged, 79 (37.1%) patients were stage I, 81 (38.0%) were stage II and 53 (24.9%) were stage III, and whereas the median survival had not been reached after 70 months for stages I and II, it was 58 months (4.8 years) for stage III.[141] This suggests that with a better understanding of risk factors and patient selection (e.g. excluding patients with advanced CMP, age more than 70 years, more than two organs involved, poor performance status, serum creatinine value more than 1.7 mg/dL) the outcomes with SCT have improved among eligible AL patients.[139,141] In selected patients with advanced AL-CMP and little or no other organ involvement, combined or sequential orthotopic heart transplantation (OHT)/SCT can significantly improve survival. Heart transplantation for amyloidosis is evolving and most centers still consider AL-CMP to be a contraindication; however, in well-selected patients, OHT can significantly improve survival so long as the underlying amyloidogenesis is successfully treated, and in some cases, survival approaches non-amyloid transplant recipients.[4-6,8,142-144]

In contrast to amyloid CMP related to AL, patients with ATTR-CMP generally have a better prognosis, although survival rates are expected to vary depending on the specific TTR variant and extent of organ involvement. One study of patients with senile ATTR-CMP showed that the 1-year survival was 97% compared with 38% ($p < 0.002$) in patients with AL-CMP despite similar echocardiographic severity of disease.[145] Similar to hereditary ATTR-CMP, patients with senile ATTR-CMP survive longer than AL-CMP. In a study by Ng et al., survival of patients with senile ATTR-CMP was 75 months, which compared favorably with AL-CMP patients whose survival was 11 months ($p = 0.003$) despite the senile group being older and having more myocardial disease by echocardiography.[44] No staging systems have been developed for these patients.

TREATMENT OF AMYLOID CARDIOMYOPATHY

HEART FAILURE MEDICAL MANAGEMENT

Cardiac amyloidosis is an invariably progressive disease with very few therapeutic options. The approach to management of amyloid CMP involves: (1) management of congestive heart failure and (2) treatment to stop the production of the amyloidogenic protein. The medical management of heart failure in patients with amyloid CMP is very challenging, and none of the traditional therapies for heart failure has been shown to improve symptoms or survival with this disease. Moreover, most patients with advanced cardiac amyloidosis often have low blood pressure because of reduced cardiac output and coexistent autonomic neuropathy making neurohormonal blocking agents poorly tolerated, and they should be used with great caution. The vasodilator effects of angiotensin-converting enzyme inhibitors may provoke profound hypotension and are rarely helpful. Beta-blockers may be useful for the management of tachyarrhythmias; however, because patients with restrictive CMP have a mostly reduced, fixed stroke volume wherein the cardiac output is heart rate dependent, the negative inotropic and chronotropic properties may lead to hemodynamic deterioration and worsened symptoms. Amyloid fibrils bind to both digitalis and calcium channel blockers, and caution must

be exercised if they are administered at all to patients with cardiac amyloidosis because their use may be associated increased susceptibility to digitalis toxicity (note that tissue digoxin levels are not reflected in serum assays) and to worsened heart failure with calcium channel blockers.[146,147] The mainstay of the medical treatment is the careful titration of diuretics and fluid volume restriction to relieve symptoms of volume overload. Due to the steep pressure-volume relationship that is present in patients with restrictive CMP, it is often challenging to find an optimal fluid balance. Anticoagulation should be considered and appears to be protective in cases of atrial fibrillation or if there is evidence of severe atrial dilatation and mechanical atrial failure.[114-116,148] Large, recurrent pleural effusions may require thoracentesis and even pleurodesis if they are diuretic-refractory.

DEVICE THERAPIES

Patients with amyloid CMP often have sinoatrial node dysfunction and/or atrioventricular block that occasionally require permanent pacemaker insertion. Sudden cardiac death is common in patients with AL amyloidosis involving the heart, and preventing death related to ventricular arrhythmias can be challenging because the amyloid protein deposition in the myocardium may interfere with the normal cardiac electric excitation and increase the defibrillation threshold. Although isolated cases of successful defibrillation of recurrent ventricular tachyarrhythmias with appropriate internal cardioverter defibrillator (ICD) function have been documented in cardiac amyloidosis, most sudden deaths appear to be due to electromechanical dissociation, and thus are not amenable to ICD therapy.[149,150] In a series of 19 patients with either non-sustained ventricular tachycardia or high-grade ventricular arrhythmia treated with a prophylactic ICD, only 2 patients received appropriate shocks for sustained arrhythmia, whereas there were 6 patients died due to electromechanical dissociation.[150] For this reason, ICD placement in AL amyloidosis should be limited to patients with documented malignant arrhythmias with the understanding that it still may not prevent sudden cardiac death.

TREATMENT OF THE UNDERLYING AMYLOID DISEASE

Since there are very few therapeutic options for managing heart failure in these patients and the disease is progressive at least as long as the amyloidogenic proteins remain in circulation, shutting off the amyloid production if possible has the best chance of preventing further cardiovascular deterioration. Moreover, in patients with AL amyloidosis where circulating monoclonal light chains have direct cardiotoxic effects, effective treatment of the plasma cell dyscrasia can lead to a significant improvement in the signs and symptoms of heart failure and may even lead to improvement in echocardiographic abnormalities and attenuation of ventricular dysrhythmias in these patients,[151-153] even in some patients with myeloma-associated AL-CMP.[154]

No therapy is uniformly effective in the management of AL amyloidosis. Currently, the best outcomes of treatment for AL amyloidosis appear to be achieved with the combination of HDM and SCT (HDM/SCT), with eligible patients who survive the post-transplant period experiencing a median survival of 57 months (4.75 years), which includes nearly 50% of patients with cardiac involvement.[136] Unfortunately, patients with advanced amyloid CMP are not candidates for SCT because of exceeding high transplant-related mortality rates of up to 75%.[155] In fact, no more than 20–25% of patients with AL amyloidosis are eligible for transplant. Contraindications to HDM/SCT generally include congestive heart failure, left ventricular ejection fraction less than 40%, hypotension, hypoxemia, persistent pleural effusions and poor performance status.[136,137,141,156,157] In addition, relative contraindications include more than two organs involved, renal failure (creatinine > 2.0) and interventricular septal thickness greater than 15 mm. Survival after HDM/SCT depends greatly on the hematologic and organ responses as well as the stage of disease based on cardiac biomarkers, but more importantly the hematologic response. In patients, who are treated with HDM and SCT, a complete hematologic response rate, partial hematologic response rate and no hematologic response rate are seen in roughly one-third each. In a recent study, the median survival of patients with a complete hematologic response had not been reached whereas the median survival with a partial response was 107 months and 32 months ($p < 0.001$) in patients with no response.[141] Patients with cardiac involvement have the highest mortality rates among AL patients undergoing HDM/SCT. With staging of disease using biomarkers and a risk-adapted approach to patient selection and treatment, the treatment-related mortality (100 days) with melphalan/SCT has decreased from up to 75% in the past to where it is currently at 7–18%.[136,137,141,156] Even when carefully selected, patients with cardiac involvement, who undergo SCT, often develop arrhythmias and hypotension, which can be life-threatening.[136] For this reason, all patients with amyloid CMP should receive telemetry monitoring during SCT. The highest cardiac risk period is during stem cell mobilization with granulocyte colony stimulating factor, possibly because of the release of cytokines and other factors that can have deleterious effects on the already diseased myocardium.

In patients considered to be too high risk for HDM/SCT, melphalan and dexamethasone combination is still considered to be the standard intervention because of its low toxicity profile, its demonstrated ability to produce hematologic responses even in the presence of advanced disease, and the orally available formulations of both agents. Older studies of chemotherapy for AL using melphalan/dexamethasone (M-Dex) demonstrated that while survival was better than with colchicine, it was only 12–18 months, and less than 6 months for those with amyloid CMP.[135] However more contemporary studies of chemotherapy have demonstrated improved survival; however, reported survival rates vary dramatically between studies depending on the study population. Predictors of outcome include the serum BNP, number of organs involved and the severity of cardiac involvement detected by echocardiography. Medical therapies shown to be effective are based on alkylators, dexamethasone or combinations of an alkylator and steroids.[158] In addition, novel agents previously shown to be effective in multiple myeloma (e.g. thalidomide, lenalidomide and bortezomib) have been shown to have efficacy in the management of AL amyloidosis. Virtually all patients are candidates for a trial of these therapies.

For cases of hereditary or familial amyloidosis caused by variant transthyretin (ATTR), fibrinogen (AFib) and apolipoprotein (AApo-AI and AApo-AII), liver transplantation may be an effective treatment because APP is produced in the liver. However, much like with SCT, the presence of cardiac amyloidosis generally excludes patients from being eligible for liver transplantation. In addition, in cases of hereditary ATTR, progressive cardiac amyloidosis has been reported to occur following liver transplantation as a result of the deposition of wild-type TTR on a background of mutant ATTR amyloid.[159-162] Therefore, patients with ATTR being considered for liver transplantation should have a careful cardiac evaluation for the presence of amyloid.[163-170] Other potential strategies for ATTR currently under investigation are: (1) stabilizers of the TTR tetramer (native state) by small molecule binding (e.g. diflusinil and Fx-1006A), (2) gene therapy with small interfering RNAs, antisense oligonucleotides and single-stranded oligonucleotides, (3) drugs that inhibit or disrupt amyloid fibril formation, such as doxycycline and immunization, and (4) solubilizers of existing amyloid protein fibrils.[171-184] Among these, native state kinetic stabilization by diflunisal and Fx-1006A, a novel therapeutic strategy against protein misfolding diseases, are currently in Phase II/III clinical trials.

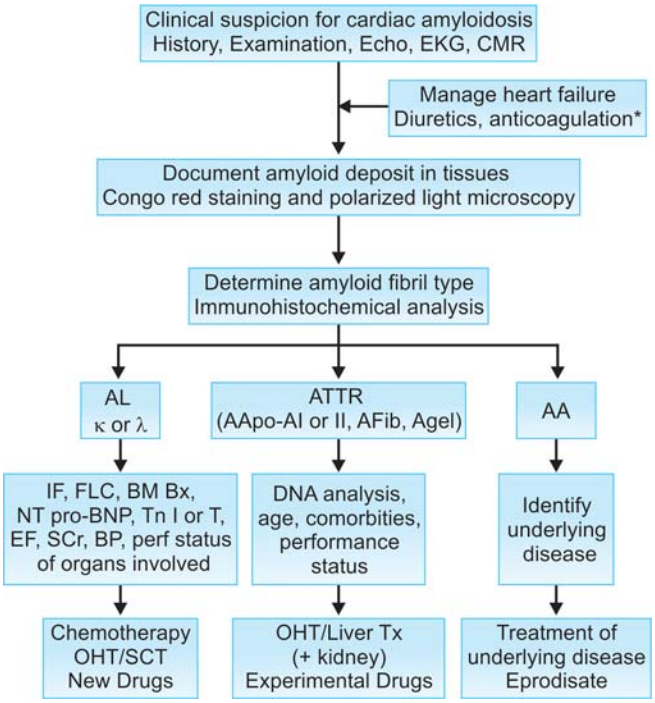
The mainstay of treatment for AA amyloidosis is directed at treatment of the underlying inflammatory or infective etiology. However, therapies under investigation include glycosaminoglycan (GAG) mimetics such as eprodisate. GAGs are important cofactors involved in amyloid fibril formation of all types of amyloid proteins and GAG mimetics can bind to and prevent amyloid fibril formation and deposition. Eprodisate has been studied for the treatment of renal disease in AA amyloidosis and it slowed the decline renal dysfunction.[185]

HEART TRANSPLANTATION

Patients with AL amyloidosis who present with severe heart failure due to cardiac amyloidosis have an extremely poor prognosis with a median survival of only 4–6 months. For this reason, cardiac transplantation has been performed in these patients beginning in the 1980s.[4-11,143,144,186-194] However survival beyond 3 months was markedly reduced after transplantation because of progression of systemic amyloid deposition, often including the cardiac allograft. Hosenpud et al. reported 4-year survival rate of 39% in heart transplant recipients for amyloid CMP.[187] Similar data have been more recently: the Heart Transplant Centers for Europe consortium reported a 5-year survival of 38% in AL amyloidosis patients compared with 67% in cardiac transplant recipients with non-AL amyloidosis. Other studies also reported worse outcomes in patients with cardiac amyloidosis undergoing OHT compared to non-amyloid recipients.[10,188] Based on these discouraging results, heart transplantation has generally been considered a contraindication for OHT. However, in 2004, Skinner et al. were the first to report significant improvement in survival with successful treatment of AL amyloidosis with HDM/SCT. The increased possibility of achieving long-term survival without progressive amyloid deposition led to the interest in examining the feasibility and outcome of performing sequential OHT followed within 6 months to a year by HDM/SCT. In 2006, Gilmore et al. first reported results from sequential OHT/SCT in 5 patients with AL amyloid CMP.[6] Two patients died from progressive amyloidosis and 3 patients survived. Of the 3 patients who survived, 1 patient had a relapse of the plasma cell dyscrasia and was treated with high-dose corticosteroids. Lacy et al. from the Mayo Clinic published a series of 11 patients who underwent sequential OHT/SCT.[143] The 5-year survival rate was 62% with only 25% alive at 8 years. Three patients died from progressive amyloidosis. More recently, Dey et al. reported the results of 26 AL amyloid patients who were considered for OHT/SCT treatment.[4] Of these, 18 patients were deemed eligible, 9 received an OHT and 8 patients subsequently had HDM/SCT. The actuarial disease-free survival was 60% at 7 years, which was not significantly different from 17,389 patients in the International Society for Heart and Lung Transplantation database who had an OHT for non-amyloid heart disease (64%; $p = 0.83$). Nine patients (35%) died on the transplant waitlist. It should be understood that patients with AL amyloid CMP who undergo cardiac transplantation represent a highly selected group with no or very limited systemic disease. Criteria for transplant eligibility is center dependent; however, the acronym DANGER has been used to predict adverse outcomes in patients undergoing evaluation for cardiac transplantation and it can be used to identify patients who are unlikely to be eligible for cardiac transplantation. DANGER stands for diarrhea, involvement of the autonomic nervous system, poor nutritional status, gastrointestinal tract (history of bleeding), elimination problems (i.e. renal impairment or nephritic syndrome) and respiratory dysfunction.[144] Less than 5% of patients with advanced heart failure related to AL amyloidosis have disease isolated to the heart. Therefore, the vast majority of AL amyloid patients are not eligible for OHT, and among eligible patients, 30–50% die on the waitlist from progressive disease. However, for selected patients with advanced amyloid CMP, sequential OHT/SCT can profoundly alter the otherwise grim prognosis.[8,194]

In contrast to cardiac transplantation for AL amyloidosis, patients with amyloid CMP from hereditary ATTR have similar survival rates compared with non-amyloid heart transplant recipients.[5,188] In order to shut off production of the amyloidogenic TTR protein, patients often undergo combined or sequential heart-liver transplantation.[163,165-170] Since the liver function of patients with hereditary ATTR who are eligible for cardiac transplantation is usually normal, a domino liver transplantation (DLT) may be performed whereby the recipient's liver is transplanted into another recipient. DLT recipients are generally older, marginal candidates who may not have been offered transplantation otherwise. It is generally believed that domino recipients may die of natural causes before developing clinically significant systemic amyloidosis; however, there are reports of de novo systemic ATTR amyloidosis developing in these recipients (typically neuropathy).[195-197] Still, the long-term survival in DLT recipients is very good, and graft shortage probably justifies DLT in selected patients, despite the risk of de novo systemic amyloidosis.[195-197] Single case reports of cardiac transplantation for senile systemic and hereditary V122I ATTR-CMP have shown survival out to 2 or 3 years post-transplant.[39,186] However, the advanced age of most senile and V122I ATTR amyloidosis patients on presentation usually precludes transplantation. Among V122I ATTR-CMP patients who are eligible for transplantation, it remains to be seen

FLOW CHART 1: Diagnostic and management algorithm for suspected cardiac amyloidosis. In suspected cases of cardiac amyloidosis, based on history, physical examination, echocardiographic findings, electrocardiogram and cardiac magnetic resonance imaging, the diagnostic workup should be based on the confirmation of the presence of amyloidosis in tissue and identification of the underlying amyloid precursor protein using immunohistochemical staining. Based upon the specific amyloid fibril type, adjunctive tests to evaluate the status of the underlying disease and other organs involved as discussed earlier in the chapter. Treatment involves management of heart failure with diuretics and anticoagulation in some cases, and also importantly, treatment directed to reducing the production of the amyloid fibril protein as previously discussed



*Recommended in patients at high risk for thromboembolic events, such as history of thromboembolic events, atrial fibrillation, or severe left atrial failure as evidenced by echo-Doppler evaluation

(Abbreviations: BM Bx: Bone marrow biopsy; BP: Blood pressure; CMR: Cardiac magnetic resonance imaging; Echo: Echocardiography; EF: Left ventricular ejection fraction; EKG: Electrocardiogram; FLC: Free light chain assay; IF: Immunofluorescence; OHT: Orthotopic heart transplantation; perf status: Performance status; SCr: Serum creatinine; SCT: Stem cell transplantation; Tn I or T: Troponin I or T levels; Tx: Transplant; AL: Light chain amyloidosis; ATTR: Senile systemic amyloidosis)

whether patients are at risk for developing amyloid infiltration in the cardiac allograft and, if so, how combined or sequential heart-liver transplantation may alter the risk.

An algorithm for the diagnosis and management of suspected cases of cardiac amyloidosis is provided in Flow chart 1. In suspected cases of cardiac amyloidosis, based on history, physical examination, echocardiographic findings, EKG and CMR imaging, the diagnostic workup should be based on the confirmation of the presence of amyloidosis in tissue and identification of the underlying amyloid precursor protein using immunohistochemical staining. Based upon the specific amyloid fibril type, adjunctive tests to evaluate the status of the underlying disease and other organs involved as discussed earlier in the chapter. Treatment involves management of heart failure with diuretics and anticoagulation in some cases, and, also importantly, treatment directed to reducing the production of the amyloid fibril protein as previously discussed.

SUMMARY

Amyloidosis is a disorder of protein folding in which normally soluble proteins undergo conformational changes that along with other cofactors ultimately leads to the deposition of insoluble extracellular material within tissues and organs. Amyloid CMP is an infiltrative disease with distinct features seen on the gross anatomy (Fig. 4), histology (Figs 1 and 2), echocardiography (Figs 6A to D) and magnetic resonance imaging (Figs 7A and B) of the heart. Amyloid CMP leads to progressive heart failure and death usually from restrictive CMP, and the presence of cardiac amyloidosis drives the prognosis in all types of systemic amyloidosis. The disease is generally associated with very poor survival, which varies depending on the underlying amyloid fibril precursor protein, severity of CMP and number of organs involved. Tissue confirmation for the presence of amyloid and identification of the amyloid fibril type is of paramount importance for determining prognosis and treatment. AL is the most common type of cardiac amyloidosis and is associated with the poorest survival. Medical management of heart failure in amyloid CMP, which is distinctly different from other CMPs, is very challenging and limited mostly to volume control. Treatment to reduce amyloidogenesis is determined by the underlying amyloid precursor protein. HDM/SCT treatment for AL amyloid has significantly improved survival in these patients, and liver transplantation is being performed for patients with hereditary ATTR amyloidosis; however, most patients with amyloid CMP are not candidates for stem cell or liver transplantation because of high treatment related mortality rates. In highly selected patients with advanced amyloid CMP, cardiac transplantation alone or in combination with HDM/SCT (AL amyloidosis) or liver transplantation (hereditary ATTR amyloidosis) may significantly improve survival in these patients. Newer therapies that are currently under clinical investigation for the treatment of amyloidosis include TTR gene manipulation, stabilizers of TTR protein conformation, drugs that disrupt or inhibit amyloid fibril formation and solubilizers of existing amyloid protein fibrils.

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Chapter 84

Peripartum Cardiomyopathy

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Chapter Outline

- Definition
- Incidence
- Etiology
- Risk Factors
- Clinical Presentation
  - Biomarkers
  - Laboratory Evaluation
- Prognosis
  - Mortality
  - Recovery of Cardiac Function
  - Outcome of Subsequent Pregnancy
- Treatment
  - Experimental Therapy
  - Implantable Cardioverter Defibrillators
  - Cardiac Assist Devices
  - Cardiac Transplantation
- Labor and Delivery

DEFINITION

In 1971, Demakis et al.[1] published data on 27 patients with cardiomyopathy associated with pregnancy that presented in the peripartum period. These investigators established the term peripartum cadiomyopathy (PPCM) and defined it by the following criteria based on the clinical profile of their patients: (1) development of heart failure (HF) in the last month of pregnancy or within 5 months of delivery, (2) absence of a determinable etiology for HF and (3) absence of demonstrable heart disease prior to the last month of pregnancy. A workshop on PPCM by the National Heart, Lung and Blood Institute in 1997[2] added an additional criterion, previously proposed by Hibbard et al.,[3] of left ventricular (LV) systolic dysfunction demonstrated by echocardiography with left ventricular ejection fraction (LVEF) lesser than 45%, fractional shortening lesser than 30% or both. Realizing that these criteria are arbitrary and that PPCM often presents earlier in pregnancy,[4-6] the definition of PPCM has been recently updated by a working group on PPCM of the European Society of Cardiology to "idiopathic cardiomyopathy presenting with HF secondary to LV systolic dysfunction toward the end of pregnancy or in the months following delivery where no other cause of HF is found. The left ventricle (LV) may not be dilated but the ejection fraction (EF) is nearly always reduced below 45%".[7]

INCIDENCE

The incidence of PPCM in the United States has ranged in different publications from 1:1149 to 1:4350 live births[8-11] with an average of 1:3186 (Table 1). Significantly higher incidence[12,13] has been reported in South Africa (1:1000) and Haiti (1:300), no information is available regarding the incidence of this condition in Europe.

ETIOLOGY

The cause of PPCM is still unknown and many potential theories have been proposed and discussed in details in a recent review.[14] Most recent hypothesis is based on experimental work that has demonstrated the development of PPCM in female mice with a cardiomyocyte-specific deletion of signal transducer and activator of transcription 3 (STAT3).[15] This study suggested that unprotected increase in oxidative stress leads to increased expression and proteolytic activity of cardiac cathepsin D which results in conversion of the nursing hormone prolactin into an antiangiogenic and proapoptotic 16 kDa form with a detrimental effect on coronary microvasculature resulting in a myocardial insult due to hypoxemia and apoptosis.

RISK FACTORS

The incidence of PPCM has been found to be higher in women older than 30 years, in patients with history of hypertension and preeclampsia, multifetal pregnancies and in the United States, in African-American women.[4] In addition, recent studies have demonstrated a high incidence of PPCM in families with dilated cardiomyopahies[16,17] suggesting that a proportion of patients with PPCM may be due to genetic cause.[6]

CLINICAL PRESENTATION

Many of the signs and symptoms of PPCM are similar to those of HF due to other etiologies. Because normal pregnancy is often associated with signs and symptoms that can mimic those of HF, the diagnosis of PPCM is often missed or delayed.[18]

BIOMARKERS

B-type natriuretic peptide (BNP) levels remain grossly unchanged during normal pregnancy and are only mildly

TABLE 1

Incidence of peripartum cardiomyopathy

Author	*Year*	*Country*	*Case series or population based*	*Retrospective (R) or prospective (P)*	*Number with PPCM*	*Incidence*	*Mean age*	*Race*	*Definition of PPCM*
Mielniczuk et al.[10]	1990–2002	USA	Population based	R	171	1990–2002: 1:3189; 2000–02: 1:2289	30	42% White; 32% African-American with PPCM	ICD 9 code 674.8 (plus at least one of 514, 428, 425.4, 648.64) and then two reviewers of each potential case—PPCM if consensus
Brar et al.[11]	1996–2005	USA	Population based	R	60	Total (all races): 1:4025; 1:4075, Whites; 1:1421, African-Americans; 1:9861, Hispanics;1:2675, Asians	32	NA	ICD 9 codes 428.0, 428.1, 428.4, 428.9, 425.4, and 425.9 and then case note review: (i) LVEF, 0.50 (ii) Framingham criteria for HF (iii) new symptoms of HF or initial echocardiographic diagnosis of left ventricular dysfunction occurred in the month before or in the 5 months after delivery
Fett et al.[13]	2000–2005	Haiti	Case series (single institution)	P	98	1:300	33	Afro-Caribbean	(i) CHF 1 month before to 5 months after delivery (ii) no pre-existing heart disease (iii) no other cause identified for CHF (iv) LVEF, 45% or FS, 30%
Chapa et al.[9]	1988–2001	USA	Case series (single institution)	P	32	1:1149	27	80% African-American; 20% White	(i) FS, 30% (ii) LVEDD, 4.8 cm (iii) no other cause identified for CHF (iv) LVEF, 45% or FS, 30%
Desai et al.[12]	1986–1989	South Africa	Case series (single institution)	P	97	1:1000	29	Black Africans; except 1 Asian	Not stated; echocardiography performed—no results presented
Witlin et al.[8]	1986–1994	USA	Case series (single institution)	R	28	1:2406	NA	21 Black; 6 White; 1 Asian	(i) CHF 1 month before to 5 months after delivery (ii) no other cause identified for CHF (iii) absence of heart disease before the last month of pregnancy

Only studies recruiting after 1985 using echocardiography are included (except Mielniczuk ML—no echocardiography). Only studies including 25 patients after 1985 patients are included.
(Abbreviations: PPCM: Peripartum cardiomyopathy; HF: Heart failure; CHF: Congestive heart failure; LVEDD: Left ventricular end-diastolic diameter; ICD: Implantable cardioverter defibrillators; NA: Not available; LVEF: Left ventricular ejection fraction. (*Source:* Adopted with permission from Sliwa et al.[7])

elevated in women with preeclampsia.[19] Similar to other form of HF, BNP levels rise significantly in symptomatic patients with PPCM.[20] Troponin can be slightly elevated especially in patients with a substantial myocardial insult at the time of diagnosis.[21]

LABORATORY EVALUATION

Electrocardiogram usually shows sinus tachycardia, nonspecific ST segment and T wave changes. LV hypertrophy and conduction abnormalities can also be seen. Chest X-ray commonly demonstrates cardiomegaly, pulmonary venous congestion and occasionally pulmonary edema and pleural effusion. Echocardiogram shows a dilated LV size in the majority of the patients but can also be within normal range, dilation of the other cardiac chambers is also commonly found. LV systolic dysfunction is the rule with moderate to severe depression of LVEF and a small pericardial effusion. Doppler evaluation usually shows moderate to severe mitral and tricuspid valve regurgitation, mild to moderate pulmonic regurgitation and pulmonary hypertension.[4,7]

PROGNOSIS

The PPCM can be associated with severe complications including pulmonary edema, cardiogenic shock, arrhythmias, thromboembolic event and mortality.[18]

MORTALITY

The PPCM continues to be an important cause of pregnancy-related death in the United States and other countries.[22,23] The rate of mortality, however, seems to vary geographically (Table 2) and is considerably higher in South Africa (between 28% and 40%), Haiti (15% and 30%) and Turkey (30%) compared to the United States where reported mortality rate from PPCM has been lower than from other forms of cardiomyopathies and has varied between 0% and 19%.[9-11,24-30] Risk of death increases with older age, severe myocardial insult (LVEF < 25%), multiparity, African-American ethnicity and when diagnosis is delayed.[18,22]

RECOVERY OF CARDIAC FUNCTION

Most recent publications in the United States have demonstrated improvement of LV function in at least 50% of patients with PPCM, mostly occurring within 6 months after diagnosis.[5,28,31] An exception to these findings was reported by Modi et al.[30] who found recovery of LV function in only 35% of 40 indigent, mostly African-American women, with a median time to recovery of 54 months. These data is similar to a low recovery rate of 21–43% reported in South Africa, Haiti and Turkey,[7] and suggest that race, ethnicity and environmental differences as well as access to medical care may be responsible for poorer outcome.

OUTCOME OF SUBSEQUENT PREGNANCY

Elkayam et al.[32] reported on the outcome of 60 subsequent pregnancies in 44 women, 28 with normal LV function (group 1) and 16 with persistent LV dysfunction (group 2). Subsequent pregnancies were associated with a significant reduction in mean LVEF in both groups. A substantial (> 20%) reduction in LVEF was seen in 21% of group 1 and 44% of group 2 patients; there was 0% mortality in group 1 women and 19% in group 2. When aborted pregnancies were excluded, rate of unfavorable maternal and fetal outcome was even higher especially in women with persistent LV dysfunction. A recent publication by Fett et al.[33] based on data mostly obtained from an internet support group in the United States, reported on 61 post PPCM pregnancies, with relapse of PPCM in 29% of the entire group and a significantly higher rate (46%) in women with LVEF of lesser than 55%.

TREATMENT

Standard drug therapy for acute and chronic HF includes the potential use of several drugs, including diuretics, angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB) as well as beta blockers, spironolactone, digoxin, intravenous (IV) and oral vasodilators and IV inotropes.[34] In general, the treatment of HF in patients with PPCM should follow recent guidelines recommendations, although, drug therapy may need to be changed during pregnancy and lactation to prevent side effects to the fetus or the lactating infant. The safety of HF therapy in pregnancy and lactation is shown in Table 3.

EXPERIMENTAL THERAPY

A successful effect of IV immune globulin was reported in a small number of women with PPCM compared with 11 historical control patients who received conventional therapy alone.[35] The study, however, was limited by an open design and a small number of patients. Sliwa et al.[36] reported a significant improvement in a combined endpoint of death, persistent LV dysfunction or NYHA functional class III to IV at the last follow-up in a group of South African women with PPCM treated with pentoxifylline. However, no further studies have been performed to confirm these results. More recently Sliwa et al.[25] have used bromocriptine, a prolactin blocker in the treatment of 10 South African patients with PPCM. The treatment was associated with a significantly larger rate of LV recovery and decreased rate of mortality and symptomatic HF at 6 months compared with a control group of 10 PPCM patients treated with standard therapy alone.

IMPLANTABLE CARDIOVERTER DEFIBRILLATORS

Since improvement of LV function is common and failure to improve cannot be predicted early after diagnosis, the use of a wearable external defibrillator[37] or an entirely subcutaneous implantable cardioverter-defibrillator[38] rather than implantable cardioverter defibrillators (ICD) should be considered in high-risk patients, as a bridge to recovery or to ICD in cases with persistent LV dysfunction in spite of appropriate trial of medical therapy.

CARDIAC ASSIST DEVICES

Intra-aortic balloon pump, extracorporeal membrane oxygenation and LV assist devices have been used successfully as bridge for recovery or transplantation in patients with PPCM and should be considered in a rapidly deteriorating patient not responding to medical therapy including vasoactive medications.[38-42]

CARDIAC TRANSPLANTATION

This procedure has been performed successfully in patients with PPCM with slightly higher risk of rejections, lower risk of infections and similar rate of vascular cardiac allograft vasculopathy and mortality compared to comparable women undergoing transplantation for reasons other than PPCM.[43]

LABOR AND DELIVERY

In a patient who is diagnosed during pregnancy continuation of pregnancy in order to allow fetal maturity may be possible under close monitoring in a woman who can be stabilized with therapy. Termination of pregnancy often results in the improvement of both symptoms and cardiac function and should be considered in a patient with deteriorating symptoms or cardiac function.
Mode of delivery in a stable patient with PPCM should be decided jointly by the obstetrician and the cardiologist. In general, vaginal delivery is preferred in the stable patient and cesarean section should be performed for obstetrical reasons or due to maternal instability. In case of vaginal delivery, instrumental delivery is recommended to reduce maternal efforts

TABLE 2

Prognosis of peripartum cardiomyopathy

Author	*Year*	*Country*	*Study type*	*Number with PPCM*	*Age (mean)*	*Mortality (mean follow-up)*	*LV function*	*Trans-planta-tion and VAD*	*Predic-tors of mortality*
Population-based studies Mielniczuk ML, et al.[10]	1990–2002	USA	Retrospective, population based	171	30	1.36% in-hospital, 2.05% 'long term'	NA	NA	NA
Brar SS, et al.[11]	1996–2005	USA	Retrospective, population based	60	34	3.3% (4.7 years)	NA	0%	NA
Case series Sliwa K, et al.[24]	2005–2008a	South Africa	Prospective, single center	80, 100% African descent	30	10% (6 months), 28% (2 years)	Mean LVEF: baseline 30%, 24 months 51%	NA	NA
Sliwa K, et al.[25]	2003–2005	South Africa	Prospective, single center	100, 100% African descent	32	15% (6 months)	Mean LVEF: baseline 26%, 24 months 43%, 23% normal LV function after 6 months	NA	Fas/Apo-1 and NYHA functional class independent predictors of mortality
Fett et al.[13]	2000–2005	Haiti	Prospective, single center	98, 100% African descent	32	15% (2.2 years)	28% normal ventricular function after 2.2 years	NA	LVEDD and LVEF at presen-tation not predictive of mortality
Fett JD et al.	1994–2001	Haiti	Prospective + retrospective, single center	47	32	14% (time period not available)	NA	NA	NA
Duran et al.[27]	1995–2007	Turkey	Prospective + retrospective, single center	33	33	30% (47 months)	24% of patients recovered completely, 39% were left with persistent LV dysfunction	6%	QRS, 120 ms 21
Modi et al.[30]	1992–2003	USA	Single center, retrospective	44 patients, 39 African-American	NA	15.9%	LV function returned to normal in 35%	NA	LVEF did not predict mortality
Sliwa et al.	1996–1997	South Africa	Single center, retrospective	29	29	27.6% (6 months)	Mean LVEF: baseline 27%, 6 months 43%	NA	NA
Desai et al.[12]	1986–1989	South Africa	Single center, retrospective	99	29	14% (time period not available)	NA	NA	NA
Felker et al.[29]	1983–1998	USA	Single center (those referred for cardiac biopsy)	51	29	6% (5 years)	NA	NA	NA
Chapa et al.[9]	1988–2001	USA	Single center, retrospective	32	27	9.6% (time period not available)	59% persistent LV dysfunction (46 months)	6.5%	NA
Witlin et al.[8]	1986–1994	USA	Single center, prospective	28; 21 black, 6 White, 1 Asian	NA	18% (time period not available)	64% persistent LV dysfunction	11%	18%
Carvalho et al.	1982–1988	Brazil	Single center, prospective	19	26	16% (21 months)	NA	NA	Increased LVEDD and late onset of symptoms
Elkayam et al.[5]	2005; 1997–1998	USA	Survey (2% response rate)	100; 19% African descent; 67% White	31	9% (2 years)	LV function returned to normal in 54%	4%	NA

Only studies including 25 patients after 1985 are included
(Abbreviations: NA: Not available; LV: Left ventricular; LVEF: Left ventricular ejection fraction; EDD: End-diastolic diameter; NYHA: New York Heart Association). (*Source:* Adopted with permission from Sliwa K, et al.[7])

TABLE 3

Drug safety during pregnancy and lactation

Drug	*Risk category*	*Information in human*	*Potential complications*	*Safety for breastfeeding*
Furosemide	C	Limited	Hypotension and decreased uterine perfusion	Compatible
Intravenous nitroglycerin	B	Modest	Hypotension and decreased uterine perfusion	Unknown
Intravenous nitroprusside	C	Limited	Thiocyanate toxicity	Unknown
Nesiritide	N/A	None	Hypotension and decreased uterine perfusion, effect on the fetus unknown	Unknown
Dopamine	C	Limited	Unknown	Unknown
Dobutamine	B	Limited	Unknown	Unknown
Milrinone	C	Limited	Unknown	Unknown
ACE inhibitors/ Angiotensin receptor blockers	C	Limited	Renal insufficiency, oligohydramnios, IUGR, prematurity, bony malformation, limb contractures, PDA, pulmonary hypoplasia, RDS, hypotension, anemia and neonatal death	Compatible
Carvedilol	C	Not available	Unknown, beta 2 receptor blocking may cause premature uterine contractions	Unknown
Bisoprolol	C	Not available	Unknown	Unknown
Metoprolol succinate	C	Not available	Unknown	Unknown
Metoprolol tartrate	C	Modest	Relatively safe	Compatible monitoring of infants for sings of beta blockade recommended
Digoxin	C	Modest used for both maternal and fetal indications	None reported	Compatible
Spironolactone	C	Limited	Possible antiandrogenic effect and feminization	Compatible
Warfarin	D	Modest	Teratogenic effect in 1st trimester (Warfarin embryopathy), increased maternal and fetal bleeding	Compatible
Heparins	C	Extensive	Do not cross the placenta	Compatible

(Abbreviations: IUGR: Intrauterine growth retardation; PDA: Patient ductus arteriosus; RDS: Respiratory distress syndrome)

and shorten labor. Hemodynamic monitoring for labor and delivery is advisable in a patient who is diagnosed during pregnancy for hemodynamic optimization prior to delivery and monitoring during and after the delivery.

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Chapter 85

Chemotherapy-induced Cardiomyopathy

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Chapter Outline

- Classification of Chemotherapy-induced Cardiotoxicity
- Risk Factors
- Pathophysiology of Anthracycline-induced Cardiomyopathy
  - Cardiac Morphologic and Functional Changes
  - Histopathologic Changes
- Mechanism of Chemotherapy-induced Cardiac Dysfunction
  - Anthracyclines
  - Alkylating Agents
  - Antimetabolites
  - Antimicrotubule Agents
  - Monoclonal Antibody-based Tyrosine Kinase Inhibitors
  - Proteasome Inhibitors
  - Small Molecule Tyrosine Kinase Inhibitors
- Diagnosis
- Monitoring
- Management
  - Preventive Strategies
- Treatment
  - Angiotensin Inhibition Therapy
  - Adrenergic Inhibition Therapy

INTRODUCTION

The overall survival of patients with cancer has improved during the last two decades due to advances in chemotherapy.[1,2] Chemotherapy-induced cardiotoxicity remains a major limitation for the use of chemotherapeutic agents. As the proportion of the cancer survival patients is increasing, the incidence of chemotherapy-induced cardiomyopathy is also increasing.

The prevalence and incidence of chemotherapy-induced cardiomyopathy is usually obtained from the registries which do not provide the specific etiologies of cardiomyopathy. Nevertheless, a prevalence of about 1% has been reported.[3] This is likely to be an underestimation as it has been reported that approximately 50% of patients exposed to adriamycin will develop some cardiac dysfunction within 10–20 years after chemotherapy and about 5% of these patients develop overt heart failure.[4]

As many cancer survivors are at a greater risk of death from cardiac complications than from the cancer, early recognition of cardiotoxicity related to anticancer treatment is highly desirable.

CLASSIFICATION OF CHEMOTHERAPY-INDUCED CARDIOTOXICITY

Chemotherapy-induced cardiotoxicities commonly classified into two types: (1) Acute or subacute which occurs anytime up to 2 weeks from the initiation to the termination of the chemotherapy (2) chronic which manifests after months or years after termination of chemotherapy. The chronic type is further classified into two subtypes: (1) early, which is evident within 1 year and (2) late, after 1 year of termination of therapy. It should be appreciated that the timing of the onset of the complications of chemotherapy-induced cardiotoxicity and classification based on this timing is arbitrary.

The incidence, relation to the dose of doxorubicin, and prognosis of chronic doxorubicin cardiotoxicity are summarized in Table 1. The manifestations of acute or subacute cardiotoxicity are usually hypertension, electrocardiographic changes such as prolongation of the QT interval and other repolarization abnormalities, supraventricular and ventricular arrhythmias, chest pain syndromes, myopericarditis and rarely acute heart failure. Most of these cardiotoxicities are reversible.[5] The manifestations of chronic cardiotoxicity are related to the type of chemotherapeutic agents used. The incidence of left ventricular dysfunction in relation to the chemotherapeutic agent used is summarized in Table 2. The risk factors, pathophysiology, manifestations and management have been discussed according to the chemotherapeutic agent used.

TABLE 1

Doxorubicin cardiomyopathy

Chronic cardiotoxicity:
Incidence: 1.7%
• Usually occurs within about 30 days
• Can occur 6–10 years after its last administration
Incidence of CHF is related to the dose:
• 4%—500–550 mg/m^2
• 18%—551–600 mg/m^2
• 36%—601 mg/m^2 or higher
The mortality with CHF is > 50%

TABLE 2

Chemotherapy associated with left ventricular dysfunction

Chemotherapy agent	*Incidence (%)*
Anthracyclines	
Doxorubicin (Adriamycin)	3–26
Epirubicin (Ellence)	0.9–3.3
Idarubicin (Idamycin PFS)	5–18
Alkylating agents	
Cyclophosphamide (Cytoxan)	7–28
Ifosfamide (Ifex)	17
Antimetabolites	
Clofarabine (Clolar)	27
Antimicrotubule agents	
Docetaxel (Taxotere)	2.3–8
Monoclonal antibody-based tyrosine kinase inhibitors	
Bevacizumab (Avastin)	1.7–3
Trastuzumab (Herceptin)	2–28
Proteasome inhibitor	
Bortezomib (Velcade)	2–5
Small molecule tyrosine kinase inhibitors	
Dasatinib (Sprycel)	2–4
Imatinib mesylate (Gleevec)	0.5–1.7
Lapatinib (Tykerb)	1.5–2.2
Sunitinib (Sutent)	2.7–11

RISK FACTORS

The risk factors for anthracycline cardiotoxicity are summarized in Table 3.

The cumulative dose of doxorubicin is an important risk factor for its cardiotoxicity. The probability of doxorubicin-induced cardiomyopathy is 3–5% with 400 mg/m^2, 7–26% with 550 mg/m^2 and 18–48% with 700 mg/m^2. The risk of cardiotoxicity with epirubicin is also dose dependent. It is recommended that the lifetime cumulative dose of doxorubicin should be less than 450 mg/m^2 and that of epirubicin less than 900 mg/m^2.

Rate and schedule of administration of anthracyclines appear to influence the risk of developing and severity of cardiotoxicity. Instead of bolus injections, prolonged infusions have been reported to be less cardiotoxic.[6] A significant reduction in the incidence of clinical heart failure with infusion duration of 6 hours or longer has been observed compared to shorter infusion duration without compromising its therapeutic efficacy.[7] The dosing schedules of doxorubicin also influence the incidence of cardiotoxicity. With single doses repeated every 3 weeks, three consecutive daily doses repeated every 3 weeks and weekly doses, the overall incidence of drug induced heart failure were 2.9%, 2.4% and 0.8% respectively.[8]

TABLE 3

The risk factors for anthracycline cardiotoxicity

Risk factors:

- High total dose
- High peak serum level
- Combination therapy with other cardiotoxic antitumor drugs
- Mediastinal radiation therapy
- Age—very young and very old
- History of cardiac diseases—hypertension, reduced LVEF
- Liver diseases
- Whole-body hyperthermia

The risks and severity of cardiotoxicity of doxorubicin increase when it is used concurrently with other chemotherapeutic agents. There was a 16% incidence of New York Heart Association (NYHA) class III/IV heart failure in patients treated with cyclophosphamide, trastuzumab and doxorubicin concurrently, compared to only 3% in those treated with doxorubicin and cyclophosphamide.[9] Doxorubicin and paclitaxel combination therapy may also be associated with a higher incidence of cardiotoxicity.[10]

Radiation therapy preceding or following chemotherapy increases the risk and severity of both early and late cardiotoxicity.[11] The extent of myocardial damage as evident from the histopathological changes is more severe in these patients.[12]

Controversy exists regarding the association of gender and doxorubicin cardiotoxicity. Female patients have been reported to be more vulnerable to develop chemotherapy-induced cardiomyopathy.[5] However, in adult patients with lymphoma receiving doxorubicin-based chemotherapy, there was a higher incidence of left ventricular dysfunction in males.[13]

The risk of developing chemotherapy-induced cardiomyopathy is higher in the older age group and also in very young.[5] Patients aged greater than 65 years are 2.25 times more likely to develop heart failure compared to younger patients receiving similar cumulative dose of doxorubicin, 400 mg/m^2.[14]

The preexisting cardiovascular disorders, such as hypertension, coronary heart disease, valvular and myocardial disease, and cardiac risk factors, such as diabetes, hyperlipidemia and obesity, increase the risk of anthracycline cardiotoxicity.[15] The cardiotoxicity is approximately three fold higher in patients with preexisting risks of cardiovascular disorders.[15]

The body mass index (BMI) is directly proportional to the risk of anthracycline cardiotoxicity. The incidence of left ventricular dysfunction was 0.9% in patients with a BMI of less than 27 kg/m^2 compared to 1.8% in patients with BMI greater than 27 kg/m^2.[16]

The type of the anthracyclines used as achemotherapeutic agent may also influence the risk of cardiotoxicity. Epirubicin and idarubicin appear to cause less heart failure than doxorubicin.[5]

PATHOPHYSIOLOGY OF ANTHRACYCLINE-INDUCED CARDIOMYOPATHY

CARDIAC MORPHOLOGIC AND FUNCTIONAL CHANGES

The cardiac morphologic and functional derangements of doxorubicin cardiomyopathy are characterized by reduced contractile and pump functions. All four cardiac chambers are dilated, similar to dilated cardiomyopathy. Severe dilatations of ventricles and atria, however, are less common than in ischemic and non-ischemic dilated cardiomyopathies. Diastolic dysfunction including ventricular filling abnormalities is observed. The left ventricular wall thickness is decreased and as a result the wall stress is increased. Mural thrombi may also be present in some patients.[17] The morphologic and functional changes in doxorubicin cardiomyopathy are summarized in Table 4.

TABLE 4

Chronic doxorubicin cardiotoxicity

Cardiac manifestations:
• Dilatation of all cardiac chambers
• Mural thrombi
• Diastolic dysfunction
• Systolic dysfunction
• Increased wall stress
• Overt systolic heart failure

TABLE 5

Doxorubicin cardiomyopathy: Light microscopy findings

Cardiac morphologic changes: Light microscopy
• Multifocal patchy interstitial fibrosis
• Scattered vacuolated cardiomyocytes (Adria cells)
• Frank necrotic cardiomyocytes are rare
• Fibroblast proliferation and histiocyte infiltration

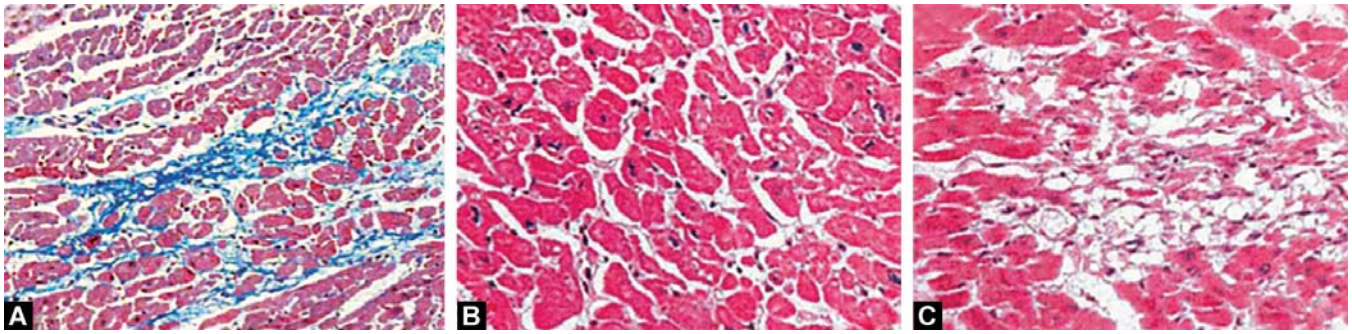
HISTOPATHOLOGIC CHANGES

It is relevant to subclassify the chronic cardiotoxicity on histological basis into type I (e.g. doxorubicin) and type II (e.g. trastuzumab). Type I agents cause cell death and biopsy changes while type II agents cause cellular dysfunction with no ultrastructural abnormalities.[5]

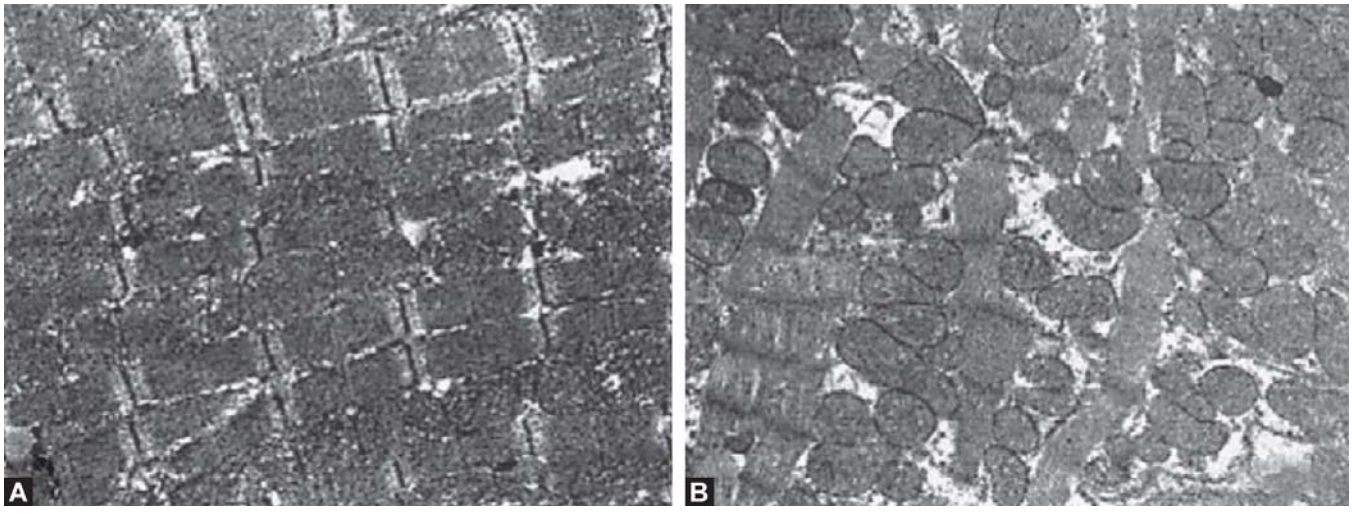
In doxorubicin cardiomyopathy, there are areas of patchy myocardial interstitial fibrosis, and scattered vacuolated cardiomyocytes (Adria cells Figs 1A to C). The Adria cells are vacuolated cardiomyocytes and are seen adjacent to areas of fibrosis. The areas of fibrosis are usually wide spread and areas of acute myocyte damage are infrequent. There is fibroblast proliferation and histiocyte infiltration in the areas of healed myocarditis.

Partial or total loss of myofibrils and myocyte vacuolar degeneration are essential features of doxorubicin cardiotoxicity (Figs 2A and B). With loss of myofilaments, the remnants of Z disks are seen. There is distention of sarcoplasmic reticulum and the T-tubules. The myocyte vacuoles coalesce and form large membrane bound spaces. The nuclei-chromatin disorganization and replacement of chromatin by pale filaments are also features of doxorubicin cardiomyopathy.[17,18]

The histopathologic changes are summarized in Tables 5 and 6.



FIGURES 1A TO C: (A) Extensive fibrosis as a manifestation of doxorubicin cardiomyopathy; (B) Scattered cardiomyocytes with vacuolar degeneration (Adria cells); (C) Foci of necrotic cardiomyocytes. Bars, 20 Im. (A) Masson's trichrome stain; (B and C) Hematoxylin-eosion stain. (*Source:* Takemura G, Fujiwara H. Prog Cardiovasc Dis. 2007;49:330-52, with permission)



FIGURES 2A AND B: Electron micrographs of the myocardium (A) Demonstrates normal myocyte structure with intact myofibrils; (B) Demonstrates myofibrillar loss and vacuolization (Adria cells). (*Source:* Takemura G, Fujiwara H. Prog Cardiovasc Dis. 2007;49:330-52, with permission)

TABLE 6

Doxorubicin cardiomyopathy: Electron microscopic findings

Cardiac morphologic changes
Cardiomyocytes:
• Partial or total loss of myofibrils
• Vacuolar degeneration
• Distention of SR and T tubules
• Formation of membrane-bound spaces
• Nuclei-chromatin disorganization
• Replacement of chromatin by pale filaments
(Adapted from Takemura G, Fujiwara H, Progr Cardiovasc Dis. 2007;49: 330)

MECHANISM OF CHEMOTHERAPY-INDUCED CARDIAC DYSFUNCTION

ANTHRACYCLINES

The mechanisms of anti-malignancy effects of doxorubicin are different from those of the mechanisms of its cardiotoxicity. The proposed mechanisms of its anti-malignancy effects include: intercalation of DNA which inhibits synthesis of macromolecules, generation of reactive oxygen species (ROS), DNA binding and DNA cross-linking. Inhibition of topoisomerase II which causes DNA damage and inhibition of apoptosis are also other potential mechanisms.[17,18]

The proposed principal mechanisms of doxorubicin cardiotoxicity are summarized in Table 7. Increased oxidative stress, as evident from increased levels of ROS and lipid peroxidation is the principal mechanism. ROS generations are associated with energy depletion in myocytes. Doxorubicin also causes depletion of cardio-protective glutathione peroxidase. In addition, anthracyclines are converted to secondary alcohol metabolites which are associated with calcium and iron dysregulation. These metabolites accumulate in the cardiac myocytes, and this leads to cumulative lifelong risk of cardiotoxicity. Other proposed mechanisms are: decreased levels of antioxidants and sulfhydryl groups, inhibition of nucleic acid and protein synthesis, release of vasoactive amines, altered adrenergic function and decreased expression of cardiac specific genes.[17,18] There is decreased expression of contractile proteins (a-actin, myosin light and heavy chains troponin-I and desmins) which leads to myofibrillar loss and decreased contractile function.[17,18] Many of these proposed mechanisms remain to be established and it is very likely that more than one mechanism causes doxorubicin cardiomyopathy.

TABLE 7

Doxorubicin cardiomyopathy: Proposed mechanisms for cardiotoxicity

• Increased levels of ROS and lipid peroxidation
• Decreased levels of antioxidants and sulfhydryl groups
• Inhibition of nucleic acid and protein synthesis
• Release of vasoactive amines
• Altered adrenergic function
• Decreased expression of cardiac-specific genes

ALKYLATING AGENTS

Cyclophosphamide

The pathogenesis of cyclophosphamide-induced cardiotoxicity is poorly understood. In 7–28% of patients treated with cyclophosphamide, left ventricular dysfunction and heart failure occurs.[19] The clinical manifestations also include pericardial effusion and myopericarditis.[5] The cardiotoxicity occurs within 1–10 days of its administration (type I) and is dose related.[5] The proposed hypothesis is that it causes direct endothelial injury followed by extravasation of plasma proteins, erythrocytes and toxic metabolites which damage the cardiomyocytes. Hemorrhagic myocarditis with fibrin-platelet capillary microemboli and fibrin strands are detected in myocardium. Intracapillary microemboli may cause ischemic myocardial necrosis. The interstitial edema and hemorrhage lead to wall thickening which is associated with decreased left ventricular compliance and restrictive cardiomyopathy.

Ifosfamide

The incidence of significant cardiovascular toxicity of 17% has been reported receiving ifosfamide as combination therapy.[20] Cardiotoxicity develops within 6–23 days of its administration (type I) and appears to be dose related.[5] The features of ifosfamide cardiotoxicity include: pericardial effusion, fibrinous pericarditis, subendocardial hemorrhage, lymphocytic infiltration of the myocardium and epicardial fibrosis. Ifosfamide is a nephrotoxic agent and reduces glomerular filtration rate. It may also produce renal tubular acidosis.[21] Reduced renal function may lead to delayed elimination of its cardiotoxic metabolites.

ANTIMETABOLITES

The risks of cardiotoxicity in humans have not been adequately studied. The antimetabolite clofarabine can produce left ventricular dysfunction which is usually reversible.[22] The animal studies have suggested that it can interfere with mitochondrial function and energy production. The features of cardiotoxicity included myofibrillar degeneration, myocardial edema, neutrophilic infiltration and endomysial proliferation.

ANTIMICROTUBULE AGENTS

There are microtubule stabilizing and destabilizing agents. For example, vincristine is a chemotherapeutic agent that disrupts microtubules and pacetaxel is a stabilizing agent. The destabilizing antimicrotubule agents enhance microtubule assembly and disrupt the normal cell division. Docetaxel, similar to pacetaxel, a microtubule stabilizing agent could potentially induce contractile dysfunction. The reported incidence of heart failure associated with docetaxel ranges from 2.3% to 8%.[23]

MONOCLONAL ANTIBODY-BASED TYROSINE KINASE INHIBITORS

The incidence of heart failure ranges from 1.7% to 3% treated with bevacizumab.[5] It ranges from 2% to 28% treated with trastuzumab, depending whether it is as monotherapy or in combination with other chemotherapeutic agents.[5] The

mechanism of heart failure with bevacizumab may be due to uncontrolled hypertension resulting left ventricular hypertrophy. It has also been suggested that there might be a reduction in myocardial capillary density, inducing myocardial ischemia, cardiac fibrosis and contractile dysfunction and heart failure. Also the vascular endothelial growth factor signaling is inhibited which may decrease angiogenesis.[5]

Trastuzumab is humanized monoclonal antibody which selectively inhibits human epidermal growth factor receptor 2 (HER2) over expressed by breast cancer cells.[1,2] Blocking of the cardiomyocyte HER2 by trastuzumab is associated with inhibition of normal physiologic pathway of growth and repair. The cardiomyocyte HER2 intracellular pathway can also modulate response to oxidative stress. The anthracycline-induced myocardial damage leads to transient upregulation in the HER2 in the myocardial cells as a compensatory mechanism. Thus, the incidence of cardiac dysfunction is increased up to 27% when trastuzumab is used concurrently with anthracyclines.[9]

PROTEASOME INHIBITORS

The proteasome is a large protein complex with proteolytic activity. Bortezomib is a reversible inhibitor of proteasome and its inhibition is associated with accumulation of poly-ubiquitinated proteins which are involved of signaling pathways that trigger apoptosis.[2] The overall incidence of cardiac dysfunction during bortezomib treatment is approximately 15% and that of cardiac failure is 5%.[5]

SMALL MOLECULE TYROSINE KINASE INHIBITORS

Imatinib Mesylate

The incidence of heart failure with imatinib treatment is about 0.5–1.7%.[5] In animal models, imatinib treatment causes impairment of left ventricular contractile function and cellular abnormalities compatible with toxic cardiomyopathy.[24]

Dasatinib

Dasatinib treatment may cause cardiac dysfunction and overt heart failure. The overall incidence is approximately 2–4% and that of severe heart failure is about 1–2%. In addition to inhibition of tyrosine kinases, other mechanisms might be involved in inducing its cardiotoxicity.

Lapatinib

Lapatinib is an oral small molecule dual tyrosine kinase inhibitor, and the incidence of combined asymptomatic and symptomatic left ventricular dysfunction with its use either alone or prior therapy with anthracyclines or trastuzumab is between 1.5% and 2.2%.[5] The average time to onset of cardiac dysfunction is 13 weeks.

Sunitinib

The incidence of heart failure reported with sunitinib ranges from 2.7% to 11%.[5] The mean time of onset of cardiotoxicity is variable, between 22 days and 27 weeks.[5] Coronary artery disease and hypertension appear to be the risk factors for the development of heart failure.

DIAGNOSIS

The diagnosis of chemotherapy-induced cardiotoxicity should consist of taking appropriate history to assess the likelihood of the diagnosis. A clinical evaluation of the cardiovascular system should be performed to determine presence of signs of overt heart failure such as elevated jugular venous pressure and S3 gallop.

An electrocardiogram should be obtained which usually demonstrates nonspecific ST-T wave changes and occasionally low voltage QRS complexes. A correlation between decreased QRS voltage and prolonged QTc interval in the electrocardiogram and abnormal left ventricular systolic and diastolic function determined by echocardiography has been observed.

A plain chest X-ray to assess the presence of cardiomegaly and signs of pulmonary venous congestion should be included during clinical evaluation. The abnormalities detected by these evaluations, however, are nonspecific and nondiagnostic of chemotherapy-induced cardiotoxicity.

Transthoracic echocardiography with Doppler studies is commonly used to detect diastolic and systolic left ventricular dysfunction. Occasionally an exercise echocardiography may be useful to assess left ventricular contractile reserve.

Doppler tissue imaging (DTI) has been employed for early detection of doxorubicin cardiomyopathy. The changes in DTI may precede changes in left ventricular ejection fraction.[25]

The Tei index which simultaneously evaluates ventricular systolic and diastolic function has been used to assess chemotherapy-induced cardiac dysfunction. The Tei index was reported to increase by 78% after anthracycline treatment which indicated myocardial dysfunction.[26] However its potential role for detection of early systolic dysfunction has not been established.[26]

Radionuclide ventriculography is also used to assess left ventricular systolic function and may provide a more accurate determination of left ventricular ejection fraction. A reduction of ejection fraction of 4% by radionuclide ventriculography has been reported to have sensitivity of 90% and specificity of 72%.[27]

Increasingly cardiac magnetic resonance (CMR) is being used not only for assessing left ventricular function but also to determine the degree of fibrosis. The irreversible myocardial damage is detected by late gadolinium enhancement in patients with chemotherapy-induced cardiotoxicity.

Cardiac adrenergic denervation occurs in chemotherapy-induced cardiomyopathy particularly in doxorubicin cardiomyopathy. Metaiodobenzylguanidine (MIBG) nuclear imaging is employed for determination of cardiac adrenergic denervation.[17] In doxorubicin cardiomyopathy, abnormal glucose and fatty acid metabolism can occur which can be assessed by positron emission tomography (PET) using fluorine-18-F-deoxyglucose.[17] The beta-methyl-branched fatty acid (123 I-BMIPP) nuclear studies can detect abnormal fatty acid metabolism. These imaging modalities, however, are not specific for doxorubicin cardiomyopathy.

Antimyosin antibody study with the use of 111-In-labeled monoclonal antimyosin antibody imaging has been employed for the diagnosis of doxorubicin cardiomyopathy.[17] The sensitivity of antimyosin antibody study is very high in patients who have received anthracyclines.

The measurements of circulating neurohormones and cardiac enzymes have been used for the diagnosis of anthracycline cardiotoxicity and also for presence of heart failure. The B-type natriuretic peptide (BNP) and N-terminal pro-BNP plasma levels are elevated in patients with established cardiac dysfunction and the magnitude of increase in the plasma levels of these natriuretic peptides correlates with the severity of congestive heart failure.[17]

The abnormal levels of troponin T or I indicate myocardial injury and should be measured in patients with anthracycline cardiomyopathy.[17] The positive troponin values are detected in about 30% of patients treated with cardiotoxic chemotherapy. If troponin level is elevated there is a significant risk of developing left ventricular dysfunction within 3 months. With a persistent elevation of troponin which indicates continued myocyte injury, there is a high probability of developing major cardiac events.

A persistently normal troponin level has a negative predictive value of 99% for developing chemotherapy-induced cardiotoxicity.[28]

The endomyocardial biopsy which can provide a definitive diagnosis of doxorubicin cardiomyopathy is occasionally employed in clinical practice. The diagnostic features are loss of myofibrils, distention of sarcoplasmic reticulum and vacuolization of the cytoplasm (Figs 1A to C). The endomyocardial biopsy is also used for grading of the severity of doxorubicin cardiotoxicity.[17] It is, however, an invasive technique, and requires considerable experience and training. The tests that are performed for the diagnosis of chemotherapy-induced cardiotoxicity are summarized in Tables 8 and 9.

MONITORING

Once the need for treatment with chemotherapy is established, evaluation for the patient's risk of developing chemotherapy-induced cardiotoxicity is indicated. The Framingham or Reynolds risk scores are usually used before initiation of chemotherapy.[29] During follow-up evaluations, cardiac function should be monitored either by echocardiography or by radionuclide ventriculography. The American Heart Association and the American College of Physicians recommend close monitoring of cardiac function during and after chemotherapy. However, how often assessment of cardiac function is necessary is not clear.

The hemodynamic grading has been proposed before institution of chemotherapy with doxorubicin. Presence or absence and severity of both right and left ventricular failure are considered for grading (Table 10). Preexisting grade 3 (severe) is associated with highest risk of developing chemotherapy-induced cardiotoxicity.

TABLE 8

Doxorubicin cardiomyopathy: Diagnostic procedures

- Physical examination
- Electrocardiography
- Echocardiography with Doppler without stress, with stress
- RNVG
- Other nuclear imaging
  - I-MIBG, IBMPP
  - PET, CMR
- Measurement of neurohormones
  - ANP, BNP, endothelins, troponins
- Endomyocardial biopsy

TABLE 9

Doxorubicin cardiomyopathy: Diagnostic and monitoring procedures

- Assessment of left ventricular function:
  - Radionuclide angiography
  - Echocardiography
- Assessment of adrenergic denervation:
  - MIBG
  - Precedes reduction in LVEF, nonspecific
- Assessment of myocardial energy metabolism:
  - F-FDG, I-BMIPP
  - Measurement of humoral factors
  - ANP, BNP, endothelins, troponins
- Detection of cardiomyocyte death:
  - In-labeled monoclonal antimyosin antibody
  - Tc-99m labeled Annexin V imaging
  - (sensitivity—high, specificity—low)

TABLE 10

Doxorubicin cardiomyopathy: Hemodynamic grading

Hemodynamic grading of patients before therapy:

- Grade 0: no RVF or LVF
- Grade 1: Mild RVF or LVF
- Grade 2: Moderate RVF or LVF
- Grade 3: Severe RVF or LVF

Worse the hemodynamic grade prior therapy, higher the incidence of cardiotoxicity and mortality

MANAGEMENT

PREVENTIVE STRATEGIES

As currently available treatment of established anthracycline-induced cardiomyopathy does not appear to be very effective to improve prognosis, there is a major emphasis on prevention, and many strategies have been proposed (Tables 11 and 12).

Several risk factors can exacerbate the risk of chemotherapy-induced cardiotoxicity. These include age, sex, preexisting cardiovascular disorders, concurrent use of other

TABLE 11

Anthracycline cardiomyopathy: Prevention—proposed approaches

- Risk factors modification
- To limit the cumulative dose of DOX to less than 450 mg/m^2
- To use anthracycline analogues
- Alternative methods of drug delivery
- Continuous slow infusion

TABLE 12

Doxorubicin cardiomyopathy: Prevention—pharmacologic

Prevention
• Mercaptopropionyl glycine (MPG)
• Probucol
• Dexrazoxane
• Amlodipine
• Carvedilol
• Angiotensin-converting enzyme inhibitors
• PDE 5 inhibitor (sildenafil)
• Nitric oxide
• Superoxide dismutase
• Endothelin receptor antagonist (bosentan)
• Erythropoetin, thrombopoetin
• Granulocyte colony-stimulating factor

chemotherapeutic agents, prior radiation, genetic predisposition and overweight. Some of these risk factors, such as age, gender and family history and genetic predisposition, are not modifiable.

Modification of preexisting hypertension, hyperlipidemia and obesity is advisable to reduce the risk of cardiotoxicity. Lipid lowering agents particularly "statins" seem to have chemoprotective and direct antitumor effect.[30]

Angiotensin-Converting Enzyme Inhibitors

Angiotensin-converting enzyme inhibitors appear to exert a protective effect against chemotherapy-induced cardiomyopathy. In patients with signs of early troponin positive doxorubicin cardiotoxicity, use of angiotensin-converting enzyme inhibitors is associated with a decrease in the magnitude of decline in ejection fraction.[31]

Beta-Adrenergic Blocking Agents

It has been suggested that the beta receptor activation enhances the risk of chemotherapy-induced cardiomyopathy and beta adrenoreceptor blockade may be useful to reduce the development of chemotherapy-induced cardiotoxicity. However experimental animal studies indicate that beta-1 adrenergic receptor blockade does not prevent doxorubicin cardiomyopathy. In contrast, carvedilol, a nonspecific beta receptor and alpha receptor blocking agent with an antioxidant property, has been shown to be effective in reducing deterioration in left ventricular ejection fraction.[32] The beneficial effect of carvedilol appears to be related to its antioxidant properties and its potential to reduce oxidative stress and mitochondrial dysfunction.[33]

Other pharmacologic agents with antioxidant properties, such as the calcium channel blocker amlodipine, anti-lipid agent probucol and oxygen radicals scavenger superoxide dismutase, have the potential to decrease anthracycline cardiotoxicity.[34,35]

Iron Chelators

The formation of oxygen-free radicals by anthracycline-iron complexes can damage myocardial mitochondria by peroxidation of lipids in the mitochondrial membranes.[36] The myocardium is particularly susceptible to the toxic effect of oxygen-free radicals as the levels of detoxifying enzymes such as glutathione peroxidase is lower than in other tissues.[37]

The iron chelators that are available for clinical use include: dexrazoxane, desferrioxamine, deferiprone and aroylhydrazone. These iron chelators decrease the generation of ROS by displacing iron bound to doxorubicin. In animal studies, addition of iron chelators to anthracyclines has been reported to decrease the histologic evidences of cardiotoxicity.[38]

In patients with breast cancer, and overall benefit of dexrazoxane in reducing anthracycline-induced cardiotoxicity has been observed.[39] However the incidence of adverse effects, such as myelosuppression, infection and fever is higher.[39] Thus, use of iron chelating agents, such as dexrazoxane, should be considered in patients with metastatic breast cancer or other malignancies who have received more than 300 mg/m^2 of doxorubicin. The patients receiving dexrazoxane should be carefully monitored for a decline in left ventricular ejection fraction and for development of heart failure, and in these patients dexrazoxane/doxorubicin treatments should be discontinued.

The mercaptopropionyl glycine (MPG), a synthetic aminothiol, has antioxidant properties and has the potential to reduce doxorubicin cardiotoxicity.[40]

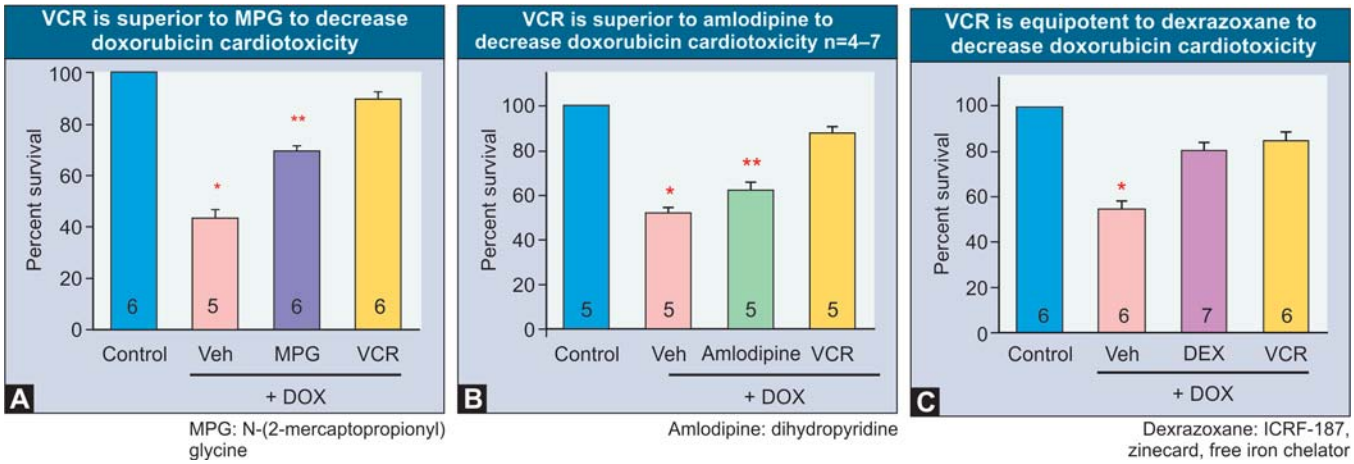
As doxorubicin may increase plasma levels of endothelin-1, endothelin antagonists can potentially decrease doxorubicin cardiotoxicity. In experimental animal studies, phosphodiesterase-5 inhibitors, erythropoietin and thrombopoietin and granulocyte colony-stimulating factor have been shown to exert protective effects against doxorubicin cardiotoxicity.[41] In transgenic mouse model, the potential protective effects of nitric oxide and superoxide dismutase have been investigated. Lack of nitric oxide was associated with enhanced myocardial mitochondrial injury which was attenuated by manganese superoxide dismutase.[42] In studies with cultured adult mouse cardiac myocytes, the vinca alkaloid vincristine exerts protective effects to chemical and hypoxic oxidative stress.[43] In this model using cultured adult mouse myocytes, the protective effects of vincristine was compared to that of MPG, amlodipine and dexrazoxane[44] (Figs 3A to C). It should be emphasized that, in these studies, specific mouse strains were used and it remains unknown whether vincristine provides similar protective effects or not in other mouse strains, and in other species including humans.

Dose Limitation and Dosing Regimens

The risks of anthracycline cardiotoxicity can be substantially reduced by limiting the cumulative dose of doxorubicin and epirubicin (< 450 mg/m^2 of doxorubicin and < 900 mg/m^2 of epirubicin). Instead of giving a bolus injection, infusion over several hours may also decrease cardiotoxicity. In addition, weekly administration of doxorubicin appears to be associated with less cardiotoxicity than the administration of higher doses every three weeks.[45]

Lyposomal Anthracyclines

Encapsulation of doxorubicin in liposomes has the potential to reduce its cardiotoxicity. Presently two types of liposomal anthracyclines—pegylated (polyethylene glycol-coated) and



MPG: N-(2-mercaptopropionyl) glycine

Amlodipine: dihydropyridine

Dexrazoxane: ICRF-187, zinecard, free iron chelator

FIGURES 3A TO C: The comparative effects of vincristine and MPG, amlodipine and dexrazoxane. Vincristine was found to be superior to MPG and amlodipine and equipotent to dexrazoxane in this model using adult cultured mouse myocytes

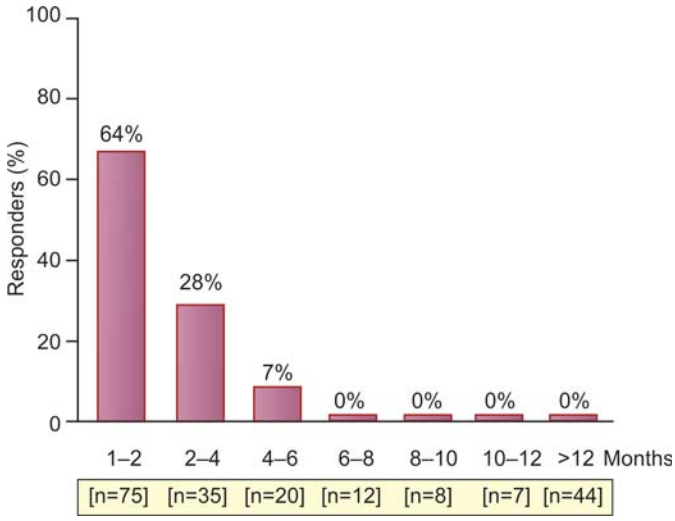


FIGURE 4: The relation between the initiations of heart failure treatment after the anthracycline administration. The sooner the heart failure treatment was initiated higher was the percentage of responders. The responders were defined who had full recovery (normal left ventricular ejection fraction) or partial recovery (improved but not normal ejection fraction) after heart failure treatment. (*Source:* Cardinale et al. JACC. 2010;55:213, reference 50, with permission)

non-pegylated—are available for clinical use. In patients with breast cancer, the use of pegylated liposomal doxorubicin was associated with a substantial reduction in the incidence of cardiotoxicity.[46] The use of non-pegylated doxorubicin was also associated with decrease in the incidence of symptomatic heart failure.[47]

TREATMENT

Presently there is no specific treatment available for the management of patients with established cardiotoxicity with or without overt heart failure. Heart failure due to chemotherapeutic agents should be managed similarly to other causes of systolic heart failure and the recommendations of the American College of Cardiology, American Heart Association and the Heart Failure Society of America should be considered.[48]

The treatment strategies for heart failure stages B, C, and D are highly desirable for chemotherapy-induced cardiomyopathy. Complete recovery of function may occur following discontinuation of the chemotherapeutic agent.[49] Early institution of standard therapy with angiotensin and adrenergic inhibition therapy may be associated with full recovery of systolic function[50] (Fig. 4).

ANGIOTENSIN INHIBITION THERAPY

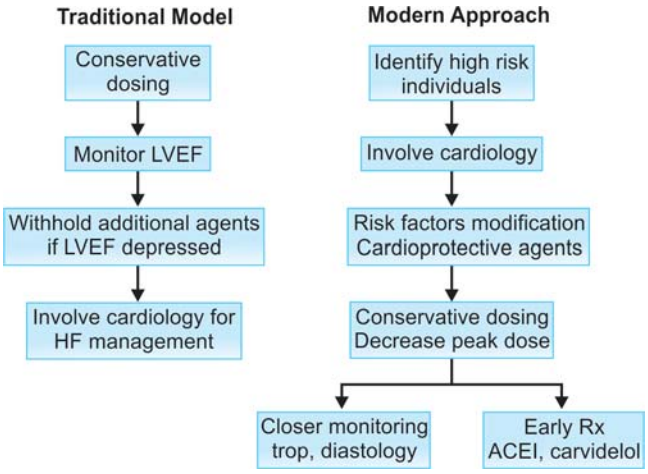
Angiotensin-converting enzyme inhibitors are indicated in patients with symptomatic (stage C) or asymptomatic left ventricular systolic dysfunction (stage B). Angiotensin-inhibition therapy has the potential to relieve symptoms and improve prognosis. In patients who develop chemotherapy-induced cardiomyopathy, improvement in left ventricular ejection fraction occur usually late after about average of 3 months after institution of treatment.

ADRENERGIC INHIBITION THERAPY

Adrenergic inhibition, such as with carvedilol, should be considered in asymptomatic (stage B) and symptomatic (stage C) patients with systolic heart failure. Early initiation of therapy may be associated with full and partial recovery of left ventricular ejection fraction.

Combination of angiotensin and adrenergic inhibition are likely to produce a greater benefit. Thus, combination therapy should be considered whenever it is feasible and not contraindicated. In patients who cannot tolerate angiotensin II inhibition or adrenergic inhibition therapy or who remain in heart failure despite these treatments, low dose hydralazine-isosorbide dinitrate combination treatment is often employed. However there is no evidence to suggest that such treatment is effective in patients with doxorubicin cardiomyopathy. Implantable cardioverter and defibrillator with or without resynchronization treatment are employed in patients with stage C systolic heart failure. However whether such treatments improve prognosis of patients with chemotherapy-induced cardiomyopathy remain unclear. Cardiac transplantation should also be considered in the appropriate patients in whom the

FLOW CHART 1: The traditional and the modern approaches for management of cancer patients at risk of developing chemotherapy-induced cardiomyopathy



(Abbreviations: LVEF: Left ventricular ejection fraction; HF: Heart failure; Rx: Treatment; ACEI: Angiotensin-converting enzyme inhibitors)

primary malignancy is cured following chemotherapy (stage D). Placement of ventricular assist devices may be required before cardiac transplantation provided there is a prospect of improved prognosis following cardiac transplantation.

CONCLUSION

Currently there are no adequate predictive models, prevention modalities or treatments. However, based on the available literature, we propose a modern approach of care of cancer patients which is based on prevention and early detection of cardiotoxicity (Flow chart 1).

Since therapeutic decisions involve trading one potentially fatal disease for another, the best care of cancer patients who are potential candidates to cardiotoxic agents is by a multidisciplinary team comprised of cardiologists and oncologists.

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Chapter 86

Pericardial Disease

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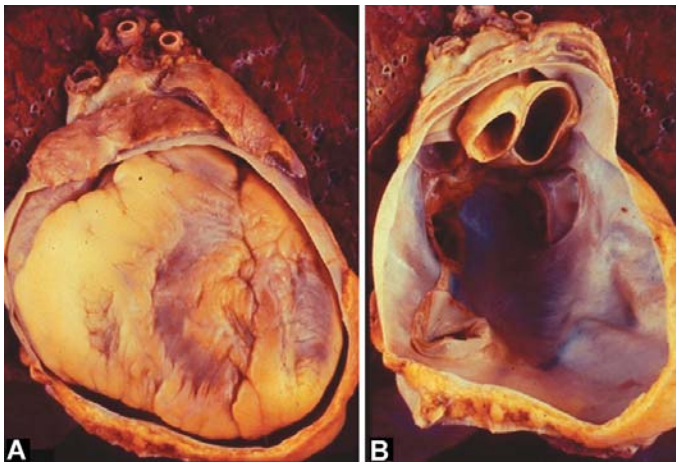
Chapter Outline

- Acute Pericarditis
  - Presentation and Etiology
  - Examination
  - Diagnosis
  - Treatment
- Chronic Relapsing Pericarditis
  - Presentation and Etiology
  - Diagnosis
- Pericardial Effusion and Pericardial Tamponade
  - Presentation and Etiology
  - Examination
  - Diagnosis
  - Treatment
- Constrictive Pericarditis
  - Presentation and Etiology
  - Examination
  - Diagnosis
  - Treatment

INTRODUCTION

The pericardium is a thin covering that separates the heart from the remaining mediastinal structures, consisting of an outer sac (fibrous pericardium) and inner double layer sac (serous pericardium). There are two layers of serous pericardium: (1) the visceral layer (epicardium) covers the heart and great vessels and (2) the parietal layer is fused to the fibrous pericardium (Figs 1A and B). The visceral and parietal layers of the serous pericardium are separated by the pericardial cavity, which normally contains less than 50 cc of a plasma ultrafiltrate. Although the pericardium does provide some mechanical protection for the heart and lubrication to reduce friction between the heart and the surrounding vessels, it is not essential, for normal cardiac function, which can be maintained in the complete absence of a pericardium.

Diseases of the pericardium may present as inflammation (acute pericarditis), exudation (pericardial effusion or tamponade) or fibrosis (constrictive pericarditis). Although these appear to be three simple pathophysiologic processes, diseases of the pericardium present one of the most misdiagnosed and undertreated cardiac problems today. It is important to understand the presentation, diagnostic tests and treatment of these pericardial disorders, as are to be outlined in this chapter.



FIGURES 1A AND B: Normal pericardium. Pathology specimens showing the double-layered pericardium with (A) and without (B) the heart in the fibrous pericardial cavity. (*Source:* William D Edwards)

ACUTE PERICARDITIS

PRESENTATION AND ETIOLOGY

Inflammation of the pericardium (acute pericarditis) can be a manifestation of an underlying systemic disease, but most commonly presents as an isolated entity. The presentation is usually that of a young otherwise healthy patient who develops sudden pleuritic chest pain accompanied by systemic symptoms of fever, malaise and myalgias. In most patients, the etiology of acute pericarditis thought to be due to a viral etiology. Known secondary causes of acute pericarditis include bacterial or tuberculosis infection, systemic diseases (such as immune mediated diseases), neoplastic invasion of the pericardium, chronic renal disease, prior myocardial infarction or bypass operation, or chest wall trauma[1-4] (Table 1).

The typical chest pain of a patient presenting with acute pericarditis is usually sharp in nature and substernal in location, radiating to the neck and arms, exacerbated by either inspiration or position. Patients with acute pericarditis typically assume an upright sitting position, which appears to lessen the pericardial pain. However, pericardial pain can also be prolonged and

TABLE 1

Etiology and estimated incidence of acute pericarditis

Condition	*Estimated incidence*[a]
Idiopathic	85–90%
Infectious:	
Viral	1–2%
Bacterial	1–2%
Tuberculous	4%
Fungal	Rare
Parasites	Rare
Neoplastic disease	7%
Systemic autoimmune disease	3–5%
Postcardiotomy or thoracic surgery	Rare (< 1%)
Aortic dissection	Rare (< 1%)
Chest wall trauma	Rare (< 1%)
Chest wall irradiation	Rare (< 1%)
Adverse drug reaction	Rare (< 1%)
Acute myocardial infarction	5–20%[b]
Myocarditis	30%[b]
Uremia	5% before dialysis and 13% after initiation of dialysis

[a](*Source:* Maisch B, et al.[1] Zayas R, et al.[2] Permanyer-Miralda G, et al.[3] and Lange RA, Hillis LD[4]
[b]Percentage related to the incidence of pericarditis in the specific population of patients

continuous, mimicking the pain of myocardial ischemia or acute aortic dissection. In some patients, acute pericarditis is accompanied by a myocarditis, and concomitant elevations of cardiac enzymes make it difficult to differentiate acute pericarditis from true myocardial ischemia.

EXAMINATION

The examination of a patient with suspected pericarditis should focus on a meticulous assessment of the blood pressure (checking for pulsus paradoxus) and the jugular venous pressure, and determining the presence of a pericardial rub. If there is a pulsus paradoxus and/or elevation of venous pressure, pericardial tamponade or constriction should be suspected. The classic pericardial friction rub is a "scratchy" three component sound heard mainly at the left sternal border. However, a pericardial rub may have only two components or even an isolated systolic component.[5] Auscultation should be performed with the patient in multiple positions, including the left lateral decubitus position, supine and sitting upright, as the pericardial rub may be effervescent and heard only in certain positions.

DIAGNOSIS

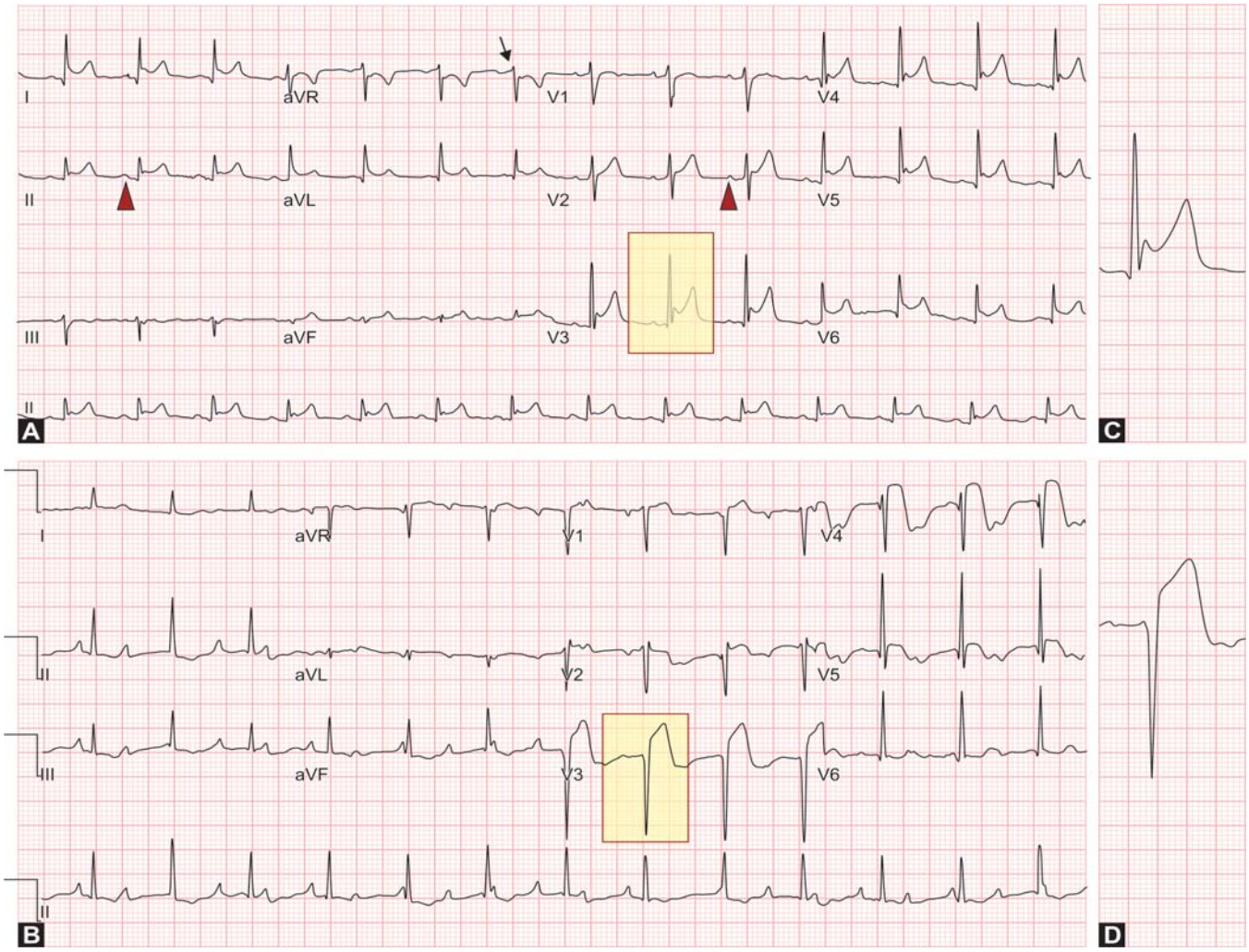
There are classic electrocardiographic abnormalities present in most patients with acute pericarditis. In the acute setting, an upward concave ST segment elevation in two or more locations as well as PR segment depression are commonly present[6-8] (Figs 2A to D). These findings need to be differentiated from the more "hump-like" convex ST segment elevation of acute myocardial injury. The evolution of electrocardiographic changes with pericarditis includes normalization of the ST and PR segments with the development of widespread T-wave inversions, some of which may persist indefinitely. It has been shown that typical presenting electrocardiographic changes of acute pericarditis are seen in over 80% of patients presenting with this entity[9] and the electrocardiographic evolution occurs in up to 60% of patients.[10]

The diagnosis of acute pericarditis should include at least two of the following criteria: (1) Characteristic pleuritic chest pain; (2) A pericardial friction rub and (3) Typical electrocardiographic changes (Flow chart 1). A new pericardial effusion on imaging studies may be helpful in equivocal cases but not required for diagnosis and/or therapy. Once the diagnosis is made, further work-up of a patient presenting with acute pericarditis is mainly to rule out other etiologies for the presenting symptoms. Echocardiography is not needed for the diagnosis if the physical examination does not show evidence of pericardial tamponade (e.g. absence of pulsus paradoxus or an elevated venous pressure). Markers of inflammation, such as a sedimentation rate or a serum C-reactive protein, should be obtained and are almost always elevated in the presence of acute pericarditis. Although most patients with an idiopathic acute pericarditis are thought to have an underlying viral infection, viral cultures or antibody titers are not clinically useful.[2,3] Routine serologic testing for antinuclear antibodies and rheumatoid factors are of low yield and should be ordered only if there are other concomitant presenting symptoms suggestive of these autoimmune diseases. Troponin levels should be performed. A cardiac troponin I level can be minimally elevated in acute pericarditis,[11,12] probably as the result of inflammation of the epicardium. Most patients with an elevated troponin level due to acute pericarditis will have normal findings on coronary angiography and the troponin levels will return to normal within 1–2 weeks. However, if there is a rapid rise and drop in serial troponin levels at 3 hours and 6 hours (a significant delta change), myocardial ischemia should be suspected. Prolonged sustained levels of marked elevation in troponin may suggest a concomitant myocarditis.

TREATMENT

Most patients presenting with acute pericarditis in the absence of underlying disorders can be treated as an outpatient. It is only those patients with high-risk features who should be hospitalized. These high-risk features include a high fever (temperature > 38°), and an immunocompromised state, concurrent oral anticoagulation, previous failure of nonsteroidal therapy or a marked elevation of troponin (> 10x upper limit normal). In the absence of these risk factors, patients do well and in one study, no serious complications were reported after nearly 40 months of follow-up.[10]

The treatment of acute pericarditis depends upon the absence or presence of an underlying etiology. For instance, if pericarditis is due to a secondary cause such as uremia, aggressive dialysis should be performed (i.e. dialysis). In the presence of systemic autoimmune diseases, appropriate treatment for the underlying disease should be implemented. However, for the majority of patients presenting with isolated acute pericarditis, the treatment should be with high dose salicylates or nonsteroidal anti-inflammatory agents. Colchicine should be used in all patients unless there is a contraindication[13] (Flow chart 1). Corticosteroids should rarely be used, as the use of



FIGURES 2A TO D: ECG abnormalities in acute pericarditis versus acute myocardial infarction. (A) Acute pericarditis reveals diffuse concave upsloping ST-segment elevation is seen in leads I, II, aVL, aVF and V2 to V6. There is also PR-segment elevation in aVR (arrow) and subtle PR-segment depression in leads II and V_2 (arrowheads). Reciprocal ST-segment depression is seen in aVR; (B) In acute myocardial infarction, the ST-segment elevation is convex upward or "humplike". (C and D) These panels demonstrate the difference in the ST-segment elevation in acute pericarditis (panel C) and acute myocardial infarction (panel D)

steroids to treat acute pericarditis has been shown to result in a higher incidence of relapsing pericarditis.[14]

The optimal treatment for an acute isolated pericarditis in a young healthy person is high dose salicylates.[1,10,14] The dosage is 900–1200 mg every 4–6 hours while awake for a period of 7–10 days, followed by gradual tapering for an additional 3 weeks. Indomethacin or other nonsteroidal anti-inflammatory agents can also be used,[15,16] but large dosages are necessary (up to 150–200 mg/day). Nonsteroidal anti-inflammatory agents should not be used in patients who present with a concomitant myocardial infarction or known coronary artery disease.[17] Proton pump inhibitors should be used in all patients on these large dosages of salicylates or nonsteroidals.

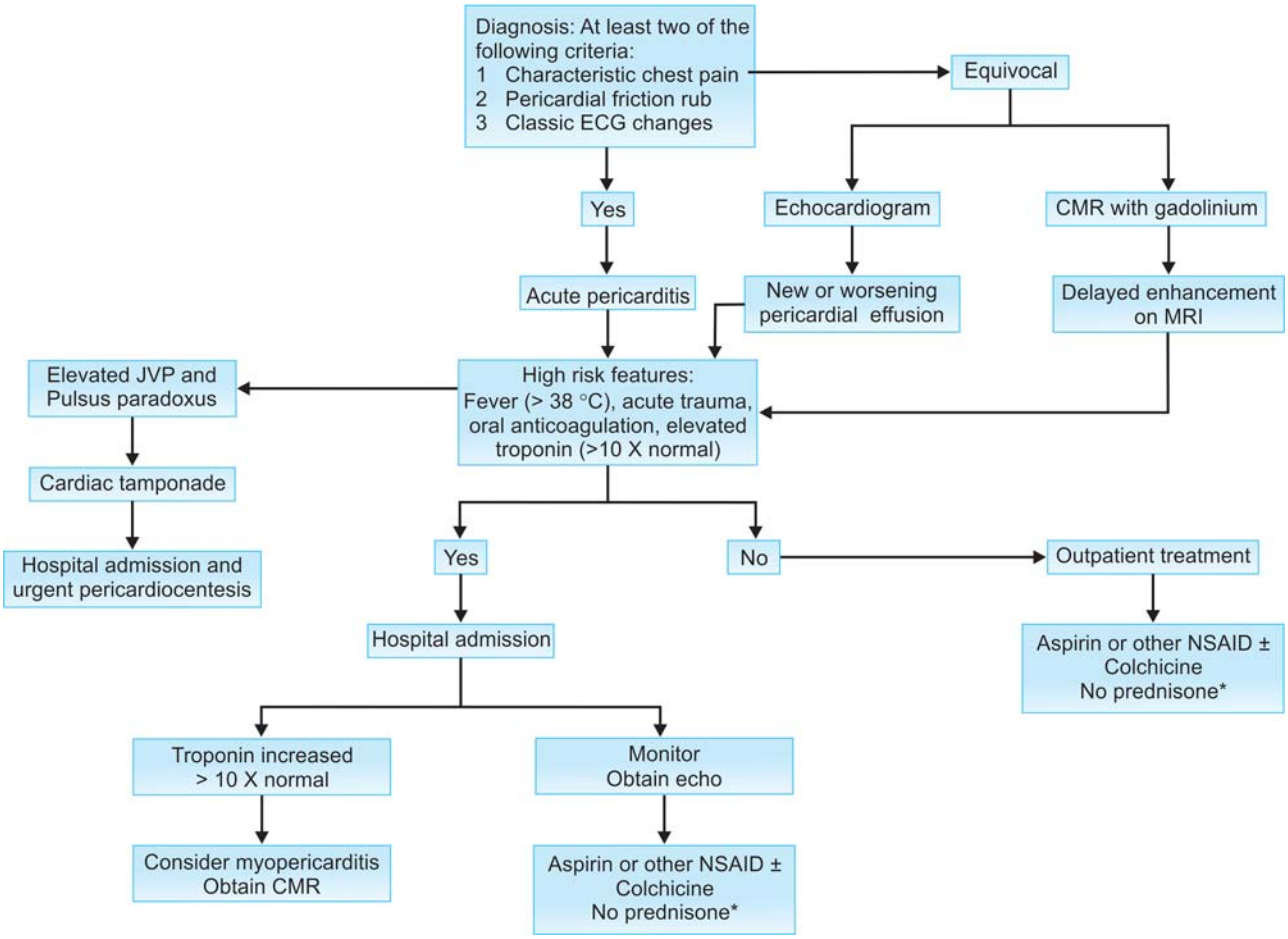
Colchicine has been shown to be effective in relieving pain with acute pericarditis and in preventing recurrences. Colchicine significantly reduced symptoms after 72 hours and recurrence at 18 months in the COlchicine for acute PEricarditis (COPE) trial.[14] It is recommended that all patients with acute pericarditis who can tolerate colchicine be treated with 0.6 mg twice a day for 1 week, then taper to 0.6 mg per day for at least 6 months. Colchicine should be avoided in patients with renal insufficiency, hepatobiliary disorders, blood dyscrasias and gastrointestinal motility disorders.

CHRONIC RELAPSING PERICARDITIS

PRESENTATION AND ETIOLOGY

Chronic relapsing pericarditis is a severe debilitating disease of the pericardium in which patients develop multiple recurrent episodes of pericarditis weeks to months after an initial episode of acute pericarditis. It is truly one of the most challenging complications of diseases of the pericardium. The frequency of chronic relapsing pericarditis following about of acute pericarditis is unknown, due to a paucity of studies with small patient populations. The frequency in many clinical series varies between 8% and 80%, but overall about one in four patients will develop chronic relapsing pericarditis.[18] The etiology is unknown but appears to be consistent with an autoimmune reaction activated by the initial episode.[19] The pericardium is

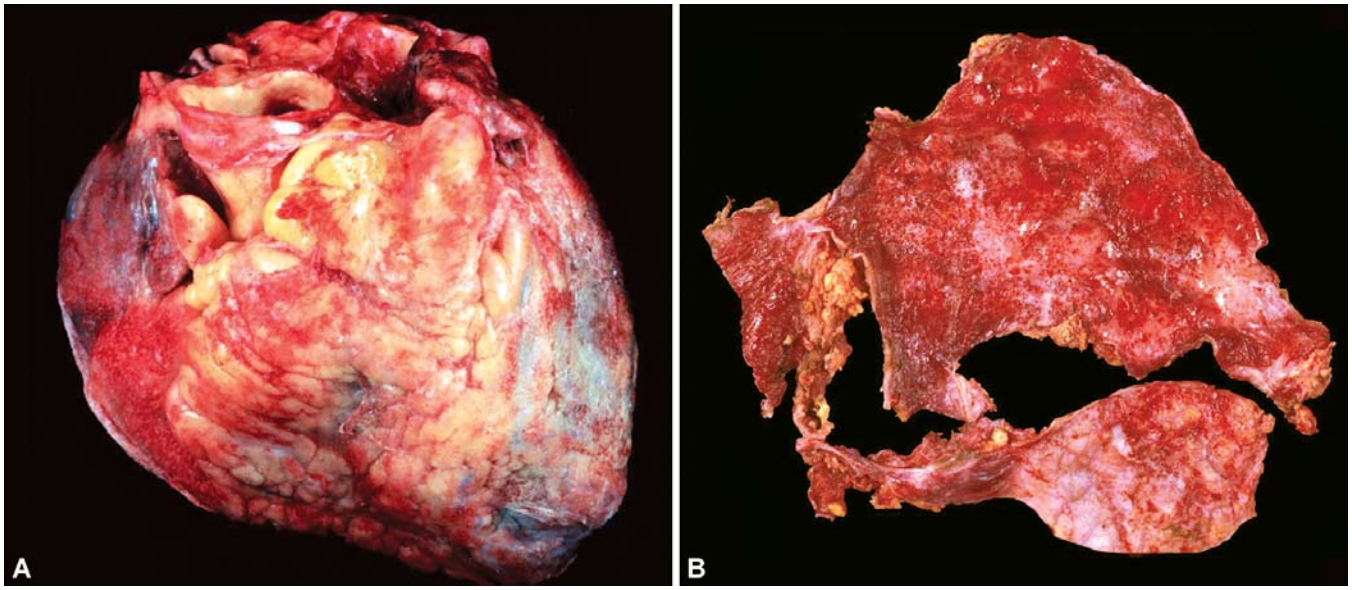
FLOW CHART 1: Overview of the diagnosis and management of acute pericarditis



*Corticosteroids should not be routinely used initially unless rheumatologic etiology or contraindication of NSAIDs and colchicine

often thickened and fibrinous due to chronic inflammatory changes (Figs 3A and B).

This devastating disease entity appears to be particularly frequent in patients who have received prior corticosteroid therapy for acute pericarditis. The mean number of relapses is much higher in those receiving corticosteroids than those who have not.[14,20,21] The typical presentation of chronic relapsing pericarditis is an otherwise healthy patient who was treated with corticosteroids for an initial bout of acute pericarditis. These relapses may occur weeks to months after the initial episode,



FIGURES 3A AND B: Gross features of relapsing pericarditis. (A) Anterior view of fibrinous pericardium in a patient with recurrent pericarditis; (B) Following surgical pericardiectomy, the thickened fibrinous pericardium is demonstrated. (*Source:* William D Edwards)

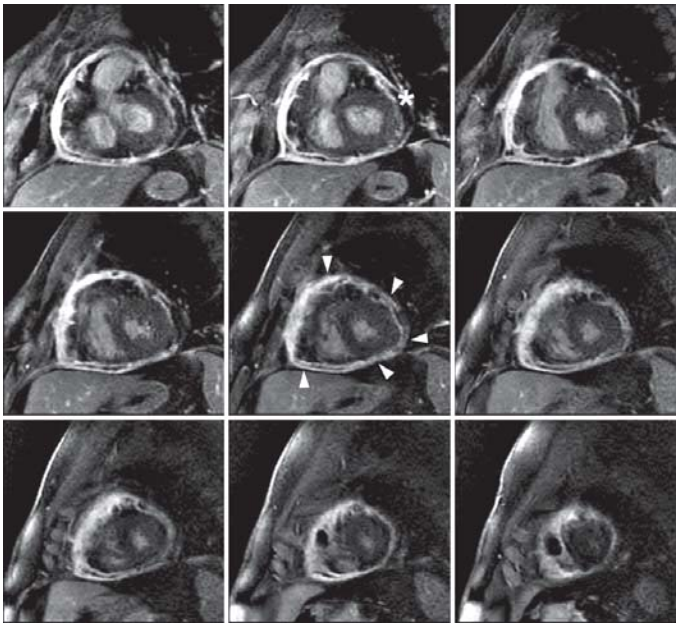


FIGURE 4: CMR in chronic relapsing pericarditis. CMR demonstrating short axis delayed gadolinium enhancement images in a patient with chronic relapsing pericarditis. A brightly enhancing pericardium (arrowheads) is suggestive of pericardial inflammation. Loculated pericardial effusions (*) are also seen

and frequently corticosteroids are restarted for pain relief. When the steroid dose is dropped below physiologic levels upon weaning, the signs and symptoms of pericarditis will then return. Increasing the steroid dose will result in temporary resolution of the pericarditis, but as soon as the steroids are dropped below a certain level (usually 10–15 mg equivalent of prednisone), the relapses will recur.

DIAGNOSIS

The diagnosis of chronic relapsing pericarditis uses the same diagnostic criteria as acute pericarditis for determining the presence of pericardial inflammation. However, these patients tend to become significantly debilitated and it is sometimes difficult to differentiate between the pain of true chronic relapsing pericarditis versus somatic complaints associated with a chronic pain syndrome. It is helpful to have concomitant findings of either an elevated sedimentation rate or CRP at the time of the relapse. MRI scanning with gadolinium enhancement will show delayed gadolinium enhancement in areas of inflamed pericardium (Fig. 4) and may be helpful in some patients in whom the diagnosis remains equivocal.[22]

The treatment of patients who present with chronic relapsing pericarditis is difficult. An aggressive medical therapy with high dose salicylates or nonsteroidal anti-inflammatory agents should be implemented while the steroid dose is above the level at which relapses occur. Following the relief of all pericardial pain by the combination of prednisone and the salicylates or nonsteroidal anti-inflammatory agents, the steroids should then be very slowly weaned over a long period of time, while maintaining high levels of salicylates or nonsteroidal anti-inflammatory agents. The weaning process should be as slow as 1 mg taper per month, necessitating a duration of up to 18–24 months before the patient is completely off the steroids. Following the taper off steroids, the salicylates and nonsteroidal anti-inflammatory agents should be continued for at least months after complete withdrawal of the steroids. Colchicine is effective in preventing recurrent episodes if given after the first episode[21] of acute pericarditis and thus should be administered during this process and continued for at least 1 year after the last episode of pericarditis.

About 50% of patients with chronic relapsing pericarditis will respond to this aggressive medical therapy. There will be a subset of patients who will not be able to respond to this very slow steroid taper and in these patients, complete pericardiectomy may be effective. In the Mayo Clinic experience, patients who underwent complete pericardiectomy for chronic relapsing pericarditis, all had symptomatic improvement and over 90% of patients were able to be weaned off steroids.[23]

PERICARDIAL EFFUSION AND PERICARDIAL TAMPONADE

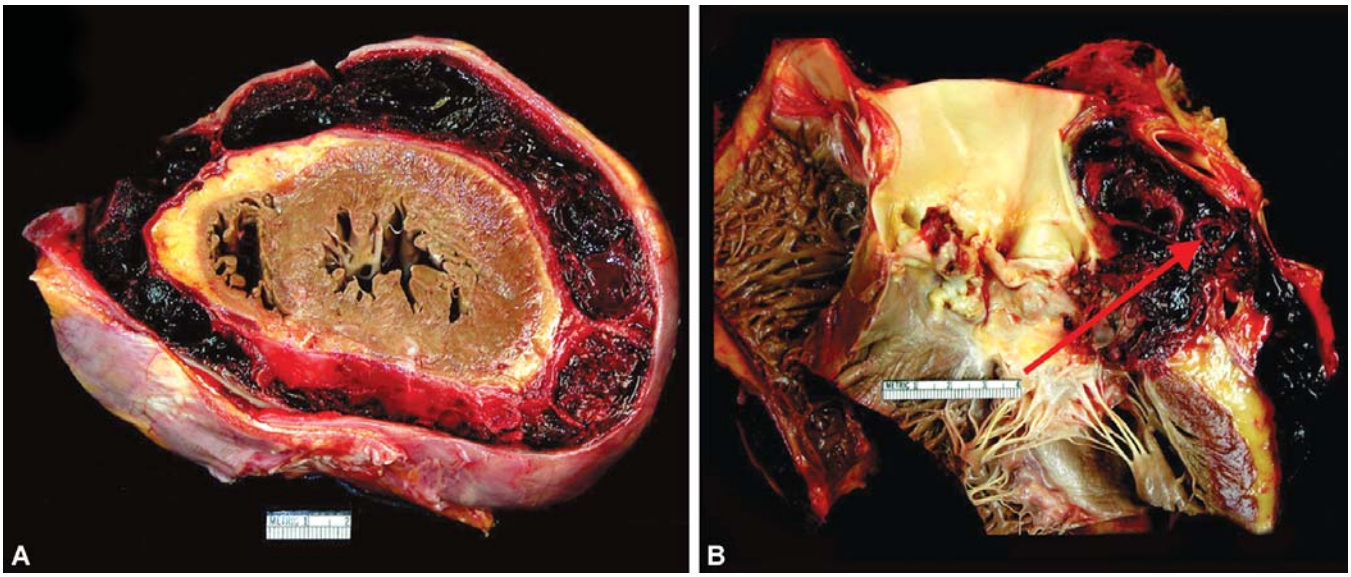
PRESENTATION AND ETIOLOGY

The development of a pericardial effusion can either be idiopathic or due to a number of underlying etiologies. The effect of the pericardial fluid on cardiac hemodynamics depends more on the rate at which the effusion accumulates rather than the amount of the effusion. In a patient with slow accumulation of pericardial fluid, the pericardium is able to expand, thus accommodating up to several liters of fluid without compromising cardiac hemodynamics. However, when the amount of fluid exceeds the ability of the pericardium to expand, all four cardiac chambers are compressed as a result of increased intrapericardial pressure comprising systemic venous return and cardiac tamponade ensues.[24] Acute pericardial tamponade can occur with rapid accumulation of less than 100 cc of fluid. This is a life-threatening entity if not treated rapidly. Acute tamponade may occur due to a malignancy or left ventricular rupture from a myocardial infarction. It is being seen more frequently as a result of complications from invasive cardiac catheterization and electrophysiologic procedures.[25] Figures 5A and B demonstrates gross anatomical features of cardiac tamponade in a patient with aortic valve endocarditis.

The pathophysiology of cardiac tamponade consists of increased intrapericardial pressure, which decreases myocardial transmural pressure reducing chamber diastolic compliance with a resultant decrease in stroke volume. During inspiration the drop in intrathoracic pressures is transmitted to the right side of the heart, resulting in an increase in systemic venous return and distention of the right ventricle. Due to the high intrapericardial pressure, the free wall of the right ventricle is not able to expand and thus the septum bulges into the left ventricle, decreasing the effective operative compliance and preload of the left ventricle with a further drop in forward stroke volume. This enhancement of ventricular interaction is the mechanism of pulsus paradoxus, which is an exaggerated drop in systemic pressure during inspiration.

EXAMINATION

In a patient with pericardial tamponade, sinus tachycardia is usually present, as the increased heart rate is a physiologic



FIGURES 5A AND B: Gross pathological features in a patient with cardiac tamponade. Pathologic examination of a patient with aortic valve endocarditis showed hemopericardium (left) due to a perforation of the proximal aorta (arrow). (*Source:* William D Edwards)

TABLE 2

Diagnostic testing in cardiac tamponade

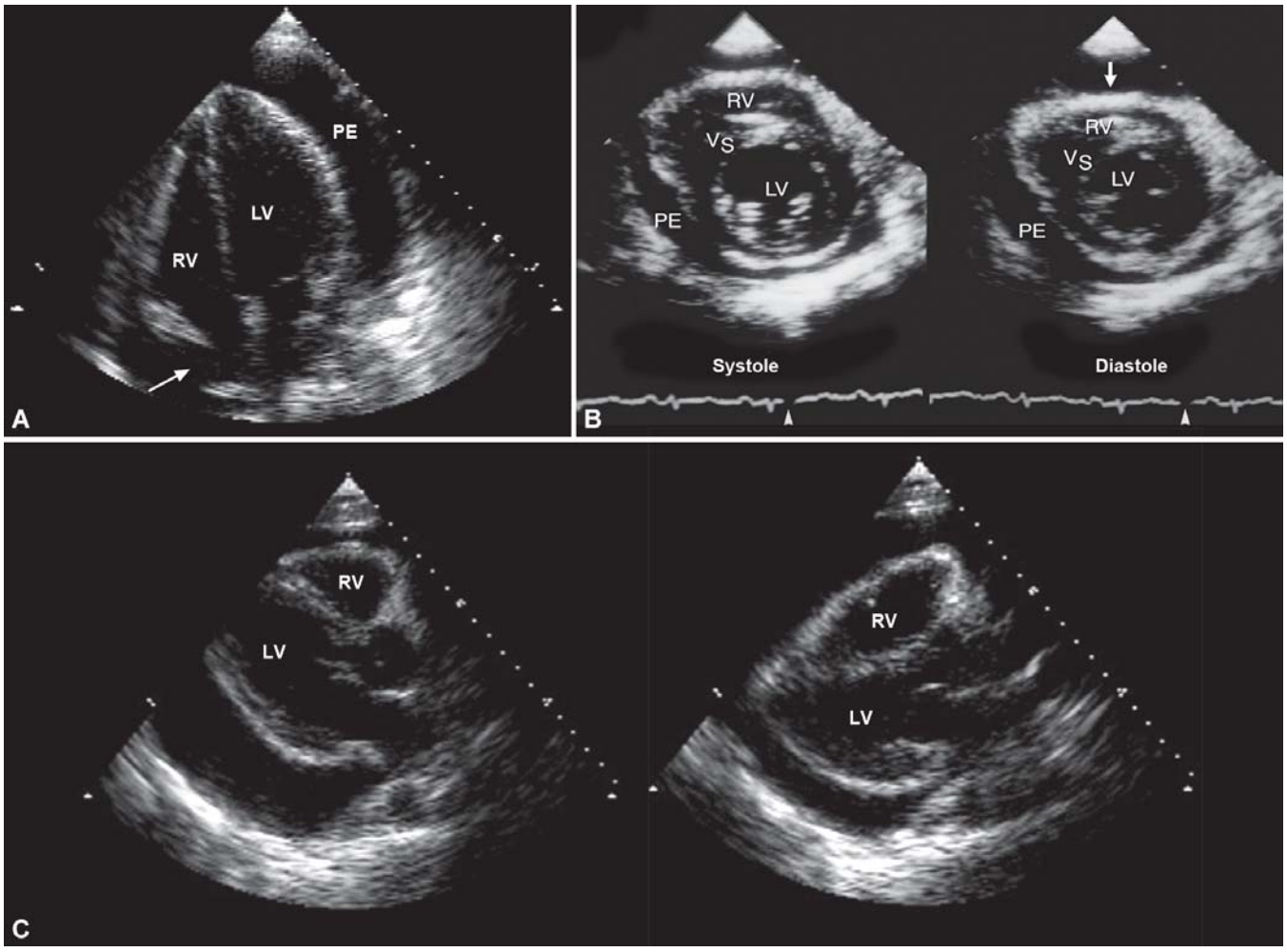
Initial findings	*Echocardiography*	*Cardiac catheterization*
Symptoms: Chest pain Shoulder discomfort Abdominal discomfort Nausea Examination: Sinus tachycardia Elevated JVP-loss "y" descent Pulsus paradoxus Friction rub ECG: Sinus tachycardia Low voltage QRS Widespread concave ST-segment elevation and PR-segment depression Electrical alternans	Two-dimensional: Late diastolic collapse of RA Early diastolic collapse of RV Collapse of LA Ventricular interdependence IVC dilatation with < 50% inspiratory collapse Doppler: Blunted initial transmitral E velocity Expiration Increased mitral E velocity Increased transmitral pressure gradient Decreased IVRT Hepatic vein diastolic flow reversal Inspiration Further drop in mitral E velocity	Early: Increased RA pressure with loss of "y" descent Late: Decreased aortic systolic pressure Decreased aortic pulse pressure Pulsus paradoxus Prominent decrease in pulse pressure with inspiration Intracardiac diastolic pressure equilibration

response to the drop in stroke volume to maintain cardiac output. The venous pressure is elevated, with preservation of the "x" descent, but there is blunting of the "y" descent, as the high pericardial pressure prevents early rapid diastolic filling of the right ventricle at the time of tricuspid valve opening. Pulsus paradoxus, is always seen in pericardial tamponade, defined as a drop of systolic pressure greater than 10 mm Hg during inspiration.

DIAGNOSIS

In a patient suspected of having pericardial tamponade, echocardiography is the diagnostic procedure of choice (Table 2). Typical findings on echocardiography include late diastolic collapse of the right atrium, early diastolic collapse of the right ventricle and a dilated inferior vena cava from the high right atrial (RA) pressure[26] (Figs 6A to C). Specifically, enhancement of ventricular interaction is seen by a septal shift from right ventricle to left ventricle during inspiration.

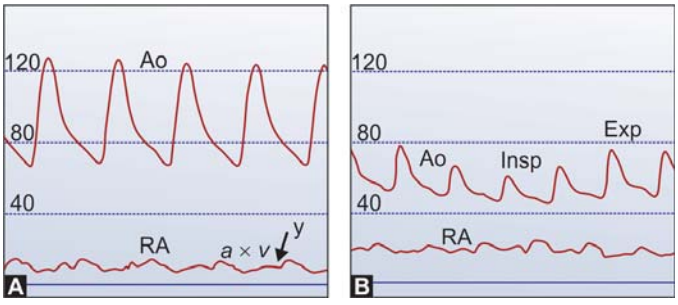
Doppler velocities show blunted initial E-velocity on the transmitral flow velocity curve due to a decrease in early rapid filling. There is a further decrease in transmitral inflow during inspiration due to the blunted inspiratory filling of the left sided chambers. There will also be expiratory reversals in the hepatic vein velocities. These findings may be present in "subclinical" cardiac tamponade and portend the development of progression to severe hemodynamic compromise. Thus, in any patient with a pericardial effusion, meticulous assessment of Doppler



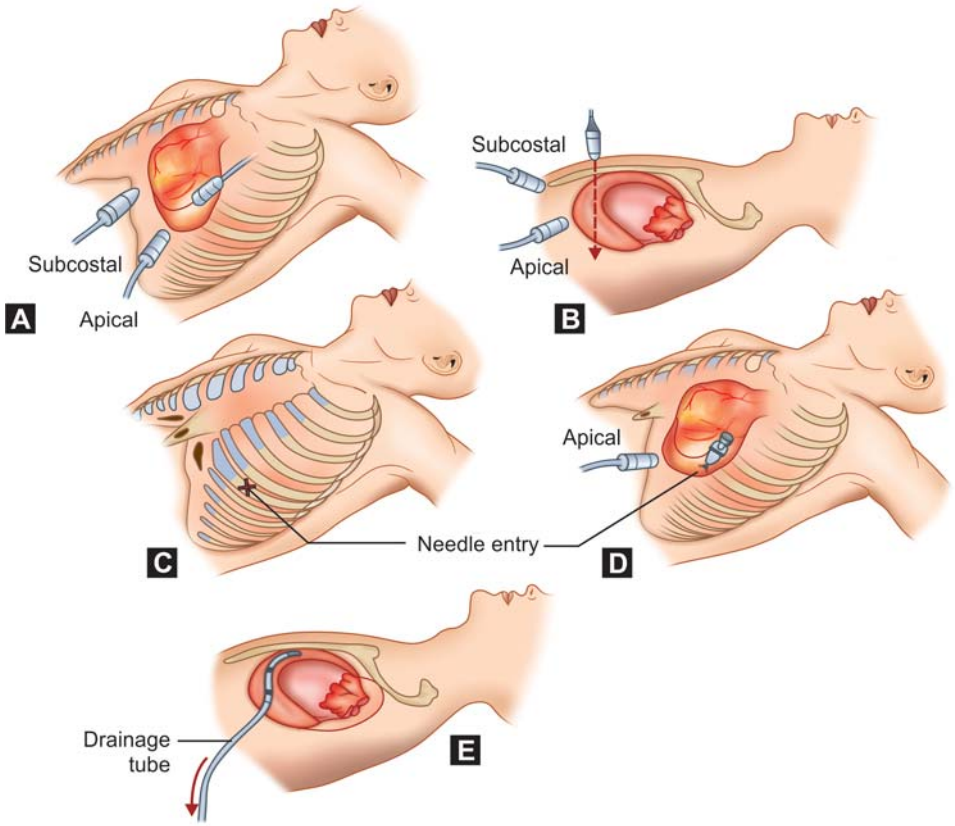
FIGURES 6A TO C: Two-dimensional echocardiographic features of cardiac tamponade. (A) Still frame image of an apical four-chamber view demonstrating late diastolic collapse of the right atrium (arrow). Persistence of right atrial (RA) collapse for more than one-third of the cardiac cycle is highly sensitive and specific for tamponade; (B) Early diastolic collapse (arrow) of the RV is specific for tamponade; (C) Parasternal long-axis views demonstrate the swinging motion of the heart within the pericardial cavity of a large pericardial effusion. The swinging motion is responsible for the electrocardiographic manifestation termed electrical alternans. (*Source:* Oh JK, Seward JB, Tajik AJ. The Echo Manual, 3rd edn. Lippincott, Williams and Wilkins; 2007)

transmitral inflows and hepatic vein are essential, even in the absence of clinically suspected pericardial tamponade.

Cardiac tamponade is increasingly seen in the cardiac catheterization or EP laboratory as interventional procedures become more invasive and complex.[25] Thus, it is important to know the sequential hemodynamic changes that can be detected by intracardiac pressure analysis. Although hypotension is a hallmark of tamponade, systemic aortic pressure and heart rate can increase in the early stages of acute tamponade as a result of the sympathetic response to pericardial irritation. In early tamponade, RA pressure will begin to increase, with a loss of "y" descent and a more pronounced a wave at the time of atrial contraction in patients who are in sinus rhythm (Figs 7A and B). As cardiac tamponade progresses, aortic systolic pressure and pulse pressure decrease and pulsus paradoxus develops, as evidence by a more pronounced decrease in pulse pressure during inspiration (Figs 7A and B). In contrast to aortic pressure, RA pressure continues to increase significantly. Severe elevation and equalization of diastolic pressures in all four cardiac chambers will occur. Fluoroscopy of the cardiac silhouette may



FIGURES 7A AND B: Hemodynamics of acute cardiac tamponade by cardiac catheterization (A) In the very early stages of cardiac tamponade, there is a mild elevation of right atrial (RA) pressure with a more pronounced a wave and a diminution of rapid y descent (arrow) suggesting RV and LV filling abnormalities. The aortic pressure has not fallen yet due to increased vasoconstriction and the pulse pressure remains normal (Abbreviations: Ao: Aortic Pressure; a: a wave; x: x descent; v: v wave) (B) As tamponade progresses, the aortic pressure and pulse pressure significantly decrease. There is also evidence of pulsus paradoxus as there is a further drop in aortic pressure during inspiration (Insp) compared to expiration (Exp). (*Source:* Modified from Khandaker MH, Espinosa RE, Nishimura RA, et al. Pericardial disease: diagnosis and management. Mayo Clin Proc. 2010)



FIGURES 8A TO E: Echographically guided pericardiocentesis. Step 1: Locate an area on the chest or subcostal region from which the largest amount of pericardial effusion can be visualized and mark it (A–C). Step 2: Determine the depth of effusion from the marked position and the optimal angulation. Step 3: After sterile preparation and local anesthesia, perform pericardiocentesis (D). Step 4: When in doubt about the location of the needle, inject saline solution through the needle and image it from a remote site to locate the bubbles. Step 5: Monitor the completeness of the pericardiocentesis by repeat echocardiography. Step 6: A long 16–18 gauge intracatheter needle should be used so that once the pericardial space is entered a 0.035 mm J wire and 6–7F introducer sheath can be placed into the pericardial space (E). Step 7: Drain any residual fluid or fluid that has reaccumulated via the pigtail catheter every 4–6 hours. If, after 24 hours, pericardial fluid has not reaccumulated, as demonstrated echocardiographically, the pigtail catheter may be removed. In the presence of a bloody pericardial effusion associated with malignancy, continued drainage for 48–72 hours is required to prevent recurrence of the effusion. Always have the pericardial fluid analyzed: cell counts, glucose and protein measurements, culture and cytology. (*Source:* Modified from Callahan JA, Seward JB, Tajik AJ, et al. Pericardiocentesis assisted by two-dimensional echocardiography. J Thorac Cardiovasc Surg. 1983)

be helpful by identifying a lack of motion of the cardiac borders, but emergency echocardiography is required for a definitive diagnosis.

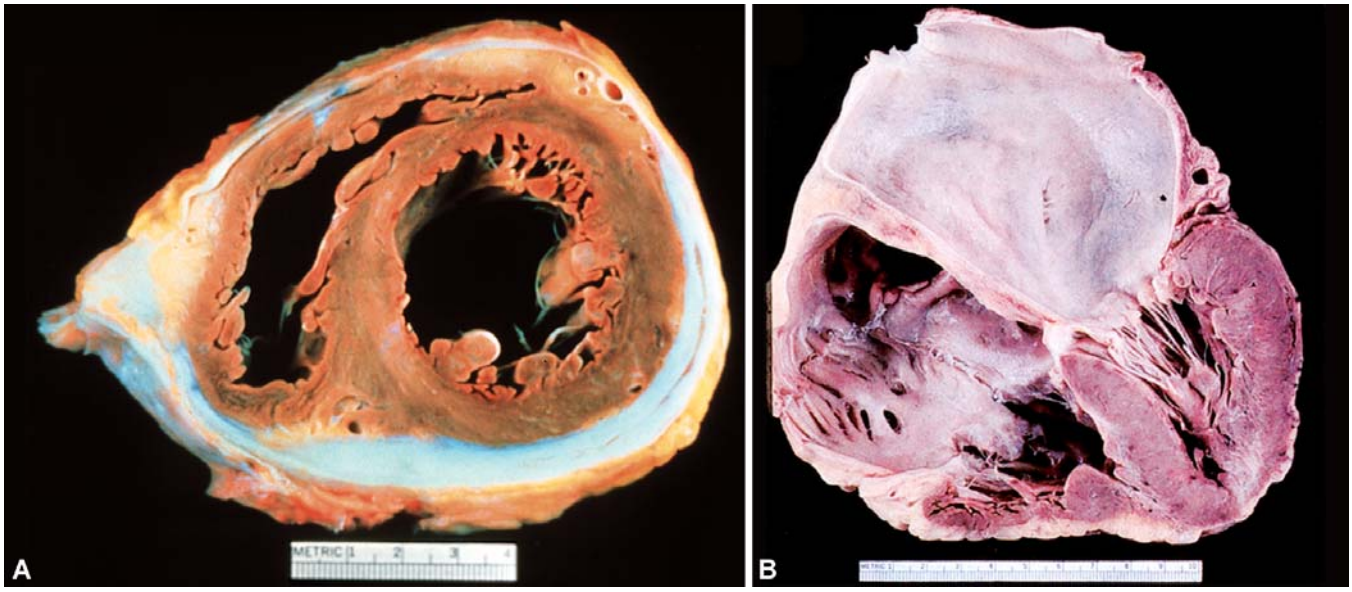
TREATMENT

The treatment of acute pericardial tamponade is drainage of the high pressure pericardial fluid. Although a rapid infusion of volume and decrease in afterload with nitroprusside can result in a mild transient improvement in hemodynamics, it is essential to remove the pericardial effusion as soon as possible by pericardiocentesis. If possible, pericardiocentesis should always be performed under echocardiographic guidance (Figs 8A to E). Two-dimensional echocardiography is able to identify the optimal site for the pericardiocentesis by visualizing the location and distribution of the pericardial effusion. The apical or periapical position is the most common site for an echo-directed pericardiocentesis, used in over 90% of cases.[27] Once the entry is located, an echocardiogram should be performed from another window during the pericardiocentesis. This allows the use of an agitated saline injection through the catheter used for the pericardiocentesis to assure that the pericardial space is being entered. A long 16–18 gauge intracatheter needle should be used for the initial entry. Once the pericardial space is entered and confirmed by contrast echocardiography, a 0.035 mm J wire and introducer sheath can be placed into the pericardial space. In most instances, a pigtail catheter can then be placed through the sheath into the pericardial space, connected to negative pressure for continued drainage. The pigtail catheter and negative pressure drainage are usually continued for at least 24 hours after the initial removal of fluid until drainage completely stops.[28] In the presence of a bloody pericardial effusion associated with malignancy, continued drainage for 48–72 hours is required to prevent recurrence of the effusion.

CONSTRICTIVE PERICARDITIS

PRESENTATION AND ETIOLOGY

Constrictive pericarditis occurs when there is thickening and fibrosis of the pericardium (Figs 9A and B), causing limitation of expansion of the cardiac chambers. Due to the resultant



FIGURES 9A AND B: Gross pathological features of constrictive pericarditis and restrictive cardiomyopathy. (A) Heart specimen of a patient who died with constrictive pericarditis. The pericardium is thickened and calcified and there is fibrosis and adhesion of the pericardial layers. Diastolic filling of the right and the left ventricles was markedly reduced; (B) Heart specimen of a patient who died with restrictive cardiomyopathy. Diastolic filling is limited by abnormal myocardium resulting in biatrial enlargement. The ventricles are not dilated in restrictive cardiomyopathy. (*Source:* William D. Edwards)

decrease in ventricular filling and an increase in diastolic pressures, constrictive pericarditis results in signs and symptoms of heart failure, similar to that seen with left ventricular systolic dysfunction. Tuberculosis was a common cause of constrictive pericarditis in the United States decades ago and remains highly prevalent in third world countries.[29,30] However constrictive pericarditis now is most commonly seen following cardiac surgery, radiation therapy for prior malignancies or years after a bout of acute idiopathic pericarditis.[31,32] There is a subset of patients who present with constrictive pericarditis in whom no obvious etiology is evident.

The most common presentation of a patient with constrictive pericarditis is that of progressive fatigue, peripheral edema and abdominal swelling. This is usually a picture of isolated right heart failure, with little pulmonary venous congestion. However there may also be a multitude of other different presentations, which makes the diagnosis of constrictive pericarditis challenging. Patients can present primarily with a low output state, so that the major complaint is decreased exercise tolerance and fatigue. Other patients may present with liver failure and cirrhosis, for the longstanding elevation of RA pressure can cause hepatic congestion and secondary cirrhosis. Recurrent pleural effusions may sometimes be the initial presentation of constrictive pericarditis.

EXAMINATION

The physical examination of a typical patient with constrictive pericarditis is that of an emaciated patient with severe ascites and edema. The sine qua non of constrictive pericarditis is a marked elevation of venous pressure with a rapid "x" and "y" descent (Fig. 10). The observation of a rise in jugular venous pressure with inspiration (Kussmaul's sign) is also often present and suggests impaired diastolic filling of the right ventricle due to restriction by an inelastic pericardium.



FIGURE 10: Jugular venous pressure tracings in constrictive pericarditis. Simultaneous jugular venous pressure tracings, phonogram and ECG tracings are shown in a patient with constrictive pericarditis. The "a" wave is generated by atrial contraction and occurs just prior to S1. The "v" wave is generated by ventricular contraction. The "x" descent reflects movement of the lower portion of the right atrium toward the right ventricle during ventricular systole. The "y" descent represents the abrupt termination of the downstroke of the "v" wave during early diastole after the tricuspid valve opens and the right ventricle begins to fill passively. In a patient with constrictive pericarditis, the "a" and "v" waves are more pronounced due to contraction against higher ventricular filling pressures resulting in marked JVP elevation. Impaired diastolic filling of the right ventricle combined with enhanced longitudinal motion of the heart in constrictive pericarditis results in unusually rapid "x" and "y" descents

Examination of the lung fields may reveal dullness in both bases consistent with pleural effusions. The heart sounds are usually distant without significant murmur. An early diastolic filling sound may be present, heard best with inspiration at the left sternal border. It is usually closer to the second heart sound than a typical third heart sound heard in patients with left ventricular dysfunction, and represents a pericardial knock.

DIAGNOSIS

Constrictive pericarditis should be suspected when a patient presents with severe right heart failure in the absence of a definable etiology such as left ventricular dysfunction, valvular

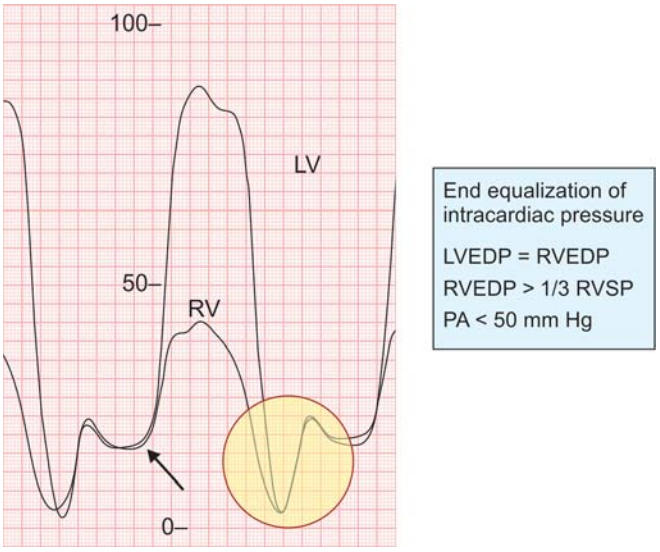
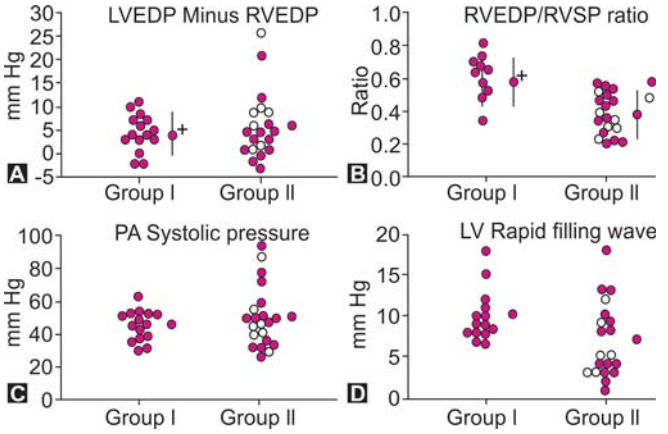


FIGURE 11: Left and right ventricular pressure tracings in constrictive pericarditis. Simultaneous pressure recordings from the left ventricle (LV) and the right ventricle (RV) in a patient with constrictive pericarditis are demonstrated. At end diastole, there is elevation and equalization of the LV and RV pressures (arrow). Other hemodynamic features include an increase in the RV end diastolic pressure (RVEDP) to greater than one-third of the RV systolic pressure (RVSP) and a pulmonary artery pressure of less than 50 mm Hg. In first third of diastole, there is rapid ventricular filling and an abrupt increase in ventricular pressure (circle), called the dip and plateau sign (circle). However these findings can also be seen in patients with restrictive cardiomyopathy



FIGURES 12A TO D: Hemodynamic variables in constrictive pericarditis versus restrictive cardiomyopathy. Scatterplots of the hemodynamic variables in patients with surgically proven constrictive pericarditis versus patients with restrictive cardiomyopathy. (A) Difference of the left ventricular end diastolic pressure (LVEDP) minus the right ventricular end diastolic pressure (RVEDP); (B) Ratio of the RVEDP to the right ventricular systolic pressure (RVSP); (C) Peak pulmonary artery systolic pressure (PASP); (D) Height of the rapid filling wave (RFW) (Group I—constrictive pericarditis; Group II—restrictive myocardial disease. (*Source:* Modified from Talreja RD, Nishimura RA, Oh JK, et al. Constrictive pericarditis in the modern era: novel criteria for diagnosis in the cardiac catheterization laboratory. JACC. 2008)

heart disease or pulmonary hypertension. Thus, right heart failure with normal left ventricular systolic function should lead the clinician to suspect the diagnosis of constrictive pericarditis. In the modern era, the differential diagnosis is usually between that of myocardial restrictive disease versus constrictive pericarditis. This is especially true since many cases occur after radiation therapy or open heart surgery, in which there may be a combination of both myocardial disease as well as pericardial disease.

It is important to understand the underlying pathophysiology that is present in constrictive pericarditis, which differentiates it from restrictive cardiomyopathy. Classic findings of constrictive pericarditis obtained at cardiac catheterization are severe elevation and end equalization of pressures in all four cardiac chambers. There is the presence of early rapid filling seen as a dip and plateau sign on the ventricular pressure traces and the rapid "x" and "y" descent on the atrial pressure traces (Fig. 11). However these findings may also be seen in restrictive cardiomyopathy. The classic findings to differentiate constrictive pericarditis from restrictive cardiomyopathy—(1) Pulmonary artery systolic pressure is less than 50 mm Hg; (2) RVEDP or RVSP is greater than 1/3 and (3) LVEDP is equal to RVEDP—are nonspecific and occur in many patients with myocardial restrictive disease as well as constrictive pericarditis[33] (Figs 12A to D).

The unique pathophysiologic features of constrictive pericarditis consist of changes during the respiratory cycle and include: (1) dissociation of intrathoracic and intracardiac pressures and (2) enhancement of ventricular interaction. In patients with a normal pericardium, there is a drop in intrathoracic pressure during inspiration. This is transmitted into the cardiac chambers so that the driving pressure from the lungs to the heart remains unchanged from expiration to inspiration. However, in patients with constrictive pericarditis, the drop in intrathoracic pressure is shielded from the intracardiac pressures. Thus, during inspiration, there will be a decrease in the driving pressure from the lungs to the heart and a decrease in filling of the left ventricle. Due to the rigid pericardium around all cardiac chambers, there is also enhancement of ventricular interaction. When there is a decrease in left ventricular volume during inspiration, there will be a concomitant increase in right ventricular volume, causing a septal shift from right ventricle to left ventricle during inspiration. Conversely, during expiration, there will be an increase in left ventricular volume, decrease in right ventricular volume, resulting in a marked decrease in the effective operative compliance of the right ventricle. This respiratory variation in filling of the right and left ventricle is the most specific hemodynamic feature of constrictive pericarditis.[34,35] These features can be delineated by both echocardiography as well as cardiac catheterization.

A comprehensive echocardiogram can many times confirm the clinical suspicion of constrictive pericarditis. It should first rule out other causes of heart failure such as left ventricular systolic dysfunction, valvular disease or pulmonary hypertension. A normal left ventricular systolic function with a dilated IVC should raise the suspicion of constrictive pericarditis. There are various two-dimensional echocardiographic features that are suggestive of constrictive pericarditis. Subtle changes in septal motion are usually present. A septal "bounce" reflects the effect of increased and equalized right ventricular and left ventricular diastolic pressures. Early rapid filling can be seen as a rapid expansion of the left ventricular cavity on M-mode (Fig. 13). A septal "shift" into the left ventricular occurs during inspiration indirectly representing enhanced ventricular interaction.[36,37] Doppler echocardiography can further delineate the respiratory

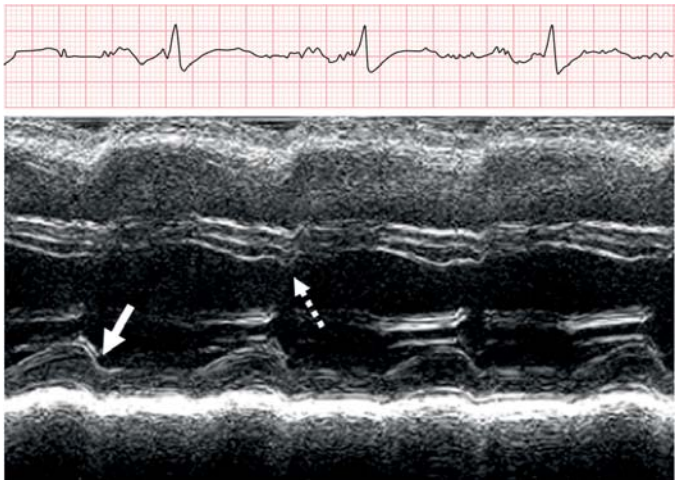


FIGURE 13: M-mode echocardiography demonstrating septal bounce and left ventricular posterior wall flattening in constrictive pericarditis. There are several M-mode signs that are indicative of the diagnosis of constrictive pericarditis. The septal bounce (dashed arrow) represents the result of increased and equalized right and left ventricular diastolic pressure. In early diastole, the left ventricular (LV) posterior wall expands rapidly and posteriorly, followed by an abrupt cessation of ventricular filling in mid to late diastole (solid arrow)

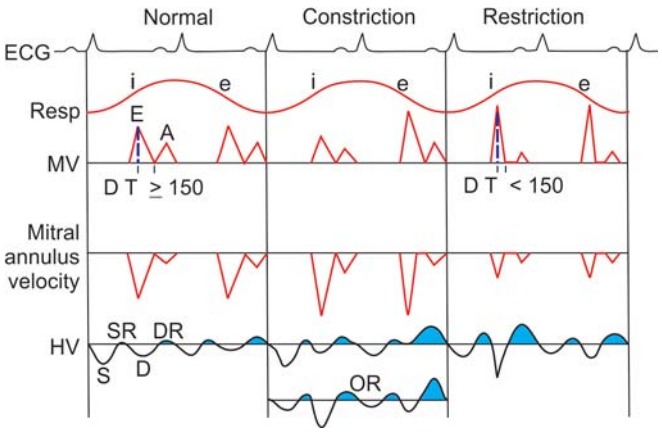


FIGURE 14: Doppler echocardiographic features in constrictive pericarditis versus restrictive cardiomyopathy. Schematic illustration of Doppler velocities from mitral inflow (MV), mitral annulus velocity and hepatic vein (HV). Electrocardiographic (ECG) and respirometer (Resp) recordings indicating inspiration (i) and expiration (e) are also shown. (Abbreviations: A: Atrial filling; S: Systolic flow; D: Diastolic flow; SR: Systolic flow reversal; DR: Diastolic flow reversal; DT: Deceleration time; E: Early diastolic filling; Stippled areas under curve—flow reversal. (*Source:* Modified from Oh JK, Seward JB, Tajik AJ. The Echo Manual, 3rd edition. Lippincott, Williams and Wilkins; 2007)

changes in hemodynamics (Fig. 14). The transmitral flow velocity curves reflect the initial driving pressure from the lungs to the heart.[38] In constrictive pericarditis, at the onset of inspiration, the pulmonary capillary wedge pressure (PCWP) decreases more than the left ventricular diastolic pressure resulting in a small driving pressure gradient and a diminution in the transmitral inflow (E)-velocity (Fig. 15). At the onset of expiration, the PCWP increases much more than the left ventricular diastolic pressure creating a large driving pressure gradient. A decrease in the transmitral early diastolic filling inflow (E)-velocity of greater than 25% during inspiration is

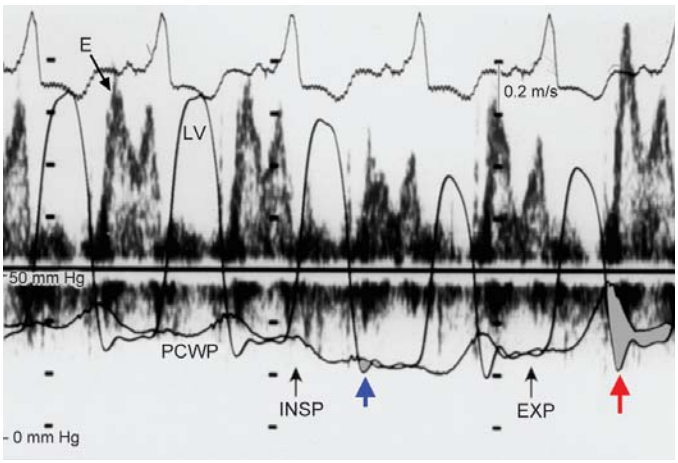
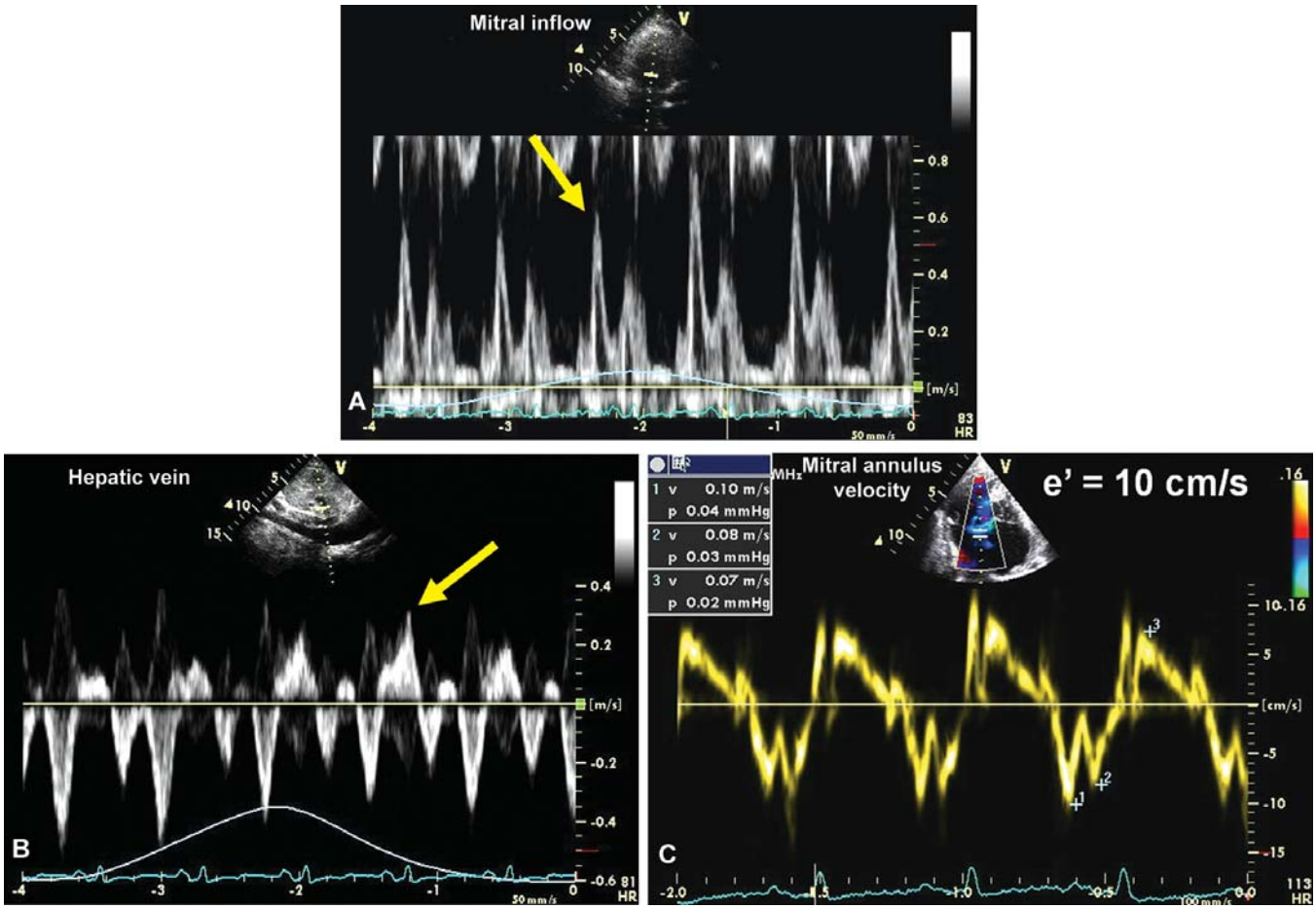


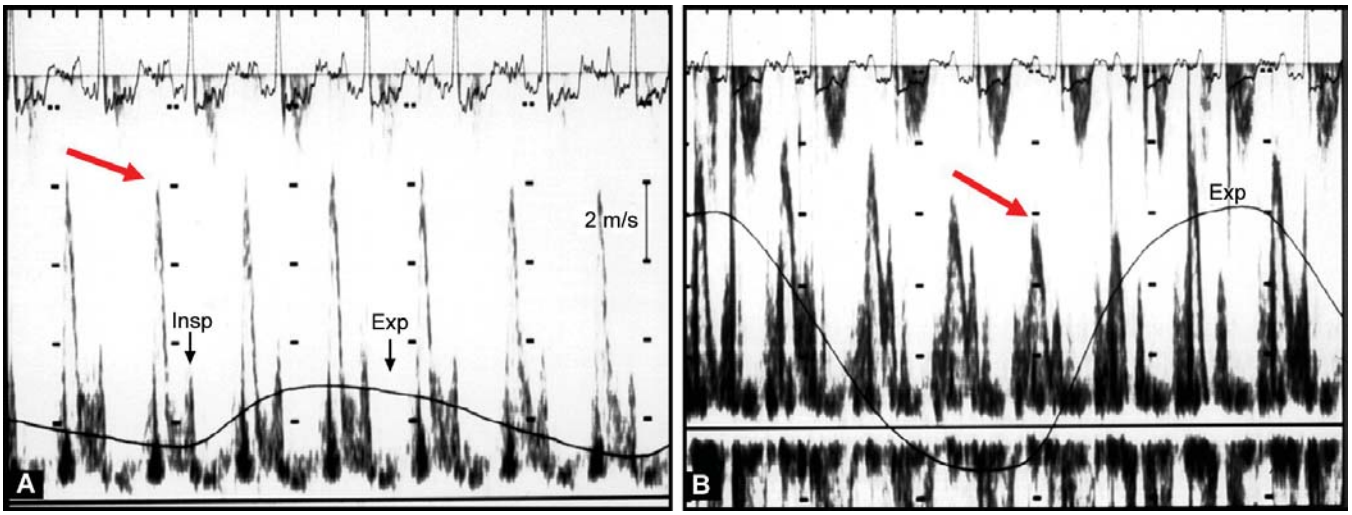
FIGURE 15: Hemodynamics of constrictive pericarditis by cardiac catheterization and Doppler echocardiogram. Simultaneous pressure recordings from the left ventricle (LV) and pulmonary capillary wedge together with the transmitral inflow (E) velocity on a Doppler echocardiogram. The onset of the respiratory phase is indicated at the bottom. (Abbreviations: EXP: Expiration; INSP: Inspiration). With the onset of inspiration, the pulmonary capillary wedge pressure (PCWP) decreases much more than LV diastolic pressure, with a very small driving pressure gradient (blue arrow; gray-shaded area). However, with expiration, the PCWP increases much more than LV diastolic pressure, creating a large driving pressure gradient (red arrow; gray-shaded area). These respiratory changes in the LV filling gradient are well reflected by the changes in the transmitral inflow velocities recorded on Doppler echocardiography

thought to be indicative of constrictive pericarditis. Examination of hepatic flow velocities will reveal an expiratory flow reversal[38,39] (Fig. 16). The mitral annulus tissue (e') velocity, which reflects shortening and lengthening of the myocardial fibers along a longitudinal plane during diastole, can be used to distinguish constrictive pericarditis from restrictive cardiomyopathy. In restrictive cardiomyopathy, the myocardium is diseased and this results in a diminution of the tissue Doppler mitral annulus velocity. In contrast, patients with constrictive pericarditis often have relatively preserved or enhanced motion of both the medial and lateral mitral annulus and thus, a medial mitral annulus tissue Doppler velocity (e') of greater than 7 cm/sec[40-42] is suggestive of constrictive pericarditis rather than restrictive cardiomyopathy (Figs 16A to C).

However there are three important clinical situations when transmitral inflow early diastolic filling (E) velocity needs to be interpreted with caution. These are: (1) patients with constrictive pericarditis who have a high preload and high LA pressure; (2) patients with constrictive pericarditis and atrial fibrillation and (3) patients with chronic obstructive pulmonary disease (COPD). In patients with constrictive pericarditis and high preload, the respiratory variation in transmitral inflow (E) velocity is blunted due to the high driving pressure from the LA during both respiratory phases. Preload reduction has been shown to unmask the characteristic Doppler features of constrictive pericarditis.[43] Demonstration of respiratory variation and an inspiratory decrease in transmitral inflow (E) velocity can be seen after the administration of a preload reducing agent such as intravenous nitroglycerin (Figs 17A and B). In patients with atrial fibrillation and constrictive pericarditis, the respiratory variation in the transmitral inflow (E) velocity may be diminished due to the lack of organized atrial contraction.



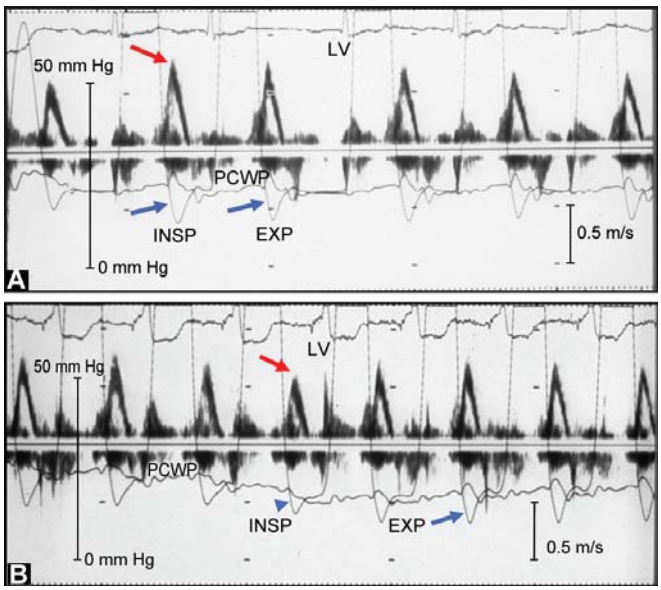
FIGURES 16A TO D: Doppler echocardiographic features in constrictive pericarditis. Typical echocardiographic features in constrictive pericarditis include diminution of transmitral inflow (E) velocity (arrow) with respiratory variation, hepatic vein expiratory diastolic flow reversal (arrow) and increased mitral annulus tissue Doppler (e') velocity



FIGURES 17A AND B: The affect of preload on transmitral inflow velocity in a patient with constrictive pericarditis. (A) Transmitral inflow (E) velocity (arrow) on Doppler echocardiography reveals no evidence of respiratory variation in a patient with proven constrictive pericarditis and high preload. A decrease in the transmitral inflow (E) velocity of greater than 25% during inspiration is thought to be indicative of constrictive pericarditis. (B) Administration of intravenous nitroglycerin reduces preload and the respiratory variation in mitral inflow (E) velocity (arrow) is now seen (Abbreviations: Insp: Inspiration; Exp: Expiration)

However, if these patients are paced, the typical pattern of an inspiratory decline in the transmitral inflow velocity is seen (Figs 18A and B). This lack of respiratory variation in the transmitral inflow (E) velocity is not always present in all patients with atrial fibrillation and constrictive pericarditis.[44]

In patients with COPD, a similar respiratory variation in the transmitral inflow (E) velocity can be seen when compared to patients with constrictive pericarditis (Figs 19A and B). However, mitral inflow velocities in COPD are less restrictive compared with those in constrictive pericarditis. In addition,

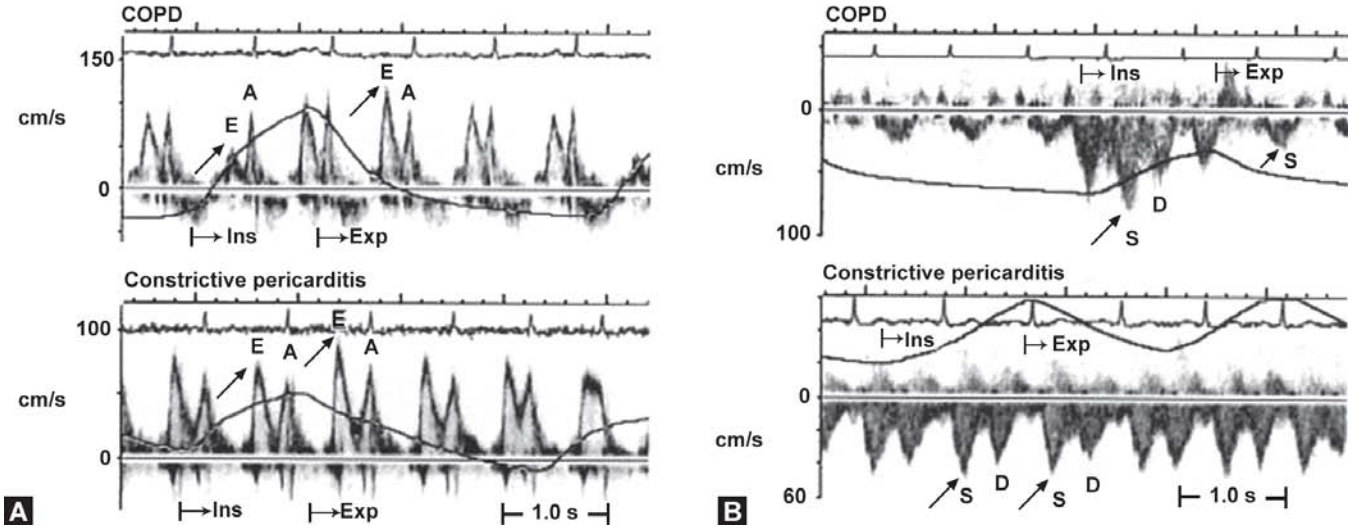


FIGURES 18A AND B: Transmitral inflow velocity in a patient with constrictive pericarditis and atrial fibrillation. Simultaneous pressure recordings from the left ventricle (LV) and pulmonary capillary wedge. Transmitral inflow velocity on Doppler echocardiography is also shown. (A) Transmitral inflow (E) velocity (red arrow) reveals an irregular and atypical pattern in a patient with constrictive pericarditis and atrial fibrillation. There is no evidence of consistent respiratory variation in the transmitral inflow velocity due to the lack of organized atrial contraction. The pressure gradient (blue arrows) between the pulmonary capillary wedge pressure (PCWP) and LV diastolic pressure does not vary with respiration. (B) Following VVI pacing, the typical pattern of inspiratory decline in the transmitral inflow E velocity (red arrow) is now seen. The PCWP increases much more than the LV diastolic pressure at the onset of expiration creating a large driving pressure gradient (blue arrow). During inspiration, the PCWP decreases more than the LV diastolic pressure resulting in a small driving pressure gradient (blue arrowhead) and a diminution in the transmitral inflow E velocity. (Abbreviations: INSP: Inspiration; EXP: Expiration)

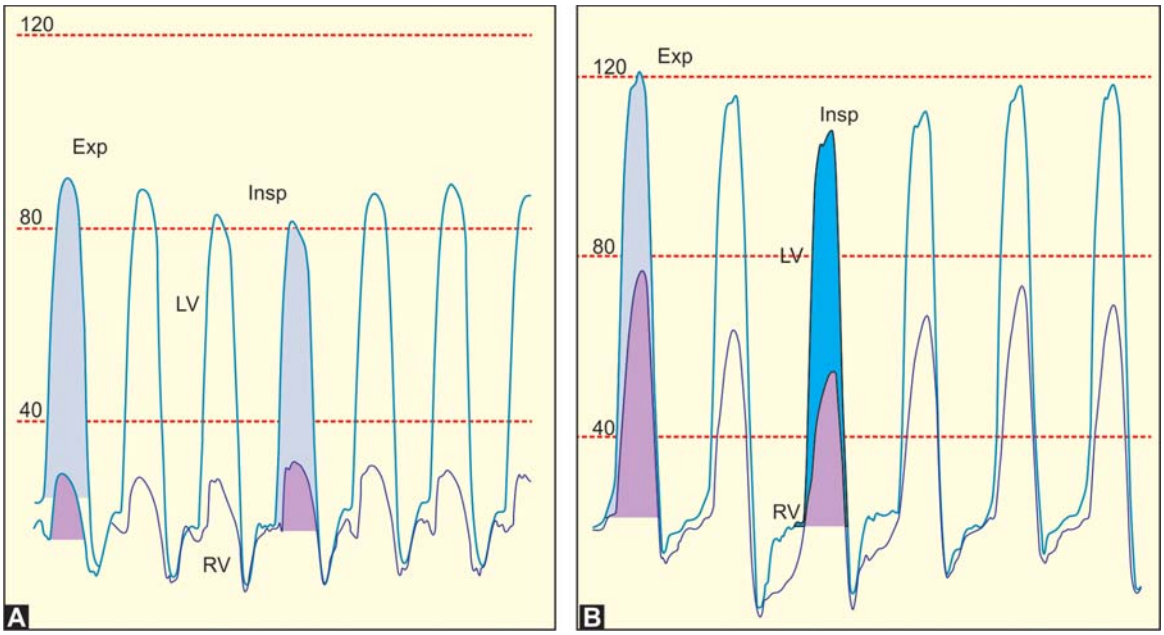
patients with chronic obstructive pulmonary disease show a marked increase in inspiratory superior vena cava systolic forward flow velocity, which is not seen in patients with constrictive pericarditis[45] (Figs 19A and B).

These Doppler velocity curves are diagnostic of constrictive pericarditis in only about 70–75% of patients. In those in whom the diagnosis is unclear, cardiac catheterization should be performed, looking at both the dissociation of intrathoracic and intracardiac pressures (relationship of the pulmonary artery wedge and left ventricular pressure) as well as enhancement of ventricular interaction (relationship of the right ventricular and left ventricular pressure). The classic findings of constrictive pericarditis due to enhanced ventricular dependence include a decrease in the area under the left ventricular curve during peak inspiration with an increase in area under the right ventricular curve during inspiration[33] (Figs 20A and B). In patients with restrictive myocardial disease, there will be a fall in both the left ventricular and the right ventricular pressure during inspiration. In addition, the relationship of the left ventricular and the right ventricular diastolic pressures are of benefit in further differentiating myocardial from pericardial disease. In patients with constrictive pericarditis, there will usually be equalization of both pressures during expiration and inspiration. In patients with myocardial restrictive disease, especially those with concomitant tricuspid regurgitation, there will be a rise in right ventricular diastolic pressure out of proportion to left ventricular diastolic pressure.[46]

Imaging modalities may also be helpful in the diagnosis of constrictive pericarditis. A lateral chest X-ray can show significant calcification of the pericardium. About 25% of patients with constrictive pericarditis will have calcification on chest X-ray.[47] However the absence of calcification does not necessarily rule out constriction. MRI and CT scanning are



FIGURES 19A AND B: Comparison of mitral inflow velocity and superior vena cava Doppler in chronic obstructive pulmonary disease and constrictive pericarditis. (A) Mitral inflow Doppler from a patient with chronic obstructive pulmonary disease (COPD) **(Top)** or constrictive pericarditis **(Bottom)** showing respiratory variation in mitral E velocity **(arrows)** (Abbreviations: Ins: Inspiration; Exp: Expiration); (B) Superior vena cava Doppler from a patient with constrictive pericarditis shows little respiratory changes in systolic forward flow velocity **(Bottom)** from inspiration to expiration **(arrows)**, in contrast to marked phasic inspiratory augmentation of forward flow velocity in chronic obstructive pulmonary disease (COPD) **(Top)** (Abbreviations: S: Systolic forward flow; D: Diastolic forward flow; Ins: Inspiration; Exp: Expiration). (*Source:* Modified from Boonyaratavej S, Oh JK, Tajik AJ, et al. Comparison of mitral inflow and superior vena cava Doppler velocities in chronic obstructive pulmonary disease and constrictive pericarditis. JACC. 1998;32:2043-8)



FIGURES 20A AND B: Ventricular interdependence and respiratory variation in ventricular filling in constrictive pericarditis and restrictive cardiomyopathy. Ventricular interdependence is observed in simultaneous recordings of left ventricular and right ventricular pressures. (A) In constrictive pericarditis, inspiration induces less filling of the left ventricle (LV) and the area of the LV pressure curve decreases (yellow-shaded area) as compared to expiration. The opposite changes occur in the right ventricle (RV) so that area of the RV pressure curve increases with inspiration (orange-shaded area). Ejection time also varies with respiration in opposite directions in LV and RV. This discordant pressure change between the LV and the RV occurs in constrictive pericarditis. (B) In restrictive cardiomyopathy, the changes in LV and RV systolic pressures with respiration are concordant. During inspiration there is a decrease in the area of the RV pressure curve (orange-shaded area) as compared with expiration. The area of the LV pressure curve (yellow-shaded area) is unchanged during inspiration as compared with expiration. Note that both patients have early rapid filling and elevation and end equalization of the left ventricular (LV) and the right ventricular (RV) pressures at end expiration. (*Source:* Modified from Khandaker MH, Espinosa RE, Nishimura RA, et al. Pericardial disease: diagnosis and management. Mayo Clin Proc. 2010;85:572-93)

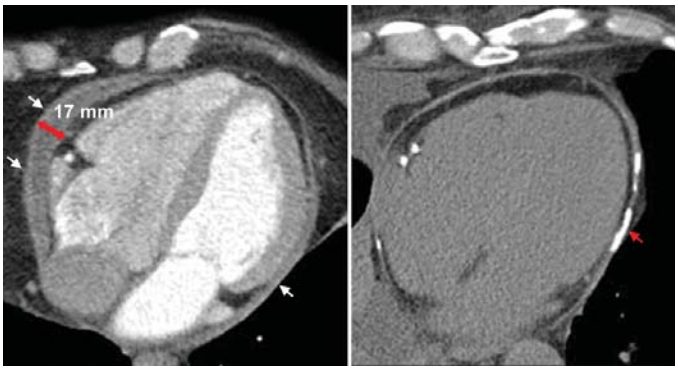


FIGURE 21: Pericardial thickening and calcification seen on cardiac CT in constrictive pericarditis. Left panel demonstrates pericardial thickening (white arrows) predominantly around the right ventricle but also covering the left ventricle. Areas of normal pericardial thickness are seen at the apex. Right panel demonstrates pericardial calcification (red arrow) adjacent to the left ventricle

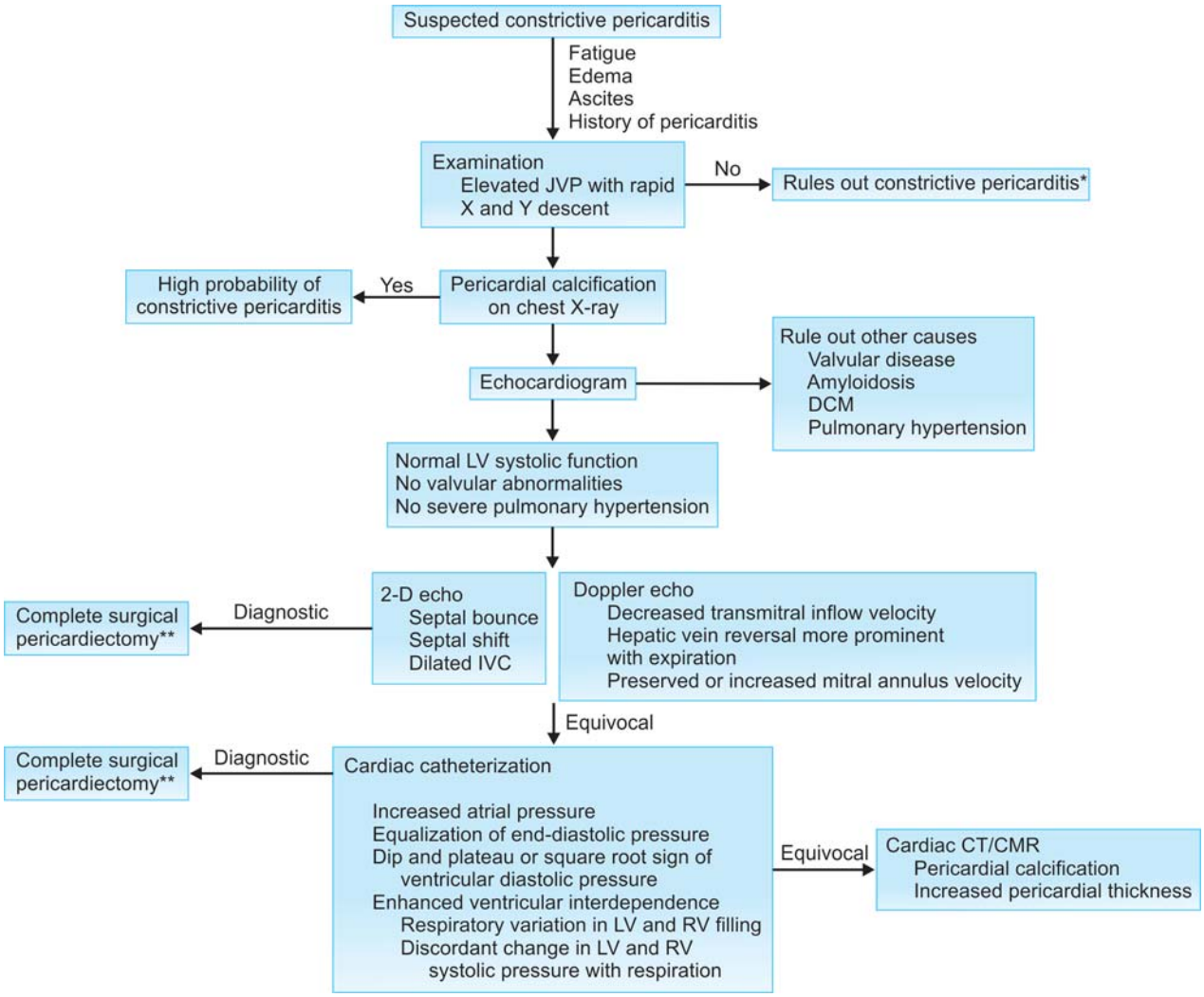
useful in demonstrating increased pericardial thickness and calcification[47] (Fig. 21). In addition, myocardial imaging can show the deformed ventricular contours, angulation of the ventricular septum and inferior vena cava dilatation.[48] Failure of pulmonary structures to pulsate during the cardiac cycle in the presence of a thickened pericardium is suggestive of constrictive pericarditis. However near 20% of patients with surgically proven constrictive pericarditis may not have increased pericardial thickness on these imaging modalities and thus does not rule out constrictive pericarditis.[35,47] In addition, many patients after radiation therapy and open heart surgery may have patchy areas of increased pericardial thickness in the absence of constrictive pericarditis. Thus the final diagnosis of constrictive pericarditis should be based upon the physiologic and not the anatomic consequences of an abnormal pericardium. At the end of all diagnostic testing, the diagnosis of constrictive pericarditis may still be uncertain and exploratory thoracotomy may be needed to make the diagnosis.

TREATMENT

Patients presenting with constrictive pericarditis should be considered for open heart surgery[31,32,49,50] (Flow chart 2). The surgery is a complete pericardiectomy, resecting the pericardium from phrenic nerve to phrenic nerve. A complete pericardiectomy does pose an increased operative mortality, greater than 5–6% even at experienced centers.[31,32] The independent adverse predictors of long-term outcome by surgery include: over age, worsening of the heart association class at presentation, renal dysfunction, left ventricular dysfunction and prior radiation.[31,32] However a complete pericardiectomy may result in significant improvement of symptoms and possibly prolongation of life. Without surgery, patients with constrictive pericarditis only have a progressive downhill course.

In any patient presenting with constrictive pericarditis, it is important to determine whether or not there is active inflammation at the time. There is a group of patients who have "transient constrictive pericarditis", in whom there is thickening of the pericardium and constriction mainly due to an acute inflammatory process in the pericardium. Thus, if there is a history of a more acute onset of symptoms coupled with laboratory findings of inflammation (elevated sedimentation rate, CRP or gadolinium enhancement defects by MRI scan), it

FLOW CHART 2: Overview of the diagnosis and management of constrictive pericarditis



*Unless aggressive diuresis; **If recent onset of symptoms. Rule out transient constrictive pericarditis. Obtain inflammatory markers +/– CMR
(Abbreviations: IVC: Inferior vena cava; RV: Right ventricle; LV: Left ventricle)

is beneficial for a trial of high dose nonsteroidal anti-inflammatory agents, salicylates or even steroids to determine whether or not resolution of the constrictive process might be possible.[51,52]

Effusive constrictive pericarditis is a unique condition in which there is both a pericardial effusion as well as constrictive pericarditis. These patients will present with a pericardial effusion and elevated filling pressures consistent with cardiac tamponade. However, once the pericardial fluid is removed, constrictive hemodynamics still persist.[53,54] In these patients, a decision then needs to be made as to whether more aggressive medical therapy or surgery is required. In those patients in whom active inflammation is present, a trial of anti-inflammatory medications should be considered. In other patients, a surgical pericardiectomy is not necessary.

CONCLUSION

Patients with pericardial disease can present a diagnostic and therapeutic challenge. It is important to understand the presentation of these diseases as well as the pathophysiology of the abnormal processes and the treatment.

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Chapter 87

Radiation-induced Heart Disease

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Chapter Outline

- Radiation-induced Pericardial Disease
- Radiation-induced Myocardial Disease
- Radiation-induced Coronary Artery Disease
- Radiation-induced Valvular Heart Disease
- Conduction System Disease
- Carotid and Other Vascular Disease
- Prevention

INTRODUCTION

During therapeutic irradiation of the chest, the heart and other intrathoracic structures are predisposed to radiation injury. Acute radiation injury is usually transient and, in general, benign. However, long-term cardiovascular complications of chest irradiation can be devastating.[1] Typically, there is a long latency period between radiation exposure and clinical manifestations of the cardiovascular complications. Radiation-induced cardiotoxicity primarily occurs in patients who received radiation for Hodgkin's lymphoma or breast cancer. However, it can also occur after radiation therapy for lung and esophagogastric cancers, thymomas and peptic ulcer disease. It should be appreciated that brachytherapy, occasionally used for coronary artery stenosis, is not associated with radiation-induced cardiotoxicity. It should also be appreciated that the extracardiac and intrathoracic structures, such as mediastinum and lungs, can sustain radiation injury. In this chapter, only the cardiovascular complications resulting from mediastinal and thoracic radiation are to be discussed.

All cardiovascular structures can sustain radiation injury: (1) pericardium; (2) myocardium; (3) cardiac valves; (4) coronary and carotid arteries and (5) conduction systems. In an individual patient, one or multiple structures can be involved.

RADIATION-INDUCED PERICARDIAL DISEASE

The cardiovascular complications of mediastinal radiation are summarized in Table 1.

Pericardial disease is the most frequent complication of mediastinal radiation therapy.[2,3] Acute radiation injury often manifests as inflammatory pericarditis with or without pericardial effusion. It has been reported that up to 40% of patients who received higher radiation dose schedule for treatment of Hodgkin's lymphoma developed acute pericarditis.[4] The tumors that are adjacent to the pericardium may become necrotic in response to radiation therapy and is a risk factor for the acute inflammatory pericarditis. Acute radiation pericarditis usually manifests a few weeks after radiation treatment. The typical clinical presentation includes fever, tachycardia, chest pain and pericardial friction rub. The pericardial fluid shows variable amount of protein rich exudates.[5] Acute pericarditis is

TABLE 1

Cardiovascular complications of mediastinal radiation

Pericardial disease

Acute inflammatory pericarditis with or without pericardial effusion
- Incidence can be as high as 40%
- It manifests within a few weeks after radiation

Constrictive pericarditis
- Usually develops 5–10 years after radiation
- Thickening, fibrosis and even calcification of the pericardium

Myocardial disease
- Overt cardiomyopathy is uncommon
- Asymptomatic myocardial fibrosis may occur up to 60% of patients
- Overt clinical heart failure results from restrictive cardiomyopathy

Coronary artery disease
- Coronary artery stenosis occurs 10–15 years after radiation
- Ostial stenosis is more frequent
- There is predilection of involvement of right, left main and proximal left anterior descending coronary arteries
- Endothelial injury, hypertension, diabetes hyperlipidemia are risk factors

Valvular heart disease
- The incidence is between 6% and 11%
- Occurs approximately 20 years after radiation
- Aortic valvular disease is most frequent complication
- Mitral annular calcification with stenosis and/or regurgitation may also occur

Conduction system disease
- Atrioventricular blocks, bundle branch blocks, sick sinus syndromes and prolonged QT intervals can occur
- Right bundle branch block is more common than the left bundle branch block
- The chronic atrioventricular block is usually infranodal
- Fibrosis is the principal mechanism

Carotid and other vascular disease
- Severe carotid artery stenosis is rare
- Latent period is about 20 years
- Radiation to the neck, diabetes, hypertension and hyperlipidemia are risk factors

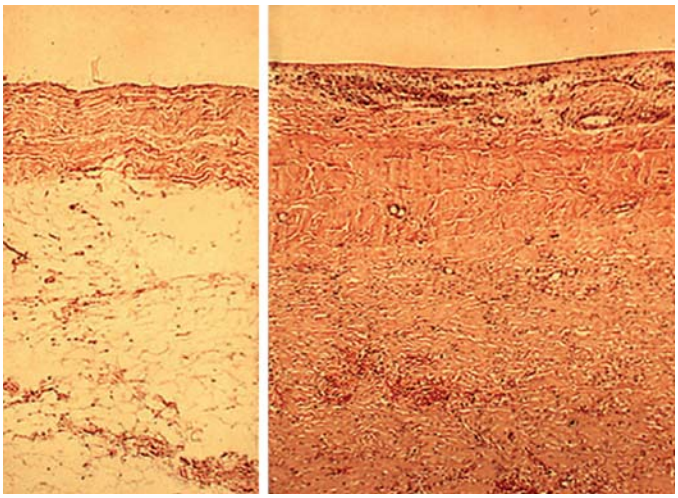


FIGURE 1: Perpendicular sections of human pericardium. The left panel illustrates the normal parietal pericardium and the right panel shows irradiated pericardium with characteristic features of constrictive pericarditis. (*Source:* Fajardo LF. Acta Oncol. 2005;44:13-22, with permission)

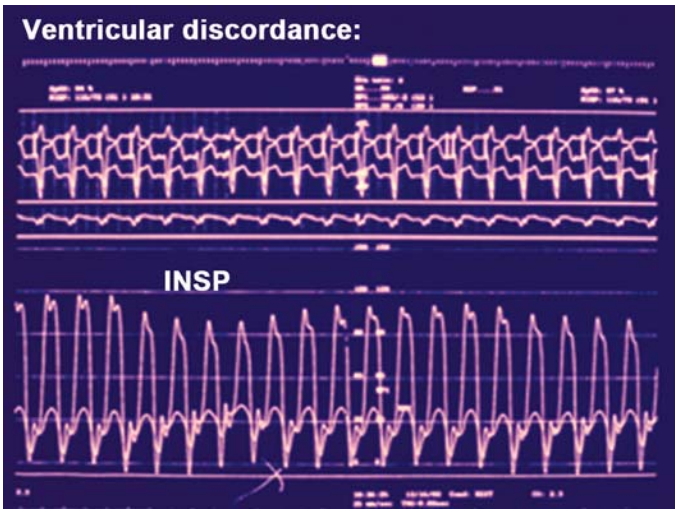


FIGURE 2: The characteristic hemodynamic features of constrictive pericarditis showing equalization of left and right ventricular diastolic pressure and exaggerated ventricular interdependence and exaggerated ventricular interdependence (the systolic pressures generated in the left ventricle and the right ventricular vary in opposite directions in relation to breathing)

not a contraindication for continuation of radiation therapy; however, a dose adjustment may be necessary.[6]

Approximately 20% of patients who develop acute irradiation-induced inflammatory pericarditis progress to develop chronic constrictive pericarditis. The rate of progression is slow and it usually takes 5–10 years to develop clinically relevant features of constrictive pericarditis. The presence of pericardial effusion, during the acute phase, increases the risk of developing chronic constrictive pericarditis.[7] However it can develop even in the absence of acute inflammatory pericarditis.

In constrictive pericarditis, the pericardium is thickened as a result of replacement of normal pericardial adipose tissue by fibrin and collagen. The fibrous layer is thickened to as much as 8 mm (normal < 0.5 mm) (Fig. 1).[8,9] Fibrosis of the parietal and visceral pericardium, with or without calcification, produces the pathophysiologic, clinical and hemodynamic features of constrictive pericarditis. The mechanism of fibrosis in radiation-induced constrictive pericarditis remains unclear. It has been postulated that ischemia resulting from injury to the microvascular network to the pericardium may be contributory.[10]

The clinical presentation of radiation-induced constrictive pericarditis is similar to that of other etiologies of constriction. The common symptoms are fatigue, dyspnea, lower extremity edema and abdominal swelling.[11] The physical findings in patients with overt constrictive pericarditis are elevated jugular venous pressure with a positive Kussmaul's sign, a quiet precordium, abdominal swelling, peripheral edema and absence of signs of pulmonary hypertension. The hemodynamic features are characterized by equalization of left and right ventricular diastolic pressures, "square root sign" and exaggerated ventricular interdependence (Fig. 2).

For the assessment of pericardial thickening, cardiac tomographic study or cardiac resonance imaging are usually employed. It should be emphasized that the presence of pericardial thickening is not necessarily associated with significant hemodynamic abnormalities of pericardial constriction.[12]

The treatment of radiation-induced constrictive pericarditis is surgical pericardiectomy. It should be appreciated, however, that pericardiectomy may not always result in significant clinical and hemodynamic improvement due to concomitant presence of restrictive cardiomyopathy.

The prognosis of patients with radiation-induced constrictive pericarditis remains poor.[3,13,14] Almost 100% mortality has been reported within a year of diagnosis.[15] Even after pericardiectomy the survival at 5 years is approximately 50%.[16] The poor prognosis is probably related to the presence of concomittant valvular, myocardial and coronary arterial diseases. Also noncardiac complications, such as pulmonary fibrosis, contribute to the adverse prognosis.[15]

Asymptomatic chronic pericardial effusion is another complication of radiation-induced pericardial disease. Its incidence is between 20% and 40%.[1] The latent period may vary from months to years after mediastinal irradiation. The pericardial fluid may be clear, hemorrhagic or serosanguinous. Most asymptomatic pericardial effusions resolve spontaneously. Only a minority of patients develop cardiac tamponade. In some patients, the constrictive physiology persists even after pericardiocentesis and in these patients a diagnosis of effusive-constrictive pericarditis should be entertained.

RADIATION-INDUCED MYOCARDIAL DISEASE

Overt clinical cardiomyopathy due to radiotherapy is rare. However, autopsy studies reported that the frequency of asymptomatic myocardial fibrosis is over 60%.[17] Myocardial fibrosis consists of proliferation of bands of collagen separating and/or replacing cardiac myocytes (Fig. 3).[8] It occurs in patches, often in the anterior wall of the left ventricle. The mechanisms of radiation-induced cardiomyopathy remain unclear. In the experimental studies, it has been suggested that microvascular injury promotes myocardial fibrosis. The injury to blood vessels is thought to be due to the generation of reactive oxygen species that disrupt DNA strands. The endothelial cells exhibit cell membrane irregularities, cytoplasmic swelling, thrombosis and

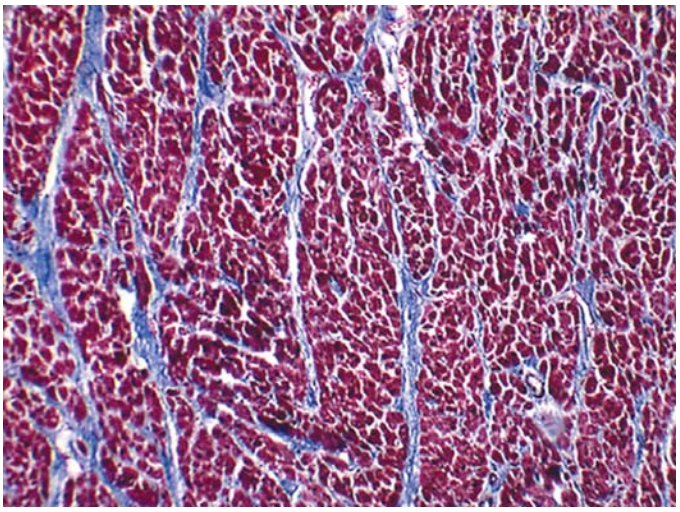


FIGURE 3: Extensive myocardial fibrosis (blue color, bands of collagen) leading to demise of patient several years arer irradiation for Hodgkin's disease. Gomori trichrome stain. (*Source:* Darby SC, et al. Int J Radiat Oncol Biol Phys. 2010;76:656-65, with permission)

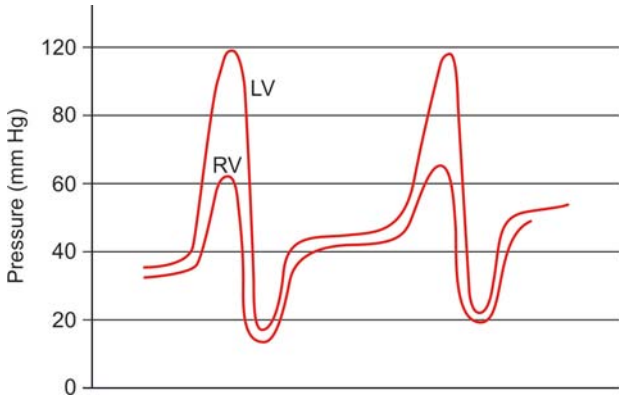


FIGURE 4: Schematic diagram showing hemodynamic features of restrictive cardiomyopathy. Left ventricular end diastolic pressure is higher than the right ventricular end diastolic pressure. Right ventricular systolic pressure is approximately 60 mm Hg suggesting pulmonary hypertension. Note the dip-and-plateau or square-root contour of the ventricular diastolic pressures (deep and rapid early decline in ventricular pressure at the onset of diastole, with a rapid rise to a plateau in early diastole)

rupture of the walls. The loss of capillary blood vessels leads to ischemia induced myocyte loss and replacement fibrosis.[18,19]

The predominant cardiac functional derangement in patients with radiation-induced cardiomyopathy is diastolic dysfunction.[20,21] The frequency of abnormalities of diastolic function is about 10%.[21] Diastolic dysfunction may or may not be associated with clinical heart failure. Older age, hypertension, diabetes and coronary artery disease are the risk factors for diastolic dysfunction. A larger dose of radiation is also associated with an increased risk of developing abnormalities of left ventricular diastolic function.

Diastolic dysfunction results from myocardial fibrosis and occurs earlier than systolic dysfunction in patients with radiation-induced cardiomyopathy.[22] It has been postulated that myocardial ischemia contributes to fibrosis. In patients receiving mediastinal irradiation for breast cancer, new left ventricular perfusion defects determined by nuclear scintigraphy have been observed in more than 50% of patients.[23] The significance of perfusion defects remains unclear, but they likely represent myocardial microvascular damage which promotes fibrosis and decrease left ventricular compliance associated with diastolic dysfunction.[24]

Thus, the diagnosis of the radiation-induced restrictive cardiomyopathy should be only made after exclusion of other more common causes.[10] Nevertheless, overt diastolic heart failure is uncommon. When it occurs, it is almost always associated with hemodynamic characteristics of restrictive cardiomyopathy.[25]

The symptoms of heart failure resulting from restrictive cardiomyopathy, irrespective of its etiology, are fatigue and dyspnea, which initially occur during exertion but later at rest, with the deterioration of the hemodynamic abnormalities. The physical findings are characterized by elevated jugular venous pressure, positive Kussmaul's sign and evidences of pulmonary hypertension. Ascitis and lower extremity edema are common in patients with advanced heart failure.

Before cardiac catheterization is undertaken, echocardiographic studies should be performed. Transthoracic echocardiography demonstrates, normal left ventricular size, normal or slightly reduced left ventricular ejection fraction (LVEF) and restrictive filling pattern.[6] In addition, impaired exercise tolerance and a decrease in LVEF during exercise have been observed.[10] Systolic dysfunction with or without clinical heart failure occurs more frequently in patients who have concurrent or prior history of exposure to chemotherapeutic agents particularly anthracyclines.[26]

The hemodynamic studies by cardiac catheterization reveal the dip-and-plateau or squre-root contour of the ventricular diastolic pressure, left ventricular end diastolic pressure higher than right ventricular end diastolic pressure and pulmonary arterial hypertension (Fig. 4).

There is no specific treatment for radiation-induced restrictive cardiomyopathy. Diuretic therapy is necessary for relief of congestive symptoms. As usually stroke volume is fixed, heart rate should not be decreased excessively, otherwise cardiac output will decrease.

RADIATION-INDUCED CORONARY ARTERY DISEASE

Epicardial coronary artery stenosis is a recognized complication of mediastinal irradiation. The coronary artery lesions have characteristic features and location.[27] The manifestations of coronary artery stenosis usually occur 10–15 years after radiation therapy. Due to the anterior location in the chest, there is a disproportionately higher incidence of ostial lesions and a predilection for the involvement of the right coronary artery, left main coronary artery and proximal left anterior descending coronary artery.[28]

The pathophysiologic mechanisms of epicardial coronary artery stenosis following radiation therapy are similar to those of established mechanisms for the development of atherosclerotic coronary artery disease. Following radiation, there is injury of the endothelial cells, followed by migration of monocytes into intima and subintima, ingestion of low-density lipoproteins and formation of atherosclerotic plaques.[29]

Subsequently the plaques become either "vulnerable" or "stable", depending on the magnitude of smooth muscle cells proliferation, thinning or thickening of the fibrous cap of the plaque and the degree of inflammatory response.[30]

Experimental studies have shown that radiation not only can initiate atherosclerosis but also can predispose plaque disruption. Radiation therapy increases the levels of the proteolytic enzymes such as matrix metalloproteinases which may cause autodigestion of the fibrous cap.[31] It should be appreciated that radiation-induced coronary artery stenosis seldom develops in absence of dyslipidemia.[32] The other risk factors are hypertension, diabetes, obesity, smoking and positive family history of coronary artery disease. It has been suggested that coronary artery disease is more prone to develop when multiple classifcal risk factors are present.[33-36] However, coronary artery disease can develop in absence of the traditional risk factors.[37-40] Higher radiation dose is also a risk factor for development of coronary artery disease.[2]

The prognosis of patients with radiation-induced coronary artery stenosis appears to be worse than that of patients with nonradiation-induced coronary artery atherosclerosis. The incidence of fatal myocardial infarction has been reported to be approximately 2–8 fold higher than in the general population.[41-45] The cumulative incidence for myocardial infarction is approximately 13% by 30 years after mediastinal radiation.[46]

Patients with radiation-induced coronary artery disease are often asymptomatic. The incidence of asymptomatic severe coronary artery disease is between 2% and 4%.[47-49] The overt clinical manifestations of irradiation-induced coronary artery disease are similar to those of nonradiation-induced coronary artery stenosis. The presentations can be typical effort angina, acute myocardial infarction or sudden cardiac death.[28,34-36,38,39] The incidence of typical angina pectoris in patients with radiation-induced coronary artery disease is approximately 20% and in patients with nonradiation-induced coronary artery disease is approximately 40%.[34] The lower incidence of angina in patients with radiation-induced coronary artery stenosis may be due to dysfunction of the cardiac nerves.[38]

The diagnosis of radiation-induced coronary artery disease can be established by both invasive and noninvasive investigations. Coronary artery angiography by cardiac catheterization, computerized contrast tomographic angiography or cardiac catheterization, or computerized contrast tomographic angiography can be used to assess presence and severity of coronary artery stenosis. Presence or absence of myocardial ischemia can be detected by pharmacologic and non-pharmacologic stress tests. Treadmill exercise test, exercise echocardiography, dobutamine stress echocardiography, nuclear myocardial perfusion imaging and positron emission tomography can be employed to assess presence and magnitude of myocardial ischemia. In clinical practice, however, these noninvasive tests have not been found useful in the detection of presence and severity of obstructive coronary artery disease.[50] In one institution study, stress echocardiography, nuclear scintigraphy and stress echocardiography were compared to assess the diagnosis of radiation-induced coronary artery disease. To detect coronary stenosis greater than 50%, the sensitivity and specificity were 59% and 89% for stress echocardiography, 65% and 11% for nuclear scintigraphy, and 38% and 100% for stress electrocardiogram respectively.[47] Similar lack of usefulness of these stress tests in the diagnosis radiation coronary artery disease has been observed in other studies.[35,48] The estimation of coronary artery calcium scores has been used to estimate the presence and severity of coronary artery stenosis.[38,49] However, its predictive values have not been adequately established. The American College of Cardiology and American Heart Association recommend the determination of coronary artery calcium scores in patients at intermediate 10-year risk (between 10% and 20%).[50] The 10-year risk of developing coronary artery disease in the survivors of Hodgkin's lymphoma treated with radiation is unknown; however, the risk appears low or intermediate. Thus, for the detection of radiation-induced coronary artery disease, it has been recommended that the estimation of coronary artery calcium scores should be repeated every 5 years.[51,52]

The treatment of radiation-induced coronary artery disease is similar to that of nonradiation atherosclerotic coronary artery disease. Adequate treatment of dyslipidemia, diabetes, hypertension and obesity should be undertaken. The cessation of smoking should be encouraged. Angiotensin inhibitors, beta-adrenergic antagonists and antiplatelet agents should be used. Coronary artery revascularization is recommended in appropriate patients. Both percutaneous coronary artery intervention and coronary artery bypass surgery have been used. Both in patients with stable or unstable coronary artery disease, coronary angioplasty has been successfully performed.[53-55]

Coronary artery bypass graft surgery using saphenous veins and radial and internal mammary arteries as conduits have also been successfully performed in patients with radiation-induced coronary artery disease. Controversy exists regarding the use of the internal mammary arteries as the grafts.[56-61] In the majority of the studies, the internal mammary arteries had excellent flow. In occasional patient, significant atherosclerotic changes were discovered and the internal mammary arteries could not be used as grafts.

RADIATION-INDUCED VALVULAR HEART DISEASE

The overall incidence of valvular heart disease following radiotherapy is variable and has been reported to be between 6% and 11% after approximately 22–23 years after radiation exposure.[33,46] The incidence of clinically relevant valvular heart disease is also variable.[12,24,35,62-65] Aortic valve disease is the most frequent valvular complication in patients with radiation-induced heart disease (RIHD).[66] The aortic root may also be calcified in these patients. The aortic valves leaflets are fibrotic, markedly thickened and calcified.[67] Valvulitis and rupture of the aortic valve have also been reported.[68]

Mitral valve may also be affected following mediastinal irradiation. Mitral valve stenosis has been reported, although mitral regurgitation is more common.[69] An unusal pattern of calcification which extends from the base of the anterior mitral leaflet to the noncoronary aortic sinus, appears to be a typical, but not specific, finding.[70] The mitral perivalvular tissue could also be heavily calcified.

Isolated tricuspid valve disease is rare; however, severe tricuspid valve regurgitation following radiation therapy has been reported.[71] A Doppler echocardiographic study reported

that the incidence of tricuspid regurgitation was 88%.[48] The severity of tricuspid regurgitation, as expected, was mild in the majority of patients. The clinical relevance of tricuspid regurgitation detected by Doppler echocardiography is minimal in the majority of cases.[72] Infundibular pulmonary valve stenosis has been reported as a complication of mediastinal radiation.[73]

Physical examination, echocardiographic studies and, if required, cardiac catheterization should be performed for establishing the diagnosis of presence and severity of radiation-induced heart valve disease. It is also essential to assess ventricular function. In asymptomatic patients, the noninvasive evaluations should be repeated to assess the changes in the severity of valvular lesions. In patients who are likely to have surgical intervention to correct the valvular heart disease, coronary angiography should also be performed to assess the presence of significant coronary artery disease. The hemodynamic severity, pulmonary artery pressure and pulmonary vascular resistance should also be determined.

The need for valve replacement surgery in patients with radiation-induced valvular heart disease is between 0.5% and 6%.[33,48,74] However, the surgical correction of radiation-induced valve disease is associated with a higher mortality (13%) than in patients with nonradiation-induced valve disease (4%).[75,76] Presence of constrictive pericarditis before and after pericardiectomy increases the risk of perioperative mortality by sixfold.[74]

The timing of surgical intervention of radiation-induced valve disease is similar to that of patients without radiation-induced valve disease. Asymptomatic patients should be followed and surgery is not recommended. There is no specific therapy for asymptomatic patients. Antibiotic prophylaxis for bacterial endocarditis is not recommended.

Surgical intervention should be considered in symptomatic patients or in patients with decreasing LVEF even in the absence of symptoms.[77] It should be appreciated that dyspnea which is the most common symptom of valvular heart disease can be caused by other causes.[64,78] In a study of 116 patients of long-term survivors of Hodgkin's lymphoma, dyspnea was present only in 12% of patients due to cardiac cause alone. Only pulmonary cause was present in 38% of patients and combined cardiopulmonary cause in 59% of patients. It is of interest that in 22% of patients, no obvious cause of dyspnea was found.[78]

Screening for the presence of valvular heart disease in patients with RIHD should be performed initially approximately 10 years after radiotherapy and then repeated on every 5 years. Presently, besides clinical examination transthoracic echocardiography is the investigation of choice to detect the presence and severity of radiation-induced valvular heart disease.[12]

CONDUCTION SYSTEM DISEASE

A variety of cardiac conduction system abnormalities have been observed following mediastinal radiation therapy. Atrioventricular blocks, bundle branch block, sick sinus syndrome and prolonged Q-T intervals have been reported.[6,12,79] The incidence of these conduction system abnormalities has been reported to be as high as 46–48% during long follow-up periods.[64,72]

The mechanisms of radiation-induced conduction system disturbances are not entirely clear. Autonomic dysfunction has been postulated as a potential mechanism.[80] However, fibrosis of the conduction system tissues is likely cause of chronic heart block.[71,79,81] The chronic atrioventricular block is usually infranodal and slowly progresses to advanced and complete heart block in 10–20 years after radiation therapy.[82,83]

Right bundle branch block is more common than left bundle branch block.[12,35,67,84] This is probably because right bundle is a thinner and longer structure, and thus is associated with increased resistance to electrical propagation.

Presyncope and syncope are the presenting symptoms of conduction system disease and the patients usually have complete heart block.[10] Electrocardiographic evaluation is essential to establish the diagnosis. In patients with intermittent symptoms, the use of Holter monitor or event recorder may be necessary. The treatment of symptomatic heart block or sick sinus syndrome is implantation of a permanent pacemaker.

CAROTID AND OTHER VASCULAR DISEASE

The precise incidence of radiation-induced carotid and other large vessels disease is not known although it has been reported in a number of studies.[85-88] In 24% of patients, intima-media thickness abnormality was identified by duplex ultrasound studies of the carotid arteries.[87] However, severe carotid artery stenosis was rare. There is usually a long latent period of about 20 years for development of carotid and other vascular disease in young survivors of Hodgkin's lymphoma. However, in older patients receiving radiation therapy, carotid disease can develop much earlier.[33]

In a large multicenter cohort study in 2001, patients who have survived Hodgkin's lymphoma had a 2–3 fold increase in the risk of stroke and transient ischemic attacks compared to the general population. The cumulative incidence of stroke or transient ischemic attacks during 30 years of follow-up was 7% and the latent period was about 17 years.[88] The most important risk factor was found to be radiation to the neck. Diabetes, hypertension and hyperlipidemia were additional risk factors. Presence of cardiac disease also increases the risk of stroke and transient ischemic attacks.

Physical examination and ultrasound studies are the initial investigations. Contrast computed tomography or magnetic resonance imaging may also be employed. The contrast angiography is performed during intervention. These investigations are recommended only in symptomatic patients. Routine screening should be avoided in asymptomatic patients.

Treatments consist of implementation of the modifiable risk factors and catheter based or surgical correction of hemodynamically significant carotid artery stenosis in the presence of symptoms.

PREVENTION

The reduction of dose of radiation is of paramount importance in reducing the risk of RIHD. The higher fractional dose is also associated with a higher risk of development of RIHD, thus it is desirable to reduce the fractional dose. When a larger volume of heart is irradiated, the higher is the risk of cardiac complications. Thus reduction of cardiac volume exposed to radiation should be attempted. The risk factors for RIHD and the strategies for its prevention are summarized in Tables 2 and 3.

TABLE 2

Risk factors for RIHD

Patient related risk factors	• Younger age at exposure • Presence of traditional cardiac risk factors • Presence of tumor next to the heart
Treatment related risk factors	• Higher total dose • Higher fractionated dose • Increased volume of heart irradiated • Longer time since exposure • Concomitant or previous cardiotoxic chemotherapy • Type of radiation source (cobalt)

TABLE 3

Strategies for prevention of RIHD

- Decreased total dose
- Decreased fraction size
- Treatment planning to reduce cardiac volume exposed
- Employ the minimum dose of adjunctive chemotherapy
- Screening and aggressive treatment for traditional cardiac risk factors
- Long-term monitoring
- Anti-free radical agents

CONCLUSION

Radiation-induced heart disease is a well recognized complication of chest irradiation. As the survival of cancer patients is increasing, the incidence of RIHD is going to increase. Although pericardial disease is the most common complication, all cardiac structures can be involved. The coronary arteries, cardiac valves, myocardium and conduction systems can be involved. These complications can occur in isolation or in combination. The increased risk of RIHD appears to be lifelong and may be progressive. Thus an index of suspicion is needed when evaluating patients who have been exposed to chest irradiation.

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Chapter 88

Chagas Disease

Diane C Kraft, Richard E Kerber

Chapter Outline

- Life Cycle
- Transmission
- Epidemiology
- Clinical Manifestations
- Echocardiography
- Cardiac Magnetic Resonance Imaging
- Treatment
  - Predictors of Mortality
- Prevention
- Chagas Disease in the United States

INTRODUCTION

Chagas disease, or American trypanosomiasis, is caused by the protozoan parasite, *Trypanosoma cruzi*. It is a disease of various clinical manifestations that in some progresses to a dilated cardiomyopathy, megaesophagus or megacolon. The pathogenesis of this disease is still incompletely understood.

Chagas disease was first described by Carlos Chagas in 1909. Chagas attended medical school in Rio de Janeiro, Brazil, studying under Dr Oswaldo Cruz. After medical school, he worked as a malaria control officer in Minas Gerais, Brazil. During this time, he observed flagellated organisms in the blood of a febrile child. After the child defervesced, the flagellated organisms were no longer present. He named the flagellated organisms, *T. cruzi*, in honor of his mentor. Carlos Chagas later went on to describe the vector and the clinical features of the disease.[1]

LIFE CYCLE

The life cycle of *T. cruzi* is complex (Fig. 1). When the vector, a triatomine bug, takes a blood meal, the *T. cruzi* is deposited on the host in the feces of the bug in the form of a metacyclic trypomastigote (Fig. 2). The *T. cruzi* gains access to the host through breaks in the skin, the nasal mucosa, the oral mucosa or the conjunctiva. There are reports of oral ingestion of the *T. cruzi* in food and drink contaminated with the *T. cruzi*-infected feces of the triatomine bug.[2] The trypomastigotes then are distributed through the body, entering host cells and transforming into amastigotes (Fig. 3). In the cell, amastigotes divide by binary fission. The amastigotes then transform into trypomastigotes and are released when the host cell ruptures. The trypomastigotes disseminate through the blood stream and lymphatics to find new cells to infect. While in the blood, the *T. cruzi* may be ingested when a vector takes a blood meal. When in the vector, the trypomastigotes, become epimastigotes in the midgut. The epimastigotes are capable of dividing. After 3–4 weeks, the epimastigotes transform into metacyclic trypomastigotes and are present in the hindgut of the vector. When the vector then takes a blood meal from a host, the *T. cruzi* is deposited on the host via the feces.[1]

The *T. cruzi* preferentially infects cells of the nervous, muscular, and reticuloendothelial system. The adipose tissue may serve as a reservoir.[3]

TRANSMISSION

T. cruzi is transmitted via the vector, the triatomine bug, which is in the order Hemiptera, family reduviidae, subfamily triatomine. The three main triatomine bugs are known to spread disease in humans are *Triatoma infestans*, *Rhodnius prolixus* and *Triatoma dimidiata*. The triatomine bug is also known as the "kissing bug" for biting the exposed skin on the faces of victims at night.[4] Most often the disease is transmitted by the vector, but can also be spread by blood transfusion, organ transplantation, contaminated food and drink,[5] transplacental and via lab accidents.[4]

EPIDEMIOLOGY

The disease is endemic in Mexico, Central and South America where an estimated 8–11 million people are infected.[6] In recent decades, there is increasing incidence in other parts of the world. It is estimated that greater than 300,000 people infected with *T. cruzi* reside in the United States.[6]

CLINICAL MANIFESTATIONS

The disease has three phases: (1) acute; (2) indeterminate and (3) chronic. The acute phase is often asymptomatic or characterized by a generally mild illness. Often patients will not recall

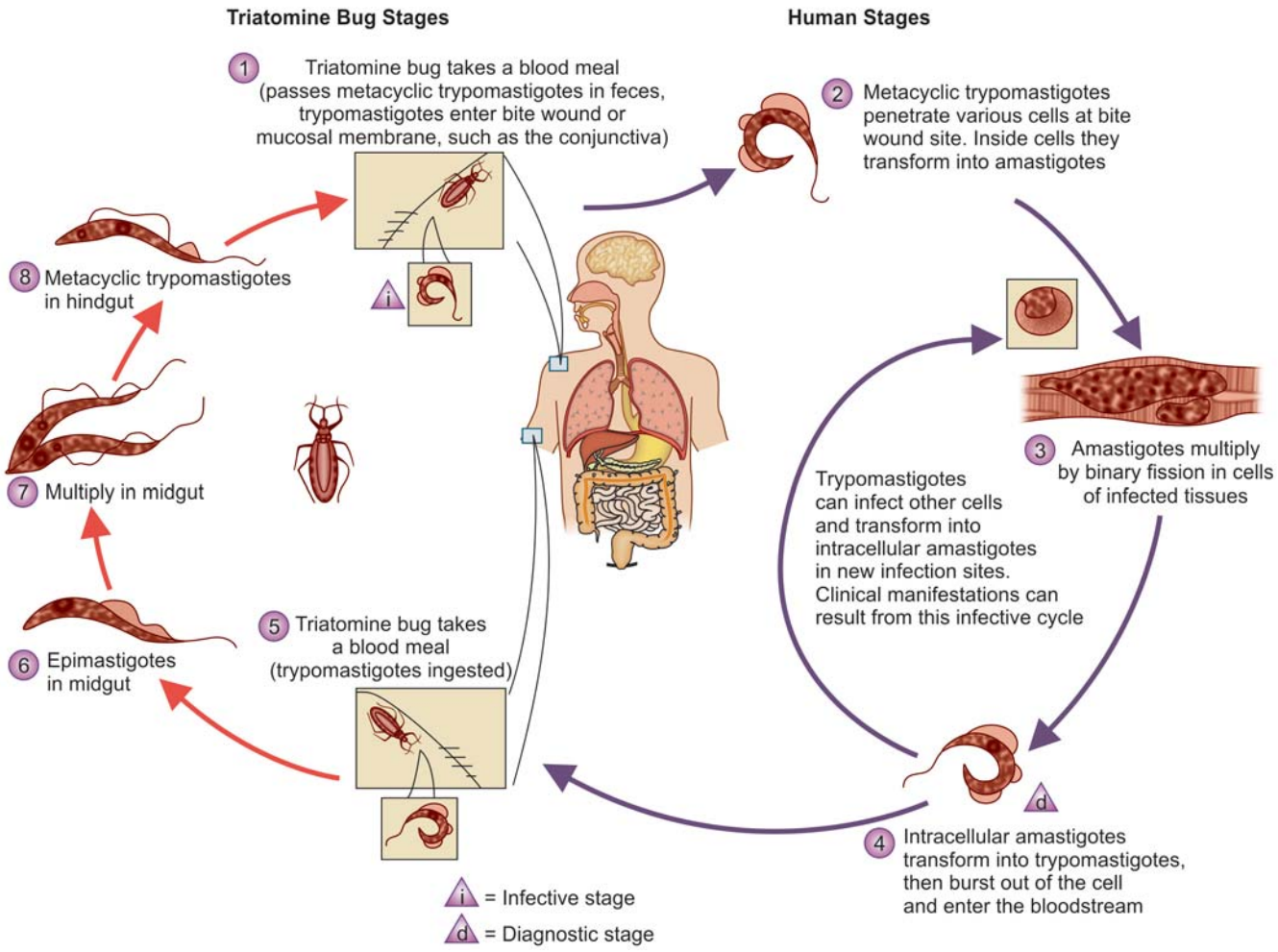


FIGURE 1: The life cycle of *T. cruzi*
(*Source:* Centers for Disease Control and Prevention)

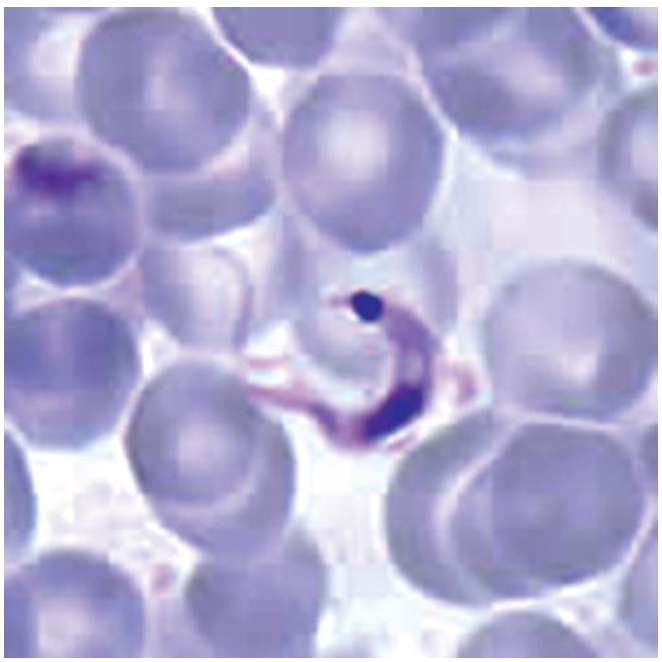


FIGURE 2: Thin blood smear with Giemsa stain of *T. cruzi* in the trypomastigote form. (*Source:* Centers for Disease Control and Prevention)

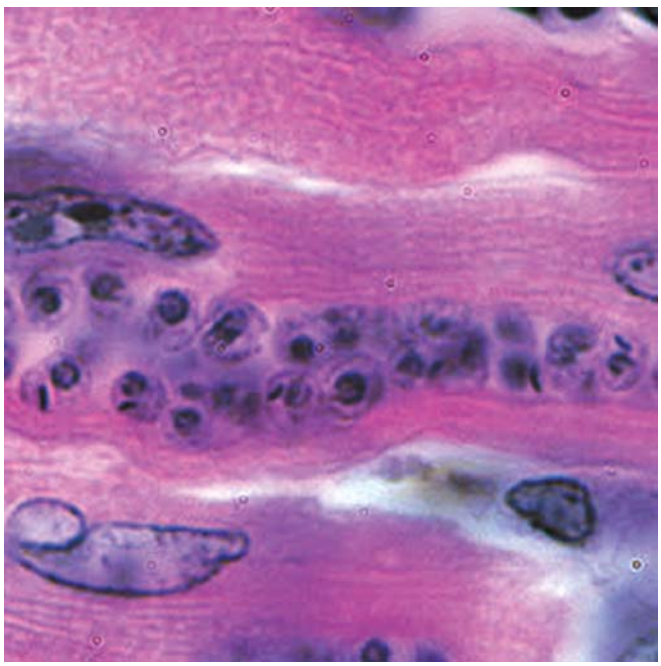


FIGURE 3: Hematoxylin and eosin stain of *T. cruzi* in amastigote form in cardiac tissue. (*Source:* Centers for Disease Control and Prevention)



FIGURE 4: Romaña's sign in acute Chagas disease. (*Source:* Reproduced with permission from the World Health Organization. Accessed 01 May, 2011 at http://www.cdc.gov/parasites/chagas/gen_info/vectors/index.html)

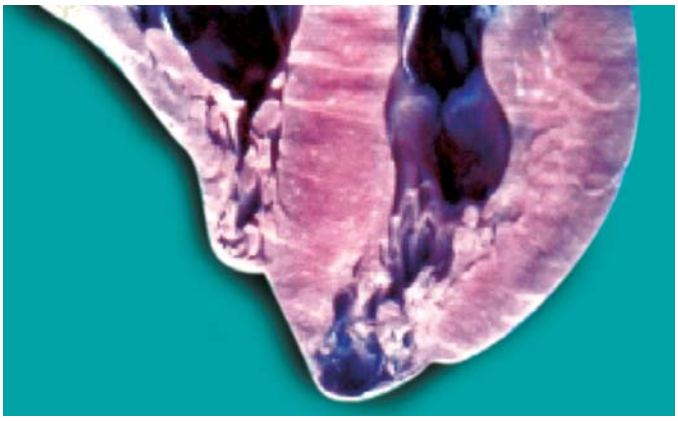


FIGURE 5: Left ventricular apical aneurysm. (*Source:* Prata A. Clinical and epidemiological aspects of Chagas disease. Lancet Infect Dis. 2001;1:92-100)

having been ill. A myriad of symptoms can be seen, including fevers, chills, nausea, vomiting, diarrhea, conjunctivitis and transient rash.[7] Associated lymphadenopathy and hepatosplenomegaly can occur. A raised lesion at the site of *T. cruzi* entry, a chagoma, can be seen. When inoculation occurs via the conjunctiva, unilateral edema of the upper and lower eyelids, conjunctivitis and regional lymphadenopathy develop, termed Romaña's sign[4] (Fig. 4). The histology of these lesions typically shows amastigote forms of *T. cruzi* in macrophages, adipocytes and muscle fibers in the subcutaneous tissue. This is associated with a lymphohistiocytic inflammatory response and edema.[8]

In approximately 5% of cases, a patient will develop myocarditis or meningoencephalitis during the acute phase.[9] It is not known if the severity of the acute phase affects the likelihood of development of chronic symptoms relating to cardiac or gastrointestinal manifestations.[1]

Laboratory findings during the acute phase are rather nonspecific, including anemia, thrombocytopenia and elevated transaminases. The diagnosis during the acute phase is primarily made by visualization of the parasites on blood smear.[4] Serologic testing during the acute phase is not recommended as IgM assays are not yet standardized and often times testing for IgG is negative during the acute phase.[10] As the immune response develops, the parasitemia wanes. There is usually complete resolution of the symptoms within 4–8 weeks.[4]

The survivors of the acute phase then enter the indeterminate phase. This is classically described as lack of clinical symptoms, a normal physical examination, a normal electrocardiogram, a normal radiographic exam of the chest, esophagus and colon, but detectable antibodies to *T. cruzi* are present.[11] This phase occurs in 60–70% of individuals and can last months to an entire lifetime.[4]

The chronic phase marks the onset of clinical symptoms and most often arises 10–30 years after the onset of the disease. It is estimated that 30% of individuals will progress to clinical Chagas cardiomyopathy.[8] The pathogenesis is complex and not well understood. It is generally accepted that the parasite persists in the body.[4] It has been hypothesized that clinical symptoms are a balance of the immune system containing the parasite and inflammation damaging the tissues.[12] The persistence of the organisms causes damage of cardiac myofibrils and Purkinje fibers with subsequently replacement by fibrous tissue. This is particularly noted at the left ventricular apex, causing aneurysmal dilatation and mural thrombus. Left ventricular apical aneurysms are described as the "pathognomonic sign" of Chagas disease[8] (Fig. 5).

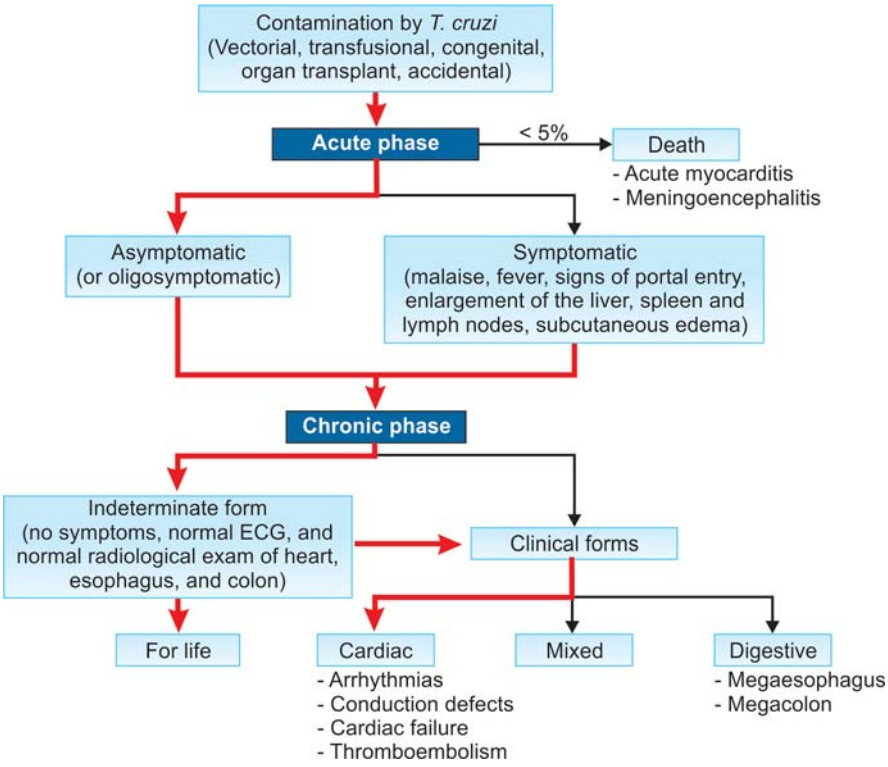
Manifestations during the chronic phase include arrhythmia and congestive heart failure, often biventricular. Electrocardiographic findings commonly encountered include complete or incomplete right bundle branch block with or without left anterior fascicular block, bradycardia, varying degrees of atrioventricular block and ventricular extrasystoles. Systemic and pulmonary embolisms often occur. Clinically, embolism to the brain, limbs and lung are most often encountered; however, at necropsy the most common sites are lung, kidneys and spleen.[12] Symptoms of atypical chest pain, palpitations and syncope are noted by patients.[11]

The diagnosis in the indeterminate and chronic phase is made by detection of antibodies to *T. cruzi*. False positive results can be obtained in patients with leishmaniasis, malaria, syphilis and collagen vascular diseases, and thus it is recommended that a patient test positive by two different assays before the diagnosis is given.[2] Currently, two ELISA tests are FDA approved for clinical testing.[10]

The disease has also been described as two phases: (1) the acute and (2) chronic form, with the indeterminate phase as a form of the chronic phase (Flow chart 1). It is not well understood why some individuals with Chagas disease develop clinical manifestations and others do not. Hypotheses include differences in host genetics, parasite strain and personal health.[1] Support for this theory could lie in the interesting finding that the digestive form is seen nearly exclusively south of the Amazon basin.[12]

The electrocardiogram often harbors the first sign of the disease. Most commonly a right bundle branch block with or without a left anterior fascicular block is seen. Other findings include bradycardia, varying degrees of atrioventricular block, ventricular extrasystoles and ventricular tachycardia, both nonsustained and sustained, atrial fibrillation, atrial flutter or left bundle branch block. However, other abnormalities can be seen.[11]

FLOW CHART 1: The natural history of Chagas disease. The thickness of the arrows indicates the relative probability of the pathway



(*Source:* Modified from Rassi A Jr, Rassi A, Rassi SG. Predictors of mortality in chronic Chagas disease: a systematic review of observational studies. Circulation. 2007;115:1101-8)

ECHOCARDIOGRAPHY

During the acute phase, segmental wall motion abnormalities can be seen; however, the global left ventricular function is usually preserved. Pericardial effusion can also be seen. During the indeterminate and chronic phases many different echocardiographic features may be seen including diastolic dysfunction, apical left ventricular aneurysms, dilated left ventricle with global hypokinesis, segmental wall motion abnormalities, isolated right ventricular dilatation, biventricular dilatation and atrial enlargement.[1]

CARDIAC MAGNETIC RESONANCE IMAGING

Cardiac MRI is an emerging modality for the diagnosis of Chagas cardiomyopathy. The high resolution images allow for visualization of subtle wall motion abnormalities, small apical aneurysms, and improved visualization and quantification of the right ventricle. In addition, delayed enhancement imaging allows for visualization of myocardial fibrosis. Both ischemic and nonischemic patterns can be seen in Chagas disease[13] (Fig. 6).

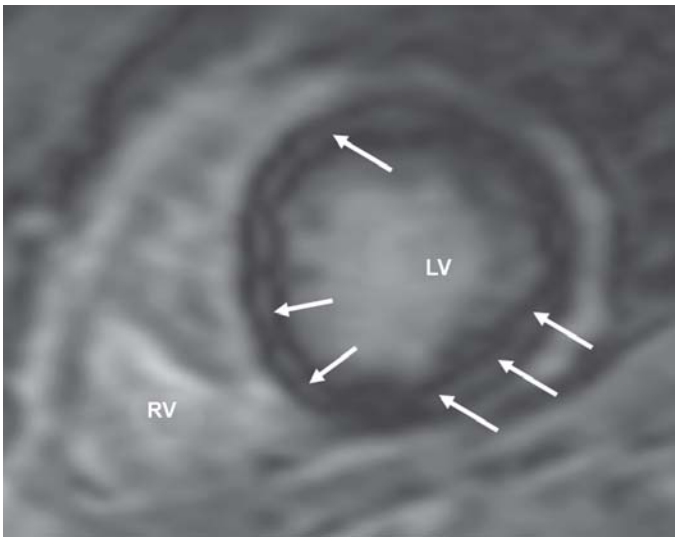


FIGURE 6: MRI of a patient with Chagas disease using late gadolinium enhancement. Note the areas of fibrosis in the midmyocardium (arrows). (*Source:* Robert Weiss, MD University of Iowa Hospitals and Clinics)

TREATMENT

Nifurtimox and benznidazole are the two present pharmacologic treatment options for Chagas disease. These drugs are old: nifurtimox was introduced in 1965 and benznidazole in 1971. Both have significant side effects of renal and hepatic failure. Nifurtimox has additional neurologic side effects including tremors, polyneuropathy and seizures.[11] Treatment is recommended for 90 days. Benznidazole side effects include exfoliative dermatitis, peripheral neuropathy in up to 30% of patients and bone marrow suppression.[11] Treatment is recom-

mended for 60 days. Frequent clinical and laboratory monitoring is required. In 2003, the Drugs for Neglected Diseases Initiative was created to assist in research and development of new treatments for neglected diseases, including Chagas disease.[14]

Treatment is indicated for individuals who are in the acute phase, those with congenitally acquired infections, those with reactivated infections due to immunosuppression, and children age 18 and younger with chronic infection. Treatment should be offered to reproductive age females, adults age 19–50 with the indeterminate form or mild to moderate cardiomyopathy, as data suggests that treatment may slow progression of the disease. Treatment in adults older than age 50 without advanced cardiomyopathy is optional due to the risk of drug toxicity. Treatment is generally not recommended in individuals with advanced Chagas cardiomyopathy due to the risk of drug toxicity in light of the existing pathology and is contraindicated in those who are pregnant and those with severe hepatic or renal insufficiency.[11]

Cure rates are estimated at 60–85% during the acute phase and greater than 90% in congenitally acquired infections when treated in the first year.[11] There is a lack of reliable assays to document response during the indeterminate and chronic phases. An unfortunate lack of well-designed studies to guide treatment length and retesting also exists.

There is hope for better understanding of treatment goals and new medications to treat the disease. The BENEFIT trial is an international, double-blind, multicenter randomized trial that at the time of submission of this manuscript was not yet published. The trial is designed to assess if benznidazole treatment reduces mortality or other major cardiovascular outcomes in patients with chronic Chagas heart disease versus placebo.[15] Completion of sequencing the genome of the *T. cruzi* occurred in 2005[16] and may allow for new drug targets.

PREDICTORS OF MORTALITY

Impaired left ventricular function is the most consistent predictor of mortality risk. New York Heart Association Class III and IV symptoms as well as cardiomegaly present on the chest radiograph were also predictive of mortality. These likely reflect an advanced degree of myocardial damage.[9]

In patients with Chagas heart disease, sudden death is the most frequent cause of death, most often secondary to ventricular tachycardia or ventricular fibrillation. Rarely atrioventricular block or sinus node dysfunction causes death. Refractory heart failure is the cause of death in approximately 25–30% of patients. In approximately 10–15% of patients death occurs as a complication of thromboembolism.[12]

PREVENTION

A key in prevention is elimination of the vector. An insecticide campaign was undertaken in the 1990s in endemic countries to eliminate the vector from home dwellings. In addition, mud walls and thatched roofs that are common in rural Central and South America allow the triatomine bug to thrive,[6] and thus housing improvements to eliminate the nesting of the vectors in human dwellings have been undertaken. Mandated screening of donated blood in all endemic countries, except Mexico, has also been instituted.[1] In 2007, screening of donated blood for Chagas disease was instituted in the United States.[6] The US Food and Drug Administration has approved Ortho *T. cruzi* enzyme-linked immunosorbent assay test system which is currently being used as the initial screening test. The test is based on parasite lysate antigen. This test will cross-react with leishmaniasis. For donated units of blood that test positive with the ELISA, confirmatory testing is completed with a radioimmune precipitation assay (RIPA)[17] developed by Dr Louis V Kirchhoff of the University of Iowa.[1] Since screening began, 1,417 blood donations have been confirmed positive.[18]

CHAGAS DISEASE IN THE UNITED STATES

Reports of seven autochthonous cases of Chagas disease have occurred in the United States, one each in California, Tennessee and Louisiana, and four in Texas.[19] There are approximately six species of vectors known to inhabit the United States. Reservoirs of the disease include opossums, raccoons, ungulates, skunks, dogs and rodents.[8] In a study by Reisenman CE, et al. volunteers in the Tuscon, Arizona area were asked to collect bugs in or around their houses. About 41% of bugs were found to be infected with *T. cruzi*.[20] A noted limitation of the study was that the insects were collected by volunteers; however, the information raises the question of how how well protected countries are outside of the known endemic areas.

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Section 10

PULMONARY VASCULAR DISEASE AND ADULT CONGENITAL HEART DISEASE

Chapter 89

Pulmonary Arterial Hypertension

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Chapter Outline

- Definitions and Classifications
  - Hemodynamic Classification of Pulmonary Hypertension
  - Clinical Classification of Pulmonary Hypertension
- Pathophysiology and Epidemiology of Pulmonary Arterial Hypertension
  - Idiopathic Pulmonary Arterial Hypertension
  - Heritable Pulmonary Arterial Hypertension
  - Drug-induced and Toxin-Induced Pulmonary Arterial Hypertension
  - Pulmonary Arterial Hypertension Associated with Connective Tissue Diseases
  - Pulmonary Arterial Hypertension Associated with Human Immunodeficiency Virus Infection
  - Portopulmonary Hypertension
  - Congenital Heart Disease Associated with Pulmonary Arterial Hypertension
  - Pulmonary Arterial Hypertension Associated with Schistosomiasis
  - Pulmonary Arterial Hypertension Associated with Chronic Hemolytic Anemias
  - WHO Group 1: Pulmonary Capillary Hemangiomatosis and Pulmonary Veno-Occlusive Disease
- Diagnostic Evaluation
  - Clinical Presentation and Physical Examination
  - Role of Echocardiography
  - Laboratory Studies
  - Pulmonary Function Testing
  - Nocturnal Polysomnography
  - Screen for Chronic Thromboembolic Pulmonary Hypertension
  - Right Heart Catheterization
  - Vasoreactivity Testing
- Survival and Prognostic Factors of Pulmonary Arterial Hypertension
  - Survival in Pulmonary Arterial Hypertension Associated with Connective Tissue Disease
  - Survival in Human Immunodeficiency Virus Related with Pulmonary Arterial Hypertension
  - Survival in Pulmonary Arterial Hypertension Associated with Portal Hypertension
  - Survival in Congenital Heart Disease Associated with Pulmonary Arterial Hypertension
  - Survival in Pulmonary Arterial Hypertension Associated with Schistosomiasis
- Therapeutic Options for the Treatment of Pulmonary Arterial Hypertension
  - Adjuvant/Conventional Therapies
  - Disease Specific Therapies for Pulmonary Arterial Hypertension
  - Invasive and Surgical Options
- Treatment Algorithm and Evaluating Response to Therapy
- Therapy of Decompensated Right Heart Failure in Pulmonary Arterial Hypertension

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a rare disease that affects approximately 15 patients per million and is characterized by progressive increases in pulmonary vascular resistance (PVR) and pulmonary arterial pressure, which ultimately leads to right ventricular (RV) failure and death.[1] Substantial progress in research over the last several decades has revealed much about its pathophysiology, molecular pathways, genetics, survival and treatment. However mortality remains high and therapeutic options are costly and limited. This chapter reviews the definition and clinical classification of pulmonary hypertension (PH), including a brief discussion of the more common causes of PH that are not PAH, followed by a discussion about the pathophysiology, epidemiology, diagnosis, prognosis and treatment of PAH.

DEFINITIONS AND CLASSIFICATIONS

HEMODYNAMIC CLASSIFICATION OF PULMONARY HYPERTENSION

Pulmonary hypertension is defined hemodynamically by invasive right heart catheterization (RHC) as a mean pulmonary artery pressure (mPAP) greater than 25 mm Hg. Formerly, PH was also diagnosed if the mPAP reached greater than 30 mm

Hg during exercise; however, the exercise criteria was removed during the 4th World Symposium on PH due to the lack of data regarding its meaning and clinical relevance. Given the diverse array of diseases that can lead to PH, it can be useful to classify PH based on the anatomical location of the "lesion" that results in elevated pulmonary pressures (Fig. 1).[2]

PH from lesions proximal to the pulmonary capillary bed are hemodynamically classified as "precapillary" and are characterized by an mPAP greater than 25 mm Hg, pulmonary arterial wedge pressure (PAWP) or left ventricular end-diastolic pressure (LVEDP) less than or equal to 15 mm Hg and PVR greater than three Wood units (WU)(or > 240 dynes sec cm^{-5}). In contrast, "postcapillary" PH is defined as an mPAP greater than 25 mm Hg, PAWP and/or LVEDP greater than 15 mm Hg, and PVR less than three WU. Some patients have "mixed" precapillary and postcapillary PH, which is defined as an mPAP greater than 25 mm Hg, PAWP greater than 15 mm Hg, and PVR greater than 15 mm Hg. Rarely, increased pulmonary blood flow from a high cardiac output (CO) state leads to PH without elevations in PAWP or PVR.[2]

World Health Organization (WHO) Group 1 PH (PAH) is a type of precapillary PH and should be discriminated from other causes of precapillary PH, as the pathophysiology, prognosis and therapies are distinct. The other types of precapillary PH include WHO Group 3 PH (PH associated with hypoxia and parenchymal lung disease), WHO Group 4 PH (PH associated with chronic thromboembolic PH) and most cases of WHO Group 5 PH (PH with miscellaneous or multifactorial causes). Lesions found distal to the pulmonary capillary bed are classified as postcapillary and can result from any condition that leads to chronically elevated left atrial and/or pulmonary venous pressure.

CLINICAL CLASSIFICATION OF PULMONARY HYPERTENSION

The clinical classification system for PH continues to evolve as our understanding of the pathological basis of the various diseases that underlie the syndrome improves. The most current clinical classification was developed in 2008 during the 4th World Symposium on PH in Dana Point, California, which resulted in a revision of the Venice clinical classification of 2003[3] (Table 1).

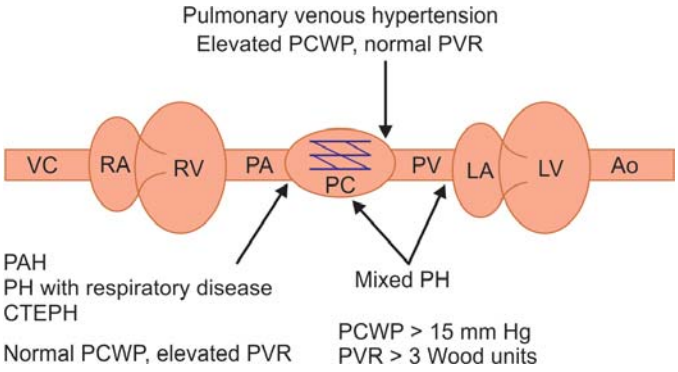


FIGURE 1: Schematic of precapillary and postcapillary pulmonary hypertension
(Abbreviations: Ao: Aorta; CTEPH: Chronic thromboembolic pulmonary hypertension; LA: Left atrium; LV: Left ventricle; PA: Pulmonary artery; PAH: Pulmonary arterial hypertension; PC: Pulmonary capillary; PCWP: Pulmonary capillary wedge pressure; PH: Pulmonary hypertension; PV: Pulmonary veins; PVR: Pulmonary vascular resistance; RA: Right atrium; VC: Vena cava)

TABLE 1

Clinical classification of pulmonary hypertension (Dana Point, 2008)[3]

1. Pulmonary arterial hypertension (PAH)
1.1 Idiopathic PAH (IPAH)
1.2 Heritable
1.2.1 BMPR2
1.2.2 ALK, endoglin (with or without hereditary hemorrhagic telangiectasia)
1.2.3 Unknown
1.3 Drug and toxin induced
1.4 Associated with:
1.4.1 Connective tissue diseases
1.4.2 HIV infection
1.4.3 Portal hypertension
1.4.4 Congenital heart diseases
1.4.5 Schistosomiasis
1.4.6 Chronic hemolytic anemia
1.5 Persistent pulmonary hypertension of the newborn
1′ Pulmonary veno-occlusive disease (PVOD) and/or pulmonary capillary hemangiomatosis (PCH)
2. Pulmonary hypertension owing to left heart disease
2.1 Systolic dysfunction
2.2 Diastolic dysfunction
2.3 Valvular disease
3. Pulmonary hypertension owing to lung diseases and/or hypoxemia
3.1 Chronic obstructive pulmonary disease
3.2 Interstitial lung disease
3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
3.4 Sleep-disordered breathing
3.5 Alveolar hypoventilation disorders
3.6 Chronic exposure to high altitude
3.7 Developmental abnormalities
4. Chronic thromboembolic pulmonary hypertension (CTEPH)
5. Pulmonary hypertension with unclear multifactorial mechanisms
5.1 Hematologic disorders: myeloproliferative disorders, splenectomy
5.2 Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis: lymphangioleiomyomatosis, neurofibromatosis, vasculitis
5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
5.4 Other: tumoral obstruction, fibrosing mediastinitis, chronic renal failure on dialysis
Sarcoidosis, histiocytosis X, lymphangiomatosis, compression of pulmonary vessels (adenopathy, tumor, fibrosing mediastinitis)

(Abbreviations: ALK: Activin receptor-like kinase; *BMPR2*: Bone morphogenetic protein receptor type 2; HIV: Human immunodeficiency virus)

Pulmonary Arterial Hypertension (WHO Group 1 PH)

Pulmonary arterial hypertension has an estimated prevalence of 15 cases per million.[1] Women are far more often affected than men, with female to male ratios from 1.5:1 to 4.1:1.[4,5] Age of onset is typically in the fourth to fifth decade although it appears to be increasing based on findings from the Registry to Evaluate Early And Long-term PAH Disease Management (REVEAL Registry™).[4] Causes of PAH include idiopathic and

heritable cases, drug and toxins, PAH associated with connective tissue disease (CTD), human immunodeficiency virus (HIV) infection, portal hypertension, congenital heart disease (CHD), schistosomiasis, chronic hemolytic anemia and persistent PH of the newborn. Pulmonary veno-occlusive disease (PVOD) and pulmonary capillary hemangiomatosis (PCH) are classified as PAH; however, because they differ from other types of PAH with the variable amounts of disease affecting the pulmonary capillaries and pulmonary veins, which leads to differences in their prognosis and variable responses to treatment compared with other WHO Group 1 (PAH) diseases. PVOD and PCH are therefore classified as WHO Group 1 PH.

PAH has been the major focus of the classification and therapeutic clinical trials of PH since the first classification done in 1973. To date, the majority of randomized controlled trials of all the currently available therapeutic drugs for PH (prostanoids, endothelin antagonists and phosphodiesterase 5 inhibitors) have been performed in patients with PAH as opposed to other WHO groups of PH, and these PH specific therapies are currently only approved by the Federal Drug Administration (FDA) to treat patients with WHO Group 1 PH.

Pulmonary Venous Hypertension (WHO Group 2 PH)

Add the following sentence as the first sentence in this paragraph and replace the yellow highlighted portion with: "Elevated pulmonary artery pressure may also be related to upstream high left atrial pressure as a consequence of left-sided heart disease (WHO Group 2 PH). Any cause of elevated left atrial pressure, including left ventricular (LV) systolic and/or diastolic dysfunction (most common), left-sided valve disease (e.g. mitral or aortic regurgitation or stenosis), pericardial disease, or a congenital membrane within the left atrium (cor triatriatum)[6] can all lead to this type of pulmonary hypertension. In these cases, the PCWP and/or LVEDP is greater than or equal to 15 mm Hg. WHO Group 2 PH has been often described as "pulmonary venous" or "post-capillary" pulmonary hypertension, and most often the PVR is normal. Due to the prevalence of left-sided heart failure, postcapillary PH accounts for the majority of cases of PH.

However, in the setting of chronically elevated left-sided filling pressures, pulmonary vascular remodeling can occur such that the PVR and transpulmonary gradient increase out of proportion to the degree of PCWP and/or LVEDP elevation. In such cases, the transpulmonary gradient (TPG) is greater than the normal 10 mm Hg or less (usually 12-15 mm Hg or greater).[7] Chronically elevated endothelin levels leading to pulmonary arterial medial hypertrophy and obliterative arteriopathy may play a role in the pathogenesis of this type of PH.[8] This hemodynamic profile with an elevated mPAP, elevated PCWP and/or LVEDP, and elevated PVR and TPG is variably described in the literature as "PH out of proportion to left heart disease", "mixed" or "reactive" PH. Moreover, when the PVR fails to decrease to less than 3 Wood Units with acute pulmonary vasodilators, the PH may be described as "fixed" or "non-reactive". In each of these instances, however, the underlying etiology of PH is left-heart disease and it is not considered to be pulmonary arterial hypertension.

If despite normalization of the left-sided filling pressures with medical therapy the mPAP and PVR remain elevated, pulmonary vasodilator therapy may in certain cases be used to treat these patients, but the use of PH specific therapies for this indication is still undefined, and in some cases could be harmful.[9-12] That being said, clinical trials of vasomodulating therapies are currently underway for the treatment of specific types of left heart disease-related PH. In particular, inhibition of phosphodiesterase type 5 does not appear to increase left-sided filling pressures, and it is currently being used in an off-label manner in selected patients with advanced systolic heart failure and mixed PH who are being considered for heart transplantation. For now, however, the currently available PH therapies are not approved to treat patients with postcapillary or mixed PH.

Pulmonary Hypertension due to Lung Disease and/or Chronic Hypoxemia (WHO Group 3 PH)

Precapillary PH can develop in patients with parenchymal lung disease and/or chronic hypoxia. Examples of this type of PH include chronic obstructive pulmonary disease (COPD), interstitial lung disease (ILD), other pulmonary diseases with mixed restrictive and obstructive lung pattern, sleep-disordered breathing, alveolar hypoventilation disorders, chronic exposure to high altitude, and developmental abnormalities. Of the parenchymal lung diseases, ILD most commonly results in PH through capillary destruction and hypoxic vasoconstriction.[13,14]

Patients with CTD, in particular those with the scleroderma spectrum of CTD, are at increased risk for development of ILD. As these patients can also suffer from PAH, it is important to distinguish, as much as possible, between PH from ILD versus PAH. In general, coexistent pulmonary vascular disease is suggested in patients with ILD and PH in whom the degree of reduced diffusion capacity for carbon monoxide (DLCO) is out of proportion to the reduction in lung volume, as suggested by a forced vital capacity to DLCO ratio greater than or equal to 1.4.[15]

To date, randomized, placebo-controlled clinical trials of prostacyclins, endothelin receptor antagonists (ERAs) and inhibitors of phosphodiesterase type 5 (PDE5I) have failed to demonstrate clear benefits of PH specific therapies in the treatment of WHO Group 3 PH.[16,17] A concern about using systemic vasodilators to treat PH in ILD is that the suppression of physiologic vasoconstriction and shunting in low ventilation/perfusion lung units may cause or worsen ventilation-perfusion mismatching and hypoxemia. Although inhaled vasodilator therapy may overcome this problem due to drug delivery to well ventilated segments, the "A Clinical Trial in IPF to Improve Ventilation and Exercise (ACTIVE)" trial of inhaled iloprost to treat PH in patients with idiopathic pulmonary fibrosis (IPF) failed to show any benefit; in fact, patients experienced worsening of the six-minute walk distance (6MWD) with treatment.[17] The Sildenafil Trial of Exercise Performance in Idiopathic Pulmonary Fibrosis (STEP-IPF) trial, which evaluated the PDE5I sildenafil in patients with IPF, but without documentation of PH, did not achieve the primary endpoint of improvement in 6MWD, but did show improvement in

secondary variables including oxygenation, dyspnea and quality of life.[18] The clinical importance of these secondary endpoints is controversial and STEP-IPF is the only trial that has shown any efficacy in IPF patients. The Bosentan Use in Interstitial Lung Disease (BUILD-1) trial in patients with IPF failed to demonstrate an improvement in the primary endpoint 6MWD in patients with IPF who were treated with bosentan; however, positive trends for the predefined secondary endpoint, combined incidence of disease progression or death at 12 months were observed.[16] This positive trend led to the BUILD-3 trial, which enrolled a total of 616 patients with IPF, and it failed to demonstrate a reduction in the primary endpoint of morbidity/mortality in patients with IPF, who were treated with bosentan.[19]

Sleep disordered breathing, as occurs with obstructive sleep apnea (OSA) and obesity hypoventilation syndrome, can cause significant elevations in pulmonary pressure, possibly through prolonged episodes of nocturnal hypoxia, although the exact mechanism are unclear.[20] Other factors could include oxidative stress[21] and impaired endothelial nitric oxide release.[22] While typically considered to be associated with precapillary PH, OSA can also be caused by and is associated with left-sided heart failure and can coexist with pulmonary venous hypertension.[23,24]

There are no clear estimates of the prevalence of PH in OSA, but OSA is common in the general population and likely to increase with increasing rates of obesity and heart failure.[25] In addition to continuous positive airway pressure ventilation for patients with obstructive episodes, therapy should be directed toward correction of hypoxia, fluid overload and weight reduction. Treatment of PH associated with OSA with pulmonary vasodilator therapies are not expected to significantly improve symptoms or outcomes beyond usual therapy in these patients and especially since their use comes at great cost ($13,000 to > $100,000 annually). PH specific therapies should not be used for this indication unless future studies demonstrate improved outcomes with therapies directed at treating the PH.

Prolonged exposure to high altitudes (HA) can also lead to PH, chronic mountain sickness and in some cases fatal pulmonary edema.[26,27] The etiology of HA related PH is unclear, but contributing factors likely include hypoventilation, hypoxic mediated pulmonary vasoconstriction and free radical mediated reduction in nitric oxide.[28,29] There is some evidence that treatment with sildenafil may protect against the development of HA associated PH and improve gas exchange, but further studies are needed.[30-32]

Chronic Thromboembolic Pulmonary Hypertension (WHO Group 4 PH)

The defining features of chronic thromboembolic pulmonary hypertension (CTEPH) are pulmonary arterial mural thrombi, webbing, bands and obliteration of the larger pulmonary vessels. In addition, patients with CTEPH may have pathologic changes in non-occluded pulmonary artery segments that are typically seen in PAH, including medial hypertrophy and intimal hyperplasia.[33] Although acute pulmonary embolism (PE) can lead to PH and RV dysfunction, in the majority of patients it resolves after the acute episode. There is limited evidence that patients treated with thrombolysis due to RV dysfunction following acute PE have decreased incidence of CTEPH.[34] Approximately 2–4% of patients, who suffer from PE, go on to develop CTEPH despite anticoagulation.[35,36]

CTEPH can lead to severe PH and RV failure with reduced survival. Because in select patients, CTEPH can be treated with surgical removal of the emboli via pulmonary endarterectomy (PEA), it is extremely important to identify patients with CTEPH even when other causes of PH have been diagnosed. In eligible patients, hemodynamics and functional status have markedly improved with low in-hospital mortality after PEA.[37,38] Patients diagnosed with CTEPH should be referred for evaluation at specialized centers with expertise in PEA.

Because CTEPH shares pathologic features of PAH, there have been several small studies of PH specific therapies, including prostacyclins, PDE5I and endothelin antagonists. The largest of these trials was a randomized, placebo-controlled trial of bosentan in patients who were ineligible for PEA or had persistent PH following PEA surgery.[39-41] Among the 157 patients enrolled in the study, patients treated with bosentan demonstrated improvements in hemodynamics and quality of life; however, exercise capacity did not improve.[39] Further trials are needed to establish the safety and efficacy of treating CTEPH patients with PH specific therapies.

Pulmonary Hypertension with Unclear Multifactorial Mechanisms (WHO Group 5 PH)

Group 5 consists of several forms of PH for which the etiology is unclear or multifactorial. For instance, PH may be related to hematologic disorders such as chronic myeloproliferative disorders including by polycythemia vera, essential thrombocythemia, chronic myeloid leukemia, and post-splenectomy state. In addition, systemic disorders that are associated with an increased risk of developing PH include sarcoidosis, pulmonary Langerhans cell histicytosis and neurofibromatosis type 1 (also known as von Recklinghausen disease). Finally, metabolic disorders, such as type Ia glycogen storage disease (a rare autosomal recessive disorder caused by a deficiency of glucose-6-phosphatase), Gaucher disease, and thyroid disease (both hyper- and hypothyroidism) have been associated with a risk for developing PH. In each of these disorders, the pathophysiology of PH is either unclear or related to multiple potential underlying mechanisms.

PATHOPHYSIOLOGY AND EPIDEMIOLOGY OF PULMONARY ARTERIAL HYPERTENSION

Pulmonary arterial hypertension (WHO Group 1 PH) occurs in a diverse group of disease states that demonstrate similar hemodynamic and pathologic characteristics. There is no unifying pathobiologic mechanism to explain the development of PAH in all cases, and multiple independent factors may play a role, such as mutations in bone morphogenetic protein receptor type 2 (BMPR2), high volume systemic to pulmonary shunts and inflammatory changes in CTD that lead to similar disease phenotypes.

The normal pulmonary circulation is a high-flow, low resistance circuit with great capacity to recruit more pulmonary capillaries and reduce PVR when needed without an increase pulmonary artery pressure. For instance, the pulmonary

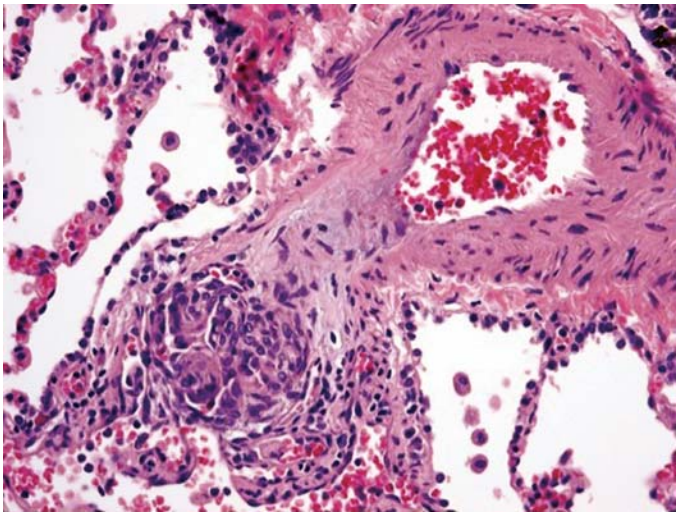


FIGURE 2: Pulmonary arterial hypertension. Plexiform lesion: a tangle of slit-like vascular channels are noted adjacent to a pulmonary arterial branch (Hematoxylin and eosin stain, 400x)

circulation can accommodate an increased CO of three to four times normal or removal of an entire lung without a significant rise in PAP because the PVR decreases. Fundamental to the development of PAH is smooth muscle cellular proliferation, decreased apoptosis, vasoconstriction, platelet dysregulation and inflammation.[42] Pathologically, these changes manifest as medial hypertrophy, intimal hyperplasia, adventitial proliferation of the small pulmonary arteries and *in situ* thrombosis (Fig. 1).[43] The hallmark of advanced PAH is the plexiform lesion, which consists of endothelial cell channels lined by myelofibroblasts, smooth muscle cells and connective tissue matrix (Fig. 2).[44,45]

On a molecular level, multiple pathways have been identified which have served as therapeutic targets. Arachidonic acid metabolism is altered in PAH which leads to decreased activity of prostacyclin synthase and reduced levels of prostaglandin I_2 (prostacyclin) with a shift toward increased thromboxane A_2 production.[46] This imbalance favors cellular proliferation, vasoconstriction and platelet aggregation. PAH is also characterized by a deficit of nitric oxide through decreased endothelial nitric oxide synthase activity. The effects of nitric oxide are mediated through cyclic guanosine monophosphate (cGMP), which is an important modulator of vascular tone and is broken down by cGMP phosphodiesterase type-5A (PDE5A). PDE5A is found in high concentrations in the pulmonary vascular bed, which has made it an attractive target for drug development.[47] Endothelin-1, which leads to smooth muscle cell vasoconstriction and proliferation is elevated in PAH, and higher levels are associated with worse outcomes.[48] Other mediators that appear to impact the development and progression of PAH include increased activity levels of serotonin, angiopoietin-1 and angiopoietin-2, plasminogen activator inhibitor-1, growth factors, oxidant stress, and inflammation and reduced activity levels of vasoactive intestinal peptide, K_v channels and fibrinolysis.[49-53] The role of estrogen in the development of PAH, if any, remains unclear; however, altered estrogen levels, signaling and metabolism may play a role in idiopathic PAH (IPAH).[54]

The pathologic outcome of the above physiologic and molecular changes is progressive elevation in PAP and PVR, leading to RV failure, poor LV filling, decreased CO, ventricular dysrhythmias and ultimately death. Under normal conditions, the right ventricle is a thin-walled, trabeculated structure that, in contrast to the LV, pumps against a low impedance and high capacitance circuit. The RV is very responsive to loading conditions with both increased pressure and/or volume resulting in significant RV enlargement and failure, which can occur acutely depending on the rate of pulmonary disease progression. During exercise, PVR normally decreases, allowing RV CO to increase without adversely increasing cardiac work. In contrast with PAH, increasing PVR leads to abnormal loading conditions, forcing the RV to undergo pathologic changes and remodel (Flow chart 1).

In the initial stages of the disease, the RV adapts to increased PVR by increasing RV wall thickness, which tends to decrease RV wall stress. During this phase, both CO and right atrial pressure (RAP) are normal. However, progressive increases in PVR lead to RV chamber enlargement, fibrosis and distortion of the normal RV architecture. As the RV begins to fail, right ventricular end-diastolic pressure (RVEDP) and thus RAP begin to rise. Due to decreased ability of the pulmonary vasculature to dilate in response to exercise, the RV is unable to augment CO and exercise tolerance decreases.

As the RV begins to dilate, the typical triangular shape of the RV is distorted, resulting in tricuspid annular dilatation and regurgitation, which further increases RV preload and decreases CO. Because the RV and LV are interdependent and contained within the pericardium, RV morphologic distortion affects LV filling, compliance and shape.[55-57] As RV pressure continues to increase, the septum flattens during systole. However, once RV volume overload develops, the LV becomes progressively "D" or crescent shaped as the septum flattens in both systole and diastole. In addition to direct compression of the LV, decreased RV CO leads to poor filling of the LV and decreased LV CO. Increased RVEDP leads to increased coronary sinus pressure, which leads to ventricular edema and decreased ventricular compliance.[58] Decreased CO further exacerbates RV ischemia due to decreased coronary perfusion pressure in the setting of low MAP and high RVEDP. Furthermore, in decompensated RV failure, LVEDP can increase as a result of ventricular interdependence and pericardial constraint.

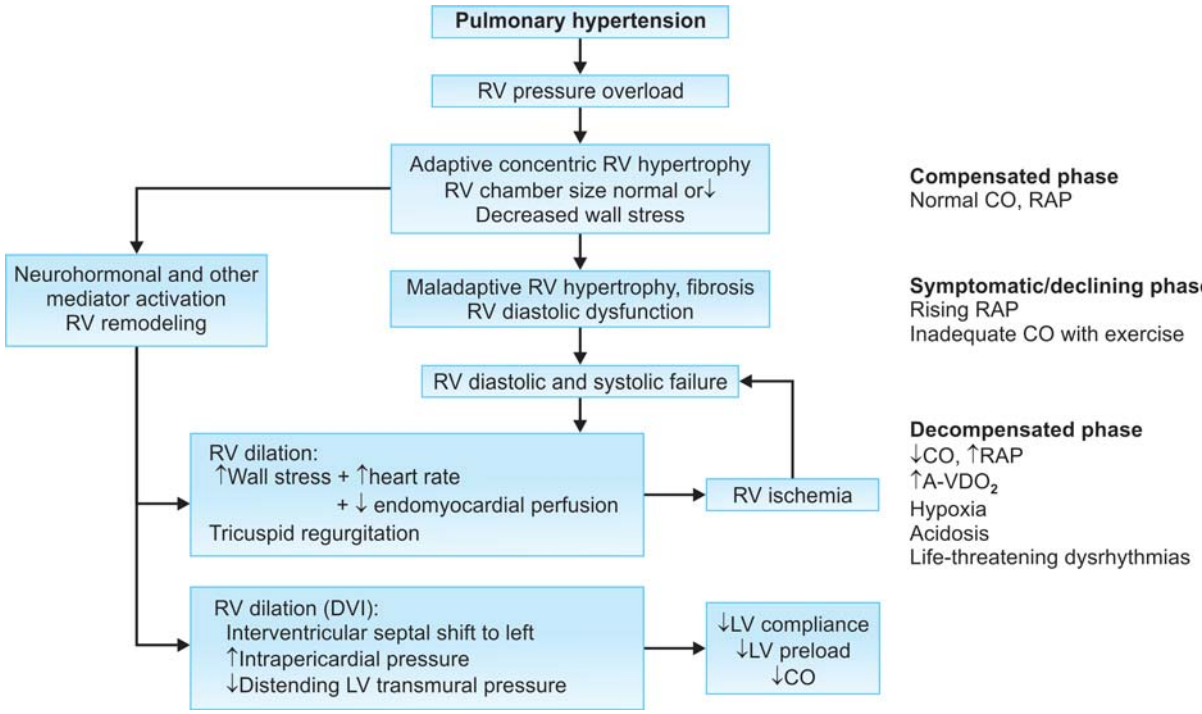
IDIOPATHIC PULMONARY ARTERIAL HYPERTENSION

Idiopathic PAH represents a sporadic and very rare disease where no identifiable cause or risk factor exists. The prevalence of IPAH is six cases per million, accounting for approximately 40% of cases of PAH.[1] While there is no known cause of IPAH, mutations in the *BMPR2* gene are found in 10–40% of patients characterized as idiopathic.[59-61] In the past, the term primary pulmonary hypertension (PPH) was used to describe patients with IPAH or familial PAH (FPAH), and all other causes of PH were considered to be secondary PH. However, these terms have been abandoned in favor of more clinically meaning terms.

HERITABLE PULMONARY ARTERIAL HYPERTENSION

The subgroup of heritable PAH (HPAH) includes patients with PAH and either germline mutations, which are transferred to

FLOW CHART 1: Pathophysiology of right ventricular failure in pulmonary arterial hypertension



(Abbreviations: A-VDO_2: Arterial venous oxygen difference; CO: Cardiac output; LV: Left ventricle; RAP: Right atrial pressure; RV: Right ventricular). *(Source:* DeMarco T, McGlothlin D. Managing right ventricular failure in pulmonary arterial hypertension—An algorithmic approach. Advances in pulmonary hypertension. 2005;4(4):16-26)

offspring or familial cases without identified germline mutations.[62,63] Several germline mutations have been identified in familial cases of PAH. The most common involves the *BMPR2* gene, a member of the transforming growth factor beta (TGF-β) signaling family. *BMPR2* gene mutations are found in approximately 58–74% of patients with FPAH.[59,64-66] Inheritance is autosomal dominant with incomplete penetrance (only 20% of patients with *BMPR2* mutations develop PAH) and genetic anticipation, whereby future generations in familial cases tend to develop clinical disease at a younger age. It has been suggested that cases of HPAH associated with *BMPR2* mutations represent a subgroup with less acute vasoreactivity and more severe disease.[64] In addition, women tend to be affected more frequently than men, although sex does not appear to be associated with outcome.[59]

In addition to *BMPR2*, mutations of the activin receptor-like kinase type 1 (ALK-1) and endoglin, both members of the TGF-β signaling family, have been identified in patients with PAH, primarily associated with hereditary hemorrhagic telangiectasia. These patients tend to present earlier than those with *BMPR2* mutations and have more severe clinical course.[66]

DRUG-INDUCED AND TOXIN-INDUCED PULMONARY ARTERIAL HYPERTENSION

An epidemiologic association between PAH and aminorex fumarate was first observed in the 1960s and was followed by associations between the disease and fenfluramine in the 1990s in France.[67] The risk of PAH following exposure to dexfenfluramine appears to increase with total exposure to the drug and can occur following short exposure.[67] Despite the earlier findings, fenfluramine and dexfenfluramine were widely used in the 1990s for weight control. Due to reports of the development of valvular abnormalities following their use, they were withdrawn for the US market in 1997.[68] The exact cause of anorexigen associated PAH is unclear, but may be due to altered serotonin metabolism and increased levels of plasma serotonin.[69] However, no association between PAH and the selective serotonin release inhibitors has been observed. *BMPR2* mutations have rarely been identified in patients with PAH associated with CHD or fenfluramine use.

Illicit drugs, including cocaine and methamphetamines, have also been associated with PAH.[70] Although the incidence is uncertain, methamphetamine associated PAH poses a significant public health risk as methamphetamines are cheap and easy to make, and use has increased rapidly throughout the world over the last few decades. Indeed, methamphetamines are the most commonly used illicit drug amongst high-school students in the United States.[71] In a retrospective analysis of patients treated at a tertiary care center for PAH, almost 30% of patients diagnosed with IPAH reported stimulant usage, primarily methamphetamine.[72] Treatment of these patients can be complicated by recurrent drug use, unstable social support and complications associated with intravenous therapy.

PULMONARY ARTERIAL HYPERTENSION ASSOCIATED WITH CONNECTIVE TISSUE DISEASES

Pulmonary arterial hypertension has been associated with a variety of autoimmune diseases; however, the highest risk of

PAH is found among patients with the scleroderma spectrum of diseases, particularly with limited cutaneous systemic sclerosis (SSc) and CREST syndrome (Calcinosis, Raynaud's phenomenon, Esophageal dysfunction, Sclerodactyly, Telangiectasias). Currently, the prevalence of systemic sclerosis associated PAH (SSc-PAH) is approximately 2.93 per million.[73] Systemic lupus erythematosus (SLE-PAH)[74-76] and mixed connective tissue disease (MCTD)[76] are associated with PAH less frequently than SSc, whereas PAH has been rarely reported among patients with other types of CTD including Sjögren syndrome,[77] rheumatoid arthritis[78] and polymyositis.[79] Chronic inflammation may play a role, and macrophages, T and B lymphocytes, and dendritic cells have been identified surrounding plexiform lesions.[80]

In early studies of patients with CTD including SSc, Doppler echocardiography without confirmation by RHC led to an overestimation of the prevalence of PAH.[81] Subsequent prospective studies using screening echocardiography followed by diagnostic RHC for confirmation of PAH have found that the prevalence of PAH in patients with SSc is between 5% and 12%.[82,83] A meta-analysis by Avouac and colleagues found a prevalence of 9% for PAH in SSc patients.[84] In the French PAH registry, CTD-PAH accounted for 15.3% of cases of PAH.[1]

It is important to recognize that PAH is not the only cause of PH in patients with SSc. Patients with SSc are also at risk for the development of pulmonary fibrosis, which is a frequent cause of PH (WHO Group 3 PH).[85] Moreover, PAH and PH due to ILD may coexist in these patients. In addition, LV diastolic heart failure related to myocardial fibrosis inpatients with SSc can lead to pulmonary venous hypertension (WHO Group 2 PH). Therefore, distinguishing between the relative contribution of each disease process through hemodynamic assessment of PAWP with RHC, radiographic evaluation for ILD and assessment of DLCO is important to guide therapy, as vasodilators have not been well studied in SSc patients with PH related to ILD or diastolic heart failure, and could be harmful.

PULMONARY ARTERIAL HYPERTENSION ASSOCIATED WITH HUMAN IMMUNODEFICIENCY VIRUS INFECTION

Pulmonary arterial hypertension is a well-established complication of HIV infection and was first recognized in 1987.[86-89] The prevalence of HIV associated PAH is estimated to be 0.5% and has not changed with the introduction of highly active antiretroviral therapies (HAART).[90,91] In contrast to IPAH, the male to female ratio is approximately 1.5:1 and the average age of diagnosis is 33 years.[92] Patients with HIV tend to present with worse functional class than do other patients with PAH and they tend to have more rapid progression in symptoms.[92]

Although the mechanism for its development is unclear, the clinical, hemodynamic and histologic characteristics of HIV associated PAH (HIV-PAH) are similar to IPAH.[89,93] Neither the virus nor viral DNA have been found in pulmonary endothelial cells and, therefore, an indirect mechanism of action through second messengers such as cytokines, growth factors, endothelin or viral proteins are suspected.[88,94-97] Importantly, there is no clear association with HIV viral load or CD4 cell count and the development of PAH or its progression.[87]

PORTOPULMONARY HYPERTENSION

Pulmonary arterial hypertension associated with portal hypertension, better known as portopulmonary hypertension (PoPAH), can be distinguished from other forms of PAH by the presence of PAH in association with elevated portal hypertension as measured by a hepatic venous pressure gradient greater than 5 mm Hg or the presence of esophageal varices.[98] While cirrhosis is not necessary for the diagnosis, cirrhotic liver disease is the most common underlying etiology.[98] Prospective studies have found that 2–6% of patients with portal hypertension have elevated pulmonary pressures. In the French Registry of PAH, 10% of cases of PAH were due to PoPAH.[1]

Characteristically, patients with PoPAH have increased or preserved CO despite elevated mPAP and PVR, although CO may decrease as the disease becomes advanced. It is important to note that PoPAH is not the only cause of PH in patients with advanced liver disease. Such patients are also at risk for PH due to high CO state and pulmonary venous hypertension related to fluid overload and/or underlying LV disease, such as the so-called "cirrhotic cardiomyopathy", alcoholic cardiomyopathy and hemochromatosis. The PVR is usually normal in these cases. Therefore, an RHC is mandatory for the definitive diagnosis of PoPAH.

CONGENITAL HEART DISEASE ASSOCIATED WITH PULMONARY ARTERIAL HYPERTENSION

Approximately 5–10% of patients with CHD develop PAH, and the prevalence of CHD-PAH in Europe and North America ranges between 1.6 and 12.5 cases per million adults.[99-101] The clinical classification of congenital heart defects may be useful to distinguish between four distinct phenotypes. PAH typically develops in the presence of large systemic to pulmonary shunts, such as ventricular septal defects (VSD), atrial septal defects (ASD), anomalous pulmonary venous drainage and patent ductus arteriosus. Patients with large VSDs tend to develop PAH at an earlier age than do patients with interatrial communications.[101] Over time, pulmonary pressures can gradually increase to systemic levels and the shunt flow can reverse, leading to central cyanosis and the Eisenmenger syndrome, which occurs in 25–50% of patients with CHD-PAH and carries a high mortality rate.[102-105]

PULMONARY ARTERIAL HYPERTENSION ASSOCIATED WITH SCHISTOSOMIASIS

Due to its worldwide prevalence of approximately 200 million, schistosomiasis is likely the most common cause of PAH with the vast majority of cases in Africa.[106,107] Prior to the Dana Point meeting, PAH associated with schistosomiasis was categorized in WHO Group 4 PH related to chronic thrombotic and/or embolic disease because embolic obstruction of the pulmonary arteries by schistosoma eggs was thought to be the primary mechanism responsible for the development of PH. More recently, however, studies have indicated that PAH associated with schistosomiasis can have similar histopathologic features, including plexiform lesions, and clinical presentation as in IPAH, and for that reason it is now subcategorized within WHO Group 1 PH (PAH), under the new classification system.

It is now better understood that the development of PAH related to schistosomiasis may be multifactorial and related to

vascular inflammation from impacted schistosoma eggs, as well as potentially by the coexistence of PoPH, which is a common consequence of this disease.[106] Pulmonary embolic obstruction by schistosoma eggs appears to play a minor role in the development of PH in these patients. Data from a recent hemodynamic study of patients with hepatosplenic schistosomiasis showed that the prevalence of PAH in these patients was 4.6%, whereas 3% of the patients had pulmonary venous hypertension.[108] These findings reinforce the need for a diagnostic RHC in patients with schistosomiasis and suspected PH.

PULMONARY ARTERIAL HYPERTENSION ASSOCIATED WITH CHRONIC HEMOLYTIC ANEMIAS

Evidence that PAH can be a consequence of the chronic hereditary and acquired hemolytic anemias has been mounting. PAH has been reported in a wide range of conditions that result in hemolytic anemia, including sickle cell disease (SCD), thalassemia, paroxysmal nocturnal hemoglobinuria, hereditary spherocytosis, malaria and others.[109,110] Due to the worldwide prevalence of SCD, thalassemia and malaria, hemolytic anemias may account for a significant portion of the global burden of PAH.

The exact mechanism(s) of the development of PAH in these patients is unclear. Hemolysis may result in a nitric oxide deficient state through free hemoglobin scavenging of nitric oxide and through release of arginase, which depletes the substrate for nitric oxide synthesis, L-arginine.[111] In common with other causes of PAH, endothelin levels are also increased.[112] In the case of sickle cell anemia, hypoxic mediated vasoconstriction and direct injury to the pulmonary vascular bed during sickle crises may also play a role.[110] Splenectomy, which is used to treat certain hemolytic disorders, has also been associated with the development (WHO Group 5 PH).

Among patients with chronic hemolytic anemias, SCD related PAH has been described most frequently with histologic findings that are similar to patients with IPAH. However, because of the lack of invasive diagnostic hemodynamic studies, the prevalence of PAH in SCD has not been established. Similar to PoPAH, it is important to understand that PAH is not the only cause of PH in patients with chronic hemolytic anemias. Such patients may develop a high CO state from anemia and/or LV diastolic heart failure with pulmonary venous hypertension as the etiology of PH. Therefore, an invasive hemodynamic study is of paramount importance for the diagnosis of PAH in these patients as well.

WHO GROUP 1: PULMONARY CAPILLARY HEMANGIOMATOSIS AND PULMONARY VENO-OCCLUSIVE DISEASE

Although classified as a subgroup of PAH, PCH and PVOD are distinguished from other causes of PAH by variable pathologic obstruction within the pulmonary capillaries (PCH) and veins (PVOD) that can lead to the development of pulmonary edema in the absence of left-sided heart failure.

The etiologic basis for PVOD and PCH is unclear, but mutations in *BMPR2*, toxin exposure and inflammatory disorders have been implicated.[113] Expression of platelet-derived growth factor appears to be involved in the angiogenic proliferation seen in PCH.[114,115] Some investigators have hypothesized that PVOD and PCH are on the same spectrum of disease and patients with associated forms of PAH, in particular SSc associated PAH, may show characteristics of PVOD.[116,117] Pathologic findings in PVOD include fibrotic obliteration of the preseptal pulmonary venules, and thrombotic occlusion of small postcapillary vessels.[113] Similar to PAH, the small pulmonary arteries demonstrate intimal thickening and medial hypertrophy, but plexiform arteriopathy is typically absent.[113] In contrast, PCH tends to present as a tumorigenic proliferation of the capillaries (Fig. 3).

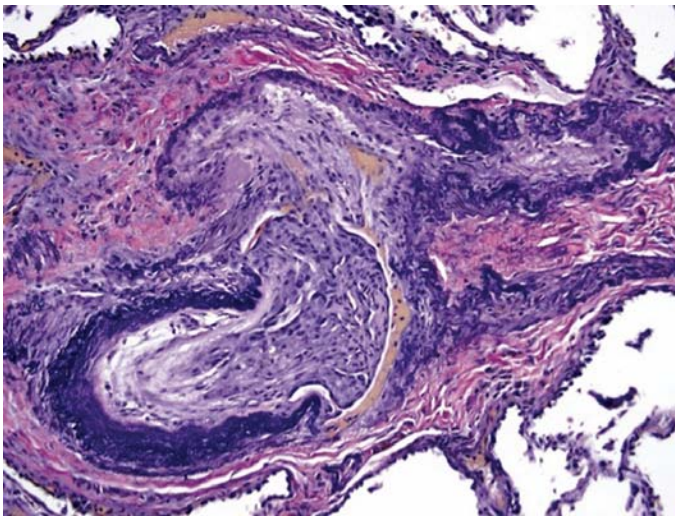


FIGURE 3: Pulmonary occlusive venopathy. An elastic tissue stain reveals fibrous obliteration of the pulmonary venous lumen. There is associated adventitial thickening (Verhoeff-Van Gieson elastic stain, 200x)

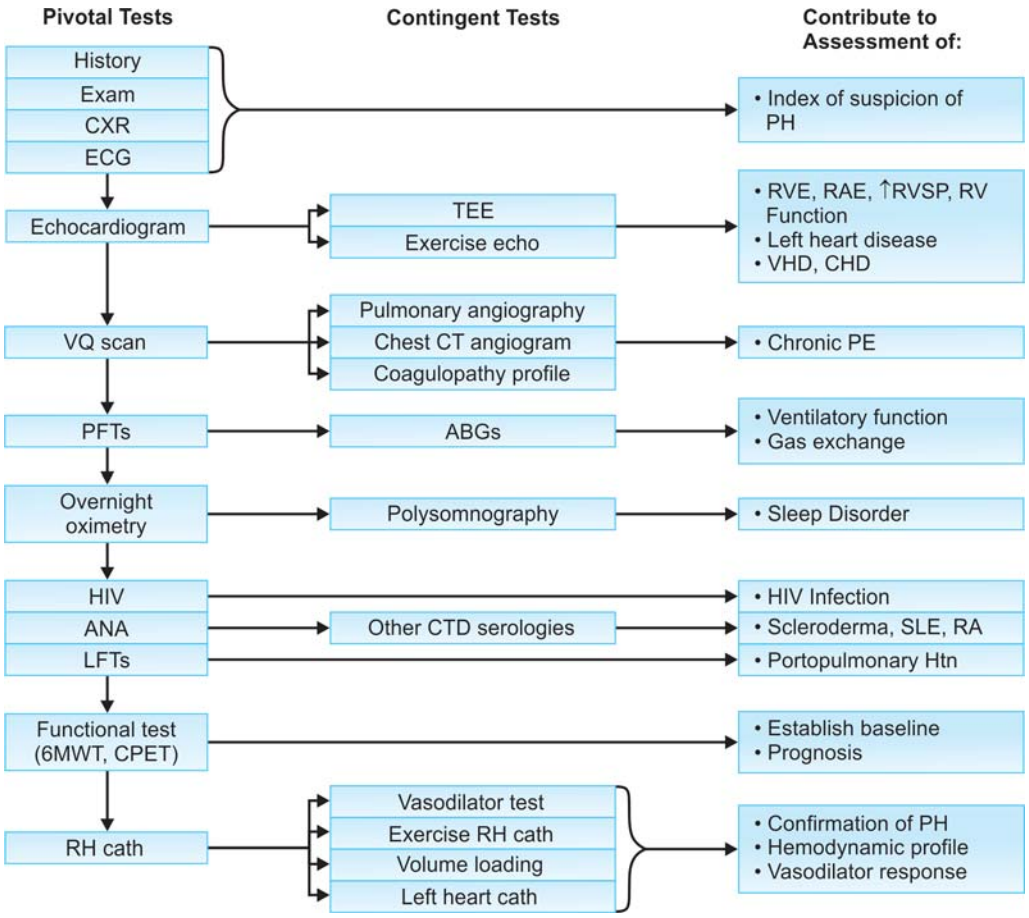
PVOD and PCH accounted for less than 0.5% of patients with PAH in the REVEAL Registry, but estimates are difficult to make given the rarity of the disease and the difficulty of making a diagnosis.[4] Both diseases appear to occur with equal frequency in men and women. PCH tends to present in patients aged 20–40 years, and PVOD can present in any decade of life.[118]

Diagnosis of PVOD and PCH are suspected based on imaging findings, and clinical deterioration on vasodilators. Computed tomograhic scans of the chest show evidence of pulmonary edema in the form of interlobular septal thickening, as well as diffuse ground glass opacities, and sometimes mediastinal lymphadenopathy. Findings on bronchoalveolar lavage are nonspecific, but may show hemosiderin-laden macrophages, suggesting occult alveolar hemorrhage.[119] Lung tissue biopsy is the only reliable diagnostic method, but it carries high risk in this patient population. Pulmonary vasodilators should be used with extreme caution, if at all, in patients with known or probable PVOD or PCH, because life-threatening pulmonary edema can develop with their use in these patients.[120] Patients with PVOD and PCH should be promptly referred for consideration of lung transplantation because of the generally rapid progression of disease and poor survival.

DIAGNOSTIC EVALUATION

In patients, suspected of having PH based on the clinical history and/or physical examination including unexplained dyspnea, a methodical and thorough diagnostic work-up should be

FLOW CHART 2: Diagnostic approach to pulmonary arterial hypertension[121]



(Abbreviations: 6MWT: Six-minute walk test; ABGs: Arterial blood gases; ANA: Antinuclear antibody serology; Cath: Catheterization; CHD: Congenital heart disease; CPET: Cardiopulmonary exercise test; CT: Computed tomography; CTD: Connective tissue disease; CXR: Chest X-ray; ECG: Electrocardiogram; Exam: Examination; HIV: Human immunodeficiency virus screening; Htn: Hypertension; LFT: Liver function test; PE: Pulmonary embolism; PFT: Pulmonary function test; PH: Pulmonary hypertension; RAE: Right atrial enlargement; RA: Rheumatoid arthritis; RH Cath: Right heart catheterization; RVE: Right ventricular enlargement; RVSP: Right ventricular systolic pressure; SLE: Systemic lupus erythematosus; TEE: Transesophageal echocardiography; VHD: Valvular heart disease; VQ Scan: Ventilation-perfusion scintigram)

undertaken in order to confirm or exclude the presence of PH and identify all potential contributing factors, as suggested by the latest published guidelines. Of fundamental importance in the evaluation of patients suspected of having PH is to perform a diagnostic RHC to assess the hemodynamics and confirm the presence of PH, characterize its anatomic location (e.g. precapillary versus postcapillary), determine severity of disease, exclude CHD with oxygen saturation evaluation and (in the case of precapillary PH) perform vasodilator testing. In addition, the patient's New York Heart Association (NYHA)/WHO functional classification and 6MWD at baseline should be noted, as they are strong prognostic markers in patients with PAH and will serve as benchmark from which to assess response to therapy or progression of disease (Flow chart 2).

The steps, necessary to establish the diagnosis of PH and which WHO Group patients belong to, are outlined in the diagnostic algorithm (Figs 4A and B), which was published as part of the most recent ACCF/AHA consensus statement guidelines on PH.[121] These are general guidelines for the evaluation of PH. Since the suspicion of PH may arise in various ways, the sequence of tests may vary. The diagnosis of PAH requires that the totality of the data support a specific diagnosis and, in the case of IPAH, all other reasonable causes are excluded. In general, pivotal tests are those that are essential to establishing a diagnosis of any type of PH. All pivotal tests are required for a definitive diagnosis and baseline characterization. An abnormality of one assessment, such as obstructive pulmonary disease on pulmonary function tests (PFTs), does not preclude that another abnormality (e.g. chronic thromboembolic disease) is contributing or predominant. Contingent tests are recommended to elucidate or confirm results of the pivotal tests, and the combination of pivotal and contingent tests contributes to assessment of the differential diagnoses. It should be recognized that definitive diagnosis might require additional specific evaluations not necessarily included in this general guideline.

CLINICAL PRESENTATION AND PHYSICAL EXAMINATION

Patients with PAH most often present with unexplained shortness of breath. Indeed, dyspnea, which is typically exertional early in the disease course, is the initial symptom in 60% of patients with PAH. Other presenting symptoms, in order of frequency include general fatigue (19%), syncope or near-

syncope (13%), chest pain (7%), palpitations (5%) and leg edema (3%).[5,122] Physical examination findings may be very few in early stages of the disease, which probably contributes to the delay in diagnosis. The presence of PH is suggested by an increased intensity of the pulmonic component of the second heart sound. In addition, RV enlargement can be detected by the presence of a left parasternal lift. In the presence of RV enlargement, a dilated tricuspid annulus often leads to a pansystolic tricuspid regurgitant murmur at the left lower sternal border. Likewise, pulmonary artery enlargement leads to pulmonary valve insufficiency, which may be auscultated as a high-pitched decrescendo murmur heard best at the left upper sternal border.

As the disease advances, the development of RV failure may become apparent with elevated jugular venous pressure, RV S3 and S4 gallops, hepatomegaly, abdominal distention from ascites and lower extremity edema. The pulmonary examination in patients with PAH is typically unremarkable in patients with pure PAH, and abnormalities such as rales may suggest a secondary cause of PH from parenchymal lung disease or left heart failure. Skin changes, such as sclerodactyly, telangiectasias, Raynaud's phenomenon or calcinosis, may point toward CTD. Likewise, spider angiomata and other stigmata of liver disease can suggest portal hypertension (Table 2).

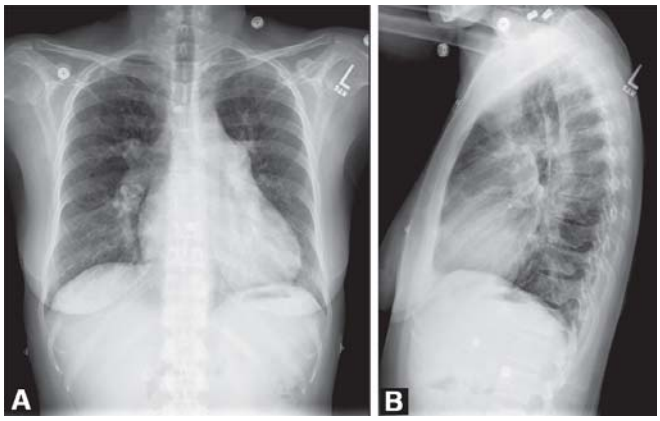
An abnormal chest radiograph (X-ray) is present in 90% of IPAH patients at diagnosis. Typical findings include clear lung fields with enlarged central pulmonary arteries and "pruning" of the peripheral vasculature. In addition, the presence of RV enlargement can be suggested on a lateral chest X-ray by a reduction or obliteration of the normal retrosternal space (Figs 4A and B). Infiltrates on the chest X-ray may suggest the presence of ILD or pulmonary venous hypertension due to left heart abnormalities as the cause of PH. In addition, hilar adenopathy may be suggestive of sarcoidosis. Of note, a normal chest X-ray does not exclude postcapillary PH since many patients with chronic pulmonary venous hypertension may not have pulmonary venous congestion on chest imaging.[5,122,123]

The electrocardiogram (ECG) (Fig. 5) may provide evidence of PH by showing RV hypertrophy (R > S wave in lead V1 and/or V2, right axis deviation, S1Q3T3 pattern); incomplete or complete right bundle branch block; strain pattern (ST depressions and/or T wave inversions in the anterior precordial leads and occasionally in the inferior leads) and right atrial enlargement (tall P wave in lead II). RV hypertrophy on the ECG is present in 87% and right axis deviation in 79% of patients with IPAH. It is important to note that the ECG has

TABLE 2

Physical examination findings in pulmonary arterial hypertension

Findings in pulmonary arterial hypertension
• Left parasternal lift
• Increased intensity of P2
• Holosytolic murmur of tricuspid regurgitation
• Diastolic murmur of pulmonary regurgitation
• Right ventricular S3 and S4
• Elevated jugular venous pressure
• Positive hepatojugular reflux
• Hepatomegaly
• Ascites with abdominal distention
• Lower extremity edema
Findings that may suggest causes of associated pulmonary arterial hypertension or pulmonary hypertension
• Pulmonary rales
• Central cyanosis
• Digital clubbing
• Raynaud's phenomenon
• Sclerodactyly, telangiectasias, Raynaud's phenomenon, calcinosis
• Spider angiomata



FIGURES 4A AND B: Chest radiograph of a patient with pulmonary arterial hypertension. (A) Posteroanterior chest radiograph showing enlarged pulmonary arteries with pruning of peripheral vasculature. (B) Lateral view demonstrating obliteration of retrosternal space due to right ventricular enlargement

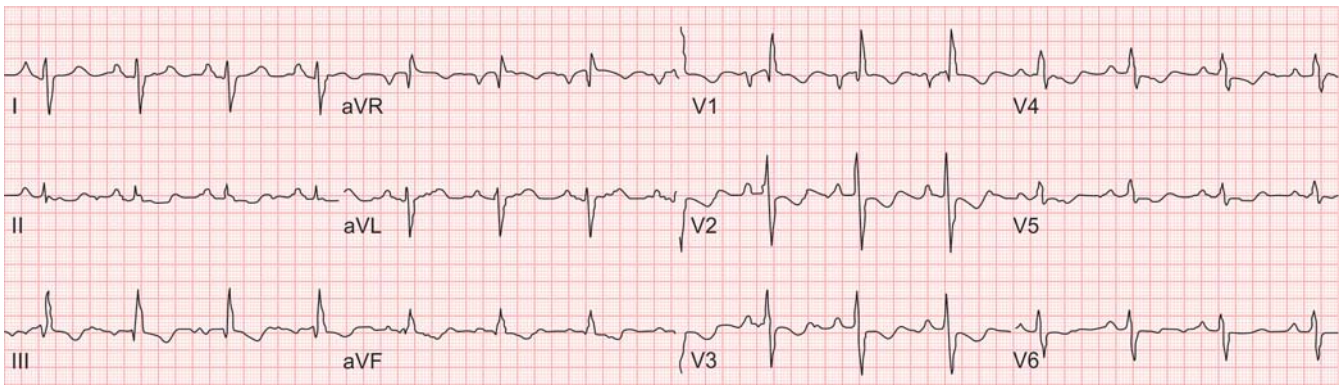


FIGURE 5: Electrocardiogram of 44-year-old woman with right axis deviation, right ventricular hypertrophy with repolarization abnormality and right atrial abnormality

insufficient sensitivity (55%) and specificity (70%) to be the sole screening tool for detecting significant PAH.[5,122,124]

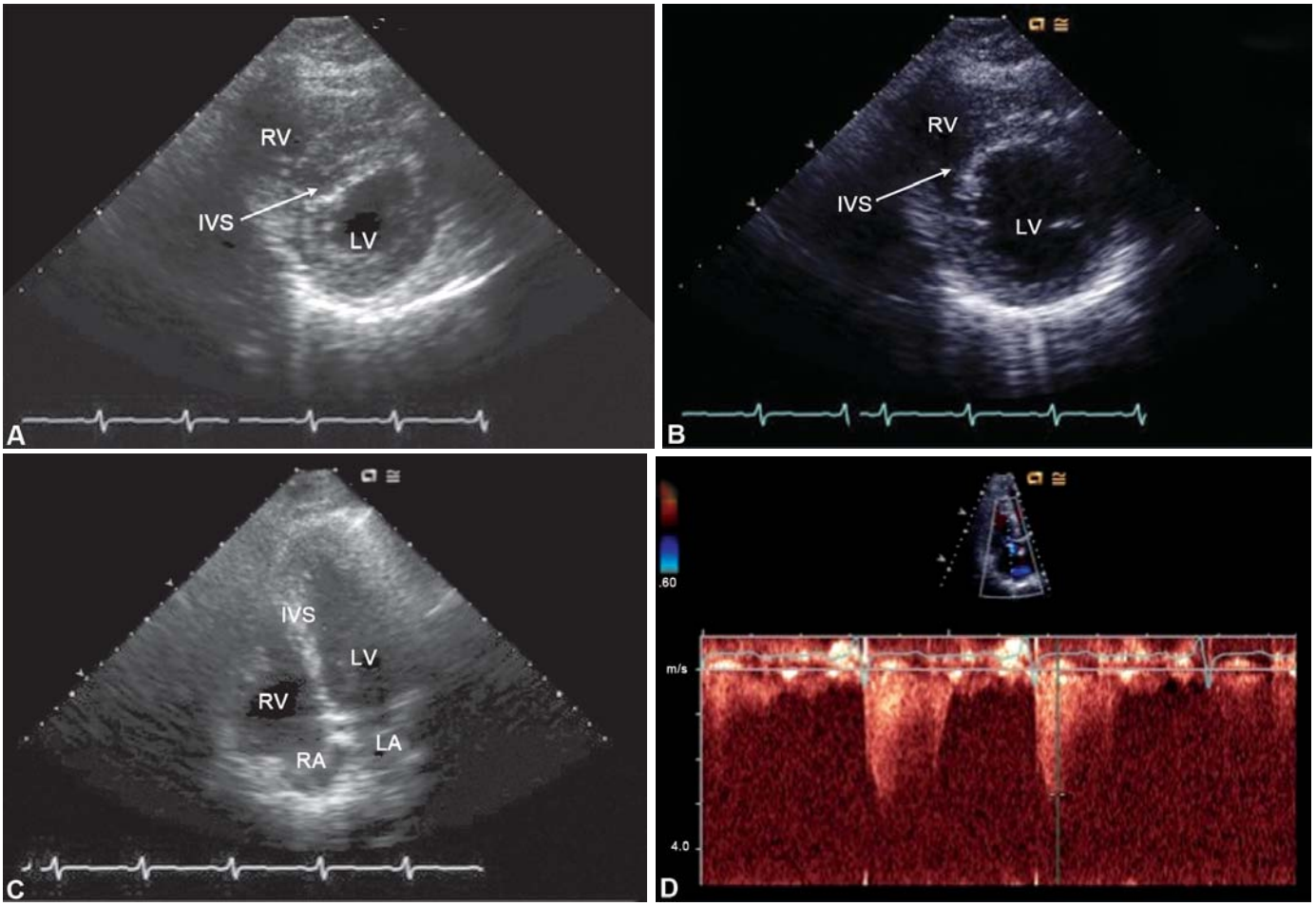
ROLE OF ECHOCARDIOGRAPHY

Transthoracic echocardiography (TTE) with Doppler interrogation is the most useful and readily available noninvasive tool to screen for PH. In most cases of moderate-to-severe PH, the RV is hypertrophied and dilated, often with reduced systolic function. The right atrium is often dilated to various degrees, depending on the degree of RV failure and tricuspid regurgitation, and the left heart chamber volumes are typically reduced, also depending on the degree of RV enlargement and severity of PAH disease.

Although LV ejection fraction can be difficult to quantitate because of compression by right heart enlargement, LV systolic function usually appears normal to hyperdynamic. In a parasternal short axis view, the left ventricle appears "D" or crescent shaped as the interventricular septum flattens and displaces toward the left ventricle. Septal flattening during systole suggests RV pressure overload, whereas septal flattening during diastole occurs with RV volume overload. Septal flattening during systole may be the only finding suggestive of PH in cases where the tricuspid regurgitant (TR) velocity is underestimated due to a lack of complete TR jet, and where the RV is well compensated and not dilated. Ventricular septal flattening from RV volume overload occurs because of an increase in RV diastolic pressure, which results from RV failure and/or TR. Therefore, as a marker of RV failure, it is not surprising that greater degrees of ventricular septal flattening during diastole, as measured by the LV eccentricity index, are associated with worse prognosis[125] (Figs 6 to 8).

Because of the unique shape of the RV, accurate estimations of RV chamber volume and ejection fraction based on assumptions used for analysis of the LV are not possible. Therefore, analyses of RV size and function for the most part have been based on subjective interpretations. However, a relatively recent technique to quantitate RV systolic function via measurement of longitudinal shorting of the RV during systole, as measured by the tricuspid annular plane systolic excursion (TAPSE) has proved to be a simple measure with prognostic significance.[126] Another method to quantify RV function in patients with PAH is known as the RV myocardial performance index (also known as the Tei index), which is a Doppler-derived measure of global RV function that correlates with survival in patients with PAH.[127]

Patients with significant PH often have tricuspid annular dilatation, which results in varying degrees of tricuspid valve insufficiency. In addition, pulmonary arterial dilation leads to



FIGURES 6A TO D: Mild pulmonary arterial hypertension suggested by parasternal short axis views showing flat IVS during (A) systole, but not in (B) diastole indicating RV pressure overload. (C) Apical four-chamber view showing borderline increased RV volume. (D) Continuous wave Doppler image of the TR jet velocity of 2.7 m/sec, equivalent to a PASP of 30 mm Hg plus the RA pressure. (Abbreviations: LA: Left atrium; LV: Left ventricle; RA: Right atrium; RV: Right ventricle; IVS: Interventricular septum; TR: Tricuspid regurgitation; PASP: Pulmonary artery systolic pressure)

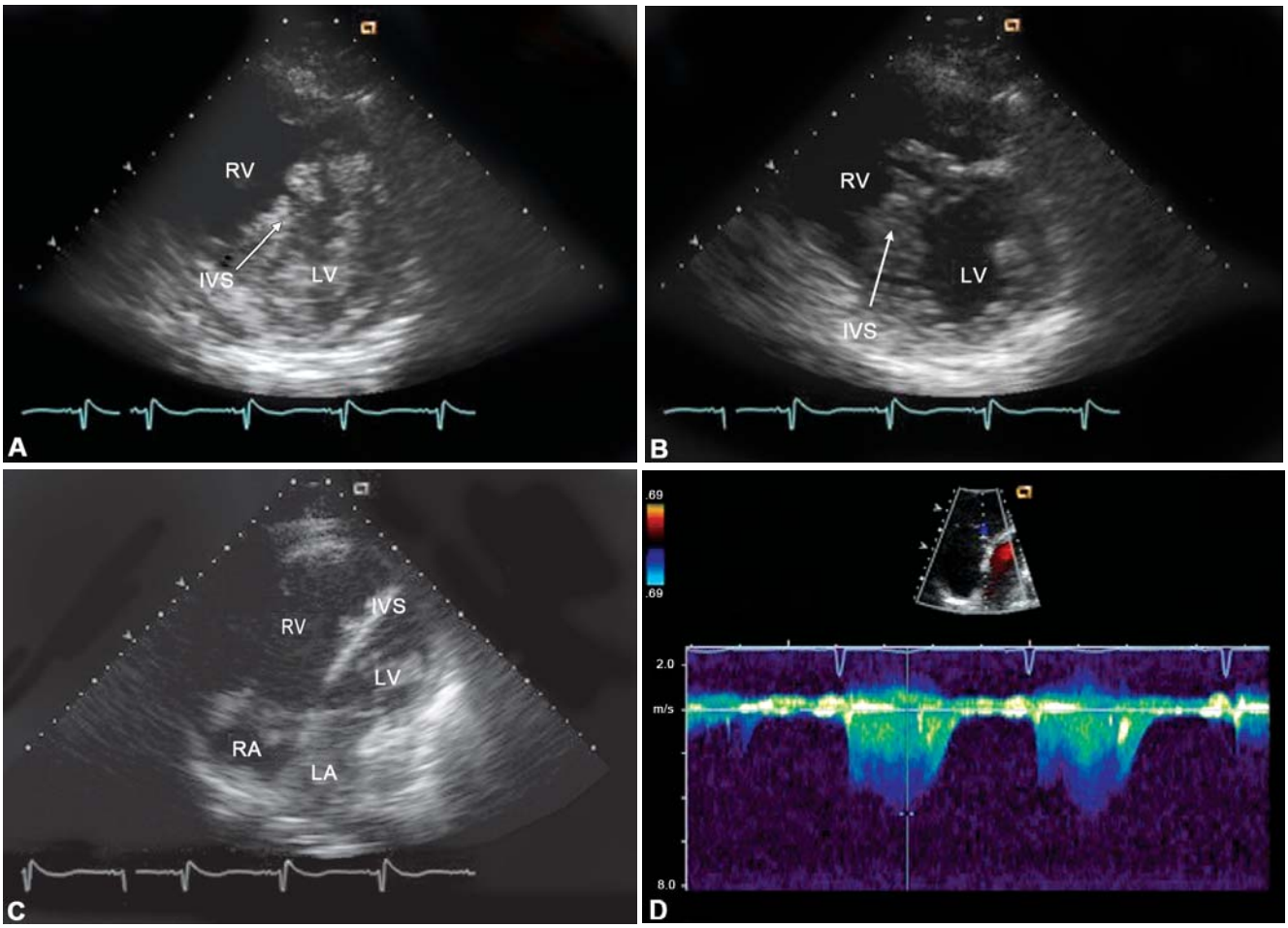


FIGURE 7A TO D: Moderately severe pulmonary arterial hypertension. (A) Parasternal short axis view demonstrates flattening of the IVS during systole, indicating RV pressure overload, (B) but not in diastole. (C) Apical four-chamber view showing moderately to severely enlarged RV. (D) Continuous wave Doppler image of the TR jet velocity of 4.7 m/sec, equivalent to a PASP of 89 mm Hg plus the RA pressure. (Abbreviations: LA: Left atrium; LV: Left ventricle; RA: Right atrium; RV: Right ventricle; IVS: Interventricular septum; TR: Tricuspid regurgitation; PASP: Pulmonary artery systolic pressure)

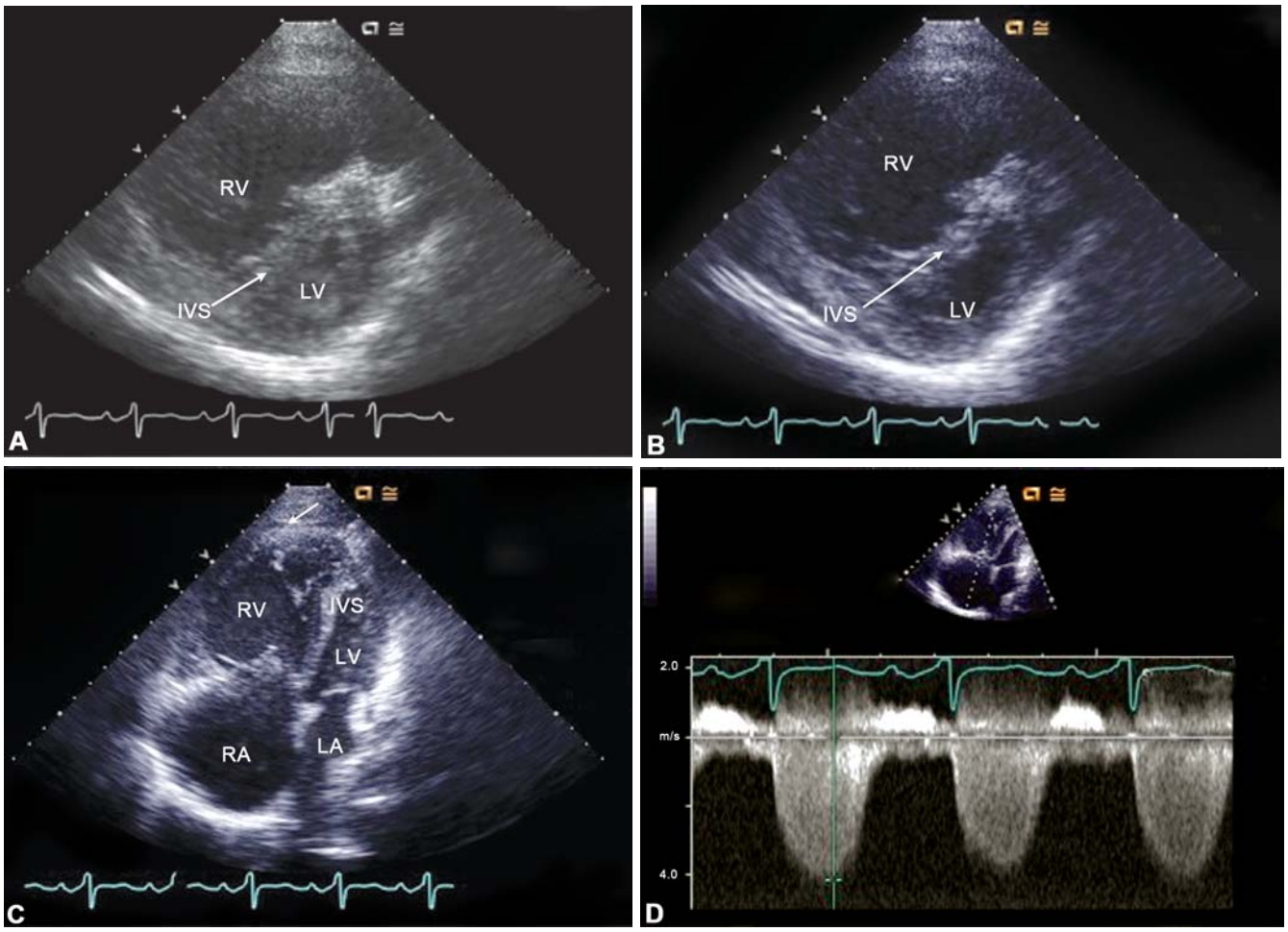
insufficiency of the pulmonary valve. As a result of ventricular interaction or interdependence, an enlarged RV that is pressure and/or volume overloaded often leads to impairment of LV diastolic function. In the vast majority of cases, this results in a Doppler pattern of mild, grade I LV diastolic dysfunction (as evidenced by a transmitral E/A wave ratio of < 1.0). An E wave dominant Doppler transmitral filling pattern (e.g. normal, pseudonormal or restrictive LV filling patterns) in patients with significant PAH are much less common and should raise the suspicion for LV diastolic heart failure as a possible cause of PH.

The pulmonary artery systolic pressure (PASP) can be estimated by the Doppler peak tricuspid regurgitant velocity (TRV)[128] and the RA pressure, which is determined by the size and collapsibility.[129] A TRV of greater than 3.2 m/sec is typically used as the threshold for PH,[121] which corresponds to a PASP of greater than 40 mm Hg. Approximately 20% of patients may not have an adequate tricuspid regurgitant jet to allow an accurate estimation of the PASP and other characteristics, such as septal flattening during systole and RV enlargement may suggest the diagnosis of PH.

Pulsed-wave Doppler in the RV outflow tract may reveal a reduced velocity-time integral, which is a surrogate of RV stroke volume and CO. Agitated saline contrast not only will aid in the diagnosis of congenital systemic-to-pulmonary shunts by indicating right to left shunting, such as ASD and VSD, but may also detect a patent foramen ovale (PFO) in one quarter of patients. The presence of a PFO has been associated with better survival in observational studies of patients with PAH.[130] An atrial septal communication, such as a PFO in patients with PAH, provides a pressure release mechanism or "pop off valve" for a failing RV whereby shunting across the PFO into the left heart chambers can preserve LV preload and CO (at the expense of arterial oxygen desaturation).

The presence of a pericardial effusion is a poor prognostic sign in patients with PAH, probably because pericardial fluid accumulates in PAH patients with RV failure in the setting of right heart failure and high diastolic filling pressure that does not allow resorption of the fluid. The pericardial effusions are rarely hemodynamically significant; however, it should be noted that two-dimensional signs of cardiac tamponade, such as right atrial and RV diastolic collapse, can be masked in the presence of high right-sided pressures from PAH.

Echocardiographic predictors of a poor prognosis include the degree of right atrial enlargement, presence and degree of interventricular septal flattening during diastole (LV eccentricity index), presence of a pericardial effusion, TAPSE less than 1.8 cm, and Doppler global RV index greater than 0.88.[131-135]



FIGURES 8A TO D: Severe pulmonary arterial hypertension. (A) Parasternal short axis demonstrating flattening of the IVS during both systole and (B) diastole, suggesting both pressure and volume overload. (C) Apical four-chamber view demonstrates severe enlargement and hypertrophy of the RV and severe RA enlargement with small, compressed left heart chambers. (D) The RV/RA pressure gradient in this case is estimated to be 69 mm Hg, so depending on the RA pressure, the PASP may be severely elevated, or it could be relatively lower because of RV failure and inability of the RV to generate a higher PASP. (Abbreviations: arrow: RV hypertrophy; LA: Left atrium; LV: Left ventricle; RA: Right atrium; RV: Right ventricle; IVS: Interventricular septum; TR: Tricuspid regurgitation; PASP: Pulmonary artery systolic pressure)

LABORATORY STUDIES

Laboratory evaluation for CTD, HIV infection and liver disease should be performed including serologic studies for antinuclear antibody, HIV and liver function tests. A history of stimulant or toxin exposure, in particular anorexigens, methamphetamines and cocaine should be queried and toxicology studies should be performed if indicated. Thyroid function tests should also be evaluated as hyperthyroidism can contribute to PH (WHO Group 5 PH).

PULMONARY FUNCTION TESTING

Pulmonary function tests with arterial blood gas sampling are helpful to identify patients with obstructive or restrictive lung disease, as well as to measure the DLCO, which is often moderately to severely decreased in patients with significant PAH. DLCO corrected for alveolar volume can be useful in discriminating between SSc related PAH and SSc associated ILD. A disproportionately low DLCO in patients with SSc (Forced vital capacity/DLCO ratio of $\geq$ 1.4) suggests that pulmonary arterial disease may also be present.[15]

If PFT testing indicates the presence of a significant obstructive or restrictive ventilatory defect, then high resolution computed tomography (HRCT) should be considered to evaluate for the presence of COPD/emphysema or ILDs such as IPF, usual interstitial pneumonia, nonspecific interstitial pneumonia and hypersensitivity pneumonitis, etc. (Fig. 9). Dynamic exhalation sequences can help to detect air trapping in small airway disease. In addition to discriminating between pulmonary parenchymal abnormalities, mosaic perfusion abnormalities can be suggestive of the presence of CTEPH, although this finding can also be present in PAH. Interlobular septal thickening is a finding related to interstitial pulmonary edema, which is most commonly seen in patients with left heart failure. However, pulmonary edema in the form of interlobular septal thickening may also be present in patients with the PVOD and PCH. In addition to interlobular septal thickening, other findings supportive of the diagnosis of PVOD or PCH include ground glass opacities and mediastinal lymphadenopathy.[136] Indeed, the presence of interlobular septal thickening on HRCT in a patient with precapillary PH may be the only clue to the diagnosis of PVOD or PCH.[136]

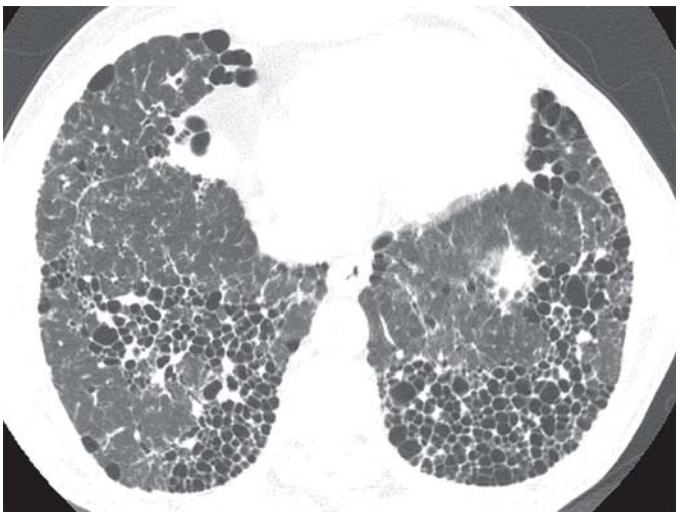


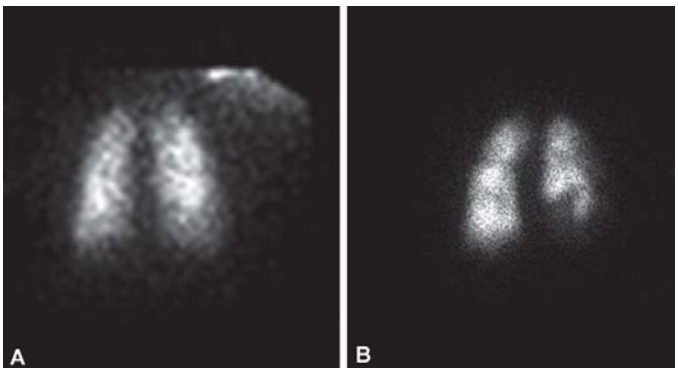
FIGURE 9: High resolution computed tomography of the chest showing severe interstitial lung disease with diffuse honeycombing

NOCTURNAL POLYSOMNOGRAPHY

All patients should be screened for a clinical history suggestive of OSA, such as snoring and daytime somnolence. Those with symptoms suggestive of a sleep disorder should be referred for evaluation with nocturnal oximetry and/or a formal nocturnal polysomnography (sleep study).

SCREEN FOR CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION

All patients with PH should be screened for CTEPH, which in selected patients can be surgically treated. Although chest computed tomographic angiography (CTA) has adequate sensitivity for the detection of acute PE, it can miss chronic thromboemboli affecting the more distal, small pulmonary arteries. The ventilation/perfusion (V/Q) scan has greater sensitivity for detecting chronic pulmonary thromboemboli and is, therefore, the preferred initial screening modality for CTEPH (Fig. 10). A patient whose V/Q scan is suggestive of CTEPH should be further evaluated with chest CTA and/or pulmonary angiography to evaluate the extent and location of pulmonary emboli and to exclude other causes of pulmonary arterial obstruction such as endovascular tumors or extrinsic compression from mass lesions. Chronic pulmonary emboli involving the segmental and subsegmental arteries can often be removed surgically with PEA; however, obstructive lesions affecting more distal pulmonary arteries are not usually surgically accessible.



FIGURES 10A AND B: Pulmonary Ventilation-Perfusion (V/Q) Scan. (A) Ventilation image demonstrating homogenous uptake of radioisotope. (B) Perfusion image demonstrating multiple bilateral peripheral subsegmental mismatched defects consistent with chronic thromboembolic disease

RIGHT HEART CATHETERIZATION

All patients suspected of having PAH by non-invasive studies should have a diagnostic RHC by clinicians trained in its performance and hemodynamic interpretation. In addition to providing confirmation of PH as suggested by echocardiogram and measuring its severity, the RHC provides important prognostic information including RAP, PVR and CO. Determination of the PAWP is of fundamental importance to distinguish between precapillary and postcapillary PH, as the treatment is distinct. If the PAWP is elevated despite multiple attempts and, especially, if blood obtained in the wedge position is not fully saturated, direct measurement of LVEDP should strongly be considered so as not to incorrectly diagnose patients with pulmonary venous hypertension who in fact have PAH. A shunt evaluation with blood oximetry sampling from the superior vena cava and pulmonary artery should be obtained in every case; however, in patients suspected of having CHD, a complete shunt evaluation should always be performed. Coronary angiography is also frequently indicated to exclude coronary artery disease as the potential cause of a patient's symptoms when there are risk factors.

VASOREACTIVITY TESTING

A vasodilator challenge should be performed in all patients with IPAH to identify the small proportion (~12% of IPAH patients) who might respond to calcium channel blocker (CCB) therapy. Common agents used for acute vasoreactivity testing include inhaled nitric oxide (iNO), intravenous epoprostenol and intravenous adenosine. Other vasodilators, such as nitroprusside or CCBs should not be used in cases of precapillary PH due to the possibility of profound systemic hypotension and hemodynamic collapse. In patients with pulmonary venous hypertension from left-heart disease who are being considered for heart transplantation, vasodilator testing with nitroprusside may be performed. A typical vasoreactivity test protocol for PAH is to administer iNO at 20 ppm for 10 minutes after which hemodynamics are reassessed. The current definition of a positive test is defined as a decrease in the mPAP greater than 10 mm Hg to an mPAP to less than 40 mm Hg with near normal or improved CO.[121] In patients with a positive acute vasoreactivity test, hemodynamic assessment to confirm the response to CCBs should be performed before discharging the patient on this therapy. Patients with severe RV failure (cardiac index < 2.2 and/or RAP > 15 mm Hg) are not candidates for CCB therapy because of their negative inotropic properties.

The importance of identifying acute responders is that these patients have near normal survival, which is much better than nonresponders, and compared to PH specific therapies, CCBs are inexpensive and easy to administer. The utility in non-IPAH varies based on subtype and is not well established. Since in most cases the diagnostic evaluation has not been completed

prior to the RHC, most PH centers perform acute vasoreactivity testing during the initial RHC once precapillary PH is confirmed.

SURVIVAL AND PROGNOSTIC FACTORS OF PULMONARY ARTERIAL HYPERTENSION

Due to survival and prognostic factors rarity, determining the epidemiologic characteristics of PAH have been difficult and several registries have been established toward this end. The National Institutes of Health (NIH) established the first prospective registry of PAH and was conducted from July 1981 to August 1988, and followed 194 patients with primary pulmonary hypertension (IPAH, FPAH and anorexigen associated PAH).[137] Patients were treated with conventional therapy at that time, which included oral anticoagulants, diuretics, oxygen, digoxin and CCBs. Mean age at diagnosis was 35 years and median survival was 2.8 years with 1-, 3- and 5-year survival estimates of 68%, 48% and 34% respectively. Mortality rates were significantly higher in patients with NYHA functional classes III and IV symptoms. Predictors of survival included NYHA functional class, mean RAP, mPAP and cardiac index.[137]

Based on the results from the NIH registry, an equation was modeled from baseline hemodynamics to predict likelihood of survival.[137] This equation is still used for estimated survival in untreated patients in lieu of a placebo control group in clinical studies.[138-140] Since the original NIH Registry, several other large cohort studies have greatly improved our understanding of the epidemiology and prognosis of PAH in the modern era with available therapies.

The French Network on Pulmonary Hypertension was a prospective registry that consecutively enrolled 354 patients between October 2002 and October 2003 at 13 centers with IPAH, familial and anorexigen associated PAH.[141] Previously diagnosed patients were receiving various therapies that included prostacyclin analogs, ERAs and PDE5A inhibitors.[141] Of the 56 patients with newly diagnosed PAH at the time of enrollment, the 1-, 2- and 3-year survival rates were 85.7%, 69.6%, and 54.9% respectively. A combined analysis of newly diagnosed patients and patients diagnosed within three years of enrollment showed 1-, 2- and 3-year survival rates of 82.9%, 67.1% and 58.2% respectively. Multivariate analysis demonstrated improved survival with female patients, greater 6MWD, and higher CO.

The multicenter US based REVEAL Registry was initiated in 2006 to identify predictors of short-term and long-term survival in the modern therapeutic era.[142] With enrollment of over 3,500 patients with PAH, it represents the largest such registry thus far. The REVEAL investigators recently published 1-year survival analysis of 2,716 enrolled patients, 47% of whom had IPAH.[142] The mean age of the cohort at diagnosis was 50 years, 79.5% were women, out of which 73% were white. Being a registry, there were no mandated therapies.[4] Prostacyclin analogs were used in 42%, PDE5A inhibitors were used in 50% and ERAs in 47%. Combination therapy was used in 40% of patients. Overall 1-year survival was 91% although survival was substantially worse with high-risk patients.[142] Multivariate analysis of the REVEAL Registry demonstrated that a PVR greater than 32 WU, PoPAH diagnosis, NYHA/WHO functional class IV, men greater than 60 years of age,

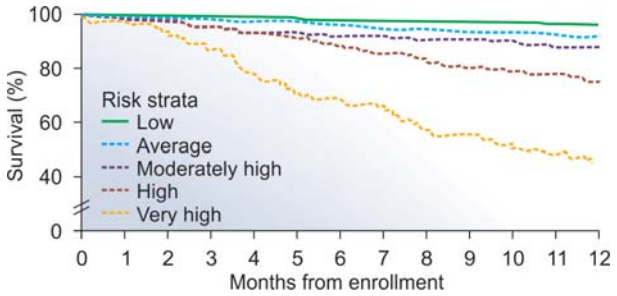


FIGURE 11: Observed one-year survival from time of enrollment according to predicted risk strata from the REVEAL Registry[142]

and family history of PAH were associated with higher mortality.[142] CTD-PAH, renal insufficiency, NYHA/WHO functional class III, resting systolic blood pressure less than 110 mm Hg, resting heart rate greater than 92 beats/min, 6MWD less than 165 m, BNP greater than 180 pg/ml, presence of pericardial effusion, percentage of predicted DLCO less than or equal to 32% and mean RAP greater than 20 mm Hg within the year preceding enrollment were also associated with significantly increased risk of death, as were scleroderma and non-scleroderma CTD subcategories. In contrast, NYHA/WHO functional class I, 6MWD greater than or equal to 440 m, BNP less than 50 pg/ml and percent predicted DLCO greater than or equal to 80% were associated with improved survival. Based on the multivariable analyses, a prognostic equation was derived and validated for predicting 1-year survival and patients were placed into five risk groups determined by fifteen possible risk factors and four possible protective factors. One-year survival in the low, average, moderately high, high and very high-risk groups was greater than 95%, 90–95%, 85–90%, 70–85% and less than 70% respectively (Fig. 11).

In addition to the predictive models generated from the above registries, several small studies have identified many prognostic variables in univariate and multivariate analyses.[143] However, due to the small size of most trials and differences in study design, determining which factors are confounders or independently associated with prognosis is challenging. The variables consistently associated with poor clinical outcome include high mean RAP (> 10–15 mm Hg), functional class III or IV, low cardiac index (< 2.2), tachycardia, reduced 6MWD, the presence of a pericardial effusion, low mixed venous oxygen saturation or hypoxia and low stroke volume index. Serum NT-proBNP levels greater than or equal to 1,400 pg/ml and BNP levels greater than or equal to 180 pg/ml have been associated with worse clinical outcomes and increased mortality.[144,145] Other markers, such as uric acid and detectable cardiac troponin, have also been found to be associated with increased mortality.[146] For patients hospitalized for right heart failure, hyponatremia, low systolic blood pressure and CTD have been associated with increased in-hospital mortality.[147]

Of particular note, the 6MWD is an important predictor of outcomes that is inexpensive, easy to administer in the office setting and results are reproducible. Because of these reasons, the six-minute walk test has been used as the primary endpoint in the majority of therapeutic clinical trials in PAH.[121,148] In a study of 178 patients with NYHA functional class III–IV symptoms who were treated with intravenous epoprostenol,

6MWD less than or equal to 250 m at baseline and less than 380 m after three months of therapy were associated with significantly worse survival.[149] Given the lack of clear cutoffs for worse survival, the American College of Chest Physicians/American Heart Association guidelines use a distance of greater than 400 m to characterize patients as lower risk and patients with a 6MWD of less than 300 m as higher risk.[121] Cardiopulmonary exercise testing has also been used to risk stratify patients, but is more difficult to perform than the 6MWD. However, a peak VO greater than 10.4 ml/kg/min is associated with better clinical course and outcomes.[150]

SURVIVAL IN PULMONARY ARTERIAL HYPERTENSION ASSOCIATED WITH CONNECTIVE TISSUE DISEASE

The survival among patients with PAH associated with SSc is worse than IPAH and other causes of CTD-PAH, with reported 3-year survival rates less than 60%.[80,151] Among patients enrolled in the REVEAL Registry, those with CTD-PAH (n = 641) compared with patients with IPAH (n = 1, 251) had better hemodynamics and favorable RV echocardiographic findings, but a higher prevalence of pericardial effusions, lower 6MWD (300.5 ± 118.0 vs 329.4 ± 134.7 m, p = 0.01), higher BNP levels (432.8 ± 789.1 vs 245.6 ± 427.2 pg/ml, p < 0.0001) and lower DLCO (44.9% ± 18.0% vs 63.6% ± 22.1% predicted, p < 0.0001) respectively. One-year survival and freedom from hospitalization was lower in the CTD-PAH group compared to IPAH patients (86% vs 93%, p < 0.0001; 67% vs 73%, p = 0.03). Patients with PAH associated with CTDs other than scleroderma (SLE, n = 110; MCTD, n = 52; RA, n = 28) when compared to SSc-PAH (n = 399) had similar hemodynamics, lower BNP levels (552.2 ± 977.8 pg/ml), higher DLCO (41.2% ± 16.3% predicted) and better 1-year survival (94% in SLE-PAH, 88% in MCTD-PAH, 96% in RA-PAH, 82% in SSc-PAH).[152] Among patients with SSc-PAH, risk factors for mortality include male sex, late age at diagnosis, pericardial effusion, severity of symptoms and hyponatremia.[80] Although advances in the treatment of PAH have led to increasing numbers of therapeutic options, the response to therapy is limited and survival remains very poor in all patients with CTD-PAH.

SURVIVAL IN HUMAN IMMUNODEFICIENCY VIRUS RELATED WITH PULMONARY ARTERIAL HYPERTENSION

Prognosis and long-term survival with HIV related PAH is worse than with IPAH and patients with NYHA class III–IV symptoms and survival is limited.[90,153] Investigators in France prospectively studied 77 consecutive patients with HIV as their only risk factor for PAH from 2000 to 2008.[87] Eighty percent were on therapy with HAART and 65% received therapy with vasodilator therapy at the time of diagnosis. One-, three- and five-year survival were 88%, 72% and 63% respectively. In multivariate analysis, cardiac index less than 2.8 l/min and lymphocyte count were significantly related to increased mortality.

There is some evidence that treatment with HAART, regardless of CD4 cell count can improve 6MWD, but not hemodynamics.[87] HIV-PAH patients rarely have a positive vasodilator challenge response.[154] Prostanoids and ERAs can produce clinical and hemodynamic improvements in these patients, but the response to PDE5A inhibitors has not been studied and should be used cautiously with patients on therapy with protease inhibitors because of drug-drug interactions.[92]

SURVIVAL IN PULMONARY ARTERIAL HYPERTENSION ASSOCIATED WITH PORTAL HYPERTENSION

A retrospective review of 154 cases of PoPAH in France from 1984 to 2000 demonstrated a 1-, 3- and 5-year survival rate of 88%, 75% and 68% respectively.[98] In multivariate analysis, risk factors for increased mortality included cirrhosis, Child-Pugh B and C score and lower cardiac index. Survival did not appear to be affected by PAH specific therapy in a subgroup of 45 patients and therapy in patients with PoPAH has not been fully evaluated.

Patients with PoPAH have increased mortality as compared to patients with cirrhosis and no PH, and PoPH is one of the greatest risk factors for mortality identified among all patients with PAH in the REVEAL Registry. Patients with PoPAH typically do not have a positive vasodilator challenge and do not typically respond to CCB therapy.[98] Due to mortality rates as high as 90% in patients undergoing liver transplantation with moderate-to-severe PAH, patients who are evaluated for liver transplantation should be screened for PH prior to listing.[155] Therapy with vasodilator agents can improve outcomes and candidacy for liver transplantation and patients who have decrease in mPAP to less than 35 mm Hg and PVR less than 3WU have post-transplant outcomes similar to patients without PoPAH.[156]

SURVIVAL IN CONGENITAL HEART DISEASE ASSOCIATED WITH PULMONARY ARTERIAL HYPERTENSION

While mortality associated with CHD-PAH is high, survival is better than that of IPAH. However, survival is heavily impacted by the type of defect and whether or not palliative surgery has been performed. PAH specific vasodilator therapy, in particular with ERAs, has been shown to improve morbidity and possibly survival.[157,158] However, the use of intravenous prostanoid therapy must be done cautiously given the increased risk of embolic and infectious complications.

SURVIVAL IN PULMONARY ARTERIAL HYPERTENSION ASSOCIATED WITH SCHISTOSOMIASIS

Hemodynamic profiles and survival appear to be better in patients with PAH associated with schistosomiasis than in patients with IPAH regardless of therapy.[106] While schistosomiasis can be effectively treated with praziquantel,[159] the impact of therapy on progression of PAH is unclear and no specific pulmonary vasodilator therapy has been adequately studied in its management.

THERAPEUTIC OPTIONS FOR THE TREATMENT OF PULMONARY ARTERIAL HYPERTENSION

Pharmacologic therapy of PAH has been changed dramatically over the last 20 years since the introduction of epoprostenol in

the 1990s.[148] Conventional therapy with coumadin, diuretics and digoxin, and CCBs are largely based on empiric evidence and retrospective studies. The currently approved disease specific therapies for PAH are directed primarily toward three distinct pathways that are involved in the pathogenesis of PAH, including the endothelin, nitric oxide and prostacyclin pathways. In general, the goals of therapy with these agents are to improve functional capacity, decrease time to clinical worsening and to improve mortality.

There are many challenges to conducting clinical trials in patients with PAH which make interpretation of results and comparisons between trials problematic. Because of the rarity of the disease, studies are frequently underpowered and rely on several centers with few patients enrolled at each center. As baseline 6MWD is correlated with survival, change in 6MWD is often used as the primary endpoint in many trials.[148] However, short-term improvements in 6MWD may not equate with long-term clinical improvements and some trials have shown no correlation between survival or time to clinical worsening and improvements in 6MWD.[149,160] In addition, methodological problems in handling missing 6MWD data and long-term follow-up of responder only populations can complicate the validity of conclusions drawn from studies.[161] However, it is ethically challenging to construct long-term placebo-controlled trials and, in general, investigators are unwilling to conduct such studies due to the clinical improvements seen with active therapy. In the absence of a placebo group, many trials rely on historical controls or predicted survival based on the NIH Registry equation, both of which can lead to overestimation or underestimation of treatment effect. Contemporaneous studies are further complicated by baseline and combination therapy. Despite these concerns, there is compelling evidence from registry data and from meta-analyses that survival has improved in the modern therapeutic era.[161]

ADJUVANT/CONVENTIONAL THERAPIES

Anticoagulation

The pathologic evidence of *in situ* thrombosis and abnormal platelet function provides a rational basis for anticoagulation in patients with PAH,[162] however randomized, controlled trials are lacking. The evidence for favorable effects of oral anticoagulant treatment in patients with IPAH, HPAH or PAH associated with anorexigens is based on retrospective analyses from seven studies, of which five were positive and two were negative.[162-165] The survival of anticoagulated patients selected on the basis of clinical judgment was improved, as compared with a concurrent population that was not treated with oral anticoagulants. Three-year survival improved from 21% to 49% in the series reported by Fuster et al., and the 3- and 5-year survival rates increased from 31% to 47% and from 31% to 62% respectively, in the series reported by Rich et al. Despite the weaknesses in this data related to their non-randomized, uncontrolled nature, anticoagulation is generally recommended to prevent the development of in situ pulmonary arterial thrombosis. Some subgroups of patients may have increased bleeding risk, such as patients with SSc or liver disease, and use of warfarin in these patients should be done with caution. A goal international normalized ratio (INR) of 1.5–2.5[121] is currently recommended for patients with PAH. The role of newer oral anticoagulants, such as dabigatran, is uncertain.

Diuretics

Diuretics are frequently required to control congestion in patients with PAH and RV failure. In particular, loop diuretics, such as furosemide, bumetanide and torsemide, are used in clinical practice. Goals of therapy should be to reduce jugular venous pressure to normal, and eliminate renal venous and hepatic congestion while avoiding hypotension. Care should be taken to closely monitor serum urea, creatinine and electrolytes. In addition to the loop diuretics, aldosterone receptor antagonists, such as spironolactone, can be used in patients to help correct potassium losses and they may have beneficial yet unproven antifibrotic effects on RV myocardium.

Oxygen

Patients with PAH that develop hypoxia should be evaluated for contributing factors, such as concurrent PE or the development of a right to left shunt. To avoid the potential for hypoxic mediated vasoconstriction, oxygen therapy should be commenced when necessary to maintain arterial oxygen saturations above 90% at rest as well as during exercise and sleep.[121]

Digitalis

Digitalis is a cardiac glycoside that leads to increased inotropy through inhibition of the sodium-potassium-ATPase pump, leading to increased sodium concentrations and subsequent increases in intracellular calcium levels. In general, digoxin is administered in patients with evidence of right heart failure or in patients with atrial arrhythmias for whom rate control is indicated.[121] However, data regarding the use of digoxin in PAH is limited to a single study, which demonstrated that the short-term administration of digoxin was associated with increase in CO and reduction in neurohormonal activation.[166] As with all patients treated with digoxin, there is a narrow therapeutic window and the goal serum digoxin concentration should be less than 0.8 ng/ml. Increased vigilance should be maintained for digoxin toxicity in the elderly, women, patients with renal dysfunction and the acutely ill who may develop toxicity at lower serum concentrations.

Calcium Channel Blockers

Patients with IPAH who during RHC have a positive vasodilator may benefit from therapy with CCBs, and 5-year survival can be as high as 95% for those who have clinical response.[163] Patients who have not had a vasodilator study should not be started on CCBs. Typical agents include the dihydropyridines amlodipine or nifedipine or the non-dihydropyridine diltiazem. These drugs should be initiated cautiously as hypotension and hemodynamic collapse can occur. Verapamil should not be used due to its potential negative inotropic effects. Patients being treated with CCBs should have invasive hemodynamics monitored at least yearly to ensure a sustained response (mPAP < 40 mm Hg with normal or near-normal CO and NYHA/WHO class I or II) since a substantial proportion of patients fail to respond long term and should be considered for PAH specific

therapy. Indeed, only approximately 8% of IPAH will continue to respond to CCB therapy over the following year.[154]

DISEASE SPECIFIC THERAPIES FOR PULMONARY ARTERIAL HYPERTENSION

Prostacyclin Analogs

Prostacyclin is generated through the breakdown of arachidonic acid and leads to vasodilation and antiproliferation of pulmonary arterial smooth muscle cells through production of cyclic adenosine monophosphate.[167] Prostacyclin and its analogs also inhibit platelet aggregation. PAH is a prostacyclin deficient state, with arachidonic acid metabolism shifted toward production of thromboxane, which contributes to the pathologic changes. Currently, there are three approved prostacyclin analogs and three different modes of delivery, each of which poses unique challenges.

Epoprostenol (Flolan® and Veletri®), a prostacyclin analog, is administered as a continuous intravenous infusion through a central venous catheter. Flolan was the first FDA approved therapy for PAH and remains the only therapy proven to improve survival. Epoprostenol (Flolan®) has to be reconstituted into solution and it is characterized by a short half-life of 3–6 minutes and instability at room temperature that requires it to be maintained on ice in order to prevent degradation.[168] Recently, room temperature stable (Veletri®) and generic formulations of epoprostenol have been developed, but they have yet to replace the widespread use of brand Flolan. Importantly, because epoprostenol has a short half-life, if the drug infusion is interrupted, patients can develop rebound worsening of PH, which can be life threatening. Likewise, inadvertent bolus administration can lead to life-threatening systemic vasodilation and hypotension.

In the landmark 12-week prospective, randomized, multicenter, open-label trial by Barst et al., 81 patients with IPAH and FPAH were studied in an open-label trial of intravenous epoprostenol versus conventional therapy.[148] Patients, all of whom had NYHA functional class III–IV symptoms at enrollment, were randomized to intravenous epoprostenol plus optimal conventional therapy versus optimal conventional therapy alone. At 12 weeks, patients in the epoprostenol group had significant increases in the primary endpoint of 6MWD from 315 m to 362 m as compared to a decrease from 270 m to 204 m in the control group. The difference in change between the two groups was 60 m. There were significant improvements in mPAP, cardiac index, stroke volume and PVR with epoprostenol therapy. Most importantly, eight patients in the control group and none in the treatment group died during the 12-week study period, the difference of which was highly statistically significant.

Badesch et al. conducted a randomized, controlled, open-label trial of intravenous epoprostenol plus conventional treatment versus conventional treatment alone in 111 patients with moderate to severe SSc-PAH.[169] Patients treated with intravenous epoprostenol experienced an increase in the primary endpoint, 6MWD, from 270 m to 316 m at 12 weeks. Differences in 6MWD were apparent by week 1 and statistically significant by week 6 ($p = 0.003$). At 12 weeks, patients treated with conventional therapy alone experienced a decrease from 240 m to 192 m. The difference between treatment groups in the median distance walked at week 12 was 108 m (95% CI, 55.2–180.0 m; $p < 0.001$).

Although intravenous epoprostenol is being used for PAH associated with other diseases, randomized, placebo-controlled studies demonstrating efficacy and safety in these subgroups of PAH are lacking. It should also be noted that there are limited data regarding the use of epoprostenol in treating other WHO Groups of PH and its use is currently restricted to PAH (WHO Group 1 PH). Moreover, its use can be associated with increased pulmonary shunt flow and hypoxemia in patients with ILD (WHO Group 3 PH) and reduced survival in patients with systolic heart failure (WHO Group 2 PH).[12,170,171]

Due to its longer half-life of 4.5 hours and stability at room temperature, treprostinil (Remodulin®) can offer an alternative to epoprostenol.[168] It was originally developed and studied as a subcutaneous infusion, but currently can be administered as an intravenous infusion, or as an inhaled formulation. When given as a subcutaneous infusion, approximately 85% of patients experience infusion pain and/or infusion site reactions, which can be mitigated by rotating the infusion site. However, 5–23% of patients discontinue subcutaneous infusion due to this complication.[168]

Simonneau et al., conducted a 12-week, double-blind, placebo-controlled multicenter trial in 470 patients with PAH and NYHA functional classes II–IV symptoms who were randomized to subcutaneous treprostinil versus placebo.[172] Patients enrolled had PAH due to IPAH, HPAH, CTD or congenital systemic-to-pulmonary shunts. 6MWD in the treprostinil group improved at week 12 by 10 m but was unchanged in the placebo group with a difference in mean distance walked between the two groups of 16 m (95% CI, 4.4–27.6 m, $P = 0.006$). Improvements in 6MWD were dose dependent. For instance, among the 53 patients in the highest dose quartile (treprostinil dose > 13.8 ng/kg/min), the improvement in 6MWD was 36.1 ± 10 m whereas the 45 patients who received a dose less than 5 ng/kg/min experienced only a 3.3 ± 10 m improvement in the 6MWD. In addition, improvements in walk distance were greatest among the sicker patients but were independent of PAH disease etiology.

Intravenous treprostinil was studied in patients with PAH in the TRUST study, a 12-week placebo-controlled study in India of 44 patients with NYHA class III symptoms due to IPAH and FPAH.[173] 6MWD improved by a placebo corrected median of 83 m in patients treated with treprostinil (95% CI 7.0–187 m, $p = 0.0008$). Treprostinil patients also had a reduction in Borg scale of dyspnea by a median of two units ($p = 0.02$) and improved NYHA class by a median of 1.0 class ($p = 0.051$).[168,172]

Inhaled delivery exists for both iloprost (Ventavis®) and treprostinil (Tyvaso™). Iloprost is administered via the hand-held portable *I-neb* Adaptive Aerosol Delivery System every two hours while the patient is awake for a total of six to nine times daily. It is breath activated and tailors the administration to the patient's breathing pattern to precisely deliver the intended amount of drug. The device also contains a computer microchip, which can be analyzed with insight software that provides useful information such as patient compliance and treatment times. Inhalational treprostinil is administered via an ultrasonic

nebulizer and the total dose is administered in less than one minute with 3–9 breaths. Dosing is four times daily (approximately every four hours while awake).

In the Aerosolized Randomized Iloprost Study (AIR trial), which studied 203 patients with NYHA functional class III–IV symptoms due to IPAH, FPAH, PAH associated with anorexigens or inoperable CTEPH, patients were randomized to inhaled iloprost verus placebo for 12 weeks.[174] Sixteen percent of patients in the iloprost group as compared to 4.9% of the placebo group patients met the combined primary endpoint of improvement by at least one NYHA class and 6MWD increase by 10%, and the absence of clinical deterioration or death. The placebo-corrected change from baseline in 6MWD for patients treated with inhaled iloprost was 36.4 m ($p = 0.04$) in the entire group and 58.8 m in the subgroup of patients with IPAH.

The recently published randomized, double-blind, 12-week placebo-controlled TRIUMPH-1 trial (*TReprostinil* Sodium Inhalation Used in the Management of Pulmonary Hypertension-1) studied inhaled treprostinil in 235 patients with NYHA function class III–IV symptoms with PAH who remained symptomatic on bosentan or sildenafil.[175] At baseline, 70% of patients were on therapy with bosentan and 30% were on therapy with sildenafil. The primary endpoint, or change from baseline to week 12 in 6MWD measured at 10–60 minutes after treprostinil inhalation, was 21.6 m in the treprostinil group and 3.0 m in the placebo group. Between the group median difference was 20 m (95% CI 8.0–32.8 m, $p = 0.0004$). Although quality of life measures and NT-proBNP improved with therapy, there was no change in the secondary endpoint of time to clinical worsening, perhaps because to overall event rate was lower than expected.

The choice of prostacyclin or prostacyclin analog and the route of administration are determined by a combination of degree of illness and patient factors, including strong preference of route, social support, manual dexterity and distance of the patient from hospitals with staff trained their management. Common side effects of prostacyclins and prostacyclin analogs include headache, flushing, jaw pain, nausea, diarrhea, hypotension, dizziness and leg pain. Patients with intravenous catheters are at risk for infection and thrombosis, as well as interruption of therapy. The inhaled agents are commonly associated with a cough.

Endothelin Receptor Antagonists

Endothelin receptor antagonists were the first oral therapy approved by the FDA for treatment of PAH and offered an alternative to the more complex prostacyclin based therapies. Endothelin-1 levels are upregulated in PAH and increased levels are associated with worse survival.[176] The actions of endothelin-1 are mediated via two endothelin receptors, ET-A and ET-B. Although activation of ET-A leads to vasoconstriction and ET-B tends to lead to vasodilatation and release of antiproliferative factors, selective versus nonselective blockade does not appear to affect clinical outcomes.[167,177]

Channick et al. initially evaluated the dual ERA bosentan (Tracleer®) as compared to placebo in a 12-week pilot trial (Study 351) of 32 patients with PPH (IPAH or FPAH) and SSc-PAH, and WHO functional class II–III symptoms.[178] Patients treated with bosentan increased 6MWD at week 12 from 360 m to 430 m. In contrast, placebo treated patients decreased from 355 m to 349 m. The mean change in 6MWD was 76 m further for treated as compared to placebo patients (95% CI 12–139 m, $p = 0.021$). In addition, significant benefits were seen in cardiac index, PVR, mPAP, PAWP and mean RAP. The BREATHE-1 trial corroborated these findings in a pivotal 16-week, double-blind, placebo-controlled randomized trial in 213 patients with WHO functional class III–IV symptoms due to IPAH/FPAH or CTD-PAH.[179] Bosentan resulted in an increase in 6MWD by 36 m whereas patients receiving placebo experienced a decrease in 8 m (mean difference of 44 m) (95% CI 21–67 m, $p < 0.001$). Notably, patients in BREATHE-1 experienced a significantly greater time to clinical worsening as compared to placebo treated patients and 89% of the patients on bosentan were event free after 28 weeks as compared to 63% of the patients treated with placebo ($p = 0.0038$).[179] The 2-year survival rate among 169 patients, who were enrolled in an extension study of these two trials, was 89%, and 70% of these patients remained on monotherapy throughout the study period.[180]

A similar delay in clinical worsening as was seen in BREATHE-1 was also observed in the EARLY study (Endothelin Antagonist Trial in Mildly Symptomatic PAH), which randomized 185 patients with WHO functional class II PAH to either bosentan or placebo for 6 months.[181] The study did not meet the co-primary endpoint of change in 6MWD; however, it did result in a significant improvement in hemodynamics. The EARLY study is the only trial to date to demonstrate efficacy of PH therapies specifically in patients with mild PAH symptoms (WHO functional class II). Post hoc analyses of other clinical trials have indicated that patients randomized to receive placebo never quite "catch up" to those who received investigational PH therapies. Taken together, the results suggest that it is important to identify and treat patients with PAH as early in their disease course as possible.

Ambrisentan (Letairis®), which is an endothelin receptor-A selective antagonist, was studied as an alternative to bosentan. The ARIES-1 and -2 studies were concurrent, randomized, double-blind, placebo-controlled studies that compared different doses of ambrisentan versus placebo.[182] The ARIES-1 trial compared 5 mg and 10 mg of ambrisentan, whereas the ARIES-2 trial compared 2.5 mg and 5 mg of bosentan versus placebo. The majority of patients were functional class II (38%) or III (55%) and had IPAH (42%). The placebo-corrected 6MWD at 12 weeks was significantly improved with all doses of ambrisentan as compared to placebo. As noted in other studies, the improvement in 6MWD was less pronounced in the 21% of patients with CTD-PAH. Time to clinical worsening was also significantly delayed in patients taking ambrisentan as compared to placebo in the combined analysis of ARIES-1 and -2, although the difference were not significantly different in the ARIES-1 trial alone.

Side effects of ERAs include peripheral edema, potential for liver toxicity, anemia, reduced hormonal contraceptive efficacy, reduced sperm count and drug-drug interactions with strong inducers or inhibitors of cytochrome P450 enzymes.

Bosentan leads to dose related increases in liver transaminases in 10–15% of patients.[179,180] For this reason, until

recently the FDA has mandated that liver function tests (aspartate transaminase, alanine transaminase and total bilirubin) be monitored monthly with all ERAs. The rate of elevations in serum aminotransferase levels greater than 3x upper limit of normal in patients taking ambrisentan was zero compared with 2.3% in patients taking placebo (not statistically different) in the ARIES trials. The FDA recently removed the monthly liver function tests monitoring requirement for patients taking ambrisentan based on post-marketing data indicating that it is not associated with increased risk of liver toxicity. However, periodic liver function testing is still recommended as part of the routine management of all patients with PAH, who may develop right heart failure and associated liver dysfunction.

Lower extremity edema can develop in up to 28% of patients treated with ambrisentan and occurs less frequently with bosentan.[179,182] Although the etiology of edema has not been clearly established, it is generally accepted to be related to fluid retention rather than peripheral vasodilation. This side effect can usually be anticipated and controlled with diuretic adjustment without the need for drug discontinuation in most patients, but it may be favorable to avoid initiating these therapies in patients with acutely decompensated right heart failure until the congestion has been adequately treated.

As with other vasodilator therapies, the benefits of therapy with ERAs in other groups of PH are unclear and can result in harm. In a double-blind study of 87 patients with chronic left heart failure and pulmonary venous hypertension as assessed by echocardiography, at 20 weeks there were no hemodynamic improvements in PAP with bosentan, and more patients treated with bosentan stopped therapy due to adverse effects, including worsened heart failure symptoms, and had serious adverse events including death.[10] In addition, the large, randomized, double-blind VERITAS trial, which compared the dual receptor ERA tezosentan with placebo in patients with acute left heart failure found no clinical benefit with therapy.[9] In patients with PH due to severe COPD, bosentan has been found to decrease exercise capacity and to worsen hypoxemia and its use in these patients should be avoided.[183]

Phosphodiesterase Type 5 Inhibitors

Cyclic GMP mediates the downstream effects of nitric oxide by causing pulmonary vascular smooth muscle cell relaxation and vasodilation, as well as having antiproliferative effects. Cyclic GMP is hydrolyzed by PDE5 which is abundant in lungs.[184] Expression of nitric oxide synthase and cGMP activity are reduced in patients with PAH.[185] By preventing the breakdown of cGMP, PDE5 inhibitors prolong the vasodilatory effects of NO, promoting smooth muscle vasodilation and antiproliferation.

Galie et al. tested the safety and efficacy of sildenafil (Revatio) in the SUPER-1 trial (Sildenafil Use in Pulmonary Arterial Hypertension), a 12-week randomized, double-blind, placebo-controlled dose-ranging trial that evaluated 278 patients with IPAH (68%), CTD-PAH and CHD-PAH.[160] The mean placebo corrected 6MWD improved by 45 m (99% CI 21-70, $P < 0.0001$), 46 m (99% CI 20-72, $P < 0.001$) and 50 m (99% CI 23-77, $p < 0.001$) with patients treated with 20 mg, 40 mg and 80 mg three times daily of sildenafil respectively. The improvement in walk distance between patients receiving sildenafil at doses of 20 mg, 40 mg or 80 mg did not differ significantly. Significant improvements in hemodynamics, Borg dyspnea scale and WHO functional class were demonstrated; however, there was no difference in time to clinical worsening. The reason for a lack of demonstrated benefit in clinical worsening is unclear, although the overall event rate was low in the study population. Due to the lack of significant difference in 6MWD among the dosing regimens, the FDA only approved sildenafil for PAH at 20 mg three times daily, although the study had shown a trend toward improved walk distances with higher doses.[186] Because of this finding as well as a trend toward improved hemodynamics in the higher doses, sildenafil is used occasionally at doses of up to 80–100 mg three times daily, if sustained responses are not maintained with lower dosages.

In contrast to sildenafil, tadalafil (Adcirca®) is longer acting with a half-life of 17.5 hours, and can be dosed once daily.[187] The PHIRST (PAH and Response to Tadalafil) trial evaluated 405 patients with idiopathic or associated PAH in a 16-week randomized, double-blind, dose-ranging double-dummy, placebo-controlled trial.[188] Patients were randomized to 2.5 mg, 10 mg, 20 mg or 40 mg daily of tadalafil versus placebo. A statistically significant improvement in 6MWD was only seen in the 40 mg dose strata with mean placebo-corrected treatment effect of 33 m (95% CI, 15–50 m, $p < 0.01$). Additionally, tadalafil at 40 mg daily, but not in the other dosing groups, demonstrated increased time to clinical worsening as compared to placebo ($P = 0.041$). Notably, there were no significant differences in change in WHO functional class or Borg dyspnea score between any of the treatment groups, although improvements in quality of life were seen with 40 mg daily of tadalafil as compared to placebo.

Sildenafil and tadalafil are metabolized by the cytochrome P450 (CYP) 3A4 pathway, although about 20% of sidenafil's metabolism is also by CYP2C9.[189,190] As mentioned above, coadministration with bosentan can increase sildenafil concentrations by approximately 50%.[191] Of particular note, ritonavir can increase exposure to sildenafil by 11-fold.[192] Simultaneous use with other inhibitors of CYP3A4 or CYP2C9, such as ketoconazole, erythromycin, HIV protease inhibitors and grape fruit juice, should be used with caution.[193]

It is an absolute contraindication to use nitrates with any of the PDE5Is as life-threatening hypotension can develop.[194] Patients prescribed sildenafil or tadalafil should be advised to avoid all nitrates including nitroglycerin, glyceryl trinitrate, isosorbide mononitrate and amyl nitrate. In patients who develop acute coronary syndrome, nitrates can be administered with close hemodynamic monitoring 24 hours after the last dose of sildenafil and 48 hours after the last dose of tadalafil, although these time considerations may be longer in patients taking drugs that inhibit PDE5I metabolism.[193-195] Sildenafil has synergistic effects when coadministered with iNO, and can be used to wean patients off the therapy with nitric oxide.[196] Use of alpha-blockers and PDE5Is should be with caution given the potential for orthostatic hypotension.[197]

Clinically relevant side effects of PDE5 inhibitors include headaches, dizziness, nausea and priapism. Sildenafil, and to a lesser extent, tadalafil, can cause epistaxis, possibly through inhibition of platelet aggregation.[198] There have been rare reports

of patients treated with PDE5Is developing anterior ischemic optic neuropathy and optic atrophy, but a causal association has not been clearly defined.[199,200] Patients who develop visual changes while taking PDE5I should seek medical attention and evaluation by an ophthalmologist and discontinue PDE5I use in the event of sudden vision loss. Hearing loss has been reported with use of PDE5Is, but causality and mechanisms remain unclear.[201,202]

INVASIVE AND SURGICAL OPTIONS

Atrial Septostomy

Atrial septostomy (AS) can be a useful strategy to increase CO and unload the right ventricle by creating an interatrial communication to allow right to left shunting in patients with severe RV failure despite vasodilator therapy or intolerance to vasodilator therapy. In addition, in resource poor settings where the cost of vasodilator therapy may be prohibitive, it can be a viable alternative.[203] The procedure can be performed either surgically or in the catheterization laboratory with balloon septostomy; however, a percutaneous approach is preferred in most patients because of the very high risk of surgery.[204] Occasionally, a stent is placed within the AS and gradually dilated in order to better control the size and degree of shunt and to prevent spontaneous closure, which occurs frequently after AS. Few studies have evaluated the impact of AS; however, there have been reports of improvement in hemodynamic parameters, including CO and RVEDP, improvements in 6MWD and NYHA class, and in mortality.[203,205-210] The morbidity and mortality associated with AS are significant, and patient selection is important. The procedure is best considered for patients with recurrent syncope despite pharmacotherapy as a bridge to lung transplantation or palliation in patients who are not transplant candidates. The procedure should not be performed in patients with severely decompensated right heart failure (RA pressure > 20 mm Hg) because the degree of right to left shunting with resultant hypoxemia can be substantial and outcomes are worse. AS should only be performed in centers with experience in its use and management of potential complications.

Lung Transplantation

As medical therapy continues to be associated with high short-term and long-term mortality, the eventual need for lung transplantation should be anticipated early in the course of the disease and patients with advanced disease (WHO functional class III–IV) should be referred to centers that specialize in lung transplantation. Patients who are listed for lung transplantation with PAH are less likely to be transplanted and more likely to die on the waiting list than patients with other diagnoses because of the current lung allocation scoring (LAS) method, which biases against patients with PAH because the clinical characteristics used to calculate the lung allocation score do not reflect the severity of disease and mortality risk in PAH patients. Although the LAS has been revised to help mitigate this bias using hemodynamic data, further revisions that include different thresholds for 6MWD, cardiac index, and RAP are being sought to help reduce this disparity.[211] Patients who undergo lung transplantation for PAH have higher perioperative mortality, reflecting the hemodynamic severity of the disease; however, the long-term post-transplant outcomes among those who survive the first post-transplant year are similar to lung transplant recipients with other indications.[212]

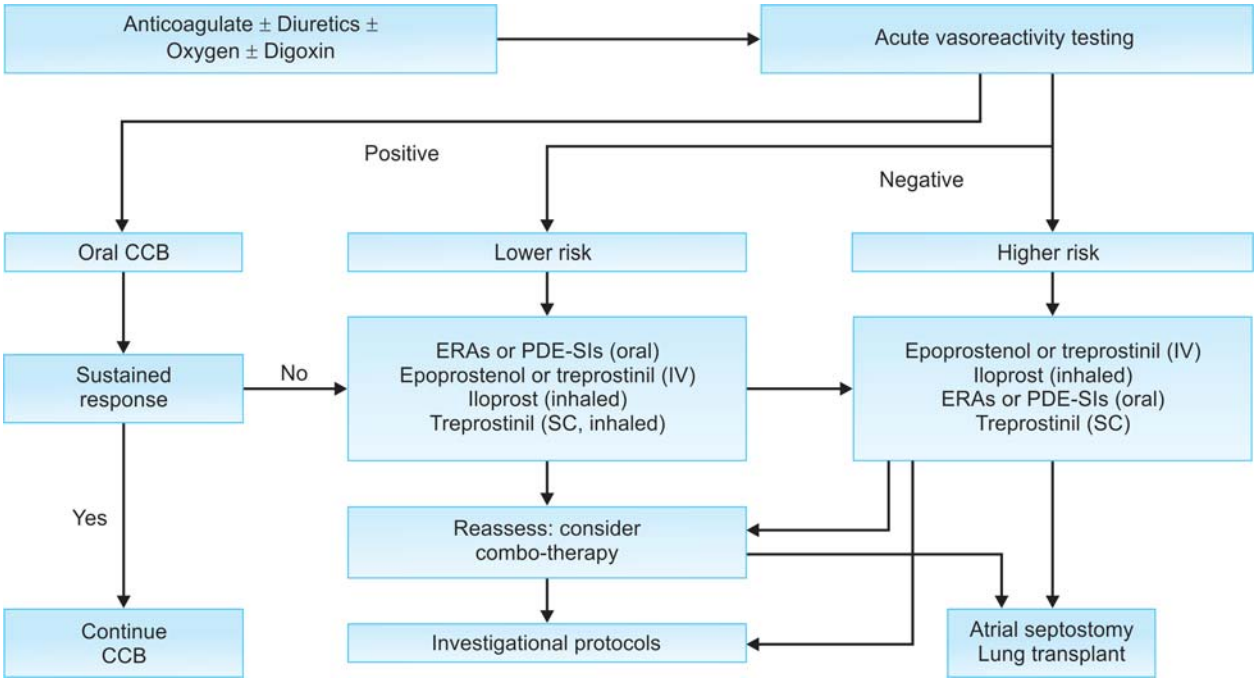
TREATMENT ALGORITHM AND EVALUATING RESPONSE TO THERAPY

Therapeutic decisions should be based on assessment of clinical status, risk factors for deterioration or death and response to vasodilator testing. Flow chart 3 shows the algorithm for the management of PAH as outlined in the latest American College of Cardiology Foundation/American College of Chest Physicians guidelines.[121] In general, anticoagulants are recommended for patients with PAH unless there is a contra-indication. Most patients require diuretics to control right-sided congestion and improve symptoms. Digitalis is often reserved for patients with clinical right heart failure. As noted earlier, oral CCBs are used only in patients with positive vasoreactivity testing, and the drugs should be continued only if there is sustained clinical response with improvement in functional capacity and near normal hemodynamics.

There is emerging evidence that earlier initiation of therapy when patients are mildly symptomatic improves functional and clinical status.[181] The decision to initiate vasodilator therapy, and the specific agents used depend on each patients particular risk profile. For patients deemed to be at low risk for deterioration without high-risk features, initiation with oral agents, either ERAs or PDE5I is acceptable. Patients who are at higher risk, such as those with multiple poor prognostic factors, or for whom rapid decline in function is expected, should be started initially on therapy with prostacyclins.

Theoretically, combination therapy is attractive as targeting the separate pathways (i.e. endothelin, nitric oxide and prostacyclin pathways) may have additive effects. However, there are few studies to guide this approach, and combination therapy is an active area of research.[213] BREATHE-2, a small, underpowered, randomized trial evaluated up-front combination therapy with bosentan versus placebo and epoprostenol in 33 patients with IPAH and CTD-PAH, and NYHA functional class III–IV symptoms. At 16 weeks, there were nonsignificant decreases in the primary endpoint of total PVR. There were also nonsignificant decreased in mPAP, PVR and confidence interval with no difference in change in 6MWD or functional class.[214] The STEP-1 (Safety and pilot efficacy Trial in combination with bosentan for evaluation in pulmonary arterial hypertension) trial randomized 67 patients with IPAH, CTD-PAH and CHD-PAH; NYHA functional class III–IV symptoms and background therapy with bosentan to inhale iloprost versus placebo.[215] At 12 weeks, the post-inhalation placebo-corrected change in the primary endpoint of 6MWD was 26 m ($p = 0.051$). However, there was evidence of delay in time to clinical worsening ($p = 0.02$), which led the FDA to approve combination therapy with iloprost and bosentan in 2005. The COMBI (Combination therapy of bosentan and aerosolized iloprost in idiopathic pulmonary arterial hypertension) trial similarly randomized patients with IPAH on background therapy with bosentan to open-label inhaled iloprost.[216] Patients in COMBI were sicker than those in STEP-1 with higher baseline PVR and lower 6MWD. Despite goal enrollment of 72 patients, the trial was stopped after 40 patients were enrolled due to futility

FLOW CHART 3: Algorithm for the treatment of PAH[121]



(Abbreviations: CCB: Calcium channel blocker; ERAs: Endothelin receptor antagonists; IV: Intravenous; PDE-5Is: Phosphodiesterase type 5 inhibitors; SC: Subcutaneous)

of achieving significant reductions in the primary endpoint of change in 6MWD after 12 weeks. As discussed earlier, the TRIUMPH-1 trial demonstrated significant improvements with inhaled treprostinil in 235 patients on baseline therapy with bosentan or sildenafil in the 12-week post-inhalation 6MWD.[175] However, there was no change in time to clinical worsening. The PACES (Pulmonary Arterial Hypertension Combination Study of Epoprostenol and Sildenafil) study randomized 267 patients with IPAH, anorexigen associated PAH, CTD-PAH and CHD-PAH with predominantly WHO functional class II–III symptoms on stable therapy with epoprostenol to either sildenafil or placebo.[217] Patients treated with sildenafil had a placebo-adjusted increase in 6MWD of 28 m (95% CI 13.9–43.8 m, $p < 0.001$). Time to clinical worsening was also improved with sildenafil therapy ($p = 0.002$ by stratified log-rank test).

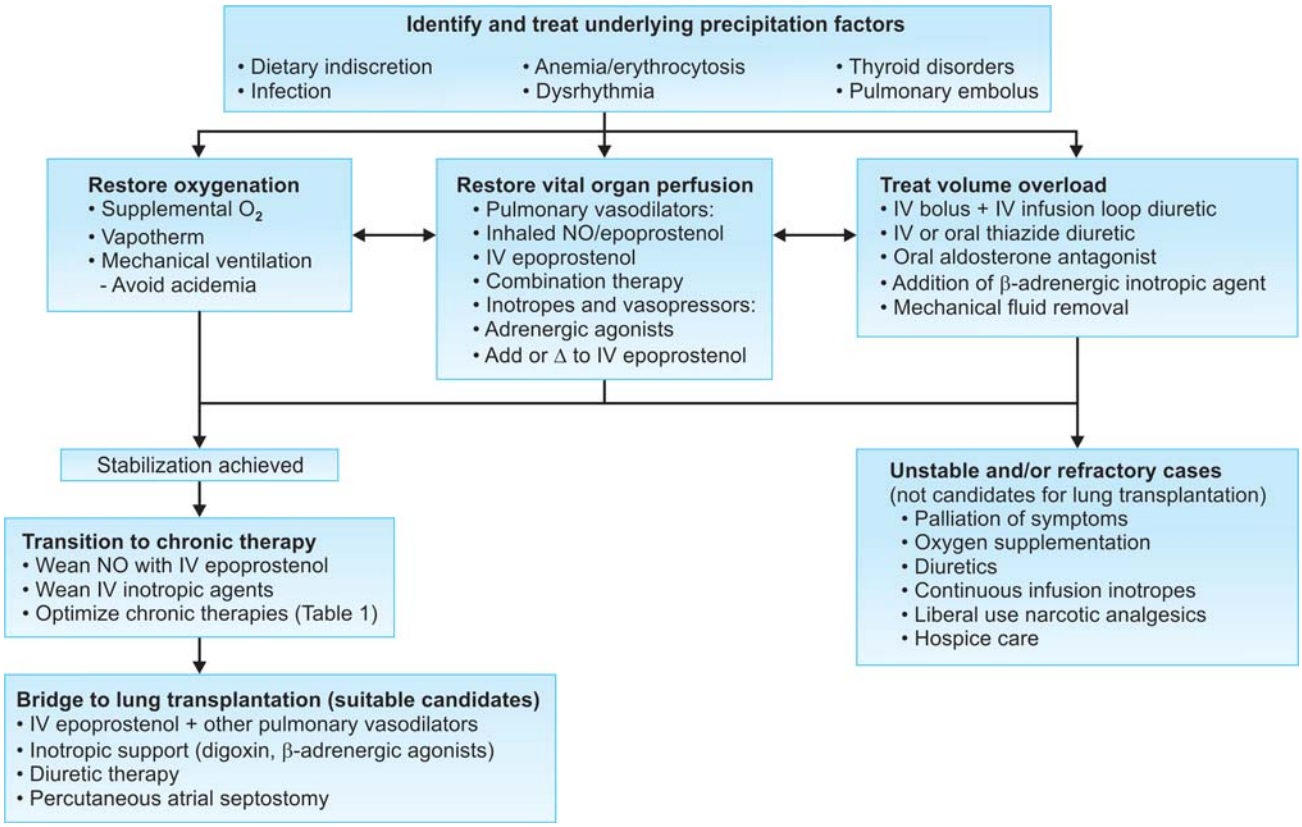
Based on the very poor expected survival and few therapeutic options, as well as the results of the above studies, most PAH specialists will institute combination therapy in higher risk patients, patients who do not improve to functional class I or II, or those patients whose disease progresses while on monotherapy. Patients may experience increased side effects, such as flushing and headaches, with combination therapy and the potential for drug interactions should be closely monitored.

All patients with PAH should be referred to centers of excellence in the management of PAH to ensure accurate diagnosis and help in intiating appropriate therapy. However, in most cases it is best to have patients with PAH co-managed by the local physician and PAH specialist. In general, patients should be evaluated on every 3–6 months for changes in clinical status and evidence of deterioration, or more frequently in patients with functional class III or IV symptoms with right heart failure. Patients, who have been recently started on therapy or discharged after a hospitalization for heart failure, should be seen more frequently, beginning within a week or two of hospital discharge. Clinic visits should include an assessment of blood pressure, heart rate, oxygenation and volume status, with particular attention to elevated jugular venous pressure and evidence of hepatic congestion. The role of serial monitoring of BNP and pro-BNP is not well studied, but can be useful to guide therapy. A six-minute walk test should be measured at each clinic visit and, as discussed earlier, is an important prognostic indicator. Failure to improve 6MWD to greater than 380 m on stable therapy and decreases in 6MWD along with other clinical parameters may signal a need for augmentation of therapy. In general, an echocardiogram should be ordered if there is a change in clinical status or if a new baseline needs to be established following initiation of therapy. The decision to perform annual or routine follow-up RHCs to assess hemodynamics vary from center to center; however, most PAH experts will perform a follow-up RHC if they are considering infused prostanoid therapies or referral for lung transplantation.

THERAPY OF DECOMPENSATED RIGHT HEART FAILURE IN PULMONARY ARTERIAL HYPERTENSION

Patients presenting with acute or progressive right heart failure with decompensation pose a unique clinical challenge. An algorithm for the management of acutely decompensated RV failure in patients with PAH has been outlined in Flow chart 4.

FLOW CHART 4: Algorithm for management of acutely decompensated right ventricular failure



(Abbreviations: IV: Intravenous; NO: Nitric oxide). (*Source:* DeMarco T, McGlothlin D. Managing right ventricular failure in pulmonary arterial hypertension: an algorithmic approach. Advances in pulmonary hypertension. 2005;4(4):16-26)

Patients may present with significant congestion, decreased CO, arrhythmias and syncope. Efforts should be made to distinguish acute decompensation due to progressive right-sided failure as compared to events that can acutely lead to decompensation, such as PE, anemia, thyroid disorders and hypoxia. In patients with a central venous catheter for infusion of a prostacyclin analog, infection should always be considered.

Patients should be monitored in an intensive care unit or transferred to a facility skilled in the management of patients with PAH. A central line can be useful to administer inotropes, measure central venous pressures and to obtain central venous oxygen saturation, which can be used to estimate CO. If central access cannot be obtained, echocardiographic estimates of CO through pulmonary and LV outflow tract velocity time integral can give estimates of CO, which can be helpful to guide therapy.

Management is directed toward decreasing right-sided congestion and elevated filling pressures, while maintaining adequate CO. Patients often present with significant intra-abdominal congestion, which can decrease oral absorption of diuretics. Because of this, intravenous diuretics are required through either continuous infusion or intermittent boluses. Typical doses are 5–20 mg/hr of intravenous furosemide or 0.5–1 mg/hr of intravenous bumetanide. Patients with severe diuretic resistance may require intravenous thiazide diuretics to achieve negative fluid balance. If diuretics are unsuccessful, ultrafiltration can be used cautiously with careful monitoring of blood pressure, renal function and developing hemoconcentration.

Patients who are hypotensive and have evidence of low CO should be treated with inotropes. It is important to note that patients with decompensated right heart failure, who are congested on examination and are hypotensive, will not respond to or improve with intravenous volume infusions. In contrast, giving additional volume will only lead to increased RV size and tricuspid regurgitation, both of which lead to decreased RV CO. Patients with RV failure and evidence of low CO with reduced organ perfusion may respond well to low dose dobutamine at a dose of 1–2 mcg/kg/min; however, it can lead to a drop in the systemic blood pressure. The combination of dobutamine and vasopressin can be effective at increasing CO and organ perfusion while maintaining systemic blood pressure. In patients who are hypotensive at baseline with low CO, agents with both beta- and alpha-adrenergic properties, such as norepinephrine or dopamine are preferred. Every attempt to maintain adequate systemic blood pressure (mean arterial pressure at least 60 mm Hg) to prevent a reduction in coronary artery perfusion pressure and myocardial ischemia that can lead to a vicious cycle of worsening right (and left) ventricular failure, hypotension and shock. Inhaled nitric oxide is another useful, but expensive agent that through selective pulmonary vasodilation can decrease PVR and improve oxygenation by selectively improving perfusion to well ventilated lung segments. Because

iNO is rapidly scavenged by hemoglobin, it has no systemic effects and will not lead to hypotension.

Atrial arrhythmias should be treated by slowing heart rate with amiodarone, digoxin and occasionally the cautious use of CCBs. Beta-blockers and verapamil should not be used as these agents have significant negative inotropic properties and may decrease CO and further exacerbate decompensation. Patients with significant bradycardia or greater than first-degree heart block are at particular risk and should be treated with permanent or temporary transvenous pacemakers as clinically appropriate. Arterial oxygen saturations should be maintained at greater than 92% at rest as well as during exercise and sleep, and there is some evidence that high-flow oxygen even in normoxic patients can reduce PVR and increase cardiac index.[218] While standard criteria for intubation apply to patients with PAH who develop respiratory failure, every effort should be made to avoid the need for intubation as it can lead to variable acute increases in RV afterload, decreases in LV preload and decreases in systemic vascular resistance (the latter related to induction agents), which can lead to rapid deterioration and hemodynamic collapse that can be fatal.[55] When available, intensivists or cardiac anesthesiologists with experience in managing patients with PAH should be present during the intubation. Decreased systemic vascular resistance and hypotension during induction can lead to decreased coronary perfusion pressure, RV ischemia, decreased CO and cardiac arrest. Patients with poor RV function and near systemic to suprasytemic PAPs are at high risk for decompensation. In these patients, treating with intravenous vasopressors such as norepinephrine or epinephrine prior to the development of hypotension should be considered. Once intubated, the lowest level of positive end-expiratory pressure should be used so as not to increase transpulmonary pressures. There is evidence that small degrees of alkalemia may improve pulmonary vasoconstriction and acidemia should be avoided.[219]

If initial measures are unsuccessful and patients continue to have poor tissue perfusion despite inotropes and diuretics, consideration should be given to extracorporeal mechanical circulatory support (MCS), if available. However, MCS should be reserved for patients who may be candidates for lung transplantation or for whom recovery from a reversible event is expected.

CONCLUSION

In summary, PAH is a rare disease with poor survival, especially if left undiagnosed and inadequately. There are many disease states that are associated with PAH, each of which has unique prognosis and epidemiology, but all of which result in similar pathologic manifestations. All patients suspected of having PAH should be screened for other causes of PH, as multiple etiologies can coexist within the same patient, and alternate diagnoses can have a strong impact on therapeutic decisions. Likewise, ensuring that a proper hemodynamic diagnosis is obtained with RHC is essential. Each patient should be risk stratified to help guide prognosis and therapeutic decisions, and close follow-up is required. Therapy for PAH has evolved significantly in the modern era, and outcomes have improved with treatment with prostacyclin analogs, ERAs and PDE5Is. Continued research is needed to further improve the prognostication, treatment and outcome of this devastating disease.

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Chapter 90

Congenital Heart Disease in the Adult Patient

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Chapter Outline

Acyanotic Heart Disease

- Congenital Valvar Aortic Stenosis
  - General Considerations
  - Associated Anomalies
  - Genetic Inheritance
  - Clinical Findings
  - Diagnostic Studies
  - Treatment
  - Prognosis
  - Pregnancy
- Supravalvar Aortic Stenosis and Subvalvar Aortic Stenosis
- Coarctation of the Aorta
  - General Considerations
  - Pathophysiology
  - Associated Anomalies
  - Genetic Inheritance
  - Clinical Findings
  - Diagnostic Studies
  - Prognosis and Treatment
  - Pregnancy
  - Guidelines
- Right Ventricular Outflow Tract Obstruction
- Valvar Pulmonic Stenosis
  - General Considerations
  - Pathophysiology
  - Associated Anomalies
  - Genetic Inheritance
  - Clinical Findings
  - Diagnostic Studies
  - Treatment and Prognosis
  - Pregnancy
  - Endocarditis Prophylaxis
  - Guidelines
- Subvalvar and Supravalvar Pulmonic Stenosis
  - General Considerations
  - Guidelines
- Atrial Septal Defects
  - General Considerations
  - Pathophysiology
  - Associated Anomalies
  - Genetic Inheritance
  - Clinical Findings
  - Diagnostic Studies
  - Treatment and Prognosis
  - Pregnancy
  - Endocarditis Prophylaxis
  - Guidelines
- Ventricular Septal Defects
  - General Considerations
  - Pathophysiology
  - Associated Anomalies
  - Clinical Findings
  - Diagnostic Studies
  - Treatment and Prognosis
  - Pregnancy
  - Guidelines
- Patent Ductus Arteriosus
  - General Considerations
  - Pathophysiology
  - Associated Anomalies
  - Clinical Findings
  - Diagnostic Studies
  - Treatment and Prognosis
  - Pregnancy
  - Guidelines

Other Acyanotic Lesions

- Ebstein's Anomaly
  - General Considerations
  - Associated Anomalies
  - Pathophysiology
  - Genetic Inheritance
  - Clinical Findings
  - Diagnostic Studies
  - Treatment and Prognosis
  - Pregnancy
  - Guidelines

Cyanotic Congenital Heart Disease

- Palliative Shunts
- Endocarditis
- Pregnancy and Contraception
- Tetralogy of Fallot
  - General Considerations
  - Pathophysiology
  - Associated Anomalies
  - Clinical Findings

- — Diagnostic Studies
- — Treatment
- — Prognosis
- — Pregnancy
- — Guidelines
- Truncus Arteriosus
  - — General Considerations
  - — Genetic Inheritance
  - — Clinical Findings
  - — Diagnostic Studies
  - — Treatment and Prognosis
  - — Pregnancy
- d-Transposition of the Great Arteries
  - — General Considerations
  - — Associated Anomalies
  - — Clinical Findings
  - — Diagnostic Studies
  - — Treatment
  - — Prognosis
  - — Pregnancy
  - — Guidelines
- Congenitally Corrected Transposition of the Great Arteries
  - — General Considerations
  - — Recommendations for Evaluation and Follow-up of Patients with Congenitally Corrected Transposition of the Great Arteries
  - — Recommendations for Surgical Intervention
- Total Anomalous Pulmonary Venous Return
- Double-outlet Right Ventricle
  - — General Considerations
  - — Associated Anomalies
  - — Treatment and Prognosis
- Tricuspid Atresia/Univentricular Heart
- Double-inlet Left Ventricle
  - — Fontan Operation
  - — Clinical Findings
  - — Diagnostic Studies
  - — Treatment and Prognosis
  - — Guidelines for Management Strategies in Patients with Fontan Repair
  - — Recommendations for Medical Therapy
  - — Recommendations for Surgery for Adults with Prior Fontan Repair
- Hypoplastic Left Heart
- Eisenmenger's Syndrome
  - — Congenital Heart Disease: Pulmonary Arterial Hypertension
  - — Recommendations for Evaluation of the Patient with Congenital Heart Disease—Pulmonary Arterial Hypertension
  - — Recommendations for Medical Therapy of Eisenmenger's Physiology
  - — Recommendations for Reproduction

Until the mid-20th century, congenital heart disease (CHD) was rarely recognized during life and was a matter of interest only to the pathologist. The advent of cardiopulmonary bypass and the work of pioneer surgeons, such as Dr Robert E Gross and Dr Alfred Blalock, created viable options for patients with congenital cardiovascular heart disease.

The enormous success of congenital cardiovascular surgery has resulted in 85% survival to adulthood among infants currently born with congenital cardiovascular anomalies. It is estimated that approximately one million adults in the United States alone have CHD. The increase in number of adults with these complex conditions requires that cardiologists, managing their care, have a deep understanding of complex anatomy, physiology and the history of evolution of the surgical procedures.

Acyanotic Heart Disease

Acyanotic heart disease includes the following lesions: left-sided heart obstructive lesions, aortic valve disease, subvalvular and supravalvular aortic stenosis and coarctation of the aorta

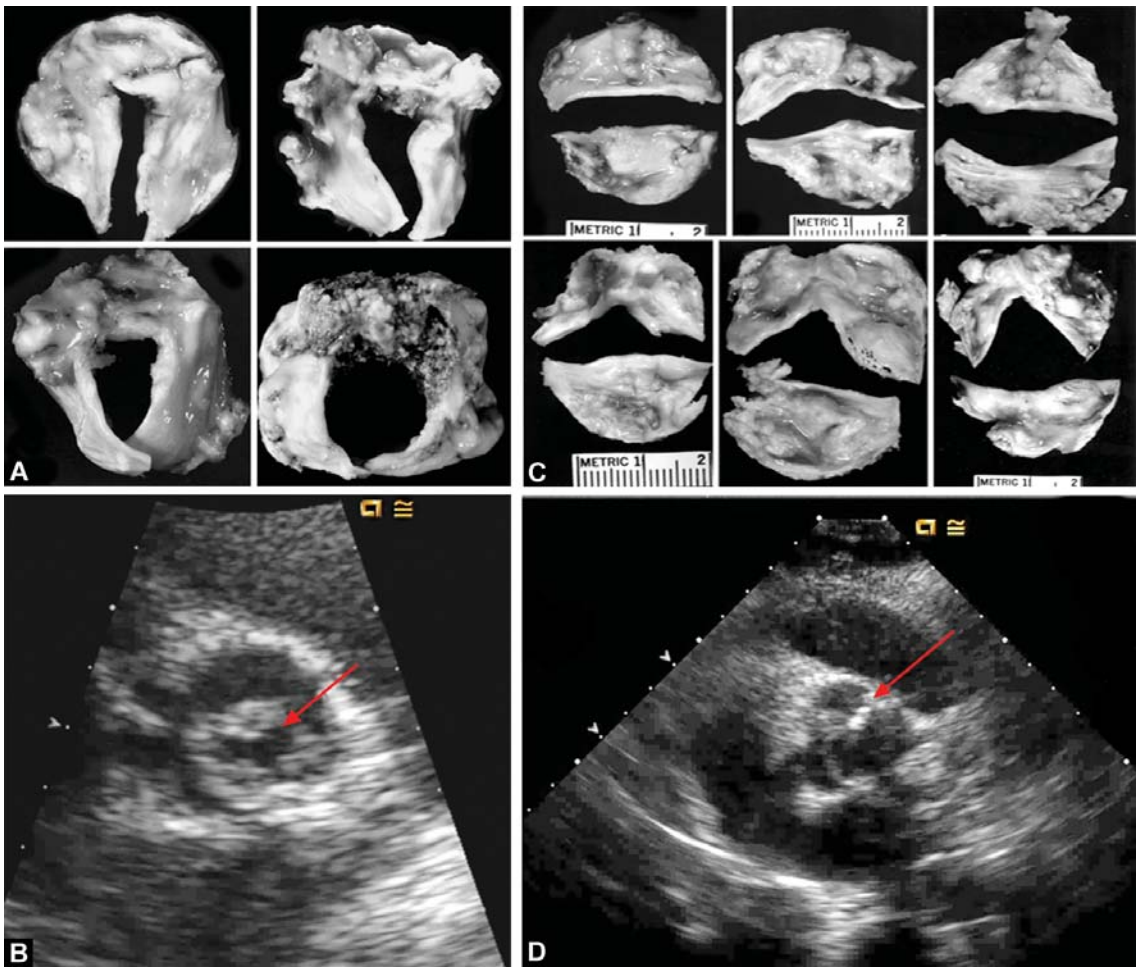
Congenital left-sided heart obstructive lesions can occur at multiple levels in relation to the aortic valve. In order of frequency, there may be valvar aortic stenosis, subvalvar aortic stenosis and supravalvar aortic stenosis. Valvar aortic stenosis is the most common of these congenitally acquired lesions.

CONGENITAL VALVAR AORTIC STENOSIS

GENERAL CONSIDERATIONS

Congenital aortic stenosis in children and young adults occurs secondary to leaflet dysplasia and/or fusion of one or more leaflets, creating a functionally bicuspid or unicuspid aortic valve. Unicuspid aortic valves can produce severe obstruction are more likely to present in infancy or before 1 year of age. Bicuspid aortic valves (BAVs) occur more frequently than unicuspid valves[1] and can be asymptomatic until middle age (Figs 1A to D). The valve is often dysplastic and, with time, may become thickened with rolled and calcified leaflets. As a consequence, stenosis and/or regurgitation develop with a left ventricular (LV) to aortic pressure gradient. The resultant hemodynamic stress may lead to further deterioration of the valve function.

The prevalence of BAV is estimated about 1–2% of the population. The most common fusion is of the right and left coronary cusp, in which case both coronaries arise from the same large anterior sinus.[2] The second most common pathology of fusion is the right and noncoronary cusp, in which case the coronaries arise from two separate cusps. Fusion of the left and



FIGURES 1A TO D: (A) Pathologic specimens from excised valves demonstrating unicommissural morphology. (B) Still frame of parasternal short axis (PSAX) view demonstrating unicommissural valve in end-systolic frame with a "keyhole" appearance (arrow). (C) Excised specimens of bicuspid aortic valves. (D) Still frame of PSAX view at end-systole demonstrating bicuspid valve with fusion of the raphe between the right and left coronary cusps (arrow). (*Source:* Roberts WC, Ko JM. Frequency by decades of unicuspid, bicuspid, and tricuspid aortic valves in adults having isolated aortic valve replacement for aortic stenosis, with or without associated aortic regurgitation. Circulation. 2005;111:920-5, with permission)

noncoronary cusp is rare. The male-to-female ratio is approximately 2–3:1.

The natural history of a BAV depends upon the severity of aortic valve disease and the presence of associated aortopathy. Progressive stenosis usually becomes hemodynamically significant in the fifth and sixth decade of life. Once symptoms of aortic stenosis develop, the prognosis worsens; prompt intervention is indicated at the time of symptom onset. Sudden cardiac death accounts for approximately half of the cardiac-related deaths.

Flow turbulence with valve thickening renders the valve prone to endocarditis, which can result in further leaflet destruction and associated regurgitation.

ASSOCIATED ANOMALIES

The BAV can be associated with subaortic stenosis, parachute mitral valve, coarctation of the aorta, ventricular septal defect (VSD) and patent ductus arteriosus (PDA). Shone's syndrome is the presence of multiple left-sided heart obstructions, which may include subaortic stenosis, BAV, coarctation, parachute mitral valve or supravalvular mitral valve ring. Abnormalities in the elastin of the aortic wall results in pathology of the aorta even in the absence of valvular stenosis.[3] The aortopathy associated with BAV may lead progressive dilatation of the aortic root, formation of an aortic aneurysm, aortic rupture and aortic dissection.

GENETIC INHERITANCE

A mutation in the NOTCH1 gene has been described in families with an inheritance pattern for BAV.[4] It is autosomal dominant with incomplete penetrance pattern.

CLINICAL FINDINGS

Signs and Symptoms

An individual with congenital BAV is usually asymptomatic unless hemodynamically significant stenosis or regurgitation is present. The symptoms are identical to those patients with acquired aortic valve disease. Dyspnea, chest pain and exertional syncope are the classic presenting symptoms.

Physical Examination

A patient with BAV reveals an early systolic click and a crescendo-decrescendo systolic murmur at the second right

intercostal space radiating to the left carotid. With increasing severity of stenosis the murmur will peak later in systole. If complicated by aortic regurgitation there will be an early diastolic murmur over the aortic area. Once stenosis predominates, the carotid upstroke is delayed and diminished, and the systolic click is no longer present. S2 is single.

The finding of upper extremity hypertension should alert the examiner to the possibility of concomitant aortic coarctation. Patients with subvalvular and supravalvar stenosis do not have a systolic ejection click. In supravalvar stenosis, the murmur usually radiates to the right carotid.

DIAGNOSTIC STUDIES

Electrocardiogram and Chest X-ray

Electrocardiogram (ECG) findings depend on the extent of the hemodynamic derangement, which leads to left ventricular hypertrophy (LVH). Left atrial enlargement may also be present.

Chest X-ray findings are also nonspecific. A dilated ascending aorta may be present. The cardiac silhouette may be enlarged in patients with moderate to severe aortic regurgitation.

Echocardiogram

Regardless of the etiology, echocardiography is the primary imaging modality for evaluation of aortic stenosis and aortic regurgitation. Echocardiography along with symptom status evaluation of the patient determines further management and intervention.

On M-mode interrogation, the point of BAV closure may be eccentric. Subaortic stenosis may be associated with early closure of the aortic valve.

Two-dimensional (2D) imaging allows for structural assessment of the valve and location of the fused leaflets as well as the origin of the coronary arteries in young patients. In systole, the valve opening is elliptical which confirms the diagnosis. Imaging in diastole may be misleading as the presence of three raphae may still be detected.

The primary hemodynamic measurement for echocardiographic evaluation of aortic stenosis are: jet velocity, peak and mean transaortic gradients valve area by continuity equation, planimetry of the anatomic aortic valve and velocity ratio [LVOT VTI (left ventricular outflow tract velocity time integral)/AV VTI (aortic valve velocity time integral)].

According to the 2006 ACC/AHA guidelines for the management of patients with valvular heart disease, the severity of aortic stenosis is assessed by jet velocity, mean gradient, valve area by continuity equation and valve area indexed to body surface area (m^2).

The primary echocardiographic parameters for the evaluation of aortic regurgitation are color Doppler jet width, vena contracta width, regurgitant volume, regurgitant fraction, regurgitant orifice area, LV size.

The echocardiographic evaluation of the aorta should be emphasized in patients with BAV. Attention should be given to the sinuses of Valsalva, size of the ascending aorta and presence of coarctation of the aorta.

Magnetic Resonance Imaging and Computed Tomography

Patients with dilated aortic roots must be followed routinely for disease progression. Gadolinium-enhanced magnetic resonance angiography imaging provides an accurate and reproducible alternative for follow-up without exposure to radiation.

Post-repair patients also require routine surveillance of the aorta and repair site for which magnetic resonance angiography is accepted as standard of care.

Catheterization

Given the accuracy of diagnosis of aortic stenosis by noninvasive imaging, the indications for catheterization are as follows:

Cardiac catheterization for hemodynamic measurement is recommended for the assessment of severity of aortic stenosis in symptomatic patients when noninvasive tests are inconclusive or where there is discrepancy between noninvasive tests and clinical findings regarding severity of aortic stenosis.

Coronary angiography should be performed before valve surgery in high-risk individuals.

TREATMENT

Medical

Current guidelines do not recommend endocarditis prophylaxis for the native valve.

Beta-blockers to prevent or delay the aortic root dilatation has been studied only in Marfan syndrome patients with propranolol.[5] It can be extrapolated from this data that patients with aortopathy associated with BAV could benefit from beta-blockers; however, there is no direct evidence to recommend their use except in the setting of hypertension.

In patients with moderate to severe aortic regurgitation, aggressive afterload reduction to reduce LV wall tension with nifedipine and angiotensin-converting enzyme (ACE) inhibitors has been studied and conflicting data exists. There is no data that afterload reduction in these patients delays the need for surgery or intervention[6] and current guidelines recommend their use only in hypertensive patients who are otherwise not candidates for surgery.

Surgical

Decision for intervention is based on the severity of the aortic valve disease and the presence of symptoms. Surgery is indicated in symptomatic patients with severe aortic stenosis and in asymptomatic patients with severe aortic stenosis who require other cardiac surgery or have reduced ejection fraction less than 50%. Asymptomatic patients present more of a dilemma. The need for repeat surgical operation in the future in younger patients needs to be balanced against risk for sudden cardiac death.

The surgical approach to aortic valve disease is, most frequently, aortic valve replacement. There is now increased experience with surgical aortic valve repair and it is now a viable option for selected patients, primarily, with aortic valve

regurgitation. Torn leaflets, prolapsed leaflets and perforated leaflets are more amenable to aortic valve repair.[7,8]

Percutaneous valvuloplasty has been successful in children and adolescents with noncalcified aortic valves. However, in adult patients, the presence of significant calcification often limits the efficacy of this technique even when the underlying pathology is a BAV.[9]

Patients with BAV and concomitant annuloaortic ectasia may show a more rapid progression of aortic regurgitation and require surgical intervention earlier than those patients with aortic stenosis.

PROGNOSIS

The natural history of congenital aortic stenosis depends largely on the severity of the stenosis at the time of diagnosis. During a 25-year follow-up period one-third of the children with a peak gradient less than 50 mm Hg required surgery. Eighty percent of children with an intermediate gradient (50–79 mm Hg) require surgery. The overall 25-year survival rate is approximately 85%; sudden cardiac death accounts for one-half of the cardiac related deaths.

Once the need for surgery is determined, the difficult decision is the ideal replacement type of aortic valve. Homografts and bioprosthetic valves can develop rapid calcific degeneration and require redo surgery particularly in the younger cohort. Mechanical valves are extremely durable; however, require lifelong anticoagulation. The Ross procedure (autologous pulmonary valve replaces the aortic valve and a homograft valve replaces the pulmonary valve) has been increasingly performed for a variety of left ventricular outflow tract (LVOT) disease. The procedure is more complex; it can be performed with low mortality by experienced surgeons. Its advantages are freedom from anticoagulation and growth of the autograft. The Ross procedure is primarily performed in infants and children; however, is an alternative in adults. Increasingly recognized late sequelae include, dilatation of the neoaortic root, pulmonary conduit stenosis and neoaortic valve regurgitation.[10] The reoperation rate at 10 years for these sequelae is as high as 20–30%.[11]

PREGNANCY

Women with mild aortic stenosis and normal LV function can be carried through term with conservative medical management throughout pregnancy.

Symptomatic women with moderate to severe aortic stenosis should be advised to delay conception until the aortic stenosis has been treated surgically.

A difficult medical situation is the asymptomatic woman with severe aortic stenosis contemplating pregnancy. Valve replacement prior to pregnancy should be considered if there is evidence of LV dysfunction or reduced exercise tolerance. If a woman, who was asymptomatic prior to pregnancy, develops new symptoms balloon valvotomy prior to labor and delivery may be required. This is a high-risk procedure for both mother and the fetus and should be performed in centers with experience.

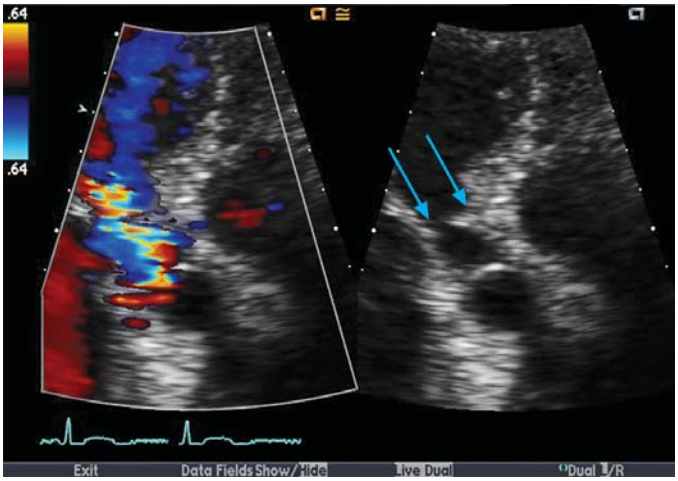


FIGURE 2: Magnified apical long axis view demonstrating aortic regurgitation jet (left panel) and subaortic membrane attached to both the anterior mitral leaflet and septum (arrows) (right panel)

SUPRAVALVAR AORTIC STENOSIS AND SUBVALVAR AORTIC STENOSIS

Congenital subvalvar aortic stenosis in the adult is most often due to a fibrous membrane below the aortic valve or in the LVOT. Tunnel stenosis is more likely to present in childhood. Similar to congenital valvar aortic stenosis, subvalvar aortic stenosis is more common in males.

Subvalvar stenosis appears to be a progressive disease, some physicians consider it an acquired rather than a congenital lesion and it is the underlying distorted LVOT anatomy, which creates flow turbulence and progressive fibrosis and scarring (Fig. 2). Most patients have associated aortic regurgitation secondary to trauma to the leaflets from the high velocity jets. Definitive therapy includes surgical correction; balloon dilatation does not correct these defects.

Supravalvar aortic stenosis is the least common level of LVOT obstruction. It may be associated with congenital valvar aortic stenosis, approximately 8–14% of patients with congenital valvar aortic stenosis have supravalvar aortic stenosis.[12] The stenosis can be localized or diffuse. The histopathology is consistent with a dysplastic medial layer and disorganized elastin fibers.

Supravalvar aortic stenosis is associated with other cardiovascular abnormalities such as coarctation of the aorta, coronary artery stenosis, dysplastic aortic valve leaflets.

It is associated with Williams syndrome.[13] Williams syndrome occurs from a mutation in the elastin gene is characterized by varying degrees of mental retardation, elfin facies, hypercalcemia, loquacious personality, sensitive hearing and supravalvar aortic stenosis.

COARCTATION OF THE AORTA

GENERAL CONSIDERATIONS

Coarctation of the aorta is a stenosis of the proximal descending thoracic aorta (usually adjacent to the origin of the subclavian artery) or the abdominal aorta. The most common location is

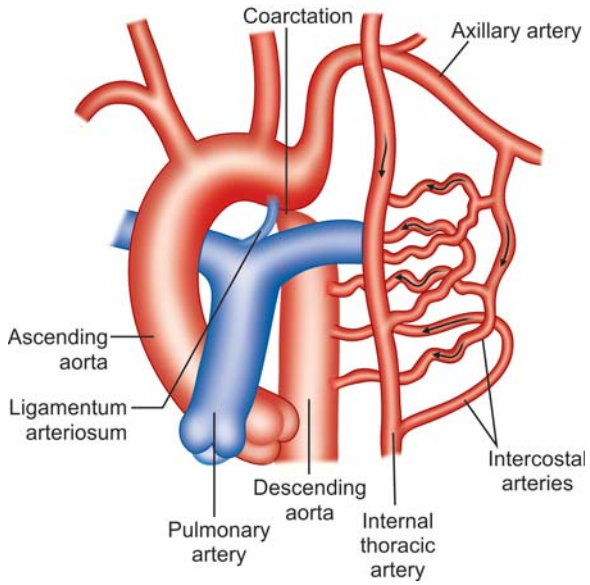


FIGURE 3: Coarctation causes severe obstruction of blood flow in the descending thoracic aorta. Collateral channels from the axillary and internal thoracic arteries through the intercostal arteries (arrows) perfuse the descending aorta and its branches. (*Source:* Brickner ME, Hillis LD, Lange RA. Congenital heart disease in adults. First of two parts. N Engl J Med. 2000;342:256-63, with permission)

distal to the origin of the left subclavian artery (postductal); however, an uncommon manifestation of this disease is stenosis proximal to the left subclavian artery (preductal) (Fig. 3). Multiple discrete sites are rarely encountered. There can be a considerable variability in the degree and extent of narrowing, ranging from a localized shelf to a long tubular narrowing or with considerable arch hypoplasia. Coarctation of the abdominal aorta is well described in the literature; however, is far less common and is often acquired.

Coarctation of the thoracic aorta is a fairly common defect accounting for 5% of all the congenital heart lesions. It is two to five times more common in males than in females. Natural history of unrepaired coarctation of the aorta shows a mean age of death of 34 years.[14] Fifty percent of these uncorrected patients died secondary to proximal aortic rupture before the age of 30 years, and cerebral hemorrhage often occurs before the age of 30 years.

Coarctation of the aorta is usually diagnosed during childhood in the asymptomatic phase by routine examination of blood pressure and femoral pulse palpation. In the case of severe obstruction, children can present with congestive heart failure (CHF). The clinical presentation in early adulthood may include upper extremity hypertension, claudication, headaches and symptoms and signs of left heart failure.

PATHOPHYSIOLOGY

The pressure in the aorta proximal to the coarctation is increased leading to upper extremity hypertension and reduced blood flow to the lower body. Collateral circulation to the distal aorta develops mainly via the subclavian and intercostal arteries in addition to the vertebral and anterior arteries. Extensive collateral supply to the distal aorta in the older child or adult may restore the femoral pulse to near normal, although there still may be a considerable delay in pulse arrival and the systolic pressure in the lower extremities is reduced. The left ventricle develops concentric hypertrophy in response to pressure overload, which can lead to diastolic dysfunction and eventually heart failure.

Intrinsic abnormalities of the aortic wall predispose the patient to risk of dissection or rupture of the ascending aorta, or at the site of coarctation even following repair.

ASSOCIATED ANOMALIES

Coarctation of the aorta is often associated with an abnormal aortic valve, most commonly a bicuspid valve, which occurs in up to 50% of patients. Left-side heart obstruction may occur at other levels including discrete subaortic stenosis and parachute mitral valve. When more than one level of obstruction is present, this is termed Shone's syndrome. Additional associated conditions are VSD and berry aneurysms in the circle of Willis occur in 3–5% of the patient with coarctation.[15]

A preductal coarctation can be present in combination with an anomalous origin of the right subclavian artery distal to the coarctation, and thus the pressure in the right arm may be lower than that of the left arm.

Up to 10% of individuals with Turner syndrome have a coarctation of the aorta, which appears to be more common in those with 45,X than in those with mosaicism.

GENETIC INHERITANCE

Recent data suggests a hereditary component in some cases, with an increased occurrence in twins, siblings and first-degree relatives.[16] A possible environmental influence is seen with an increased incidence of coarctation in the late fall and winter months.[17] NOTCH1 mutations have been identified in association with BAV.

CLINICAL FINDINGS

Signs and Symptoms

The clinical presentation of the disease can vary in the adult. Patients with isolated coarctation of the aorta are usually asymptomatic and diagnosis is commonly made on routine physical examination presenting with hypertension. There may be exertional dyspnea, headaches, epistaxis and claudication or leg fatigue.

Occasional acute catastrophic presentations may include aortic rupture or dissection of the proximal thoracic aorta or an aneurysm distal to the coarctation. Less common is infective endocarditis on the associated BAV or endarteritis at the site of coarctation and subarachnoid hemorrhage associated with rupture of berry aneurysm.[15]

Physical Examination

The systolic blood pressure is elevated in the right arm and usually in the left arm (postductal) with reduced systolic blood pressures in the lower extremities. Diastolic blood pressures are generally unaffected. Delayed arrival of the femoral pulse is noted during simultaneous palpation of the brachial and femoral

pulses. Adult patients with highly developed collateral circulation may not have reduced lower extremity pressure but will still exhibit brachial to femoral delay.

Cardiac examination reveals a nondisplaced, but is sustained LV impulse. The first heart sound is normal; the aortic component of the second heart sound may be accentuated. Jugular venous pulse is normal. Carotid upstrokes are brisk. A late systolic murmur, heard best between the scapulae, might be heard as a result of the coarctation. An ejection click and a systolic murmur may be associated with BAV along with a blowing diastolic murmur associated with aortic regurgitation.

Every patient with systemic arterial hypertension should have the brachial and femoral pulses palpated simultaneously to assess timing and amplitude evaluation for the "brachial-femoral delay". Supine bilateral arm blood pressures and prone leg blood pressure should be measured.[18]

DIAGNOSTIC STUDIES

Electrocardiogram and Chest X-ray

The ECG is nonspecific with LVH and in later stages left atrial enlargement. As in other patients with long-standing hypertension, atrial fibrillation may occur but is uncommon.

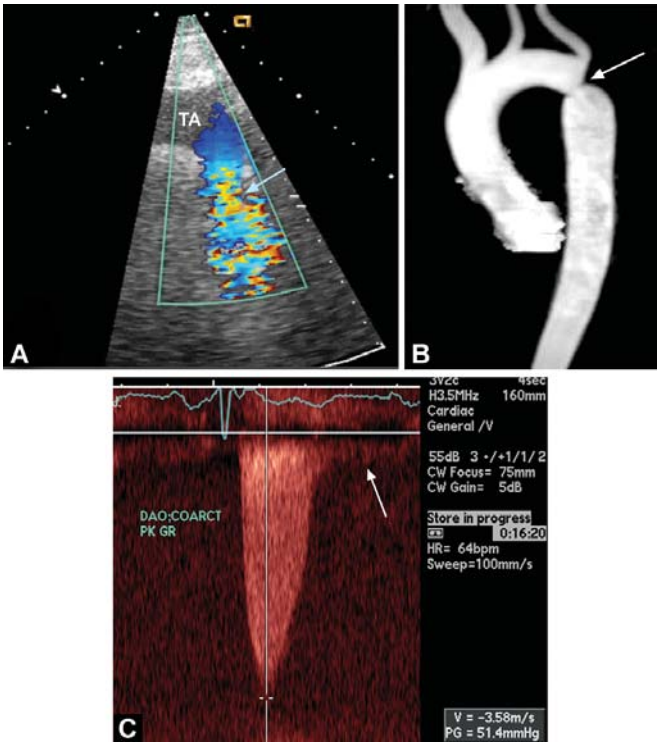
The finding of rib notching is highly specific for coarctation of the aorta. Notching is present on the bottom of the rib where the intercostal arteries are located. In patients with preductal coarctation, the notching is present only on the right side. Another classic radiographic finding is the "3" sign, with the dilated left subclavian forming the upper curvature and the dilated distal aorta forming the lower curvature.

Echocardiogram

It is difficult to visualize the region of coarctation and its presence may be missed if routine suprasternal notch images are not obtained. Doppler evidence of flow acceleration in the descending aorta can be useful even when the 2D images are suboptimal (Figs 4A to C). The peak systolic velocity can be used to estimate the gradient, but the presence of persistent antegrade flow in diastole and decreased acceleration time beyond the coarctation provide additional confirmation of hemodynamic significance. Localization of the coarctation is possible with multiplanar transesophageal echocardiography (TEE). The anatomy of the aortic and mitral valve should be carefully examined to exclude BAV and parachute mitral valve.

Magnetic Resonance Imaging and Computed Tomography

Gadolinium-enhanced cardiac magnetic resonance angiography can localize, define and magnify the extent of the coarctation. It provides an estimate of the extent of collateralization, which is helpful in therapeutic decision-making (Fig. 4B). Computed tomography (CT) angiography provided excellent anatomic definition; however, it does not provide physiologic information. Patients with coarctation often require a lifetime of repetitive imaging and, therefore, careful thought to radiation exposure should be given.



FIGURES 4A TO C: (A) Suprasternal notch view demonstrating flow acceleration by color Doppler through the narrowed region of coarctation (arrow); (B) corresponding image from magnetic resonance angiography of the aorta demonstrating discrete coarctation; (C) continuous wave Doppler peak velocity of 3.5 m/sec through region of coarctation in descending aorta with diastolic runoff (arrow). The gradient, as estimated by the modified Bernoulli's equation, may not correlate with invasively measured gradient, although the presence of diastolic runoff suggests hemodynamically significant coarctation. (Abbreviation: TA: Transverse aorta)

Patient with repaired coarctation should be evaluated by magnetic resonance imaging (MRI) or CT angiography at intervals of 5 years or less, depending on the specific anatomic findings before and after the repair.[18]

Catheterization

Aortography for diagnosis is only necessary when all of the noninvasive imaging methods are inconclusive. When surgical repair is planned, it is reasonable to perform coronary angiography in men 35 years or older, or premenopausal women 35 years or older, or older women who have coronary risk factors.[18]

Cardiac catheterization with percutaneous intervention is often an essential part for treatment.

PROGNOSIS AND TREATMENT

Medical

All patients require aggressive blood pressure and risk factor therapy. Medical therapy should be geared toward treating hypertension with beta-blockers, ACE inhibitors or angiotensin II receptor blockers as first-line medications. When hypertension persists following either percutaneous or surgical intervention, these medications should be continued.

Surgical and Interventional Correction

Early detection and repair are highly desirable because early repair will prevent the associated accelerated development of coronary artery disease and decrease the likelihood of persistent hypertension. The repair strategy often depends upon the age of presentation as well as the anatomy and location of the coarctation.

Children often undergo surgical correction.[19] The removal of the abnormal coarctation followed by end-to-end anastomosis is the most desirable procedure. The morphologic variability has precluded the dominance of any one single method. The repair depends on the length of the coarctation and the location of the subclavian artery relative to the coarct.

Surgery for correction in patients, over the age of 15 years, can be challenging because of huge intercostal aneurysms and atheromatous changes in the shelf near the coarctation site.[19] Hypertension persists in approximately one-third of the patients operated upon after the age of 14 years. Over the last 10 years, endovascular repair of coarctation has grown in popularity. Compared with surgery, endovascular stents have similar morbidity and mortality but are associated with higher degree of recoarctation, need for repeat interventions, and persistent hypertension.[19,20] In the light of these differences, there is ongoing controversy about the best treatment. It is generally accepted that recoarctation in adults can be managed by percutaneous balloon angioplasty with or without stent implantation. Morbidity in adults with reoperation can be considerable and severe including aneurysm formation at the repair site after the use of a Dacron patch and false aneurysms at the repair site.[21] There have been reports of late ruptures of these aneurysms, so they should be repaired.[22] Paraplegia is an uncommon but can be seen in patients with poor collateral circulation as a result of spinal cord ischemia. Subclavian steal syndrome is rare; however, it is noted primarily after subclavian flap technique.

Treatment of coarctation, either primary or repeat, is indicted if (a) the peak-to-peak coarctation gradient is greater than or equal to 20 mm Hg, or (b) peak-to-peak coarctation gradient is less than 20 mm Hg in the presence of significant coarctation with radiological evidence of significant collateral flow.

The causes of late cardiovascular deaths include coronary artery disease, sudden death, aortic regurgitation, hypertension and heart failure and stroke.

PREGNANCY

It is essential to screen women of childbearing age for post-repair aortic dilatation because of high risk of rupture during pregnancy. The concern is about the integrity of the para-coarctation tissue in these young women. Now, in these patients consideration for removal of the para-coarctation tissue is given.

The need for screening pregnant women for intracranial aneurysms is controversial.[23]

GUIDELINES

Class I

- Intervention for coarctation is recommended in the following circumstances:
  - — Peak-to-peak coarctation gradient greater than or equal to 20 mm Hg. (*Level of Evidence: C*)
  - — Peak-to-peak coarctation gradient less than 20 mm Hg in the presence of anatomic imaging evidence of significant coarctation with radiological evidence of significant collateral flow. (*Level of Evidence: C*)
- Choice of percutaneous catheter intervention versus surgical repair of native discrete coarctation should be determined by consultation with a team of adult congenital heart disease (ACHD) cardiologists, interventionalists and surgeons at an ACHD center. (*Level of Evidence: C*)
- Percutaneous catheter intervention is indicated for recurrent, discrete coarctation and a peak-to-peak gradient of at least 20 mm Hg. (*Level of Evidence: B*)
- Surgeons with training and expertise in CHD should perform operations for previously repaired coarctation and the following indications:
  - — Long recoarctation segment. (*Level of Evidence: B*)
  - — Concomitant hypoplasia of the aortic arch. (*Level of Evidence: B*)

Class IIb

Stent placement for long-segment coarctation may be considered, but the usefulness is not well established, and the long-term efficacy and safety are unknown. (*Level of Evidence: C*)

RIGHT VENTRICULAR OUTFLOW TRACT OBSTRUCTION

The obstruction within the right ventricular outflow tract (RVOT) can occur at the pulmonary valve level (valvar), above the valve and at the branch pulmonary arteries (supravalvar), or below the pulmonary valve. The most common of these is valvar pulmonic stenosis (PS).

VALVAR PULMONIC STENOSIS

GENERAL CONSIDERATIONS

The normal pulmonary valve has three leaflets. Congenital pulmonary valve stenosis is characterized by a conical or dome shaped valve formed by the fusion of the valve leaflets. The valve may be tricuspid, bicuspid, unicuspid or dysplastic. Acquired PS is rare but may occur with rheumatic disease and carcinoid heart disease; these conditions have not been discussed in this chapter.

Valvar PS is the second most common form of CHD and comprises 7% of all congenital heart lesions in adults.[24,25]

The natural history of the isolated mild PS is benign and rarely progresses to severe obstruction.[26] Patients with moderate to severe PS can be improved by valvotomy or surgery with excellent prognosis. The goal of a clinician is to treat those in whom it is moderate or severe, and follow-up on those with mild disease intermittently.

PATHOPHYSIOLOGY

Pulmonary stenosis causes pressure overload to the right ventricular (RV), which develops hypertrophy. When the hypertrophy extends to the infundibulum, there may be secondary

dynamic subpulmonic stenosis. RV failure and systemic venous congestion can occur late in the course of the disease.

Also, if an associated patent foramen ovale (PFO) or atrial septal defects (ASDs) is present and RV compliance is reduced sufficiently, a subsequent elevation in right atrial pressure will allows right-to-left shunting and cyanosis. This also increases the risk of paradoxical emboli.

ASSOCIATED ANOMALIES

Congenital PS often coexists with other congenital cardiac abnormalities such as ASD, VSD or PDA. PS may also occur as a part of a more complex congenital heart process such has tetralogy of Fallot (TOF), aortic valve (AV) canal defect, double-outlet RV and a univentricular heart.

GENETIC INHERITANCE

Pulmonic stenosis, secondary to dysplasia of the valve leaflets, is most often present in Noonan syndrome, an autosomal dominant disorder associated with pectus carinatum, short stature, developmental delay, hypertelorism and webbed neck.[27,28] These valves are often stenotic and require repair during childhood.

Congenital rubella syndrome occurs via maternal fetal transmission of maternal viremia. The syndrome refers to a constellation of birth defects including CHD (most common defects PS or PDA), hearing impairment, cataracts and retinopathy.

CLINICAL FINDINGS

Signs and Symptoms

Patients with severe PS usually have exercise intolerance and present with exertional fatigue, dyspnea or chest pain. Exertional syncope or light-headedness may occur if there are systemic or suprasystemic RV pressures, especially in association with dehydration leading to decreased preload.

Physical Examination

The physical examination demonstrates a parasternal RV heave and delayed or diminished P2 and a late peaking crescendo-decrescendo murmur. If the valve is pliable, an ejection click may be heard before the murmur.

The murmur increases in intensity during inspiration and decreases during expiration. However the ejection click will decrease in intensity during inspiration and increase with expiration. With increasing severity, the murmur peaks later in systole and the ejection click will move closer to the first heart sound because the valve opens earlier as a consequence of the higher RV pressure.

The jugular venous pressure shows a prominent wave as a result of diminished RV compliance. Once RV failure occurs, the jugular venous pressure increases.

DIAGNOSTIC STUDIES

Electrocardiogram and Chest X-ray

The ECG demonstrated right ventricular hypertrophy (RVH) with right axis deviation, prominent R waves in the right precordial leads and deep S waves in the left precordial leads. There may also be evidence of P pulmonale with peaked inferior P waves.

On chest X-ray the cardiac silhouette may become enlarged in severe PS especially with right heart failure occurs. The left pulmonary artery (PA) is often dilated.

Echocardiogram

Echocardiography is the method of choice for the diagnosis, assessment of PS. Associated findings, such as RVH, subpulmonic stenosis, septal defects, can also be identified.

2D images in the parasternal short-axis or subcostal short-axis views are the most optimal to align parallel Doppler signal.

Color flow Doppler imaging demonstrates high-velocity flow within the PA. Continuous wave (CW) Doppler interrogation demonstrates the high velocity jet and estimates the gradient across the RVOT.

According to the 2006 ACC/AHA guidelines on the management of valvular heart disease,[29] the severity of pulmonary stenosis is defined as follows:

Severe stenosis: A peak jet velocity of 4 m/s (peak gradient 64 mm Hg).

Moderate stenosis: A peak jet velocity of 3–4 m/s (peak gradient 36–64 mm Hg).

Mild stenosis: A peak jet velocity of 3 m/s (peak gradient < 36 mm Hg).

Other echocardiographic hemodynamic parameters used to determine the severity of PS include tricuspid regurgitation (TR) to estimate the right ventricular systolic pressure (RVSP) and imaging of the inferior vena cava (IVC) to estimate right atrial pressure. The PA systolic pressures can be estimated by subtracting the transpulmonary valve gradient from the estimated RVSP as long as an adequate, well-aligned TR jet is present. The pulmonary regurgitation jet velocity will be low. Associated subpulmonic stenosis can be identified by the presence of second population of velocity signals superimposed on the CW jet, which peaks later in systole. A saline contrast study should be performed to detect shunting at the atrial level, especially in the presence of cyanosis.

Transesophageal echocardiography is indicated when there is uncertainty as to the level of outflow tract obstruction. This technique provides excellent definition of the RVOT and pulmonary valve in the basal longitudinal views. The interatrial septum should be carefully imaged with color flow Doppler and during saline contrast injection to differentiate a PFO from an ASD. As a result, noninvasive methods are almost always adequate for establishing the diagnosis, even in adults.

Magnetic Resonance Imaging and Computed Tomography

These modalities are rarely needed to diagnose pulmonary stenosis. Cardiac MRI may be adjunctive in patients with subpulmonic stenosis to define the level of muscular hypertrophy.

Cardiac Catheterization

Cardiac catheterization is now reserved for patients in whom balloon valvuloplasty is indicated and should be performed in

centers capable of this procedure to avoid duplicated procedures. During right heart catheterization, the level of stenosis can be confirmed during pullback from the PA. In valvular stenosis, there is a rise in gradient as the catheter crosses from PA to RV. In contrast, when the stenosis is in the infundibulum, the systolic pressure increases when the catheter is pulled into the body of the RV. If the infundibular stenosis is a consequence of valvar PS, a pressure differential may be present at both levels on pullback. If the level of obstruction remains uncertain then infundibular cineangiography may help delineate the anatomy.

TREATMENT AND PROGNOSIS

Surgical and Interventional

In children treated conservatively for PS, the likelihood of requiring surgery is dependent on the initial gradient less than 25 mm Hg, 5%; 25–49 mm Hg, 20%; and 50–79 mm Hg, 76%.

Most patients, including adults, are treated with balloon valvuloplasty. Recent technical improvements leading to low profile balloon have decreased the risk of pulmonary regurgitation after dilatation. The long-term results after balloon valvuloplasty are excellent.

Infundibular stenosis secondary to valvar PS often regresses over time[30] after pulmonary valvuloplasty has been performed. Beta-blockade has been suggested; however, the effectiveness of this is unknown.

Surgery is still usually required for the dysplastic valve often seen in Noonan syndrome. Surgical valvotomy via transpulmonary artery incision can be effective with excellent long-term outcomes to avoid prosthetic valve replacement. Should valve replacement be the only alternative? Bioprosthetic valve is preferred over mechanical valve to avoid thrombotic complications.

PREGNANCY

Volume overload combined with a low systemic vascular resistance in pregnancy may precipitate right heart failure in patients with severe PS. Women of child-bearing age with known congenital PS should consult with their cardiologist for assessment of treatment prior to pregnancy and a potential irreversible state. Symptomatic patients with severe stenosis during pregnancy may require pulmonary valvotomy during pregnancy, which can be performed safely with uterine shielding especially during the second trimester (reference).

ENDOCARDITIS PROPHYLAXIS

The incidence of endocarditis with isolated PS is low. However patients with PS have approximately two time higher risk of endocarditis than the general population.[31] According to current guidelines, patients with untreated or treated pulmonary valve stenosis do not require antibiotics for endocarditis prophylaxis.

GUIDELINES

In adults, the treatment for PS according to the "2008 focused update incorporated into the ACC/AHA 2006 guidelines for the management of patients with valvular heart disease"[32] are:

- Patient with mild gradients should be observed
- Symptomatic patients in whom the catheterization peak-to-peak gradient is more than 30 mm Hg (class I)
- Asymptomatic patients, intervention is recommended when gradients across the stenosis is more than 40 mm Hg (class I); however, may be reasonable with gradient 30–39 mm Hg (class IIa)
- Intervention in the absence of pulmonary insufficiency is almost always performed in the catheterization laboratory with balloon valvuloplasty.[33] Some pulmonary regurgitation almost invariably occurs after valvuloplasty, but it is rarely clinically important
- If severe pulmonary insufficiency is present, treatment is surgical, often with a pulmonary valve with a conduit

SUBVALVAR AND SUPRAVALVAR PULMONIC STENOSIS

GENERAL CONSIDERATIONS

Subvalvar PS is primarily seen in TOF patients. It is also associated with a congenital VSD or a VSD jet lesion or a congenital double chamber RV (the development of infundibular muscle bundles). Other uncommon causes include a hypertrophic cardiomyopathy or glycogen storage disorder and compression by tumor. In most of these cases, correction of the stenosis is done during surgical correction of the primary lesion.

Supravalvar stenosis may occur in the main PA or in the branches. Central and peripheral congenital PA stenosis may be a major cardiovascular feature in the Alagille and Keutel syndromes. Acquired PA stenoses can be sequelae of the congenital rubella syndrome, Williams syndrome or scarring at the site of a previous PA band or aortopulmonary shunt.

Evaluation of supravalvular PS should be with baseline echocardiography plus one alternative imaging modality such as magnetic resonance angiography or CT angiography. These methods provide superior definition of the pulmonary architecture compared to echocardiography and both can help confirm the diagnosis.

GUIDELINES

Based on the 2008 ACC/AHA guideline for management of ACHD, percutaneous interventional therapy is the treatment of choice in the management of appropriate focal branch and/or peripheral PA stenosis with greater than 50% diameter narrowing, an elevated RVSP greater than 50 mm Hg and/or symptoms.

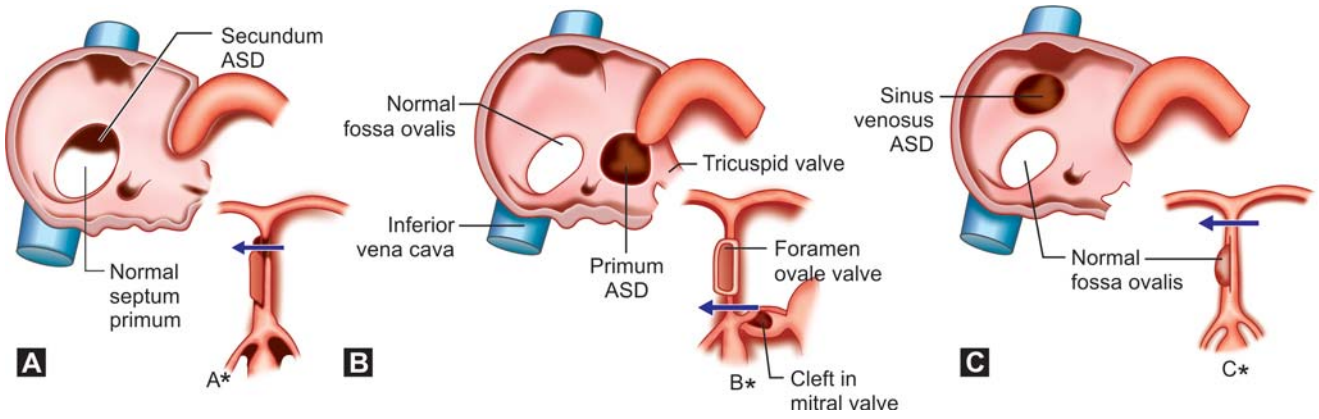
ATRIAL SEPTAL DEFECTS

GENERAL CONSIDERATIONS

An ASD results in an interatrial communication due to deficient septal tissue causing left-to-right shunting. ASDs make up 7% of CHD in newborns and are relatively commonly encountered in adults.[34]

Classification of ASDs is based on anatomic location (Figs 5A to C):

- Ostium secundum—in the region of the fossa ovalis
- Ostium primum—in the lower portion of the atrial septum
- Sinus venosus defect of the superior vena cava (SVC) results in the SVC overriding both atria



FIGURES 5A TO C: Classification of ASDs based on anatomic location

- Coronary sinus defects are rare with an opening of the wall of the coronary sinus communicating to the left atrium allowing left-to-right shunting

It is important to note that the most common interatrial communication is a PFO, which is anatomically and physiologically not classified as an ASD as there is no missing septal tissue, and intermittent shunting is predominantly right-to-left.

As opposed to congenital aortic stenosis, ostium secundum ASD have a 2:1 female preponderance. The ostium primum and sinus venosus ASDs have a 1:1 ratio.

PATHOPHYSIOLOGY

The pathopysiological consequences and treatment decision of an ASD depend upon the degree of systemic to pulmonary shunting, the size of the defect and the compliance of the RV and LV. Small ASDs, which are unrecognized at a young age, may become apparent in adulthood. Diminishing LV compliance due to aging, coronary artery disease and hypertension can increase the left-to-right shunting and, consequently, lead to right heart failure.

Shunt size is characterized by a ratio between the pulmonic blood flow (Q_p) to systemic blood flow (Q_s). The greater the pulmonic blood flow, the greater the degree of shunting. A small shunt is defined as a Q_p/Q_s less than 1.5, a moderate size shunt as Q_p/Q_s greater than 1.5–2.0, and a large shunt as Q_p/Q_s greater than 2.0. Large shunts can cause CHF in infants and children.

ASSOCIATED ANOMALIES

Important associated anomalies are anomalous drainage of the right upper pulmonary vein into left SVC (sinus venosus), persistent left SVC draining into the coronary sinus (secundum and primum), cleft mitral valve leaflet (primum).

Trisomy 21 (Down's syndrome) patients commonly have a primum ASD. This is a part of the spectrum of atrioventricular septal defect.

Holt-Oram syndrome, an autosomal dominant syndrome with abnormalities of the forearm and hand associated with an ASD, VSD or other cardiac malformations.

GENETIC INHERITANCE

An autosomal dominant inheritance pattern has been demonstrated in some patients with an ostium secundum ASD with associated first-degree AV block. Cases of ASD in monozygotic twins have been reported. Recent studies have shown mutations in the genes GATA4 and NKX2.5 in non-syndromic ASD. Point mutation in the gene TBX5 is known to cause the Holt-Oram syndrome.

CLINICAL FINDINGS

Signs and Symptoms

A young adult with a small, uncorrected ASD and normal pulmonary pressures may be asymptomatic. The most common presenting symptoms in adults are exercise intolerance and palpitations. Patients with large shunts will have signs and symptoms consistent with right heart failure because of pulmonary hypertension and volume overload.

Physical Examination

A pathognomonic finding is a fixed split second heart sound. A prominent RV impulse along the left lower sternal border and a palpable PA can be palpated. A systolic ejection murmur is heard secondary to increased flow across the pulmonary valve.

DIAGNOSTIC STUDIES

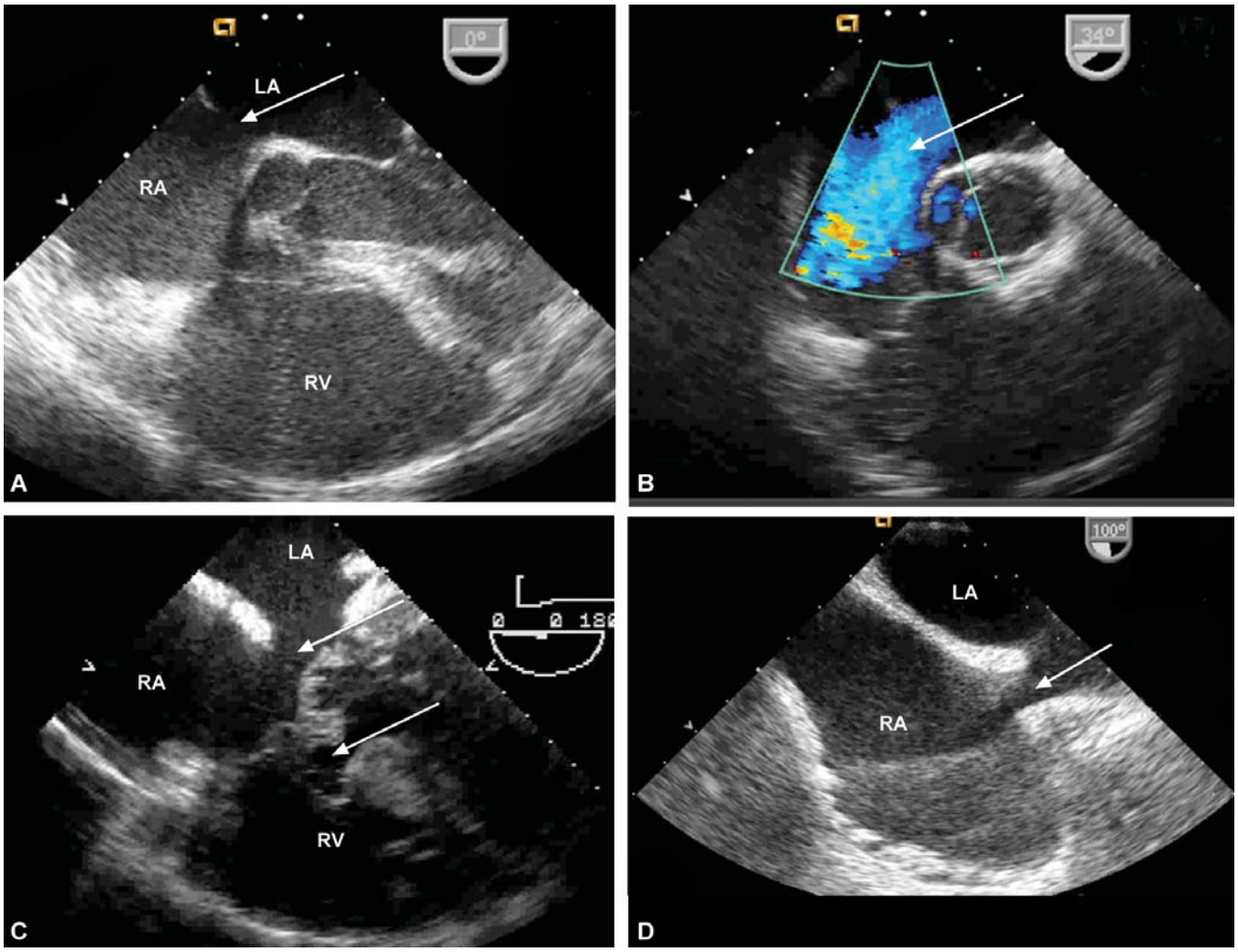
Electrocardiogram and Chest X-ray

The ECG shows RV conduction delay ["incomplete right bundle branch block (RBBB)"] in 90% of the cases. In ostium secundum ASDs and sinus venosus ASDs, the QRS axis is vertical or rightward. In patients with ostium primum ASDs, the axis is superior and leftward. Abnormal sinus node function in patients with sinus venosus ASD often results in ectopic atrial rhythm with superior P wave axis.

The chest radiograph shows prominent aortic and pulmonary arteries and RV enlargement. In the absence of pulmonary hypertension, the lung markings are increased as a result of increased pulmonary blood flow.

Echocardiogram

In most cases of primum and secundum ASDs, the septal defect can be visualized on 2D imaging. However only 70% of sinus venosus defects are visualized by transthoracic imaging and



FIGURES 6A TO D: Transesophageal echocardiographic views of atrial septal defects. (A) Ostium secundum (arrow) on four-chamber transesophageal echocardiographic view with dilated right ventricle. (B) Left-to-right shunting by color flow Doppler jet (arrow). (C) Ostium primum (arrow) on four-chamber transesophageal echocardiographic view with dilated right ventricle. There is a common atrioventricular valve with right-sided attachments to the crest of the interventricular septum closing the ventricular septal defect (small arrow). (D) Sinus venosus atrial septal defects (arrow) on bicaval longitudinal plane transesophageal echocardiographic view with right atrium. (Abbreviations: LA: Left atrium; RA: Right atrium; RV: Right ventricle)

require a high level of clinical suspicion and further imaging with TEE or magnetic resonance.[35]

Echocardiographic findings of an ASD include RV enlargement, paradoxical septal motion consistent with volume overload and increased PA flow. Color flow Doppler can identify in the interatrial flow, especially in the four-chamber view. Intravenous saline contrast injection should be used in all patients with suspected ASD, a negative contrast effect can be seen in the right atrium.

Echocardiographic measures can be used to determine the degree of shunt flow, which can eliminate with need for invasive assessment and assist with management decisions. The shunt calculations are performed by calculating the RV and LV stroke volumes using the PA diameter, the VTI at the pulmonary valve to calculate pulmonary blood flow and the LVOT diameter and the VTI in the LVOT to calculate systemic blood flow.

Transesophageal echocardiography has been found to be more accurate in determining the size and location of atrial communication. However anomalous pulmonary venous connections may be difficult to ascertain on TEE (Figs 6A to D).

Magnetic Resonance Imaging and Computed Tomography

MRI and CT imaging are especially useful in patients with ASDs to assess anatomy of the pulmonary veins and SVC. Also, phase contrast MRI is another noninvasive way of determining the Q_p/Q_s ratio, with good correlations to invasive measures.[36]

Catheterization

Equivocal finding on noninvasive imaging can require invasive measurement of shunt size. Right heart catheterization with repeat blood sampling for oxygenation levels reveals oxygen step-up from the vena cava to the right atrium. A value greater than 90% suggests a large shunt. The ratio of pulmonary to systemic flow can be calculated by the following formula:

$Q_p/Q_s = (S_aO_2 - M_vO_2)/(P_vO_2 - P_aO_2)$

S_aO_2 = systemic arterial oxygen saturation

M_vO_2 = mixed venous oxygen saturation [Calculated: (3 x SVC + IVC)/4]

P_vO_2 = pulmonary venous oxygen saturation

P_aO_2 = pulmonary arterial oxygen saturation

Surgical and Interventional

In adults, hemodynamically insignificant ASDs with Q_p/Q_s less than 1.5 do not require closure unless there is concern for paradoxical emboli. Symptomatic or large ASDs should be closed. In patients with pulmonary hypertension, closure can be considered as long as the pulmonary blood flow is greater than 70% of systemic blood flow. Closure of a symptomatic ASD improves function status and exercise capacity.

Ostium secundum ASDs have been surgically repaired for more than 40 years. In one series, there was no late cardiac mortality occurs in patients who had surgical repair before the age of 18 years.[37] Percutaneous device closure is widely available for secundum defects less than 41 mm in diameter. Studies have suggested results comparable with surgical closures.[38,39] Device closures are safe and effective, and offer lower complication rates than surgery. The major reported complications are device embolization, atrial perforation and thrombus formation on the device.[40] Atrial arrhythmias have been reported but are less common than following surgery. Although there has never been a randomized trial comparing device closure to surgery, device closures have become the procedure of choice for adolescents and adults when appropriate. Associated defects of an anomalous pulmonary venous connection or proximity to the coronary sinus will mandate surgical repair. Sinus venosus ASDs and primum ASDs must be surgically closed. Surgical closures involve pericardial or synthetic patch or just primary suture closure.

Small ASDs may lead to heart failure in late adulthood with progression of acquired cardiovascular disease. These patients should undergo continued echocardiographic surveillance as the degree of shunting may increase and they may require closure.

Patients with large uncorrected ostium secundum ASDs generally survive into adulthood; however, their life expectancy is not normal.

Atrial arrhythmias are common over the age of 50 years, especially atrial fibrillation. Late surgical or percutaneous closures do not prevent late onset atrial arrhythmias. Paradoxical embolism or stroke can be the initial presentation of an ASD.

PREGNANCY

Pregnancy in the absence of pulmonary hypertension is generally uncomplicated and well-tolerated. The risk or paradoxical is increased in the peripartum and postpartum period. In women with large shunts detected prior to conception, closure of the ASD is recommended. Pregnancy is contra-indicated in Eisenmenger's syndrome.

ENDOCARDITIS PROPHYLAXIS

Endocarditis is rare in patients with ASDs, and prophylaxis is not routinely indicated. Prophylaxis is, however, indicated for the 6 months after surgical and percutaneous ASDs closure.

GUIDELINES

Class I

- Closure of an ASD either percutaneously or surgically is indicated for right atrial and RV enlargement with or without symptoms. (*Level of Evidence: B*)
- A sinus venosus, coronary sinus or primum ASD should be repaired surgically rather than by percutaneous closure. (*Level of Evidence: B*)
- Surgeons with training and expertise in CHD should perform operations for various ASD closures. (*Level of Evidence: C*)

Class IIa

- Surgical closure of secundum ASD is reasonable when concomitant surgical repair/replacement of a tricuspid valve is considered or when the anatomy of the defect precludes the use of a percutaneous device. (*Level of Evidence: C*)
- Closure of an ASD, either percutaneously or surgically, is reasonable in the presence of:
  - Paradoxical embolism. (*Level of Evidence: C*)
  - Documented orthodeoxia-platypnea. (*Level of Evidence: B*)

Class IIb

- Closure of an ASD, either percutaneously or surgically, may be considered in the presence of net left-to-right shunting, PA pressure less than two-thirds systemic levels, pulmonary vascular resistance (PVR) less than two-thirds systemic vascular resistance, or when responsive to either pulmonary vasodilator therapy or test occlusion of the defect (patients should be treated in conjunction with providers who have expertise in the management of pulmonary hypertensive syndromes). (*Level of Evidence: C*)
- Concomitant Maze procedure may be considered for intermittent or chronic atrial tachyarrhythmias in adults with ASDs. (*Level of Evidence: C*)

Class III

Patients with severe irreversible pulmonary arterial hypertension (PAH) and no evidence of a left-to-right shunt should not undergo ASD closure. (*Level of Evidence: B*)

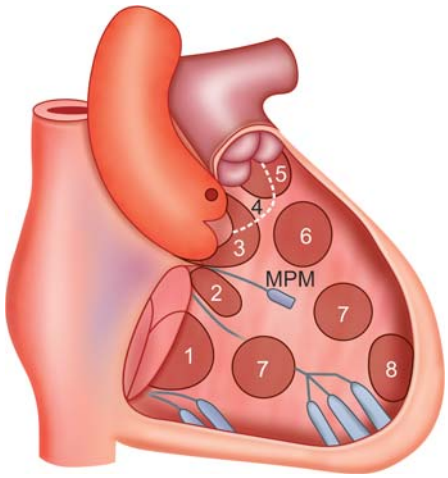
VENTRICULAR SEPTAL DEFECTS

GENERAL CONSIDERATIONS

Ventricular septal defect is a birth defect with abnormal connections between the systemic and pulmonary circulation at a level, which reflects arterial pressures, in contrast to ASDs, and pulmonary venous anomalies, which connect at venous pressure levels. VSD is the most common of all forms of CHD. Twenty percent of all children with CHD have an isolated VSD.[24] This figure is as high as 30% in the newborn population and 10% in the adult congenital population. Acquired VSDs secondary to trauma and ischemia have not been discussed in detail in this chapter.

Most VSDs present in childhood as a murmur or with CHF. Up to 40% close spontaneously so it is uncommon to encounter adults with a previously unrecognized significant VSD. Therefore, most adults present with either small defects of no hemodynamic consequence or large defects associated with Eisenmenger's syndrome.

The small VSDs will generally demonstrate a benign uncomplicated course. The biggest concern is the development



FIGURES 7: Classification of the site of ventricular septal defects as viewed from ventricle. (1–5) subvalvular: 1. Inlet; 2. Subtricuspid; 3. Subaortic; 4. Subarterial doubly committed; 5. Subpulmonary. (6–8) muscular: 6. Outlet; 7. Central; 8. Apical. (Abbreviation: MPM**:** Medial papillary muscle)

of endocarditis. The natural history of large VSDs is development of pulmonary vascular obstruction or Eisenmenger's syndrome.

Classification of VSDs can be based on anatomic location and/or physiology. The anatomic classification includes both the membranous and muscular portions of the ventricular septum (Fig. 7).

a. *Membranous VSDs*: This is the most common site for VSDs. The membranous septum lies beneath the aortic valve and behind the tricuspid septal leaflet. Membranous VSDs are subclassified as supracristal (also know as doubly committed subarterial), perimembranous (the inlet portion of the membranous septum) and malalignment (found in TOF with the overriding aorta). These latter defects occur as a result of anterior malalignment of the conal septum; however, the anatomical location is similar to perimembranous VSDs.

   The supracristal VSDs are located immediately below the pulmonic and aortic valve. Approximately 5% of the patient with VSDs will have it localized in the subpulmonary position. They tend to be more common in the Asian population.

   It is possible, although rare, to have a communication between the left ventricle and the right atrium in a relatively small area of the membranous septum which divides the two chambers. The defect is known as a Gerbode defect and is often seen as a part of the atrioventricular septal defect.

b. *Muscular VSDs*: About 10% of the VSDs are muscular defects. They are often multiple and may be located in the inlet or outlet regions or within the trabeculae portion of the septum. Muscular defects often close spontaneously in infants. The condition associated with multiple muscular VSDs is often referred to as "Swiss Cheese" septum.

Physiologically they can be divided into two categories:

a. *Restrictive VSDs*: A small defect with a large gradient between the ventricles such that the RVSP is less than 50% of the LV systolic pressure.

b. *Non-restrictive VSDs*: A large defect with a small gradient between the ventricles such that the RVSP is more than 50% of the LV systolic pressure.

PATHOPHYSIOLOGY

Left-to-right shunting occurs only after the PVR falls in the first month of life and the murmur may not be detected in the newborn. In the presence of a large nonrestrictive defect, the PVR may not fall. If the defect is not closed by age 2, irreversible pulmonary vascular disease may develop. The volume overload caused by a large VSD may lead to CHF in the first 6 months of life. Approximately 40% of all VSDs close spontaneously by age 3. Generally, the smaller defects are more likely to close. Even in infants with CHF, 7% will close spontaneously.

Spontaneous closure of a VSD may occur through development of a ventricular septal aneurysm, formed by adhesion of a portion of the tricuspid septal leaflet to the septum, in as many as 20–25% of all spontaneous VSD closures. TR may result as a consequence. However, given that the tricuspid valve is normally sufficiently redundant often no disabling defects are observed. Severe aortic regurgitation may complicate doubly committed subarterial VSDs (supracristal), resulting from herniation of the right aortic cusp into the defect. Aortic regurgitation may also occur in perimembranous VSDs but is usually not as severe. Hypertrophy of muscle bands related to the septomarginal trabeculation divides the RV into a high-pressure inflow chamber and a low-pressure outflow chamber, a condition termed as "double-chambered right ventricle". If a sufficient pressure gradient develops, RVSP can exceed LV systolic pressure and right-to-left shunting can occur across the VSD. Thus, resulting in hypoxia may occur only during exercise.

In adults with a large unrepaired VSD, there will nearly always be evidence of pulmonary hypertension leading to Eisenmenger's syndrome, with all of the associated pathology of pulmonary vascular disease, including medial hypertrophy of the arteries and intimal hyperplasia. Terminally, there may be *in situ* pulmonary thrombosis and pulmonary infarction. In these advance stages, the shunt will be reversed with right-to-left shunting and cyanosis.

ASSOCIATED ANOMALIES

Ventricular septal defects often occur as isolated defects. However, they accompany many other complex congenital cardiac anomalies, including pulmonary stenosis (in which case TOF may be diagnosed), congenitally corrected transposition of the great arteries (l-TGA) and right-sided aortic arches. VSDs can be seen with other left-sided heart obstructive lesions such as supravalvar aortic stenosis, valvar aortic stenosis and coarctation.

Ventricular septal defects are associated with genetic disorders, most commonly Trisomy 21. Patients with trisomy 21 may have simple VSDs as well as variants of the atrioventricular septal defect (see AVSD). In these patients, a cleft mitral valve is often present.

The presence of a VSD has been associated with genitourinary tract abnormalities in approximately 10% of patients.

Males and females are equally affected. Rare familial patterns have been demonstrated. Generally speaking no genetic pattern has been detected.

CLINICAL FINDINGS

Signs and Symptoms

Adults with small uncorrected VSDs with normal PA pressures are usually asymptomatic. Rarely, large VSDs without pulmonary hypertension may cause dyspnea, especially if the condition is complicated by aortic regurgitation.

Adults with Eisenmenger's syndrome are markedly symptomatic with diminished exercise tolerance, air hunger, headaches, hemoptysis and angina on exertion.

Physical Examination

The patient with an uncomplicated VSD is acyanotic. Generally it is held that small VSDs produce the loudest murmurs, but if they are small enough, they may produce little to no acoustic energy and may be soft in intensity. The murmur associated with a VSD is pansystolic and begins during isovolumic contraction before the aortic and pulmonic valve open. It is generally heard at the left sternal border in the fourth or fifth intercostal space, radiating rightward except in the case of a supracristal VSD, where radiation is usually to the left clavicle. The murmur does not vary with respiration. The intensity of the murmur will decrease with amyl nitrite as the fall in systemic vascular resistance will decrease the left-to-right shunt. Tricuspid and mitral regurgitation can mimic a VSD; however, mitral regurgitation will be heard best at the apex and TR will generally have a lower pitch and will vary with respiration.

The murmur is often associated with a systolic thrill. Due to increased flow across the mitral valve, an S3 gallop and diastolic rumble across the mitral valve may be present. Also, murmurs for aortic regurgitation may be audible if it is associated with the defect.

When Eisenmenger's physiology develops, the systolic murmur across the VSD diminishes. The patient will have a loud P2 with a wide but physiologically split S2. The murmurs of pulmonic regurgitation and TR may be audible as a result of the pulmonary hypertension. The cardiac examination is similar from patients with other forms of pulmonary hypertension, although patients with Eisenmenger's physiology due to an ASD will have a fixed split S2. Clubbing and cyanosis are usually absents in pulmonary hypertension patients without CHD and patients with Eisenmenger's physiology due to a PDA have differential cyanosis and clubbing (see *Patent Ductus Arteriosus*).

The few patients who develop double-chambered right ventricle will have an ejection murmur rather than a pansystolic murmur and the S2 will be soft, even if the patient is cyanotic.

DIAGNOSTIC STUDIES

Electrocardiogram and Chest X-ray

The ECG may be normal. In presence of a large shunt, the ECG is suggestive of LVH or biventricular hypertrophy with biphasic QRS complexes in the precordial leads.

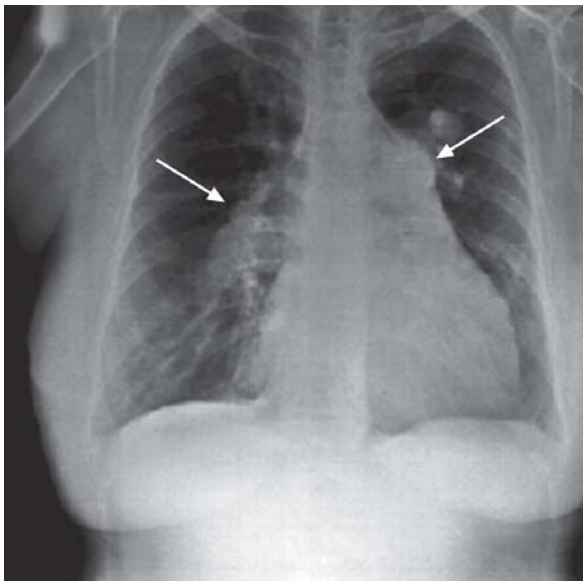


FIGURE 8: Pulmonary arterial view of chest radiograph in a patient with Eisenmenger's syndrome showing severely dilated pulmonary arteries (arrows)

A postoperative patient whose VSD has been closed will often show the presence of a RBBB.

The chest X-ray in a patient with a VSD shows a normal to slightly increased cardiothoracic ratio due to an increase in size of the left atrium and left ventricle. Increase pulmonary vascular markings consistent with large pulmonary blood flow are common. Pulmonary vascular plethora will not be present in adults or in Eisenmenger's syndrome.

In stable Eisenmenger's syndrome, the cardiothoracic ratio will be normal, although RV prominence may be noted on the lateral chest X-ray. The main PA will be very prominent and central hilar vessels will be enlarged (Fig. 8). Late Eisenmenger's syndrome will cause an enlarged heart due to PI and TR.

Associated right-sided aortic arch can be seen on chest X-ray.

Echocardiogram

2D echocardiography and color flow Doppler interrogation can define the size and location of the VSD. The basal short axis view allows for assessment of perimembranous (Fig. 9) and supracristal VSDs (Fig. 10). Mid ventricular and apical short axis views can visualize muscular VSDs (Fig. 11), which are also well seen in the apical and subcostal views.

The presence of left atrial and LV enlargement suggest that the left-to-right shunt is hemodynamically significant. The method of shunt calculation is similar to that of ASDs. The right-sided chambers are normal in the absence of pulmonary hypertension. The main PA may be dilated. The presence of RVH usually signifies pulmonary hypertension or associated RVOT obstruction.

2D imaging may visualize and ventricular septal aneurysm with complete or partial closure of the VSD by the tricuspid septal leaflet. This is primarily seen in the short axis view at the base just below the aortic valve. Saline contrast will show negative contrast effect in the right ventricle, and occasionally a small degree of bidirectional shunting is seen.

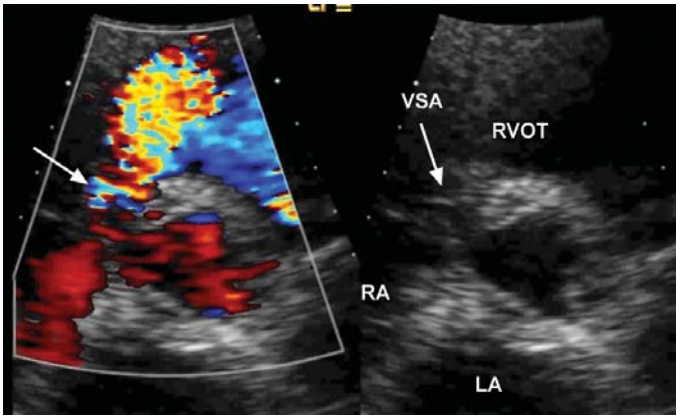


FIGURE 9: Parasternal short axis view demonstrating small muscular ventricular septal defect with color flow jet on the right panel (arrow) and small defect with ventricular septal aneurysm on left panel (arrow). (Abbreviations: LA: Left atrium; RA: Right atrium; RVOT: Right ventricular outflow tract; VSA: Ventricular septal aneurysm)

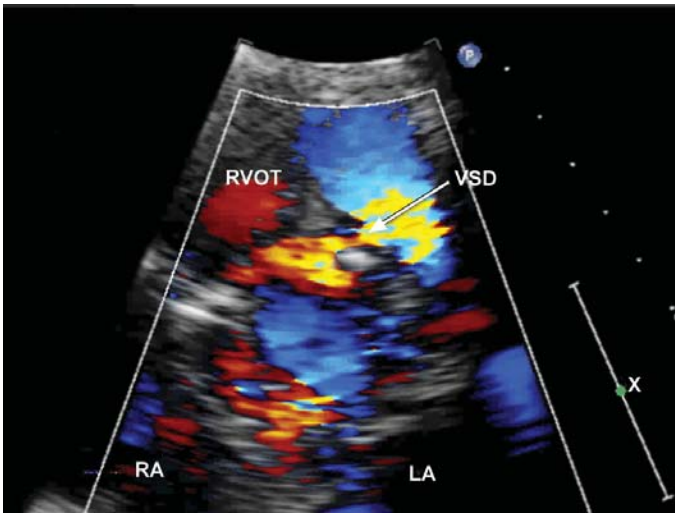


FIGURE 10: Parasternal short axis view demonstrating small subarterial ventricular septal defect with color flow jet on the right panel (arrow). (Abbreviations: LA: Left atrium; RA: Right atrium; RVOT: Right ventricular outflow tract; VSA: Ventricular septal aneurysm)

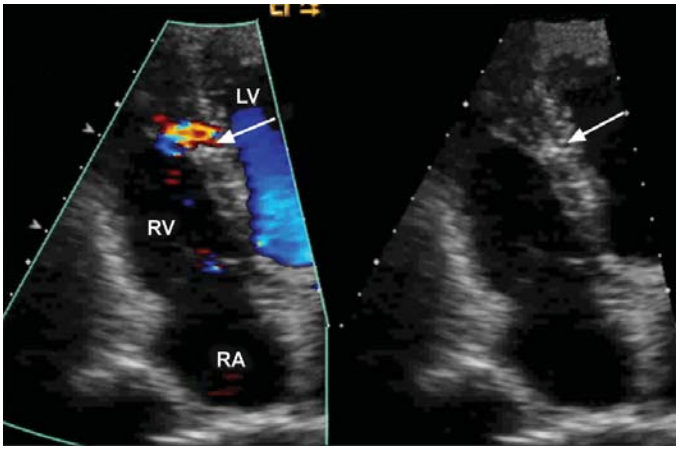


FIGURE 11: Modified four-chamber view demonstrating small muscular ventricular septal defect with color flow jet on the right panel (arrow) and small defect on left panel (arrow). (Abbreviations: LV: Left ventricle; RA: Right atrium; RV: right ventricle)

In the absence of pulmonary hypertension, the color jet demonstrates high velocity flow (aliased jet) through the VSD into the right ventricle and will be directed toward the transducer producing a positive systolic flow pattern. When the right ventricle pressure is elevated due to pulmonary hypertension or less commonly, obstruction, there is a low velocity color flow jet that is usually bidirectional. Using CW Doppler, the peak velocity of the jet provides the peak LV-RV gradient. Subtracting the gradient from the simultaneously measured systolic blood pressure provides an estimate of the peak RVSP, which is equal to the PA systolic pressure in the absence of a pressure gradient across the RVOT.

In post-repair patients, the VSD patch may or may not apparent. Color flow Doppler helps demonstrate patch leaks. Cases of repaired VSDs are reported to occasionally develop subaortic stenosis or double-chambered right ventricle, which can be seen and assessed by 2D echocardiography and color Doppler echocardiography.

Catheterization

There is very little indication for diagnostic cardiac catheterization in patients with small VSDs. However, the decision to close a VSD requires accurate measurements of shunt fraction and PVR.

Right heart catheterization with sequential measurements of oxygen saturation reveals a step-up in the right ventricle. The higher the RV oxygen saturation the greater is the degree of shunting. For shunt calculations, same formula is used as for the ASDs; however, the mixed venous saturation is taken from the RA. Pulmonary artery pressures and vascular resistance should be measured and gradients across the RVOT should be sought by careful pullback of the PA catheter. LV angiogram in the cranial left anterior oblique projection will reveal the location of the defect as contrast enters the right ventricle.

Patients with Eisenmenger's syndrome will have pressures similar to patients with pulmonary hypertension.

In the instance of the adult who has developed muscular subpulmonic stenosis angiographic demonstration of the RVOT as well as the site of the VSD should be obtained. In addition, evaluation of the coronary arteries is indicated preoperatively to exclude anomalous coronary branches crossing the RVOT. Cardiac catheterization can be performed to assess the operability of adults with VSD and PAH.

TREATMENT AND PROGNOSIS

Surgery for closure of VSDs has been available for more than 40 years. Surgery prior to the age of 2 years in infants with large VSDs, high pulmonary blood flow and preoperative pulmonary hypertension almost always prevents the development of pulmonary vascular obstructive disease.[41] However, current guidelines do not recommend closure of small VSDs in the absence of a history of endocarditis when the shunt ratio (Q_p:Q_s) is less than 1.5.

Closure of a VSD is indicated when the Q_p/Q_s is greater than 2.0 and is reasonable with the Q_p/Q_s is greater than 1.5 with a PA pressure less than two-thirds of the systemic pressure and the PVR is less than two-thirds of the systemic vascular closure. Closure of a VSD is indicated when the patient has a

history of infective endocarditis. VSD closure is not recommended in patients with severe irreversible PAH. Pulmonary vasodilator therapy should be considered in these patients. There are two options for closure catheter base device and surgical patch closure.

Catheter based device closure of muscular VSDs in a location remote from the tricuspid valve has been gaining attention. Initial results show high success rates and low complication rates. Indications for closure of restrictive VSDs in the adult population include a history of bacterial endocarditis or a hemodynamically significant left-to-right shunt (Q_p/Q_s > 1.5:1). However, there is about a 20% incidence of residual shunting and a persistent risk of endocarditis. Ventricular arrhythmias and RBBB are common after surgery involving right ventriculotomy. These patients are at risk of developing complete heart block over time and should be followed with periodic ambulatory or exercise ECG monitoring. The risk for endocarditis is approximately 1% per year.[42]

Surgery with patch closure has a low perioperative mortality and high success rate. Patch leaks can occur, however, are often small and seldom require reoperation.[43]

Device closures also show good short-term outcome. Most common complications reported at tricuspid and mitral valvar regurgitation and complete heart block.[44]

PREGNANCY

In women with small VSDs and no pulmonary hypertension pregnancy is generally well-tolerated. These women should be followed closely throughout pregnancy period. The increase is volume overload is counterbalanced by the decrease in systemic vascular resistance. Women with VSD and severe PAH (Eisenmenger's syndrome) have excessive maternal and fetal mortality and should be counseled strongly against pregnancy with appropriate contraceptive measures.

GUIDELINES

Class I

- Surgeons with training and expertise in CHD should perform VSD closure operations. (*Level of Evidence: C*)
- Closure of a VSD is indicated when there is a Q_p/Q_s (pulmonary-to-systemic blood flow ratio) of 2.0 or more and clinical evidence of LV volume overload. (*Level of Evidence: B*)
- Closure of a VSD is indicated when the patient has a history of infective endocarditis. (*Level of Evidence: C*)

Class IIa

- Closure of a VSD is reasonable when net left-to-right shunting is present at a Q_p/Q_s greater than 1.5 with PA pressure less than two-thirds of systemic pressure and PVR less than two-thirds of systemic vascular resistance. (*Level of Evidence: B*)
- Closure of a VSD is reasonable when net left-to-right shunting is present at a Q_p/Q_s greater than 1.5 in the presence of LV systolic or diastolic failure. (*Level of Evidence: B*)

Class III

VSD closure is not recommended in patients with severe irreversible PAH. (*Level of Evidence: B*)

PATENT DUCTUS ARTERIOSUS

GENERAL CONSIDERATIONS

The PDA is a remnant of the normal fetal circulation, which connects the main PA to the proximal descending aorta (just distal to the left subclavian) to deliver systemic venous return from the right ventricle to the placenta for oxygenation (Fig. 12). The ductus normally closes within the first hours to days of life. If it does not close and a shunt persists then it is considered a PDA. Patients who survive into adulthood with a large uncorrected PDA, generally have CHF or pulmonary hypertension by the age of 30 years. Most adults with a small PDA or mildly elevated PVR (< 4 Wood Units) are asymptomatic or mildly impaired.

PATHOPHYSIOLOGY

Transition of an open ductus at birth to a closed ligamentum arteriosus is facilitated by an increase in PO_2 and fall in the PVR. If the ductal patency persists after birth, the direction of blood flow reverses, now producing a left-to-right shunt. The degree of shunting is dependent upon the size of the shunt and the resistance in the pulmonary and vascular beds. Early on, the degree of pulmonary hypertension depends on the directly transmitted aortic pressure, which in turn depends on the size of the channel and the amount of pulmonary blood flow. With persistently high pulmonary blood flow, the infant can develop

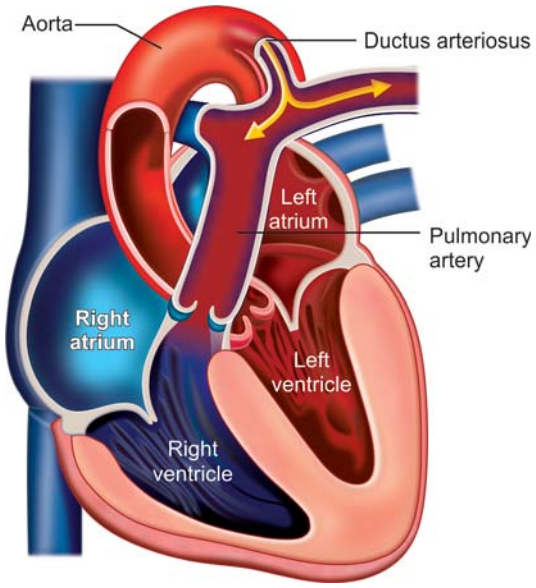


FIGURE 12: Patent ductus arteriosus with resultant left-to-right shunting. Some of the blood from the aorta crosses the ductus arteriosus and flows into the pulmonary artery (arrows). (*Source:* Brickner ME, Hillis LD, Lange RA. Congenital heart disease in adults. First of two parts. N Engl J Med. 2000;342:256-63, with permission)

CHF due to LV volume overload. The high pulmonary blood flow can subsequently lead to pulmonary vascular disease.

Very few patients develop severe pulmonary vascular disease leading to shunt reversal and Eisenmenger's physiology. It is important to note because the PDA is usually distal to the left subclavian, the head and neck vessels will continue to receive oxygenated blood from the left ventricle. However, the descending aorta will receive the desaturated blood, with development of differential cyanosis.

ASSOCIATED ANOMALIES

A PDA can be seen in isolation. However, it is common in occurrence in conjunction with other forms of CHD. There may have a history of maternal rubella.

CLINICAL FINDINGS

Signs and Symptoms

Most small PDAs are asymptomatic in adults. CHF rarely develops in early adulthood. This is largely dependent on the shunt size, if large enough to cause LV volume overload, the patient may experience exertional dyspnea, chest pain and palpitations.

When pulmonary vascular disease has progressed to cause right-to-left shunting, cyanosis and clubbing are predominantly seen in the lower extremities often sparing the upper extremities (the left hand may show clubbing if the left subclavian origin is distal to the PDA).

Physical Examination

The LV impulse is hyperdynamic and often laterally displaced. The classic murmur of the uncomplicated PDA is best heard below the left clavicle. The murmur is a continuous machinery-like murmur. With significant LV volume overload caused by a large shunt, a mitral diastolic rumble and a left-sided S3 may be heard.

As the PVR increases and shunt reverses, the murmur changes. Initially there is a decrease in the diastolic component and then a decrease in the systolic component. Finally, the murmur is silent with physical findings consistent with Eisenmenger's syndrome and pulmonary hypertension.

DIAGNOSTIC STUDIES

Electrocardiogram and Chest X-ray

The ECG is normal if the shunt is small. Larger shunts will show findings consistent with LVH. With pulmonary hypertension and shunt reversal the ECG may show P pulmonale, right axis deviation and evidence of RVH.

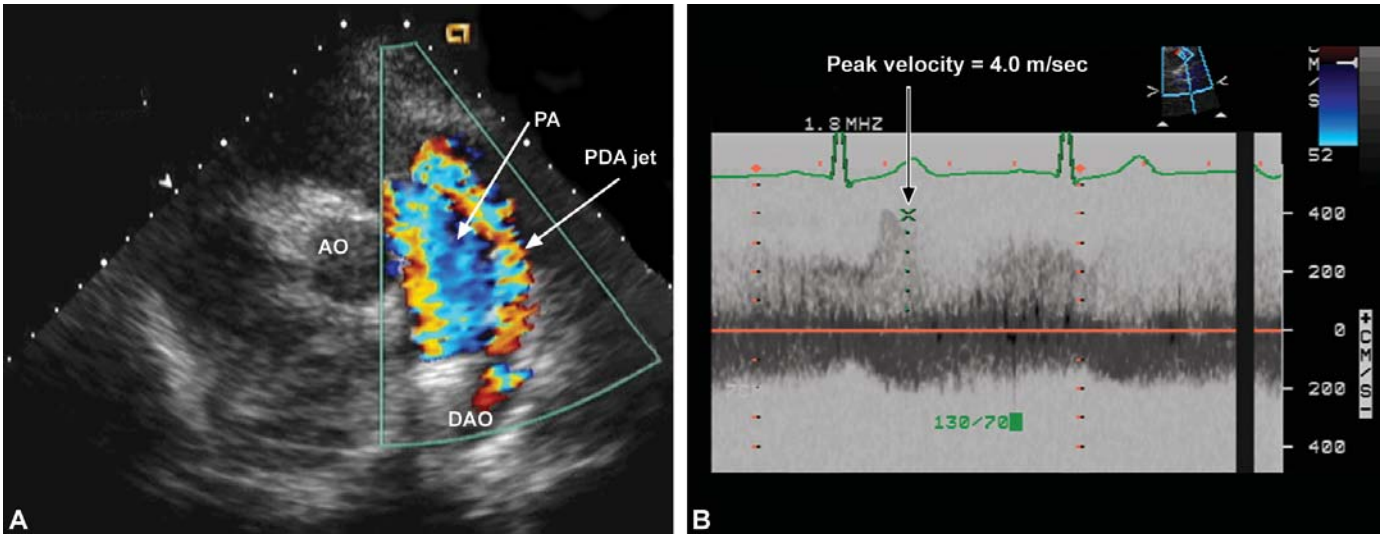
The chest X-ray is normal in the presence of a small shunt. With a large shunt, LV prominence is evident with an enlarged cardiac silhouette and pulmonary vascular plethora. The ductus may be calcified in the older adults.

Echocardiogram

The 2D echocardiogram will show left atrial and ventricular enlargement. The ductus itself can be difficult to visualize; however, it can be detected in the basal short axis and suprasternal notch views by the presence of continuous flow signal into the PA using color Doppler. Spectral Doppler shows a continuous jet with a peak velocity in systole (Figs 13A and B).

Magnetic Resonance Imaging and Computed Tomography

Magnetic resonance angiogram can be used to evaluate the anatomic location and structure of the PDA. Phase contrast imaging can determine flow through a designated plane. This can be used to quantitate the degree of shunting Q_p:Q_s ratio.[36]



FIGURES 13A AND B: The high velocity jet from the patent ductus arteriosus into the pulmonary artery is visualized (blue arrow). It arises from the descending aorta. The high velocity jet seen on continuous wave peaks at 4.0 m/sec with a gradient of 64 mm Hg between the aorta and the pulmonary artery at point when systolic blood pressure was 130 mm Hg. The estimate pulmonary artery systolic pressure of 65 mm Hg suggested only mildly increased pulmonary vascular resistance on the basis of extremely high pulmonary blood flow due to the large and persistent left-to-right shunt. (Abbreviations: AO: Aorta; DAO: Descending aorta; PDA: Patent ductus arteriosus; PA: Pulmonary artery)

Right heart catheterization may be performed to measure the PA pressure, PVR and flow ratio (Q_p:Q_s). The oxygen step-up is at the level of the PA.

Given the ability to diagnose and quantify the degree of shunting noninvasively a diagnostic cardiac catheterization is not indicated for uncomplicated PDA (class III)[18] and catheterization should be performed at a center capable of closing the PDA percutaneously to avoid multiple invasive procedures.

TREATMENT AND PROGNOSIS

Medical

Treatment in premature infants who are not dependent on the PDA flow consists of indomethacin administration to stimulate closure, surgical ligation or percutaneous closure with coils or a device.

Surgical and Interventional

In adults, surgical ligation or percutaneous coil or device occlusion of a PDA can be performed with low morbidity and mortality and is recommended because of high risk of endocarditis in uncorrected cases.

Adults with mildly elevated PVR (< 4 Wood units) can undergo surgical ligation or percutaneous closure with good results.[45] In patients with elevated PVR (> 10 Wood units), survival is poor and right heart failure may occur if the ductus is closed. Pulmonary vasodilator therapy can be used to decrease PA pressures, but limited data are available on the long-term outcomes associated with this approach. Fifteen percent of the patients older than 40 years have aneurysmal dilatation of the ductus, which can complicate surgery, increasing the risk of bleeding.

Once noninvasive testing makes the diagnosis cardiac catheterization should be combined with a therapeutic intervention. Techniques for coil and, more recently, device occlusion are well established and currently represent the treatment of choice for simple PDAs.

Closure of a PDA, either percutaneously or surgically, is indicated if: (a) left atrial size and/or LV enlargement or if PAH is present as long as there is net left-to-right shunting; (b) prior history of endocarditis.

PDA closure is not indicated in patients with PAH and net right-to-left shunt.

Follow-up is recommended approximately every 5 years due to lack of long-term outcome data on device closures.

PREGNANCY

Generally, pregnancy is well-tolerated in women with a small PDA. In women with larger shunts, pregnancy may precipitate right heart failure. Closure of these shunts is recommended prior to conception.

GUIDELINES

Class I

- Closure of a PDA either percutaneously or surgically is indicated for the following:
  - — Left atrial and/or LV enlargement or if PAH is present, or in the presence of net left-to-right shunting. (*Level of Evidence: C*)
  - — Prior endarteritis. (*Level of Evidence: C*)
- Consultation with ACHD interventional cardiologists is recommended before surgical closure is selected as the method of repair for patients with a calcified PDA. (*Level of Evidence: C*)
- Surgical repair by a surgeon experienced in CHD surgery is recommended when:
  - — The PDA is too large for device closure. (*Level of Evidence:C*)
  - — Distorted ductal anatomy precludes device closure (e.g. aneurysm or endarteritis). (*Level of Evidence: B*)

Class IIa

- It is reasonable to close an asymptomatic small PDA by catheter device. (*Level of Evidence: C*)
- PDA closure is reasonable for patients with PAH with a net left-to-right shunt. (*Level of Evidence: C*)

Class III

PDA closure is not indicated for patients with PAH and net right-to-left shunt. (*Level of Evidence: C*)

Other Acyanotic Lesions

EBSTEIN'S ANOMALY

GENERAL CONSIDERATIONS

Ebstein's anomaly is a rare congenital heart defect and comprises of less than 1% of all congenital heart lesions.[46]

Ebstein's anomaly is characterized by the apical displacement of the attachment of the posterior and/or septal leaflets of the tricuspid valve and adherence to the underlying myocardium. A variable portion of the inflow of the right ventricle lies above the tricuspid valve creating "atrialization" of the right ventricle.[47] The anterior leaflet is often large and redundant and is often described as "sail-like" and may contain fenestrations, contributing to the TR.

The prognosis and natural history of patients with Ebstein's is variable and depends upon the severity of the malformation and size of the functioning right ventricle.[48] Patients with mild Ebstein's anomaly may have a long, uncomplicated course with normal life span. In contrast, patients with hemodynamically significant TR and/or right-to-left shunting through an interatrial communication may develop CHF and/or cyanosis.

There is a high frequency of atrial arrhythmias with or without an accessory pathway, predominantly paroxysmal supraventricular tachycardia, but also atrial fibrillation and flutter and a smaller percentage of patients with paroxysmal ventricular tachycardia or ventricular fibrillation. Sudden cardiac death related to arrhythmias has been reported.

ASSOCIATED ANOMALIES

More than 50% of the patients have a shunt at the atrial level with either a secundum ASD or PFO,[47] which results in varying

degree of cyanosis. The degree of cyanosis is greater with severe TR and high right atrial pressure.

Right-sided accessory conduction pathways are seen in approximately 25% of these patients.

Other infrequent associations are RVOT obstruction and PDA, VSD and mitral valve prolapse. Another recently described association is with noncompaction of the left ventricle, which can lead to left-sided CHF.

PATHOPHYSIOLOGY

Depending upon the degree of "atrialization" of the right ventricle and leaflet coaptation, these patients have a varying degree of tricuspid valve regurgitation. Significant degree of tricuspid valve regurgitation can lead to RV dilatation and right heart failure. The presence of an ASD or PFO can cause increase right atrial pressures (secondary to the TR) and subsequent right-to-left shunting.

GENETIC INHERITANCE

Rare mutations in GATA4 have been described in association with Ebstein's anomaly. There may be a history of lithium exposure *in utero.*

CLINICAL FINDINGS

Signs and Symptoms

Patients over the age of 10 years often present with electrophysiological rather than hemodynamic manifestations at presentation. Hemodynamic symptoms in adulthood can include dyspnea on exertion, fatigue, palpitations and cyanosis (depending on degree of right-to-left shunting). Cyanosis may be present only during exercise.

Physical Examination

Physical examination reveals right parasternal lift, widely split S1, systolic clicks (from delayed tricuspid valve closure) and systolic murmur of the TR. The latter does not increase in intensity with inspiration because the noncompliant right ventricle cannot accept an increase in venous return. The jugular venous pulse is usually normal. An early diastolic snap from opening of the elongated anterior leaflet may be present. Pulse oximetry at rest and at stress can be useful in the diagnostic evaluation of Ebstein's anomaly in adult patients.

DIAGNOSTIC STUDIES

Electrocardiogram and Chest X-ray

The ECG shows right atrial enlargement and right ventricular conduction defect of the RBBB type. The PR interval may be prolonged, except in the presence of an accessory pathway.

Approximately 25% of the patients show ECG findings consistent with Wolff-Parkinson-White syndrome, i.e. short PR interval and delta waves from a posterolateral or posteroseptal bundle of Kent. Older patients may present with atrial fibrillation.

Chest radiography can be normal in mild cases. In more severe cases, right atrial enlargement with reduced pulmonary vascularity. The LV and Left atrium are normal size.

Echocardiogram

The diagnosis of Ebstein's anomaly is often made by transthoracic echocardiography. Classic M-mode description of this anomaly included increased excursion of the anterior tricuspid valve leaflet and delayed tricuspid valve closure (> 40 ms) following mitral valve closure.[49] Often, the mitral and tricuspid valves are seen simultaneously on M-mode.

The 2D four-chamber apical and subcostal views provide most of the necessary information. The right atrium is enlarged and the RV is usually small. The septal and/or posterior leaflets are apically displaced, and color flow Doppler imaging shows regurgitant jet arising from the apical point of coaptation. The degree of TR, which is frequently severe, can be estimated by color and Doppler echocardiography. The RVSP estimated from the CW TR jet is nearly always normal.

It is mandatory to perform a saline contrast examination to reliably exclude a PFO or an ASD. TEE should be used for confirming diagnosis and defining the anatomy of the interatrial communications.

Catheterization

Right heart cardiac catheterization is rarely necessary for diagnosis. However, simultaneous recording of a RV ECG and a right atrial pressure tracing are obtained with a specialized catheter in the atrialized portion of the right ventricle.

When surgical repair is planned, it is reasonable to perform coronary angiography in men 35 years or older, or premenopausal women 35 years or older, or older women who have coronary risk factors.[18]

TREATMENT AND PROGNOSIS

Medical Treatment

Anticoagulation is recommended for patients with Ebstein's anomaly with a history of paradoxical embolus or atrial fibrillation. Supraventricular tachycardias may be resistant to medical therapy.

Catheter-based Intervention

In patients with mild TR, who have cyanosis due to an interatrial shunt or a history of paradoxical embolus, percutaneous closure of the interatrial septal defect may provide symptomatic relief. Many of the supraventricular arrhythmias are now amenable to catheter ablation at experienced centers. Given that, often there is presence of multiple accessory pathways, the overall success rates are lower than those reported in a structurally normal heart.[50]

Surgical Intervention

Surgery for the tricuspid valve is dependent on the degree of anatomic and physiologic abnormalities. Surgery for the mild cases usually involves tricuspid valve repair when feasible or valve replacement. Tricuspid valve annuloplasty and tricuspid valve reconstruction, with creation of a monocuspid valve are often possible in experienced centers. However, valve replacement with a mechanical or heterograft bioprosthesis may be required in some patients. A right reduction atrioplasty is often performed.

Improvement in exercise tolerance after valve replacement surgery has been observed, especially in patients with an associated ASD. Long-term complications after surgery are usually related to arrhythmias.[51]

Some patients with severe Ebstein's anomaly may require a Glenn operation with the tricuspid valve repair or even Fontan-type surgery. Accessory pathways that are difficult to ablate in the catheterization laboratory can be attempted during surgery, usually not done in isolation.

Tricuspid valve surgery, with concomitant closure of ASD, for patients with (a) symptoms of deteriorating capacity, (b) cyanosis, (c) paradoxical embolus, (d) progressive cardiomegaly on chest X-ray and (e) progressive RV dilatation or reduction of RV systolic function. However, the decision to proceed to surgery for Ebstein's anomaly should be carefully considered and performed in centers with experience in this disease.

PREGNANCY

Women with known Ebstein's anomaly should undertake prepregnancy counseling by a physician with an expertise in ACHD. Most women can have a successful pregnancy. However, if there is significant right-to-left shunting and cyanosis, there is increased risk of low-birth weight and fetal loss. The risk of CHD in the offspring is approximately 6%.[52] It may be higher in patients with a family history of Ebstein's anomaly. Thromboprophylaxis should be considered in those with interatrial shunts and a modified delivery plan may be needed.

GUIDELINES

Class I

- Surgeons with training and expertise in CHD should perform tricuspid valve repair or replacement, with concomitant closure of an ASD, when present, for patients with Ebstein's anomaly with the following indications:
  - — Symptoms or deteriorating exercise capacity. (*Level of Evidence: B*)
  - — Cyanosis (oxygen saturation < 90%). (*Level of Evidence: B*)
  - — Paradoxical embolism. (*Level of Evidence: B*)
  - — Progressive cardiomegaly on chest X-ray. (*Level of Evidence: B*)
  - — Progressive RV dilatation or reduction of RV systolic function. (*Level of Evidence: B*)
- Surgeons with training and expertise in CHD should perform concomitant arrhythmia surgery in patients with Ebstein's anomaly and the following indications:
  - — Appearance/progression of atrial and/or ventricular arrhythmias not amenable to percutaneous treatment. (*Level of Evidence: B*)
  - — Ventricular pre-excitation not successfully treated in the electrophysiology laboratory. (*Level of Evidence: B*)
- Surgical repair or replacement of the tricuspid valve is recommended in adults with Ebstein's anomaly with the following indications:
  - — Symptoms, deteriorating exercise capacity, or New York Heart Association functional class III or IV. (*Level of Evidence: B*)
  - — Severe TR after repair with progressive RV dilatation, reduction of RV systolic function, or appearance/progression of atrial and/or ventricular arrhythmias. (*Level of Evidence: B*)
  - — Bioprosthetic tricuspid valve dysfunction with significant mixed regurgitation and stenosis. (*Level of Evidence: B*)
  - — Predominant bioprosthetic valve stenosis (mean gradient > 12–15 mm Hg). (*Level of Evidence: B*)
  - — Operation can be considered earlier with lesser degrees of bioprosthetic stenosis with symptoms or decreased exercise tolerance. (*Level of Evidence: B*)

Cyanotic Congenital Heart Disease

INTRODUCTION

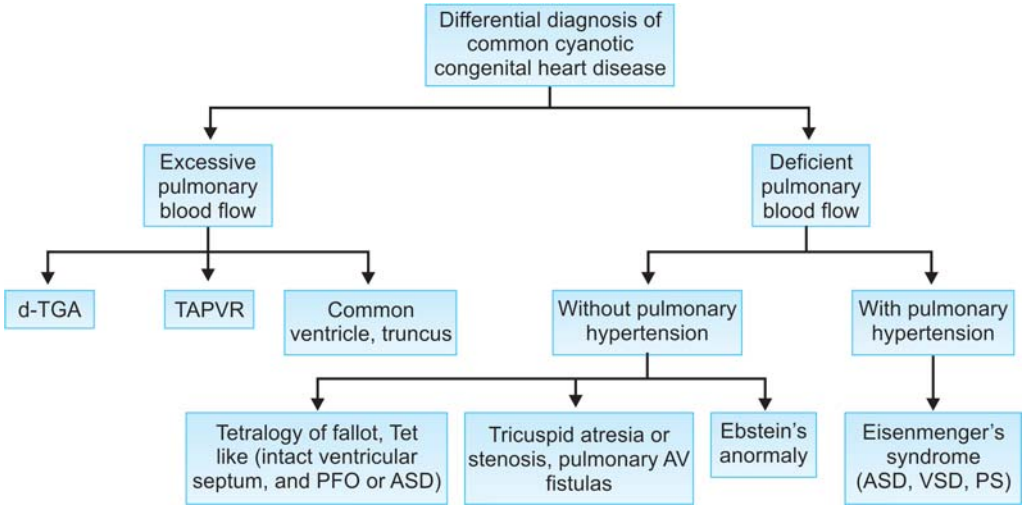
In 1945, Dr Alfred Blalock and Dr Helen Taussig reported an operation that changed a patient's color from blue to pink. The initial collaboration of Taussig and Blalock led to the development of pediatric cardiology and pediatric cardiovascular surgery, making it possible for many cyanotic patients to survive into adulthood. Given that these patients now survive. It is imperative for adult cardiologists to understand their history, disease process and be aware of potential complications. While these patients can live normal lives, every medical decision must be carefully considered. Ideally these patients are managed at Centers of excellence, which specialize in the management of adults with CHD patients and allow for focused and informed care.

All abnormalities resulting in cyanosis require a right-to-left shunt, which may be at the atrial, ventricular or vascular level. Cyanotic heart lesions can be further divided into categories based on the degree of pulmonary blood flow, excessive or deficient, and the pressure in the pulmonary circuit. The status of the PVR, pulmonary blood flow and pulmonary vascular anatomy determine survival, functional capacity and operability. The various cyanotic CHDs can be systematically classified based on one of two categories: excessive pulmonary blood flow or deficient pulmonary blood flow (Flow chart 1). This classification is based on the initial presentation in childhood and is altered by the various palliative procedures performed.

The status of pulmonary blood flow determines the ability of that person to survive, to function and to undergo cardiac surgery. Cyanotic infants with excessive pulmonary blood flow present with respiratory distress, tachypnea and CHF. These patients may develop pulmonary hypertension and early intervention is often required in infancy to prevent irreversible pulmonary vascular changes and Eisenmenger's syndrome.

The most common cyanotic CHDs are associated with deficient pulmonary blood flow and normal PVR is TOF. In these patients, PS or atresia protects them from developing pulmonary hypertension and CHF. The shunt is at the level of

FLOW CHART 1: Systematical classification of various cyanotic heart diseases



the ventricular septum. In childhood, patients have had varying degrees of cyanosis depending upon the RVSP (determined by the degree of RVOT obstruction) and the size of the VSD.

Chronic cyanosis in adult is associated with increased erythropoietin production and secondary erythrocytosis (isolated increase in red blood cells) as a physiological response to tissue hypoxia. This in turn may result in symptoms of hyperviscosity syndrome accompanied by headaches, myalgias, altered mental status, visual disturbances paresthesias and fatigue. Patients who are in a stable chronic cyanotic state without symptoms of hyperviscosity should not undergo phlebotomy. Phlebotomy is only indicated in patients with severe symptoms who are not dehydrated and who have hematocrits above 65. Simultaneous, hydration during phlebotomy and avoidance of dehydration is critical.

Cyanotic patients have various forms of *coagulopathies* and are at increase risk for both bleeding and coagulation. Their platelet counts are generally reduced and they have abnormal platelet function. Several factor deficiencies can be present along the coagulation cascade including factors V, VII, VIII and IX. If anticoagulation is warranted as treatment in these patients, it should be monitored closely. Measurement of the INR in patients treated with vitamin K antagonists who have elevated hematocrits needs to be done in specialized laboratories and can be inaccurate if done in routine blood laboratories.

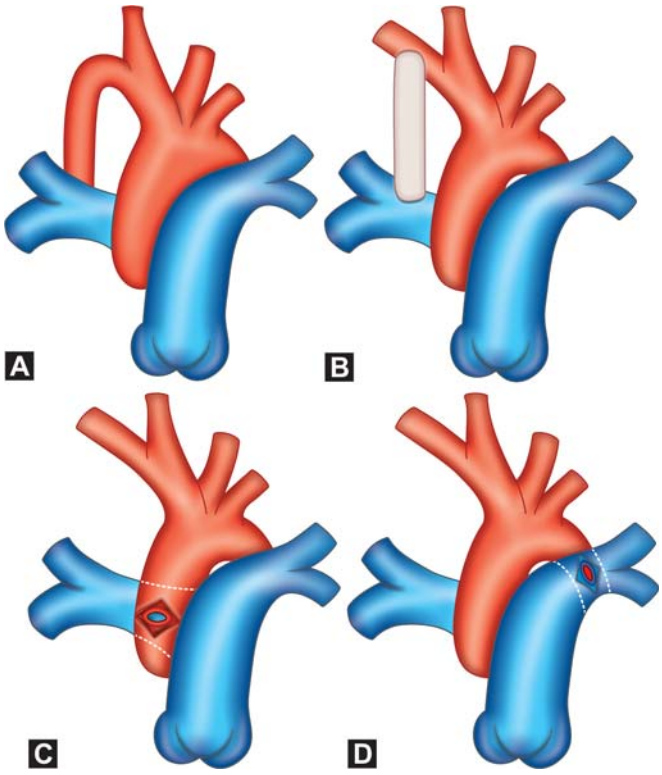
Hyperuricemia, proteinuria and renal dysfunction are common sequelae of chronic cyanosis as a consequence of increased urate production and decreased renal clearance. Urate nephropathy/nephrolithiasis and gouty arthritis may occur. Treatment options are with colchicine, probenecid or allopurinol. Nonsteroidal anti-inflammatory drugs should be avoided as they can lead to renal insufficiency, sodium retention and hypertension.

Hypertrophic osteodystrophy and consequent arthralgias are a common complaint among cyanotic adult congential heart disease patients. Right-to-left shunting causes megakaryocyte release and entrapment in the systemic arterioles with promotion of local cell proliferation.

Neurologic complications, including *cerebral hemorrhage* in anticoagulated patients and brain abscess, should be suspected in patients with a new headache. Platelet transfusion, fresh frozen plasma, vitamin K, desmopressin and cryoglobulin infusions can be used to control bleeding. Patients with a right-to-left shunt may be at risk for paradoxical cerebral emboli. Air filters should be used in peripheral and central lines in cyanotic patients to help prevent these complications.

PALLIATIVE SHUNTS

Wide spectrums of palliative shunts have been used in patients with cyanotic CHD (Figs 14A to D). They are broadly classified



FIGURES 14A TO D: (A) Classic Blalock-Taussig shunt. (B) Modified Blalock-Taussig shunt. (C) Waterston shunt. (D) Potts anastomosis. (*Source:* Khairy P, Poirier N, Mercier LA. Univentricular heart. Circulation. 2007;115:800-12, with permission)

into those that increase pulmonary blood flow through a systemic artery to PA connection or those that divert systemic venous blood flow directly to the PA. The systemic artery to PA shunts includes the Blalock-Taussig shunt, Waterston shunt, Potts anastomosis and central shunts. The systemic venous to PA shunts include the Glenn anastomosis and the Fontan operations. The Fontan circulation will separate the systemic and PA circulations.

ENDOCARDITIS

All patients with cyanotic CHD are at increasing risk of endocarditis. Cardiac structural abnormalities, presence of prosthetic material, shunt and conduits increase their likelihood to develop an infection. A persistent shunt is also associated with a risk for brain abscess. According to the 2008 ACC/AHA management for patients with ACHD, antibiotics for endocarditis prophylaxis is indicated before dental procedures in patients with CHD is recommended in all patients with both unrepaired and palliated cyanotic CHD.

PREGNANCY AND CONTRACEPTION

When patients with CHD reach childbearing age, pregnancy and contraception become important issues and the risks of both should be discussed in detail with the patients. Preconceptual counseling is ideal but often the patients present after conception, making clinical decision more complicated.

Patients with Eisenmenger's syndrome, severe pulmonary hypertension, severe LVOT obstruction and dilated aortic roots are at high risk for complications. The low risk lesions include small left-to-right shunts, repaired TOF, mild LVOT obstruction.[53,54]

The choice of contraceptive methods is complicated in patients with cyanotic CHD. Estrogen-containing oral contraceptives are associated with an increased risk for thromboembolic complications and are contraindicated in cyanotic patients. Progesterone-only pills are associated with irregular bleeding and fluid retention. Intrauterine devices are generally contraindicated in patients with CHD because of risk of infection. However, in monogamous women, the risk of infection with an intrauterine device is low and devices that elude progesterone-like hormones are a reasonable choice. Surgical or nonsurgical sterilization methods should be considered in women who are in the highest risk categories for complications of pregnancy such as those with Eisenmenger's syndrome and severe cyanosis.

For the purposes of this chapter, cyanotic heart disease is classified as (a) conotruncal abnormalities, (b) single ventricles and (c) Eisenmenger's syndrome. The clinical presentation will focus on the adult patient—the focus of this chapter.

TETRALOGY OF FALLOT

GENERAL CONSIDERATIONS

Tetralogy of Fallot is the most common cyanotic congenital heart lesion, accounting for 10% of all CHD.[55] It consists of a malalignment VSD in conjunction with RVOT obstruction,

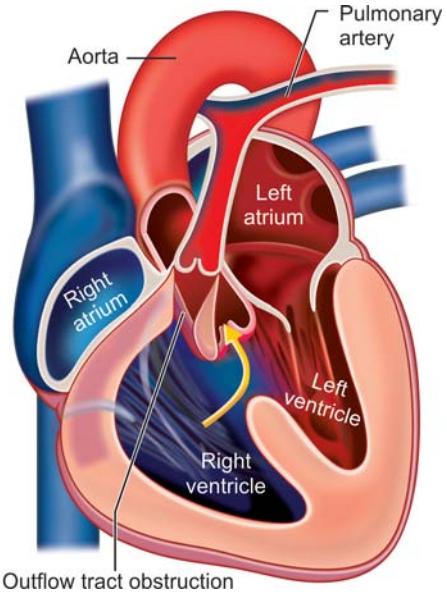


FIGURE 15: Tetralogy of Fallot. (*Source:* Brickner ME, Hillis LD, Lange RA. Congenital heart disease in adults. Second of two parts. N Engl J Med. 2000;342:334-42, with permission)

overriding aorta and consequent RVH (Fig. 15). The RVOT obstruction may be subvalvar, valvar or supravalvar. Often it is a combination of infundibular stenosis with valvar stenosis. Only 11% of individuals, born with this lesion, survive without palliative surgery beyond the age of 20 years and only 3% beyond the age of 40 years.[56] However adults who undergo restorative surgery can live a long life.

PATHOPHYSIOLOGY

Although it is called tetralogy, the pathophysiology of this disorder is dependent on the degree of RVOT obstruction and the size of the VSD. The severity of the RVOT obstruction determines the RVSP and, therefore, the degree of right-to-left shunting. Commonly, the RVOT obstruction occurs at multiple levels with valvular abnormalities with or without hypertrophied obstructing muscle bands in the RVOT. Occasionally, a patient may present with an acyanotic picture because the degree of PS is mild to moderate with minimal right-to-left shunting (pink TOF). However, as these patients get older, their PS can worsen and they may develop cyanosis. The anatomy of the pulmonary arterial circulation varies widely. The most severe form of TOF is pulmonary atresia. In this variant, the source of pulmonary blood flow is predominantly aortopulmonary collateral vessels arising from the descending aorta.

Another variant of TOF is absent pulmonary valve syndrome, which is associated with severe pulmonic regurgitation and enlarged pulmonary arteries.

ASSOCIATED ANOMALIES

Common associates anomalies include an interatrial setpal defect (ASD or PFO is present in 15%; the "pentalogy" of Fallot), right-sided aortic arch (25%, most commonly seen in pulmonary atresia), branch pulmonary stenosis (15%) and anomalous coronary distribution.

Tetralogy of Fallot may occur in conjunction with DiGeorge syndrome.[57] The chromosome 22q11.2 microdeletion is present in up to 15% of the patients with TOF and is higher in those with pulmonary atresia. In addition, mutations in the genes encoding the cardiac transcription factor NKX2-5 and the Notch ligand Jaged have been reported in patients with TOF. Screening for heritable causes of their condition should be offered to all patients with TOF.

CLINICAL FINDINGS

Signs and Symptoms

Most adult patients presenting with TOF have often undergone palliative or restorative surgery. They usually present with symptoms related to long-term complications of surgery.

Physical Examination

Physical examination in an adult with TOF depends on the type of repair performed and the residual defect. In the increasingly rare adult patient with a persistent aortopulmonary shunt, such as Blalock-Taussig shunt, Waterston shunt or Potts anastomosis, there should be a continuous murmur, a single S2 and a harsh systolic murmur. In the patient with tetralogy with pulmonary atresia, continuous murmurs may be audible over the patient's back due to the aortopulmonary collaterals.

After total repaired of TOF, there is usually a prominent and often sustained right ventricular impulse, a single S2, a systolic ejection murmur with intensity and timing dependent on the severity of residual stenosis and, a low-pitched decrescendo murmur of pulmonary valve insufficiency. A right-sided S3 and/or S4 may be present. In the presence of dilated aortic root, a second high-pitched diastolic murmur of aortic valve regurgitation may be present.

Patients with a pulmonary valve conduit and a competent pulmonary valve may have an early systolic murmur and a widely and physiologically split S2 due to the common RBBB. With time, valve degeneration may lead to the development of a diastolic pulmonary regurgitation murmur.

DIAGNOSTIC STUDIES

Electrocardiogram and Chest X-ray

Right ventricular hypertrophy with right axis deviation is usually seen on ECG in childhood. RBBB with left anterior hemiblock is seen commonly in patients after tetralogy repair surgery. The degree of QRS prolongation should be noted and followed as it has been used as clinical marker for sudden death risk.

Chest X-ray in the unrepaired is typically shows the boot-shaped heart (Coeur en sabot), which is seen when the PS is severe and a prominent right ventricle. Right-sided aortic arch (25%) is a variant seen with TOF may be seen on chest X-ray. The pulmonary blood flow usually reduced in the unrepaired state and normal after repair. The PA may be dilated in patients with absent pulmonary valve syndrome. Patients who have undergone total repair and have residual severe pulmonic regurgitation may have a dilated right ventricle with filling of the retrosternal air space on lateral chest radiography.

Echocardiography

In the rare adult with unrepaired TOF, there is a perimembranous VSD, RVOT obstruction, RVH and an overriding aorta (Figs 16A to D and 17A and B). The large overriding aortic root can be appreciated and attention must be paid to the presence of aortic regurgitation and prolapse of the aortic valve leaflets. The right ventricle is rarely dilated and the tricuspid regurgitant jet velocity reflects the degree of outflow tract obstruction. The level of RVOT obstruction is variable. There may be a small PA with a thickened pulmonary valve. The infundibulum is usually hypertrophied. Color flow Doppler shows right-to-left shunting across the VSD unless the outflow obstruction is mild. The velocity across the VSD by CW Doppler is usually low.

The increasingly rare Waterston or Potts shunt can be visualized with continuous color flow Doppler. A Blalock-Taussig shunt should be interrogated for continuous flow; the gradient through the shunt will reflect the aortic to PA gradient and permit estimation of the PA systolic pressure.

In the adult with repaired TOF, echocardiography should focus on the right ventricular infundibular region, the pulmonary valve and RV size and function. Residual RVOT obstruction with a persistent subvalvular gradient or valvular gradient is less common that severe pulmonary valve regurgitation (Figs 18A to D). When a gradient is detected, the shape of the jet can provide a clue as to the level of obstruction; a late peaking "dagger-shaped" jet suggests dynamic subvalvular obstruction and an early to mid-peaking jet is consistent with valvular obstruction. Residual VSDs due to patch leaks and ASDs should be sought. While color flow Doppler is sensitive for detection of VSDs, saline contrast is often necessary to detect shunts at the atrial level. There may be aortic dilatation with varying degrees of aortic regurgitation. Increasingly recognized is the development of LV dysfunction in the older patient with TOF.

Transesophageal echocardiogram can be useful to define the anatomy of the RVOT and the pulmonary valve when precordial imaging is suboptimal.

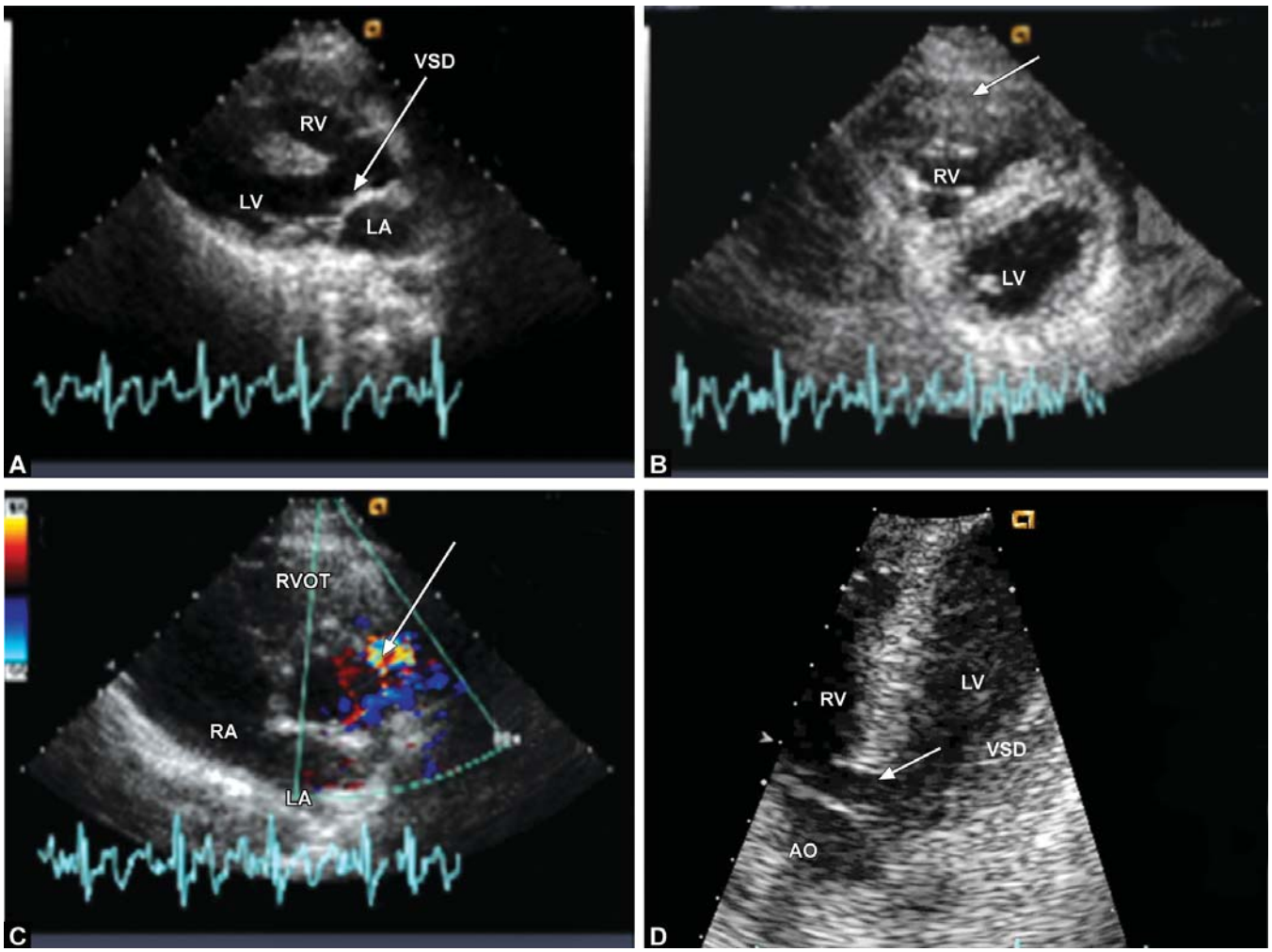
Magnetic Resonance Imaging and Computed Tomography

Magnetic resonance imaging is an important noninvasive modality in assessing patients with repaired TOF, primarily to provide accurate assessment of RV size, ejection fraction, volume and the pulmonic regurgitant fraction.

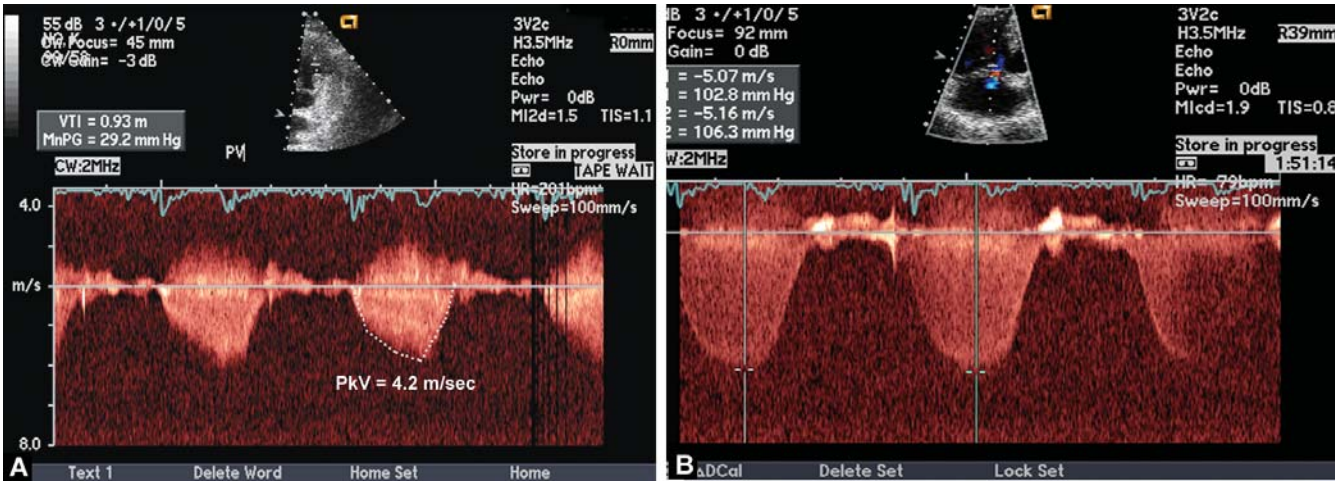
Computed tomography scanning can be used as a secondary alternative to make measurements of the right ventricle and systolic function and is potentially helpful in patients who cannot have an MRI due to a pacemaker or defibrillator.

Catheterization

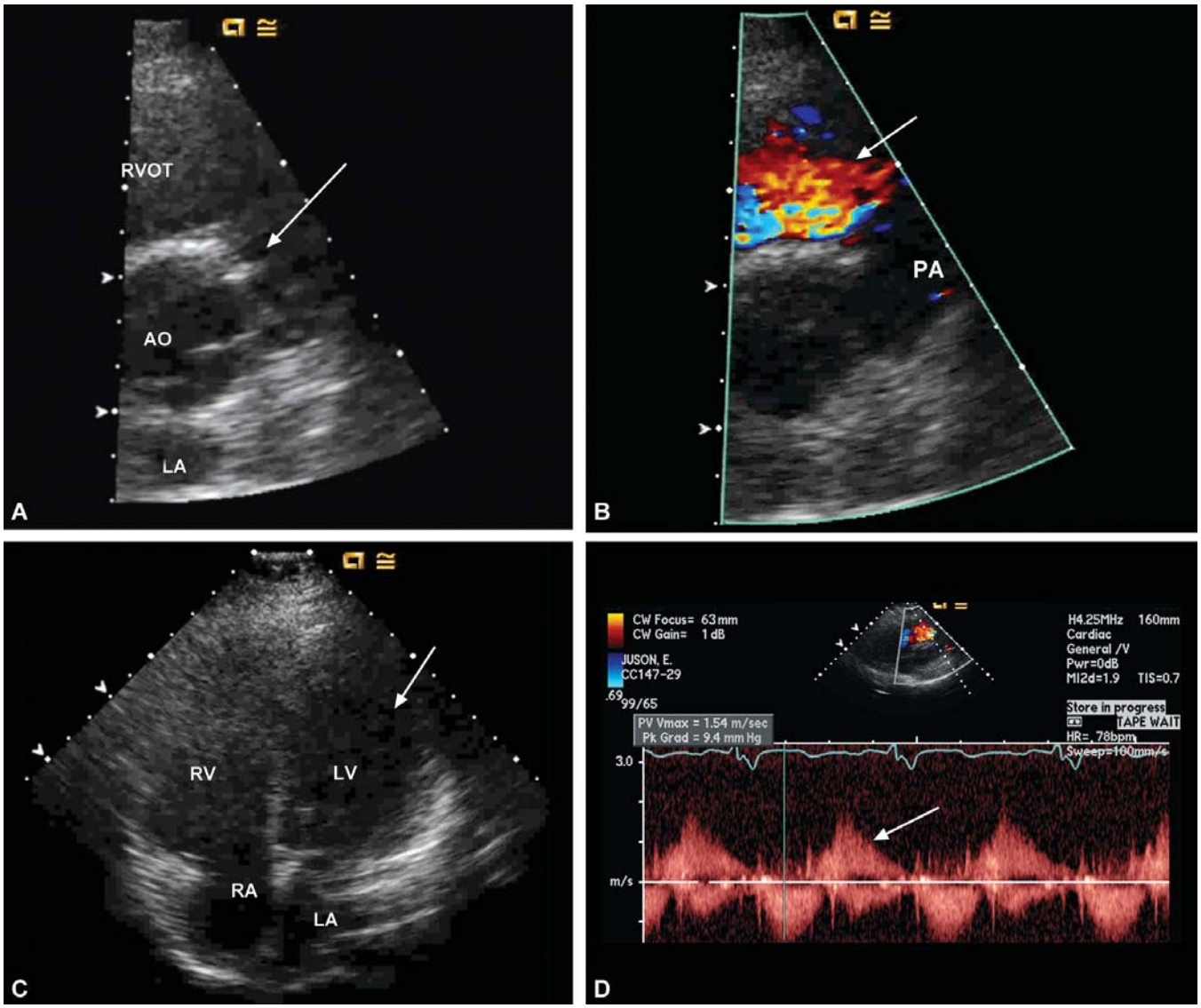
Catheterization should be performed prior to any surgical intervention in patients with TOF, whether it is for primary surgery or repeat surgery. It is important to identify the origin of the coronary arteries. If the LAD originates from the right coronary cusp, it may cross the RV infundibulum, a potential incision site for the repair and surgical modifications may be required. Prior to repair in TOF with pulmonary atresia



FIGURES 16A TO D: Transthoracic echocardiogram in cyanotic patient with unrepaired tetralogy of Fallot. (A) Parasternal long axis view in a patient with large malalignment ventricular septal defect and overriding aorta (arrow). (B) Parasternal short axis view demonstrating flattened septum consistent with right ventricular pressure overload and severe right ventricular hypertrophy (arrow). (C) Parasternal short axis view showing the narrowed right ventricular outflow tract and high velocity jet at the level of the hypoplastic pulmonary valve (arrow). (D) Magnified apical five-chamber view showing aorta overriding septum with moderate sized ventricular septal defect. (Abbreviations: AO: Aorta; LA: Left atrium; LV: Left ventricle; RV: Right ventricular; RVOT: Right ventricular outflow tract; VSD: Ventricular septal defect)



FIGURES 17A AND B: (A) Continuous wave Doppler jet through the right ventricular outflow tract with a peak velocity of 4.2 m/sec consistent with a peak gradient of 70 mm Hg suggestive of severe right ventricular outflow tract obstruction. The late peaking jet suggests a component of dynamic obstruction associated with infundibular hypertrophy. (B) High velocity tricuspid regurgitant jet estimated right ventricular systolic pressure as 110 mm Hg based on a right atrial pressure of 5 mm Hg. Therefore, the pulmonary artery systolic pressure is low enough (110–70 mm Hg = 40 mm Hg) to consider a total repair in this patient



FIGURES 18A TO D: Transthoracic echocardiogram in a patient with repaired tetralogy of Fallot. (A) Parasternal short axis view in a patient with dilated right ventricular outflow tract, remnants of pulmonary valve tissue (arrow). (B) Parasternal short axis view demonstrating broad low velocity jet of pulmonary valve regurgitation (arrow). (C) Four-chamber view showing dilated right ventricle. (D) Continuous wave Doppler jet of low-velocity dense pulmonary valve regurgitant jet with steep slope and short pressure half-time consistent with severe pulmonary valve regurgitation. There was no evidence of residual stenosis. (Abbreviations: AO: Aorta; LA: Left atrium; LV: Left ventricle; PA: Pulmonary artery; RA: Right atrium; RV: Right ventricular; RVOT: Right ventricular outflow tract)

catheterization defines aortopulmonary collateral which primarily arise from the descending thoracic aorta.

Additionally, in post-repair patients, catheterization can offer therapeutic interventions to eliminate residual native or palliative systemic to PA shunts, such as ASDs or VSDs, and to address branch pulmonary stenosis. Percutaneous pulmonic stent valves for patients who develop PR, remains investigational; however, this procedure is promising.

TREATMENT

Many older adults require palliative aortopulmonary shunts prior to total repair, which is often not performed until age 4–5 years. Large shunts may have led to pulmonary vascular disease with PAH, although this complication is relatively uncommon. Kinking of the PA adjacent to the Waterston shunt may have led to decreased pulmonary blood flow to a solitary lung and eventual loss of lung function.

Restorative surgery involves closure of the VSD and relief of the pulmonary or infundibular stenosis (Fig. 19). Closure of the VSD is usually done with a synthetic patch. Relief of the RVOT obstruction is achieved by resection of muscle in the infundibulum and pulmonary valvotomy. However often resection alone will not suffice and the pulmonary annulus may have been enlarged with a transannular synthetic patch, which disrupts the integrity of the pulmonary annulus. In patients with pulmonary atresia, a valved conduit from the right ventricle to the PA may be required.

PROGNOSIS

Late survival after surgery is excellent and 35-year survival nears 85–95%.[58] There are significant complications associated with restorative surgery. Hemodynamic sequelae include pulmonary valvular regurgitation, RV aneurysms, VSD patch leaks, aortic regurgitation and LV dysfunction.[59] It is imperative to follow

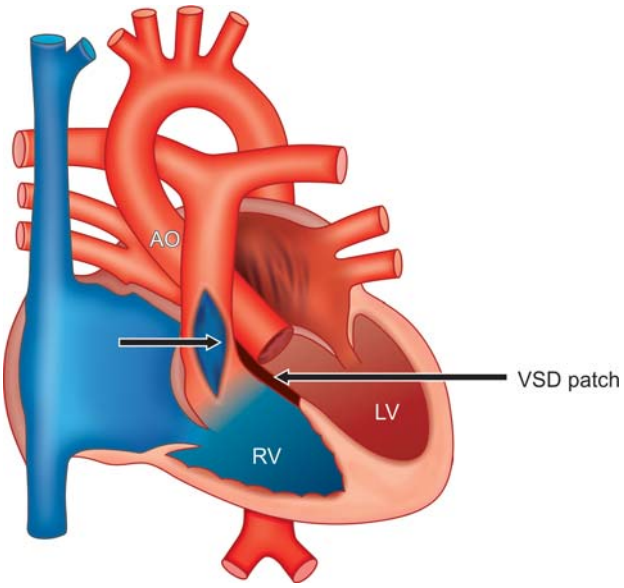


FIGURE 19: Repaired tetralogy of Fallot with ventricular septal defect patch, patch augmentation of the pulmonary artery (small arrow). (Abbreviations: AO: Aorta; LV: Left ventricle; RV: Right ventricular; VSD: Ventricular septal defect). (*Source:* Mayer CD, Mullins CE. Congenital Heart Disease: A Diagrammatic Atlas. New York: Alan R Liss Inc; 1988. p. 5)

these patients closely for supraventricular tachyarrhythmias and ventricular tachycardia.

Pulmonary regurgitation develops as a consequence of surgical repair of the RVOT and enlargement of the pulmonary annulus. It is the most common hemodynamic derangement encountered after repair. Eventual RV enlargement occurs, and repair or replacement of the pulmonary valve is often required usually after the second decade of life.[60] Percutaneous pulmonary valve implantation is becoming a viable option for selected patients.

Atrial fibrillation and flutter are common in older patients with TOF. The substrate is thought to be surgical scar in the atria. However, development of these arrhythmias is often indicative of hemodynamic compromise and volume overload in the presence of RV failure with TR.

Although ventricular ectopy is common in these patients, sustained ventricular tachycardia is relatively uncommon. QRS widening of greater than 180 ms is a marker in these patients for VT and sudden cardiac death.[61] It is imperative for physician to remains vigilant for symptoms of palpitations, presyncope or syncope. Some experts advocate routine annual screening with Holter monitoring and referral to electrophysiologists with experience in CHD when complex ectopy is detected. Documented sustained VT is usually managed by ICD implantation.

Postoperative progressive QRS widening often accompanies RV dilatation and is commonly seen in patients with transannular patch repair and severe pulmonary regurgitation. A large retrospective study of risk stratification underscored the importance of assessment of QRS duration, degree of PR and obstruction and timely intervention to modify risk of sudden cardiac death. Surgical replacement of the pulmonic valve has been shown to stabilize the QRS prolongation and reduce the incidence of arrhythmias. Recent modifications to the surgery including avoidance of RVOT incision by avoidance of transannular patch and early surgical intervention may further reduce incidence of arrhythmias.

Patients with pulmonary atresia and diminutive PA present more of a management challenge. Their survival depends upon presence of aortopulmonary collaterals. An extracardiac conduit may be placed in these patients from the right ventricle to the PA in patients with adequate main pulmonary arteries. In patients, with absent or small pulmonary arteries, complex surgery that "unifocalizes" the pulmonary circulation is required with centralization of the pulmonary blood flow and connection to the PA. In addition, their management may require multiple interventional catheterizations for balloon dilatation of stenosis for the distal pulmonary arteries, intravascular stent placement and coil embolizations of the aortopulmonary collaterals after corrective surgery.

PREGNANCY

In uncorrected patients, pregnancy poses significant risks to both mother and fetus. The fall in systemic vascular resistance may increase cyanosis due to increase in right-to-left shunting.

In corrected patients, the risks depend upon their hemodynamic status. In patients with good hemodynamics and minimal symptoms, pregnancy is fairly low-risk.

However, in women with severe PR, residual RVOT obstruction and RV dysfunction pregnancy may lead to worsening RV failure and arrhythmias.[62] Pregnancy should be managed and delivery should be performed in a center for ACHD.

GUIDELINES

Evaluation and Follow-up

Class I

- All patients should be seen at least yearly by a cardiologist who has expertise in the management of ACHD. (*Level of Evidence*: *C*)
- Echocardiograms and MRIs should be performed by staff with expertise in ACHD. (*Level of Evidence*: *C*)
- Screening for heritable causes of their condition (e.g. chromosome 22q11 deletion) should be offered to all patients with TOF. (*Level of Evidence: C*)
- Before pregnancy or if a genetic syndrome is identified, consultation with a geneticist should be arranged for patients with TOF. (*Level of Evidence: B*)
- Patients with unrepaired or palliated forms of tetralogy should have a formal evaluation at an ACHD center regarding suitability for repair. (*Level of Evidence: B*)

Recommendations for Surgery in Patients with Previous Repair of Tetralogy of Fallot

Class I

- Surgeons with training and expertise in CHD should perform operations in adults with previous repair of TOF. (*Level of Evidence: C*)
- Pulmonary valve replacement is indicated for severe pulmonary regurgitation and symptoms or decreased exercise tolerance. (*Level of Evidence: B*)

- Coronary artery anatomy, specifically the possibility of an anomalous anterior descending coronary artery across the RVOT, should be ascertained before operative intervention. (*Level of Evidence: C*)

Class IIa

- Pulmonary valve replacement is reasonable in adults with previous TOF, severe pulmonary regurgitation, and any of the following:
  - — Moderate to severe RV dysfunction. (*Level of Evidence: B*)
  - — Moderate to severe RV enlargement. (*Level of Evidence: B*)
  - — Development of symptomatic or sustained atrial and/or ventricular arrhythmias. (*Level of Evidence: C*)
  - — Moderate to severe TR. (*Level of Evidence: C*)
- Collaboration between ACHD surgeons and ACHD interventional cardiologists, which may include preoperative stenting, intraoperative stenting or intraoperative patch angioplasty, is reasonable to determine the most feasible treatment for PA stenosis. (*Level of Evidence: C*)
- Surgery is reasonable in adults with prior repair of TOF and residual RVOT obstruction (valvular or subvalvular) and any of the following indications:
  - — Residual RVOT obstruction (valvular or subvalvular) with peak instantaneous echocardiography gradient greater than 50 mm Hg. (*Level of Evidence: C*)
  - — Residual RVOT obstruction (valvular or subvalvular) with RV/LV pressure ratio greater than 0.7. (*Level of Evidence: C*)
  - — Residual RVOT obstruction (valvular or subvalvular) with progressive and/or severe dilatation of the right ventricle with dysfunction. (*Level of Evidence: C*)
  - — Residual VSD with a left-to-right shunt greater than 1.5:1. (*Level of Evidence: B*)
  - — Severe AR with associated symptoms or more than mild LV dysfunction. (*Level of Evidence: C*)
  - — A combination of multiple residual lesions (e.g. VSD and RVOT obstruction) leading to RV enlargement. (*Level of Evidence: C*)

Recommendations for Arrhythmias: Pacemaker/ Electrophysiology Testing

Class I

Annual surveillance with history, ECG, assessment of RV function, and periodic exercise testing is recommended for patients with pacemakers/automatic implantable cardioverter defibrillators. (*Level of Evidence: C*)

Class IIa

Periodic Holter monitoring can be beneficial as part of routine follow-up. The frequency should be individualized depending on the hemodynamics and clinical suspicion of arrhythmia. (*Level of Evidence: C*)

Class IIb

Electrophysiology testing in an ACHD center may be reasonable to define suspected arrhythmias in adults. (*Level of Evidence: C*)

TRUNCUS ARTERIOSUS

GENERAL CONSIDERATIONS

Truncus arteriosus (TA) is a rare lesion, accounting for only 1% of all congenital heart defects. TA is defined as a single arterial trunk arising from both ventricles due to failure of septation of the TA, which gives rise to the systemic, pulmonary and coronary circulation. It is always accompanied by a VSD.

Truncus arteriosus defects are in the family of conotruncal abnormalities similar to TOF. The pulmonary arteries arise from the arterial trunk in a variety of configurations. A large VSD results in the right-to-left shunting and subsequent cyanosis. The common truncus overrides this large VSD with a common truncal valve, which can be trileaflet, bileaflet and four or more leaflets may be present.[63,64] The majority of adults with TA have had surgery.

Classifications

Several anatomic classifications based upon the PA anatomy are available (Fig. 20). The variant that was called Type IV

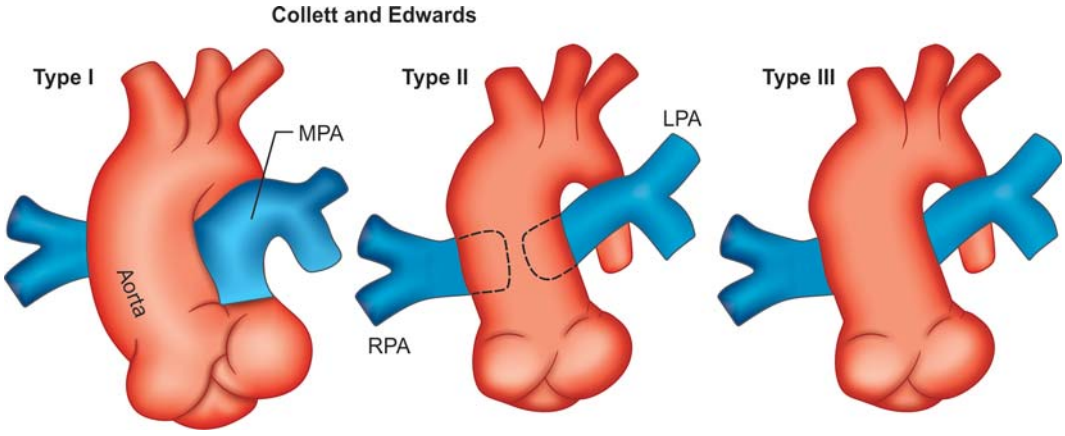


FIGURE 20: Variations of truncus arteriosus; adapted from Figure 11 (Abbreviations: LPA: Left pulmonary artery; MPA: Main pulmonary artery; RPA: Right pulmonary artery). (*Source:* Bashore TM. Adult congenital heart disease: right ventricular outflow tract lesions. Circulation. 2007;115:1933-47, with permission)

where there were no main pulmonary arteries, and the flow arose from the descending aorta is now classified as pulmonary atresia with VSD.

Type I truncus—The common PA exits the lateral aspect of the trunk, near the truncus valve. This is the most common type, and lends itself to easier repair.

Type II truncus—There are separate origins of the right and left pulmonary arteries from the posterior aspect of the ascending trunk.

Type III truncus—Each PA arises from the lateral aspect of the truncus.

GENETIC INHERITANCE

There is a strong association of chromosome 22q11 deletions and DiGeorge syndrome with TA.

CLINICAL FINDINGS

Signs and Symptoms

Most infants, if not surgically corrected before one year, die from CHF. As the PVR increases in infancy, there degree of cyanosis and right-to-left shunting increases.

Adults presenting with unrepaired TA typically present with Eisenmenger's syndrome.

DIAGNOSTIC STUDIES

Electrocardiogram and Chest X-ray

Biventricular hypertrophy is common in infants. If pulmonary vascular disease develops, there is RVH. In repaired adults, the ECG findings will depend on the presence of residual lesions. A RBBB may found due to VSD closure.

In the infant, there is cardiomegaly with prominent pulmonary arterial markings. In the repaired adult, the appearance depends on the presence of residual lesions. Approximately 30% of patients have a right-sided aortic arch.

Echocardiography and Magnetic Resonance Imaging

Diagnosis can be made by 2D Echocardiography. In the absence of repair, there is an overriding common arterial trunk with a common truncal valve, which has a variable number of truncal valve cusps. Truncal valve may associated with stenotic or regurgitant lesions. The origin of the pulmonary arteries is more readily visualized in Type I lesions. Also, the VSD size and location should be noted.

In the adult with repaired TA, the truncal root may show varying degrees of dilatation with valvular regurgitation. The gradient across the conduit should be evaluated as well as the presence of conduit valve regurgitation. The right and left ventricles may show varying degrees of dilatation and dysfunction depending on the severity of valvular regurgitation. Cardiac MRI is indicated to evaluate truncal size and may be useful to follow RV size and function in the presence of conduit insufficiency.

TREATMENT AND PROGNOSIS

Surgery consists of VSD closure, surgical separation of the pulmonary arteries from the truncus followed by placement of a valved conduit from the RV to the PA. Adults with repaired TA must be followed for progressive RV to PA conduit obstruction, ventricular dysfunction, truncal root dilatation and truncal valve regurgitation.

Repeat surgery in the adult is usually required when there is conduit obstruction due to pseudointimal hyperplasia and regurgitation due to degeneration of the bioprosthetic valve. There is increasing investigational use of implantable percutaneous valves similar to patients with TOF. There can be progressive truncal root dilatation and progressive regurgitation of the native truncal valve, which serves as the systemic semilunar valve. When this valve has been replaced in childhood, repeat surgery may be required for prosthetic mismatch with the growth of the patient or bioprosthetic valve degeneration.

PREGNANCY

Patient with successful repairs and no residual lesions are able to tolerate pregnancy. Patients with residual lesions/conduit obstructions may require correction prior to considering a safe pregnancy. In uncorrected adults with Eisenmenger's syndrome, pregnancy is contraindicated. Genetic testing with chromosome analysis is recommended prior to conception, and fetal echocardiography is advised.

d-TRANSPOSITION OF THE GREAT ARTERIES

GENERAL CONSIDERATIONS

In d-transposition of the great arteries (d-TGA), the aorta arises from the right ventricle and the PA from the left ventricle. There is atrioventricular concordance with ventriculoarterial discordance (Fig. 21). The "d" (meaning right) refers to the rightward looping of the cardiac tube in embryologic development, which results in normal ventricular orientation. However, the arterial transposition results in independent,

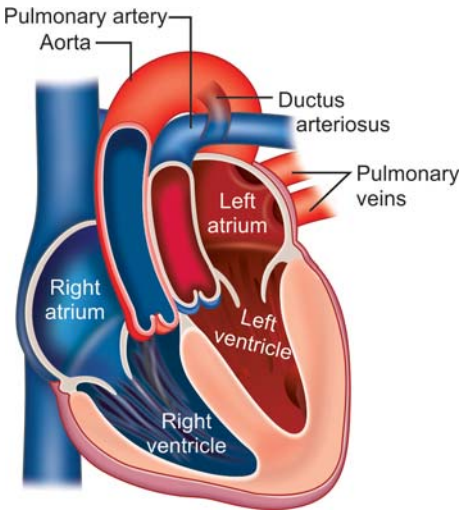


FIGURE 21: Transposition of the great arteries. (*Source:* Brickner ME, Hillis LD, Lange RA. Congenital heart disease in adults. First of two parts. N Engl J Med. 2000;342:256-63, with permission)

parallel pulmonic and systemic circuits. Survival depends upon mixing of the right-sided systemic and left-sided pulmonic circuits via a PDA, ASD or VSD.

More males than females are affected by this condition, with an approximate 3:1 ratio. There is an increased incidence in infants with diabetic mothers.[65]

Without any treatment, the survival is low and mortality rate is greater than 90% in the first year of life.[66] Infants with shunting have a higher survival rate. At birth, if there is no shunting of blood, atrial communication must be created to permit survival. In the interim, Prostaglandin E1 may be given to maintain patency of the ductus arteriosus.[66] Survival in adults depends upon the type of corrective surgery and the function of the right ventricle.

ASSOCIATED ANOMALIES

d-transposition of the great arteries may be associated with VSDs, PDAs and with subpulmonic or valvar PS.

CLINICAL FINDINGS

Symptoms

Adults with atrial switch surgery may have symptoms of fatigue and exertional dyspnea due to systemic RV failure. Symptoms suggestive of SVC syndrome can be seen with superior baffle obstruction and occasionally peripheral edema may be due to inferior limb baffle obstruction. Palpitations are common; presyncope and syncope may be due to hemodynamically important arrhythmias.

Patients with arterial switch operations (ASOs) are often asymptomatic with excellent exercise tolerance.[67] However exertional chest pain should be carefully investigated as coronary artery obstruction of the reimplanted coronaries may occur.

Physical Examination

Atrial switch: Prominent and sustained RV impulse; loud anterior A2; holosystolic murmur of TR.

Arterial switch: Diastolic murmur of aortic regurgitation; systolic murmur of pulmonary stenosis.

DIAGNOSTIC STUDIES

Electrocardiogram

Atrial switch: The ECG demonstrates a rightward QRS axis and RVH.

Arterial switch: The ECG is usually normal.

Chest X-ray

Atrial switch: The RV is prominent. There may be a narrow mediastinum with an oblong shape cardiac silhouette; "egg-on-side".

Arterial switch: Normal mediastinal borders are present.

Echocardiography

d-transposition with atrial switch: The ventricles are in normal position. The systemic right ventricle shows severe RVH and an increase in right ventricle size. The interventricular septum is flattened toward the subpulmonic left ventricle. The great vessels are discordant with an anterior rightward aorta arising from the RV, and leftward and posterior PA arising from the LV. The interatrial baffles can be visualized in the apical views. The four-chamber view demonstrates the pulmonary venous limb of the baffle. The point of drainage is rarely narrowed with a gradient that can lead to pulmonary venous hypertension. The tricuspid valve serves as the systemic AV valve and varying degrees of regurgitation may result from RV dilatation and dysfunction. The systemic venous limb of the baffle diverting flow to the mitral valve is usually best seen in the apical two-chamber view.

High-velocity flow from the IVC with aliasing on color flow Doppler suggests IVC obstruction. The SVC should be interrogated from right supraclavicular region to detect normal venous flow. Obstruction should be suspected if high flow velocities are detected or if flow signals are not detected. Baffle leaks are not usually detected with color flow Doppler, and agitated saline contrast should be done at least once in every patient to detect a shunt. With systemic to pulmonary shunting, contrast will be seen in the systemic venous limb of the baffle and the left ventricle, and then appear on the right side of the heart. Because an obstructed SVC will decompress through the azygous vein to the IVC, agitated saline injected into an upper extremity will appear first in the IVC on subcostal imaging before appearing in the baffle, when this complication is present.

In the patient with a history of associated VSD, residual leak across the VSD should be identified with color flow Doppler. The LVOT should be interrogated for evidence of subpulmonic or valvar stenosis.

After arterial switch procedure, echocardiography may show neoaortic dilatation with neoaortic valve regurgitation. Branch pulmonary stenosis can also be present.

Magnetic Resonance Imaging

Magnetic resonance imaging is primarily indicated in patients who need further delineation of cardiovascular anatomy. In patients with atrial switch, it provides additional information about the baffles and potential leaks, and obstructions and quantitation of the systemic RV volume and ejection fraction.

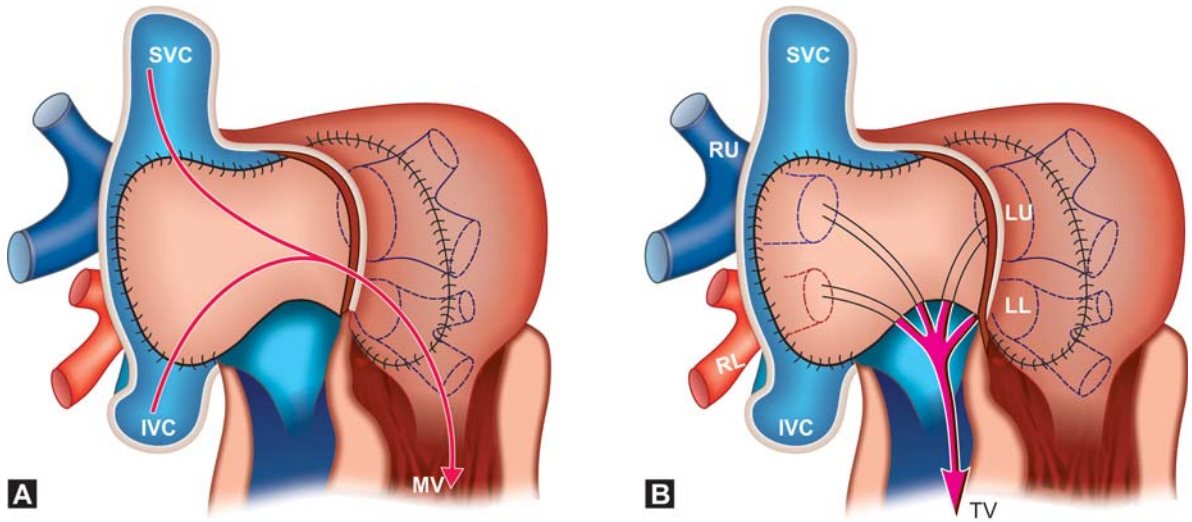
Catheterization and Percutaneous Intervention

In adults, cardiac catheterization is rarely required for diagnosis. However there are percutaneous options for closure of baffle leaks and stenting for relieving baffle obstruction. An important but uncommon used is to evaluate for coronary ostial stenosis in patients with arterial switch.

TREATMENT

Atrial Switch

Physiologic correction was first introduced in 1959 by Senning[68] and in 1964 by Mustard[69] (Figs 22A and B). These operations redirect the pulmonary and systemic returns at an atrial level. The atrial septum is excised, and a baffle is created to direct the systemic venous return to the mitral valve into the left ventricle, and the pulmonary venous flow to the tricuspid valve into the



FIGURES 22A AND B: Arterial switch correction of d-transposition of the great arteries. (A) The systemic venous blood from the superior vena cava (SVC) and inferior vena cava (IVC) is diverted through the baffle to the mitral valve (MV). (B) The pulmonary venous blood is diverted to the tricuspid valve. (Abbreviations: IVC: Inferior vena cava; LL: Left lower pulmonary vein; LU: Left upper pulmonary vein; MV: Mitral valve; RL: Right lower pulmonary vein; RU: Right upper pulmonary vein; SVC: Superior vena cava; TV: Tricuspid valve). (*Source:* Warnes CA. Transposition of the great arteries. Circulation. 2006;114:2699-709)

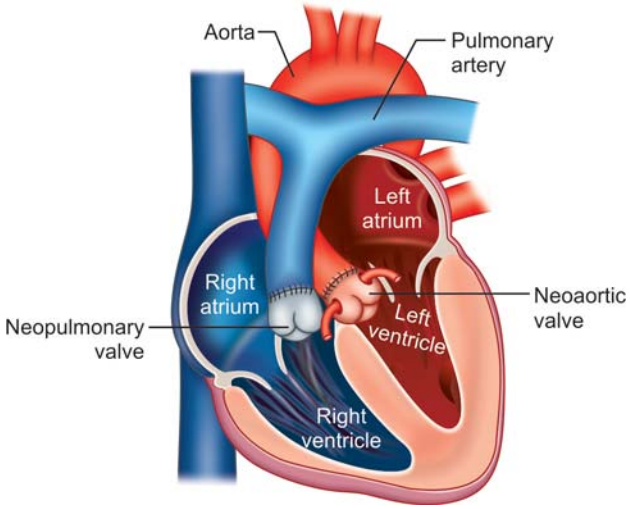


FIGURE 23: Arterial switch for d-transposition of the great arteries. (*Source:* Brickner ME, Hillis LD, Lange RA. Congenital heart disease in adults. Second of two parts. N Engl J Med. 2000;342:334-42)

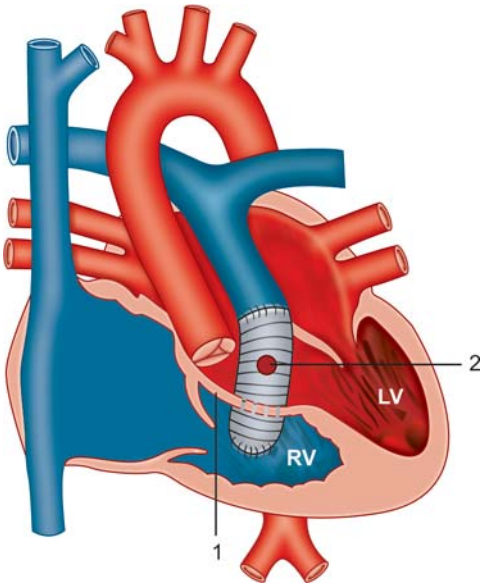


FIGURE 24: The Rastelli operation
(*Source:* Warnes CA. Transposition of the great arteries. Circulation. 2006;114:2699-709, with permission)

right ventricle. The Senning used right atrial wall and atrial septal tissue to create the baffle, whereas the Mustard procedure used pericardium or synthetic material to create the baffle.

In 1976, Jatene introduced an ASO,[70] which reestablishes the left ventricle as the systemic chamber (Fig. 23). The aorta and pulmonary are transposed and the coronary arteries are reimplanted onto the neoaorta. An accompanying LeCompte maneuver leaves both branches of the PA anterior to the aorta.

Rastelli Procedure

One surgical option in patients with large VSDs and with significant PS (valvar or subvalvar) is a Rastelli repair (Fig. 24). This includes an LV to aorta valve baffle through the VSD and an RV to PA conduit.

PROGNOSIS

After an atrial switch procedure, complications, such as sinus node dysfunction, tachyarrhythmias (atrial and ventricular arrhythmias), AV valve regurgitation, RV (systemic ventricle) failure and baffle leaks and obstruction, are common. Pulmonary hypertension is rare. Surgical reintervention or cardiac transplantation may be considered in certain patients. Atypical atrial flutter is present in approximately 20% of the patients.[71] Bradyarrhythmias, mostly due to sinus node dysfunction, may require pacemaker implantation in approximately 10% of these patients. Ventricular arrhythmias and systemic ventricular failure are risk factors for late mortality.

Baffle obstructions are most common at the superior vena caval site. Facial plethora and symptoms suggestive of superior vena caval syndrome may occur. The presence of SVC narrowing may complicate pacemaker insertion. Obstruction of the inferior vena caval limb may cause hepatic congestion and lead to cirrhosis. Baffle leaks pose a risk for paradoxical emboli, which can occur in patients with pacing leads and associated thrombus.

The ASO eliminated the problem of late failure of the systemic right ventricle. It is now usually performed in the first week of life unless a VSD is present. Follow-up in these patients has been reported with low mortality rates and low occurrence of arrhythmias. LV function is usually normal; the presence of reduced LV systolic function should raise the concern of coronary artery compromise. Development of premature coronary ostial stenosis occurs in 7% of patients; neoaortic root dilatation and aortic regurgitation are of concern.

PREGNANCY

Before women with d-TGA following either an atrial or arterial switch contemplate pregnancy they should undergo comprehensive evaluation. Patients with atrial baffle procedure carry and increase risk of RV dysfunction that may be irreversible. Atrial arrhythmias are relatively common during pregnancy. However, in women, who are asymptomatic or minimally symptomatic, pregnancy is usually well-tolerated.

Pregnancy is reported in few patients after ASO and appears to be well-tolerated. However, if there is a history of chest pain or exercise intolerance, or evidence of LV dysfunction, the patient should be screened for coronary artery obstruction.

GUIDELINES

Evaluation, Follow-up and Imaging

Class I

- All patients should be seen, at least yearly, by a cardiologist who has expertise in the management of ACHD. (*Level of Evidence*: *C*)
- Echocardiograms and MRIs should be performed by staff with expertise in ACHD. (*Level of Evidence*: *B*)
  - — In patients with d-TGA repaired by atrial baffle procedure, comprehensive echocardiographic imaging should be performed in a regional ACHD center to evaluate the anatomy and hemodynamics.(*Level of Evidence: B*)
  - — Additional imaging with TEE, CT or MRI, as appropriate, should be performed in a regional ACHD center to evaluate the great arteries and veins, as well as ventricular function, in patients with prior atrial baffle repair of d-TGA. (*Level of Evidence: B*)
  - — Comprehensive echocardiographic imaging to evaluate the anatomy and hemodynamics in patients with d-TGA and prior ASO repair should be performed at least every 2 years at a center with expertise in ACHD. (*Level of Evidence: C*)
  - — After prior ASO repair for d-TGA, all adults should have at least 1 evaluation of coronary artery patency. Coronary angiography should be performed if this cannot be established noninvasively. (*Level of Evidence: C*)

Class IIa

- Echocardiography contrast injection with agitated saline can be useful to evaluate baffle anatomy and shunting in patients with previously repaired d-TGA after atrial baffle. (*Level of Evidence: B*)
- Transesophageal echocardiography can be effective for more detailed baffle evaluation for patients with d-TGA. (*Level of Evidence: B*)
- Periodic MRI or CT can be considered appropriate to evaluate the anatomy and hemodynamics of patients with d-TGA after ASO in more detail. (*Level of Evidence: C*)
- Coronary angiography is reasonable in all adults with d-TGA after ASO to rule out significant coronary artery obstruction. (*Level of Evidence: C*)

Recommendations for Interventional Catheterization in Patients with d-Transposition of the Great Arteries

Class IIa

- Interventional catheterization of the adult with d-TGA can be performed in centers with expertise in the catheterization and management of ACHD patients. (*Level of Evidence: C*)
- For adults with d-TGA after atrial baffle procedure (Mustard or Senning), interventional catheterization can be beneficial to assist in the following:
  - — Occlusion of baffle leak. (*Level of Evidence: B*)
  - — Dilatation or stenting of SVC or IVC pathway obstruction. (*Level of Evidence: B*)
  - — Dilatation or stenting of pulmonary venous pathway obstruction. (*Level of Evidence: B*)
- For adults with d-TGA after ASO, interventional catheterization can be beneficial to assist in dilatation or stenting of supravalvular and branch PA stenosis. (*Level of Evidence: B*)
- For adults with d-TGA, VSD and PS, after Rastelli-type repair, interventional catheterization can be beneficial to assist in the following:
- Dilatation with or without stent implantation of conduit obstruction (RV pressure > 50% of systemic levels or peak-to-peak gradient greater than 30 mm Hg; these indications may be lessened in the setting of RV dysfunction). (*Level of Evidence: C*)
- Device closure of residual VSD. (*Level of Evidence: C*)

Recommendations for Surgical Interventions: After Atrial Baffle Procedure (Mustard, Senning)

Class I

Surgeons with training and expertise in CHD should perform operations in patients with d-TGA and the following indications:

- Moderate to severe systemic (morphological tricuspid) AV valve regurgitation without significant ventricular dysfunction. (*Level of Evidence: B*)
- Baffle leak with left-to-right shunt greater than 1.5:1, right-to-left shunt with arterial desaturation at rest or with exercise, symptoms and progressive ventricular enlargement that is not amenable to device intervention. (*Level of Evidence: B*)
- SVC or IVC obstruction not amenable to percutaneous treatment. (*Level of Evidence: B*)

- Pulmonary venous pathway obstruction not amenable to percutaneous intervention. (*Level of Evidence: B*)
- Symptomatic severe subpulmonary stenosis. (*Level of Evidence: B*)

Recommendations for Surgical Interventions: After Arterial Switch Operation

Class I

It is recommended that surgery be performed in patients after the ASO with the following indications:

- RVOT obstruction peak-to-peak gradient greater than 50 mm Hg or right ventricle/left ventricle pressure ratio greater than 0.7, not amenable or responsive to percutaneous treatment; lesser degrees of obstruction if pregnancy is planned, greater degrees of exercise are desired, or concomitant severe pulmonary regurgitation is present. (*Level of Evidence: C*)
- Coronary artery abnormality with myocardial ischemia not amenable to percutaneous intervention. (*Level of Evidence: C*)
- Severe neoaortic valve regurgitation. (*Level of Evidence: C*)
- Severe neoaortic root dilatation (> 55 mm) after ASO. (This recommendation is based on data for other forms of degenerative aortic root aneurysms). (*Level of Evidence C)*

Recommendations for Arrhythmias: Pacemaker/ Electrophysiology Testing

Class I

- Clinicians should be mindful of the risk of sudden arrhythmic death among adults after atrial baffle repair of d-TGA. These events usually relate to VT but may be caused in some cases by rapidly conducted IART or progressive AV block. (*Level of Evidence B*)
- Consultation with an electrophysiologist who is experienced with CHD is recommended to assist with treatment decisions. (*Level of Evidence: B*)
- Pacemaker implantation is recommended for patients with d-TGA with either symptomatic sinus bradycardia or sick sinus syndrome. (*Level of Evidence: B*)

Class IIa

Routine surveillance with history, ECG, assessment of RV function and periodic Holter monitoring can be beneficial as part of routine follow-up. (*Level of Evidence: B*)

CONGENITALLY CORRECTED TRANSPOSITION OF THE GREAT ARTERIES

GENERAL CONSIDERATIONS

In congenitally corrected transposition of the great arteries (CCTGA or l-TGA), the ventricles and the AV valves are transposed so that the systemic venous blood drains into the right atrium and through a bileaflet mitral valve into a morphological LV pumping into a posterior and rightward PA (Fig. 25). Similarly, the pulmonary venous blood drains into the left atrium and through the tricuspid valve into the morphological right ventricle and to the aorta. It is also termed as l-TGA, meaning left, refers to the leftward looping of the cardiac tube in development resulting in a ventricular inversion. As a result, there is physiological correction of the circulation; however, the right ventricle is the systemic ventricle. These patients are acyanotic and usually asymptomatic. However, in the presence of VSD and pulmonary valve stenosis, the physiology is similar to TOF and varying degrees of cyanosis are present. There are case reports of these patients surviving into the seventh and eighth decade of life.

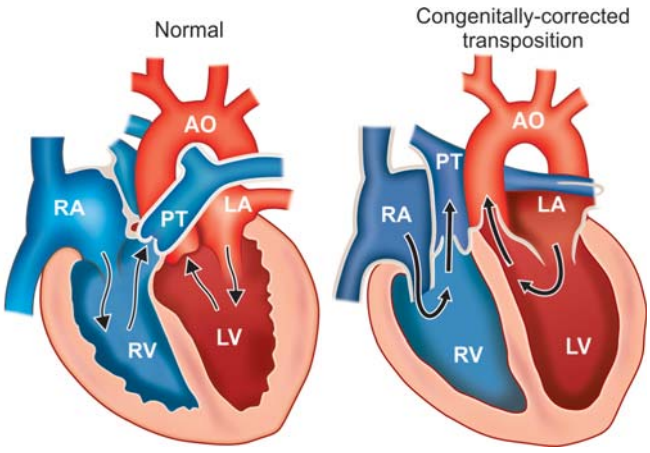


FIGURE 25: Congenitally corrected transposition of the great arteries. (*Source:* Warnes CA. Transposition of the great arteries. Circulation. 2006;114:2699-709, with permission)

The patients are prone to a number of complications, including failure of the systemic right ventricle and hemodynamically significant tricuspid valvular regurgitation. Systemic (tricuspid) AV valve regurgitation often develops prior to systemic ventricular failure and is sometimes due to apical displacement of the valve (Ebstein-like anomaly). In patients with moderate to severe tricuspid valve regurgitation consideration should be given to the systemic AV valve replacement.[72]

There is a high prevalence of complete heart block, which may present as exercise intolerance, syncope or sudden death, estimated 2% per year[73] (Fig. 26). Seventy-five percent of patients with this anomaly will require pacemaker placement. In the presence of an uncorrected shunt, it is generally recommend that transvenous pacing be avoided because of the risk of paradoxical embolization.

RECOMMENDATIONS FOR EVALUATION AND FOLLOW-UP OF PATIENTS WITH CONGENITALLY CORRECTED TRANSPOSITION OF THE GREAT ARTERIES

Class I

- All patients with CCTGA should have a regular follow-up with a cardiologist who has expertise in ACHD. (*Level of Evidence: C*)
- Echocardiography-Doppler study and/or MRI should be performed yearly or at least every other year by staff trained in imaging complex CHD. (*Level of Evidence: C*)
- The following diagnostic evaluations are recommended for patients with CCTGA:
  - Electrocardiogram. (*Level of Evidence: C*)
  - Chest X-ray. (*Level of Evidence: C*)

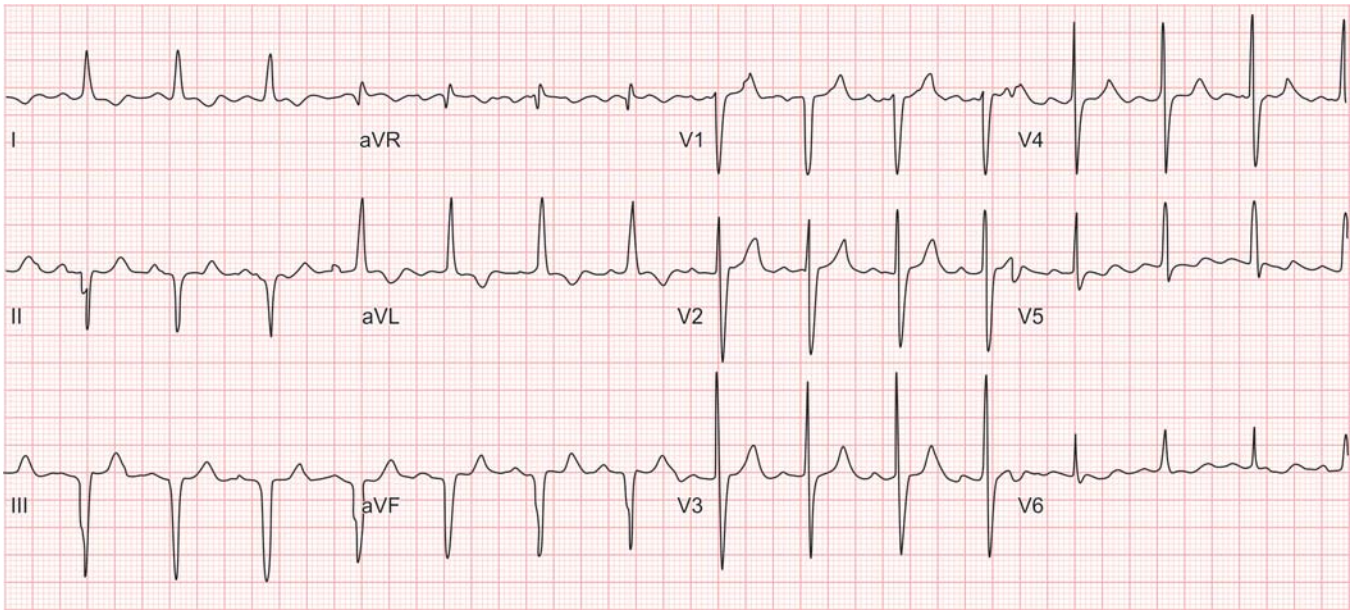


FIGURE 26: Electrocardiogram of a patient with congenitally corrected transposition of the great arteries showing atrial fibrillation and superior axis with absence of septal Q waves. (*Source:* Warnes CA. Transposition of the great arteries. Circulation. 2006;114:2699-709, with permission)

  - — Echocardiography-Doppler study. (*Level of Evidence: C*)
  - — Magnetic resonance imaging. (*Level of Evidence: C*)
  - — Exercise testing. (*Level of Evidence: C*)
- Catheterization may be indicated for evaluation of hemodynamic status in the setting of arrhythmia, unexplained systemic ventricular dysfunction, degree of shunting and unexplained volume retention. (*Level of Evidence: C*)

RECOMMENDATIONS FOR SURGICAL INTERVENTION

Class I

Surgeons with training and expertise in CHD should perform operations for patients with CCTGA for the following indications:

- Unrepaired CCTGA and severe AV valve regurgitation. (*Level of Evidence: B*)
- Anatomic repair with atrial and arterial level switch/Rastelli repair in cases in which the left ventricle is functioning at systemic pressures. (*Level of Evidence: B*)
- Simple VSD closure when the VSD is not favorable for LV-to-aorta baffling or is restrictive. (*Level of Evidence: B*)
- LV-to-PA conduit in rare cases with LV dysfunction and severe LV outflow obstruction. (*Level of Evidence: B*)
- Evidence of moderate or progressive systemic AV valve regurgitation. (*Level of Evidence: B*)
- Conduit obstruction with systemic or nearly systemic RV pressures and/or RV dysfunction after anatomic repair. (*Level of Evidence: B*)
- Conduit obstruction and systemic or suprasystemic LV pressures in a patient with nonanatomic correction. (*Level of Evidence: B*)
- Moderate or severe AR/neo-AR and onset of ventricular dysfunction or progressive ventricular dilatation. (*Level of Evidence: B*)

TOTAL ANOMALOUS PULMONARY VENOUS RETURN

In total anomalous pulmonary venous return (TAPVR), the pulmonary venous flow enters the right atrium either directly or by connecting to the coronary sinus, SVC, IVC, portal vein, hepatic vein and ductus venosus. If pulmonary venous obstructions are present, it is called "obstructed TAPVR". Obstruction can be within the pulmonary venous system or compression from adjacent structures like left bronchus or PA.

Several anatomic variants exist based on the level of the drainage:

1. Supracardiac (49%)[74]: The pulmonary vein confluence drains upward through a vertical vein into the left innominate vein and into the SVC (Fig. 27).
2. Cardiac (25%)[74]: All pulmonary veins drain directly into the right atrium or into the coronary sinus.
3. Infradiaphragmatic (18%)[74]: The pulmonary vein confluence passes down thorough the diaphragm into the portal vein, ductus venosus or hepatic vein and into the IVC (Fig. 28).

There is an atrial communication and the degree of cyanosis depends upon the size of the ASD and the PVR. If the flow is unobstructed the clinical presentation is similar to an ASD. Infants with obstructive TAPVR present more cyanotic. This anomaly often requires emergency surgery in infancy and 80% of patients will die if not treated within the first year of life. In the rare patient who is diagnosed in adulthood, the lesion is most commonly the supradiaphragmatic type. There is usually mild cyanosis and the chest X-ray shows the typical "snowman" pattern (Fig. 29). Surgical repair can usually be done with low morbidity and mortality.

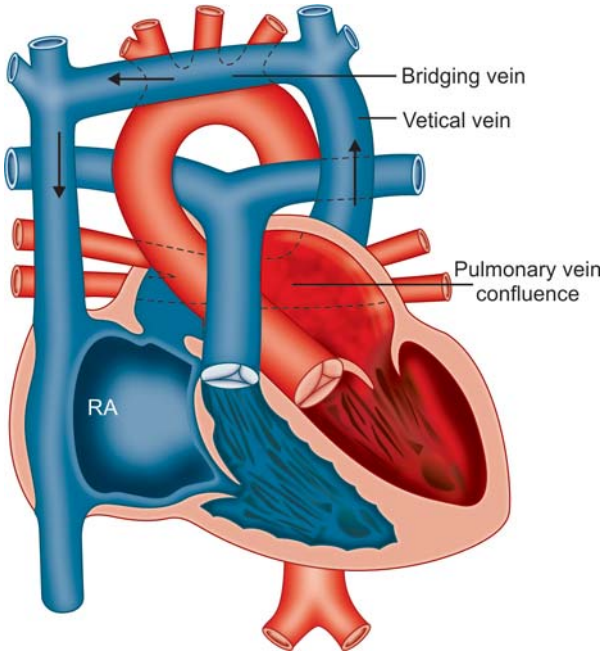


FIGURE 27: Supradiaphragmatic variant of total anomalous pulmonary veins. (Abbreviation: RA: Right atrium). (*Source:* Mayer CD, Mullins CE. Congenital Heart Disease: A Diagrammatic Atlas. New York: Alan R Liss Inc; 1988. p. 5, with permission)

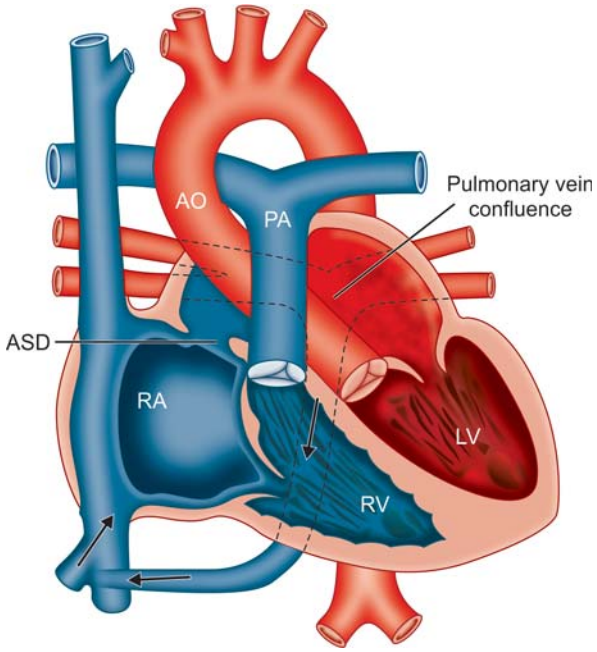


FIGURE 28: Infradiaphragmatic variant of total anomalous pulmonary veins. (Abbreviations: AO: Aorta; ASD: Atrial septal defect; LV: Left ventricle; PA: Pulmonary artery; RA: Right atrium; RV: Right ventricular). (*Source:* Mayer CD, Mullins CE. Congenital Heart Disease: A Diagrammatic Atlas. New York: Alan R Liss Inc; 1988. p. 5)

Surgical correction consists of connecting the common pulmonary venous channel to the left atrium. The postoperative course is usually uncomplicated and they can live a normal life span as adults without CHD.

However, late postoperative supraventricular arrhythmias in adulthood have been reported.[75] The recommendations for follow-up are similar to those for patients with repaired ASD.

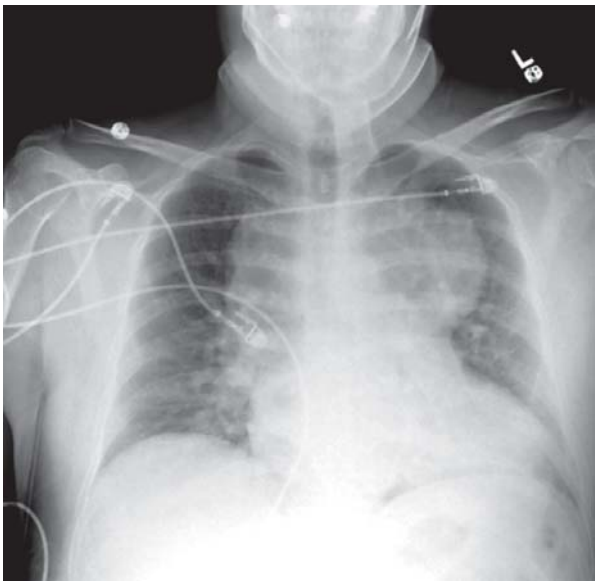


FIGURE 29: Chest radiograph of 45-year-old man with uncorrected total anomalous pulmonary venous drainage demonstrating the "snowman" appearance of the mediastinal structures

DOUBLE-OUTLET RIGHT VENTRICLE

GENERAL CONSIDERATIONS

In double-outlet right ventricle (DORV), more than 50% of both the aorta and the PA originate above the morphological right ventricle. DORV almost always occurs with a large VSD, which serves as the outlet for the left ventricle. The anatomy of DORV varies greatly. In most patients, the aorta and the pulmonary arteries are transposed. A VSD is almost always present. Very few patients survive to adulthood without surgical intervention.

ASSOCIATED ANOMALIES

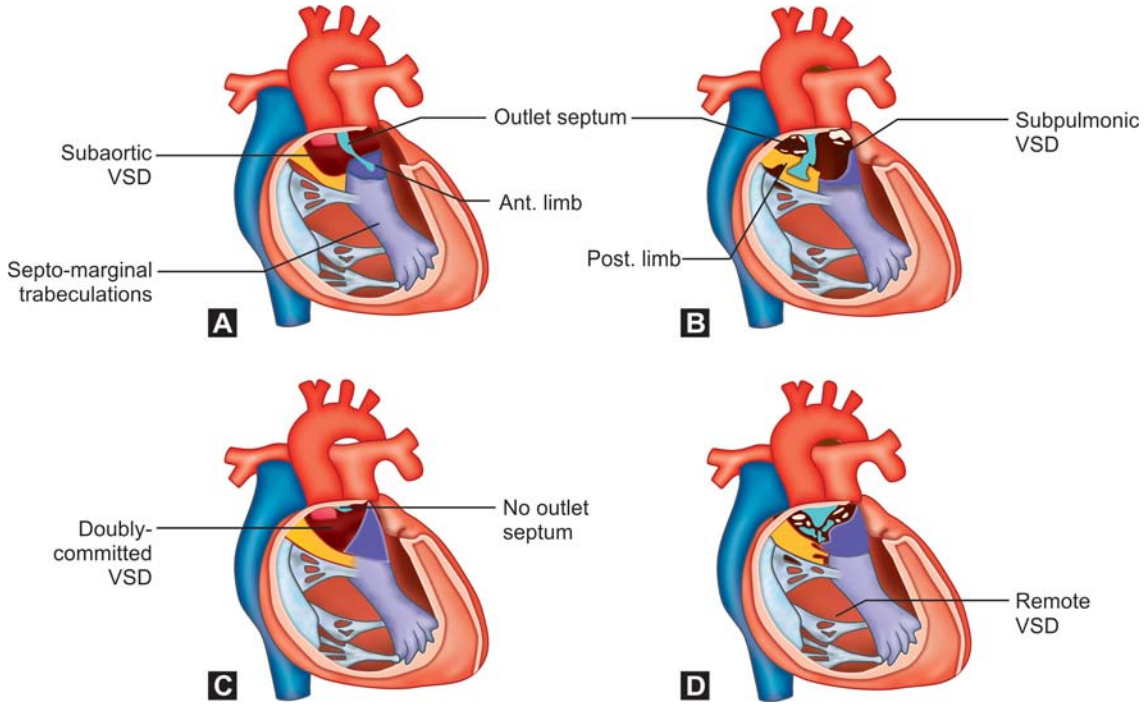
Other common associated malformations include pulmonary stenosis, overriding atrioventricular valve, RVOT obstruction and aortic arch obstruction (coarctation, aortic arch interruption, arch hypoplasia).[76] More complex associations with heterotaxy and situs inversus (dextrocardia) can occur which can complicate surgical repair.

A classification scheme introduced by Lev and colleagues[77] categorizes biventricular heart with DORV based on the site of the VSD, which can affect the clinical manifestation and the surgical treatment options[78] (Figs 30A to D):

a. DORV with a subaortic VSD (similar to TOF). Ventricular blood is directed from the left ventricle into the aorta.
b. DORV with a subpulmonic VSD. The ventricular blood is directed to the PA. The Taussig-Bing defect is a variant in which both arteries arise from the right ventricle.
c. DORV with a VSD committed to both arterial outlets (doubly committed VSD)
d. DORV with a VSD that is remote from either arterial outlet. (Uncommitted VSD).

TREATMENT AND PROGNOSIS

The hemodynamics of this lesion varies based upon the location of the VSD, the presence of outflow obstruction and the



FIGURES 30A TO D: Variations of double outlet right ventricle. (Abbreviation: VSD**:** Ventricular septal defect). (*Source:* Bashore TM. Adult congenital heart disease: right ventricular outflow tract lesions. Circulation. 2007;115:1933-47)

associated lesions. The blood ejected from the left ventricle flows across the VSD into the right ventricle. Based on the location of the VSD, blood flow will preferentially flow to either the PA or the aorta. As in the case with any large VSD, in the absence of obstruction, the pulmonary circulation is exposed to high pressures and increased blood flow.

When the VSD is subaortic, the blood from the LV is primarily directed to the aorta. The surgical repair in this case involves the creation of an intraventricular tunnel, which directs blood to the aorta.

The repair of the subpulmonic VSD is more complex repair because the LV blood flow is directed primarily to the PA. The clinical presentation is similar to transposed great vessels. This defect is now primarily treated with an ASO with a patch in the RV, which directs blood flow into the aorta. These patients may have complex coronary anatomy, which needs to be considered prior to an ASO.

Prior to the ASO, the procedure of choice for these patients was a Damus-Kaye-Stansel (DKS) operation (Fig. 31). This operation involved closing the VSD, dividing the main PA and connecting the proximal main PA to the ascending aorta. A conduit from the morphological right ventricle to the distal PA is placed. The DKS operation is still used in patients with complex coronary anatomy or in patients with Taussig-Bing defect associated with hypoplastic aortic arch.

The doubly committed VSD defects and distant VSD can involve more complex repair with a tunnel, which connects the aorta to the LV through the VSD without obstructing pulmonary flow. If there is potential for RVOT obstruction, then a Rastelli procedure is performed which would add an external conduit from the RV to the PA. Sometimes complex surgeries are not possible, and a palliative Fontan procedure may be performed which will direct caval blood flow into the PA.

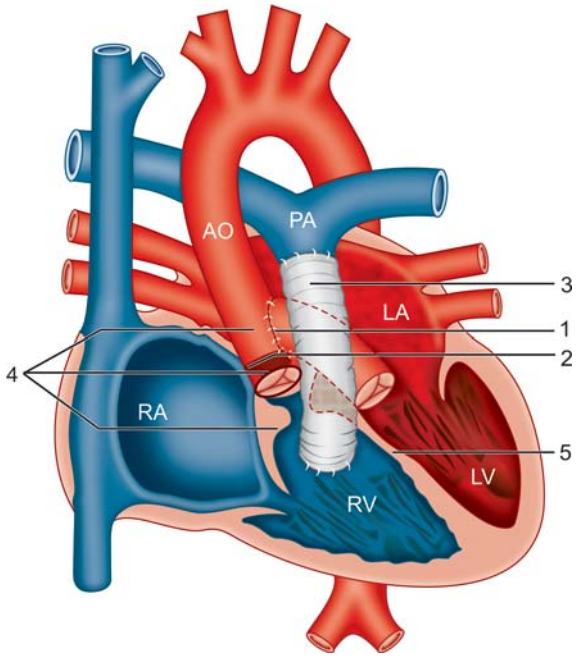


FIGURE 31: Damus-Kaye-Stansel operation plus Rastelli repair for transposition of the great arteries. Labels: (1) Main pulmonary artery to ascending aorta (end-to-side) anastomosis. (2) Patch closure of aortic orifice. (3) Conduit interposition from right ventricle to distal pulmonary artery. (4) Transposition of the great arteries with valvular and subvalvular aortic stenosis. (5) Patch closure of ventricular septal defect. (Abbreviations: AO: Aorta; LA: Left atrium; LV: Left ventricle; PA: Pulmonary artery; RA: Right atrium; RV: Right ventricular). (*Source:* Mayer CD, Mullins CE. Congenital Heart Disease: A Diagrammatic Atlas. New York: Alan R Liss Inc; 1988. p. 5, with permission)

The late follow-up of these patients will depend on the primary anatomy and the type of repair performed. Like patients

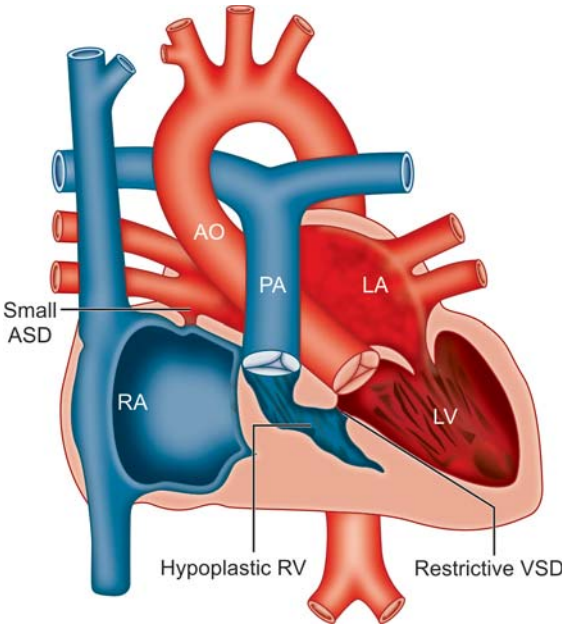


FIGURE 32: Truncus arteriosus with normally related great vessels. (Abbreviations: AO: Aorta; ASD: Atrial septal defect; LA: Left atrium; LV: Left ventricle; PA: Pulmonary artery; RA: Right atrium; RV: Right ventricular; VSD: Ventricular septal defect). (*Source:* Mayer CD, Mullins CE. Congenital Heart Disease: A Diagrammatic Atlas. New York: Alan R Liss Inc; 1988. p. 5)

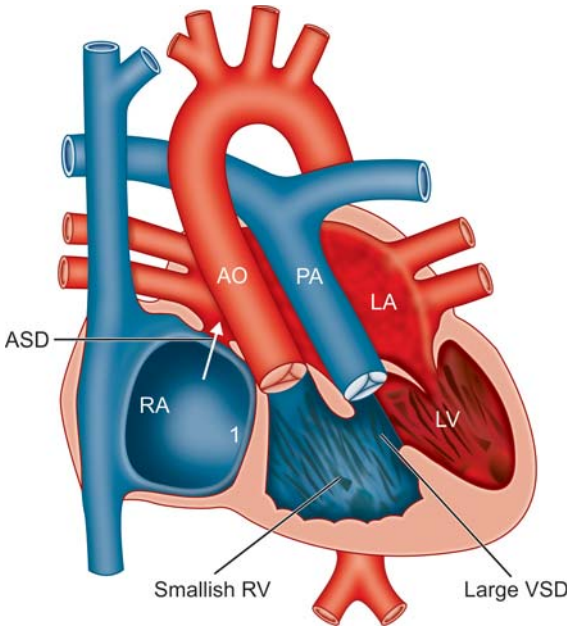


FIGURE 33: Tricuspid atresia with transposed great vessels. (Abbreviations: AO: Aorta; ASD: Atrial septal defect; LA: Left atrium; LV: Left ventricle; PA: Pulmonary artery; RA: Right atrium; RV: Right ventricular; VSD: Ventricular septal defect). (*Source:* Mayer CD, Mullins CE. Congenital Heart Disease: A Diagrammatic Atlas. New York: Alan R Liss Inc; 1988. p. 5)

with TOF, these patients are at risk for both atrial and ventricular arrhythmias as well as sudden death. They should be monitored for progressive conduction system disease. Residual hemodynamic concerns include conduit stenosis and insufficiency, residual subvalvular stenosis and valvular disease.

TRICUSPID ATRESIA/UNIVENTRICULAR HEART

Tricuspid atresia is defined as the absence of the inflow portion of the RV, an incomplete or absent tricuspid valve and a hypoplastic right ventricle. An ASD is present to allow for right-to-left shunting. The degree of cyanosis depends upon the size of the ASD. In tricuspid atresia, the great arteries are normally related in 70% and transposed in 30% of patients. The patients with transposed vessels a VSD is usually present with no pulmonary obstruction. With normally related arteries, there is usually valvar or subvalvar PS.[79]

Without palliative surgery, there is a high mortality in infancy. Palliative surgery varies, depending upon the patient's underlying anatomy. Patients with tricuspid atresia have generally undergone multiple surgeries by the time they reach adulthood.

Tricuspid atresia is classified based on the anatomy of the great arteries. Initially blood passes from the right atrium to the left atrium through the ASD and, subsequently, into the left ventricle. Based on the location of the great arteries, the blood flow will be further directed as follows:

Type I: Normally related great vessels (70%) (Fig. 32). When the great vessels are normally related, blood flow from the left ventricle passes into the aorta. This type is further subdivided according to the presence of VSD, the size of the VSD and the presence or absence of pulmonary valve stenosis.

Type II: d-transposition of the great arteries (25%) (Fig. 33). There is a VSD and these patients are further classified according to the presence or absence of pulmonary stenosis or atresia.

Type III: L-transposition and malposition of the great arteries (5%).

Older adults with reduced pulmonary blood flow frequently have had an initial Blalock-Taussig shunt. Aortopulmonary shunts may be required in infants under the age of 6 months in whom PVR has not yet fallen. Currently, older infants with reduced pulmonary blood flow undergo a bidirectional Glenn procedure (Fig. 34). As the child grows, the Glenn alone does

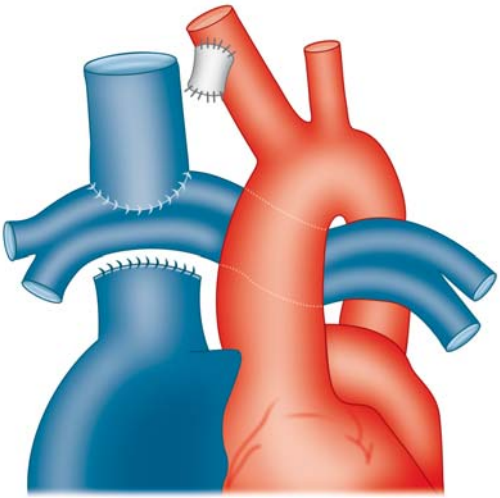
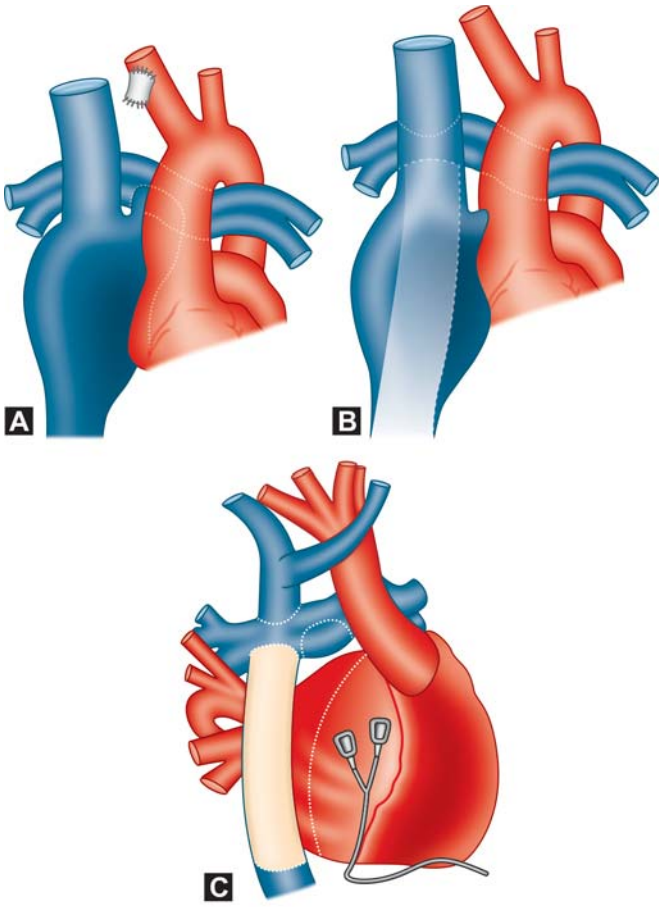


FIGURE 34: Bidirectional Glenn. (*Source:* Khairy P, Poirier N, Mercier LA. Univentricular heart. Circulation. 2007;115:800-12, with permission)



FIGURES 35A TO C: (A) The modified classic Fontan; (B) the intracardiac lateral tunnel Fontan; (C) the extracardiac Fontan. In (A), the modified Blalock-Taussig shunt, shown in white, was taken down and oversewn. In (C), permanent atrial epicardial pacemaker leads are illustrated in gray. (*Source:* Khairy P, Poirier N, Mercier LA. Univentricular heart. Circulation. 2007;115:800-12, with permission)

not provide adequate pulmonary blood flow and cyanosis worsens. Patients who have only a Glenn operation are also at risk for the development of pulmonary arteriovenous malformations. In most cases, the patient then undergoes a complete cavopulmonary anastomosis (Fontan procedure). However, while there are a variety of surgical approaches to the Fontan, the principle behind the surgery remains constant; the systemic venous blood is diverted to the PA (Figs 35A to C). Overall prognosis is good but there are many late complications associated with the Fontan circulation described below.[80-82] An alternative to the Fontan is the addition of a central systemic to pulmonary shunt in association with the Glenn but this approach has fallen out of favor.

Patients with increased pulmonary blood flow may require initial PA banding to prevent development of pulmonary vascular disease, which would limit options for later Fontan surgery.

DOUBLE-INLET LEFT VENTRICLE

In 75% of patients with single ventricle, the morphology is that of a left ventricle with a rudimentary right ventricle. In approximately 20% of these cases the single ventricle may be a morphological right ventricle.

The most common connection is with two atrioventricular valves (double-inlet). Rarely, there is only one AV valve or a common inlet.

In majority of the cases, the double-inlet LV is associated with l-transposition in which the aorta arises anteriorly from the rudimentary RV and the PA arises posteriorly from the left ventricle. There may be associated subpulmonic or pulmonic valve stenosis.

FONTAN OPERATION

The majority of patients with tricuspid atresia and double-inlet left ventricle are now treated with a Fontan operation.

CLINICAL FINDINGS

Symptoms

The adult with a Fontan operation frequently has decreased exercise tolerance and may have evidence of elevated systemic venous pressures with abdominal bloating and venous varicosities. Diarrhea and weight loss may be evidence of protein losing enteropathy.

Physical Examination

The patient with a Fontan operation is acyanotic unless there is a fenestration in the Fontan circuit allowing for right-to-left shunting. In patients with a Glenn with or without an additional central shunt, the patient is cyanotic to variable degrees. The left ventricle is dominant without a palpable RV. S1 and S2 are single. A murmur of mitral regurgitation may be present. If there is a systemic to pulmonary shunt, there is a continuous murmur over the base of the heart.

DIAGNOSTIC STUDIES

Electrocardiogram and Chest X-ray

In tricuspid atresia, the ECG reveals right atrial enlargement and LVH. This is the most common cyanotic heart lesion associated with LVH at birth. In double-inlet left ventricle, there is also predominance of LV forces. AV nodal disease may be manifest with first-degree AV block. In patients with single ventricles of RV morphology, there is RVH with a superior frontal plane axis.

The chest X-ray is variable depending on the specific anatomy and the type of palliative procedure performed.

Echocardiography

The echocardiogram is the primary imaging modality for evaluation and follow-up of these individuals. Atrioventricular and ventriculoarterial connections should be determined. The large single ventricle is smooth-walled. A right ventricle is heavily trabeculated. The atrioventricular valves should be carefully evaluated for stenosis and regurgitation.

The appearance of the Fontan circulation on echocardiography depends on the type of Fontan performed. The right atrium may be extremely dilated in patients with a direct connection from the RA to the PA. In this case, the ASD is no

longer present and there may be a small right ventricle with a VSD of variable size. If there is transposition of the great arteries, the size of the VSD is important as restriction to aortic blood flow can occur. The IVC is usually dilated and respirophasic blood flow with inspiratory augmentation should be demonstrated in both the IVC and SVC to assure patency of the Fontan circuit.

In patients with a lateral tunnel Fontan, the circular conduit is visualized within the right atrium, which carries the IVC flow to the PA. The ASD persists. When the Fontan is extracardiac, visualization may be difficult but Doppler flow interrogation ensures patency.

Transesophageal echocardiography may be important in patients with direct right atrial to PA connections to detect thrombus in the large right atrium.

Magnetic Resonance Imaging and Computed Tomography

These methods may be very helpful to elucidate the anatomy especially when Fontan revision is being considered. They are the optimal methods for visualizing the extracardiac Fontan.

Catheterization

Cardiac catheterization may be important in the adult to directly measure pressures in the Fontan circuit and in preparation for Fontan revision. It is important to measure the LV diastolic pressures as well as the PA pressures.

TREATMENT AND PROGNOSIS

There are many long-term complications associated with the Fontan circulation. With the direct RA to PA connections, conduits were often used. There may be severe RA enlargement, atrial arrhythmias and thrombus formation within the Fontan circuit, conduit obstruction, hepatic congestion and protein losing enteropathy. Atrial arrhythmias and thrombus formation within the conduit make it necessary to anticoagulate these patients. Sinus node dysfunction may necessitate pacemaker insertion; when needed, the leads are placed on the epicardium.

Protein losing enteropathy is uncommon; it usually presents in early adulthood. It results from increased systemic venous pressures causing lymphangiectasia. Gastrointestinal protein loss results in malnutrition, edema, effusions, ascites and hypogammaglobulinemia. This enteropathy is difficult to treat and the 5-year survival is less than 50%.[83]

One option for patients with the direct atriopulmonary connection is a conversion either to a lateral tunnel repair or an extracardiac Fontan circulation. The mortality associated with conversion remains relatively high and, if undertaken, this procedure must be undertaken with careful consideration of the risk/benefit ratio. It is usually combined with a maze operation to reduce the burden of atrial arrhythmias.

GUIDELINES FOR MANAGEMENT STRATEGIES IN PATIENTS WITH FONTAN REPAIR

Class I

- Management of patients with prior Fontan repair should be coordinated with a regional ACHD center. Local cardiologists, internists and family care physicians should develop ongoing relationships with such a center with continuous availability of specialists. (*Level of Evidence: C*)
- At least yearly follow-up is recommended for patients after Fontan repair. (*Level of Evidence: C*)
- Arrhythmia management is frequently an issue, and consultation with an electrophysiologist is recommended as a vital part of care. (*Level of Evidence: C*)
- New-onset atrial tachyarrhythmia should prompt a comprehensive noninvasive imaging evaluation to identify associated atrial/baffle thrombus, anatomic abnormalities of the Fontan pathway or ventricular dysfunction. (*Level of Evidence: C*)

RECOMMENDATIONS FOR MEDICAL THERAPY

Class I

Warfarin should be given for patients who have a documented atrial shunt, atrial thrombus, atrial arrhythmias or a thromboembolic event. (*Level of Evidence: C*)

Class IIa

It is reasonable to treat SV dysfunction with ACE inhibitors and diuretics. (*Level of Evidence: C*)

RECOMMENDATIONS FOR SURGERY FOR ADULTS WITH PRIOR FONTAN REPAIR

Class I

- Surgeons with training and expertise in CHD should perform operations on patients with prior Fontan repair for single-ventricle physiology. (*Level of Evidence: C*)
- Reoperation after Fontan is indicated for the following:
  - — Unintended residual ASD that results in right-to-left shunt with symptoms and/or cyanosis not amenable to transcatheter closure. (*Level of Evidence: C*)
  - — Hemodynamically significant residual systemic artery to PA shunt, residual surgical shunt or residual ventricle to PA connection not amenable to transcatheter closure. (*Level of Evidence: C*)
  - — Moderate to severe systemic AV valve regurgitation. (*Level of Evidence: C*)
  - — Significant (> 30 mm Hg peak-to-peak) subaortic obstruction. (*Level of Evidence: C*)
  - — Fontan pathway obstruction. (*Level of Evidence: C*)

HYPOPLASTIC LEFT HEART

The hypoplastic left heart syndrome (HLHS) is characterized by a diminutive left ventricle and varying degree of hypoplasia of the left heart structures such as mitral stenosis or atresia and aortic stenosis or atresia. ASDs, VSDs and coarctation of the aorta are also known to occur in conjunction with HLHS. It occurs in 1% of all congenital heart defects and is the most common cause of death in the first month of life.

In the initial days of life, circulation is entirely dependent on blood flow through the ductus. Newborns with a known

diagnosis are administered prostaglandin E1 to maintain ductal patency followed by a balloon atrial septostomy.

Palliative surgical repair options are the Norwood procedure and heart transplantation. The Norwood procedure is a complex three-staged surgical procedure. *Stage 1* includes atrial septectomy and division of the main PA. The proximal main PA is anastomosed with the ascending aorta creating a neoaorta and the distal main PA is ligated. A modified Blalock-Taussig shunt is created to provide blood to the pulmonary circulation. *Stage 2* creates a bidirectional Glenn (SVC to right PA). *Stage 3* involves completion of the Fontan circulation.

Patients undergoing Norwood procedure often have long complicated postoperative courses. Adult survivors are likely to have complications related to the Fontan operation as described above. Unlike in patients with tricuspid atresia and double-inlet left ventricle, the right ventricle is the systemic ventricle and may be more subject to late failure. There are currently no adult series of survivors of the Norwood procedure.

EISENMENGER'S SYNDROME

CONGENITAL HEART DISEASE: PULMONARY ARTERIAL HYPERTENSION

Eisenmenger's syndrome is a general term applied to pulmonary hypertension and shunt reversal in the presence of CHD such as VSD, ASD, atrioventricular septal defect or PDA. In VSDs and atrioventricular septal defects, there is an increase in pulmonary flow along with increase in pulmonary pressure, which can results in pulmonary vascular obstructive disease.[84] The increased pulmonary arterial pressures lead to the transition of a left-to-right shunt to a right-to-left shunt with unoxygenated blood mixing with oxygenated blood.

Eisenmenger's syndrome results in erythrocytosis, hemoptysis, pulmonary infarction and right heart failure. It may present as recurrent bronchitis or pneumonia in children.

Life expectancy is markedly shortened in these patients. However, meticulous management with oxygen, pulmonary vasodilator therapy, anticoagulation and endocarditis prophylaxis can improve their longevity and quality of life.[85] The causes of death include pulmonary infarction, uncontrollable arrhythmias, progressive RV failure and brain abscesses.

Surgical repair of the underlying defect is essentially contraindicated with fixed pulmonary hypertension. Currently, some patients with reversible pulmonary vascular disease may become candidates for repair after prolonged treatment with pulmonary vasodilators. Heart and lung transplant has been supported in some literature.

Pregnancy accompanies an extremely high rate of maternal and fetal mortality and is contraindicated in patients with Eisenmenger's syndrome.

RECOMMENDATIONS FOR EVALUATION OF THE PATIENT WITH CONGENITAL HEART DISEASE—PULMONARY ARTERIAL HYPERTENSION

Class I

- Care of adult patients with CHD-related PAH should be performed in centers that have shared expertise and training in both ACHD and PAH. (*Level of Evidence: C*)
- The evaluation of all ACHD patients with suspected PAH should include noninvasive assessment of cardiovascular anatomy and potential shunting, as detailed below:
  - — Pulse oximetry, with and without administration of supplemental oxygen, as appropriate. (*Level of Evidence: C*)
  - — Chest X-ray. (*Level of Evidence: C*)
  - — Electrocardiogram. (*Level of Evidence: C*)
  - — Diagnostic cardiovascular imaging, via TTE, TEE, MRI or CT, as appropriate. (*Level of Evidence: C*)
  - — Complete blood count and nuclear lung scintigraphy. (*Level of Evidence: C*)
- If PAH is identified but its causes are not fully recognized, additional testing should include the following:
  - — Pulmonary function tests with volumes and diffusion capacity (diffusing capacity of the lung for carbon monoxide). (*Level of Evidence: C*)
  - — Pulmonary embolism—protocol CT with parenchymal lung windows. (*Level of Evidence: C*)
  - — Additional testing as appropriate to rule out contributing causes of PAH. (*Level of Evidence: C*)
  - — Cardiac catheterization at least once, with potential for vasodilator testing or anatomic intervention, at a center with expertise in catheterization, PAH and management of CHD-PAH. (*Level of Evidence: C*)

Class IIa

It is reasonable to include a six-minute walk test or similar nonmaximal cardiopulmonary exercise test as part of the functional assessment of patients with CAD-PAH. (*Level of Evidence: C*)

RECOMMENDATIONS FOR MEDICAL THERAPY OF EISENMENGER'S PHYSIOLOGY

Class I

- It is recommended that patients with Eisenmenger's syndrome avoid the following activities or exposures, which carry increased risks:
  - — Pregnancy. (*Level of Evidence: B*)
  - — Dehydration. (*Level of Evidence: C*)
  - — Moderate and severe strenuous exercise, particularly isometric exercise. (*Level of Evidence: C*)
  - — Acute exposure to excessive heat (e.g. hot tub or sauna). (*Level of Evidence: C*)
  - — Chronic high-altitude exposure, because this causes further reduction in oxygen saturation and increased risk of altitude-related cardiopulmonary complications (particularly at an elevation > 5,000 feet above sea level). (*Level of Evidence: C*)
  - — Iron deficiency. (*Level of Evidence: B*)
- Patients with Eisenmenger's syndrome should seek prompt therapy for arrhythmias and infections. (*Level of Evidence: C*)
- Patients with Eisenmenger's syndrome should have hemoglobin, platelet count, iron stores, creatinine and uric acid assessed at least yearly. (*Level of Evidence: C*)
- Patients with Eisenmenger's syndrome should have assessment of digital oximetry, both with and without supplemental oxygen therapy, at least yearly. The presence

of oxygen-responsive hypoxemia should be investigated further. (*Level of Evidence: C*)
- Exclusion of air bubbles in intravenous tubing is recommended as essential during treatment of adults with Eisenmenger's syndrome. (*Level of Evidence: C*)
- Patients with Eisenmenger's syndrome should undergo noncardiac surgery, and cardiac catheterization only in centers with expertise in the care of such patients. In emergent or urgent situations in which transportation is not feasible, consultation with designated caregivers in centers with expertise in the care of patients with Eisenmenger's syndrome should be performed and sustained throughout care. (*Level of Evidence: C*)

Class IIa

- All medications given to patients with Eisenmenger's physiology should undergo rigorous review for the potential to change systemic blood pressure, loading conditions, intravascular shunting and renal or hepatic flow or function. (*Level of Evidence: C*)
- Pulmonary vasodilator therapy can be beneficial for patients with Eisenmenger's physiology because of the potential for improved quality of life. (*Level of Evidence: C*)

RECOMMENDATIONS FOR REPRODUCTION

Class I

- Women with severe CHD-PAH, especially those with Eisenmenger's physiology, and their partners should be counseled about the absolute avoidance of pregnancy in view of the high risk of maternal death, and they should be educated regarding safe and appropriate methods of contraception. (*Level of Evidence: B*)
- Women with CHD-PAH who become pregnant should:
  - Receive individualized counseling from cardiovascular and obstetric caregivers collaborating in care and with expertise in management of CHD-PAH. (*Level of Evidence: C)*
  - Undergo the earliest possible pregnancy termination after such counseling. (*Level of Evidence: C*)
- Surgical sterilization carries some operative risk for women with CHD-PAH but is a safer option than pregnancy. In view of advances in minimally invasive techniques, the risks and benefits of sterilization modalities should be discussed with an obstetrician experienced in management of high-risk patients, as well as with a cardiac anesthesiologist. (*Level of Evidence: C*)

Class IIb

Pregnancy termination in the last two trimesters of pregnancy poses a high risk to the mother. It may be reasonable; however, after the risks of termination are balanced against the risks of continuation of the pregnancy. (*Level of Evidence: C*)

Class III

- Pregnancy in women with CHD-PAH, especially those with Eisenmenger's physiology, is not recommended and should be absolutely avoided in view of the high risk of maternal mortality. (*Level of Evidence: B*)
- The use of single-barrier contraception alone in women with CHD-PAH is not recommended owing to the frequency of failure. (*Level of Evidence: C*)
- Estrogen-containing contraceptives should be avoided. (*Level of Evidence: C*)

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Section 11

SECONDARY DISORDERS OF THE HEART

Chapter 91

Alcohol and Arrhythmia

Mary Gray

Chapter Outline

- Direct Effects of Ethanol Exposure on Heart Cells and Tissues
- Ethanol Ingestion and the Normal Cardiac Conduction System
- Binge Drinking and Transient Clinical Arrhythmias—Holiday Heart
- Alcohol Consumption, Chronic Atrial Fibrillation and Atrial Flutter
- Alcohol Consumption and Sudden Cardiac Death
- Guidelines

DIRECT EFFECTS OF ETHANOL EXPOSURE ON HEART CELLS AND TISSUES

Alcohol has long been recognized as an important modulator of cell membrane potentials, action potential duration, conduction and contractility in the heart tissues. For example, Gimeno and colleagues[1] found that ethanol at concentrations between 100 and 900 mg/100 ml reversibly shortened the action potential duration and depressed contractility in isolated rat atria. Williams and colleagues[2] later showed that treatment with 100–300 mg/100 ml ethanol caused reversible, concentration-dependent shortening of action potential duration in isolated Purkinje fibers. Treatment of Purkinje fibers with 80 mmol/l acetaldehyde, the highest plasma concentration documented in humans and experimental animals following heavy drinking,[3] prolonged action potentials through mechanisms that could be blocked by the α-adrenergic antagonist phentolamine. Action potential amplitudes, transmembrane resting potentials and conduction times were not altered by physiologically relevant[4] concentrations of ethanol or acetaldehyde. Acetate had no effect on action potential configuration or conduction time.

Interestingly ethanol, acetaldehyde and acetate at every concentration examined did not increase the rate of spontaneous depolarization of the guinea pig atria. Williams and colleagues[2] proposed that direct interactions between ethanol and Purkinje fiber membranes shorten the action potential duration through selective modulation of ionic conductance. Furthermore, the magnitude of change in action potential duration could contribute to arrhythmia mechanisms in the individuals who consume moderate-to-large amounts of ethanol. Habuchi and colleagues[5] used whole-cell patch-clamp techniques to investigate direct effects of ethanol on the guinea pig ventricular myocytes. At clinically relevant concentrations, ethanol shortened the action potential duration and reduced L-type Ca^{2+} currents (I_{Ca}), by shifting channel availability curves toward more negative potentials. In contrast, there were no changes in fast Na^{+} currents (I_{Na}) in the same experimental system.[5] The group proposed I_{Ca} inhibition as one major contributor to the negative inotropy, action potential shortening and arrhythmia seen in heavy drinkers.

ETHANOL INGESTION AND THE NORMAL CARDIAC CONDUCTION SYSTEM

Heavy drinking is consistently linked to the clinical arrhythmias. However there is controversy as to whether alcohol-mediated rhythm disorders are primarily triggered by direct effects on cardiac conduction or indirect effects on nutritional status and myocardial viability. To address this issue, Ettinger and colleagues[6] fed 11 mongrel dogs and gave them 36% of their total daily calories as ethanol while adequate nutrition was maintained for 14 months. The investigators determined that heavy ethanol consumption did not cause cardiac hypertrophy, inflammation or necrosis. Resting left ventricular pressures, volumes and stroke outputs were also normal in alcoholic animals.[6] In contrast, bundle of His and left bundle branch electrograms recorded under general anesthesia showed QRS widening and prolongation of H-Q time in ethanol-fed dogs versus controls. Both conduction abnormalities were correlated with the duration of ethanol intake and could not be reproduced in controls by acute ethanol infusion.[6] Interestingly, no abnormalities of atrial conduction were noted. Histological evaluation revealed the accumulation of Alcian Blue-positive interstitium and swelling of intercalated discs in ventricular muscle and Purkinje fibers.

Randomized controlled studies of humans who drink are rare but suggest the dose-related effects of ethanol on cardiac conduction. In a simulation of acute binge drinking, Lorsheyd and colleagues[6] assigned ten healthy volunteers to ingest three glasses of red wine (Rioja, 11.4 gm ethanol each) over 45 minutes. The electrocardiogram (ECG) was recorded and blood alcohol concentration (BAC) measured 45 minutes after the last drink to allow for slow uptake into the circulation. Additional red wine was administered as needed to achieve a target BAC

of 0.45%. The cycle was repeated to generate ECG recordings at a target BAC of 0.80%. Control participants were required to ingest three glasses of a sweet designer drink (Bacardi Breezer, 11.0 gm ethanol each) to differentiate alcohol effects from those of the polyphenols in wine. The investigators showed that BACs of 0.45% and 0.80% were associated with PR and QTc prolongation.[7] Binge drinking produced no changes in systolic blood pressure (BP), diastolic BP and heart rate or QRS interval. There were no differences in conduction intervals between the red wine group and control group. The authors speculated that ethanol-mediated inhibition of Na, K-ATPase, L-type calcium channels, and HERG potassium channels might explain their findings.[7]

More recently, Spaak and colleagues[8] examined dose-related effects of red wine and ethanol on heart rate variability (HRV). The 13 healthy participants were randomly assigned to ingest red wine (Pinot noir), ethanol (pharmaceutical grade diluted with Perrier) or water (Perrier). The BAC and vital signs were monitored throughout the protocol. The BAC peaked at 40 mg/dL after the first drink and 90 mg/dL after the second.[8] For HRV measurements, ECG signal was sampled at 1,000 Hz and digitized for blinded analysis in the time and frequency domains. All subjects completed three separate experimental sessions. There was no significant change in the BP after 1 or 2 drinks of red wine, ethanol or water.[8] In contrast, the second glass of both alcoholic beverages increased the heart rates and reduced all time domain parameters except standard deviation (STD) of R-R intervals. Both alcohols decreased high frequency (HF) spectral power, increased low frequency (LF) spectral power, and increased LF-to-HF ratio.[8] The investigators concluded that moderate alcohol ingestion diminishes time and frequency indices of parasympathetic heart rate modulation in a dose-dependent manner and augments frequency domain indices of sympathetic rate modulation. Spaak's findings are most consistent with centrally mediated sympathoexcitatory and vagolytic actions on HRV, with no differences between intakes of red wine versus other ethanol solutions.

BINGE DRINKING AND TRANSIENT CLINICAL ARRHYTHMIAS—HOLIDAY HEART

Of more immediate interest to the general public and health professionals is the association between heavy drinking and acute cardiac rhythm disorders, better known as "Holiday Heart". More than 30 years ago, Ettinger and colleagues[9] published an important case series that documented experience with patients who drink heavily and habitually with superimposition of especially heavy ingestion prior to the cardiac arrhythmia. Thirty-two episodes of alcohol-associated arrhythmias with normal post-conversion ECGs and chest radiographs and no clinical evidence of heart disease were assessed. Systolic time interval measurements were performed after return to sinus rhythm. Most patients also underwent diagnostic cardiac catheterization to rule out coronary artery disease and evaluate ventricular performance. Data were compared to those from 12 normal individuals studied in the core laboratory. Investigators determined that a history of at least 10 years of heavy ethanol intake was usually present.[9] Patients smoked heavily, drank everyday and increased the alcohol intake over the weekend. When studied plasma potassium concentrations were usually normal. Plasma magnesium concentrations were not measured.

Importantly, most admissions occurred after weekends and holidays, prompting staff to coin the term "Holiday Heart".[9] The most common arrhythmia was atrial fibrillation (AF), followed by atrial flutter (AFL) or isolated ventricular premature beats. Several patients had supraventricular beats, paroxysmal atrial tachycardia (PAT) and junctional tachycardia. The mean heart rate of alcoholics during systolic time interval testing was higher than controls, as was the ratio of pre-ejection period (PEP) to left ventricular ejection time (LVET). Mean PRc, QRS, and QTc intervals were higher in alcoholic patients compared to controls.[9] Mean cardiac index (MCI) was lower in heavy drinkers, and stroke volume index did not increase normally in response to angiotensin infusion, further supporting alcohol-related left ventricular dysfunction. Ettinger concluded that preclinical cardiomyopathy was likely to be present in the majority of cases.

ALCOHOL CONSUMPTION, CHRONIC ATRIAL FIBRILLATION AND ATRIAL FLUTTER

Recent prospective cohort studies validate the association of heavy ethanol intake with a higher risk of AF. Mukamal and colleagues[10] tested the association between self-reported alcohol use and incident AF among more than 16,000 women and men enrolled for up to 18 years in the Copenhagen City Heart Study (CCHS). Participants with AF on baseline ECG and those with histories of coronary heart disease (CHD), stroke or regular cardiovascular medication use were excluded from analysis. Participants reported alcohol use in standardized interviews as intake of beer (bottles), wine (glasses) and spirits (units). Usual weekly alcohol intake was classified as less than 1 serving, 1–6 servings, 14–20 servings, 21–28 servings, 28–34 servings and at least 35 servings. The investigators documented 1,071 cases of AF—68 by study ECG, 891 from the hospitalization records and 112 from both sources. In both age- and multivariable-adjusted analyses, risk of AF was similar between abstainers and those consuming up to 14 drinks per week.[10] The risk of AF increased significantly at a threshold of 35 drinks per week (HR, 1.45; 95% CI, 1.02–2.04), with a relatively flat relationship at lower levels of intake.

Blood pressure, incident CHD during follow-up and incident congestive heart failure during follow-up were independently associated with the risk of AF. However adjustment for these recognized precipitants of AF had no significant effect on the relationship between alcohol use and arrhythmia. There was no clear evidence that beverage type or drinking frequency correlated with risk of AF. Mukamal and colleagues[10] concluded that high risk was restricted to heavy drinking. Their investigation was not designed to identify mechanisms of alcohol-induced AF. Other limitations include self-reporting of alcohol consumption and long intervals between study examinations.

Conen and colleagues[11] evaluated the association between self-reported alcohol use and AF among 34,000 participants in the Women's Health Study. Individuals with AF at baseline, cardiovascular disease or cancer before randomization, or missing data were excluded from the analysis. Women reported alcohol intake via mailed questionnaires as average frequency

of consumption of beer (12 ounces), wine (4 ounces) and liquor (shot) during the preceding 12 months. Usual daily intake of alcohol was categorized as none, more than 0 and less than 1 drink per day, 1 or more and less than 2 drinks per day and 2 or more drinks per day. The investigators documented 653 events of incident AF during a median follow-up of 12 years—504 by study ECG and 149 by physician report in the medical record.[11] After multivariate adjustment, intake of at least 2 alcoholic beverages per day was significantly associated with increased risk of AF (HR, 1.6; 95% CI, 1.13–2.25).

When examined as a continuous measure, each additional alcoholic drink consumed per day was associated with increased risk of incident AF. However a test for linear trend across consumption categories was not significant. Conen and colleagues[11] concluded that the small cohort of women who consumed 2 or more alcoholic beverages per day had 1.6-fold greater risk for AF than nondrinkers, suggesting a possible threshold effect. Factors mediating the observed association between drinking and incident AF were unclear. Other limitations of the research include self-reporting of alcohol consumption, absence of screening ECGs and generalizability of the Women's Health Study population.

Marcus and colleagues[12] address mechanisms connecting alcohol and atrial arrhythmia in their investigation of 200 patients presenting for ablation or cardioversion of AF or AFL to a university medical center. They performed a prospective case-control study to assess the association between alcohol intake and right or left coronary sinus atrial effective refractory period (AERP). Control groups included patients presenting for ablation of paroxysmal supraventricular tachycardia (PSVT) and normal subjects with no arrhythmias. Each patient underwent a structured interview that included a question about average alcohol intake. The AERPs were obtained at 400 millisecond drive cycle length at twice pacing threshold from the right atrium, proximal coronary sinus and distal coronary sinus (DCS).[12] The AERPs were not obtained when patients presented with arrhythmias at the start of their invasive procedures.

After multivariate adjustment, patients less than or equal to 60 years of age who drank daily had greater odds of having AFL than non-drinkers.[12] Patients less than or equal to 60 years of age exhibited a significant linear association between increasing amounts of alcohol and greater odds of having AFL. Greater intake was associated with decreased high right atrial AERP, approximately 50 milliseconds shorter than in non-drinkers. Interestingly, neither proximal nor DCS ERPs showed a linear association with self-reported alcohol ingestion. Marcus and colleagues[12] postulated that the lack of association between alcohol and AF may be a consequence of the relatively small patient cohort. However, their observations advance the field by (a) suggesting that the association between alcohol and AFL may be stronger than between alcohol and AF and (b) raising the possibility that AERP shortening may be a key atrial arrhythmia mechanism.

ALCOHOL CONSUMPTION AND SUDDEN CARDIAC DEATH

Beyond Holiday Heart and chronic atrial arrhythmias looms the specter of alcohol-induced sudden cardiac death. Wannamethee and Shaper[13] used data from the British Regional Heart Study to show that heavy drinking is associated with an increased risk of sudden death. In this study, 7,735 men aged 40–59 at screening were selected at random from general practices in England, Wales and Scotland, and followed for 8 years. These men were classified into groups according to weekly alcohol intake: (1) None; (2) Occasional [< 1 unit/week]; (3) Light [1–15 units/week]; (4) Moderate [16–42 units/week] and (5) Heavy [> 42 units/week]. These men were also classified based on pre-existing ischemic heart disease (IHD): (1) no evidence of IHD on WHO chest pain questionnaire, ECG or doctor's diagnosis; (2) evidence suggesting IHD short of myocardial infarction (MI) and (3) previous definite MI. Sudden death was defined as an event in which death occurred within 1 hour of onset of symptoms.

The investigators found that mortality from IHD actually decreased with greater alcohol intake up to levels of moderate drinking.[13] In contrast, heavy drinkers had a higher rate of sudden death than all other groups combined (relative risk 1.6; 95% confidence interval 1.0–2.6; p = 0.05). Heavy drinkers did not have excess risk of overall death from IHD, but death was more likely to be sudden. Subsequent adjustments for social class and cigarette smoking did not alter the association between heavy alcohol intake and sudden cardiac death.[13] However, adjustment for age showed that heavy drinking was associated with increased risk of sudden death only in the older participants (50–59 years).

In men with no evidence of IHD, more than 80% of deaths in heavy drinkers were sudden. In men with pre-existing IHD, more than 70% of deaths in heavy drinkers were sudden. The authors concluded that death in the event of a heart attack in heavy drinkers was likely to be sudden and that alcohol intake discriminated between sudden death and non-sudden death, perhaps by triggering ventricular arrhythmias. British Regional Heart Study findings were concordant with analyses of heavy drinking and sudden cardiac death performed in Auckland,[14] Puerto Rico[15] and Yugoslavia.[16]

Mukamal and colleagues[17] subsequently evaluated the effects of binge drinking on mortality after acute myocardial infarction (AMI) using data from the Determinants of MI Onset Study. In this study of 1,919 men and women in 45 communities and tertiary care medical centers in the United States were interviewed a median of 4 days after MI. For inclusion, patients were required to have a creatine kinase (CK) level above the upper limits of normal, positive MB isozymes, an identifiable onset of symptoms of infarction and the ability to complete a structured interview.[17] Participants reported the usual frequency of consumption during the preceding year of wine, beer or liquor. Usual weekly ethanol consumption was categorized as None, Light (< 105 gm) or Heavier (≥ 105 gm). Binge drinking over the preceding year was determined as the usual frequency with 3 drinks or more were consumed within 1–2 hours.[17] Whereas alcohol intake was inversely associated with mortality with patients who did not report binge drinking, investigators observed a doubling of total mortality among current binge drinkers, in both age- and sex-adjusted models. Adjustments for usual alcohol consumption further strengthened the association between binge drinking and death.

Interestingly, there were similar associations between binge drinking and mortality among Light and Heavier drinkers, based on usual alcohol intake, and among patients who reported binges up to once per week and more often.[17] Risks associated with binge drinking were similar among patients who reported heavy intake of beer, wine, liquor or multiple beverages. For the majority of binge drinkers, there was a positive relation between binge frequency and mortality. Further adjustments for use of nicotine, caffeine, marijuana, cocaine or heroin did not alter these findings. Mukamal and colleagues[17] concluded that potential health benefits of light-to-moderate alcohol consumption among patients with AMI were completely eliminated by binge drinking, findings with public health relevance because most Americans who are light-to-moderate drinkers have reported occasional binge episodes.[18] The investigators postulated that binge alcohol use could be a trigger for lethal ventricular arrhythmias. Heavy intake appears to lower ventricular fibrillation threshold and increase risk in postinfarction patients, who are susceptible to sudden cardiac death.[19-24]

In the Onset Study, few women reported binge drinking but associated cardiovascular risks appeared to be similar among men and women.[17] Chiuve and colleagues[25] performed a more targeted analysis of the relationship between sudden cardiac death and light-to-moderate alcohol consumption in women using data from the Nurses' Health Study. Those investigators prospectively explored the role of alcohol intake on risk of sudden cardiac death compared to other forms of CHD. Female nurses aged 30–55 years at baseline in 1976 completed questionnaires about medical history and cardiovascular and lifestyle risk factors. Chiuve's excluded women missing information on alcohol consumption and those reporting cardiovascular disease or cancer prior to 1980. Importantly, nondrinkers were separated into lifetime abstainers versus former drinkers to reduce bias from inclusion of "sick quitters".[25]

Women were categorized into groups based on alcohol intake: (1) Abstainers; (2) Former Drinkers; (3) 0.1–4.9 gm/day [< ½ drink]; (4) 5.0–14.9 gm/day [½ –1 drink]; (5) 15.0–29.9 gm/day [1–2 drinks] and greater than or equal to 30 gm/day [≥ 2 drinks]. Study endpoints were sudden cardiac death, other fatal CHD and non-fatal MI. Deaths were initially identified through next of kin, postal authorities, or National Death Index and confirmed by death certificate. Approximately 26% of women were nondrinkers, 50% consumed up to 15 gm/day (1 drink), 4% consumed 30.0–49.9 gm/day (2–4 drinks), and less than 1% consumed greater than or equal to 50.0 gm/day (≥ 4 drinks). Heavy drinkers tended to be smokers but had lower prevalence of diabetes, lower body mass index (BMI), lower intake of trans fat and higher intake of omega-3 fat.

Chiuve and colleagues[25] found a U-shaped association between light-to-moderate alcohol ingestion and risk of sudden death in age-adjusted, calorie-adjusted and multivariate-adjusted models. Sudden cardiac death was least common among women who consumed ½–1 drink daily: 36% lower risk than in nondrinkers. Risk among women drinking more than or equal to 2 drinks per day did not differ significantly from risk among nondrinkers. Benefits were not restricted to one type of beverage (beer, wine or liquor). Subsequent analysis showed no difference in the association between drinking and sudden cardiac death in participants with history of coronary disease.[25]

The investigators noted that the U-shaped association for sudden cardiac death in women was generally consistent with that of men participating in the Physicians Health Study.[26] In contrast to other prospective studies, there was no increase in risk of sudden cardiac death at any level of alcohol intake. Few women reported moderate-to-heavy ethanol consumption, and heavy drinking was rare.[26] Importantly, Chiuve and colleagues[25] were unable to determine the influence of binge drinking. They also noted that their study design might not eliminate all confounding by healthy lifestyle or the evolution of drug therapy during the follow-up period.

SUMMARY AND CLINICAL GUIDELINES

- Physiologically relevant concentrations of ethanol cause direct, acute and reversible shortening of action potential duration in isolated heart cell and tissue preparations
- Randomized controlled studies of ethanol consumption by humans and experimental animals demonstrate slowing of cardiac conduction and modulation of HRV that are independent of ethanol-mediated effects on nutritional status and myocardial viability
- Chronic heavy drinkers are more likely to develop "Holiday Heart", a condition in which transient supraventricular arrhythmias develop after weekend and holiday binge episodes
- Individuals who consume more than 2 drinks everyday are more likely to develop sustained atrial arrhythmias, possibly through effects on the AERP
- Heavy consumption is also associated with increased risk of sudden cardiac death, possibly through ethanol-mediated effects on the threshold for ventricular fibrillation
- Binge drinking is a major risk factor for cardiovascular mortality, including sudden death, even among individuals who are usually light-to-moderate consumers of alcoholic beverages

In response to these important findings, the American College of Cardiology, American Heart Association and European Society of Cardiology recommend: (1) complete abstinence from alcohol when there is a suspected correlation between intake and ventricular arrhythmias and (2) optimal evidence-based treatment, including an implantable cardioverter defibrillator (ICD), if necessary, for individuals who have an expectation of survival of greater than 1 year.[27]

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Chapter 92

Insulin-resistance and Cardiomyopathy

Dipanjan Banerjee, Ronald Witteles, Michael B Fowler

Chapter Outline

- Epidemiology
- Diastolic Heart Failure and Insulin-resistance
- Pathophysiology
- Myocardial Energy Metabolism
- Metabolic Effects of Insulin-resistance—Energy Metabolism
- Other Metabolic Effects of Insulin-resistance
  - — Dyslipidemia or Lipotoxicity
- Detection of Metabolic Effects of Insulin-resistance
- Structural Effects of Insulin-resistance
  - — Diastolic Dysfunction
  - — Systolic Dysfunction
  - — Antiadrenergic Therapy
  - — Insulin Therapy
  - — Insulin Sensitization
  - — Metabolic Modulators

INTRODUCTION

Insulin-resistance, the underlying abnormality responsible for the metabolic syndrome, is associated with the development of hypertension, adiposity, glucose intolerance and the characteristic dyslipidemia that are used to define the metabolic syndrome (Fig. 1). Insulin-resistance is important in the progression of heart failure, while in some patients insulin-resistance may also serve a primary role in the development of heart failure. This relationship is most clearly manifest in the epidemiology of heart failure, as hypertension and diabetes, two important components of the metabolic syndrome, are closely linked to the development of heart failure. The hereditary and environmental factors that combine to produce insulin-resistance provide the nidus for the development of heart failure; both by contributing to the causes of heart failure, and by aggravating the response to myocardial injury or stress which characterizes the progression of cardiomyopathy.

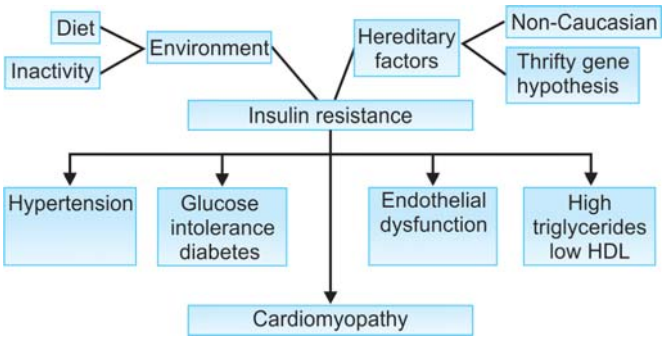


FIGURE 1: Insulin-resistance and cardiomyopathy. (*Source:* Modified from Michael B Fowler)

EPIDEMIOLOGY

The Framingham study revealed the importance of diabetes in the development of heart failure, with diabetic men and women being four and six times, respectively, more likely to develop heart failure than nondiabetics.[1] Direct evidence for the important relationship between the insulin-resistance and the development of heart failure can be found in a study from Uppsala University, Sweden.[2] This study was designed to examine the relationship between the development of heart failure and the evidence of insulin-resistance at the time of study entry. In this longitudinal study, 1,107 elderly men (age $\geq$ 70 years) were followed for an average of 8–9 years. All were free from heart failure or valvular heart disease at baseline. At the end of the study, 104 individuals had developed heart failure. Insulin-resistance was measured using euglycemic insulin clamp glucose disposal rate, as well as measurements from a 2 hour glucose tolerance test and measurement of proinsulin levels and waist circumferences. Multivariate cox proportional hazard models adjusted for known determinants for risk of heart failure found that an increased risk for heart failure was related to parameters of insulin-resistance: a 1-SD increase in the 2 hours glucose level of an oral glucose tolerance test [hazard ratio (HR) 1.44], fasting proinsulin levels (HR 1.29) and waist circumference (HR 1.36). A 1-SD increase in glucose disposal rate was associated with a reduced risk of developing heart failure by 34% (HR 0.66; 95% CI, 0.51–0.86) (Fig. 2). Obesity was no longer related to the development of heart failure when clamp glucose disposal rate was included as a covariate. Jeppesen et al. corroborated these results by showing that insulin-resistance predicts cardiovascular disease, including heart failure, in a similar cohort of patients.[3]

Initially, the relationship between insulin-resistance and heart failure was thought to be mediated by coronary artery disease

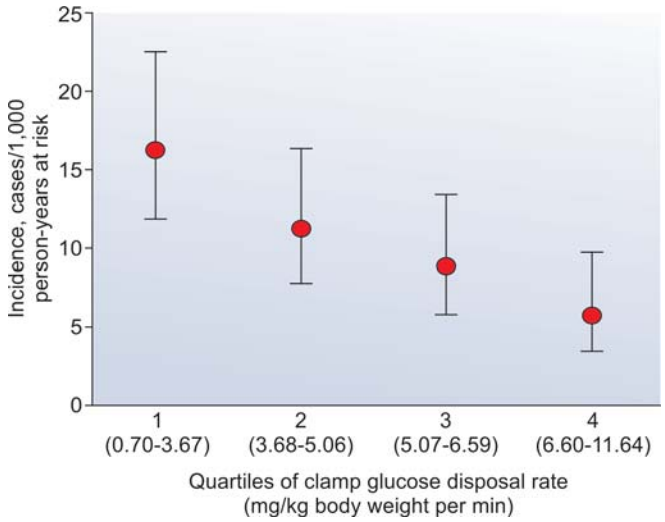


FIGURE 2: Incidence rates of congestive heart failure by glucose disposal rate. (*Source:* Modified from Ingelsson E et al. JAMA. 2005;294:334-41)

(CAD) and the resultant systolic dysfunction. One of the strongest arguments for this paradigm was a study by Haffner and colleagues, which found that individuals with diabetes were as likely to experience a myocardial infarction as nondiabetics who had already suffered a myocardial infarction.[4] This strong relationship between diabetes and CAD, and the finding that diabetics with multivessel CAD benefit from more complete revascularization than nondiabetics[5] suggested that the insulin-resistance-CAD interaction was paramount.

The demonstration that patients with nonischemic cardiomyopathy exhibit higher degrees of insulin-resistance than matched controls[6] suggests that the link between insulin-resistance and cardiomyopathy is not necessarily mediated by coronary disease. Further support for this hypothesis was demonstrated in a study which examined the relative risk of heart failure incidence in diabetics as compared to controls;[7] the study cohort was further subdivided into a population without ischemic heart disease. The relative risk of incident heart failure was higher in diabetics than in nondiabetics, but this effect was more pronounced in the cohort without ischemic heart disease (Fig. 3). This study established that insulin-resistance is an important risk factor for heart failure in the absence of CAD, and suggested that it may in fact be a more significant factor in the development of heart failure in the absence of CAD.

Interestingly, the original description of a diabetic cardiomyopathy from autopsy findings in patients with diabetic nephropathy suggested that the observed cardiomyopathy was not explained by the presence of small vessel disease.[8] The changes seen were principally myocardial structural changes, including the development of left ventricular hypertrophy (LVH) with myofibrillar hypertrophy and diffuse fibrosis. Shirley Rubler, who first described this 'diabetic cardiomyopathy', did note, however, that a coexisting microangiopathy, while only observed in one of four cases, may also contribute to the cardiomyopathic state.

DIASTOLIC HEART FAILURE AND INSULIN-RESISTANCE

As it became more apparent that the relationship between insulin-resistance and heart failure is not necessarily mediated by CAD, attention turned to the relationship between insulin-resistance and diastolic heart failure. Diastolic heart failure has been described as the syndrome of heart failure in patients with preserved left ventricular (LV) systolic function. It is characterized by abnormal LV diastolic filling due to structural and functional changes in the myocardium, which include myocardial fibrosis and hypertrophy, hypertension, with increased ventricular or arterial stiffness.[9] In epidemiologic studies, the pathologic state most strongly linked with diastolic dysfunction is hypertension. Data from the Framingham study reveal that as many as 70% of patients who develop heart failure have had prior hypertension[10] (Fig. 4). Hypertension is especially likely to have been present in women who subse-

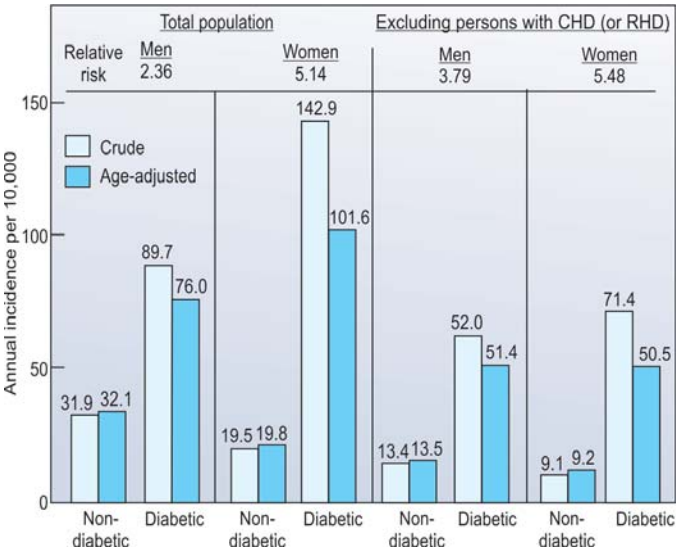


FIGURE 3: Relative risk of congestive heart failure with diabetes mellitus. (*Source:* Modified from Zoneraich S. Diabetes and the heart. Springfield Ill: Charles C. Thomas, Publisher; 1978)

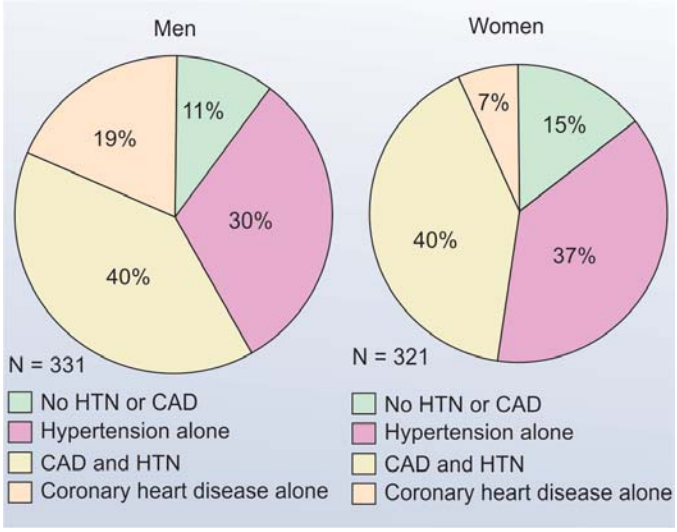


FIGURE 4: Presence of risk factors in patients with heart failure, stratified by gender. (*Source:* Modified from Ho KKL et al. JACC. 1993;22: 6A-13A)

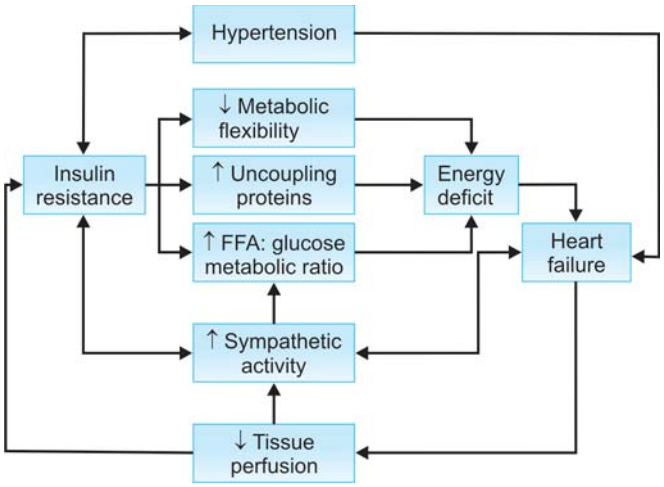


FIGURE 5: Relationships/mechanisms linking insulin-resistance to heart failure. (*Source:* Modified from Witteles and Fowler, JACC. 2008)

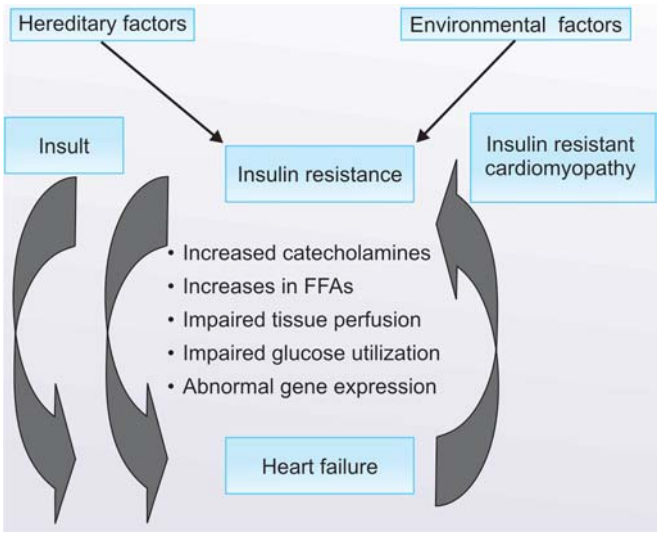


FIGURE 6: Vicious cycle of insulin-resistance in HF. (*Source:* Modified from Michael B Fowler)

quently develop heart failure, and is a significant risk factor in patients with or without CAD.

The association between insulin-resistance and hypertension is well established. Multiple prospective studies have noted that insulin resistant individuals are more likely to develop hypertension than insulin sensitive individuals.[11,12] Epidemiological studies have also demonstrated the relationship between the insulin-resistance and the myocardial abnormalities characteristic of diastolic heart failure, which develop independently of the changes in body mass index (BMI) or hypertension.[13,14] LVH, an important factor closely linked to the development of heart failure in epidemiological studies, is closely related to the presence of hypertension. An interaction between insulin-resistance and hypertension has been described in the development of LVH.[15] Not all who exhibit hypertension are insulin resistant (roughly 50%), but those with hypertension who are insulin resistant have worse cardiovascular outcomes.[16]

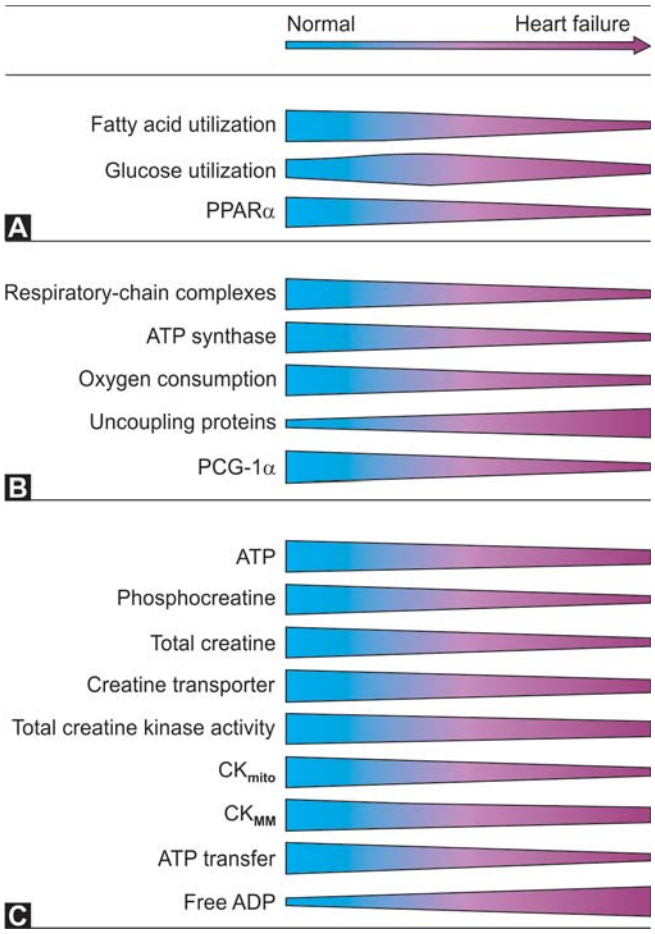
PATHOPHYSIOLOGY

Insulin-resistance is often described as a cofactor in the development of heart failure (Fig. 5). Evidence supports the concept that a superimposed myocardial insult (such as ischemia or pressure overload) and the presence of insulin-resistance contributes to the development of a cardiomyopathic state. Other studies support the concept of insulin-resistance in cardiomyopathic patients resulting in worsening heart failure. Many studies have focused on the insulin resistant state which develops in advanced heart failure, and compromises the failing heart's adaptation to use glucose, its more efficient fuel source.[17-19] This causes a progressive deterioration in myocardial function. It has been noted that the presence of insulin-resistance in heart failure is associated with adverse clinical features, including decreased exercise capacity.[20] Recent animal studies have provided evidence that insulin-resistance can lead directly to myocardial stress (i.e. decreased contractile function) and initiate, not just perpetuate, the process of myocardial deterioration. This has led to a more balanced view of the role of insulin-resistance in heart failure, as both initiator and cofactor.[21]

Insulin-resistance contributes to the development of heart failure due to the direct effects of hyperinsulinemia upon the myocardium and its vasculature, including chronic adrenergic stimulation, cellular apoptosis and endothelial dysfunction, as well as indirect effects such as impairment of myocardial energy metabolism, hypertension and dyslipidemia. The importance of the alterations in gene expression that accompany these changes in the setting of heart failure is being increasingly recognized.[22,23] These changes in gene expression largely recapitulate the heart's fetal gene program, an adaption presumably made to improve myocardial efficiency in the setting of energy and oxygen deprived environment. However these genetic changes cannot compensate for myocardial inefficiency in the insulin resistant environment, and often paradoxically further impair myocardial efficiency. Importantly, whether insulin-resistance initiates myocardial damage or impairs the response to myocardial injury, in both cases, the resultant myocardial performance leads to worsening insulin-resistance, compounding myocardial stress and engendering a cycle of ever worsening cardiac function and insulin metabolism (Fig. 6).

MYOCARDIAL ENERGY METABOLISM

To explain the role of insulin-resistance in heart failure, an understanding of myocardial energy metabolism is required. The heart turns over its ATP supply in 4–5 seconds and has a limited capacity for intracellular energy storage. Thus the myocardium needs a steady supply of energy to function optimally and safely. Two major energy sources are available to the heart. Glucose, the more efficient fuel, which yields a higher number of ATP per amount of oxygen consumed, and free fatty acids (FFA) which in the setting of abundant oxygen yield a greater total amount of ATP. In the normal heart, the predominant fuel used is FFA, as the relative abundance of FFA in the serum directly suppresses glycolysis by inhibiting pyruvate dehydrogenase, and leads to the storage of glucose as glycogen.[24]



FIGURES 7A TO C: Changes in cardiac energy metabolism in the failing heart. (*Source:* Modified from Neubauer S. The failing heart—an engine out of fuel. N Engl J Med. 2007;356:1040-51)

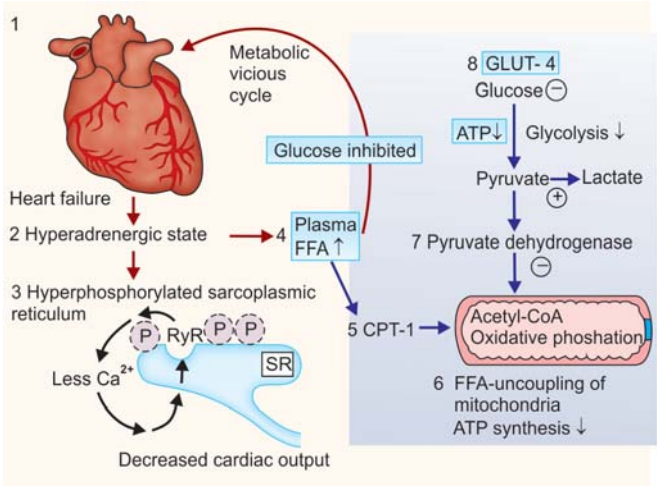


FIGURE 8: Metabolic vicious cycle in heart failure. Heart failure, a hyperadrenergic state, increases free fatty acids in plasma with inhibitory effects on cardioprotective glycolysis. Steps in cycle are detailed in text. (Abbreviations: FFA: Free fatty acids; RyR: Ryanodine receptor; SR: Sarcoplasmic reticulum). (*Source:* Modified from Lionel Opie. The metabolic vicious cycle in heart failure. Lancet. 2004;364:1733-4)

In the failing heart, a switch is initially made to the more efficient fuel glucose, in an attempt to reduce myocardial oxygen consumption and thus myocardial workload[25] (Figs 7A to C). Typically, a stressor leads to this switch in myocardial energy metabolism, which can be pressure-induced hypertrophy (i.e. hypertension), ischemia, toxic drug use (methamphetamines), chronic beta-adrenergic stimulation or insulin-resistance itself. This switch is accompanied by a reversion of the failing heart to the fetal gene program (the fetal condition itself an energy deprived environment), with increased transcription of genes such as glucose transporters (GLUT-1 and GLUT-4), atrial natriuretic peptide, MHC beta and skeletal actin, and by the repression of metabolic 'adult' genes alpha myosin heavy chain and SERCA.[26] Energy metabolism is closely linked to gene expression: increased myocardial work spurs increased glucose uptake via insulin secretion, which stimulates transcription of genes encoding glucose transporters and inhibits nonesterified fatty acid (NEFA) release, leading to lower NEFA levels.[27]

METABOLIC EFFECTS OF INSULIN RESISTANCE—ENERGY METABOLISM

In the insulin resistant state there is decreased Ser473 phosphorylation of Akt-1, resulting in decreased translocation of the GLUT-4 transporter to the cell membrane and decreased myocardial cellular glucose influx. The result is a decrease in GLUT transporters present in the cellular membrane, and an increase in NEFA levels.[28,29] Insulin-resistance thus counteracts the fetal gene program's attempt to adapt during cardiomyopathy. The inhibition of this adaptive response leads to increased reliance of the failing heart on FFA, which in the setting of insulin-resistance actually makes the heart less efficient by increasing myocardial oxygen consumption. This inefficiency arises because FFAs direct uncouple mitochondrial respiration,[30] but also because elevated FFA levels directly impair glycolysis (Fig. 8). The resultant lower levels of glucose thus compound the effects of insulin-resistance, and the excess of FFAs lead to myocardial triglyceride accumulation and lipotoxicity due to peroxidation of these lipids.[24]

Mouse models of insulin-resistance induced by streptozocin have noted preferential metabolism of FFA rather than glucose in the presence of pressure overload, resulting in apoptosis and cardiomyopathy.[31] Overexpression of GLUT-1 in these models preserves glucose utilization and protects the mouse heart from the myocardial inefficiency caused by pressure overload, maintaining cardiac function. The adverse strategy of FFA utilization in insulin-resistance appears to be correlated with the severity of the cardiomyopathy. In animals with moderate cardiomyopathy, FFA oxidation is maintained.[32] In humans with moderate idiopathic dilated cardiomyopathy, myocardial glucose uptake increases slightly with a concomitant decrease in FFA uptake.[33] As cardiomyopathy progresses, insulin-resistance worsens with a concomitant increase in plasma NEFA levels and preferential use of FFAs as a fuel source, which leads to a further decrease in myocardial ATP levels.[34] Thus, there is a progressive impairment in energy utilization as heart failure worsens.

In summary, the switch to the fetal gene program and resultant increase in glucose utilization is an adaptive response to myocardial stress. In the setting of insulin-resistance, however, this switch is ineffective, since glucose utilization is impaired, and the heart enters an 'energy starved state'. It should

be emphasized here that insulin-resistance can both initiate this cycle, by producing the stress that leads to reversion to the fetal gene program, and perpetuate this cycle, by subverting the metabolic efficiency of the fetal gene program by inhibiting glucose utilization. Heart failure can in turn worsen insulin-resistance by increasing sympathetic activity, endothelial dysfunction and inflammatory cytokine production. Thus, insulin-resistance can initiate a cardiomyopathic state and subsequently exacerbate a cardiomyopathic state. Importantly, heart failure itself engenders insulin-resistance, and a cycle of worsening efficiency perpetuates until there is either treatment or correction of the underlying insult.

OTHER METABOLIC EFFECTS OF INSULIN-RESISTANCE

DYSLIPIDEMIA OR LIPOTOXICITY

Characteristic of insulin-resistance is a dyslipidemia with an increase in triglycerides and decrease in high density lipoprotein concentration.[35] This is partially due to the increased level of NEFAs in the serum that results from impaired utilization of glucose. These excess fatty acids bind to PPAR alpha and influence gene transcription. The excess of FFA in the heart also leads to an accumulation of triglycerides in myocardial cells, causing mitochondrial dysfunction, lipid peroxidation and myocardial dysfunction, a phenomenon known as lipotoxicity[36] (Fig. 9). These effects increase reactive oxygen species through impairment of mitochondrial beta oxidation, apoptosis and impair nitric oxide synthase, which decreases myocardial contractility.

Among the most deleterious effects of insulin-resistance upon the heart is an increase in serum catecholamine levels (norepinephrine) and beta-adrenergic receptor density, leading to augmentation in chronic beta-adrenergic receptor stimulation.[37,38] Multiple investigations have shown that excess beta-adrenergic stimulation can lead to deterioration of LV systolic function and increased LV size. Pharmacologic agents that block the beta-adrenergic receptor can improve this cardiomyopathy, and may be particularly effective in patients with insulin-resistance.[39]

Insulin-resistance is also an inflammatory state, and, as with atherosclerosis, this inflammatory milieu leads to adverse effects upon the vasculature, particularly the endothelium of blood vessels. Decreased eNOS activity in insulin resistant individuals leads to increased plasma asymmetric dimethylarginine and increased free radical formation, which promotes microvascular dysfunction.[38] There are increased hsCRP, IL-6 and TNF-alpha levels in insulin-resistance and these factors promote apoptosis of myocardial cells via the NFKB pathway.[29,40]

In its most extreme form, insulin-resistance leads to hyperglycemia when the excess insulin produced by the pancreas is insufficient to maintain normal blood glucose levels. Hyperglycemia replicates and compounds many of the effects of insulin-resistance including increased inflammation (IL-6, TNF-alpha and IL-18), increased reactive oxygen species generation (peroxidation of LDL) and impaired microcirculation (nitric oxide derangement).[38] Hyperglycemia also causes increased platelet aggregation, reduced fibrinolysis and the formation of advanced glycosylation end products, which accumulate in many tissues, including the myocardium.[41]

DETECTION OF METABOLIC EFFECTS OF INSULIN-RESISTANCE

Detection of the metabolic effects of insulin-resistance requires specialized, often investigational tools. Energy use in the myocardium can be examined through phosphorous magnetic resonance (MR) spectroscopy; the phosphocreatine to ATP ratio is low in heart failure, and a low ratio independently predicts mortality in heart failure.[25,42] Fluorodeoxyglucose positron emission tomography (FDG PET) cardiac imaging has revealed impaired myocardial glucose uptake in diabetics and shown that this uptake worsens in advanced heart failure[43] (Figs 10A and B). Others have used cardiac 1H MR spectroscopy in conjunction with FDG PET to demonstrate the intramyocardial triglyceride accumulation characteristic of insulin-resistance, and decreased myocardial glucose uptake with increased NEFA uptake in diabetics as compared to controls.[44,45] These tools,

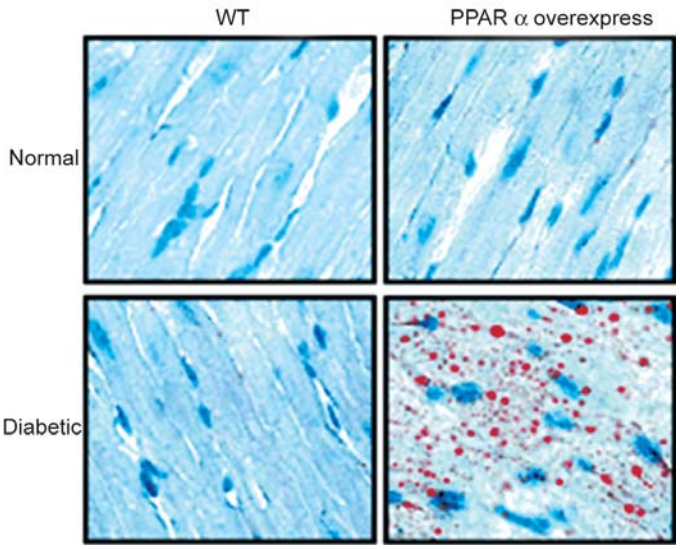
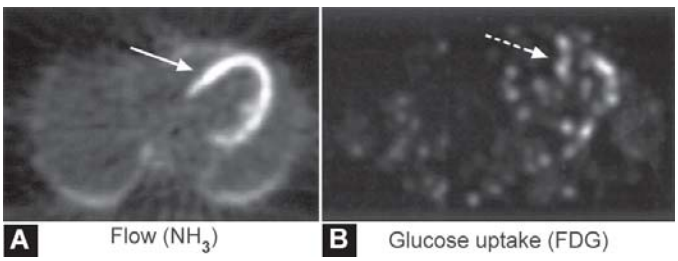


FIGURE 9: Lipotoxicity in diabetes. Red droplets indicate neutral lipid staining. (*Source:* Modified from Finck et al. Proc Natl Acad Sci. USA. 2003;100:1226-31)



FIGURES 10A AND B: Insulin-resistance and abnormal glucose metabolism in nonischemic heart failure patients.

Myocardial perfusion (A) and glucose uptake (B) in a patient with idiopathic dilated cardiomyopathy and insulin-resistance, as assessed by N-ammonia (NH_3) and F-fluoro-2-deoxyglucose (FDG) positron emission tomographic imaging. Note the strong, consistent signal in the left ventricle for blood flow (solid arrow) compared with the weak, scattered signal for glucose uptake (dashed arrow), implying inefficient energy metabolism. (*Source:* Modified from Witteles and Fowler, JACC. 2008)

once they have been established as reproducible and cost-effective, could be used to identify early evidence of insulin resistant cardiomyopathy in asymptomatic individuals.

STRUCTURAL EFFECTS OF INSULIN-RESISTANCE

Numerous investigators have noted a direct relationship between the degree of cardiac structural abnormalities as measured by echocardiography and the severity of insulin-resistance or metabolic syndrome.[46-48] The metabolic effects of insulin-resistance, as they accumulate over time, eventually lead to macroscopic changes in the structure and function of the heart. Both diastolic and systolic dysfunction can arise from long-standing insulin-resistance.

DIASTOLIC DYSFUNCTION

Insulin-resistance leads to cardiomyocyte hypertrophy, which can increase myocardial oxygen demand, further stressing a compromised heart. Insulin resistant individuals, both diabetic and nondiabetic, exhibit increased LV mass when compared to insulin sensitive individuals.[15,17] Histologically, this is represented by myocyte hypertrophy, LVH, and diffuse fibrotic strands as first noted in an autopsy study in patients with diabetes and heart failure, but without CAD or hypertension.[8,13] These findings can be partially explained by the nonenzymatic glycation of vascular and membrane proteins that result from hyperglycemia.

The direct hypertrophic effect of insulin-resistance upon cardiomyocytes plays a primary role in LVH, and is largely mediated by the the Akt-1 pathway in the acute phase as well as by B2 adrenergic receptors in chronic insulin resistant states.[27] Other contributing factors to diastolic dysfunction in the insulin resistant state include myocardial fibrosis (arising from myocardial cell apoptosis and collagen deposition in the gaps left by cellular death), endothelial dysfunction (which can lead to reactive fibrosis and cellular injury) and altered calcium metabolism (decreased sarcoplasmic reticulum calcium protein expression occurs in diabetes, leading to slower myocardial relaxation).[14,41] Finally, myocardial steatosis, another effect of insulin-resistance described above, is increased in insulin resistant individuals compared with controls and is associated with diastolic dysfunction.[49]

Further clinical evidence for the influence of insulin-resistance on the myocardial response to injury was recently obtained from an analysis of the LV remodeling that occurs in aortic stenosis. The aortic stenosis progression observation measuring effects of rosuvastatin (ASTRONOMER) study was designed to evaluate statin use on the progression of calcific aortic stenosis. In a substudy,[46] the impact of insulin-resistance on LV remodeling in patients with asymptomatic aortic stenosis was analyzed according to the presence or absence of components of the metabolic syndrome.

Figures 11 and 12 display the observed relationship between the pattern of LV remodeling and hypertrophy and the metabolic syndrome (MetS); Figure 11 focuses upon the relationship between the number of MetS criteria present on relative wall thickness ratio, a measure calculated from echo parameters:

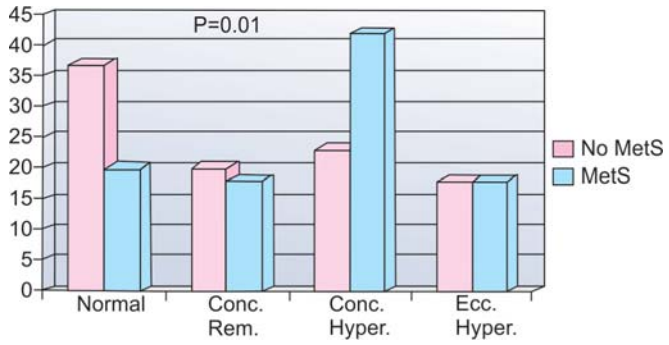


FIGURE 11: Left ventricular remodeling in the presence and absence of metabolic syndrome. (*Source:* Modified from Page et al. J Am Coll Cardiol. 2010;55:1867-74)

Relative wall thickness = (posterior wall thickness + interventricular septal thickness)/left ventricular internal diameter, or

$$RWT = (PWT + IVST)/LVID.$$

In both cases, cardiac structural abnormalities were linked to the degree of MetS.

In the Strong Heart study of Pima Indians, 1,810 individuals with DM were compared to 944 with normal glucose tolerance.[13] The subjects with DM were found to have a higher LV mass and wall thickness, and lower LV functional shortening, wall shortening and stress-connected mid-wall shortening as compared to controls. Arterial stiffness was also higher in the diabetic cohort. The investigators concluded that the adverse cardiovascular effects from diabetes were independent of changes in associated increases in BMI or hypertension. Other investigators have demonstrated that similar changes can be detected in populations of patients with insulin-resistance before the development of overt diabetes.[50,51]

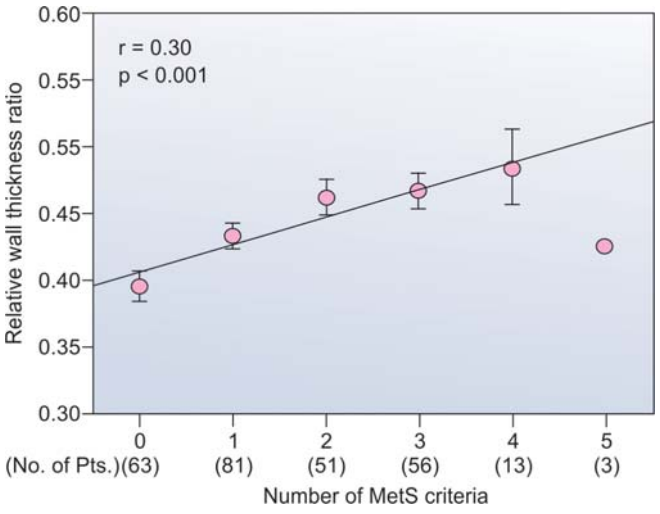


FIGURE 12: Relation between degree of left ventricular concentric remodeling and number of MetS criteria relative wall thickness ratio as a function of the number of NCEP-ATPIII (National Cholesterol Education Program, Adult Treatment Panel III) criteria for the metabolic syndrome (MetS). Error bars represent standard errors of the mean. (*Source:* Modified from Page et al. J Am Coll Cardiol. 2010;55:1867-74)

Thus insulin-resistance, by increasing the propensity to develop the structural abnormalities found in hypertension, greatly predisposes individuals to the development of diastolic dysfunction. Diabetes and hypertension can thus compound each other's role in the development of heart failure, and both of these conditions are frequently related to underlying insulin-resistance.

Detection of Diastolic Dysfunction

Since diastolic dysfunction typically predates and may also predict systolic dysfunction in insulin-resistance,[52,53] early identification of diastolic abnormalities in insulin resistant individuals could allow for early therapy and possible prevention of progression to systolic dysfunction. Most studies which have evaluated the presence of diastolic dysfunction in insulin-resistance have used echocardiography. This technology can detect increases in LV mass as well as diastolic dysfunction by measuring transmitral flow and mitral annular velocity.[51] Newer techniques, such as strain imaging, also show promise for earlier detection of diastolic dysfunction, while measures of coronary flow reserve (CFR) via echocardiography or coronary catheterization can also characterize diastolic dysfunction.[14]

Insulin-resistance is associated with worsening diastolic function compared to controls as detected by echocardiography.[50,51] Multiple studies have demonstrated increased LV mass in individuals with insulin-resistance (up to 70%) as measured by echocardiography, and the presence of diastolic dysfunction in diabetic cohorts has been described to be as high as 60%.[54] Liu et al. showed that not only is diabetes mellitus independently associated with impaired diastolic function, but that more severe diabetes (worse glycemic control) displayed the strongest association with diastolic dysfunction.[55] The concept of a graded severity of diastolic dysfunction that correlates with the severity of insulin-resistance is corroborated by other investigators who have found that the degree of insulin-resistance is positively associated with the prevalence of diastolic dysfunction.[56,57] Cardiac MR spectroscopy also shows promise in the early detection of diastolic dysfunction in insulin resistant cardiomyopathy. Rijzewijk et al. have shown that patients with diabetes exhibit increased myocardial triglyceride content in comparison to controls, and that increased myocardial triglyceride content independently predicts diastolic dysfunction[58] (Fig. 13).

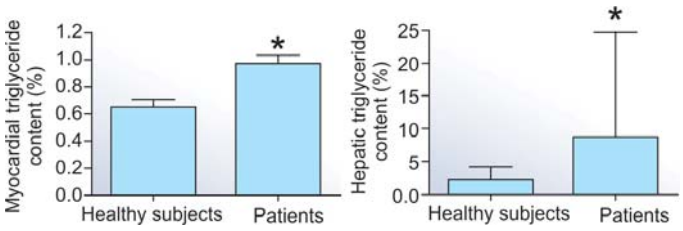


FIGURE 13: Myocardial triglyceride content in healthy controls is lower than in diabetics. (*Source:* Modified from Rijzewijk et al. JACC. 2008)

SYSTOLIC DYSFUNCTION

Systolic dysfunction in insulin resistant individuals is less well described than diastolic dysfunction, because diastolic abnormalities predate systolic abnormalities, as noted above.[4] Much of the evidence supporting a relationship between insulin-resistance and systolic dysfunction comes from animal models, where diabetes has been associated directly with decreases in contractile function.

The effects of insulin-resistance that contribute to systolic dysfunction of the heart include impairment of the coronary microcirculation, mitochondrial dysfunction and lipotoxicity.[59] The CFR is impaired in diabetic patients;[60] these findings have been extended to nondiabetic individuals, with more severe insulin-resistance associated with lower CFR.[61] One hypothesis is that impaired coronary microcirculation can lead to repetitive ischemic episodes, cell death and thus contractile dysfunction; the evidence for this is conflicting.[38] Diabetes has been shown to reduce mitochondrial oxidative capacity by suppressing genes that produce proteins active in oxidative phosphorylation and through impaired calcium homeostasis; the resultant decline in ATP production can lead to impaired myocardial contractile efficiency.[37]

Detection of Systolic Dysfunction

Echocardiographic studies have noted impairment of systolic function in patients with metabolic syndrome as compared to controls as measured by the Tei index, a combination of systolic and diastolic dysfunction,[62] while subclinical systolic dysfunction has been unmasked in diabetic individuals using dobutamine stress echocardiography: with stress, diabetics had lower measures of systolic function than controls.[63]

Others have shown cardiac steatosis detected by cardiac MRI in patients with impaired glucose tolerance when compared to normal controls, which is also associated with systolic dysfunction.[44] Though not specific to insulin resistant cardiomyopathy, late gadolinium enhancement detected by cardiac MRI predicts subsequent cardiovascular outcomes, likely due to an association with ventricular tachycardia; the prevalence of this in patients with insulin-resistance is not known.[64,65] Finally, invasive angiography and measurement of CFR had been shown to predict prognosis in both diabetic and nondiabetic patients: patients with abnormal CFR exhibited higher rates of death and myocardial infarction than those with normal CFR.[60] The patients in this study had negative stress ECHO findings by wall motion criteria. Impairment of CFR may indicate that abnormal coronary vascular reactivity is an important mechanism in the development of systolic dysfunction in insulin resistant cardiomyopathy.

As the role of insulin-resistance in the development and propagation of cardiomyopathy has only recently been investigated, there are no large scale clinical trials of therapy targeting insulin-resistance in individuals with heart failure. Thus, much of the evidence supporting treatment modalities for this condition are based upon extrapolation from other clinical populations or from small scale animal and human studies[21] (Table 1).

ANTIADRENERGIC THERAPY

Our group has speculated that in a significant proportion of patients with idiopathic dilated cardiomyopathy, insulin-

TABLE 1

Potential therapeutic options

Medication	*Mechanism*	*Other/side effects*
Metabolic modulators		
Trimetazidine	↓ FFA metabolism	Not approved in US
Prehexiline	↓ FFA metabolism	Not approved in US, liver/neuro-toxicity
Ranolazine	↑ Glu metabolis,	Might not be primary mechanism, ↑ QT interval
L-carnitine	↑ FFA/Glu metabolism	
Diabetic medications		
Insulin	↑ Ins	Hypoglycemia
Sulfonylureas	↑ Ins	Hypoglycemia
Metformin	↑ Ins sensitivity	Lactic acidosis (rare)
TZDs ("glitazones")	↑ Ins sensitivity	Fluid retention/edema
GLP-1	↑ Ins/↑ Ins sensitivity	Very short half-life (1–2 min)
Exenatide	↑ Ins/↑ Ins sensitivity	Nausea/weight loss, subcutaneous injection
DPP-IV inhibitor	↑ Ins/↑ Ins sensitivity	

(Abbreviations: DPP: Dipeptidyl peptidase; FFA: Free fatty acid; GLP: Glucagon-like peptide; Glu: Glucose; Ins: Insulin; TZD: Thiazolidinedione). (*Source:* Modified from Witteles and Fowler. JACC. 2008)

resistance is an important, and even a primary component in the development of cardiomyopathy. This patient group appears to have a particularly good response to antiadrenergic therapy. Since insulin-resistance worsens with heart failure, therapies that lead to significant myocardial remodeling and improved systolic function could conceivably lead to improved insulin-resistance. Thus, the recommended therapies for heart failure, including beta-blockers (BB), angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor blockers, and aldosterone antagonists will improve the insulin resistant state in patients with systolic heart failure. Antineurohormonal therapy can also directly modify insulin-resistance. ACEIs have been shown to reduce insulin-resistance in various patient cohorts,[66-68] although BB have been shown to adversely affect insulin-resistance and increase fasting glucose levels in diabetics.[69]

The BB have a separate important benefit in patients with heart failure, analogous to their benefit in patients with myocardial ischemia. In the latter case, BB improve the mismatch between oxygen demand and supply by reducing myocardial oxygen demand. Similarly, in patients with heart failure, BB improve the imbalance between myocardial energy demand and supply by decreasing myocardial energy demand, particularly in the insulin resistant state of heart failure. This may be one of the most important mechanisms explaining the benefit of beta-blocking agents across the spectrum of heart failure. This concept is supported by the observation that BB have been shown to reverse fetal gene expression.[26]

The effect of BB on insulin-resistance depends or appears to be determined both the patient population and the type of BB used. With respect to the former, in a study of patients with dilated cardiomyopathy, investigators found a significant decrease in insulin-resistance after BB therapy.[39] As for the latter, in the GEMINI study, adult hypertensive patients were randomized to carvedilol or metoprolol tartrate and indices of insulin-resistance were measured.[70] The carvedilol group exhibited no change in hemoglobin A1C level, improved insulin sensitivity and decreased microalbuminuria when compared to baseline, while the metoprolol group exhibited an increase in HbA1C, decreased insulin sensitivity and an increase in microalbuminuria.

Vasodilatation appears to be the property which is largely responsible for the differing degree of impact observed between different beta blocking drugs. In this respect, nonselective agents, such as propranolol, which tend to have vasoconstrictive actions, particularly increase insulin-resistance. Meta-analyses have shown that nonvasodilating beta blocking drugs are associated with the development of diabetes in patients being treated with this class of agents in hypertension. This finding should be a concern when conventional beta blocking drugs are used in Stage A or Stage B populations to prevent heart failure. Corroborating the beneficial effect of carvedilol (which has vasodilating properties) upon myocardial energy metabolism, Wallhaus et al. found that carvedilol use reduces FFA utilization by 57% in patients with heart failure,[71] (Fig. 14) and other investigators comparing carvedilol and metoprolol in heart failure have found that carvedilol reduced myocardial consumption of FFA, while metoprolol did not.[72] The BB nebivolol, which has nitric oxide donating properties, may be of particular beneficial in insulin resistant cardiomyopathy, which is associated with endothelial dysfunction and nitric oxide derangement.[73] These findings suggest that the specific properties of BB used in patients with heart failure may lead to differing outcomes, especially in insulin resistant cardiomyopathy.

INSULIN THERAPY

The benefit of insulin therapy in modifying the progression of cardiovascular disease has become more controversial due to recent data. The large, prospective trials of glycemic control including UK Prospective Diabetes Study (UKPDS) have shown

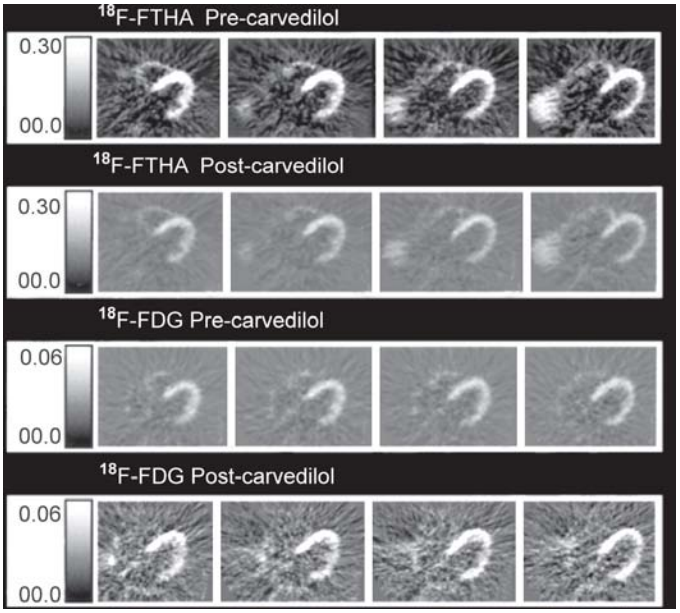


FIGURE 14: Reduced free fatty acid utilization in patients with heart failure after carvedilol use. (*Source:* Modified from Wallhaus et al. Circulation. 2001;103:2441-6)

a decrease in microvascular complications with better glucose control, whether with provision of insulin or insulin secretagogues such as the sulfonylureas.[74] In a surgical intensive care unit setting, tight glycemic control was shown to have a beneficial effect upon overall mortality and sepsis.[75] These findings were in keeping with a large prospective study that showed poor glycemic control was associated with increased hospitalization in patients with heart failure.[76]

Macrovascular complications have not been shown to decrease with tight glycemic control in patients with diabetes. While there is evidence that tight glycemic control reduces myocardial remodeling after myocardial infarction,[77] other data is not so robust. Tight glycemic control has been shown in the ADVANCE[78] and ACCORD[78] trials, respectively, to have either no effect on macrovascular complications or a harmful effect as compared to usual care, while tight glycemic control proved to have a detrimental effect on medical ICU patients.[79] This may in part be due to the reduced effect of insulin in patients with heart failure, an insulin resistant state; insulin infusions have been shown to improve systolic function in nondiabetics more than in diabetics.[80] Studies specifically investigating tight glycemic control with insulin or insulin secretagogues in heart failure would help determine whether patients with heart failure represent a subgroup in which the above agents are beneficial.

INSULIN SENSITIZATION

While adrenergic antagonists can directly affect insulin-resistance, more specific agents that target insulin-resistance exist. Among these are the thiazolidinediones, rosiglitazone and pioglitazone. These directly affect insulin-resistance by altering DNA expression, binding to the PPAR gamma receptor in cell nuclei.[59] In a small pilot study, the authors administered rosiglitazone to patients with nonischemic cardiomyopathy and assayed myocardial glucose metabolism via FDG PET before and after rosiglitazone administration, finding that myocardial glucose uptake improved after rosiglitazone administration.[43] Another study randomized patients with cardiovascular disease or risk factors for cardiovascular disease to rosiglitazone or placebo and performed peak VO_2 max testing and cardiac MRI at baseline and at 6 months; there was an increase in peripheral edema in the rosiglitazone group, but no significant change in VO_2 max or MRI parameters. The side effects of rosiglitazone include significant fluid retention, and this medication now includes a black box warning against use in patients with heart failure, precluding its use in insulin resistant cardiomyopathy. Dargie et al. showed that, while the use of rosiglitazone in heart failure led to more hospitalizations for congestive heart failure, there was no significant change in ejection fraction or increased mortality, suggesting that the fluid retention may be related to a separate process from the fluid retention characteristic of heart failure.[81] It is possible that the adverse effects of rosiglitazone on salt and water retention were in fact balanced by an improvement in myocardial performance due to the beneficial effect of rosiglitazone on insulin-resistance. Pioglitazone has been shown to reduce the incidence of myocardial infarction and stroke in diabetics, but also increased the number of heart failure events.[82] The adverse impact of thiazolidinediones on fluid retention in heart failure effectively has barred further investigation of any putative beneficial effect these agents may have on the insulin resistant state in heart failure.

Other ancillary data suggesting improved outcomes with agents that directly improve insulin-resistance include a study by Shannon and colleagues that employed infusions of GLP-1, a peptide that increases insulin sensitivity, which was found to increase glucose uptake and improve LV performance in patients with reduced LV systolic function following acute infarct.[34] In a porcine model of ischemic heart disease, exenatide, an agent that increases insulin sensitivity as a GLP-1 analog, was also found to reduce infarct size[83] (Fig. 15). Sitagliptin is another compound that enhances carbohydrate metabolism by inhibiting the breakdown of GLP-1 (dipeptidyl peptidase IV inhibitor), and has been proposed as a possible therapy for insulin resistant cardiomyopathy.

Some promising data has arisen from the bariatric surgery field. The striking weight loss from bariatric surgery has been

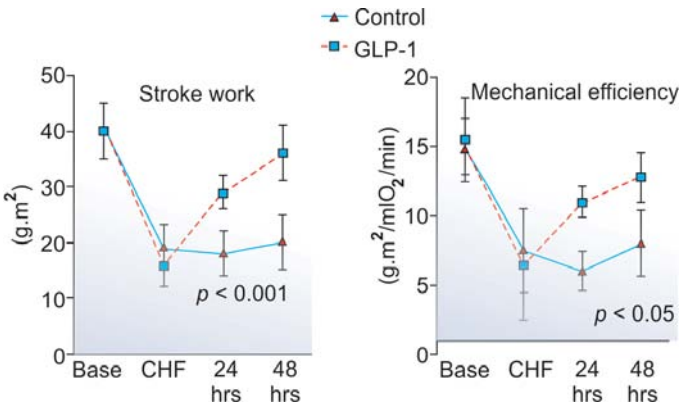


FIGURE 15: Improvement in myocardial work indices after GLP-1 infusion. (*Source:* Modified from Nikolaidis et al. Circulation. 2004;110:995)

shown to improve insulin-resistance and to improve LV mass and diastolic function as measured by cardiac MRI.[84,85] There are case reports of patients with nonischemic cardiomyopathy who have had improvements in systolic function with bariatric surgery,[86] although these are confounded by concomitant antiadrenergic therapy. Whether lesser degrees of weight loss in heart failure through diet and exercise will yield similar effects is uncertain and unstudied; in patients without heart failure, diet and exercise have yielded improvement in parameters of insulin-resistance but not in cardiac size or function.[87]

METABOLIC MODULATORS

Given the preference for glucose utilization in the failing heart but a paradoxical increase in FFA concentrations, another hypothetical approach to treating insulin resistant cardiomyopathy would be to decrease FFA utilization or production, or increase carbohydrate metabolism. Trimetazidine, etoxomir and perhexiline are agents that decrease FFA metabolism, the former by inhibiting beta-oxidation of FFAs, and the latter two by inhibiting mitochondrial transport of FFAs. Trimetazidine is one of the more promising agents to be studied in patients with heart failure and has been found to improve LV systolic function while reducing LV dimensions[88-91] (Fig. 16). This agent is available in Europe, but not in the United States. The use of etoxomir and perhexiline has been limited by hepatotoxicity, although one randomized trial of perhexiline in heart failure yielded positive results: improved LV ejection fraction was noted in the group receiving perhexiline.[92]

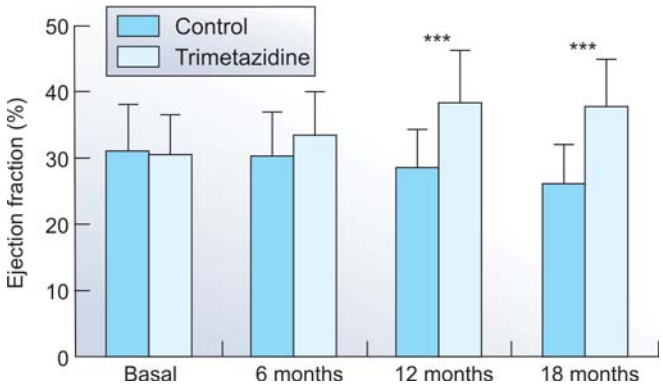


FIGURE 16: The effect of trimetazidine in heart failure. ***p < 0.001 v control. (*Source:* Modified from Di Napoli et al. Heart. 2005)

Dichloroacetate increases carbohydrate metabolism by activating pyruvate dehydrogenase, allowing glucose to be metabolized by the Krebs cycle and undergo oxidative phosphorylation, rather than produce lactate, which yields significantly lower amounts of ATP. Dichloroacetate infusion by Bersin and colleagues in patients with NYHA III/IV heart failure led to augmented LV contractility and reduced myocardial oxygen demand[93] (Fig. 17).

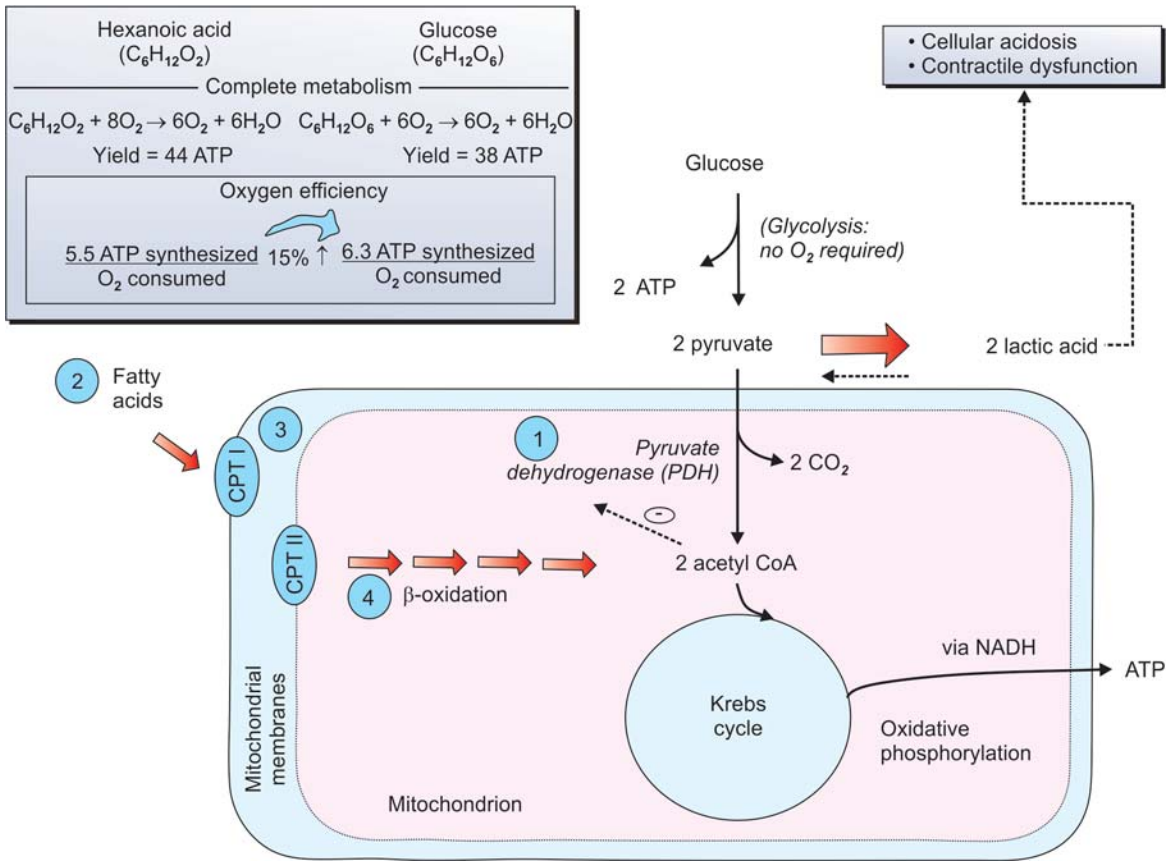


FIGURE 17: Modulation of myocardial energetics. (*Source:* Modified from Morrow DA, Givertz MM. Circulation. 2005;112:3218-21)

CONCLUSION

Insulin-resistance has emerged as an important contributor to the development and propagation of cardiomyopathy, and therapies targeted toward treating insulin-resistance show promise in modifying the course of this disease. As this emerging field develops and a better understanding of insulin resistant cardiomyopathy ensues, earlier detection and more specific treatment of this condition will follow.

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Chapter 93

Cardiac Complications of Substance Abuse

Hugh H West

Chapter Outline

- Magnitude of the Problem
  - Adolescents
  - College and Medical Students
  - Unemployed Adults
  - Trauma Associations
  - Iatrogenic Issues
- Substances of Abuse
  - Cocaine
  - Methamphetamine
  - Phencyclidine
  - Phenylpropanolamine
- Marijuana, Tetrahydriocannabinol, Hashish
  - Cardiac Complications
- Club Drugs: MDMA, GHB, Ketamine, Rohypnol
  - Methylenedioxymethamphetamine
  - Gammahydroxybutyrate
  - Ketamine
  - Rohypnol
- Hallucinogenic Drugs
  - Lysergic Acid Diethylamide
- Body Image Drugs
  - Anabolic Steroids
  - Diet Drugs
  - Anorexia and Bulemia
- Inhalants
- Narcotics
  - Heroin
  - Methadone
- Prescription and Over the Counter Drugs
- Alcohol and Tobacco

INTRODUCTION

The use of mood-altering substances occurs quite frequently in modern society and ranges from the social use of alcohol to the intravenous administration of cocaine, heroin and other illegal substances. Many of these substances produce cardiac complications, particularly if taken in large enough quantities over long enough periods of time. Cardiac complications of alcohol abuse are fairly common, as are the infectious complications of parenteral drug use such as cellulitis, abscess formation and endocarditis. Patients with an acute drug overdose manifested by cardiac signs and symptoms such as arrhythmias or shock present for medical care with some regularity. This chapter discusses substance abuse issues with a focus on cardiac complications. The spectrum of pathology ranges from the acute overdose at one end to the more subtle chronic issues related to long standing usage patterns at the other. The distinction between these two ends of the spectrum offers some value to the clinician as the clinical presentations are generally quite different. With an acute overdose, the patient often presents with a history of substance use or circumstances suggesting that diagnosis, and often the patient has an altered mental status. The clinical presentation fits the picture of substance abuse such that cardiac signs and symptoms can promptly be connected with the offending substance in the clinician's mind, and appropriate diagnosis and treatment follow in a relatively straightforward manner. That situation differs from the chronic problems in that patients with chronic abuse complications often present with a normal mental status, and their cardiac signs and symptoms present well after the phase of acute intoxication has passed. The possibility of substance abuse may not occur to the physician and often the patient will minimize that possibility, neglect to mention it or deny it altogether. Furthermore, while the acute overdose often results in a single medical encounter, which can be treated in a very satisfactory manner with a good outcome, chronic substance abuse issues are much more complicated for everyone involved. They generally result from long-standing behavior patterns. The physician who makes the correct diagnosis of a chronic complication of the use of some substance of abuse has the additional substantial task of modifying the patient's behavior patterns by convincing the patient of the danger of the practice. Involvement with the underlying behavioral issues may in turn involve engaging some of the more vexing economic and social issues that our society has yet to solve.

Although the problem of substance abuse complications represents a significant challenge, there exists a paucity of scientific research of these issues and, with some exceptions, there are few reports in the literature addressing the underlying science and pathophysiology, especially considering the frequent use and the wide variety of the offending substances. In addition, although the state of medical knowledge regarding these

complications has progressed to some degree, the changing spectrum of substances provides a moving target, and research generally lags well behind the current usage patterns. At best, the scope of the needed scientific work vastly exceeds the available resources for investigation and funding.

MAGNITUDE OF THE PROBLEM

From 2002 until 2008, the rate of illicit drug use by youths aged 12–17 declined significantly overall, from 11.6% to 9.3%. That fact notwithstanding, in 2008 some 20 million Americans over the age of 11 were considered to be active current users of illicit drugs. This data comes from approximately 67,500 interviews per year conducted by the Substance Abuse and Mental Health Services Administration, which falls under the purview of the U.S. Department of Health and Human Services. "Active and current usage" in these interviews meant that subjects had used illicit drug during the month immediately prior to the survey. The drugs termed "illicit" for the purposes of the survey included marijuana, cocaine, heroin, hallucinogens, inhalants and prescription medications used nonmedically. The tally of 20 million represented approximately 8% of the population of that age range, over age of 11, and this incidence did not change significantly from 2007 to 2008.[1]

ADOLESCENTS

In 2009, the National Institute of Drug Abuse reported on the adolescent age group, showing a similar decline in illicit drug use seen since about the mid-1990s, with the greatest proportional decline in the 8th grade population and the smallest in 12th graders. Most recently, from 2008 to 2009, few changes in drug use reached statistical significance. One that did involve marijuana, the use of which had increased from 12% to 14%. The particular importance of marijuana lies in the fact that it was the most prevalent illicit drug in any survey for this age group. Although the usage of drugs other than marijuana has been declining, the illicit drug spectrum of abuse in this age range according to the "Monitoring the Future" survey done at the University of Michigan under the auspices of the National Institutes of Health included lysergic acid diethylamide (LSD), cocaine, amphetamines, rohypnol, ketamine, ecstasy, sedatives, anabolic steroids, and over the counter cough and cold remedies.[2] Unless one has active dialog with an adolescent, the incidence and the scope of illicit drug use will probably come as a surprise.

COLLEGE AND MEDICAL STUDENTS

As one might expect, these usage patterns continue on the college campus where alcohol and marijuana are the most commonly used drugs. Drug abuse is thought to be a major contributing factor to poor academic performance and failure to graduate from college.[3] As the chosen few go on to medical school, the problem continues. One review of medical student use of club drugs (LSD, cocaine, MDMA, ketamine, methamphetamine and others) showed that the usage by medical students of these drugs was 16.8% overall. The most common drugs used were MDMA (11.8%) and cocaine (5.9%).[4] As adolescents and young professionals move into adulthood, the problem persists. Among those aged 50–59, for example, the rate of illicit drug use has increased from 2.7% in 2002 to 4.6% in 2008. This may reflect the aging of the baby boom generation, whose lifetime rate of illicit drug use has been higher than that of other groups.[1]

UNEMPLOYED ADULTS

Not surprisingly, the incidence of drug use among unemployed adults 2008, those aged 18 or older, was 19.6%, approximately twice the rate of the fully employed (8%) and those with part time employment (10.2%). The number of unemployed illicit drug users increased from 1.3 million 2007 to 1.8 million 2008, primarily because of an overall increase in unemployment. Since 2008, the ranks of the unemployed have continued to swell and the timing of the resolution of the current economic problems is the subject of some debate. The current unemployment rate in the United States was 9.5% as of May 2010[5] and the unemployment statistics for the first half of 2010 were the highest since the 1982-83 period. In addition, those two periods, 1982-83 and the present, represent the highest rate of unemployment since one particular index was started in 1948.[6]

The inverse, of course, means that the majority of illicit drug users continue to be employed. Approximately 12.9 million of the 17.8 million current illicit drug users aged 18 or older in 2008 had either full or part time jobs (72.7%).[1] Although a job does confer immunity to the problem, the unemployment contribution thus rests at historic highs, and the timing of the improvement of that issue remains to be seen.

TRAUMA ASSOCIATIONS

Driving under the influence of illicit drugs during the year prior to 2008 was reported by 10 million persons aged 12 or older, approximately 4% of the population. This rate did not change from 2007, but was lower than the reported rate in 2002. In the year 2002, approximately 4.7% of the population reported driving under the influence. In 2008 subgroup analysis, the rate was highest among those aged 18–25, approximately 12.3%.[1] The incidence of motor vehicle accidents associated with driving under the influence of alcohol or some other substance of abuse will continue to bring these people, as well as the innocent bystanders, to our trauma centers. In addition, we can expect the issue of substance and alcohol abuse to affect the incidence and severity of motorcycle, all terrain vehicle (ATV) and boating accidents on an ongoing basis.

IATROGENIC ISSUES

There are numerous questions that arise regarding the question of health care provider responsibility for some of the abuse of prescription medications. This set of problems ranges from an overdose of a prescribed medication by the intended patient to the use of a legitimately prescribed medication by someone other than the intended user, and also includes loss, theft, or sale of prescriptions and medications. Another set of issues involves the patient who sees multiple physicians or visits multiple facilities for the purposes of seeking medications for other than medical purposes. The ability of our society to track this kind of activity has been problematic at best. In examining the sources

of pain medication used for nonmedical purposes, for example, a study of people aged 12 or older done in 2008, which examined their usage during the previous 12 months, revealed that 56% got the drug from a friend or relative. Another 18% got the drug from one doctor, while only 4.3% got pain relievers from a drug dealer. Less than 1% bought them online.[1] Another set of issues in this regard relates to misbehavior by health care providers. The State Board administrative action taken with regard to such problems categorizes them in various ways, but among the categories one finds prescribing medications without prior examination or medical indications, prescribing without maintaining an office in the state, and ordering large quantities of controlled substances which may have been for self use. Of course, relevant to this same unfortunate category, health care providers are no more immune to the attraction of substance abuse than other members of society, so there are also State Board administrative actions involving such issues as possession of cocaine, use of a controlled substance, opiate and cocaine addiction, alcohol and drug dependence, misuse of alcohol, and driving under the influence.[7] By almost any criteria, these numbers represent a significant problem for our society. They will also represent a continuing challenge to healthcare providers for the foreseeable future.

SUBSTANCES OF ABUSE

COCAINE

Coca leaves, the source of cocaine, have been chewed and ingested for thousands of years, making cocaine one of the oldest known stimulants. Cocaine was originally extracted from the leaf of the coca bush in Peru and Bolivia. Following crop reduction efforts in those countries after the 1990s, Columbia became the nation with the largest cultivated crop. Today cocaine is a Schedule II drug, thus one with a high potential for abuse, but it can be administered by a health care provider for a legitimate use which may include local anesthesia for eye or ENT surgery. The purified form, cocaine hydrochloride, was used medically a century ago as the active ingredient of many tonics and elixirs for a wide variety of reasons. It has been a substance of abuse for at least that long.[8]

Epidemiology

Cocaine was second only to marijuana as the most commonly used illicit drug in the United States from 2005 to 2006 and was first in terms of the illicit drug leading to the most emergency department evaluations from 1995 to 2002.[9] In 2005, there were 448,481 cocaine-related visits to Emergency Departments in the United States.[9,10] The estimated number of people aged 12 and older who used cocaine the previous month in 2008 was 1.9 million, approximately 0.7% of the population. This was similar to the statistics gathered for the years 2007 (2.1 million users, 0.8% of the population) and 2002 (2.0 million users, 0.9% of the population). The users of crack cocaine in 2008 (359,000 people, 0.1% of the population) decreased by a significant margin compared to 2007 (610,000 people, 0.2% of the population).[1] In the adolescent population, in a narrower age range from 12 to 17 years old, the rate of cocaine use dropped from 0.6% to 0.4% for the period of 2007 to 2008. In addition, for young adults in the age range from 18 to 25 years old, the rate of cocaine usage also dropped significantly during that same period, from 2.6% in 2005 down to 1.5% in 2008.[1] Although there appears to be significant movement in terms of decreasing usage patterns, the current numbers still fall near the two million mark, and will continue to present the health care community with the various cocaine related issues that have been seen and studied in the past.

Pharmacology

Cocaine sold on the street comes as a fine white crystalline powder often diluted with inert material such as cornstarch, talcum powder or sugar. Pharmacologically active diluting agents include procaine (with its local anesthetic effect), methamphetamine and others. The two forms of cocaine that are abused are the water soluble hydrochloride salt and the water insoluble cocaine base (freebase). The water soluble form, the fine white crystalline powder, can be snorted or injected. The insoluble base form results from processing with ammonia or sodium bicarbonate and water, and heating to remove the hydrochloride. The final product can then be smoked. The term "crack" refers to the street name given to freebase cocaine which produces a crackling sound when smoked.[8]

More has been published about the mechanisms of action involved in the cardiac effects of cocaine than any other drug covered in the chapter. Much of the underlying pathophysiology has been delineated and more work continues to be done. The American Heart Association's Acute Cardiac Care Committee of the Council on Clinical Cardiology recently summarized much of the clinical information.[9] The local anesthetic effect of cocaine, which was recognized as early as 1984,[11] results from the prevention of the rapid increase in the nerve cell membrane permeability to sodium ions during depolarization, which blocks the initiation and conduction of electrical impulses within the nerve cells. The systemic effects on the nervous system are mediated by alterations in synaptic transmission. Cocaine blocks the uptake of the norepinephrine and dopamine at the presynaptic adrenergic terminals, producing an excess of the neurotransmitters at the postsynaptic receptor sites. The accumulation of norepinephrine at the postsynaptic receptor has a sympathomimetic action.[9,12,13] The dopaminergic effects of cocaine have been regarded as contributory in producing addiction. Short-term use of cocaine appears to stimulate dopaminergic neurotransmission by blocking the reuptake of dopamine and thus causing euphoria. With long-term use of cocaine, however, the nerve terminals may become depleted of dopamine. It has been suggested that dopamine depletion may be a potential mechanism for the dysphoria and craving for the drug that develops during withdrawal. There has also been extensive recent work regarding the effect of cocaine on the cardiac ion channels.[14,15] Generically termed the channelopathies (discussed below), these have both intrinsic interest and serve as examples of past research being carried to deeper levels of understanding. Cocaine metabolism occurs via plasma and liver cholinesterases which produce the water-soluble metabolites, benzoylecgonine and ecgonine methyl ester.[16] The concentrate of the ecgonine methyl ester, also metabolically active, correlates nicely with recurrent vasospasm approximately

90 minutes after initial administration.[17] Both metabolites are excreted in the urine.[16]

Cardiovascular Complications

Adrenergic physiology (tachycardia, hypertension, increased myocardial demand): The activation of the postsynaptic alpha-adrenergic receptors in the vascular system causes vasoconstriction and hypertension, while activation of the beta-adrenergic receptors of the myocardium causes tachycardia and enhanced contractility.[11] The cocaine induced tachycardia and hypertension are dose dependent[18,19] and the tachycardia effect of cocaine is intensified by alcohol.[9,20] In addition, cocaine increases end-systolic wall stress and reduces left ventricular function.[9] By increasing heart rate, blood pressure and contractility, cocaine causes increased myocardial demand.[9,21] Of interest in this regard is that plasma levels of cocaine are not linearly related to central nervous system effects, and the subjective "high" sought by the user dissipates at a time when plasma levels are still significantly elevated. The practice of repeating cocaine administration to maintain the "high" over a number of hours can lead to progressively more elevated plasma levels (with corresponding cardiac toxicity) without the similarly improved mood sought by the user.[22]

Coronary Artery Vasoconstriction

Cocaine has been shown to cause coronary vasospasm in the catheterization laboratory.[23,24] Small medically indicated doses of intranasal cocaine (10% cocaine hydrochloride, 2 mg/kg) have been shown to cause vasoconstriction of coronary arteries, increased heart rate and BP, and reduction of coronary sinus blood flow in patients with or without atherosclerotic coronary artery disease (CAD).[23] This dose represents one commonly used for local anesthesia and vasoconstriction of the nasal passages, as compared to much larger dosages in the substance abuse situation. Focal spasm of segments of epicardial coronary arteries has been noted during angiographic studies of patients with cocaine-related acute myocardial infarction (AMI).[22,25,26] Coronary artery vasospasm occurs in the absence of significant epicardial artery spasm, of intrinsic CAD and of myocardial infarction (MI).[17] The degree of vasoconstriction may be more prominent in patients with CAD.[27]

Cocaine-induced vasoconstriction has been shown to be alpha-adrenergic receptor mediated, more pronounced in stenotic as opposed to nonstenotic coronary segments (as above), and is generally believed to be accentuated by beta-adrenergic-blockade (unopposed alpha-adrenergic effects).[17] As expected per this discussion, alpha-adrenergic antagonists reduce the degree of coronary vasoconstriction.[28] Vasoconstriction may also occur via other mechanisms, including cocaine precipitated release of plasma endothelin-1 which causes vasoconstriction[17,29] and impaired production of nitric oxide, a vasodilator.[17,30] Finally, recurrent vasospasm also occurs approximately 90 minutes after initial administration, an event which is temporally related to increasing blood concentration of the main cocaine metabolite ethyl methyl ecgonine.[17] This has obvious implications in the substance abuse scenario, when the user may redose continually seeking the ephemeral high and run into a combination of primary and recurrent vasospasm. There are thus a number of different mechanisms involved in cocaine vasoconstriction of the coronary arteries.[28]

Acute Coronary Artery Thrombosis

Acute occlusion of the coronary arteries immediately after cocaine use has been reported.[31] There are a number of different mechanisms by which the propensity for clot formation and coronary artery thrombosis increases in the presence of circulating cocaine. There is an increase in plasminogen-activator inhibitor.[28] There are also a number of changes in the platelets, including an acute increase in the number of platelets,[32] an increased platelet activation, and increased platelet aggregation.[33] Cocaine has been found to lower the threshold level of platelet aggregation.[34] In one case in which a 21-year-old man died of infarction within two hours after cocaine abuse and was examined at autopsy within six hours, acute coronary obstruction was found due solely to platelet thrombi.[35] This is of particular significance because other causes of thrombosis were ruled out and, because platelet thrombi are fragile, do not persist long, and are seldom seen unless autopsy occurs within a short time, making their occurrence usually very difficult to document.[22] Cocaine users have also been found to have increased levels of C-reactive protein, von Willebrand factor and fibrinogen which probably contribute to the coagulopathic issues.[36]

Direct Myocardial Damage

Sudden cardiac deaths have long been reported to occur in cocaine addicts.[25] Autopsy studies of patients who used cocaine but died from an unrelated cause (trauma) have demonstrated that cocaine may exert direct toxic effects on the heart, with myocardial inflammation and interstitial fibrosis.[37,38] Myocardial biopsy specimens in the setting of acute cocaine toxicity have demonstrated focal myocyte necrosis, focal myocarditis, sarcoplasmic vacuolization, and myofibrillar loss.[17]

Contraction band necrosis has been reported to occur in the myocardium of patients who died of complications of cocaine abuse. The incidence noted historically varied between 25% and 93%.[39,40] The term, however, has been used somewhat ambiguously. Histologically, myocardial contraction bands are characterized by irreversible hypercontraction of the myocytes with markedly thickened Z-lines and extremely short sarcomeres. This finding may be seen in otherwise normal subjects who die accidental deaths, correlating with survival time, which suggests an agonal adrenergic stimulation. Contraction band necrosis probably represents this adrenergic stress and may be linked to malignant terminal arrhythmias such as ventricular fibrillation. It has been produced experimentally with catecholamine infusion and seen in patients with pheochromocytoma.[41] The association with cocaine therefore probably occurs as a manifestation of the adrenergic physiology discussed above.

Animal studies have shown that cocaine alters cytokine production in the endothelium and in circulating leukocytes, inducing the transcription of genes responsible for changes in the composition of myocardial collagen and myosin.[17]

Recent animal studies of neonates born from cocaine treated hamster mothers demonstrate irreversible focal ischemic damage to the Purkinje cells, as well as endocardial damage and myocardial cell vacuolization. These findings were felt to be consistent with the pharmacotoxicity of cocaine. The damaged Purkinje cells underwent autolysis but remained in contact with the adjacent myocardial cells. The researchers correlated these results with the clinical occurrence of cardiac arrhythmias including sudden death in cocaine abused babies and with similar events in young individual cocaine users.[42]

Coronary Artery Atherosclerosis

Accelerated atherosclerosis has been demonstrated at autopsy in young cocaine users[43] and in patients with cocaine related sudden death.[39] This has also been demonstrated quantitatively (by cross-sectional coronary plaque area) in a case-controlled autopsy study of cocaine addicts.[44] Premature coronary atherosclerosis is common in young cocaine abusers. Obstructive CAD is found in 35–55% of patients undergoing coronary angiography for cocaine-associated chest pain.[44]

Cardiac Arrhythmias

The appearance of cardiac arrhythmias in this spectrum of pathology comes as no surprise. Among the rhythms seen, sinus tachycardia is commonplace. In anesthesia, cocaine is associated with a greater incidence of arrhythmias, particularly premature ventricular beats.[45] Cocaine has also been implicated in the production or exacerbation of supraventricular tachycardias, ventricular tachycardia (VT), torsades de pointes, accelerated idioventricular rhythm, sinus bradycardia, asystole and ventricular fibrillation.[17,46]

A case of self resolving accelerated ventricular rhythm after intravenous cocaine abuse has been reported.[47] Accelerated idioventricular rhythm with hypotension was also noted in the clinical setting of frank cocaine poisoning.[48] Ventricular fibrillation and asystole have also been reported.[22] The mechanisms of the arrhythmogenic effects of cocaine have not been precisely delineated, but the multifactorial spectrum of causation includes the effects of catecholamines, direct effects on the myocardium and cocaine-induced myocardial ischemia or infarction.[22] In addition, the increase in LV mass due to chronic cocaine abuse and the development of contraction band necrosis may make some contribution.[17]

Animal studies have shown that cocaine overdose can cause prolongation of the QRS complex and can induce bundle branch block.[49] In conscious dogs, intravenous cocaine infusion produced sinus bradycardia progressing to VT and fibrillation and asystole, and these arrhythmias occurred up to several hours after cocaine infusion.[50] In other canine experiments, cocaine reduced ventricular fibrillation thresholds.[17]

The conduction system of the heart has a prominent place in these discussions as cocaine disrupts normal electrical activity, causing increased PR, QRS and QT intervals on the electrocardiogram (ECG).[50-55] These effects are generally attributed to direct effects on the potassium, sodium and calcium channels.[14]

Monomorphic VT associated with inhibition of the sodium channel has been described as the most common arrhythmogenic effect of cocaine, and there is evidence that cocaine can also induce torsades de pointes, the term used for polymorphic VT characterized by twisting of the QRS axis around the isoelectric line of the ECG.[56,57] Drug induced torsades is associated with QT interval prolongation[58,59] and cocaine-induced torsades has been reported in patients with idiopathic long QT syndrome[60,61] as well as in patients taking medication with a risk of QT interval prolongation, notably methadone.[62,63] Another study of the acute effects of cocaine on habitual cocaine users also showed prolongation of rate-corrected QT (QTC) interval.[14,64] Patients hospitalized for cocaine abuse often have ECG evidence of altered repolarization, including QTC prolongation.[14,65,66] In one study of emergency department patients treated for cocaine abuse, 26% of ECGs exhibited QTC intervals greater than 440 ms, and in a smaller group who died suddenly, the figure was 75%.[14,65]

Channelopathies

Cocaine has also been shown to block K^+ channels, increase L-type Ca^{2+} channel current, and inhibit Na^+ influx during depolarization, all possible causes for arrhythmia.[67]

Electrocardiogram changes in the setting of cocaine abuse are generally attributed to the direct effects of cocaine on these cardiac ion channels where multiple sites of action have been demonstrated.[14,56,68] Cocaine inhibits L-type calcium currents, delays potassium channel currents and inhibits sodium currents providing influx during repolarization[49,67,68a,69] and these actions are thought to have direct effects in the arena of cocaine induced arrhythmia.[14] The sympathomimetic effects of cocaine may also be related to actions on the cardiac ion channels.[14]

Sodium channel: In acute myocardial ischemia there is a localized increase in extracellular potassium[70,71] resulting in depolarization of the resting membrane potential of cardiac muscle cells.[14,71-73] This depolarization causes inactivation of sodium channels. Cocaine binding to the inactivated sodium channels decreases the functioning sodium channels in the ischemic area, slowing electrical conduction overall and increasing the risk of arrhythmias.[14,74-77] Ischemia also produces acidosis,[14,78-80] and local acidosis near the Na channels may also lead to more stable binding of cocaine to the inactive state of the sodium channel and therefore to further decreases in electrical conduction. In addition, the sympathomimetic provoked vasoconstriction causes tachycardia which may in turn worsen the cocaine induced effect on the sodium channels.[14] Because cocaine binds to the inactive state of the sodium channel, the degree of binding is affected by the heart rate. Tachycardia causes increased cycling of the sodium channel between inactive and active states, which allows more binding of cocaine to the inactive sodium channels.[15,53,81] This effect has been termed “use-dependent kinetics,” and the increase in heart rate associated with the adrenergic physiology of cocaine can thus exacerbate the risk of arrhythmias.[15]

The major metabolites of cocaine, benzoylecgonine and ecgonine methyl ester have little or no effect on the sodium channel, but the ethanol-derived metabolite, cocaethylene, does.

This metabolite exceeds the effect of cocaine itself in terms of slowing sodium channel function.[15,82]

The Brugada syndrome was first described in 1992. It is characterized by specific ECG changes: a right bundle branch block with coved ST segment elevation in leads V1 to V3.[15,83] This syndrome is caused by a genetic disease which has been associated with the risk of sudden death due to tachyarrhythmia in young individuals with structurally normal hearts.[15,84-86] The genetic issue involves a mutation of the cardiac sodium channel gene, SCN5A, which codes for the alpha subunit of the sodium channel.[15,87] Approximately 25% of the Brugada cases arise from this mutation in the cardiac sodium channel, although several non-genetic inductors of Brugada-type ECG patterns have also been recognized.[85,86] Cardiac arrest in cocaine toxicity with a transient post-resuscitation Brugada pattern ECG has also been reported. In this report, the patient was 33 years old, ingested 14 grams of cocaine, and had a seizure shortly after arrival followed by pulseless VT. She had successful cardioversion and the post-arrest ECG showed sinus rhythm, right bundle branch block and coved ST elevation in leads V1 to V3, a Brugada pattern, which resolved on serial ECGs. The authors felt this case represented an association between cocaine toxicity and a malignant arrhythmia that may have been due to "poisoning" of the cardiac sodium channels manifested by the transient Brugada pattern ECG.[86] ECG changes with a Brugada pattern have been reported elsewhere with cocaine use.[15,84,88-90] In some of these patients with Brugada syndrome, subsequent pharmacological testing with other sodium channel antagonists, such as flecainide, which is known to precipitate Brugada pattern ECG changes in those with the genetic sodium channel mutation, has not replicated the changes that would be expected.[15,89,90] The Brugada pattern ECG provocation by cocaine has been attributed to an effect on the sodium channel by others as well.[91] Wide-complex dysrhythmias responding to sodium bicarbonate (therefore pH-dependent) may also occur after cocaine as a result of the direct effects on the sodium channels.[17]

Potassium channel: Potassium channels also have a role in the cocaine mediated cardiac dysfunction. The pore-forming subunit of the potassium channel is encoded by the human ether-a-go-go related gene (hERG) and mutations of this gene were found to be associated with one form of congenital long QT syndrome.[14,92-95]

hERG channels have unique biophysical properties[14,59,95,96] and drugs that reduce hERG currents have been shown to produce long QT syndromes that predispose healthy individuals to ventricular arrhythmias and sudden death.[14,97,98]

Cocaine blocks hERG channels and produces an acquired form of long QT syndrome that may promote arrhythmias. One suspected trigger for sudden death in patients with long QT syndromes is emotional or physical stress, which is believed to act via an increase in sympathetic stimulation,[97] and this may be related to adrenergic regulation of hERG channels.[14,99] Acute myocardial ischemia (with acidosis and local increases in potassium concentration) enhances cocaine binding to potassium channels as well as sodium channels, further increasing electrical dysfunction and increasing the risk of arrhythmias.[14]

Myocardial Ischemia and Infarction

It is not surprising that there have been many reports of a temporal association between the use of cocaine and MI.[100-103] As one might expect from the demographics, the patients were predominantly male, with an average age of 31, but case reports include a 28-year-old woman and a 21-year-old man, both with normal coronary arteries.[22,104,105] Most of these patients had neither seizures nor other major manifestation of cocaine overdose, and about a third had no risk factors for CAD. In several cases, there have been recurrent episodes of ischemia and infarction associated with cocaine use in the same person, and cessation of use resulted in complete absence of further ischemic symptoms.[22,100,106]

Several mechanisms may contribute to cocaine related MI. The adrenergic physiology with tachycardia and hypertension may produce ischemia in patients with pre-existing atherosclerotic CAD. Decrease or total interruption of coronary blood flow resulting from spasm or thrombosis may also occur, and this likelihood seems higher in patients with normal coronary arteries at cardiac catheterization or autopsy. Thrombosis may also cause AMI in the presence of anatomically normal coronary arteries.[22,107,108] Catecholamine mediated direct myocardial injury is another potential mechanism. Angina or silent myocardial ischemia may occur in patients using cocaine and the incidence of episodes of silent ischemia may be as high as 87% in these patients[22,106] and may be observed during the first weeks of withdrawal.[22]

Many studies have looked at the rate of MI in patients with cocaine associated chest pain. The rate was thought to be approximately 6%,[101,109] but other studies have reported a somewhat lower incidence of infarction in this population, from 2.8%[110] down to a dubious low of 0.7%.[111] Although the incidence of infarction in cocaine chest pain varies, a prudent approach to these patients would suggest that the higher number of 6% enter into the deliberations as to management options, especially given the various underlying pathophysiological mechanisms making contributions to acute coronary thrombosis as discussed above. Cocaine and methamphetamine are probably the major risk factors for young people who present with an acute coronary syndrome (ACS). The average age in one study for cocaine associated MI patients was 38 years old.[112] Finally, although approximately a third of patients with cocaine-induced MI develop complications, such as congestive heart failure (CHF) or arrhythmias, the overall mortality in hospitalized patients remains exceedingly low.[17,112]

ECG Changes

Cocaine can cause prolongation of the PR interval, of the QRS duration, and of the QT interval of the ECG.[14] The interpretation of ECGs in patients with cocaine-associated chest pain can be challenging. Cocaine induced MI has been documented in patients with normal ECGs as well as with abnormal ECGs. On the other hand, a significant proportion of patients meeting the electrocardiographic criteria for ST-elevation myocardial infarction (STEMI) may not have MI. The sensitivity of the ECG for detecting MI is reportedly as low as 36%.[17,101]

Chest Pain

The acute clinical syndrome of chest discomfort (cocaine chest pain) occurs in 40% of cocaine users,[9,113] but the incidence of MI in this clinical setting varies widely as discussed above. In the setting of confirmed MI associated with cocaine use, the average age in one recent study was 38 years old which reflects the population of users.[9] Cocaine chest pain is a frequent presentation in routine emergency medical practice.

Many other causes of chest pain occur in the setting of cocaine abuse, and due consideration should be given to them in terms of differential diagnosis. Aortic dissection should always be a consideration in patients with severe chest pain. Acute rupture of the ascending aorta has been reported in cocaine users.[22,114] The surge in catecholamine levels with cocaine use can lead to elevated shear-stress forces, and increase the proclivity for intimal tears and aortic dissection. In a retrospective study by Hsue and colleagues,[17,115] cocaine was implicated in 37% of aortic dissections studied in an inner city population. The location of dissection seemed to be equally distributed between types A and B, as is the case with dissections not related to cocaine. Aortic intramural hematoma and coronary artery dissection have also been reported to be associated with cocaine abuse.[17]

Cocaine has also been reported to cause coronary artery aneurysms and ectasia.[17] Dissection can be difficult to diagnose and the various diagnostic approaches short of a contrast CT with dissection protocol, such things as history, characteristics of the pain, physical examination, pulse deficit, PA and lateral chest X-ray and laboratory testing including d-dimer all leave something to be desired.

Barotrauma also occurs in this population. Smoking free-base cocaine may cause lung damage and noncardiac pulmonary edema.[22,116] Spontaneous pneumomediastinum and pneumopericardium have been reported after "free-base" smoking, which probably results as a consequence of alveolar rupture due to a sudden rise in intra-alveolar pressure.[22] Pneumothorax also should be considered, but this would commonly show up on a simple chest X-ray. In addition to the above, the timing of the recurrent vasospasm and chest pain occurring 90 minutes after ingestion related to the increasing blood concentration of the main cocaine metabolite ethyl methyl ecgonine should be considered.[17]

Treatment

Volume adjustment: Management of the basics in cocaine abuse patients requires careful attention. The usual emergency medicine ABC precepts apply, but the next step should involve assessment of volume status and treatment in that regard. If some degree of tachycardia arises from a volume down status, poor oral intake or blood loss for example, that should be addressed. Likewise, if the patient has pump problems, ACS or CHF for example, the underlying issues must be identified and the management adjusted accordingly. Treating tachycardia due to a volume down issue with benzodiazepines alone rather than in combination with volume resuscitation can occur, particularly in a patient who may be altered from toxic amounts of cocaine or some other stimulant, but can also be avoided if the underlying issues are identified and addressed.

Analgesics: Likewise, if the patient has pain, this should be treated and that component of the adrenergic physiology removed from the equation. If the pain arises from some source other than cocaine, some secondary orthopedic injury for example, that should be addressed in the appropriate fashion.

Benzodiazepines: These drugs form the mainstay of initial medication management in adrenergic stimulated cocaine abuse patients. Benzodiazepines reduce heart rate and systemic arterial pressure,[17] thereby decreasing myocardial demand and directly addressing the agitation and anxiety which occurs so commonly in these patients. In animal studies, benzodiazepines also attenuate some of the toxic effects of cocaine on the heart.[17] The downside of sequential IV benzodiazepine titration in these patients should be minimal unless specific mental status or neurological examination findings mandate inclusion of differential diagnoses such as intracranial hemorrhage, meningitis or traumatic brain injury, all of which may be seen and any of which may dictate a more nuanced approach to the situation.[117] In patients with cocaine related chest pain, benzodiazepines alone have been shown to be effective in resolving the chest pain and improving cardiac performance.[117]

Nitroglycerin: The usual approach to the use of nitroglycerin in any patient with chest pain applies here. In patients with cocaine associated chest pain it has been shown that nitrates or benzodiazepines are effective when used alone or in combination.[117] These drugs can resolve chest pain and improve cardiac performance. The agent of choice may be influenced by CNS symptomatology as above.[117] Benzodiazepines represent a viable alternative to nitroglycerin in this situation in the eyes of some authors.[17] The absence of predictive value of the response of chest pain to nitrates, in terms of a cardiac versus some other etiology, has also been well documented, so the clinician must remember that the response to nitrates in this setting has no diagnostic value.[118-120]

Oxygen, Aspirin, Heparin, PCI, Thrombolytics: Oxygen should be a part of the routine management of cocaine associated chest pain patients, along with venous access, cardiac monitoring, ECG, and laboratory work with troponins. This falls into the usual emergency department approach to potential cardiac patients. Aspirin administration to inhibit platelet aggregation in patients with cocaine-induced myocardial ischemia is reasonable[17] and should also be done. Heparin and coronary catheterization and thrombolytics should be the next consideration, and these are site specific in terms of availability. A cardiologist should be involved in this decision making process. There is limited specific data on thrombolytics in this patient population and there are reports of severe complications associated with thrombolytic use in cocaine abuse.[17,121] Often contraindications to thrombolytics preclude their use. Such issues as intractable hypertension, altered mental status with the differential diagnoses of seizures or intracranial pathology, and the chest pain differential of aortic dissection will mandate a cautious approach to thrombolytics or preclude their use altogether. In addition, ECG criteria for STEMI do not reliably predict cocaine precipitated MI. If chest pain persists after treatment with oxygen, aspirin, nitrates, benzodiazepines and analgesics, thrombolytics should be considered if immediate

coronary angiography is not available.[17,46] The American College of Cardiology/American Heart Association guidelines[122] advocate the use of thrombolytic therapy if ST segments remain elevated despite nitroglycerin and calcium antagonists and if coronary arteriography is not possible (class II A indication).[17] The updated ACC/AHA guidelines for STEMI management[123] and for PCI[124] do not offer any additional recommendations regarding cocaine, other than to include the recent use of cocaine as a low likelihood factor in determining whether the patient's signs and symptoms represent an ACS secondary to CAD. Unfortunately, the use of this low likelihood criterion applies only in the absence of high or intermediate risk criteria such as chest or left arm pain as well as most ECG abnormalities.[124] The decision-making process therefore should parallel that of other chest pain patients, with the understanding that something less than 6% of this patient population will actually infarct, that their morbidity and mortality rate if they do infarct will be low, and that some of those taken to cardiac catheterization for PCI because of STEMI criteria will have normal coronary arteries.

Bicarbonate: The potential use of sodium bicarbonate in cocaine induced sodium channel blockade arises from the action of bicarbonate in reversing QRS prolongation and stabilizing arrhythmias due to sodium channel blocking drugs, such as tricyclic antidepressants and Class Ic anti-arrhythmic drugs like flecainide.[15,125,126] Models of flecainide toxicity, a drug which has similar properties to cocaine, show that sodium bicarbonate partially reversed the QRS prolongation.[15,125] This effect does not occur in patients with mild QRS prolongation due to therapeutic use of flecainide.[15,127]

This suggests that bicarbonate might benefit patients with an overdose of Class Ic anti-arrhythmic agents like flecainide, and therefore that bicarbonate might potentially benefit patients with cocaine precipitated sodium channel dysfunction as well. Local alkalinization should decrease the percent of ionized cocaine, reduce binding to the cardiac sodium channel and potentially decrease cardiac arrhythmias.[15] Isolated cell studies show that alkalinization does reverse cocaine binding and associated toxicity.[15,81] There have been no reported studies to date regarding the effect of alkalinization in patients with regard to an effect on their cocaine associated QRS prolongation.[15]

Beta-blockers: There has been a perennial debate regarding the use of beta-blockers to manage the adrenergic physiology of cocaine, particularly with cocaine precipitated ACS.[17] Historically, the argument has been made to avoid them altogether in this setting because they may accentuate cocaine precipitated coronary artery spasm. In the study which demonstrated this effect,[128] 30 patients catheterized for the evaluation of chest pain were given intranasal cocaine versus saline followed by intracoronary propranolol versus placebo. The cocaine caused coronary vasoconstriction and the propranolol caused further increases in coronary vascular resistance. Labetalol, on the other hand, which has both alpha- and beta-adrenergic blocking activity, reversed the cocaine precipitated hypertension but did not affect the degree of coronary artery vasoconstriction.[17,129]

Underlying theoretical support for the use of beta blockade involves the use dependent kinetics of cocaine binding to sodium channels described above, in which the degree of cocaine binding increases with tachycardia. Reduction of the heart rate in isolation, in this model, could theoretically reduce cocaine binding to sodium channels resulting in normalization of the QRS prolongation. This was tested in animals and found not to be true. Neither beta-blockers (propranolol) nor combined alpha- and beta-adrenergic antagonists (labetalol) were beneficial in this model. The authors recommend avoiding beta-blockers and labetalol in the management of cocaine related cardiac arrhythmias.[15] In a recent clinical study of ACS patients actively using cocaine, comparing labetalol to diltiazem in addition to standard ACS therapy, there were no adverse events during hospitalization and the authors conclude that labetalol appears to be safe in this setting.[130] There were only 90 patients; however, and the parameters measured included heart rate and BP at baseline and 48 hours later. In a relatively strong toxicology editorial, on the other hand, it was noted that the majority of patients with cocaine chest pain will continue to use cocaine after discharge, and the usual practice of starting patients on long-term beta blockade may be unwise. The editorial concludes that this approach would "not only repeat a practice abandoned by its pioneers nearly 30 years ago for good reason but also subject an unpredictable subset of these individuals to the lethal drug interaction so well described in controlled animal investigations".[131] There are other options for patient management in this clinical setting, and a conservative approach to this particular question would probably be wise.

Miscellaneous: The issue of alpha-adrenergic blockers should also be addressed, as in one animal study the use of the alpha-adrenergic receptor antagonist prazosin attenuated cocaine-induced ventricular arrhythmias.[15,132] This has not come into general use. Another drug which has been studied and shown to be potentially safe in cocaine related myocardial ischemia is lidocaine.[15,133] This study had a small number of patients, occurred some years ago, and used lidocaine for issues such as arrhythmia prophylaxis which are not current clinical indications. The timing was such that the majority of the drug was given over five hours after ingestion, arguably well after the cocaine related abnormal sodium channel activity, such that potential adverse effects of lidocaine were unlikely to be seen. This also has not come into general use.

Subacute and Chronic Problems

More complex and more obscure are the subacute to chronic problems related to cocaine abuse. These include chest pain presentations beyond the period of acute intoxication, an advanced rate of atherosclerosis, the issue of hypercoagulable states with non-cardiac related clot formation, myocarditis, cardiomyopathy and CHF.

The acute adrenergic presentations of cocaine intoxication generally last a matter of hours and can be comfortably treated as discussed above. Chest pain presentations beyond this time frame, without historical evidence of cocaine use or hyper-adrenergic vital signs, particularly in young individuals with few other cardiac risk factors, can be challenging and problematic. The suggested approach includes careful assessment of the substance abuse issue and a heightened suspicion of the potential drug abuse contributions during a clinical encounter in which

a cardiac etiology for a chest pain evaluation seems quite unlikely based on age and the usual cardiac risk factors.

The advanced rate of atherosclerosis causes earlier onset of CAD and should be factored into the clinical evaluation. This particular issue may be helpful in terms of deterring patients from chronic usage patterns. The problem of cocaine related hypercoagulable states which bring DVT, pulmonary embolism and stroke into the differential diagnosis may be particularly relevant to a patient with complaints referable to these arenas having an onset shortly after cocaine intoxication. Of note, and relevant to the discussion of cocaine cardiomyopathy below, ischemic stroke from cardiac embolization, temporally related to cocaine use, has been reported in young patients with cocaine cardiomyopathy.[38,134]

Myocarditis may occur from the direct cardiac muscle effects discussed above, and secondary to the adrenergic physiology of recurrent usage patterns. Several studies have reported the presence of lymphocytic and eosinophilic myocarditis in patients with cocaine use.[22,39,50,102] Focal myocyte necrosis, focal myocarditis, sarcoplasmic vacuolization and myofibrillar loss have been demonstrated in myocardial biopsy specimens obtained in the setting of acute cocaine toxicity[17,135] and these would be expected to have residual effects.

Cardiomyopathy related to cocaine use has been known for decades.[22,136] Cocaine may cause an acute or chronic deterioration of LV performance.[17,135] Chronic LV systolic dysfunction occurs in approximately 7% of the patients who have asymptomatic long-term cocaine abuse patterns.[17,135] Cardiomyopathy from cocaine use may present as CHF and the management may be complicated by persistent use of cocaine. The incidence of cocaine cardiomyopathy is not clear, as current data consists primarily of case reports.

In one study of otherwise healthy asymptomatic cocaine users, LV systolic dysfunction was diagnosed in 7% by radionuclide angiography. This was a small study (84 patients) and they were examined two weeks after their last cocaine use.[38,137]

The mechanism of cocaine related cardiomyopathy is also unclear, neither do we have any good idea of how much cocaine can precipitate cardiomyopathy, nor do we know the duration of cocaine use that puts patients at risk.[38] Extensive or recurrent MI may contribute to the LVD and cardiomyopathy, but many cocaine abuse patients with severe LVD do not have a history of CAD or MI. In one study, 33 patients with cardiac symptoms and a history of cocaine abuse had coronary angiography. Eighteen of those patients (55%) had LVD (ejection fraction < 50%), whereas only twelve patients had CAD and regional wall motion abnormalities. Six patients exhibited nonobstructive CAD but still showed diffuse LVD.[38,135] These findings suggest that myocardial dysfunction may result from transient ischemia, or perhaps from nonischemic myocyte injury.[38]

Pathology studies have shown contraction band necrosis in the myocardium of patients with cocaine cardiomyopathy and also in patients with pheochromocytoma. The pathologic similarities suggest that chronic or recurrent adrenergic stimulation may play a role.[38,40] In other studies of cocaine abuse patients who died traumatic deaths show myocardial inflammation, interstitial fibrosis and ventricular dilation.[37,38]

The clinical presentation of cocaine cardiomyopathy resembles that of other patients with dilated cardiomyopathy. Cocaine associated chest pain patients tend to be young male tobacco users[38,138,139] so cocaine cardiomyopathy should be considered in patients of this demographic who present with heart failure or LVD. The same diagnosis should also be considered in any patient who presents with no clear etiology of ventricular dysfunction as cocaine use spreads across the age spectrum. Presenting symptoms of cocaine cardiomyopathy may occur suddenly, without a long prodrome or antecedent cardiac illness, but otherwise they resemble those of patients who have heart failure of any etiology. The symptoms may include dyspnea, diaphoresis, anxiety, palpitations, dizziness and nausea.[38]

Obtaining the history of cocaine use may confirm the diagnosis and guide therapy. Eliciting the required information by direct questioning history should be the first approach and many patients will be relatively straightforward in this regard. Given the appropriate clinical suspicions, however, when the patient's history does not provide the expected historical details, urine toxicology screening should be obtained.[38]

The findings on physical examination are similar to those in other patients with heart failure. There are a few exceptions worthy of mention such as the acute onset. The findings of chronic CHF, such as pedal edema, are less common.

Patients with heart failure due to drug use may show physical signs such as superficial thrombophlebitis of accessible veins (tracks) or scars from subcutaneous injection (skin-popping). They may also have nasal cavity findings such as nasal septal irritation or perforation from cocaine insufflation (snorting). Patients presenting with acute heart failure related to recent cocaine use will often show signs of the adrenergic physiology of the drug, such as tachycardia and hypertension. They may also present with cardiac arrhythmias or with an altered mental status.[38]

Both cardiomyopathy and cocaine precipitated chest pain often present with an abnormal ECG. Sinus tachycardia occurs most frequently and repolarization abnormalities are also common given the young male demographic. In one study of cocaine associated chest pain,[38,140] an early repolarization pattern was found in 32% of the patients. Another 16% of the patients demonstrated a pattern of LV hypertrophy pattern, and only 32% of patients had a normal ECG. On echocardiogram, cocaine abuse patients had a higher LV mass index compared to nonusers and were more likely to demonstrate increased thickness of the posterior wall compared to nonusers. It is difficult to distinguish cocaine cardiomyopathy from other forms of heart failure by echocardiographic imaging alone.[38,141]

With regard to treatment, there appear to be no well conducted trials regarding the management of cocaine cardiomyopathy. Treatment recommendations are based on animal and autopsy studies, case reports, and American Heart Association guidelines on the management of heart failure, cocaine-associated chest pain and MI.[9,38,142] Patients with cocaine cardiomyopathy should be treated the same as those with other forms of heart failure, with a few exceptions.[38] One exception is that patients with cocaine cardiomyopathy who present with hypertension and tachycardia should receive benzodiazepines.[38] Patients who use cocaine and present with

cardiac symptomatology often also demonstrate signs of central nervous system hyperactivity. These neuropsychiatric symptoms of cocaine toxicity are closely tied to the cardiac manifestations of heart failure. Aggressive treatment of the neuropsychiatric symptoms with benzodiazepines, to provide sedation, will help treat the heart failure. Anxiety relief usually improves and often normalizes the hypertension and tachycardia.[38] Another exception is the use of beta-blockers, which are recommended for the patients with heart failure unrelated to cocaine use. In the non-cocaine using population, beta-blockers decrease the symptoms of heart failure, decrease the risk for hospitalization, and improve the survival. The American College of Cardiology/American Heart Association heart failure guidelines state that treatment with beta-blockers "should be initiated as soon as LVD is diagnosed".[142] In patients using cocaine, beta-blockers should probably not be used in the acute phase of therapy (see discussion above). There is disagreement about the utility and safety of chronic beta-blocker therapy in this population given the high rate of continued use of cocaine after discharge.[38,112] Some authors feel that beta-blockers should not be routinely prescribed at discharge. They argue that the high rate of continued cocaine use and the theoretical risk of hypertensive and ischemic events by combined cocaine and beta-blockers argues against this strategy. They would suggest following the advice of the American Heart Association guidelines for the management of cocaine-associated chest pain, which also applies to patients with cocaine cardiomyopathy: "this decision should be individualized on the basis of careful risk-benefit assessment and after counseling the patient about the potential negative interactions between recurrent cocaine use and beta blockade".[9,38]

With regard to long-term therapy and outpatient management, the primary goal should be abstention from cocaine. Many case reports have shown improvement in LVF after stopping cocaine. LVD and heart failure may recur if the patient returns to cocaine use.[38] Patients should be advised that continued cocaine use increases their risk of heart attack, heart failure, stroke and sudden death. Unfortunately the rate of continued cocaine use is high, with 60% of patients using cocaine again within one year.[112] Cardiology involvement during the hospitalization and for follow-up would be ideal. Chronic pharmacotherapy in patients with cocaine cardiomyopathy is similar to that recommended for patients with other forms of heart failure. Diuretics, ACE inhibitors, angiotensin receptor antagonists, vasodilators, and digoxin should be prescribed as recommended by published evidence-based guidelines.[38,142]

Miscellaneous: Cocaine washout: The syndrome of "cocaine washout" (also seen as methamphetamine washout) occurs as a state of deep depression of the level of consciousness following a hyperadrenergic state, particularly one which has gone on for some time. The cocaine washout phase of the acute intoxication may disguise any number of underlying issues such as trauma with intracranial pathology, infection from some obscure source, intoxication with other substances and clinically unsuspected overdose. Sorting out these issues may present a fairly complex clinical problem. The acuity of the situation often dictates the specific evaluation and workup required, and the clinical question often becomes not just whether cocaine was involved, but whether only cocaine was involved. A perennial concern lies with deciding whether the washout phase may really represent some other underlying pathology requiring an approach other than observation and watchful waiting. If the patient has evidence of parenteral substance abuse [intravenous drug use (IVDU)], such as superficial venous thrombophlebitis of the upper extremities (tracks) or evidence of multiple subcutaneous abscesses from injection (skin popping), the constellation of potential underlying pathology expands dramatically. The acuity of the presentation again drives the clinical evaluation, and the inclusion of bacterial endocarditis in the differential diagnosis of such patients who have clinical support for that diagnosis (Chapter "Infective Endocarditis" by Chamers), or the inclusion of spinal epidural abscess in such patients who present with lower extremity motor, sensory or sphincter problems poses a quite different but still relatively straightforward set of emergency medicine issues.

Miscellaneous: Polysubstance abuse: The use of cocaine in combination with tobacco causes more tachycardia and more vasoconstriction than does the use of tobacco or cocaine alone.[28] The addition of tobacco to the use of cocaine has been shown to increase the adrenergic physiology effects of the cocaine on myocardial supply-demand balance.[142a] This combination increases the metabolic requirements of the myocardium for oxygen and simultaneously decreases the diameter of coronary arteries[17,28] together also increases myocardial oxygen demand. This use of both of these substances together is considered to be more lethal than the use of either one in isolation or this has also been reported as the most frequent substance abuse combination encountered in the emergency department. The metabolism of cocaine with ethanol (transesterification) occurs in the liver and results in the metabolite cocaethylene, which is considered to be more lethal than the parent cocaine. Cocaethylene blocks re-uptake of dopamine and may be responsible for the increase in cardiovascular complications observed in this setting.[17]

METHAMPHETAMINE

The amphetamines are a group of chemically related drugs, which produce similar effects. Methamphetamine (also referred to as meth, speed, ice, crystal, chalk and glass) may be the most widely circulated compound of this group. The following discussion of methamphetamine may be taken as generically applicable to the group. Methamphetamine is longer lasting than cocaine, toxic to CNS dopaminergic nerve terminals, and is used by nasal insufflation (snorting), smoking or injection.[10] Methamphetamine causes tachycardia and hypertension due to the same type of adrenergic stimulation discussed under cocaine[143] and the amphetamines have been said to possess cardiac stimulant properties virtually identical to those of cocaine.[19,22] Chronic use of these drugs can produce insomnia, anxiety, confusion, mood and other psychiatric disorders, behavioral disorders, violence as well as severe dental problems. With parenteral use, the usual infectious complications of IVDU also occur. These may include hepatitis, endocarditis and HIV/AIDS.[143]

Epidemiology

Methamphetamine was initially recognized as a clinical problem in Hawaii and the western United States, but spread eastward and increasingly affected both rural and urban areas throughout the United States and elsewhere.[144] The risk to minority populations in some areas still appears to be somewhat greater, especially ethnic groups such as Native Hawaiians and Pacific Island Peoples (Micronesian, Samoan, Tongan) in the western United States. From 1995 to 1998, there was a tenfold increase in methamphetamine use among Native Hawaiians.[144] Between 2004 and 2005, emergency department visits for methamphetamine abuse rose by almost 50% to 108,905 visits per year, and treatment admissions for methamphetamine abuse increased to 150,000 admissions per year in 2004.[144]

More recent trends among the younger generation suggest that the use of methamphetamine may be waning, but the absolute numbers still offer reason for concern. Among youths aged 12–17, from the years 2002 to 2008, the use of methamphetamine decreased significantly from 0.3% to 0.1%.[1] In the next older group, ages 18–25, there was a decrease in methamphetamine use from 2002 to 2008 as well, with the usage numbers dropping from 0.6% to 0.2%.[1] In the year 2008, however, the total of all users age 12 and older (at least once in the year prior to survey) still added up to 850,000.[1] The total number of users of methamphetamine during the month immediately prior to the survey dropped from 731,000 (in 2006) to 529,000 (in 2007) to 314,000 (in 2008). Among the Native Hawaiians and the Pacific Island People, younger age and unmarried status (either never married or divorced or separated) appear to be particular risk factors.[144] In another survey, covering over 19,000 young people aged 16–23, and including multiethnic urban, suburban and rural groups, the focus was club drugs (see below). Recent users of methamphetamine in this club drug survey showed a predominance in the adolescent female age 16 or 17 group.[145]

Pharmacology

Synthetic amphetamine compounds may be synthesized in clandestine laboratories with variable purity and potency. The potential routes of administration may be oral, inhalation or parenteral (intravenous). The oral route involves absorption delays and the time of onset occurs about one hour after ingestion. The plasma concentration peaks approximately two to three hours after oral ingestion, but the rage of metabolism varies widely. With inhalation or parenteral use, the onset of symptoms occurs within a few minutes, and the peak plasma concentrations occur in approximately 5 minutes. The plasma half-life from the peak concentration varies in a range that spans from five hours to as long as thirty hours. Up to 30% of the parent compound may be excreted unchanged in the urine, and the excretion rate depends upon urine flow and the urine pH.[146] Intravenous dextroamphetamine produces a dose dependent hypertension virtually identical to that seen with cocaine.[22,147]

Cardiovascular Complications

A number of complications have been connected to methamphetamine use including the usual adrenergic physiology findings of tachycardia and hypertension. Other cardiovascular complications include myocarditis, necrotizing vasculitis, cardiomyopathy, pulmonary hypertension (cor pulmonale) and cardiac arrhythmias.[146] There have also been reports of acute coronary syndromes (ACS)[146,148-151] and sudden death.[152] One recent review mentions accelerated atherosclerosis, hypercoagulable states and epicardial coronary artery spasm similar to those issues with cocaine. This particular report focuses on yet another issue, global slow flow of all of the coronary arterial systems in the absence of significant stenoses. This global microvascular spasm was unrelieved by intracoronary vasodilator therapy and resulted in MI. The authors review the pathophysiology and treatment of this condition.[153]

Cardiomyopathy may result from intravenous or oral use of the amphetamines.[22,154] One report, of four patients with LVD and congestive cardiomyopathy attributed the problem to chronic IV use of propylhexedrine, an amphetamine analogue.[22,155] In another study, fifteen deaths due to IV propylhexedrine abuse, most patients had hypertrophy of the right ventricle and pulmonary hypertension.[22] Recent studies have found an increase of the patients presenting with CHF who report current or prior use of methamphetamine. The CHF of methamphetamine cardiomyopathy appears in a somewhat younger age group and in racial and ethnic minorities.[144] In a recent echocardiography study of 59 patients with cardiomyopathy or heart failure, 28 patients were methamphetamine users by history or urine toxicology (47%). The patients were hospitalized between 2001 and 2004, and they were less than 46 years of age. Both groups were predominantly male (64%). The patients using methamphetamine had echocardiographic findings of more severe dilated cardiomyopathy compared with the controls, but the confidence intervals were so wide that there was significant overlap. Echocardiography found nothing distinctive in this study that would reliably point to a methamphetamine etiology for the cardiac findings.[156]

Acute coronary syndrome: The occurrence of an ACS in the setting of methamphetamine abuse has been reported many times.[148-151] A representative recent case report details the presentation of a 23 year old who arrived hypotensive to 77/40 with a STEMI in the anterior leads and complete heart block. He was taken to the cardiac cath lab for PCI where he was found to have normal coronary arteries. His LV ejection fraction (EF) at that time was 15–20%. He required a pacemaker, and follow-up ECHO done seven days later demonstrated an improved EF of 35–30%. He survived this episode and was discharged nine days later.[146]

Death: It is not surprising that fatalities occur in this group, and that their occurrence goes back for decades. One report, for example, described a number of propylhexedrine deaths related to abuse of that drug with a suggestion of precipitation by sudden exertion or stress.[22,157] In a more recent study from Australia, a total of 371 cases were identified where methamphetamine was listed as the cause of death. The patients had a mean age of 32.7 years. They were predominantly male (77%) and unemployed (65%). The most common route of administration employed was injection (89%). Other drugs were

found frequently in the patient's system (89% of the time). The most commonly found drugs were benzodiazepines (41%) and morphine (36%). Deaths were termed accidental for the most part and occurred in the setting of a private home (71%). Approximately 14% were determined to be suicides.[152]

Noncardiac Complications

Among the other complications seen with methamphetamine abuse are aortic dissection,[146,158] central nervous system pathology such as ruptured berry aneurysms[146,158] and cerebral hemorrhage,[152] and rhabdomyolysis.[146,159]

PHENCYCLIDINE

Phencyclidine or PCP, (angel dust, ozone, whack, rocket fuel) comes as tablets or powder and can be used by nasal insufflation, smoking or taken by mouth. PCP was developed in the 1950s as a parenteral (IV) anesthetic but did not receive approval for human use because of problems during clinical studies which included intensely negative psychological effects. PCP has "dissociative" actions, distorting visual and auditory perceptions and producing feelings of detachment. Accompanying unpleasant psychological effects includ hallucinations, delusions, markedly disordered thinking and profound anxiety states.[143] It has been limited to veterinary use.[22,160] PCP was a popular drug of abuse during the 1970s and was known to provide stimulant properties similar to those found with amphetamines.[22,161] Emergency department visits related to this drug peaked in 1979 and deaths peaked in 1983. Nineteen deaths were reported due to this drug in two counties in California over a six year period, but in none of those could a cardiac cause be considered primary.[160]In a review of 1,000 cases found self-limited systolic and diastolic hypertension in 75% of the patients.[22,162] The hypertension resolved without treatment. There were no cases of the delayed "dopaminergic storm", with malignant hypertension described by one author with an onset 72–96 hours after ingestion.[22,163] Phencyclidine does not appear to have major cardiovascular toxicity even in the overdose scenario, and particularly not with the usual doses taken for recreation.[22] Researchers continue to publish laboratory work on this drug, but there are no recent clinical studies. That issue notwithstanding, approximately 99,000 Americans aged 12 and older used PCP in the year prior to the survey in 2008.[1]

PHENYLPROPANOLAMINE

Phenylpropanolamine (PPA) hydrochloride is a sympathomimetic compound, structurally and functionally similar to amphetamine and ephedrine. It is a component of more than one hundred over the counter medications, including nasal decongestants, anorectics and stimulants.[164-166] The authors of one survey in the mid of 1990s found that 9 million adults used over the counter diet medications containing PPA. They ranked it as the fifth most used drug in the United States at that time.[165] PPA may be taken by mouth for the symptomatic treatment of nasal congestion and appears frequently in combination preparations for cough and cold symptoms. Other uses of PPA include urinary incontinence and some forms of priapism. PPA has been used in the treatment of obesity as an appetite suppressant, as well as by those seeking simply to lose weight, but stimulants are no longer recommended in this clinical setting.[166]

Pharmacology

Phenylpropanolamine has sympathomimetic actions similar to that of ephedrine but with less central nervous system stimulation.[166] It is well absorbed from the GI tract, and peak plasma concentrations occur one to two hours after ingestion. There is some degree of liver metabolism (over 10%), but up to 90% of a dose is excreted unchanged in the urine within 24 hours. The plasma half-life averages about three to five hours.[166]

The cardiovascular effects of PPA, including vasoconstriction and increased cardiac output, are related to its alpha- and beta-adrenergic activity. This may or may not benefit weight control effort programs or symptoms of the common cold, but the use of PPA in patients with heart disease and hypertension can clearly be hazardous.[166] The exact cause of myocardial depression and injury after PPA ingestion is unknown and it is also unclear whether PPA has any direct effect on the myocardium.[166] One study showed that PPA caused depressed myocardial contractility without decreasing coronary artery blood flow. Inhibition of nitric oxide synthesis has been demonstrated to sensitize the heart to the myocardial depressant effects of PPA and to increase the risk of ventricular fibrillation.[166,167] Nitric oxide deficiency may thus play a role in endothelial dysfunction and predispose coronary arteries to PPA provoked vasoconstriction.[166]

Complications

Serious complications associated with the use of PPA include quite a number of pathological entities. The sympathomimetic effects are well recognized and more an effect of the drug than a complication, but the elevated BP can present as a hypertensive emergency.[164,165] Additional cardiac complications may include atrial and ventricular arrhythmias,[165] myocarditis,[165] myocardial damage,[166] MI,[165,166] and cardiac arrest.[166] The noncardiac complications relate to the central nervous system with psychosis,[164,165] headaches,[164] seizures,[165] and fatal CVAs[164,165] with an area of predilection, hemorrhagic strokes in young women.[166] Another complication related to vasospasm includes ischemic bowel.[165] Another interesting issue involves a case report of PPA abuse that surfaced during workup for pheochromocytoma. The patient was a 16-year-old girl with recurrent paroxysmal hypertension and seizures who sustained cardiac arrest before surreptitious ingestion of PPA was discovered.[22,164] The authors suggest that the abuse of sympathomimetics should always find a place in the differential diagnosis of paroxysmal hypertension and should be pursued.

MARIJUANA, TETRAHYDRIOCANNABINOL, HASHISH

Marijuana is the most commonly used illegal drug in the US. It is made up of dried parts of the cannabis sativa hemp plant, and can be smoked or taken orally. Tetrahydrocannabinol (THC) is the main found in the plant. Hashish is a concentrated form

of marijuana which is smoked, the use of which is much more common in Europe. Marijuana has been the most widely used illicit drug throughout the 35 years that the National Institute on Drug Abuse (NIDA) has been performing surveys on these issues in their "Monitoring the Future series".[2] The use of marijuana among 12th graders peaked in 1979 at 51% after a rise that began in the 1960s. Usage declined for over a decade, dropping by more than half, and bottomed at 22% in 1992. At that point, usage began to increase among 8th graders and, a year later, among 10th and 12th graders whose usage peaked in 1996 and 1997. Since that time usage declined in all three grades until 2006 and 2007, at which point there was the start of small but important increases in all three grades, indicating another possible period of resurgence of use.[2] In a survey done by the Substance Abuse and Mental Health Survey Administration (SAMHSA) a branch of the U.S. Department of Health and Human Services, the decline in the use of marijuana from 2002 to 2006 among the age group 12–17 years was confirmed. The usage dropped from 8.2% to 6.7%. This survey also noted significant decreased usage between 2002 and 2008 for prior year marijuana use (15.8–13.0%) and for lifetime marijuana use from 20.6% to 16.5%).[1] This survey also found somewhat different recent trending in that the usage among youths aged 12–17 remained unchanged in 2007 and 2008.[1] Among a somewhat older age spectrum, aged 12 or older, the rate of marijuana used in the month prior to the survey in 2008 was 6.1%, similar to the rate in 2007 at 5.8%. Recent trending aside, these lower numbers still amount to 25.8 million people.[1]

CARDIAC COMPLICATIONS

Given the prevalence of the use of this drug, there are surprisingly few complications. In one study of IV cocaine and smoked marijuana, alone and in combination, marijuana use alone produced blood level dependent increases in the mean arterial pressure. These changes were asymptomatic and devoid of clinical significance.[168] In one recent case report discussed the occurrence of syncope in a patient who smoked more than his usual amount of marijuana and sustained a shock from his implantable cardioverter defibrillator (ICD) device prior to losing consciousness. Interrogation of the device revealed an episode of ventricular fibrillation which was sensed and treated with a single shock of 35 Joules. The authors called this the first report of ventricular fibrillation triggered by marijuana use in a patient with an ICD.[169] In another case report, coronary vasospasm diagnosed by cardiac magnetic resonance imaging was reported in an adolescent who had used marijuana. This 17-year-old patient presented with severe chest pain, ECG changes and urine toxicology positive for cannabis. He was diagnosed as having transient myocardial ischemia. In the follow-up echocardiogram 1 month later revealed normal LV systolic function. The authors considered this an example of marijuana provoked transient coronary vasospasm leading to myocardial ischemia.[170] Again, the merits of these case presentations and the authors' conclusions aside, the prevalence of the use of this drug at 25.8 million users per month in the 2008 survey[1] makes drawing any conclusions relation these clinical events to the drug use somewhat dubious.

CLUB DRUGS: MDMA, GHB, KETAMINE, ROHYPNOL

The term "club drugs" refers to a group of drugs used by young adults often associated with nightclubs and parties, particularly all night dance parties called "raves" that take place in nightclubs and other venues. The U.S. Office of National Drug Control Policy identifies four specific club drugs: (1) Methylenedioxymethamphetamine or "Ecstasy" (MDMA); (2) Gamma-hydroxybutyrate (GHB); (3) Ketamine and (4) Rohypnol (flunitrazepam).[171] The NIDA 2008 Monitoring the Future Study showed the annual usage of these club drugs during the prior year by 12th graders to be GHB (1.2%), ketamine (1.5%) and rohypnol (1.3%). In the younger group of 10th graders, the numbers were somewhat less at GHB (0.5%), ketamine (1.0%) and rohypnol (0.4%). The numbers for the youngest group of 8th graders was slightly higher than the 10th graders at GHB (1.1%), ketamine (1.2%) and rohypnol (0.5%).[172] In terms of breakdown by gender and other age groups, it has been reported that approximately 20% of young people aged 16–23 have used one or more of these drugs in the past, and that females were more likely than males to use multiple club drugs. Club drug use was highly associated with the presence of criminal behavior and recent alcohol abuse or dependence.[145]

A study of club drug usage by medical students encompassed a somewhat larger group of drugs, classifying them as Generation I (cocaine and LSD) and Generation II (MDMA, ketamine, GHB, methamphetamine, rohypnol and dextromethorphan). These categories were based upon "their initial widespread use in club settings". The usage pattern was based upon an anonymous questionnaire. The overall prevalence of club drug usage by medical students was 16.8%, while the most frequent two drugs used were MDMA (11.8%) and cocaine (5.9%).[4] Drugs outside of the initial four categories above have been addressed elsewhere in the text. LSD is covered below under hallucinogenics for example, while cocaine and methamphetamine are covered above under stimulants. Since the category still contains multiple drugs, the expected effects vary, and they are addressed individually below.

METHYLENEDIOXYMETHAMPHETAMINE

Methylenedioxymethamphetamine (MDMA) or Ecstasy is a synthetic drug with stimulant and psychoactive properties.[1] MDMA affects neurotransmitters, principally in the serotonin system where it acts as a serotonin agonist. MDMA increases serotonin production, increases the release of serotonin and blocks serotonin re-uptake. MDMA also depletes serotonin stores, such that subsequent doses of the drug produce less euphoria and increased adverse effects. MDMA also affects the noradrenergic, dopaminergic and cholinergic neurotransmitter systems.[171]

The effects of MDMA sought by users include increased physical energy, increased self-confidence and a feeling of well-being. It produces a positive mood, heightened sensory awareness and increased responsiveness to emotions accompanied by a sense of closeness to others. Adverse effects include derealization, depersonalization, anxiety and thought disorders, difficulty concentrating, blurred vision, sweating anorexia,

bruxism, muscle cramping, hypertension and problems with thermal regulation.[2,171]

Complications

MDMA has been associated with nine deaths due to severe hyperthermia in the setting of physical exertion without adequate hydration and ventilation. These cases involved diaphoresis, hypertension, tachyarrhythmias, papillary dilation and seizures, which resulted in renal failure and death. There have also been reports of liver failure in patients using MDMA but the causation link was not clear. Neurotoxicity has been described, including the above complications as well as cerebral hemorrhage and infarction. Psychiatric disturbances such as depression, panic attacks and flashback hallucinations have also been described, but these findings often emerge in patients at risk for mental illness, and thus the specific contribution of MDMA to the situation remains ambiguous.[171]

Cardiac Complications

Given that MDMA is structurally related to the amphetamines, there is less by way of cardiac complications than one might expect. One recent study to investigate the association of cardiac arrhythmias with MDMA found that chronic use was not associated with any higher prevalence of abnormalities than controls.[173] In another study to address the occurrence of valvulopathy in young adults taking MDMA, 29 patients with a history of using MDMA were matched with controls and evaluated in a blinded fashion by echocardiography. Eight of the 29 MDMA patients (28%) had abnormal ECHO results compared with none in the control group. The abnormalities included mitral regurgitation, tricuspid regurgitation and mild aortic regurgitation. Valvular "strands" were present in six of the MDMA patients (21%) and in none of the controls. The p values were significant and the authors concluded that MDMA may lead to mild to moderate valvular heart disease and valvular strands.[174] Dilated cardiomyopathy has been reported in conjunction with liver damage attributed to MDMA.[175] MI has also been reported in a single patient who sustained two MIs, the second one fatal, that were attributed to MDMA abuse.[176]

GAMMAHYDROXYBUTYRATE

Gammahydroxybutyrate (GHB) occurs naturally in the brain and may be a neurotransmitter. It is structurally related to gamma-amino butyric acid (GABA). GHB inhibits dopamine release and activates tyrosine hydroxylase, both of which increase central dopamine levels which may be associated with the clinical effects. GHB has been discussed and in some cases implemented in the areas of anesthesia, obstetrics, psychiatry, alcohol withdrawal, narcotic withdrawal, fibromyalgia, narcolepsy and cataplexy. By the 1990s, GHB was marketed for illicit use in weight control and it was popular with body builders for supposed anabolic properties and associated muscle growth. Illicit indications for this drug, along with the body image uses, include euphoria, increased relaxation, relief of anxiety and enhanced libido. It has also been implicated in sexual assault (date rape) because victims have difficulty resisting due to the deep level of intoxication. The associated memory problems and rapid clearance also inhibit prosecution efforts.[171]

Adverse Effects

GHB causes drowsiness which can segue into loss of consciousness, coma and respiratory failure. In the absence of the appropriate medical measures, including intubation and ventilation, the outcome of an overdose may be fatal. In addition GHB may cause agitation, tremors, seizure-like activity, vertigo, confusion and hallucinations. GI upset may also occur with vomiting and incontinence of bowel and bladder. Given the rapid metabolism, most adverse symptoms clear within a few hours.[171] In one study of 170 patients over 30 months with GHB ingestion in Australia, it was noted that the incidence of usage doubled during the study period. The presenting complaint was altered level of consciousness in 90% of the patients and more than half of them had a Glasgow Coma Scale (GCS) in the range of 3-8. Only eight percent required intubation, but over half of them required other more conservative airway management. Approximately 70% of the patients were hypothermic, and the expected respiratory acidosis occurred in 75% of the study population. Other manifestations of GHB toxicity varied widely and included agitation (12%) and vomiting (17%). *Cardiovascular complications* were not a major issue. Those occurred in less than 10% of the patients, and included only bradycardia, tachycardia and hypertension. The expected prompt resolution occurred in patients who were not intubated and mean time to discharge from the emergency department for that group was less than two hours. No serious complications were seen overall and there were no fatalities.[177]

KETAMINE

Ketamine distorts perception producing a dissociative state which may be quite useful clinically, in controlled settings and dosages. This drug finds daily use across the United States in emergency department pediatric procedural sedation. In the club drug setting, ketamine dissociation involves feelings of detachment from one's self and from the environment, and may be accompanied by amnesia and delirium.[2] Interestingly enough, ketamine users tend to be primarily employed youths.[145]

Pharmacology

Ketamine is an *N*-methyl-D-aspartate (NMDA) receptor antagonist. It decreases excitatory amino acid neurotransmission mediated by NMDA receptors through calcium channel blockade, and has been associated with altered perception, memory and cognition. Ketamine has been used as an approved anesthetic for both humans and animals since the 1970s. The nonmedical use of ketamine became popular in the 1980s, wherein low doses are associated with feelings of relaxation called "K-land." Higher doses produce dreamlike states, hallucinations, visual distortions and the sensation of a near-death experience called a "K-hole." The use of ketamine has been associated with unintentional injuries which occur because the user is insensitive to pain, and with sexual assault because of its dissociative effect.[171]

Adverse Effects

The usual clinical responses to medical dosages for pediatric procedural sedation include tachycardia and hypertension, so those would also be expected in the club drug setting. The additional effects described are numerous and many are directly related to the actions of the drug. Impaired motor functioning and immobility, for example, which could lead to abnormally low body temperature in the club setting, is exactly the effect required in the pediatric procedural sedation arena. Respiratory depression has also been mentioned in this regard,[171] but this is not seen in current emergency medicine usage where an intact gag reflex and no evidence of respiratory depression is expected. Other psychiatric adverse effects in the club drug setting include anxiety, amnesia, impaired attention, delirium with confusion and disordered speech, hallucinations, learning disability, depression, recurrent flashbacks and symptoms of schizophrenia. Chronic use has led to cognitive difficulties in areas such as attention, learning, and memory.[171] There appear to be no specific cardiac complications associated with ketamine, other than issues with the tachycardia and hypertension is patients for whom these issues would be problematic.

ROHYPNOL

Flunitrazepam (Rohypnol) is a benzodiazepine used as a sedative hypnotic. It acts as a gamma-aminobutyric-acid (GABA) agonist, mediating inhibitory neurotransmission in the brain and spinal cord. Benzodiazepines bind to GABA receptors, open the chloride channels of neurons, and result in chloride influx and hyperpolarization of the cell, which decreases excitability. The clinical effects of benzodiazepines include sedation, anticonvulsant activity and anxiety reduction. Rohypnol can also completely incapacitate users and cause amnesia.[2] Overdoses can lead to loss of consciousness and respiratory depression.[171] Rohypnol has been associated with sexual assault (date rate) due to profound sedation accompanied by anterograde amnesia in which an individual cannot recall events that took place while sedated. It is odorless, tasteless and easily dissolved, allowing a perpetrator to add it to the beverage of a potential victim. The manufacturers are now adding a blue dye to the pill that will make it more visible in that regard.[171] A recent review, however, examining the issue of drug-facilitated sexual assault, concluded that when one removed voluntary drug ingestion from the study group, only 2% of alleged date rape could be attributed to surreptitious drug administration. The reviewers quoted a study from the U.K. which found no evidence that Rohypnol had been used for drug facilitated sexual assault during a three year investigation. The study pointed out that Rohypnol is used recreationally in the United States, providing an explanation for its presence in samples of some alleged date rape victims.[178] In addition to the association with sexual assault, high rates of misuse by teenagers and young adults at nightclubs and raves have been reported. Some studies have reported that Rohypnol is preferred over other benzodiazepines in this setting, possibly having to do with faster onset (15–20 minutes), longer duration of action (12 hours or more), and stronger effects at lower dosages. Rohypnol may be used illicitly to reduce anxiety in social settings, to achieve a feeling euphoria, and to induce a relaxation resembling alcohol intoxication. It may also be used with heroin to ameliorate withdrawal symptoms.[171]

Adverse Effects

Adverse effects include the expected sedation and impaired functioning, along with visual disturbances, confusion, GI disturbances and urinary retention. In terms of cardiovascular complications, hypotension has been noted, but as with any benzodiazepine overdose, the process may include loss of consciousness and respiratory failure if sufficient quantities of the drug have been taken.[171]

HALLUCINOGENIC DRUGS

The use of hallucinogens among youths aged 12–17 increased from 0.7% in 2007 to 1.0% in 2008. Among young adults aged 18–25, from 2007 to 2008, there was no change in the incidence of use of these drugs (1.7%). In the group aged 12 and older, prior month hallucinogenic drugs were used by 1.1 million people in 2008, again similar to usage numbers for the prior year.[1]

LYSERGIC ACID DIETHYLAMIDE

The prototype of this group of drugs is lysergic acid diethylamide (LSD) which has a long and colorful history. It may be taken as tablets, capsules, liquid or on blotter paper. It distorts the perception of reality and produces hallucinations. In 2008, the group aged 12 and older using LSD in the prior year totaled 802,000.[1] LSD produces the expected psychological side effects of hallucinations which may turn decidedly unpleasant (a bad trip).

Adverse Effects

Adverse effects of LSD may include increased body temperature, heart rate and BP, as well as anorexia and insomnia.[172] In one case report of LSD ingestion led to lower extremity vasospasm requiring percutaneous transluminal angioplasty.[179] In another case report delineates the role of LSD in rhabdomyolysis which has been seen in a number of other drugs discussed here.[180] Other hallucinogens, such as mescaline and peyote, have not been known to produce any major cardiac complications.

BODY IMAGE DRUGS

ANABOLIC STEROIDS

Synthetic anabolic androgenic steroids are widely used by professional athletes in many sports, perhaps somewhat less at present given the rigid proscriptions and testing now in place, but for weight lifters and body builders the issue persists. Steroids have major effects on muscle mass, performance, libido and aggression, and particularly on the cardiovascular system. Their use is a major risk factor for CAD as they are potent atherogenic agents, and they also cause a predisposition to clotting.[22] They can cause high cholesterol, high BP, fluid retention, liver damage and hormonal issues which differ by

gender.[2] Anabolic steroids are usually synthetic substances similar to the hormone testosterone. They can be taken orally or injected.[2] As of 2008, the adolescent usage numbers were just under 1% of 8th graders (0.8%) and 10th graders (0.9%), increasing to 1.5% of all 12th graders. These were adolescents who had used anabolic steroids at least once during the previous year.[2]

Cardiovascular Complications

Use of anabolic steroids causes a variety of cardiovascular effects. One recent review goes through most of these in some detail. Although many of the complications are listed and discussed, the authors note that there have been no prospective, randomized studies on the long-term cardiovascular effects of anabolic steroids to date.[181] Among the various cardiovascular complications which have been reported are sudden cardiac death, LV hypertrophy, reduced LVF, cardiomyopathy, CHF, arterial thrombosis, pulmonary embolism and AMI.[181-185] In a discussion of some of the underlying pathophysiology, the review points to alterations of diastolic function and ventricular relaxation, and to a mild transient hypertension. Anabolic steroids also cause a thrombotic state by increasing platelet aggregation. There is also data showing alterations of lipid metabolism, with elevations of low-density lipoprotein (LDL) and decreases of high-density lipoproteins (HDL), which increase the risk of CAD.[181] In an autopsy study accompanied by an animal study, the animals showed histopathological changes consisting of coronary thrombosis associated with left ventricle hypertrophy in a few cases, and myocarditis in the others. These findings were very similar to those observed in the autopsy study of cardiac sudden death in 6 athletes with a history of anabolic steroid abuse.[185] One interesting case report details the admission of a previously healthy 40-year-old bodybuilder for acute hepatic failure attributed to toxic hepatitis associated with anabolic steroid abuse. There were no signs of CHF on admission, but workup revealed dilated cardiomyopathy with thrombus in both ventricles as the underlying cause of the liver pathology. Treatment for the heart failure restored the liver function to normal. The authors felt this was the first reported case of acute liver failure due to an unrecognized anabolic steroid-induced cardiomyopathy.[184]

In this body image anabolic steroid category, GHB should be mentioned, as it has been used by body builders for theoretical anabolic properties and associated muscle growth.[171] GHB is discussed under the section on club drugs. Physicians who encounter cardiovascular complications such as the above, particularly in young patients devoid of risk factors, should actively pursue the possibility of anabolic steroid use and should discuss the risk of these drugs with any of their patients who engage in athletic competition.[22]

DIET DRUGS

Fenfluramine, dexfenfluramine and phenteramine (fen fen) have an established role in the development of valvular heart disease; along with other drugs such as MDMA (ecstasy) (see club drugs). Clinical trials have shown that dose and duration affect both the incidence and the severity of the problem. The natural history remains unclear, but regression of valvular lesions with cessation of treatment has been reported. Fenfluramine and phenteramine were approved by the FDA in 1959 and 1973, and they soared in popularity after reports of their effectiveness in obesity.

Fenfluramine is a racemic mixture of two isomers (levofenfluramine and dexfenfluramine). Dexfenfluramine stimulates serotonin release from neurons and platelets.[186] It was thought to be less toxic than fenfluramine and was approved for use in 1996. The first reports of valvular disease associated with fenfluramine came from Mayo Clinic in 1997, a year later. A series of 24 women using the drug presented with valve pathology. The ECHO features of the valves and microscopic examination of excised valves showed features seen in carcinoid and ergot alkaloid valve disease.[187] The FDA received five reports of similar series of patients on these drugs with an overall incidence of 32% having valvular heart disease. The risk was increased for patients taking the drug for more than 6 months. On the basis of these reports, fenfluramine and dexfenfluramine were voluntarily withdrawn from the market.[188] Although this improvement is reassuring in the short term, there are no long-term follow-up studies of these patients.[188] GHB was marketed in the 1990s as an illicit weight control agent. This drug is discussed with the club drugs. PPA is discussed under stimulants.

ANOREXIA AND BULEMIA

There continue to be issues among young people (mostly female) with pathologic concerns about weight leading to induced vomiting, abuse of furosemide and other diuretics, and purging with emetics and laxatives.[22] These patients generally view themselves as overweight even though they are usually underweight. They may present with hypokalemia and ECG abnormalities including low voltage, bradycardia, ST and T wave changes, prolonged QT interval, and U waves due to hypokalemia. The prolonged QT interval in anorexia nervosa has led to ventricular arrhythmias and death.[22] Cardiomyopathy has been seen as well.[22] Ipecac may present a particular risk, as patients who misuse the drug may ingest very large quantities over long periods of time, accumulating a large tissue burden of the cardio toxic ingredient emetine.[22] A fatal overdose may be ingested in only a few days, particularly by an underweight person. In reported cases, patients have presented and died with fulminant biventricular failure.[22] Ipecac was once recommended as a stocked home emetic for use in pediatric toxic ingestions, but has more recently been discouraged for use in home, and usage in emergency department settings has been abandoned. Ipecac remains available and has been associated with abuse in eating disorders and other situations. One case report involved an adolescent boy who abused ipecac in the context of parental conflict. The medical workup undertaken for proximal muscle weakness, abdominal pain, and cardiomyopathy eventually led to Ipecac.[189] There is no specific treatment. Ipecac abuse should be considered in patients with unexplained hypokalemia or cardiac failure, particularly those who meet this particular demographic.[22]

INHALANTS

Inhalants are chemical vapors inhaled intentionally for mind altering purposes. Often they are common household products

like aerosols, gases or glue. Most inhalants produce a high similar to alcohol intoxication, and also result in a loss of sensation.[190] In the age range from 18 to 25 years old, there were decreases from the year 2002 to 2008 in the use of inhalants (0.5–0.3%).[1] In terms of absolute numbers for the year 2008, approximately 2 million Americans aged 12 and older used inhalants.[1] In a poison control center database with no delimiting age parameters, a review of 35,453 inhalant cases from 1993 to 2008 showed a 33% decreased incidence of usage over that period. The highest usage of inhalants occurred among children aged 12–17, with a peak at age 14.[191]

More than 3,400 different substances were inhaled by patients in this series, with the most frequent being propellants, gasoline and paint. Propellants were the single category which increased over this time period. The highest fatality rates occurred with the inhalation of butane, propane and air fresheners. The geographic distribution of use varied with the substance, but the overall incidence was highest in western mountain states and in West Virginia. Gasoline appeared to be a greater problem for younger children while propellants were more often misused by older children.[191]

A lack of consensus as to classification and subclassification of these numerous inhalant substances has been felt by some to hamper research in the area. One review suggested moving beyond classifications based on chemical structure, or pharmacological properties, or intended use of the product into another yet-to-be-determined combination of chemistry, pharmacology and shared patterns of abuse.[192] This may eventually prove fruitful but there is much work to be done. The work to date often involves examining binge use during adolescence, a key stage of development. Human studies have consistently shown that chronic use causes significant CNS effects, including neuropsychological impairment, with subtle diffuse changes in the white matter. There does appear to be growing evidence that common inhalants share common cellular mechanisms. The majority of acute behavioral effects appear to relate to changes in receptor or ion channel activity. Recent studies examining toluene exposure during the early postnatal period, for example, suggest long-term alterations in NMDA and GABA receptors.[193]

In terms of complications, inhalants can cause suffocation, anoxia and brain damage including irreversible hearing loss. Bone marrow damage and heart failure have also been described.[190] The cardiac complications of toluene, one of the major components of glue, include arrhythmias and sudden sniffing death syndrome. One recent study examined QT dispersion as a risk marker for cardiac arrhythmias and sudden cardiac death. The intent was to study the effects on the QT interval and QT dispersion of glue inhalation. The study involved 44 patients with inhalant abuse and 34 healthy controls divided into three groups: glue abusers with syncope (n = 20); asymptomatic glue abusers (n = 24) and healthy controls (n = 34). The results demonstrated prolonged QT intervals and increased corrected QT dispersion in toluene abusers as compared to controls, and these changes were more marked in the syncopal symptomatic group than in the asymptomatic inhalant patients.[194]

In summary, there exist a true multitude of inhalants subject to abuse, and the spectrum includes typewriter correction fluid, which contains chlorinated hydrocarbons, the contents of fire extinguishers, which contain bromochlorotrifluoroethane, and chloroform which in one instance caused loss of consciousness and VT.[22] There is no specific treatment for the arrhythmias caused by inhalants. These generally occur before the patient arrives in the medical setting, and the recommended approach when they do arrive would include oxygenation, acid-base and electrolyte management and conventional pharmacological therapy. The cause of such arrhythmias may be suspected from the patient age and appearance, from the history, or from findings on the physical exam such as traces of paint on the hands, nose or mouth. One of the most useful services the physician can provide, in addition to the usual support of the patient's physiological difficulties, includes informing patients and their families of the risk of permanent brain damage and death from continuation of this practice.[22]

NARCOTICS

HEROIN

Heroin, the prototype of illicit drugs, is processed from morphine and is highly addictive. It can be used by injection, nasal insufflation, or by smoking and usually causes euphoria, clouded thinking and altered mental states. Heroin depresses the respiratory drive and overdose scenarios can cause fatal respiratory failure. When used parenterally, heroin poses the usual infectious risks of IVDU including hepatitis and HIV/AIDS.[172] As with any IVDU, other infectious complications, such as endocarditis, sepsis, septic emboli and spinal epidural abscess, must be considered. From the years 2002 to 2008, nonmedical use of pain relievers (not specifically narcotics) by the age group 12–17 years old decreased significantly from 3.2% to 2.3%.[1] For the year 2008, however, with the expanded age grouping of 12 years and older, that still amounted to 453,000 Americans using heroin during the prior year.[1]

The complications of the parenteral use of heroin are mentioned above and would also include rhabdomyolysis and compartment syndrome requiring fasciotomy.[195] One case report involved a patient who inhaled heroin presenting with rhabdomyolysis and cardiogenic pulmonary edema complicated by retroperitoneal hemorrhage caused by spontaneous rupture of renal artery aneurysms. The patient then developed oliguria, pulmonary edema and anterior T wave inversion. On ECHO he was found to have severe global systolic LVD with an EF of 15% that was attributed to heroin cardiomyopathy. He survived this horrendous course of events. The authors describe heroin associated cardiomyopathy in some historical detail along with a number of other cases. The pathophysiology of heroin-induced cardiomyopathy was felt to be uncertain, but one fatal case had microscopic findings at autopsy in the myocardium that resembled those in skeletal muscle with focal myolysis.[196] Another study described myocardial fibrosis associated with opiate abuse whose origin was unclear. The study involved 21 chronic drug use patients who died of heroin or morphine intoxication compared to 15 controls who died noncardiac deaths with no history of drug use. A quantitative study of myocardial interstitial leucocyte infiltrates was performed with conventional techniques to characterize the leucocytes, T lymphocytes and macrophages. The total number

of cells was found to be increased up to fivefold in heroin addicts as compared to controls but this did not reach the cut-off values for the immunohistochemical diagnosis of myocarditis.[197]

METHADONE

Methadone appears in the clinical arena as an analgesic for chronic pain patients, particularly cancer-related pain, and as a pharmacologic adjunct to assist in weaning patients from illegal opiates. Given the accepted benefits of methadone in these legitimate clinical arenas, the finding of an association between methadone use and QT prolongation and torsades de pointes was of great concern.[198] The long half-life of methadone, as compared to the opiate antagonist naloxone, for example, poses a number of clinical problems in the emergency medicine arena. Methadone may also be misused, abused and taken for nonmedical purposes. Methadone is used orally, and the clinical presentation generally involves a known user having taken an overdose of their own medication, or with the use of their medication by someone else. The accidental ingestion by children can be particularly problematic and clear cut abuse situations occur with some frequency.

Cardiac complications with methadone may involve QT interval prolongation, which has been noted to provoke ventricular arrhythmias and particularly torsades de pointes.[62,196,199] Recent studies indicate the QT prolongation with methadone is context dependent, meaning occurring more frequently with higher doses of methadone, with hypokalemia, with hepatic failure, with pre-existing heart disease, and with the use of QT prolonging drugs.[198] A reasonable approach to this situation involves measuring the QT interval in patients on methadone before adding another drug which causes QT prolongation.[62]

Torsades de pointes has also been reported to occur with the use of cocaine in patients who have idiopathic long QT syndrome.[60,61] Methadone associated torsades may result from large dosages or from a recent increase in dosage. One case report involved a patient with a recent methadone dose increase to 135 mg/day presenting with symptomatic torsades. Initial stabilization included IV magnesium and lidocaine and direct current (DC) cardioversion. Definitive treatment involved reduction of the daily methadone dose and an implanted cardioverter-defibrillator.[200] A recent set of recommendations for physicians prescribing methadone has been promulgated and includes the following: (1) Disclosure—informing patients about the risk of arrhythmia; (2) History—asking patients about the history of heart disease, arrhythmia or syncope; (3) Screening—ECG performed before treatment, with follow-up ECG in 30 days, and follow-up ECG annually. Additional ECG indications include dosage in excess of 100 mg/dL, syncope, or seizures; (4) Risk stratification—if QTc is greater than 450 ms and less than 500 ms, monitor more frequently and discuss risk and benefits with the patient. If QTc exceeds 500 ms consider reducing dose or discontinuing the drug or eliminating any contributing factors that can be identified (such as hypokalemia) or alternative therapy; and (5) Drug Interactions—physicians should be aware of methadone interactions with other drugs that cause QT prolongation or decrease methadone clearance.[200a]

Sudden cardiac death also occurs with methadone therapy. In an autopsy study of 22 sudden cardiac death patients with therapeutic levels of methadone compared with 106 controls (consecutive sudden cardiac death cases without evidence of methadone), sudden death-associated cardiac findings appeared in only 23% of the methadone patients (n = 5) with no cause discerned in the remaining 77% (n = 17). Among the controls, sudden death-associated cardiac abnormalities were identified in 60% of the patients (n = 64, p = 0.002). The authors concluded that sudden death occurred in methadone users out of proportion to the cardiac abnormalities at autopsy (with a lower incidence of cardiac pathology than would otherwise be expected) therefore that methadone, even at therapeutic levels, was implicated as a likely cause of sudden death.[200b]

PRESCRIPTION AND OVER THE COUNTER DRUGS

The subject of the "prescription drug abuse epidemic" was addressed at a Congressional Hearing in 2006. According to Dr Laxmaiah Manchikanti, the chief executive officer of the American Society of Interventional Pain Physicians, "Prescription drug abuse today is second only to marijuana abuse. In the most recent household survey, initiates to drug abuse started with prescription drugs (especially pain medications) more often than with marijuana. The abuse of prescription drugs is facilitated by easy access (via physicians, the Internet and the medicine cabinet) and a perception of safety (since the drugs are FDA approved)".[201] "He goes on to point out that added to the personal toll of prescription drug abuse, there are associated indirect costs including product theft, criminal activity to support addiction, law enforcement costs and encouraging the practice of defensive medicine." [201] Despite these assertions, the epidemiologic data reflects an overall decline in this problem in the youngest group monitored. Among youths aged 12–17, from the years 2002 to 2008, usage rates for nonmedical use of prescription drugs decreased from 4.0% to 2.9%, and that of pain relievers from 3.2% to 2.3%.[1] During this same time frame, however, there was an increase of this problem among young adults aged 18–25 where the rate of nonmedical use of prescription pain relievers increased from 4.1% to 4.6%.[1] The absolute numbers involve 6.2 million people aged 12 or older (2.5% of this group) who used prescription psychotherapeutic drugs nonmedically during the month prior to the survey. The estimates fall below that of the previous year of 2007, during which the numbers were 6.9 million people of this age grouping (2.8%). [1]

Another review called this a "growing problem in the United States affecting all age groups, including adolescents" which is somewhat at odds with the above, but this author points out that advances in the medical management of chronic pain, depression, anxiety and attention-deficit/hyperactivity disorder have brought medications such as opiates, benzodiazepines, and psychostimulants to our shelves, and that these medication have significant potential for abuse.[202] Yet another review calls our attention to gender issues. In this population of 55,023 people, it was noted that among women but not men, the first use of illicit drugs beginning at the age of 24 years or older was associated with past-year non-medical use of prescription opioids. In addition, among all respondents, 4.8% of the

population reported nonmedical use during the past year of prescription opioids. The incidence for both men and women of alcohol abuse and dependence, as well as the use of marijuana, hallucinogens, cocaine, and nonmedical use of stimulants, sedatives and tranquilizers was firmly associated with nonmedical use of prescription opioids during the previous year.[203]

From a problem solving point of view, another review calls our attention to the risk factors for adolescent (ages 12–17) misuse of prescription medication. In a population of 18,678 patients, the risk factors identified were poorer academic performance, higher risk-taking levels, past year use of alcohol, cigarettes, marijuana, cocaine, inhalants, major depression in the previous year and 10 or more episodes of prescription misuse in the past year. The authors conclude these risk factors could help clinicians identify those at risk for prescription misuse.[204] At the Congressional Hearings mentioned above, other future strategies were discussed at length. These included prescription drug monitoring programs, reducing mal-prescriptions, public education, eliminating internet drug pharmacies and development of drugs which would be tamper-resistant and non-addictive. The parents who lost children to drugs advocated a focus on education at all levels, development of resistant drugs and non-opioid treatment of chronic pain.[201]

ALCOHOL AND TOBACCO

These topics have been covered under Section 5 (Chapter: Coronary Heart Disease), Section 11 (Chapter: Alcohol and Arrhythmia) and Section 13 (Chapter: Smoking and Air Pollution).

CONCLUSIONS

Substance abuse statistics boggle the mind, especially given the spectrum of relatively nasty drugs, the severity of some of the complications, and the young ages of people with the highest usage statistics. We probably do not consider these issues as often as we should in clinical settings, particularly in patients who meet the demographic profile or who have the social settings or risk factors as outlined above. A number of these drugs can cause long-term and irreversible damage to the heart and other organ systems, and the inhalants can cause fatal arrhythmias at the time of intoxication. The treatment of the side effects of these agents generally follows the same approach as when these effects are induced by nondrug causes, with a few notable exceptions which are detailed above. The physician who identifies the use of these agents and convinces the patient and their family members of the seriousness of the situation has made the first step toward rectifying an appalling situation. The most useful service we can perform as clinicians, in addition to supporting the patient physiologically through the various acute crises, involve in arranging for them to seek counseling and to abstain from the offending substance.

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Chapter 94

HIV/AIDS and Cardiovascular Disease

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Chapter Outline

- HIV and Coronary Heart Disease
  - Epidemiology
  - Clinical Characteristics of CHD in HIV-infected Individuals
  - Pathogenesis of Coronary Heart Disease in HIV Infection
  - Treatment
- Surrogate Measures of Atherosclerosis
  - Carotid Artery Intima-media Thickness
  - Brachial Artery Flow-mediated Dilation
  - Coronary Artery Calcium Scoring
- Other Cardiovascular Conditions
  - HIV-associated Pulmonary Arterial Hypertension
  - HIV-related Left Ventricular Dysfunction and Myocarditis
  - Cerebrovascular Disease
  - Miscellaneous

INTRODUCTION

According to data from the Joint United Nations Programme on HIV/AIDS and the World Health Organization in 2008, an estimated 1.4 million people were living with human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS) in North America and there were over 33 million living with HIV or AIDS worldwide.[1] The advent of highly active antiretroviral therapy (HAART) in 1996 has resulted in dramatically decreased HIV-related mortality,[2] and it is estimated that, by the year 2015, HIV patients aged 50 and older will account for half of all HIV/AIDS cases in the United States.[3] As patients are living longer, chronic health complications, such as cardiovascular disease (CVD), represent an increasing important health issue in this patient population. The mechanism underlying CVD in the setting of HIV is most likely multifactorial and related to inflammation in the setting of HIV infection, side effects from antiretroviral medication and HIV-related immune responses. This review will focus on cardiovascular manifestations of HIV infection, with particular emphasis on coronary heart disease (CHD) and cardiovascular risk factors.

HIV AND CORONARY HEART DISEASE

EPIDEMIOLOGY

In 1998, the first case reports of myocardial infarction (MI) in HIV-infected patients on antiretroviral treatment were described.[4,5] Since these initial reports, an increasing number of observational studies have reported higher rates of CHD among HIV-infected individuals. However, the relative contributions of HIV infection versus potential adverse effects of HAART to CHD risk remain uncertain. While the data regarding coronary events in HIV disease are conflicting, the majority of studies shown in Table 1 suggest the concept that antiretroviral therapy is associated with increased CHD risk among individuals with HIV.

The Veterans Affairs study was a retrospective cohort of 36,766 HIV-infected patients followed for a mean of 40 months. There was no significant increase in cardiovascular or cerebrovascular events in patients treated with HAART or protease inhibitors (PIs) compared with age-adjusted US population rates.[9] In contrast, the French Hospital Database was a prospective cohort study that followed 34,976 HIV-infected individuals for a median of 42 months. The rate of MI was increased in subjects with greater than 30 months of exposure to PI, when compared with lesser than 18 months of PI exposure (33.8 vs 10.8 events per 10,000 PY), suggesting a duration-related effect.[15] Similarly, the data collection on adverse effects of anti-HIV drugs (DAD) study prospectively followed 23,468 HIV-infected individuals, and showed an increased incidence rate of MI with longer exposure to HAART.[20] Specifically, PI exposure greater than 6 years was associated with increased risk of MI (1.53 vs 6.01 events per 1000 PY), a finding that was only partly explained by dyslipidemia related to PI use. In particular, further analysis from the DAD study revealed that indinavir, lopinavir-ritonavir, didanosine and abacavir were associated with a significantly increased risk of MI.[19,21] A recent controversy has been the potential adverse cardiovascular effect of abacavir (a nucleosidase reverse transcriptase inhibitor (NRTI), which appeared to increase risk of MI in the DAD study (relative rate 1.89, $p = 0.0001$).[22] This finding has also been corroborated in the more recent strategies for management of antiretroviral therapy (SMART) study, where abacavir was associated with increased CHD events when compared with didanosine.[23] However, this finding has not been demonstrated in other studies.[24]

TABLE 1

Observational studies of CHD in HIV infection

Authors	*Population*	*Number of Patients*	*Study years*	*HIV-infected compared with noninfected controls*	*Effect of HAART*
Klein et al.[6]	Kaiser Permanente, Northern California	4,159	1996–2001	Higher incidence rate of CHD hospitalization: 6.5 vs 3.8 events per 1,000 PY, p = 0.003 Nonsignificant increase in incidence rate of MI: 4.3 vs 2.9 events per 1,000 PY, p = 0.07	No difference in age-adjusted CHD and MI hospitalization rates before versus after PI: 6.2 vs 6.7 events per 1,000 PY
Currier et al.[7]	California Medicaid	28,513	1994–2000	Increased relative risk of CHD in men < 35 years and women < 45 years	Increased relative risk of CHD in those on HAART vs no HAART: 2.06, p < 0.001 (covariate adjusted)
Vittecoq et al.[8]	French cohorts			Incidence rate MI: 5–5.5 vs 1.52 events per 1,000 PY	
Bozette et al.[9]	VA hospital system	36,766	1993–2001	No significant increase in CHD admissions or mortality compared with US population	No difference between PI vs no PI
Triant et al.[10]	Health care-based cohort	3,851	1996–2004	Increased incidence rate of MI: 11.13 vs 6.98 events per 1,000 PY, p < 0.0001, adjusted relative risk 1.75, 95% CI 1.51–2.02, p < 0.0001	No PI comparison
Rickerts et al.[11]	Frankfurt HIV cohort	4,993	1983–1998	No controls	Incidence rate MI increased after introduction of HAART: 0.86 events per 1,000 PY 1983–1986 to 3.41 events in 1995–1998, p = 0.002
Coplan et al.[12]	Meta-analysis of phase II/III randomized studies on PIs	10,986	30 studies done before 1999	No controls	No significant difference in incidence rate of MI in PI vs NRTI in randomized trials: 1.82 vs 1.05 events per 1,000 PY, RR 1.69, 95% CI 0.54–7.48
Holmberg et al.[13]	HIV outpatient study (HOPS)	5,672	1993–2002	No controls	Nonsignificant increased risk of MI with PI vs no PI: adjusted hazard ratio 6.5, 95% CI 0.9–47.8
Barbaro et al.[14]	Italian cohort	1,551	1999–2002	No controls	Increased incidence rate of MI with PI vs no PI: 5.1 vs 0.8 events per 1,000 PY, p < 0.001
Mary-Krause et al.[15]	French hospital database	34,976	1992–1999	Increased standardized morbidity ratio for MI in PI ≥ 30 months compared with general French population: risk ratio 2.9, 95% CI 1.5–5.0 No significant difference in those on PI < 18 months: risk ratio 0.8, 95% CI 0.5–1.3	Incidence rate of MI increased with > 30 month PI exposure vs < 18 month exposure: 33.8 vs 10.8 events per 10,000 PY
Obel et al.[16]	Danish national hospital registry	3,953	1995–2004	Incidence rate for CHD hospitalization increased after HAART initiation c/w uninfected population: adjusted RR 1.39 (95% CI 0.81–2.33) vs 2.12 (95% CI 1.62–2.76)	No PI comparison
Iloeje et al.[17]	HIV insight (includes HOPS cohort)	7,542	1991–2002	No controls	Incidence rate of CHD increased in PI vs no PI: 9.8 vs 6.5 events per 1,000 PY, p = 0.0008 PI ≥ 60 days associated with greater events: adjusted HR 1.71, 95% CI 1.08–2.74, p = 0.03
Kaplan et al.[18]	Multicenter AIDS Cohort Study and Women's Interagency HIV Study	931 men and 1,455 women	1984–2003	No controls	Risk of CHD in moderate-high 10-year risk patients showed no difference in PI vs no PI: OR 0.74, 95% CI 0.53–1.01
Friis-Moller et al.[19]	DAD	23,468	1999–2005	No controls	Incidence rate of MI increased with > 6 years PI: 6.01 vs 1.53 events per 1,000 PY, after adjustment for lipids relative rate 1.10 (95% CI 1.04–1.18)

(Abbreviations: HAART: Highly active antiretroviral therapy; CHD: Coronary heart disease; PY: Person-years; MI: Myocardial infarction; PI: Protease inhibitor; VA: Veterans affairs; NRTI: Nucleoside transcriptase inhibitor; HR: Hazard ratio; CI: Confidence interval; DAD: Data collection on adverse effects of anti-HIV drugs; RR: Relative rate)

Although absolute rates remain low, these observational studies suggest a 1.5–2 fold increased risk of CHD in HIV-infected individuals when compared with uninfected controls.[25] The discrepancy in findings among observational studies is likely a result of differences in study design, short follow-up times, lack of noninfected control groups, and unclear duration and specifics of HAART.[26] In contrast to these initial studies, the SMART study included 5,472 HIV-infected patients who were randomized to a strategy of viral suppression (continuous HAART) versus drug conservation (intermittent HAART) and followed for an average of 16 months. Patients assigned to continuous HAART had a decreased risk of fatal or nonfatal CVD when compared with those on intermittent HAART (HR 1.6, 95% CI 1.0–2.5, p = 0.05).[27] Furthermore, the initiation of HAART in the treatment of naïve patients results in dramatic improvement in endothelial dysfunction,[28] suggesting that in the short-term, treatment of HIV infection may actually decrease cardiovascular risk. These studies suggest that, although long-term treatment with HAART, especially PIs, may lead to detrimental cardiovascular effects, there may be beneficial effects of HAART in the short term, providing additional evidence that HIV itself is mechanistically associated with increased CHD risk.

CLINICAL CHARACTERISTICS OF CHD IN HIV-INFECTED INDIVIDUALS

Clinical presentations of CHD in HIV infection are unique compared to individuals without HIV. Compared to uninfected controls, HIV patients, who develop acute coronary syndrome, are more than a decade younger, with a mean age of 50 years. They are also more likely to be male, to be current smokers and to have low high density lipoprotein (HDL) cholesterol. As expected, HIV patients tend to have low thrombolysis in myocardial infarction (TIMI) risk scores, and tend to have single, rather than multiple-vessel coronary artery disease.[29] In general, HIV patients hospitalized with acute coronary syndrome have excellent immediate outcomes,[30-33] with successful percutaneous coronary intervention procedures.[32] However, when compared with noninfected controls, HIV patients tend to develop higher rates of future stent-related complications. Prior studies comparing outcomes of percutaneous coronary interventions in HIV patients with noninfected controls have demonstrated a higher incidence of restenosis before the era of drug eluting stents (52% vs 14%, p = 0.006),[29] and stent-related complications requiring target vessel revascularization (43% vs 11%, p = 0.02).[30] Among individuals with HIV, patients who received a drug eluting stent had lower rates of major adverse cardiovascular events compared to those with bare metal stents suggesting that treatment with drug eluting may be warranted among this patient population.[34] There are no large surgical series of HIV patients who have undergone coronary artery bypass grafting; however, one study in 37 patients after cardiac surgery, of whom 29 had undergone bypass grafting, demonstrated 81% event-free survival at 3 years.[35] In a study performed at Kaiser, 19 HIV patients undergoing cardiothoracic surgery had fewer complications compared to uninfected controls (5.3% vs 26.3%, p = 0.07).[36]

PATHOGENESIS OF CORONARY HEART DISEASE IN HIV INFECTION

Compared to the general population, atherosclerosis in HIV patients may represent a pathologically distinct entity, although autopsy studies have had mixed results. One autopsy study demonstrated and accelerated atherosclerosis in young HIV-1-infected patients, with intermediate features between lesions in common CHD and transplant vasculopathy.[37] In another study, HIV-associated atherosclerosis was characterized by diffuse and circumferential vessel involvement with unusual proliferation of smooth muscle cells mixed with abundant elastic fibers, forming endoluminal protrusions.[31] In addition, unusual patterns of calcification have been reported in the coronary arteries of HIV-infected individuals.[38,39] Advanced coronary disease has been demonstrated, with HIV patients having a three times greater odds of having a significant stenosis in the coronary arteries, even after adjustment for age and gender.[39]

Chronic inflammation and T cell activation are thought to play a central role in the development of atherosclerosis.[40] The underlying mechanism of early atherosclerosis in HIV disease is not well understood, but may be due to direct viral effects, the use of HAART and associated metabolic changes or host immune responses. Specifically, the HIV envelope protein gp-120 has been linked to higher endothelin-1 levels.[41] Clinical observations also support the potential role of HIV disease in the pathogenesis of early atherosclerosis, as both CD4+ count and viral load appear to influence cardiovascular risk. The CD4+ count nadir predicts subclinical carotid atherosclerosis,[42] and a low CD4+ count on HAART has been associated with increased risk of CVD.[43-45] A recent study showed that low CD4+ count was independently associated with increased prevalence of carotid plaques,[45] while another study has correlated CD4+ nadir less than or equal to 350 cells/mm^3 with arterial stiffness, suggesting that earlier initiation of antiretroviral therapy may be beneficial.[46] Prior studies have also shown that higher viral loads correlate with endothelial dysfunction as measured by brachial artery flow-mediated vasodilation (FMD).[47,48] From a mechanistic standpoint, endothelial cells appear to play a central role in the pathogenesis of HIV-associated atherosclerosis, as do procoagulant changes, fibrinolytic effects, and increased activation of platelets.[31] Elevations in levels of endothelial cell derived markers, such as von Willebrand factor antigen, have been reported in HIV disease, particularly in patients with a high viral burden or advanced disease.[49] Circulating levels of the adhesion molecules—intercellular adhesion molecule-1 (ICAM-1) and vascular adhesion molecule-1 (VCAM-1)—have also been shown to be elevated in HIV patients compared with noninfected controls, and were directly related to the degree of inflammation as assessed by soluble receptor type 2 for TNF-alpha (sTNFR2).[50] Increased rates of inflammation as assessed by CMV-specific T cell responses were associated with higher carotid IMT.[51] More recently, the SMART study found that untreated HIV infection was associated with high levels of interleukin-6 (IL-6) and D-dimer, and that these biomarkers were strongly associated with all cause mortality and to a lesser extent CVD.[52] HIV-infected individuals also have higher high-sensitivity C-reactive protein (hsCRP) levels and T cell activation compared with uninfected individuals.[51]

Lastly, chronic activation of the immune system in HIV infection may also be due to microbial translocation in the gastrointestinal tract, leading to elevated levels of circulating microbial products, such as lipopolysaccharide, which may activate immune and inflammatory pathways.[53] It is known that residual microbial translocation during suppressive HAART is associated with the degree of immune reconstitution, as reflected by CD4+ T cell count recovery,[54] although whether chronic microbial translocation increases cardiovascular risk directly remains unknown.

HIV and Cardiovascular Risk Factors

HIV infection and antiretroviral therapy are also associated with a variety of traditional risk factors including dyslipidemia, metabolic syndrome, hypertension and cigarette smoking. An increased prevalence of traditional risk factors among HIV-infected men without known CHD has been reported, leading to higher calculated 10-year Framingham risk scores when compared with noninfected controls (17% vs 11% 10-year risk of ≥ 25%).[18]

Lipid abnormalities: In the early stages of HIV infection before treatment, the predominant changes appear to be hypertriglyceridemia, low HDL and low LDL levels with predominant small, dense LDL particles when compared with controls.[55,56] In contrast, after initiation of HAART, LDL and total cholesterol levels appear to increase, while HDL cholesterol appears to remain low, findings that are particularly associated with the use of PIs.[57] In the Swiss HIV Cohort study, hypercholesterolemia and hypertriglyceridemia were 1.7–2.3 times more common among patients on HAART containing PIs when compared with those without PIs.[58] Thus, the overall effect of HIV infection is an atherogenic lipid profile with significant reduction in HDL, and increase in triglycerides, oxidized LDL and small dense LDL.[25] The prevalence of hyperlipidemia in HIV patients is between 28% and 80% in different studies, with the majority of cases being hypertriglyceridemia (40–80%).[59]

Specific effects of HAART are important to consider. In general, most forms of HAART may increase LDL levels. With regard to hypertriglyceridemia, the PI ritonavir has been associated with the most significant increases in triglycerides, in some cases causing extreme hypertriglyceridemia exceeding 1,000 mg/dL, although full doses of ritonavir are rarely used today.[60] Increased triglyceride levels are also seen with the use of ritonavir-saquinavir or ritonavir-lopinavir combinations. The PI with perhaps the least effect on triglyceride levels is the relatively newly developed PI atazanavir.[61] At this time, the newer classes of antiretroviral medications, including integrase inhibitors and CCR5 inhibitors do not appear to be associated with significant changes in lipid profile.

Lipodystrophy and metabolic syndrome: The HIV-associated lipodystrophy is a syndrome characterized by fat accumulation in the neck and dorsocervical region along with subcutaneous and peripheral fat loss, with relative preservation or increase in visceral fat, resulting in relative central adiposity.[56] After starting HAART, these abnormalities are clinically evident in 20–35% of patients. The use of PIs as well as the concomitant use of the two NRTIs, stavudine and didanosine are strongly associated with the development of lipoatrophy.[56] Of note, a recent study showed that the use of the newer PI atazanavir for 48 weeks was not associated with abnormal fat redistribution or metabolic disturbances commonly seen in HIV-associated lipodystrophy.[62]

Lipodystrophy in HIV patients is commonly associated with different features of metabolic syndrome, including insulin resistance, impaired fasting glucose tolerance, elevated triglycerides, low HDL cholesterol and hypertension.[63] Metabolic syndrome appears to be highly prevalent among HIV patients; in a recent cross-sectional study of 710 HIV patients, 17% had metabolic syndrome, a finding which was independently associated with the use of stavudine and lopinavir/ritonavir.[64] Progression to metabolic syndrome is substantial in the first 3 years after initiation of HAART, and incident metabolic syndrome was associated with increased risk of CHD in a study of 88 HAART-naïve patients who started on treatment (HR 2.73, 95% CI 1.07–6.96, p = 0.036).[65]

Other risk factors: Other traditional cardiovascular risk factors are prevalent in the HIV-infected population. Smoking is common among HIV patients, and in a French cohort comparing HIV patients aged 35–44 years on HAART to a population-based cohort, the estimated attributable risks due to smoking were 65% for men, and 25% for women respectively.[66] Similarly, the DAD study investigators found that smoking was the most powerful predictor of CHD in patients with HIV aside from an existing history of CHD.[19] Although smoking cessation strategies are important, the efficacy and potential drug-drug interactions of pharmacotherapies for smoking cessation have not been evaluated in HIV-infected individuals.[25] The prevalence of diabetes mellitus and hypertension also appear quite elevated when compared with the general population.[18,67]

TREATMENT

Studies focusing on treatment of CHD among individuals with HIV are limited; as a result, the treatment of CHD in HIV-infected individuals should largely be guided by existing recommendations in uninfected patients. However, two aspects particular to HIV-infected patients deserve: (1) the potential role of HAART with regard to CVD and (2) the treatment of hyperlipidemia in HIV disease, for which separate recommendations have been devised.

Highly-active Antiretroviral Therapy

Among individuals with CD4+ counts greater than 200 cells/μl, the risk of non-AIDS-related mortality may exceed the risk of AIDS-related mortality.[68] Of particular concern are increased rates of coronary events and mortality compared with noninfected controls.[13,20,42] While long-term HAART may have adverse effects, it is becoming clearer that uncontrolled HIV replication leads not only to increased cardiovascular risk, but also to other non-AIDS complications, as was shown in the SMART study.[44,68,69] Current recommendations by the International AIDS Society USA Panel guidelines, thus, support HAART initiation for asymptomatic individuals at CD4+ count less than 350 cells/μl, with 'individualized' therapy at CD4+ count greater than or equal to 350 cells/μl.[70] Whether earlier initiation of HAART at higher CD4+ counts in the course of HIV disease improves cardiovascular risk is not known; however, guidelines do support earlier initiation of HAART in

the setting of high cardiovascular risk, in addition to other high risk clinical features (high viral loads > 100,000 copies/ml, rapidly declining CD4+ count > 100/µl per year, active hepatitis B or C infections or the presence of HIV-associated nephropathy).[70]

The initial choice of HAART regimen is primarily targeted at viral suppression; however, metabolic profiles of drugs should be considered in patients at high cardiovascular risk. While traditional HAART may be constrained by HIV resistance and medication tolerability, novel antiretroviral agents, such as integrase inhibitors and viral entry inhibitors, may in the future provide better options with regard to cardiovascular side effect profiles.[71]

Hyperlipidemia

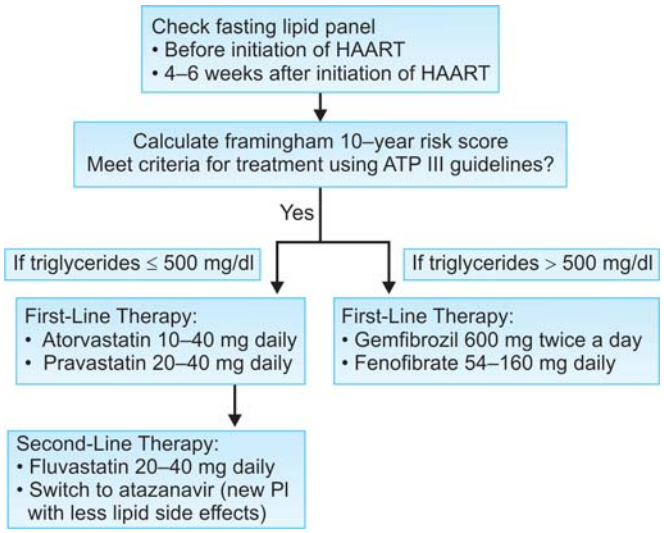
The Infectious Disease Society of America (IDSA) and Adult AIDS Clinical Trials Group (AACTG) have developed specific guidelines for the evaluation and management of HAART-related hyperlipidemia.[72] These recommendations are largely based on National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) guidelines, and advocate adjusting individual cholesterol targets to the underlying cardiovascular risk based on the Framingham predicted 10-year risk.[73] A general algorithm of treatment of hyperlipidemia has been summarized in Flow chart 1.

Specific drug-drug interactions are important to consider when initiating lipid-lowering therapy in this patient population. Both PIs and NNRTIs can affect cytochrome P450 isoforms. In general, all PIs inhibit CYP3A4, with the highest level of inhibition with ritonavir, followed by indinavir, nelfinavir, amprenavir and saquinavir. Delavirdine, an NNRTI, is also an inhibitor of CYP3A4, whereas nevirapine and efavirenz result in induction of the enzyme. Both simvastatin and lovastatin levels increase dramatically in the setting of PI use and have led to rhabdomyolysis[74] and thus, are contraindicated in this setting. As atorvastatin levels appear to be increased to a lesser degree, atorvastatin may be used at lower doses in HIV patients. Since pravastatin is not metabolized by CYP3A4, it is a first-line agent for LDL lowering in HIV patients. Similarly, fluvastatin is metabolized by CYP2C9, and can be used as a second-line agent.[72] Rosuvastatin has minimal P450 metabolism, although levels appear to be increased when used in combination with atazanavir/ritonavir and lopinavir/ritonavir, so limiting doses to 10 mg in that setting is advised.[75,76]

Current recommendations for the treatment of hyperlipidemia in HIV patients include lifestyle modifications, and dietary and exercise interventions which have been shown to decrease total cholesterol levels by 11–25% in the HIV population. When lipid-lowering therapy is indicated, pravastatin or atorvastatin are first-line therapies for the treatment of elevated LDL cholesterol in patients taking any PI or delavirdine (Flow chart 1). The recommended starting doses are pravastatin 20–40 mg daily and atorvastatin 10 mg daily. Fluvastatin 20–40 mg daily may be considered an alternative second-line agent. The treatment of hypertriglyceridemia is mainly achieved with fibrates (gemfibrozil 600 mg twice a day or micronized fenofibrate 54–160 mg daily) for triglyceride levels exceeding 500 mg/dL. Niacin can cause insulin resistance, and is therefore, not recommended as first-line therapy with concurrent PI use or the presence of lipodystrophy. In general, bile-sequestering resins are not recommended for use in HIV patients.[72] Ezetemibe appears safe and effective when added to maximally tolerated doses of lipid lowering therapy[77] and has modest lipid lowering activity when used alone in HIV patients.[78]

What remains unknown is whether HIV should be considered as a separate cardiovascular risk factor, potentially lowering LDL thresholds for starting therapy. Furthermore, given potential anti-inflammatory and other pleiotropic actions, it is unclear whether statins will have additional benefits beyond lipid-lowering in this patient population.

FLOW CHART 1: Treatment of hyperlipidemia in HIV-infected individuals



Modification of Other Risk Factors

Clearly, traditional cardiovascular risk factors are enriched in the HIV population, such that modification of underlying risk factors is essential to the clinical care of HIV patients. Smoking cessation, lifestyle changes in diet and exercise, and the appropriate treatment of hypertension and diabetes mellitus are all measures which should be pursued aggressively in this population.

Screening: None of the multivariate models of calculating probability of CHD used in the general population have been validated in the HIV-infected population. The most widely used screening tool is the Framingham risk score, which appears to underestimate CHD risk in HIV patients who are smokers.[79] HIV-specific risk prediction models of CHD have been proposed, and one such tool from the DAD study group incorporated PI exposure with traditional risk factors and appeared to be reasonably accurate in preliminary studies.[79] The IDSA/HIV Medicine Association (HIVMA) recommendations include checking fasting lipid panels before and within 4–6 weeks after starting HAART, fasting glucose levels before and during HAART, and routine measurements of body weight and changes in body shape.[80]

The sensitivity and specificity of exercise or pharmacologic stress testing are not established in HIV disease, and utilization currently follows guidelines for the general population. Similarly, the role of surrogate markers of CHD such as carotid IMT, inflammatory biomarkers, such as hsCRP, adiponectin and

apolipoprotein B100, are also unclear in HIV disease, and further work is needed to clarify their role in the early detection of CHD in HIV patients.[81] A study evaluating HIV-infected individuals presenting with acute MI found that both elevated CRP and HIV were independently associated with increased risk of MI, so CRP may be useful to predict CHD in this patient population.[82]

SURROGATE MEASURES OF ATHEROSCLEROSIS

CAROTID ARTERY INTIMA-MEDIA THICKNESS

In HIV-uninfected patients, carotid artery intima-media thickness (IMT) as assessed with B-mode ultrasound has been strongly correlated with coronary atherosclerosis, and is directly associated with increased risk of MI and stroke in older patients without known CVD.[83,84] There have been numerous studies using carotid IMT to assess the presence of subclinical atherosclerosis in HIV patients, of which the largest studies have been summarized in Table 2.

In general, the impact of HIV and HAART on subclinical atherosclerosis is still incompletely understood; however, most studies appear to demonstrate premature atherosclerosis in the HIV-infected population. The effect of HAART and PI use in particular on cardiovascular risk is no clearer in carotid IMT studies as it was in observational studies, and studies demonstrating a correlation between carotid IMT and clinical outcomes are lacking in the HIV-infected population. One of the current limitations of carotid IMT measurement is the lack of uniform methodology. Whereas, some studies examine the common carotid,[88] others measure IMT at the carotid bifurcation region.[51,92] Others still report the presence of carotid plaque within the imaged segment distinct from the underlying IMT measurement at a specified location.[45]

BRACHIAL ARTERY FLOW-MEDIATED DILATION

Endothelial dysfunction is thought to play a central role in the development and progression of atherosclerosis and in non-HIV-infected patients has been shown to predict future cardiovascular events.[96,97] The hallmark of endothelial dysfunction is impaired endothelium-dependent vasodilation, which can be non-invasively assessed using brachial artery FMD.[98] Whereas, carotid IMT is thought to reflect long-term exposure to atherogenic factors, brachial artery FMD is a measure of current vascular function and short-term exposures.

Prior work has demonstrated that HIV-infected patients have impaired endothelial function as assessed by FMD when compared with noninfected controls.[48] The mechanism of endothelial dysfunction in HIV disease is unclear. Endothelial dysfunction has been described in the setting of a higher viral load,[47,48] while improved endothelial function in HAART-treated compared with untreated individuals has also been reported.[99,100]

The relative contribution of HAART to endothelial dysfunction in HIV-infected individuals is complex. Data from numerous studies examining endothelial function and the use of HAART, in particular PI-based regimens are conflicting. Some studies suggest worse endothelial dysfunction with the use of PIs,[99-101] while others do not support this phenomenon.[48,102] The potential effect of PIs may be specific to certain HIV medications, as studies in noninfected controls demonstrated no change in brachial artery FMD taking lopinavir-ritonavir;[103] however, significantly decreased FMD after indinavir use has been described in other studies.[104,105] Adverse effects of PIs may be mediated via atherogenic lipid changes,[101] although zidovudine (AZT) and AZT + indinavir dramatically reduced endothelium-dependent vasodilatation in an animal model, without changes in cholesterol.[106] Initiation of HAART in treatment-naïve patients resulted in dramatic improvement in endothelial function both at 4 and 24 weeks of therapy, irrespective of whether a PI was used or not.[107]

CORONARY ARTERY CALCIUM SCORING

The quantification of coronary artery calcium (CAC) by electron beam computed tomography is a noninvasive marker of atherosclerosis that has been shown to predict coronary death and nonfatal MI in the noninfected population.[108] There are several studies examining CAC scores in HIV-infected individuals. One series demonstrated elevated CAC greater than 100 in 8.6% of men and 6.0% of women in a relatively young cohort; however, no direct comparison was made to HIV-uninfected controls.[89] A large series of 615 male participants and 332 seronegative controls, demonstrated that both HIV infection (OR 1.35; 95% CI 0.70–2.61) and long-term HAART (OR 1.33; 95% CI 0.87–2.05) were independently associated with presence of CAC.[109] Interestingly, a cross-sectional study of 400 HIV-infected patients showed that over 40% of individuals had evidence of increased vascular age as calculated on the basis of CAC scores published from the MESA study which was associated with current CD4+ T cell count.[110]

OTHER CARDIOVASCULAR CONDITIONS

HIV-ASSOCIATED PULMONARY ARTERIAL HYPERTENSION

While pulmonary arterial hypertension (PAH) is generally a rare condition among individuals without HIV infection, the prevalence of PAH in HIV-infected patients is several thousand times higher. Older studies had shown an incidence of 0.5%, which appears to have remained constant since the advent of the HAART era.[111,112] A more recent prospective study of HIV-infected individuals conducted in France showed a similar prevalence of 0.46%.[113] Our group has described the prevalence of asymptomatic elevations in pulmonary arterial systolic pressures (PASP) as assessed by echocardiography may in fact be much higher, with a PASP greater than 30 mm Hg in 35.2% of HIV patients, compared with 7.7% of noninfected controls.[114] This association between HIV and PAH is largely independent of secondary causes of PAH, with HIV being the sole risk factor for PAH in 82% of HIV-infected patients.[115] It has also been shown that HIV-infected patients with PAH have higher mortality rates and a more rapidly progressive disease course when compared with those without HIV, with a median survival rate of 6 months.[116]

The pathogenesis of HIV-associated PAH has not been clearly defined. Certain HIV proteins have been shown to

TABLE 2

Carotid IMT in HIV patients—major studies

Authors	*Population*	*Patients*	*F/u*	*Results*
Hsue[51] 2006	SCOPE*	93 cases 36 controls	None	Carotid IMT was higher in HIV-infected versus uninfected patients (0.95 vs 0.68 mm, p < 0.001) CMV-specific T cell responses were independently associated with IMT
Hsue[42] 2004	SCOPE	143 cases 63 controls	1 year	Carotid IMT progression at 1 year was higher in HIV-infected vs uninfected patients (0.074 ± 0.13 mm vs 0.006 ± 0.05 mm, p = 0.002) Predictors of progression included age, Latino race and nadir CD4+ count ≤ 200
Kaplan[45] 2008	WIHS MACS	1931 cases 859 controls	None	Carotid IMT was not significantly different in HIV-infected versus uninfected patients after adjustment for metabolic risk factors (women: 0.722 vs 0.716 mm, p = 0.17, men: 0.750 vs 0.771 mm, p = 0.47). CD4+ count < 200 predicted increased prevalence of carotid lesions (prevalence ratio in women: 2.00, 95% CI 1.22–3.28, in men: 1.74, 95% CI 1.04–2.93)
Maggi[85] 2007	PREVALEAT	133 cases	2 years	PI use appeared associated with a more rapid onset of carotid lesions compared to patients treated with NNRTIs, with more rapid evolution of previous lesions
Maggi[86] 2000		102 cases 104 controls	None	Carotid plaque was higher than expected in patients receiving PI therapy, when compared with those without PI use and noninfected controls (52.7% vs 14.9% vs 6.7%)
Currier[87,88] 2005	ACTG study A5078	89 cases 45 controls	144 weeks	Carotid IMT was not significantly different in HIV-infected patients on PI therapy for ≥ 2 years compared with those without prior PI use or uninfected controls (0.690 vs 0.712 vs 0.698 mm). No difference in IMT progression in HIV patients and controls. Nadir CD4 count and ritonavir use associated with IMT progression in the HIV group
Mangili[89] 2006	Nutrition for healthy living study	327 cases	None	Carotid IMT did not differ by HAART regimen. For men age and waist circumference predicted common carotid IMT, for women age and body mass index were predictors
De Saint Martin[90] 2006	SHIVA	154 cases	None	Carotid IMT predictors included age, SBP and triglyceride level (< 0.001, < 0.001, and 0.02 respectively). Duration of PI, especially that of lopinavir was also correlated with carotid IMT after adjustment (p = 0.01)
Jerico[91] 2006	Barcelona	132 cases	None	Carotid IMT > 0.8 mm or presence of plaque was found in 41.7% of patients. Risk of carotid atherosclerosis was increased in patients on HAART compared to treatment-naïve patients (OR 10.5, 95% CI 2.8–39)
Lorenz[92] 2008	Frankfurt HIV cohort	292 cases 1168 controls	None	Carotid IMT was higher in HIV-infected compared to uninfected patients (absolute difference 0.044 mm, 95% CI 0.021–0.066 mm, p = 0.0001). Use of HAART had an independent effect on IMT
Depairon[93] 2001	Swiss HIV cohort study	168 cases 68 controls	None	HIV-infected patients had more carotid or femoral plaques when compared with uninfected patients (61 vs 46%, p = 0.03). Independent predictors of plaque included age, male gender, LDL cholesterol and smoking. PI use was not associated with the presence of plaque
Grunfeld[94] 2009	FRAM	433 cases 5749 controls	None	HIV infection was associated with more atherosclerosis as assessed by IMT. There was a stronger association of HIV infection with IMT in the internal/bulb region as compared to the common carotid
Hsue[95] 2009	SCOPE	494 cases 93 controls	None	Carotid IMT was strongly associated with the presence of HIV irrespective of antiretroviral therapy, detectable viremia or over immunodeficiency. Untreated and suppressed individuals (elite controllers) had higher IMT

(Abbreviations: *SCOPE: Study of the consequences of the protease era; WIHS: Women's interagency HIV study; MACS: Multicenter AIDS cohort study; PREVALEAT: Premature vascular lesions and antiretroviral therapy study; ACTG: AIDS clinical trials group; SHIVA: Study of HIV and atherosclerosis; FRAM: Fat redistribution and metabolic change in HIV infection; IMT: Intima-media thickness; CI: Confidence interval; PI: Protease inhibitor; NNRTI: Non-nucleoside reverse transcriptase inhibitor; SBP: Systolic blood pressure; HAART: Highly active antiretroviral therapy; OR: Odds ratio)

activate endothelial cells indirectly, such as the envelope glycoprotein-120, which has been linked to higher endothelin-1 levels.[41,117] Endothelin-1 in turn is a potent vasoconstrictor and may play a central role in the pathogenesis of PAH. Increased markers of inflammation such as vascular endothelial growth factor-A, platelet-derived growth factor and interleukin-1 and interleukin-6 have also been demonstrated in HIV-associated PAH.[118] In addition, autoimmunity may play a role,[119]

and a genetic predisposition has also been suggested.[120] Coinfection with human herpesvirus-8 on the other hand, did not appear to be associated with elevated PASP.[114]

The treatment of HIV-associated PAH including the role of HAART remains unclear. Few studies have examined the role of pulmonary vasodilators: one uncontrolled study showed improvement in clinical measures of heart failure and hemodynamics with bosentan, suggesting that endothelin may play a role in the pathogenesis.[121] Of note, the recommended dosage of bosentan among individuals on PI therapy is 62.5 mg everyday or every other day in contrast to the usual dosing of 125 mg twice daily. There have not been any studies describing the use of selective endothelin receptor antagonists (ambrisentan or sitaxsentan) in the setting of HIV. No controlled trials of sildenafil in HIV-associated PAH have been reported at this time. As sildenafil is metabolized by the 3A4 isoform of the cytochrome P450 system, interactions have been described involving sildenafil and saquinavir and ritonavir[122] as well as indinavir.[123] Due to these drug-drug interactions, the dose of sildenafil in HIV-infected individuals who are concurrently on PIs should be carefully monitored. The role of prostacyclin analogs in HIV-associated PAH is limited to several small prospective studies demonstrating hemodynamic improvement.[124] Finally, with respect to the issue of HAART and HIV-associated PAH, a retrospective analysis of 77 consecutive patients with HIV-associated PAH showed that HAART was not associated with improvement in hemodynamic parameters; prognosis was related to CD4+ T cell count and cardiac index.[125]

HIV-RELATED LEFT VENTRICULAR DYSFUNCTION AND MYOCARDITIS

The incidence of HIV-related dilated cardiomyopathy before HAART was 15.9 per 1,000 person-years, and has decreased significantly after introduction of HAART.[126] The etiology of HIV-related cardiomyopathy is likely multifactorial, and may be due to direct infection of myocardial cells by HIV-1 virions, immune activation or coinfection with other viruses such as coxsackievirus B3 and cytomegalovirus, as well as nutritional deficiencies, autoimmune factors (increased anti-alpha myosin antibodies), and HAART toxicity (AZT).[127] One myocardial biopsy series prior to the HAART era demonstrated that pathology is consistent with myocarditis in more than half of patients.[128]

The treatment of HIV-related cardiomyopathy is unclear, and usual treatment for heart failure with afterload reduction appears reasonable. What remains unknown is the role of inflammation and immune response in the disease. One study in children with HIV and left ventricular (LV) dilation showed improvement in LV contractility in those with higher endogenous IgG levels or after treatment with intravenous immunoglobulin, suggesting that myocardial impairment may be immunologically mediated.[129] The prognosis of HIV-related cardiomyopathy appears to be worse than other nonischemic cardiomyopathies, and one study in children with vertical HIV transmission demonstrated that even mild LV dysfunction was associated with increased overall mortality.[130] Studies of contemporary HIV-infected adults show that in contrast to older studies, the prevalence of pericardial effusion and reduced LV systolic function are rare; in contrast, diastolic dysfunction is a common finding.[131] Further data will emerge from the ongoing HIV-Heart study, which is examining the prevalence and natural history of myocardial dysfunction in HIV-infected adults.[132]

CEREBROVASCULAR DISEASE

Although up to 40% of AIDS patients appeared to have neurologic complications, most of these were related to encephalopathy or infectious causes, although both ischemic stroke and intracranial hemorrhage have been described in HIV patients.[133] In one cohort, the prevalence of cerebrovascular disease was 1.9% (transient ischemic attack 0.8%, stroke 1.2%), with an annual incidence rate of 216/100,000. The prevalence appeared to be higher in later stages of infection and poorer immunologic state, although HAART did not change the risk of cerebrovascular events in two studies.[9,134] In contrast, DAD study results showed an incidence rate of 5.7 events per 1,000 person-years for the combined endpoint of cardiovascular and cerebrovascular disease events, with an increased risk with longer HAART exposure (relative risk per year of exposure 1.26, 95% CI 1.14–1.38, $p < 0001$).[135]

MISCELLANEOUS

Pericardial effusion is the most common cardiac manifestation of HIV infection with a prevalence up to 20%.[136] Although most patients are asymptomatic and effusions are generally small,[137] the presence of a pericardial effusion appears to be an independent predictor of mortality and poor prognosis.[138] The risk of bacterial endocarditis in HIV-infected patients is similar to cohorts with similar risk behaviors, and the diagnosis and management is the same as in uninfected patients.[139] Cardiac malignancies are quite rare in HIV patients, and include Kaposi's sarcoma and malignant lymphoma.[127] HIV patients also have been noted to have prolonged QTc intervals, a finding which may be associated with myocarditis, cardiomyopathy and autonomic neuropathy.[127]

CONCLUSION

As the HIV-infected population continues to live longer, they will face a new set of health challenges that are distinct from prior HIV-related issues, namely consequences of other chronic diseases, including atherosclerosis. HIV infection and HAART may accelerate typical problems associated with aging, particularly CVD via chronic persistent inflammation. Since CVD is so prevalent in older Americans, any process that accelerates this process further will likely lead to significant clinical and public health problems. Cardiologists should be aware of HIV-related cardiovascular complications and treatment so they can diagnose and treat these individuals appropriately.

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Chapter 95

Systemic Autoimmune Diseases and the Heart

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Chapter Outline

- Rheumatoid Arthritis
  - — Clinical Features
- Spondyloarthropathies
  - — Ankylosing Spondylitis
  - — Reactive Arthritis
  - — Scleroderma
- Polymyositis-Dermatomyositis
  - — Clinical Features
  - — Treatment
- Mixed Connective Tissue Disease
- Systemic Lupus Erythematosus
  - — Clinical Features
- Antiphospholipid Antibody Syndrome
- Coronary Arteritis
- Polyarteritis Nodosa
- Kawasaki Disease
- Churg-Strauss Vasculitis
- Wegener's Granulomatosis
- Giant Cell Arteritis
- Takayasu's Arteritis

RHEUMATOID ARTHRITIS

A discussion of the cardiovascular manifestations of connective tissue disease, appropriately begins with rheumatoid arthritis. In many respects, rheumatoid arthritis is the prototypical systemic autoimmune disease. Patients with rheumatoid arthritis have an increased mortality when compared with the general population, due in part to cardiovascular diseases.[1] The spectrum of cardiovascular involvement in rheumatoid arthritis is protean, and it may involve nearly all cardiovascular tissues, including the pericardium, myocardium, coronary arteries, conducting system, endocardium and valves, in addition to the aorta and peripheral vessels.

A comparison of findings at autopsy in 62 patients with peripheral rheumatoid arthritis and twice as many patients from the general necropsy population matched for age and gender found an 82% incidence of heart disease in the rheumatoid population, as opposed to 66% in the control group.[2] Clinical heart disease had been recorded in two-thirds of the rheumatoid population, nearly twice the prevailing rate in most clinical series. Indeed, over half of the rheumatoid patients displayed cardiac lesions at autopsy that could not be correlated with other illness or therapy, as compared with a small fraction of the control group, and the postmortem incidence of such lesions exceeded the reported incidence of attributable clinical manifestations. In 27% of patients with rheumatoid arthritis who had clinical cardiac disease, the only cardiac lesions evident at autopsy were those related to rheumatoid disease. In 8 of the 62 cases (13%), the cause of death was rheumatoid heart disease.

The diversity of histologic and clinical features of cardiovascular involvement in rheumatoid arthritis is also related to the manner, in which humoral and cellular immunity participate in the pathophysiology of this disease. The most characteristic pathologic lesion of rheumatoid arthritis is the rheumatoid nodule, a nodular granuloma that occurs in cardiovascular tissue and is usually associated with sub-rheumatoid nodules. Such nodules rarely compromise cardiac function and, indeed, were present in only 2 of the 62 autopsied cases[2] mentioned earlier. More commonly, changes in connective tissue consist of round cell infiltration, edema and fibrosis, which have a particular predilection for the pericardium, where the disease may be even more extensive than in synovial tissues. The progression of interstitial disease to secondary amyloid deposition is uncommon except in advanced cases, in which abnormalities of cardiac diastolic function may result in restrictive physiology difficult to distinguish from pericardial constriction. Coronary arteritis may be diffused or involved small vessels by intimal proliferation; neither commonly produces clinically significant myocardial ischemia.

CLINICAL FEATURES

Pericardial Involvement

The pericardium becomes involved in rheumatoid arthritis more often than the myocardium, endocardium or vascular structures of the heart. In most patients with rheumatoid arthritis, however, pericarditis has little clinical impact and generally goes undetected. The clinical diagnosis of rheumatoid pericarditis is established in up to 2% of adults with rheumatoid arthritis; the rate rises to 6% in patients with systemic juvenile inflammatory arthritis (Still's disease) and 10% of hospitalized patients with rheumatoid arthritis.[3-5] A

pericardial friction rub or echocardiographic features of effusion have been reported in approximately 30–50% of patients with rheumatoid arthritis.[6-8] In patients with subcutaneous rheumatoid nodules, echocardiographic signs of pericardial involvement are found in 50%, matching the incidence in some necropsy series.[2,9,10]

Pathophysiologically, acute fibrinous rheumatoid pericarditis involves the inflammatory interplay of leukocytes and immune complexes. The pericardial fluid contains low levels of glucose and complement factor 3 and elevated levels of lactic dehydrogenase, immunoglobulin and cholesterol; rheumatoid factor is sometimes also detected. Histologically, there is plasma cell infiltration, immunoglobulin deposition and cytoplasmic inclusion of immune complexes, but rheumatoid granulomata (nodules) are unusual. More commonly, the inflammatory changes are nonspecific and include adhesions and scarring.

It is important to distinguish rheumatoid pericarditis from viral, tuberculous or drug-induced varieties. Pericarditis is usually clinically recognized in patients with well-established rheumatoid arthritis; however, rarely, pericarditis can be the first manifestation of rheumatoid arthritis.[11] More often symptoms of chest and shoulder pain in patients with rheumatoid arthritis are mistaken for articular discomfort or masked by analgesic or anti-inflammatory medications.

Compressive complications of rheumatoid pericarditis such as acute cardiac tamponade and chronic constrictive pericarditis occur in less than 1% of cases,[5] the latter more often. Both can be fatal, if not treated rigorously; the mortality rate associated with cardiac compression has been reported to be 17–23%.[5] Diagnosis of constrictive pericarditis can be challenging; in one series, 10 months elapsed between the onset of cardiac symptoms and the diagnosis of constrictive pericarditis.[12] Most patients have positive tests for rheumatoid factor, and extra-articular features are common.[5] Echocardiography, right heart catheterization, computed tomography and magnetic resonance imaging are the mainstays of diagnosis.[13] Neither tamponade nor constriction respond well to corticosteroid or cytotoxic medications and invasive approaches are usually required. Cardiac compression may take the form of effusive-constrictive pericarditis in which fluid becomes loculated by pericardial adhesions, making needle aspiration or catheter drainage incompletely effective. In such cases, pericardectomy may be called for. Despite the antithrombotic effects of salicylates and certain other nonsteroidal anti-inflammatory medications, acute hemorrhagic pericarditis producing tamponade by hemopericardium is quite rare.

Myocardial Involvement

Disease of the myocardium associated with rheumatoid arthritis is an unusual, but recognized cause of heart failure. Myocarditis typically occurs in either a granulomatous or nonspecific form.[14] The granulomatous form is considered specific for rheumatoid arthritis with nodules. The myocardial nodules have morphology similar to subcutaneous nodules, but a predilection for the left ventricle.[2] The nonspecific form is characterized by infiltration of lymphocytes, plasma cells and histiocytes.[2,14]These varied pathologic processes and the superimposed effects of drugs and infection lead to myocardial changes evident at autopsy in 19% of patients with severe rheumatoid arthritis.[2] Rheumatoid nodules in the myocardium have been reported in 1–3% of patients with rheumatoid arthritis.[2,15,16] Amyloid infiltration rarely develops in patients with longstanding rheumatoid disease, but when it occurs, there is frequent involvement of other organs such as the spleen, liver and kidneys. Isolated cardiac amyloidosis has been described, and endomyocardial biopsy of the interventricular septum may allow more accurate estimation of the incidence of amyloidosis in the living rheumatoid population.

Most echocardiographic studies have focused on pericardial and endocardial changes. Some have reported lower diastolic closure rates (reduced E to F slope) of the anterior mitral valve leaflet in some patients with rheumatoid arthritis and suggested that abnormal ventricular compliance was responsible.[10,17] Congestive symptoms were infrequent, however, and hemodynamic measurements have not been provided to corroborate the ultrasound findings. Patients with rheumatoid arthritis have a higher prevalence of heart failure compared with controls[18] often on the basis of diastolic dysfunction,[19,20] not readily explained by ischemia; and therefore, possibly related to myocardial inflammation, but this may be difficult to distinguish from pericardial restriction.[21]

In patients with rheumatoid arthritis and cardiomyopathy, evaluation is directed to excluding reversible factors such as volume overload, hypertension, pulmonary involvement, ischemia and rhythm disturbances. Management entails conventional modalities for treating heart failure.

Endocardial and Valvular Involvement

Like rheumatoid myocarditis, the histologic pattern of endocardial involvement in rheumatoid arthritis is nonspecific. There is infiltration of lymphocytes, histiocytes, plasma cells and occasionally eosinophils accompanied by collagen deposition, fibrosis and calcific sclerosis. Valvular involvement is characterized by formation of granulomas that morphologically resemble the rheumatoid nodules encountered in subcutaneous tissue and, less commonly, in the respiratory, intestinal, musculoskeletal, reticuloendothelial and hematopoietic systems. Valvular granulomas have been described at autopsy in approximately 3% of patients with rheumatoid arthritis, but in most of these cases, the size and location of the lesions were not associated with clinical valve dysfunction.[2,22]

The order of frequency of involvement of the cardiac valves (mitral the highest, then aortic, tricuspid and pulmonic) parallels that in rheumatic fever and it is difficult to distinguish valvular disease related to rheumatoid arthritis from rheumatic heart disease following streptococcal infection without histological examination of the involved tissue. In rheumatoid arthritis, nodular granulomas usually occur in the annular skeleton and basal attachments of the valvular leaflets.[23] When the leaflet matrix becomes involved, a thin margin of normal tissue usually remains at the surface in contact with the circulation, unlike the situation in rheumatic valvular disease in which the entire thickness of the leaflet is affected without preservation of a capsule of normal valvular tissue. Several patients have been described with involvement of all four cardiac valves; in these cases, valves on the left side of the heart were more extensively

involved than those on the right side.[24,25] Hemodynamically, left-sided rheumatoid involvement tends to cause more impairment of valvular function than lesions on the right side of the heart.

As in other forms of rheumatoid heart disease, clinical features occur less frequently than histologic abnormalities. Congestive symptoms are cardinal, but auscultatory clues may be misleading. Coexisting anemia or hypertension may distort cardiac murmurs, and auscultatory findings were commonly absent altogether in patients with granulomatous involvement of valvular tissue at necropsy. The hemodynamic consequences may reflect either valvular regurgitation or stenosis. It has been suggested that reduced mid-diastolic closing velocity of the anterior mitral leaflet on echocardiography might be due to subclinical valvular pathology rather than abnormal myocardial diastolic function, but this has not been verified.[10] Although rarely severe, rheumatoid arthritis is one of the few causes of mitral stenosis other than post-streptococcal rheumatic fever. It is actually more common to encounter patients with features of both rheumatic and rheumatoid valvular heart disease and in some cases, valvular surgery may be required.[26]

Disease of the Conducting System

The first report of complete heart block due to rheumatoid granulomatous involvement of the conduction pathways appeared in 1959;[27] since then additional cases have been described. Complete atrioventricular dissociation is still a rare complication of rheumatoid arthritis, with an incidence in patients hospitalized with the disease estimated at less than 0.1%.[28] Other than direct involvement of the conducting system with granulomas, pathologic processes producing cardiac conducting system disease include extension of the inflammatory process from the base of the aortic or mitral valve leaflets, amyloidosis or hemorrhage into a rheumatoid nodule.[29]

Although progression to complete heart block seldom occurs, lesser degrees of conduction delay are fairly common. The most frequent abnormality is first-degree atrioventricular block, which occurred eight times more frequently in a series of patients with rheumatoid arthritis than in a control population.[9] Left bundle branch block occurred four times more often in the rheumatoid population, but the opposite was true of right bundle branch block, which developed in 1–2% of the control group, but in none of the 254 patients with rheumatoid arthritis in that series. Villecco reported conflicting observations, finding right bundle branch block in 35% of patients with rheumatoid arthritis.[30] Management of patients with symptomatic bradycardia resulting from involvement of the conducting system generally entails permanent cardiac pacemaker implantation. Therapeutic agents used to treat patients with rheumatoid arthritis may be associated with complete heart block. In one case report, a patient with rheumatoid arthritis developed complete heart block after treatment with infliximab associated with increased pulmonary nodularity, but not peripheral nodulosis.[31] The authors postulated that cardiac rheumatoid nodularity may have been provoked, but histological confirmation was not provided.

Other than conduction system disorders, patients with rheumatoid arthritis occasionally display abnormalities of impulse generation in the form of sinoatrial block, wandering atrial pacemaker and atrial fibrillation. A significant correlation has been reported between the severity of inflammation in patients with rheumatoid arthritis, heart rate variability on ambulatory cardiac rhythm monitoring,[32] ventricular arrhythmias, myocardial infarction and sudden cardiac death.

Pre-excitation related to a paranodal accessory pathway of atrioventricular conduction has been described in rare patients with rheumatoid arthritis, although no causal relationship has been suggested and the association seems incidental. In one study, ventricular extrasystoles occurred in twice as many patients with rheumatoid arthritis as in a control population,[9] but there is no proven association between rheumatoid arthritis and malicious ventricular dysrhythmias or sudden cardiac fibrillatory death. Patients with rheumatoid arthritis may have an increased sympathetic activity, however, which may predispose to the tachyarrhythmias,[33] and QT dispersion has been proposed as a marker of cardiovascular morbidity and mortality due to complex ventricular arrhythmias.[34,35]

Coronary Artery Disease

Several autopsy studies found coronary atherosclerosis more frequently in patients with rheumatoid arthritis than in matched controls.[2,9] In the 254 cases described by Cathcart and Spodick, angina pectoris occurred four times more often in patients with rheumatoid arthritis than in the reference population.[9] In 19 separate studies published since 1941 and encompassing over 900 patients, the incidence of coronary atherosclerosis at autopsy approached 40%.[36] In 16% of these autopsied cases, there was also evidence of myocardial infarction. In all, about 25% of myocardial infarctions in patients with rheumatoid arthritis proved fatal. Traditional risk factors for cardiovascular disease only partly account for increased rates of atherosclerosis and worse outcomes in patients with rheumatoid arthritis.[37] Although coronary arteritis is found at autopsy in about 1–5 patients[15] and intimal inflammation may lead to severe luminal narrowing or arterial occlusion, myocardial necrosis resulting from this form of vascular involvement seems relatively rare.

A relationship between inflammation and accelerated atherosclerosis has been recognized,[38] and corticosteroid therapy has also been thought to accelerate the progression of the atherosclerotic process. Inflammatory markers, such as C-reactive protein, are associated with atherosclerotic risk,[39] but the mechanisms of this relationship are incompletely understood. Tumor necrosis factor (TNF)-alpha and interleukin (IL)-6 are associated with coronary atherosclerosis in patients with rheumatoid arthritis,[40] and therapy directed against TNF may decrease cardiovascular morbidity.[41,42] Inhibition of IL-6 is another potential avenue for decreasing atherosclerosis, but in a double blind trial in patients with rheumatoid arthritis the anti-IL-6 receptor antibody, tocilizumab, raised blood cholesterol levels.[43]

Myocardial revascularization surgery is commonly performed in patients with coronary disease and rheumatoid arthritis, and the clinical course of these patients is not appreciably different from the remainder of the coronary bypass population.

SPONDYLOARTHROPATHIES

This group of diseases is distinct from rheumatoid arthritis and characterized by enthesitis (inflammation at the attachment site of ligaments to bone), sacroiliitis, peripheral arthritis and dactylitis (fusiform swelling of a digit caused by inflammation in the joint space and along tendon sheaths). The prototype is ankylosing spondylitis, but this group of diseases includes reactive arthritis (formerly called Reiter's syndrome), psoriatic arthritis and enteropathic arthritis (associated with inflammatory bowel disease, celiac disease or Whipple's disease). There is a strong association of the spondyloarthropathies with the histocompatibility antigen, HLA-B27.

ANKYLOSING SPONDYLITIS

There are four principal cardiac sites of involvement in ankylosing spondylitis: (1) the region around the aortic root; (2) the conduction system; (3) the myocardium and, rarely, (4) the pericardium.[44] The histopathologic features of proximal aortic root and subaortic involvement were described by Bulkley and Roberts[45] and include focal destruction of the muscular and elastic structures of the media, intimal and adventitial thickening, and obliterative vascular disease. The thickening and foreshortening of the aortic valve cusps and displacement and dilation of the aortic valve annulus may result in severe aortic regurgitation. The subaortic bump (fibrosis of the base of the anterior mitral leaflet) is considered a specific finding in ankylosing spondylitis.[45] Patients with spondyloarthropathies may develop subaortic changes before aortic regurgitation develops, but over time, these lesions may either progress or (in 20% of cases in one study) resolve.[46,47]

Extension of the inflammatory process into the conduction system has been associated with atrioventricular and fascicular block. The importance of ankylosing spondylitis as a cause of severe conduction disturbances is evident in the fact that the prevalence of ankylosing spondylitis in men with permanent cardiac pacemakers is significantly greater than in the general population.[48-50]

Myocardial involvement affects diastolic function before systolic contraction.[51-53] Left atrial diameter, left ventricular cavity size and wall thickness are typically normal early in the course of the disease. The histopathologic findings are nonspecific, consisting most often of interstitial fibrosis with little evidence of inflammation or amyloidosis. The fibrotic process may obliterate the pericardial cavity, but clinical pericarditis is unusual in patients with ankylosing spondylitis.[48,49]

Cardiac manifestations may precede articular findings,[53] so the diagnosis of ankylosing spondylitis should be considered when a middle-aged man develops aortic regurgitation or advanced heart block. Fibrosis may occasionally involve the endocardium at the base of the anterior mitral leaflet and upper portion of the interventricular septum. Mitral regurgitation as an isolated valvular lesion is unusual in this disease but may develop as a consequence of left ventricular enlargement in patients with severe aortic regurgitation. The valvular lesions can be difficult to distinguish from those of syphilis, rheumatic fever and Marfan's syndrome. Rheumatic fever commonly affects the mitral valve and subaortic area, but typically spares the aorta. Syphilis has similar histopathology and echocardiographic appearance, but typically does not involve the subaortic area, the mitral valve or interventricular septum. In Marfan's syndrome, tissue thickening does not typically occur, and aortic regurgitation is almost invariably associated with dilation of the aortic root.[53]

REACTIVE ARTHRITIS

The classic presentation of reactive arthritis (formerly called Reiter's syndrome) involves conjunctivitis, urethritis and arthritis, although all three of these features typically are not present. Atrioventricular block and aortic valve incompetence are the most frequent cardiac manifestations, but other forms of conduction system disease have been described in reactive arthritis as well.[54-58] The histopathology is similar to that in ankylosing spondylitis.

SCLERODERMA

Scleroderma, or systemic sclerosis, is characterized by progressive fibrosis of the skin, although much of the morbidity of the disease results from visceral involvement and vasculopathy. The pathophysiology is incompletely understood, but involves microvascular damage with intimal proliferation and subcutaneous fibrosis with accumulation of type I collagen later in the course of the disease. This may result in Raynaud's phenomenon, cutaneous sclerosis, systemic and pulmonary hypertension, abnormal enteric motility and effects on other organ systems such as the kidneys. The spectrum of disease ranges from localized to generalized forms, and the prognosis depends on the extent of visceral involvement, particularly of the lungs, kidneys and heart. The major subcategories are a limited cutaneous form, in which sclerosis is limited to the hands, distal parts of the arms and legs and the face, and a more diffuse cutaneous form. In the limited form, pulmonary hypertension is uncommon and antinuclear antibody (ANA) may be detected in a centromere pattern. The diffuse form is associated with early visceral involvement and antibodies against topoisomerase-I DNA (Scl70) in about 30% of patients.[59,60]

The pathophysiology of systemic sclerosis is not well understood, but seems to begin with vascular injury and infiltration of mononuclear cells into perivascular tissues. Tissue factors, including endothelin and platelet-derived growth factor, induce smooth muscle cell differentiation into myofibroblasts, resulting in intimal proliferation and narrowing of the vascular lumen.[61] Vascular attenuation can be appreciated by nailbed capillaroscopy, which may demonstrate abnormal capillary loop architecture and decreased capillary density. The most frequent cardiovascular manifestation is cutaneous vasospasm, classically manifesting as episodic attacks of Raynaud's phenomenon characterized by well-demarcated triphasic color change of pallor, cyanosis and rubor.[62] It is important to note that the majority of individuals with Raynaud's phenomenon do not have a systemic rheumatologic disease and the vascular abnormality reflects a primary functional disturbance of vasomotor control manifested as vasospasm, rather than structural microvascular disease. In contrast, patients with secondary Raynaud's phenomenon due to systemic sclerosis typically display both functional

abnormalities, such as impaired endothelium-dependent vasodilation and structural abnormalities such as intimal thickening of the digital arterioles. The tyrosine kinase signal transduction pathway has been implicated as a mediator of cold-induced vasoconstriction. Responses to vasoconstrictors, including serotonin and angiotensin II, were increased in response to cooling in patients with primary Raynaud's phenomenon, and this effect was reversed with protein kinase inhibitors.[63]

Arteriographic studies of patients with scleroderma most commonly demonstrate occlusions in the digital arteries and ulnar artery.[64] The coronary circulation can be affected early in disease by transient, reversible, cold-induced constriction of distal coronary arteries and arterioles and impaired coronary flow reserve thought to be due to fixed, structural abnormalities of small vessels.[65] Intramyocardial blood flow is abnormal, both at rest and after exercise in the majority of patients with diffuse systemic sclerosis.[66]

The heart was first recognized as a common target organ in scleroderma by Weiss and associates in 1943.[67] While cardiac symptoms may develop as a consequence of renal or pulmonary disease related to scleroderma, primary cardiac involvement and its hallmark, myocardial fibrosis, is increasingly appreciated. Fibrosis is typically patchy and may result from chronic microvascular ischemia. The cardiomyopathy that sometimes develops in patients with scleroderma may be a consequence of both microvascular insufficiency and myocardial fibrosis leading to heart failure and conduction defects. In a study of 108 patients with scleroderma, 70% had myocardial fibrosis compared with 37% of controls, but there was no difference in the prevalence of contraction band necrosis on biopsy.[68] Myocardial fibrosis is not specific for scleroderma and occurs in other forms of myocarditis, muscular dystrophy, rheumatic heart disease and following cardiac surgery, radiation exposure or drug toxicity.

Although histological abnormalities are prevalent in autopsy studies, symptomatic cardiac involvement is less frequent and when present is generally associated with a poor prognosis. In a meta-analysis of international scleroderma cohorts, cardiac involvement occurred in 10% of patients and was associated with serious involvement of other organs.[69] In a 10-year follow-up study of 953 patients with diffuse scleroderma, 15% had cardiac involvement and 20% of deaths were attributed to cardiac causes.[70]

Clinical Features

Pericarditis: Pericardial disease is a frequent histological finding in patients with scleroderma, reported in 33–72% of cases at autopsy, although, usually clinically silent.[71,72] In a comparative postmortem study of 44 patients, chronic pericarditis was seen in 77.5% of patients with systemic sclerosis and in only one control.[73] Echocardiography detected pericardial effusions in 21–29% of patients with scleroderma who had no clinical signs or symptoms of cardiac disease.[74-76] In contrast, pericarditis becomes clinically apparent in only 5–15% of patients with scleroderma and is sometimes recurrent. Large effusions (> 200 ml) are associated with a poor prognosis.[77] In patients with scleroderma-related interstitial lung disease, the presence of pericardial abnormalities is strongly associated with pulmonary hypertension unless cardiac tamponade develops.[78] Management of pericardial disease in scleroderma typically involves administration of nonsteroidal anti-inflammatory medications, although these agents may adversely affect renal hemodynamics and function. Administration of corticosteroid medication has not been systematically evaluated and doses of prednisone greater that 15 mg daily have been associated with an increased risk of renal crisis.[79]

Myocardial disease: Myocardial disease in scleroderma may produce systolic or diastolic dysfunction, conduction abnormalities, exertional chest pain or sudden death. Exertional dyspnea may result from elevation of left ventricular filling pressure or pulmonary involvement, and pulmonary hypertension may lead to right ventricular failure. Heart failure related to cardiomyopathy may be either insidious or fulminant and cardiac disease appears prior to cutaneous manifestations in one-fourth to one-third of cases of progressive systemic sclerosis.[67] Myocarditis is a rare, but life threatening complication, usually associated with myositis. It typically occurs early in the course of the disease and requires prompt diagnosis and treatment with immunosuppressive medications.[80]

Echocardiography and MRI have shown a variety of abnormalities in patients with scleroderma other than the pericardial findings mentioned above. At least one abnormality was seen on cardiac MRI in 75% of patients with systemic sclerosis, including reduced left ventricular ejection fraction in 23% and diastolic dysfunction in 35%.[81] Left ventricular hypertrophy may occur in the absence of hypertension in a large proportion of patients, and pulmonary hypertension may occur in the absence of left heart failure. Using gated SPECT myocardial perfusion imaging, diastolic dysfunction was apparent in over half of a series of patients with scleroderma and was associated with more severe skin involvement.[82] The plasma level of N-terminal pro-brain natriuretic peptide reliably detected cardiac involvement (sensitivity 94%; specificity 78%) in one study of patients with scleroderma and may be validated in the future as a useful screening tool.[83]

Abnormal coronary perfusion: Myocardial perfusion imaging using thallium-201 scintigraphy has identified cold-provoked and exercise-induced defects in patients with systemic sclerosis suggesting abnormal coronary vasomotor regulation[84,85] and more extensive defects are associated with subsequent cardiac disease or death.[86] In a study of 26 patients with diffuse scleroderma, 6 had clinical cardiac involvement, while 20 had abnormal thallium perfusion images, including 10 with reversible exercise-induced defects and 18 with fixed abnormalities (8 had both).[66] In a smaller study, contrast-enhanced cardiac MRI in asymptomatic patients with systemic sclerosis identified perfusion defects in 5 of 9 patients and delayed enhancement in 3.[87]

Atherosclerotic disease does not appear more pronounced in patients with systemic sclerosis than in the general population. Coronary angiography in patients with scleroderma and exercise-induced perfusion defects may show no evidence of atherosclerotic obstruction, supporting a microvascular mechanism of ischemia.[66] Vascular narrowing, fibrosis, fibrinoid necrosis and concentric intimal hypertrophy have been described

more frequently in patients with systemic sclerosis than in controls, and these lesions are similar to those found in the kidneys and other organs.[84]

Management of patients with scleroderma-associated myocardial disease is guided by predominant clinical features. For those with heart failure, standard therapy with digoxin, diuretics and vasodilator agents is employed. Control of hypertension is essential, and angiotensin converting enzyme (ACE) inhibitors are often effective. ACE inhibitors are crucial components of treatment for scleroderma renal crisis, which usually manifests as acute renal failure, hypertension and an active urinary sediment. Unfortunately, these agents were not effective for prophylaxis against renal crisis in a randomized controlled trial.[88] Cutaneous vasospastic symptoms can be managed both through lifestyle modification (avoiding cold exposure and smoking, and application of moisturizing emollients affected skin to prevent dryness and cracking) and by administration of vasodilator drugs such as α-adrenergic antagonists, calcium-channel blockers, ACE inhibitors and angiotensin-II receptor antagonists.[89] Beta-adrenergic antagonists, especially those of the non-cardioselective variety, should generally be avoided due to the potential to exacerbate peripheral, if not coronary vasospasm.

Pulmonary hypertension: Pulmonary hypertension is the leading cause of mortality in patients with systemic sclerosis and when identified is associated with a poor prognosis. Compared to patients with idiopathic pulmonary hypertension, those with pulmonary hypertension associated with systemic sclerosis are four times more likely to die.[90] In a meta-analysis, pulmonary hypertension was present in 9% of patients with systemic sclerosis and associated with limited cutaneous involvement and duration of disease.[91,92] Pulmonary function testing and right heart catheterization are recommended in symptomatic patients to guide treatment, the approach to which is similar to that for idiopathic pulmonary hypertension by often less successful.[93]

Conduction disturbances: Patients with systemic sclerosis may develop cardiac conduction abnormalities as a consequence of ischemia or fibrosis, and some require electronic pacemaker therapy. Ventricular ectopic arrhythmias should be managed as they would be for patients with coronary atherosclerotic disease. The relationship between structural microvascular disease and functional disturbances of vascular control (manifested as vasospasm), the core uncertainty about the pathogenesis in scleroderma, but cardiovascular involvement is common at the subclinical level. Those patients who develop overt cardiac symptoms typically face a poor prognosis and require aggressive management.

POLYMYOSITIS-DERMATOMYOSITIS

Polymyositis and related disorders of skeletal muscle may occur as isolated diseases or in association with rheumatologic disorders such as systemic lupus erythematosus (SLE), scleroderma or mixed connective tissue disease (MCTD). These disorders usually manifest with muscle weakness and fatigue, particularly in the proximal muscles accompanied by histological evidence of skeletal muscle inflammation. In dermatomyositis, a characteristic skin rash involving erythema over the eyelids, chest, shoulders and/or extensor aspects of the fingers and extremities typically accompanies skeletal muscle involvement. Muscle biopsy is crucial in the diagnosis of both disorders. Characteristic findings in dermatomyositis are predominantly perifascicular vascular inflammation and CD4+ T cell, macrophage and occasional B cell infiltration. The presence of the C5b-9 membrane attack complex in the vessel walls of patients with dermatomyositis suggests that complement activation plays a role in pathogenesis.[94] In contrast, inflammation in polymyositis is predominantly endomysial and consists of a larger number of CD8+ T cells.

Polymyositis was first described by Wagner in 1886,[95] and cardiac involvement was reported by Oppenheim in 1899.[96] Despite its obvious muscular persuasion, the heart was classically regarded as infrequently involved in polymyositis. Although the reported prevalence varies, cardiac involvement is often subclinical, and when present may be a predictor of mortality.[97] In a clinicopathologic study of 19 autopsied patients with polymyositis, 13 had abnormal electrocardiograms during life and at autopsy 6 had myocarditis.[98] Another study of 32 patients demonstrated conduction abnormalities in over half and left ventricular diastolic dysfunction in 42%; only 2 patients had reported cardiac symptoms.[99] Cardiac lesions have been identified most frequently in the conducting system with lymphocytic infiltration and fibrosis of the sinoatrial node. Valvular and coronary structures are generally spared. Mononuclear inflammatory cells may infiltrate the myocardial tissue as they do in skeletal muscle, leading to degeneration of cardiac myocytes, clinical myocarditis and fibrosis.[100] While associated malignancy portends the worst outcomes, respiratory muscle and cardiac involvement also have prognostically unfavorable implications.

CLINICAL FEATURES

Females predominate in a ratio of 2:1 as victims of inflammatory myositis (polymyositis and dermatomyositis) and average about 50 years of age at the time of diagnosis. Cardiovascular symptoms have been reported in 10–15% of cases and include palpitations, chest pain, dyspnea and edema.[101] Serum levels of creatine kinase (CK-MB) may be elevated due to either myocardial damage or skeletal muscle regeneration. Inflammatory myositis without cardiac involvement may be associated with a higher of CK-MB to total CK. Nearly half the patients in one study with inflammatory myositis had ratios exceeding 3% without evidence of myocardial damage. Serum troponin-I has the highest specificity for myocardial tissue and is a more reliable marker of myocardial damage in patients with polymyositis or dermatomyositis.[102] Atrioventricular and fascicular conduction block have been reported repeatedly in polymyositis and seems to correlate with the severity of skeletal muscular and myocardial involvement.[101,103] Pericarditis, although relatively rare, may take the form of intermittent acute illness or subside incompletely leaving persistent symptoms and signs of serosal irritation.

TREATMENT

Corticosteroid drugs are the accepted initial treatment for patients with polymyositis or dermatomyositis, typically augmented by immunosuppressive medication therapy. In one study, all patients with myositis-related myocarditis showed

improvement by cardiac MRI after treatment with intravenous methylprednisolone followed by prednisone and immunosuppressive medication.[104] Nonsteroidal anti-inflammatory medication may be useful for the treatment of pericarditis.[105]

MIXED CONNECTIVE TISSUE DISEASE

Given the overlap of clinical features in the polymyositis-dermatomyositis complex with other connective tissue diseases, particularly SLE and progressive systemic sclerosis, MCTD was not recognized as a discrete clinical entity until 1972.[106] In patients with MCTD, clinical manifestations typical of lupus erythematosus, systemic sclerosis and polymyositis-dermatomyositis overlap. This disease is uniquely associated with high titers of antibodies to nuclear ribonucleoprotein (anti-U1-RNP) and cardiovascular involvement is both frequent and varied. Given the spectrum of disease, clinical diversity is expected, but cardiac manifestations predominantly involve pericarditis with or without effusion, mitral valve prolapse, intimal hyperplasia of coronary arteries and pulmonary hypertension. Acute pericarditis and pericardial effusion are the most common cardiac abnormalities, identified in 25–29% of 55 patients with MCTD in two reviews.[107,108] Other manifestations include Raynaud's phenomenon, pulmonary hypertension and myocarditis. Mitral valve prolapse was detected in 26% of cases, compared to 10% of an age- and sex-matched control population. Marked intimal hyperplasia of the coronary arteries was found in all four of the hearts examined at autopsy in one study.[108] Common symptoms included dyspnea in 55% of patients, which had been attributed to mainly restrictive pulmonary pathology, and chest pain in 39% ascribed to mitral prolapse, pericarditis, angina pectoris or musculoskeletal factors. In a series of 113 patients with MCTD, 20% had conduction abnormalities, but this was not associated with clinical outcome.[109] Other common findings were right ventricular hypertrophy and right atrial enlargement, left ventricular diastolic dysfunction; those with pulmonary arterial hypertension had right ventricular diastolic dysfunction as well.[110]

Pulmonary hypertension may develop years after diagnosis and is closely associated with mortality. In a long-term study of 47 patients of MCTD, the prevalence of pulmonary hypertension was 23%.[111] Pulmonary hypertension is less common at earlier stages of the disease; in the first three years after diagnosis, the prevalence of pulmonary hypertension was 9%, but increased to 23% after 15 years in one study[112] and the incidence was 68% between 6 years and 10 years following diagnosis of MCTD in another study. In the context of MCTD, pulmonary hypertension reduced the probability of survival to 73% at 5 years compared to 96% in those without pulmonary hypertension.[113] The prostacyclin analog and pulmonary vasodilator, treprostinil, significantly improved symptoms and exercise capacity in a placebo-controlled study in patients with an array of connective tissue diseases, approximately 20% of whom had MCTD.[114]

SYSTEMIC LUPUS ERYTHEMATOSUS

Systemic lupus erythematosus is characterized by development of autoantibodies, prototypically antinuclear antibody. The pathogenesis seems to involve formation of immune complexes of these antibodies with circulating antigen and complement that are deposited on the microvascular endothelium, producing organ dysfunction. Immunohistologic studies of cardiac tissue obtained from patients with advanced SLE disclosed IgG deposition in 90% of specimens. These deposits were granular (suggesting immune complex aggregates) and occurred predominantly in the walls of pericardial and myocardial vessels. Direct immunofluorescence studies of valvular tissue and associated vegetations also revealed IgG and components in these stroma. Some discrepancy has been observed between the patterns of immunopathologic involvement and the other features of interstitial inflammation, which may indicate that these are not simultaneous processes. Anti-heart antibodies have been identified in the sera of some patients with SLE, but detection of these antibodies has not correlated with either the frequency or the severity of cardiac lesions identified clinically or histologically.[115]

Attention was drawn to the heart in SLE in 1924 when Libman and Sacks described a nonbacterial form of endocarditis characterized by verrucous valvular vegetations.[116] Clinical evidence of cardiac involvement is seldom florid, but astute physicians have identified features of cardiac disease in over 50% of patients.[117] Although the frequency of Libman-Sacks lesions seen at autopsy ranges from 3% to 74%, evidence of SLE is found in a majority of cases. Typical endocarditic lesions have been identified in approximately 50% of patients with fatal SLE.[118]

CLINICAL FEATURES

Pericarditis

Acute or chronic pericardial inflammation has been described in approximately 70% of autopsies of patients with SLE, making this the most common cardiac lesion associated with the disease.[119,120] Chest pain, usually pleuritic, is described by almost 50% of patients and is the chief presenting complaint in over 15%.[117] Echocardiography demonstrates pericardial abnormalities in up to 54% of cases.[121]

Acute pericarditis may be serous or fibrinous, but the chronic form is most often fibrinous. Pericardial effusions may cause cardiac tamponade, but constrictive pericarditis occurs rarely, and a remitting, episodic course is the rule.[122] Immune complexes likely play a role as deposition of immunoglobulin and complement factor 3 can be detected by direct immunofluorescence staining of pericardial tissue[123] and are substantially affected by corticosteroid therapy.[118] Echocardiography may disclose pericardial effusion or pericardial thickening in a large proportion of patients without symptomatic cardiac involvement.[124] In patients with large pericardial effusions associated with SLE, pericardiocentesis has been suggested to carry a greater risk of hemorrhagic complications than in patients without this disease, and it may be prudent to leave a drainage catheter in place for several hours following the procedure to reduce the need for repeated puncture. Surgical pericardiectomy is seldom required since few cases of chronic constriction have been reported in patients with SLE.

Treatment of pericarditis in patients with SLE includes nonsteroidal anti-inflammatory drugs or corticosteroids in low to intermediate doses. In moderate or severe cases, higher doses of corticosteroids (prednisone 1 mg/kg or high dose intravenous

methylprednisolone bolus administration) may be needed. In patients with recurrent or chronic pericarditis, immunosuppressive therapy with methotrexate, azathioprine, mycophenolate or intravenous immunoglobulin (IVIG) have been used.[121]

Myocarditis

In the pre-corticosteroid era, myocardial infiltration by lymphocytes and plasma cells was detected at autopsy in 20–75% of cases of SLE.[119,125] With earlier diagnosis and the advent of corticosteroid medication, this figure has fallen to less than 10%.[118,123,126] Foci of fibrinoid necrosis and plasma cell and lymphocyte infiltrates are common,[118,123,127] as are vascular and perivascular deposition of immune complexes and complement.[118] Signs and symptoms of myocarditis are similar to those in myocarditis due to other causes.

Corticosteroid therapy in high doses is indicated in patients with myocarditis complicating SLE and was associated with clinical improvement in heart failure in nearly 90% of cases in an older report.[128] Immunosuppressive therapy, such as cyclophosphamide, azathioprine or IVIG, may also be beneficial.[121] Patients with SLE who develop heart failure associated with myocarditis should also receive other standard treatment, including diuretic vasodilator and inotropic medications.

Endocarditis

The characteristic of Libman-Sacks form of endocarditis was described even before the diagnostic criteria for SLE were defined, and the earliest observations of vegetative endocardial lesions in patients with this disease appeared in the literature at the turn of the 20th century.[129] Anatomic lesions have been identified in 15–75% of autopsy studies and in 40–60% of patients by precordial or transesophageal echocardiography.[121,130] These verrucous lesions, most commonly affect the mitral and aortic valves[130] in two histologic forms: lesions with fibrin clumps, focal necrosis and mononuclear cell infiltrates or vascularized fibrous tissue occasionally accompanied by calcification.[118] An association between antiphospholipid antibodies and valvular lesions is controversial,[121] and an association between valvular abnormalities, clinical cardiovascular disease, hyperhomocysteinemia and hypertriglyceridemia has also been reported.[131]

Two theories of pathogenesis have been proposed for the development of valvular abnormalities in SLE: in one, antibodies to phospholipids and endothelium bind to and activate endothelial cells leading to platelet aggregation and thrombus formation; the other involves immune complex deposition. Verrucous valvular vegetations typically develop near the edges of the valve leaflets and are often asymptomatic, since even large lesions seldom deform valve closure,[121] but embolic complications may occur, particularly when there is a coexisting thrombophilia. Hemodynamically, significant valvular regurgitation is uncommon, occurring in 3–4% of patients with SLE, but valve replacement surgery is occasionally required.[132-134] Infectious endocarditis was reported in 7% of patients with cardiac valvular manifestations of SLE and 13% had stroke or peripheral embolism.[134] Antibiotic prophylaxis has been suggested for patients with valvular abnormalities associated with SLE receiving immunosuppressive therapy,[121] but the efficacy of this approach has not been established. Asymptomatic Libman-Sacks endocarditis generally does not require treatment; when actively symptomatic, high dose corticosteroid therapy (e.g. 1 mg/kg per day with prednisone) has been recommended[121] with surveillance for the development of clinical hemodynamic compromise.

Electrophysiological Disturbances

Electrocardiographic abnormalities develop in most patients with SLE, if nonspecific repolarization patterns, the most common disturbance, are included.[117,135] In patients with SLE who develop conducting system disease, coronary atherosclerosis or vasculitis involving the sinoatrial or atrioventricular nodal arteries are more common than active myocarditis, but progressive fibrosis of the conducting system is common in chronic cases.[118] Atrioventricular block and bundle branch blocks are rare in adults[136] but occur in approximately 2% of children born to mothers with antibodies to SSA (also called "Ro") or SSB ("La").[137,138] Maternal lupus is also a recognized cause of congenital complete heart block. This form of severe conduction disease carries considerable mortality (15–30%) if untreated, and approximately two-thirds of surviving children require permanent pacemaker implantation.[139] The risk of congenital heart block complicating subsequent pregnancies is approximately 19% or ninefold greater than the risk in a primigravida with SSA or SSB antibodies.[140] As a consequence, serial fetal echocardiography is recommended weekly between 16 weeks and 26 weeks of gestation and thereafter, alternate weeks until the 34th week for pregnant women with antibodies to SSA and/or SSB.[138] Dexamethasone therapy may ameliorate incomplete heart block, but data are insufficient to support prophylactic therapy during gestation in high-risk mothers.[138]

Coronary Artery Disease

Despite abnormal serum lipid profiles associated with the nephrotic syndrome in patients with SLE, accelerated coronary atherosclerosis was rare before the introduction of corticosteroid therapy. A report from the National Heart, Lung and Blood Institute found the lumens of at least major epicardial coronary artery more than 50% obstructed by atherosclerotic plaque in 42% of patients with SLE treated with long-term corticosteroid medication, despite an average patient age of 35 years.[118] Lipid abnormalities provoked or aggravated by corticosteroid therapy, along with hypertension, physical inactivity and hyperhomocysteinemia have been implicated in the development of atherosclerosis in patients with SLE.[141-144] The duration and activity of inflammatory disease interplay with the cumulative effects of corticosteroid exposure to accelerate atherosclerosis.[141,142,145-147] Symptomatic myocardial ischemia and myocardial infarction are now commonly encountered in young women with corticosteroid-treated SLE, altering the spectrum of cardiac involvement more than any other aspect of the disease and representing a major cause of premature mortality in this patient population. As a result of steroid therapy, the risk of developing coronary artery disease (CAD) is 4–8 times higher in patients with SLE than controls, and Manzi et al. reported a 50-fold increase risk for myocardial infarction in young women with SLE.[148]

Histologically, there are two characteristic patterns: transmural infarcts due to atherosclerotic plaque in one or more major extramural arteries or small areas of necrosis adjacent to smaller intramural arteries accompanied by inflammatory vascular infiltrates.[121] The distinction between atherosclerosis and vasculitis may be difficult, but therapeutically important. Although relatively uncommon, vasculitis tends to affect younger patients with immunologically active disease, while atherosclerosis is more common among older patients with long-standing SLE and greater net exposure to corticosteroid therapy. Coronary vasculitis is typically treated with high-doses prednisone (1–1.5 mg/kg per day).[121]

ANTIPHOSPHOLIPID ANTIBODY SYNDROME

Circulating antibodies to phospholipids have been associated with an increased risk of venous thrombosis, pulmonary embolism, arterial thrombosis and fetal loss in patients with or without SLE. Antiphospholipid syndrome (APS) may occur in association with SLE (secondary APS) or as a primary pathologic problem (primary APS). It has been suggested that APS is also associated with accelerated atherosclerosis and since the prevalence of conventional (i.e. Framingham) cardiovascular risk factors does not differ in patients with APS compared with the general population,[149] the development of atherosclerosis in patients with APS would then more likely result from inflammatory or immune mechanisms. Ischemic vascular events associated with antiphospholipid antibodies are more frequent in patients with SLE-associated (secondary) APS and can occur in patients of all ages and at any stage of SLE.[150] Management of atherosclerotic heart disease in the setting of either primary or secondary APS generally requires both aggressive drug therapy of risk factors with statin, platelet inhibitor and angiotensin inhibitor medications in addition to lifestyle changes aimed at dietary safety and exercise. Concurrent aspirin therapy may not be necessary in patients treated with warfarin.[151] The role of corticosteroid administration is controversial and not routine, but antimalarial agents, like hydroxychloroquine, may exert favorable antithrombotic effects mediated by inhibition of platelet aggregation in patients with phospholipid antibodies.[152,153]

After atherosclerosis, the most common cardiovascular abnormality in patients with APS is valvular heart disease. Thickening of the mitral and aortic valve leaflets have been identified by echocardiography in 22% and 6% of APS patients respectively,[154,155] but is usually asymptomatic. Approximately 4–6% of patients with primary APS develop severe valvular regurgitation and about half of these require surgical or catheter-based intervention.[154-156] Anticoagulation has been recommended patients with APS and symptomatic valvular disease; asymptomatic patients are generally treated with aspirin. Corticosteroid therapy is not generally recommended.[157]

CORONARY ARTERITIS

Necrotizing vasculitis is a common feature of several immune complex diseases of connective tissue. The varied clinical manifestations of these diffuse vasculitides may be produced by infectious agents such as the hepatitis B virus or bacterial endocarditis, in which persistent antigenemia results in specific autoimmune phenomena and immune complex formation. In most vasculitides, however, the etiology is unknown and classification is based on clinical and histological features, mainly the size and location of involved vessels, indices of inflammatory activity and morphology of the vascular lesions themselves. Cardiac involvement is most common in the large vessel vasculitides of giant cell arteritis (GCA) and Takayasu's arteritis, medium-size vessel vasculitides of polyarteritis nodosa and Kawasaki disease, and the small vessel vasculitides of Wegener's granulomatosis and Churg-Strauss. Kawasaki disease is associated with cardiovascular sequelae in the pediatric population. Cardiac manifestations related to vasculitis are also encountered in acute rheumatic fever, cryoglobulinemia, MCTD and as a result of exposure to various drugs.

POLYARTERITIS NODOSA

Polyarteritis nodosa may present a highly variable clinical picture affecting multiple organ systems. The most common manifestations include systemic symptoms such as fever and weight loss in addition to neuropathy, skin rash and arthralgias. It predominantly affects medium-sized muscular arteries, although smaller arteries are less commonly affected. Necrotizing inflammation is segmental and transmural, with a predilection for branch points. Small aneurysms may develop, complicated by thrombosis or rupture. Inflammatory changes consist of polymorphonuclear leukocytes and mononuclear cells; there may be evidence of leukocytoclasis. Coronary involvement is fairly frequent, and myocardial infarction is a frequent cause of death in these cases. In a retrospective study of 348 French patients with polyarteritis nodosa, 7.5% had vasculitis-related cardiomyopathy, which may be related to coronary arteritis or to hypertension, present in 34.8% of patients in the study. Pericarditis was identified in 5.5% of patients.[158]

The coronary vessels are second only to renal vessel involvement in polyarteritis nodosa, and aneurysm formation, thrombosis and active arteritis may coexist. Coronary arteritis has been described in 60% of patients with polyarteritis nodosa studied at necropsy involving the proximal left and right coronary and left anterior descending arteries and their immediate branches.[159] Myocardial infarction was found in 62% of cases, the majority of which had evidence of coronary arteritis.

Cardiovascular mortality may also be related to aneurysmal rupture and hemorrhage into the gastrointestinal tract or pericardium; cardiac arrhythmias and advanced pericardial disease occasionally produce fatality. Although conducting system involvement has been reported, clinically significant bradyarrhythmias are uncommon in polyarteritis nodosa. Atrial tachyarrhythmias, however, are encountered fairly frequently.[160-162]

In general, the management of cardiac complications in patients with polyarteritis nodosa is directed toward symptomatic relief and aggressive therapy of the underlying disease with corticosteroid or immunosuppressive medications. In a multivariate analysis of data from 342 patients with polyarteritis nodosa or Churg-Strauss vasculitis, cardiomyopathy, renal insufficiency, proteinuria and GI tract involvement were

associated with a worse prognosis, and mortality at 5 years increased to 46% when three or more of these factors were present.[163]

KAWASAKI DISEASE

The "mucocutaneous lymph node syndrome", first described by Dr Tomisako Kawasaki in 1967, affects medium-sized and smaller arteries with a predilection for the coronary circulation. It begins with an acute febrile self-limited illness manifested by inflammation of the oral and conjunctival mucosa, high fevers, cervical lymphadenopathy, rash, extremity swelling and at times desquamation of the skin of the hands and feet.[164] Over 80% of cases arise in children between the ages of six months and four years.[165] Due to the potential for cardiovascular sequelae, it is the most common cause of acquired heart disease in the pediatric population, although the etiology remains unknown.[166] Cardiac manifestations may include pericarditis, myocarditis, valvitis and inflammatory changes in the atrioventricular conduction system. About 20–25% of children who are not treated with IVIG within the first ten days develop coronary artery aneurysm, the major cardiovascular complication of Kawasaki disease.[167,168]

Autopsy studies have demonstrated panvasculitis in the absence of fibrinoid necrosis.[169] Neutrophilic inflammation predominates early in disease, later replaced by macrophages and lymphocytes. Active inflammation eventually subsides, leaving fibrosis and scar formation.[170,171]

In the acute disease, patients may display tachycardia out of proportion to fever, hyperdynamic precordium, a gallop or a flow murmur due to anemia or fever. Electrocardiographic abnormalities, such as prolonged P-R interval or nonspecific ST segment and T wave changes, also occur. In a study of 198 patients with Kawasaki disease, all of whom received IVIG, left ventricular systolic dysfunction was evident by echocardiography in 20% at the time of diagnosis. At 5 weeks follow-up, 89% of these had regained normal systolic function but persistent abnormalities were associated with a greater risk of coronary artery dilation. In this study, 27% of patients had mitral regurgitation at diagnosis, which persisted at 5 weeks follow-up in 9%.[172]

Aneurysms most commonly involve the coronary vessels, particularly the proximal left anterior descending and proximal right coronary arteries, but may develop in medium-sized peripheral arteries as well.[173] Aneurysms of the coronary arteries are most commonly saccular or fusiform rather than purely saccular, tubular or fusiform. Angiography characteristically displays multiple small aneurysms at the branch points of the coronary vessels. Development of coronary artery aneurysm is associated with age under one year or greater than 9 years and total duration of fever greater than 8 days.[174,175] During the initial 4–6 weeks after symptom onset aneurysms may increase in size, but about 50% regress within 1–2 years. The likelihood of resolution decreases markedly after that time frame.[168] Patients with uncomplicated Kawasaki disease should undergo echocardiography at the time of diagnosis, at 2 weeks and 6–8 weeks after development of symptoms. Monitoring beyond that point depends on the extent of cardiac involvement and other clinical features. The elevated long-term cardiac risk in patients without obvious cardiac sequelae from Kawasaki disease is unknown and cardiovascular risk assessment is recommended at 5 years intervals.[166]

Kawasaki disease may be complicated by myocardial ischemia, sometimes asymptomatic. Kato et al. analyzed 195 cases of myocardial infarctions related to Kawasaki disease; about 75% occurring within a year of diagnosis, and 37% of the cases reported no cardiac symptoms.[176] Patients with persistent coronary artery aneurysms or resolved coronary artery abnormalities are at a higher risk of subsequent ischemic cardiac events. Those with persistent small to medium-sized aneurysms should employ long-term antiplatelet therapy. Annual follow-up with a pediatric cardiologist, electrocardiography and echocardiography are recommended. Patients over 10 years old should undergo stress testing, approximately every 2 years. In those with large coronary aneurysms, warfarin therapy is recommended with or without aspirin. Cardiac catheterization should be performed 6–12 months after the acute illness has subsided and biannual clinical follow-up with EKG and echocardiogram is generally advised.[164] In patients with Kawasaki disease who have no echocardiographic abnormalities, the risk of ischemic events appears modest over extended follow-up of 10–20 years.[168]

The standard initial treatment for Kawasaki disease is a single infusion of 2 g/kg IVIG, which, if administered 5–10 days after fever onset, has been shown in multiple studies to significantly reduce the risk of future coronary artery aneurysm.[177] If fever persists, IVIG should be repeated. Aspirin 80–100 mg/kg per day in 4 doses is also recommended for its anti-inflammatory and antiplatelet effects, although it has not been shown to reduce coronary aneurysm formation. Aspirin should be continued at high doses until day 14 of the illness and the fever has resolved for 48–72 hours. After that, low-dose aspirin should be continued for 6–8 weeks and stopped only if there is no evidence of cardiac pathology, continuing indefinitely in patients with persistent cardiac abnormalities. The role of corticosteroids in treatment of Kawasaki disease is not well-defined, as randomized trials have yielded contrasting results.[167,178]

Coronary artery bypass graft surgery may be necessary in children with significant obstructive coronary pathology related to Kawasaki disease. Arterial grafts such as the internal thoracic (mammary) artery are most commonly used as they tend to grow with the patient. In a single center study of 114 patients with Kawasaki disease, 25-year survival was 95%, but only 60% of subjects were cardiac-event free at that time, the others requiring percutaneous coronary intervention, cardiac reoperation or developing specific adverse outcomes.[179]

CHURG-STRAUSS VASCULITIS

The necrotizing vasculitis described by Churg and Strauss in 1951 is characterized by asthma and peripheral eosinophilia.[180] Cardiovascular involvement is common, affecting about 60% of patients and is the cause in approximately half of disease-related deaths.[181,182] Cardiac involvement in Churg-Strauss syndrome includes reduced ventricular function, valvular insufficiency, pericardial effusion and endomyocarditis.

Myocardial damage may be secondary to coronary vasculitis and occlusion. Cardiac involvement is associated with higher peripheral eosinophil counts and the absence of antineutrophil cytoplasmic antibodies.[183] Patients with unfavorable prognostic features, including cardiac involvement, should be treated with corticosteroid agents and cyclophosphamide. Remission is achieved in the majority of patients; the 8-year relapse rate was approximately 65% in one series, but these episodes were generally mild.[184]

WEGENER'S GRANULOMATOSIS

Wegener's granulomatosis now referred to as granulomatosis with polyangiitis (GPA) is a necrotizing vasculitis that most commonly affects the renal, pulmonary and upper respiratory tract vascular structures. Symptomatic cardiac involvement is rare, although subclinical cardiac pathology has a reported frequency between 6% and 44%.[185] The most common manifestations are pericarditis and coronary arteritis, both occurring in about half of the patients with cardiac involvement.[186] Myocarditis, valvitis and arrhythmias, particularly of supraventricular origin, have also been reported.[185] In most cases, the clinical picture is dominated by the involvement of respiratory and renal tissue, and these represent a *sine qua non* of diagnosis. Early diagnosis of this disease is crucial, since treatment with corticosteroid agents and cyclophosphamide dramatically reduces mortality.[187]

GIANT CELL ARTERITIS

Giant cell arteritis also called temporal arteritis is a granulomatous vasculitis which affects medium and large vessels, particularly the aorta and its extracranial branches. It affects older individuals, such that age over 50 is one of the diagnostic criteria and the average age of onset is 72. Typical presenting symptoms include new headache, jaw claudication or visual disturbance in the context of an elevated erythrocyte sedimentation rate. Temporal artery biopsy demonstrates disruption of the internal elastic lamina and multinucleated giant cells, often with patchy involvement.[188] Long-term cardiovascular sequelae include a 17-fold increase in the risk of thoracic aortic aneurysm and a 2–4 fold increase in the risk of abdominal aortic aneurysm.[189] GCA also appears to associated with an increased risk of CAD.[190] Left ventricular dysfunction was found in 18% of patients with GCA and was associated with aortic involvement.[191] Corticosteroids are the only proven treatment, with initial doses of 40–60 mg/day followed by an extended taper highly effective in the majority of cases.

TAKAYASU'S ARTERITIS

Takayasu's arteritis primarily affects the aorta and its main branches, and is typically diagnosed in women before age 40. Fever and fatigue are common presenting symptoms, but as the disease progresses beyond the acute phase, granulomatous inflammation in the vessel walls may result in arterial narrowing or occlusion manifested as extremity claudication, visual loss, angina pectoris or mesenteric ischemia.[192] Physical findings may include reduced or asymmetrical peripheral pulses or reduced blood pressure in one or both arms. In one of the largest published series of 204 patients, approximately 70% of patients had hypertension at diagnosis. On initial presentation, 39% reported extremity claudication and 25% reported chest pain. Aortic valve regurgitation secondary to aortic root dilation is relatively common, occurring in 20% of patients in one study.[193]

Subtypes of Takayasu's arteritis have been delineated based upon both clinical and anatomical patterns. In one schema, pulseless disease is distinguished from a mixed, atypical coarctation and dilated types. There are several anatomical schema: one distinguishing type I, the most proximal or brachiocervical type typically involves the aortic arch and its branches, and sometimes the coronary ostia; type II a more dorsal distribution associated with thoracoabdominal aortic involvement; type III typically involves the abdominal aorta, mesenteric and renal arteries predominantly;type IV is a generalized form and type V shows a predilection for peripheral vessels, but other systems of categorization have also been proposed.[194] Arteriography (catheter-directed CT or MR angiography) is key to the diagnosis, and characteristically demonstrates areas of stenosis with some areas of arterial dilation. Glucocorticoids represent the mainstay of treatment with adjuvant immunosuppressive therapy intended in some cases to reduce the corticosteroid dose requirement. Angioplasty or stenting may be indicated to treat focal lesions.

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Chapter 96

Cardiac Neoplastic Disease

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Chapter Outline

- Clinical Symptoms
- Imaging Techniques
- Benign Cardiac Neoplasms
  - Cardiac Myxoma
  - Papillary Fibroelastoma
  - Rhabdomyoma
  - Cardiac Fibroma
  - Hemangioma
  - Lipomas and Lipomatous Hypertrophy
  - Cardiac Paraganglioma
  - Atrioventricular Node Tumors
- Malignant Tumors
  - Primary Cardiac Sarcomas
  - Angiosarcoma
  - Malignant Fibrous Histiocytoma
  - Osteosarcoma
  - Leiomyosarcoma
  - Rhabdomyosarcoma
  - Synovial Sarcoma
  - Unclassifiable or Undifferentiated Sarcomas
- Other Sarcomas
  - Primary Cardiac Lymphoma
  - Pericardial Mesothelioma
  - Metastatic Tumors

INTRODUCTION

Primary cardiac neoplasms are rare and when they occur they are most frequently benign. Although infrequently observed, they are important causes of morbidity and mortality in clinical cardiology. Although many cardiac neoplasms present with a variety of symptoms the majority of them present with some combination of heart failure, embolic disease or arrhythmias. The signs and symptoms are mostly related to their anatomic location, size and their effects on the surrounding tissues, rather than to the histological type of tumor. In the past they were mostly an autopsy curiosity, as no imaging techniques existed that could diagnose their presence in life. The autopsy incidence of cardiac neoplasms is reported to be 0.001–0.3%.[1] In several surgical series the most common neoplasm of the heart is a myxoma accounting for over 70% of cases, with the second most common being primary sarcomas (12%) (Table 1). Since the first resection of a myxoma in 1945, cardiac tumors are now being routinely resected, even when asymptomatic. Despite advances in cardiovascular imaging allowing for earlier detection and surgical removal, malignant cardiac tumors continue to carry a poor prognosis.

CLINICAL SYMPTOMS

Cardiac tumors usually present with heart failure and thromboembolism with over 50% of cases due to a large intracavitary mass; depending upon the chamber of involvement they may result in either backward, congestive heart failure or forward low-output heart failure.[2] Intracavitary tumors have a point of attachment to the wall of the heart and therefore may cause arrhythmias (Table 2). The signs and symptoms are related to the precise location within the heart, tumor size and chamber of involvement (Table 3). Myxomas as well as other primary cardiac tumors, may present with one or more of the classic symptom triad including: sequelae of valvular obstruction, embolic phenomena and constitutional symptoms. The symptoms related to embolic phenomenon include strokes, transient ischemic attacks, claudication of the extremities, renal insufficiency, myocardial infarction and when located on the right side, pulmonary embolism. Tumors of the right ventricle produce symptoms of pulmonary stenosis and usually present with syncope.

The clinical manifestation of the primary malignant tumors of the heart also depends on the location and when associated with extensive myocardial involvement, often results in congestive heart failure. The majority of angiosarcomas are located in the right atrium and almost always involve the pericardium. Therefore, patients present with either right-sided heart failure or pericardial tamponade. Other sarcomas, like osteosarcoma, fibrosarcoma, myxosarcoma, undifferentiated sarcoma or malignant fibrous histiocytoma (MFH), occur more frequently in the left atrium and will present with pulmonary symptoms, such as dyspnea from pulmonary congestion and right heart failure or may present with pneumonitis (and even mitral stenosis). Primary lymphomas of the heart are rare but may present with non-specific clinical symptoms such as chest pain, dyspnea and bradycardia.

TABLE 1

Cardiac tumors, surgical series

	Total	*Bloudeau et al.*	*Tazelaar et al.**	*Miralles et al.*	*Murphy et al.**	*Reece et al.*	*Dein et al.*	*Melo et al.*	*Verkkala et al.*	*Endo et al.*	*Odim et al.*	*Hoffmeier et al.*	*Thomas-de-Montpreville et al.*	*Patel et al.*
Myxoma	995(75%)	444	80	63	58	51	27	19	16	91	20	78	21	27
Sarcoma	148(11%)	52**	8	12	7	5	8	1	2	14	2	8	8	21
Fibroma	48(3.6%)	9	9	7	3	5	1	1	0	1	1	1	6	4
Rhabdomyoma	43(3.2%)	5	0	9	9	5	0	0	0	2	1	2	9	2
Lipoma	33(2.5%)	9	5	4	2	3	1	0	2	1	1	0	2	3
Angioma	25(2%)	7	0	3	3	2	7	0	0	0	0	0	1	2
Fibroelastoma	23(2%)	0	7	—	0	—	2	0	0	1	2	1	3	8
Lymphoma	6(0.4%)	1	0	0	0	0	0	0	0	1	0	2	0	4
Hamartoma	5(0.4%)	4	0	0	0	0	1	0	0	0	0	0	0	0
Ectopic thyroid	2(0.1%)	2	0	0	0	0	0	0	0	0	0	0	0	0
Total	1331	533	109	98	98	71	47	21	20	111	27	92	48	71

*Cases of Purkinje cell hamartoma (histiocytoid cardiomyopathy) reported in these series were excluded from this table.
**Includes two malignant neoplasms that were considered unclassifiable.

TABLE 2

Location of common cardiac neoplasms

Types of tumor	*Left atrium*	*Right atrium*	*Left ventricle*	*Right ventricle*	*Valve*	*Pericardium*
Myxoma	90%	10%	Rare	Rare	Rare	0
Sarcoma	46%*	26%	21% (right or left)†	†	0	7%
Fibroma§	Rare	Rare	80% (majority in IVS)	20%	0	0
Papillary fibroelastoma	2%	¶	10%	3% (right heart)¶	85% (AV,MV)	0
Rhabdomyoma**	0	30% (atrium or ventricle)††	70% (and ventricular septum)	††	0	0
Lipoma (LI)/Lipomatous hypertrophy (LH)	0	Majority LH	Epicardial surface (LI)	Epicardial surface (LI)	0	0
Angioma	Any location	Any location	Any location	Any location	Varix	0

*Angiosarcomas predominately arise in right atrium
†Right or left
§86% occur in children, and 1/3 are less than 1 year in age
††Atrium or ventricle
¶Right heart
**90% are multiple, and occur in newborn or children, rare in adults
(Abbreviations: AV: Aortic valve; MV: Mitral valve; IVS: Interventricular septum)
(*Source:* Modified from Burke A, Jeudy J, Virmani R. Cardiac tumours: an update. Heart. 2008;94:117-23)

TABLE 3

Cardiac symptoms by tumor type

Benign tumors

Cardiac myxomas
- Obstructive cardiac symptoms: left atrial myxoma—prolapse into (by various degrees) mitral orifice, LVOFT obstruction—shortness of breath or syncope or progressive cardiac failure
- Embolic symptoms
- Constitutional symptoms

Papillary fibroelastoma
- Embolic symptoms of obstruction of coronary or cerebral circulation as 80–90% located on the aortic or mitral valve endocardium
- Sudden death by prolapse into coronary ostia or occlusion of large coronary branch

Rhabdomyoma (most common tumor in children)
- Dependent on size, might result in cardiomegaly, congestive heart failure and cardiac arrhythmias
- Sudden death or stillbirth

Fibroma (most common resected tumor in children)
- Approximately one-third present with heart failure or cyanosis
- One-third with arrhythmias or syncope
- One-third are asymptomatic and tumor discovery incidental

Atrioventricular nodal tumors
- Majority of patients present with complete heart block, the remainder experience sudden death

Cardiac lipomas
- Asymptomatic
- Rare extrinsic compression of heart dependent on size and location

Malignant tumors

Angiosarcoma
- Non-specific, depending on the location, right atrial lesions have propensity for pericardial involvement causing hemopericardium and pericardial constriction
- Chest pain, shortness of breath, malaise and fever

Osteosarcoma
- Left atrial lesions present with respiratory symptoms
- Ventricular lesions present with recurrent ventricular tachyarrhythmia

Leiomyosarcoma
- Left atrial lesions (75%) present with pulmonary symptoms of dyspnea, chest pain and non-productive cough
- Ventricular lesions may present with right heart failure, valve stenosis, rhythm alterations, conduction abnormalities, hemopericardium and sudden death

Rhabdomyosarcoma
- Non-specific symptoms, sometimes pleuropericardial symptoms and distal embolization
- Arrhythmias and obstructive symptoms

Cardiac lymphoma
- Heart failure exertional dyspnea, atrial fibrillation and features of right-sided heart obstruction
- Cardiac tamponade

Pericardial mesothelioma
- Chest pain, cough, dyspnea and palpitations

Metastatic cardiac tumor (depends on the primary tumor as well as myocardial or pericardial involvement)
- Tachycardia, arrhythmias, cardiomegaly or heart failure in patients with carcinoma should raise suspicion of cardiac metastasis
- Rarely, cardiac involvement, such as pericardial effusion or incipient cardiac tamponade, can be first clinical feature of malignant disease, although 90% are clinically silent

(*Source:* Modified from Butany J, Nair V, Naseemuddin A, et al. Cardiac tumours: diagnosis and management. Lancet Oncol. 2005;6:219-28)

IMAGING TECHNIQUES

By far the most useful technique for establishing the diagnosis of a cardiac tumor is echocardiography. Although cardiac catheterization and selective angiography enabled the first antemortem diagnosis of a cardiac tumor, this is no longer necessary and other techniques, like magnetic resonance imaging (MRI) and electron beam computed tomography (CT), are now increasingly being used (Table 4).[2] The spatial and temporal resolution is certainly lower with CT and MRI than with echocardiography. The soft-tissue contrast of CT and MRI make them superior to that of echocardiography and also allow imaging of the surrounding mediastinum and evaluation of extracardiac extent of the disease.[3] Computed tomography, while being faster and easier to perform, offers the additional advantage of the detection of calcification, which is important in the differential diagnosis of cardiac tumors. However, MRI offers better soft-tissue contrast. Echocardiography has the

TABLE 4

Cardiac imaging findings of cardiac neoplasms

Type of tumor	*Patient age at presentation*	*Most common location*	*Typical morphology*	*Echocardiographic*	*CT*	*MRI*
Benign Tumors						
Myxoma (50% of all primary neoplasms)	30–60 years (younger associated with Carney complex	Interatrial septum at fossa ovalis, left more common than right	Myxomatous (gelatinous) calcification and hemorrhage common	Mobile tumor, narrow stock, heterogeneous with hypo-echoic and hyperechoic foci	Heterogeneous, low attenuation; occasionally with calcification	Heterogeneous, bright on T2WI, heterogeneous enhancement;isointense on T1
Papillary fibroelastoma	Middle-aged elderly	Cardiac valves, 80% left sided	Small (< 1 cm), frond like, narrow stalk, calcification rare	"Shimmering" edges	Usually not seen	Usually not seen
Fibroma	Infants, children, young adults; (associated with Gorlin Syndrome)	Ventricles, intramyocardial	Large intramural; calcification common	Intramural large, solid mass, central hyper-echoic foci	Homogeneous, low attenuation, calcification	Isointense in T1WI, dark on T2WI; minimal enhancement
Rhabdomyoma	Infants and children, 50% associated with tuberous sclerosis	Left and right ventricle and ventricular septum	Small lobulated, diameter ranges from 2 mm to 2 cm	Multiple small, solid, hyperechoic masses	Hypodense areas within the myocardium on contrast CT, isointense to myocardium	Homogeneous isointense on T1 and hyperintense on T2
Lipoma	Variable	Pericardial space or any cardiac chamber, may be mobile	Broad based, infiltrative or circumscribed, calcification rare	Usually hypoechoic in the pericardial space, echogenic in cardiac chamber	Homogeneous fat attenuation (low fat attenuation)	Homogeneous fat signal intensity (increased in T1; no enhancement
Teratoma	Intrauterine, and in children	Right atrium and ventricle or in the interatrial and ventricular septum	Heterogeneous lobulated mass with solid and cystic components, often with calcification	Very heterogeneous, with pericardial effusion	Very heterogeneous	Very heterogeneous
Hemangioma	Children and adults	Any part of the heart, lateral wall of LV and anterior wall of RV	Lobular broad base	Hyperechoic	Heterogeneous, calcification, marked enhancement	Isointense in T1, hyperintense in T2, marked enhancement
Malignant Tumors						
Angiosarcoma	Adult, more common in male than female	Right atrium (80%) as either intracavitary or polypoid, or diffuse with pericardial involvement	Pericardial involvement and cardiomegaly	Mass protruding into right atrium, and pericardial effusion	Broad based with myocardial, pericardial and mediastinal invasion. Highly vascularized and low attenuation	Infiltrative heterogeneous broad based mass, nodular areas of hyperintensity on T1, and linear area of enhancement
Other sarcoma	Adult left atrial masses	Left atrium	Large, invasive masses. They range from endo-cardial based lesions to large infiltrative lesions	Left atrial mass, broad base of attachment to posterior atrial wall	Low attenuation	Infiltrative and heterogeneous, variable intensity on T1 and isointense on T2WI
Lymphoma	Adults and rarely children	Right side of the heart, most common right atrium	Lobular, pericardial effusion	Hypoechoic masses, pericardial effusion	Low attenuation	Infiltrative, isointense to hypointense on T1, heterogeneous enhancement

(*Source:* Sabatine MS, Colucci WS, Schoen FJ. Primary tumors of the heart. In: Zipes DP, Libby P, Bonow RO, Braunwald E (Eds). Braunwald's Heart Disease: A Text Book of Cardiovascular Medicine, 7th Edition. 2005. p. 1741.
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Araoz PA, Mulvagh SL, Tazelaar HD, et al. CT and MR imaging of benign primary cardiac neoplasms with echocardiographic correlation. Radiographics. 2000;20:1303-19)

TABLE 5

Primary cardiac tumors, Armed Force Institute of Pathology 1976–1993

Benign tumors	*n (% total)*	*Surgical cases*	*< 16 years**	*< 1 year**
Myxoma	114 (29)	102	4	0
Papillary fibroelastoma	31 (8)	8	0	0
Rhabdomyoma	20 (5)	6	20	19
Fibroma	20 (5)	18	13	8
Hemangioma	17 (4)	10	2	1
Lipomatous hypertrophy, atrial septum	12 (3)	7	0	0
AV nodal tumor	10 (3)	0	2	1
Granular cell tumor	4 (1)	0	0	0
Lipoma	2	2	0	0
Paraganglioma	2	2	0	0
Myocytic hamartoma, not further classified	2	2	0	0
Histiocytoid cardiomyopathy	2	0	2	2
Inflammatory pseudotumor	2	2	1	0
Benign fibrous histiocytoma	1	0	0	0
Epithelioid hemangioendothelioma	1	1	0	0
Bronchogenic cyst	1	1	0	0
Teratoma	1	0	1	1
Total benign tumors	242	161	45	32
Malignant tumors	*Total*	*Surgical cases*	*< 16* years*	*< 1* year*
Sarcoma	137 (35%)	124	11	3
Angiosarcoma	33	22	1	0
Unclassified	33	30	3	1
MFH	16	16	1	0
Osteosarcoma	13	13	0	0
Leiomyosarcoma	12	11	1	1
Fibrosarcoma	9	9	1	0
Myxosarcoma	8	8	1	0
Rhabdomyosarcoma	6	2	3	1
Synovial sarcoma	4	4	0	0
Liposarcoma	2	0	0	0
Malignant schwannoma	1	1	0	0
Lymphoma	7 (2%)	1	0	0
Total malignant tumors	144	125	11	3
Total tumors	**386**	**286**	**56**	**35**

*Age of patient at time of diagnosis

advantage as it offers real-time, high spatial and temporal resolution and provides information about the size of the tumor. Doppler ultrasound evaluates the hemodynamic consequences.

BENIGN CARDIAC NEOPLASMS

Three quarters of all primary tumors of the heart and 90% of tumors resected at surgery are benign. Many benign proliferations of the heart have no exact histologic counterpart in extracardiac locations; these entities include myxomas, papillary fibroelastoma, lipomas, lipomatous hypertrophy, cardiac fibroma and rhabdomyoma and cystic tumor of the AV node (Table 5).

CARDIAC MYXOMA

Cardiac myxoma is the most common benign tumor in adults, accounting for approximately 75–80% of cardiac tumors in surgical series. The mean age at presentation is 50 years and two-thirds of cases are found in women.[4] Large studies have shown that 75–80% of myxomas arise in the left atrium, 15–20% in the right atrium and less than 2.5% are biatrial.[5] They are rarely found in the ventricles, on valves and attached to chordae tendineae.[6,7] Most arise from the endocardium of the atrial septum near the fossa ovalis and are attached by a broad base or narrow stalk.

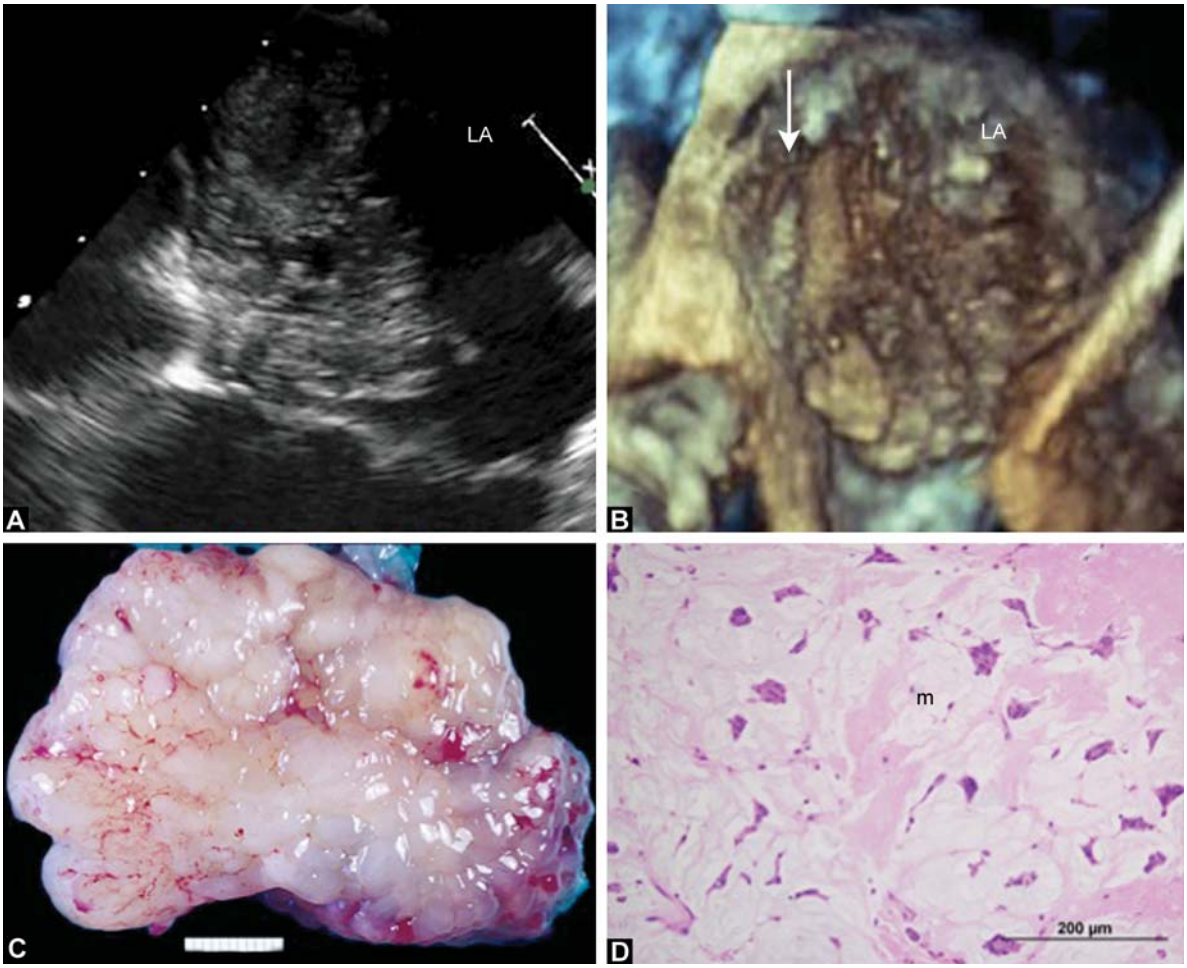
Familial tumors are more likely to be multiple, recurrent and right sided compared to sporadic myxomas. Multiple tumors

are generally found in the Carney syndrome, an autosomal dominant syndrome characterized by cardiac myxomas and extracardiac manifestations including cutaneous and neural tumors and a variety of pigmented skin lesions.[8] Genetic studies of Carney syndrome patients have identified mutations in the gene coding the type 1 alpha regulatory subunit of protein kinase A (PRKAR1A).[9]

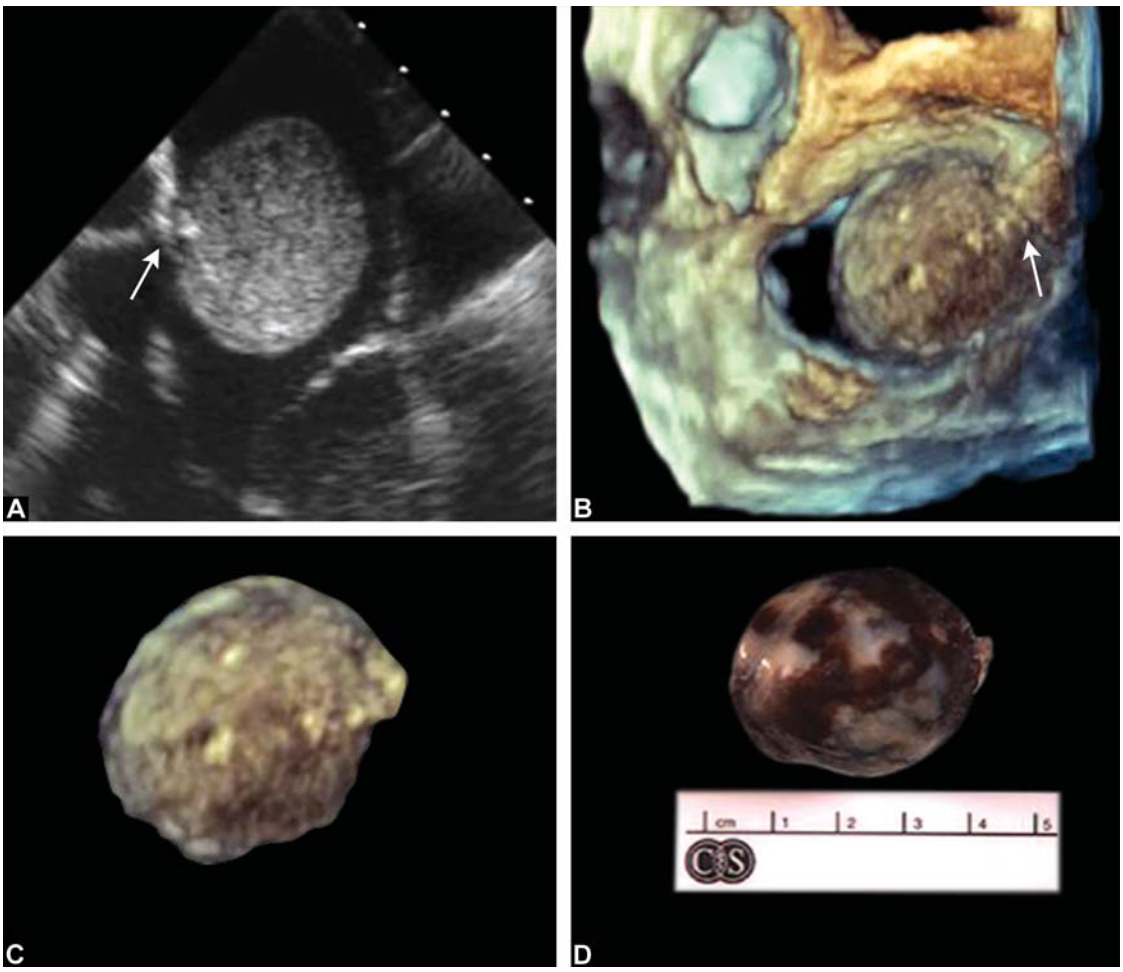
Cardiac myxomas are great mimickers owing to the multitude of non-specific presenting symptoms. These include symptoms related to sequelae of valvular obstruction, embolic phenomena and constitutional symptoms. Since the majority of cardiac myxomas occur in the left atrium, the most common presentation secondary to obstruction is mitral stenosis, leading to a clinical syndrome similar to chronic rheumatic mitral heart valve disease. In addition, the tumors are often friable resulting in embolic phenomena, including strokes, transient ischemic attacks, claudication of the extremities, renal insufficiency, myocardial infarction and pulmonary emboli (right sided tumor). Myxomas are also notorious for producing vague constitutional symptoms of weakness, malaise, fever and hematologic abnormalities such as anemia, hypergammaglobulinemia and increased sedimentation rate.

Imaging Techniques

By echocardiography, the narrow stalk is the most distinguishing feature of a myxoma, followed by tumor mobility and distensibility.[3] There is a high sensitivity for the detection of cardiac myxomas by two-dimensional (2D). However, even with transesophageal echocardiography (TEE) differentiation from thrombus is difficult despite the ability to more easily delineate the site of attachment. As a result, too often thrombi can be misdiagnosed as myxomas on TEE. Recently with the advent of real-time three-dimensional (3D) TEE (RT3DTEE), it is now feasible to differentiate a smooth, solid myxoma from one that is mobile with papillary components (Figs 1 and 2). However, differentiation between myxoma and thrombus remains difficult.[10] CT provides a high degree of soft tissue discrimination but is typically unable to assess the presence of a narrow base of attachment. Similarly, mobility and distensibility cannot be detected on CT, but tumor location can certainly be detected with high accuracy. The administration of contrast agent may further demonstrate the presence of a well-defined spherical or ovoid intracavitary mass with lobulated contours. On MRI, myxomas typically have a heterogeneous appearance with



FIGURES 1A TO D: (A) Two-dimensional transesophageal echocardiographic image of left atrial myxoma showing multiple papillary excrescences but no distinct stalk. (B) Real-time 3D transesophageal echocardiographic surgical view of the mass through a left atrial cut shows a very friable tumor with multiple frond-like extensions (white arrow, dense stalk) [*Source:* Reproduced with permission from Tolstrup K et al. J Am Soc Echocardiogr. 2011; (In Press)]. (C) Papillary myxoma after resection (*Source:* Reproduced with permission from Travis WD, Brambilla E, Muller-Hermelink H-K, et al. (Eds). Tumors of the lung, pleura, thymus and heart. World Health Organization Classification of Tumor. Geneva, Switzerland: WHO Press; 2004. p. 261). (D) High-power microscopic image showing myxoid stroma (m) with lepidic cells arranged singly and in cords, typical of myxoma. (Abbreviation: LA: Left atrium)



FIGURES 2A TO D: (A) Large homogeneous myxoma with smooth surface as depicted by 2D TEE attached to the interatrial septum by a stalk (white arrow). (B) Left atrial view looking toward the mitral valve using full-volume 3D TEE, showing spherical myxoma with mildly irregular surface attached by a stalk to the interatrial septum near fossa ovalis (white arrow). (C) Zoomed view of the myxoma with the background removed. (D) Corresponding gross pathologic specimen with similar distinct borders and slightly irregular surface appearance

intermediate signal intensity on T1WI and higher signal intensity on T2WI when there are areas of subacute or chronic hemorrhage.[11,12] However, mobility of the tumor or attachment site cannot be assessed. Myxomas show heterogeneous enhancement after gadolinium.[13]

Treatment

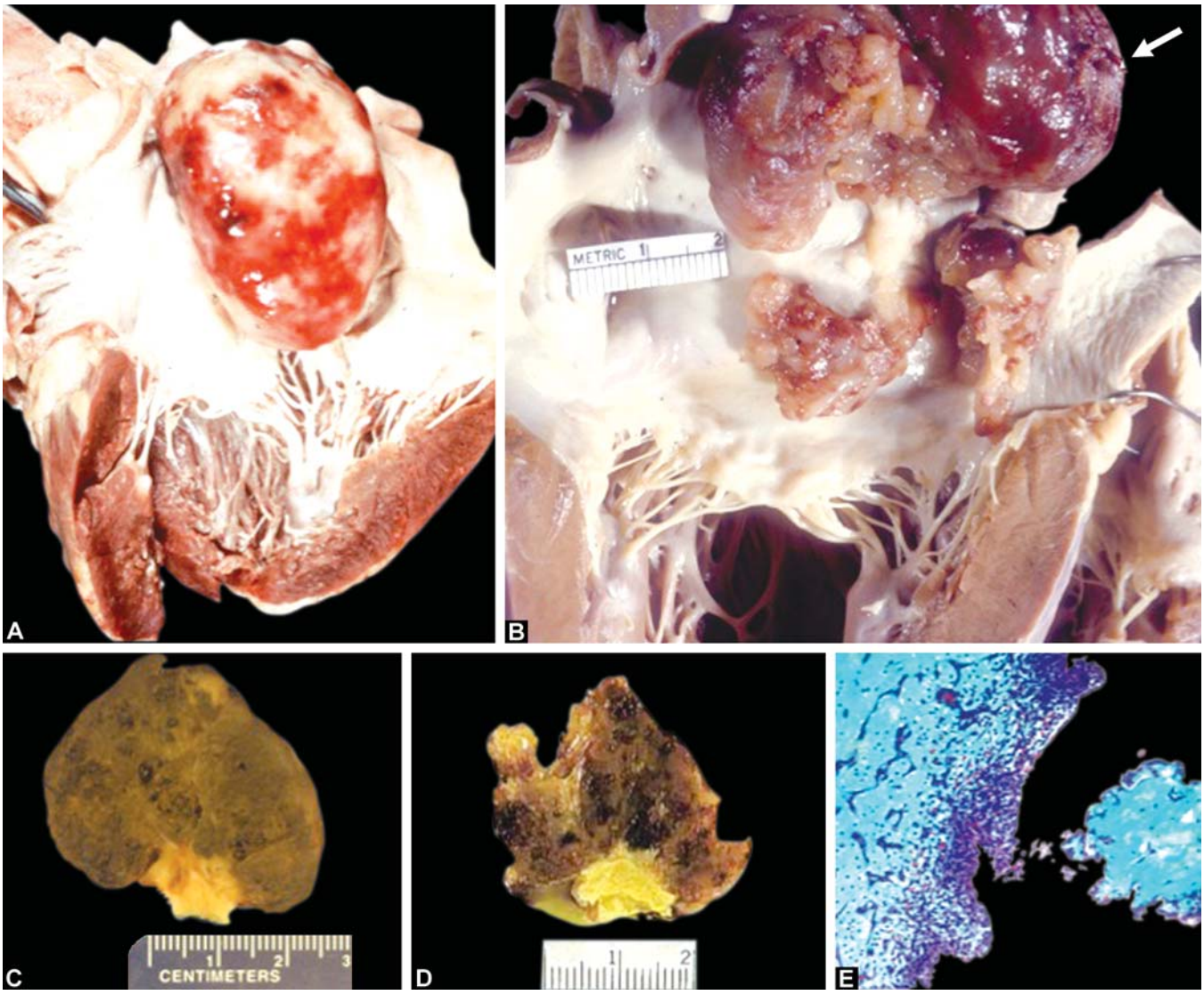
The majority of patients are cured by surgical removal. The Mayo Clinic reported that the risk of recurrence of myxoma is between 1% and 3%.[14] Other series have shown no recurrences, possibly because of the removal of a rim of uninvolved atrial wall along with the myxoma.[15] Therefore, pathologic assessment of margins is relevant to outcome.

Gross Pathology

Cardiac myxomas demonstrate great morphologic variability. They may range in size from a few millimeters to 14 cm in diameter and weigh 2–250 gm. Grossly, the tumors may be round, ovoid or polypoid and the surface may be smooth or irregular demonstrating villous-like projections with or without organized thrombi. On cut section, tumors are variegated in appearance and may be pale gray, pearly white or yellow brown admixed with hemorrhagic dark brown to red areas. Heterogeneity is a common finding in myxomas with areas of hemorrhage, necrosis, cyst formation, fibrosis or calcification (Figs 3A to E).

Microscopic Findings

The microscopic diagnosis of cardiac myxoma depends on the identification of the myxoma cell. The classic myxoma cell has an oval nucleus with an open chromatin pattern and inconspicuous nucleoli. There is abundant eosinophilic cytoplasm and indistinct cell borders. Myxoma cells may occur singly or as complex structures such as multilayered rings or cords. Rudimentary vessels are also found in myxomas and are typically thin-walled without pericytes. Thick walled vessels may be found at the basal attachment site. Variable degrees of chronic inflammation consisting of macrophages, lymphocytes, plasma cells and mast cells may be present as well. The stroma is myxoid and contains varying degrees of proteoglycan, collagen and elastin. The surface of the tumor may be quite cellular and rare mitotic figures occur near the surface of the tumor. Secondary changes of fibrosis, thrombosis and calcification are often present as well. Hemosiderin-laden macrophages are virtually always present. Other degenerative



FIGURES 3A TO E: (A) Large left atrial myxoma prolapsing into the mitral orifice, smooth surface with areas of hemorrhage. (B) Papillary myxoma filling the left atrium. There are multiple sites of attachment to the left interatrial septum; the myxoma consists of friable polypoid fronds with a distinct mucoid or gelatinous appearance. Note attached thrombus (arrow). (C) Surgically removed myxoma with relatively smooth surface but extensive areas of hemorrhage. (D) Surgically resected myxoma showing papillary fronds, which lead to a high incidence of embolic phenomenon to the brain, myocardium and kidneys. (E) Histologic appearance of irregular fronds on the surface of a myxoma that is rich in proteoglycans and are likely to embolize. (*Source:* Tolstrup K, et al. J Am Soc Echocardiogr. 2011)

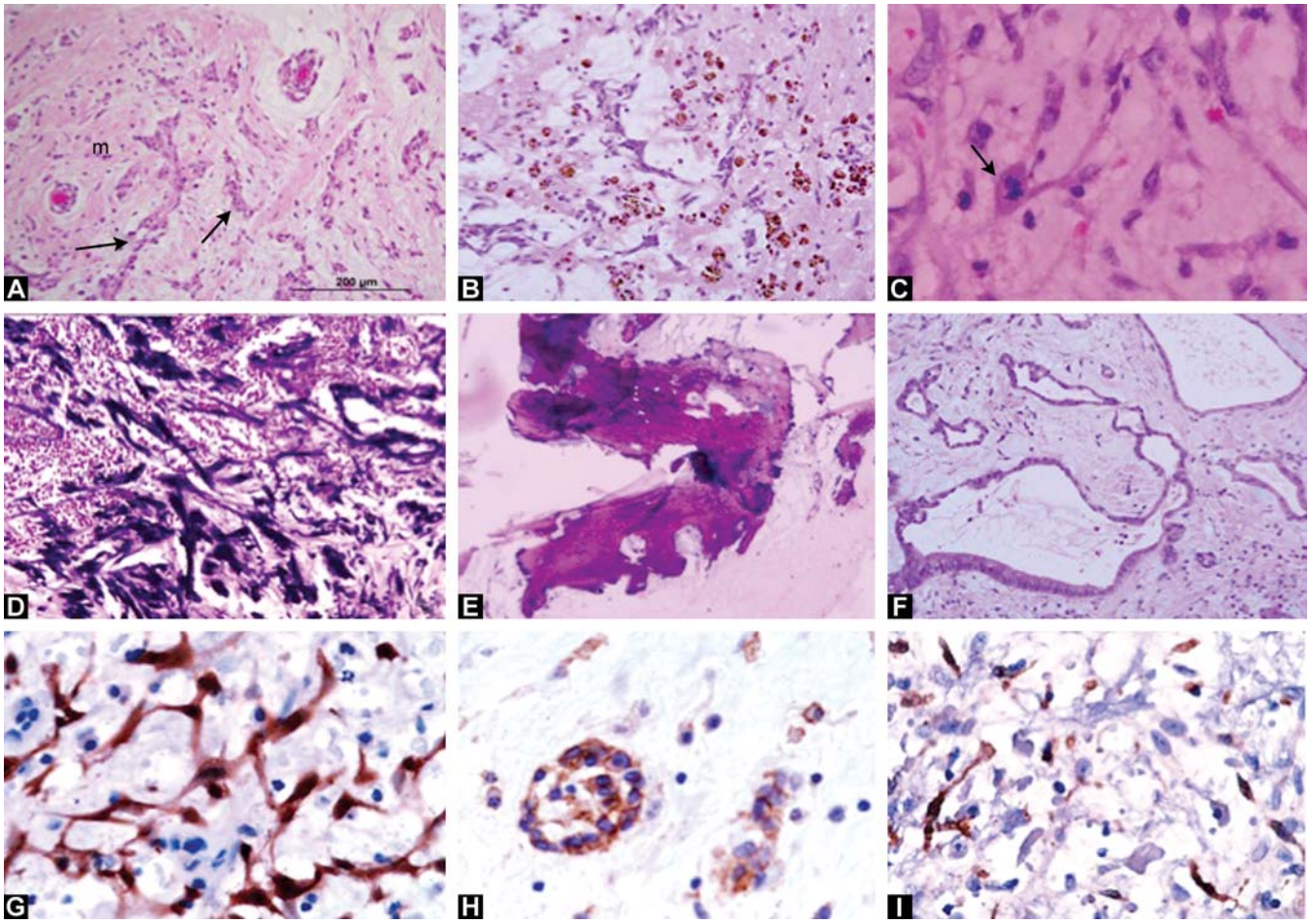
changes include ossification and Gamna-Gandy bodies. Approximately 1–2% of myxomas contain glandular structures lined by mucin-laden cells that resemble goblet cells of the gastrointestinal tract. Recognition of the glands as a component of myxoma is important since these structures may be confused with metastatic adenocarcinoma (Figs 4A to I).

In general, the immunohistochemical profile is of little use in the differential diagnosis of cardiac myxoma, but helps to explain its histogenesis. The cells are cytokeratin negative, variably S-100 positive and variably positive for smooth muscle and endothelial markers CD34 and CD31. Calretinin is expressed in about 75% of cardiac myxomas.[16]

PAPILLARY FIBROELASTOMA

Cardiac papillary fibroelastoma (CPF) is a rare benign cardiac tumor of uncertain histogenesis with an estimated frequency of 0.0017–0.3300% in autopsy series.[17] The vast majority of CPFs do not produce any symptoms and are recognized as incidental findings during echocardiography. The mean age of patients is 60 years and there is an equal gender predilection.[18,19] In most surgical series, it is the second most common mass lesion after myxoma in adults.[1,20] The true incidence, however, is difficult to determine because papillary fibroelastomas resemble Lambl's excrescences and therefore small incidental lesions may be missed. Nevertheless, important morphologic differences exist between the two entities. Papillary fibroelastomas are larger and more gelatinous than Lambl's excrescences and are present on valves away from the lines of closure as well as on the endocardial surfaces of the atria or ventricles. Lambl's excrescences occur exclusively at the sites of valve closure.

These lesions typically involve the valves, especially left sided valves and are the most common valve lesions. About 80–90% of papillary fibroelastomas are found on the valvular endocardium of the aortic and mitral valves, followed by the



FIGURES 4A TO I: (A) Histologic appearance of a typical myxoma, showing myxoid matrix (m) and cords of myxoid cells (arrows), which may be single layered, or multiple. (B) Hemosiderin laden macrophages are virtually always present in myxoma. (C) Rarely mitotic figures may be observed (arrow). (D) Gamna gandy bodies. (E) Focal calcification and rarely even bone formation within a myxoma is observed. (F) Glandular structures are seen in < 5% of cases. These are benign and should not be mistaken for metastatic adenocarcinoma. (G to I) Immunohistochemical stained sections showing myxoma cells express calretinin (approximately 75% of cardiac myxomas express calretinin), and focally CD 31/34, the moncyte/macrophages lineage stain positive for factor XIII

tricuspid valve and endocardium.[21,22] In addition, papillary fibroelastomas have been reported to arise on endocardial surfaces thickened by radiation therapy and prosthetic valves.[1] Sudden death, ischemic heart disease and neurologic symptoms have been reported secondary to embolization of surface thrombi as well as dislodged papillary fronds. Symptoms can be caused by prolapse into the coronary ostium, embolization into coronary arteries, cerebral vascular occlusion and renal vascular occlusion.[23]

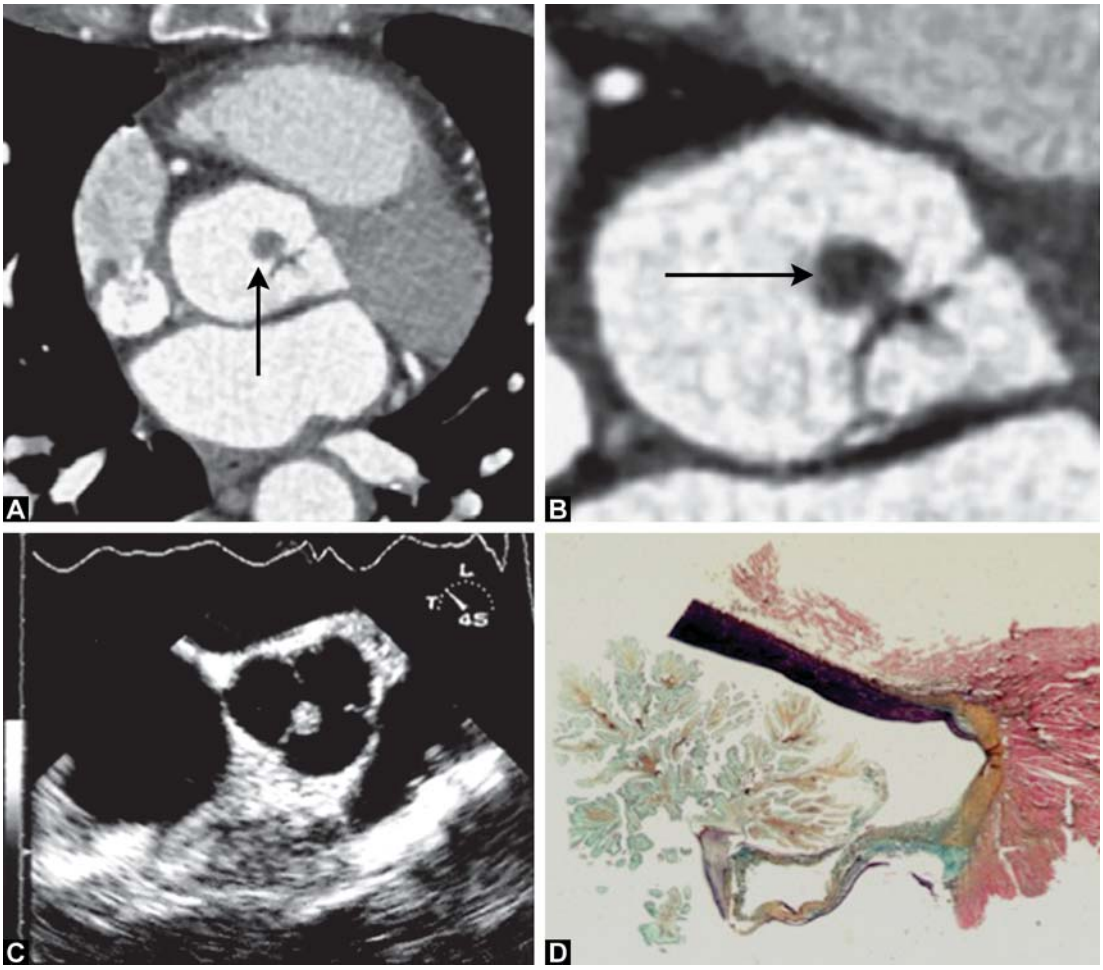
Cardiac papillary fibroelastoma have been described as neoplasms, hamartomas, unusual organized thrombi and endocardial responses to trauma. As Lambl's excrescences are believed to be unusual organizing thrombi, a similar histogenesis has been advocated for papillary fibroelastoma. However, since papillary fibroelastomas are often located in regions of low hemodynamic stress, it is likely that processes other than organizing thrombosis play a role in their histogenesis. Evidence in favor of CPF being a form of hamartoma includes the histologic appearance, which suggests a proliferation of disorganized miniature chordae tendineae. The congenital nature of some papillary fibroelastomas is supported by an early age at onset of symptoms and an association with other congenital anomalies.

Imaging

The sensitivity is close to 60% by transthoracic echocardiography (TTE) but increases to 77% with an overall accuracy close to 90% on TEE[19] (Table 3). On echocardiography they appear as round, oval or irregular mass lesions, with well demarcated borders and a homogeneous texture. Echocardiography is convenient and has resulted in the detection of small CPF lesions, which appear as round, oval or irregular on echocardiography but are usually well demarcated and homogenous. With optimal image quality they appear "speckled" with "stippling" around the edges of the lesions.[19,24] While CT imaging can detect CPF, this is not the primary mode of detection as they are of a small size, high mobility and attach to valves (Figs 5A to D).[24]

Gross Pathology

The vast majority (90%) of papillary fibroelastomas are located on left sided valves. They have a predilection for the atrial surface of atrioventricular valves with no similar predilection for side when present on semilunar valves. They have a characteristic flower-like appearance that has been likened to



FIGURES 5A TO D: ECG 64-detector dual-source gated cardiac CT coronary angiogram with intravenous contrast performed in a 53-year-old woman before noncardiac surgery demonstrated an incidentally found papillary fibroelastoma (arrow) in relation to other cardiac structures (A) a magnified image (B) demonstrates the papillary fibroelastoma (arrow) arising from the right coronary cusp. (*Source:* Anavekar NS, et al. Radiology Clin N Am. 2010;48:799-816]. (C) A papillary fibroelastoma attached to the aortic non-coronary cusp of the aortic valve, as seen by TEE in the midesophageal short axis. (*Source:* Reproduced with permission from Sun JP et al. Circulation. 2001;103:2687-93). (D) Papillary fibroelastoma of the aortic valve stained with Movat pentachrome stain. Note the mass consists of multiple papillary fronds that are rich in proteoglycans and collagen

that of a sea anemone and is best appreciated by immersing the specimen in water. Approximately 13% are multiple.[25] Although the majority of tumors are 1 cm or less in largest diameter, tumors as large as 5 cm have been reported.[26] They are usually attached to the endocardial surface by a short single stalk but multiple attachments may be observed. In one series, the stalk ranged 1–3 mm in length and all of these were mobile.[19]

Histology

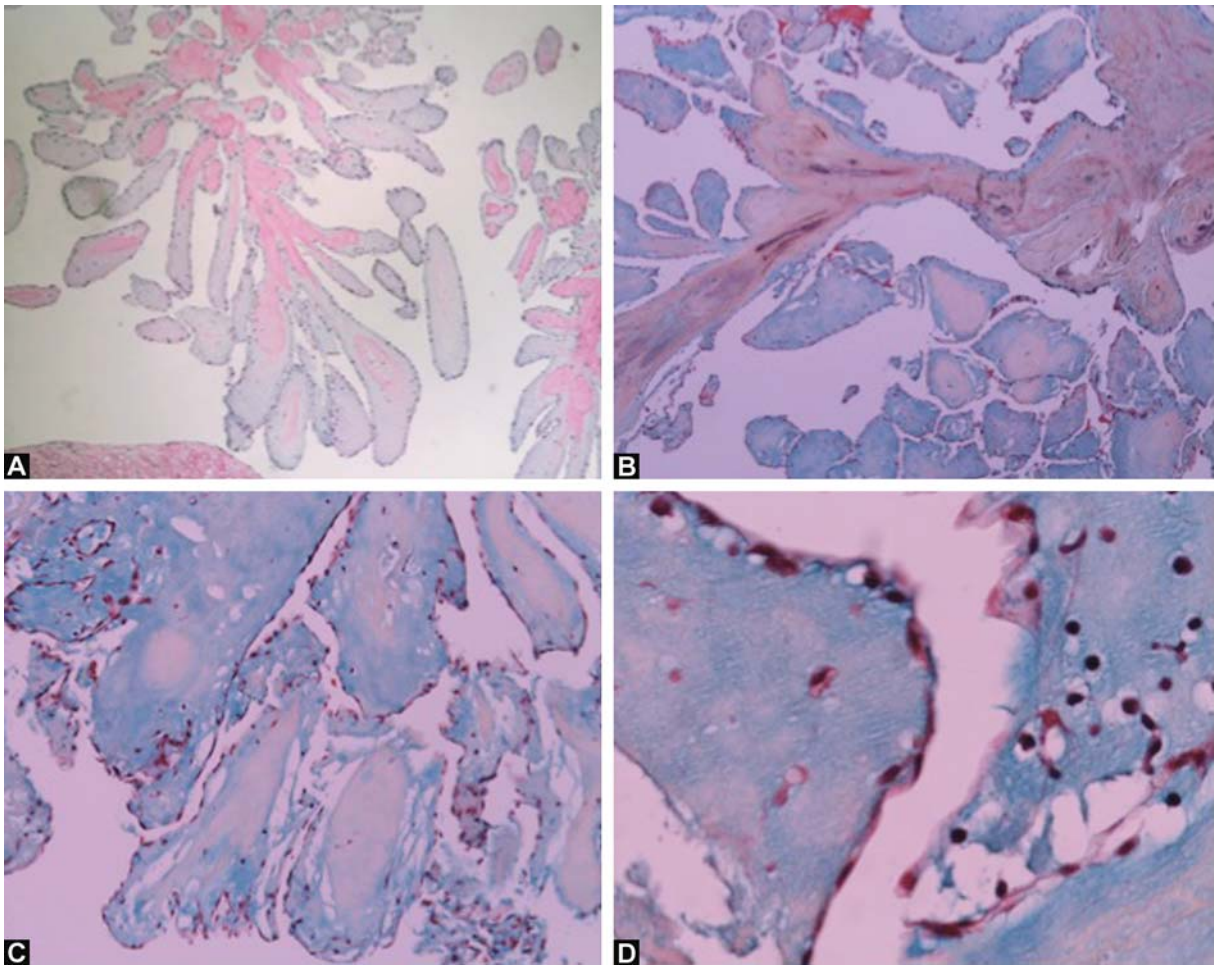
The papillary fronds of papillary fibroelastoma are narrow, elongated and branching and are longer than those seen in nodules of Aranti. The matrix consists of mucopolysaccharides, varying degrees of elastic fibers and rare spindle cells resembling smooth muscle cells and a central avascular core (Figs 6A to D). Acute and organizing thrombi may be seen on the surface. Surface endothelial cells express vimentin and CD34, with less intense CD31 and factor VIII related antigen compared to normal endocardial endothelium. Spindle cells in deeper layers may focally express S100 protein.[27-29]

RHABDOMYOMA

Cardiac rhabdomyomas are the most common primary cardiac tumor in children. Cardiac rhabdomyomas can be divided into three groups: (1) those that arise in patients with tuberous sclerosis; (2) sporadic rhabdomyomas and (3) those associated with congenital heart disease. There is no sex predilection for patients with cardiac rhabdomyoma and tuberous sclerosis.[30,31] These neoplasms have been associated with arrhythmias; heart block is the most common. Paroxysmal tachycardia, ventricular tachycardia and sudden death have also been reported. Large intracavitary tumors can give rise to congestive heart failure. In general, children with cardiac rhabdomyoma and tuberous sclerosis have an excellent prognosis since the majority of these lesions regress.[32]

Imaging

By echocardiography, cardiac rhabdomyomas are usually multiple, small, lobulated, homogenous and hyperechoic (echogenic) intramural or intracavitary tumors (Figs 7A to E).[33]



FIGURES 6A TO D: Papillary fibroelastoma. (A) Papillary fibroelastoma located on the mitral valve. Note the presence of a central stalk made up of collagen (pink area in A) and some elastic fibers (brown black area in B), from which arise papillary fronds, which are rich in proteoglycans (blue green, B and C) with interspersed mesenchymal cells and are lined by endothelial cells (D). The central core is avascular

By CT they appear as hypodense areas within the myocardium and on contrast CT, isointense to myocardium.[24] MRI is useful in atypical cases, which typically have a solid and homogenous appearance that may be hypointense compared to myocardium on T1WI and slightly hyperintense on T2WI. Typically they do not show enhancement with gadolinium.[11,12]

Gross Pathology

Rhabdomyomas are firm white circumscribed lobulated nodules that occur in any location in the heart but are more common in the ventricles. They are often multiple and can consist of numerous miliary nodules measuring less than 1 mm (Figs 7A to E). One series reported a significant size range from 0.3 cm to 9 cm.[1]

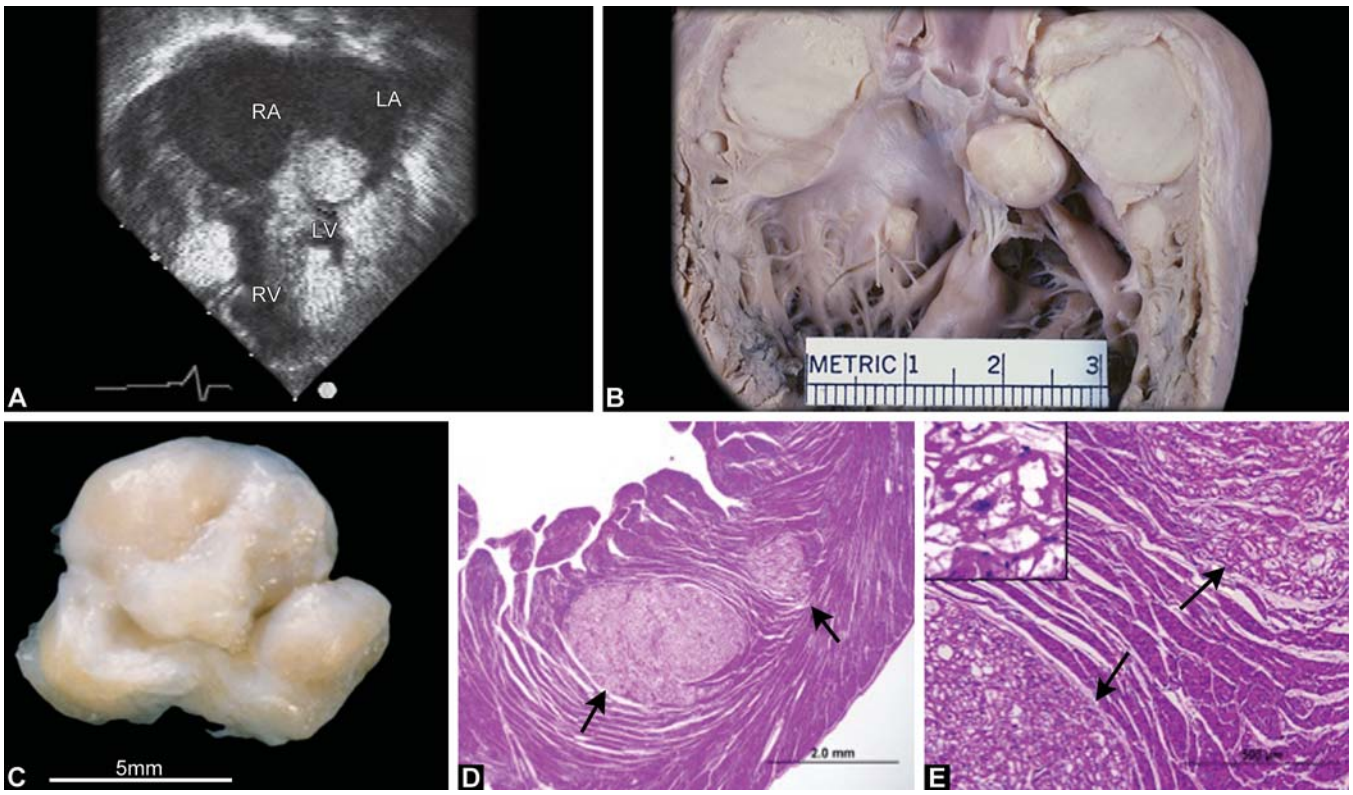
On histology, tumors are well demarcated and composed of enlarged cells with clear cytoplasm and occasional spider cells. There is uniform vacuolization of cells and cytoplasm is relatively sparse. Spider cells are characterized by a centrally located nucleus with radial cytoplasmic extensions to the cell periphery (Figs 7A to E). There is a strong reaction with periodic acid-Schiff (PAS) reflecting the glycogen content of rhabdomyoma cells. Immunohistochemical studies show features of striated muscle fibers in these cells including myoglobin, desmin, actin and vimentin.

CARDIAC FIBROMA

Cardiac fibroma is a rare benign congenital tumor that typically affects children, a third of whom are younger than 1 year at presentation. It is the most commonly resected cardiac neoplasm in children.[34] The mean age of presentation is 13 years, ranging from the newborn period to 75 years.[35,36] There is no sex or race predilection. A majority of patients are asymptomatic (36%) or present as sudden death (23%). Cardiac fibromas are also associated with congestive heart failure (21%) or arrhythmias (13%) and chest pain (3.5%).[37]

Imaging

Fibromas are usually solitary tumors that result in cardiomegaly on radiography, with 25% demonstrating calcification.[38] By echocardiography they appear as large, noncontractile, solid masses within the ventricular wall. By CT, a cardiac fibroma appears as heterogeneous mural mass with a high sensitivity for the detection of calcium. Also, by contrast CT these lesions typically enhance homogenously or heterogeneously. By MRI, fibromas appear as a discrete solitary mural masses, usually involving the interventricular septum or free wall or as focal myocardial thickening. They appear as isointense to slightly hyperintense on T1WI and hypointense on T2WI relative to



FIGURES 7A TO E: Rhabdomyoma. (A) Echocardiogram of an infant who presented with supraventricular tachycardia. There are multiple rhabdomyomas. (B) Echocardiographic imaging of the apical four chamber view, showing multiple cardiac rhabdomyomas involving the left and right ventricles. Multiple rhabdomyomas in an infant with tuberous sclerosis complex. (*Source:* William D Edwards). (C) Subaortic rhabdomyoma in a 5-month-old child. (D and E) Histologic section shows two subendocardial rhabdomyomas (arrows) inset in Figure E shows "spider" cells, several vacuolated tumor cells and cells with abundant eosinophilic cytoplasm

the myocardium (Figs 8A to E).[11] MRI does not directly visualize calcium, which is a considerable disadvantage when compared to CT. There is no enhancement with gadolinium injection compared to surrounding myocardium.[12,38]

Gross and Histology

Grossly, fibromas are nearly always solitary mural lesions. The cardiac sites of fibromas are in order of decreasing frequency: the ventricular septum, left ventricular free wall, right ventricle and rarely the atria. Morphologically, cardiac fibromas are solitary circumscribed, firm, gray-white whorled masses. They are often centrally calcified, a useful imaging feature. The mean diameter has been reported as 5 cm but tumors as large as 8 cm have been reported.[36] Histologically, the cardiac fibroma shows a homogenous proliferation of monomorphic fibroblasts with little if any atypia. The degree of cellularity decreases with the age of the patient, whereas the amount of collagen increases (Figs 8A to E). There can be occasional perivascular lymphohistiocytic infiltrates or mild chronic inflammation at the junction of the tumor and endocardium. Elastic fibers may also be present.

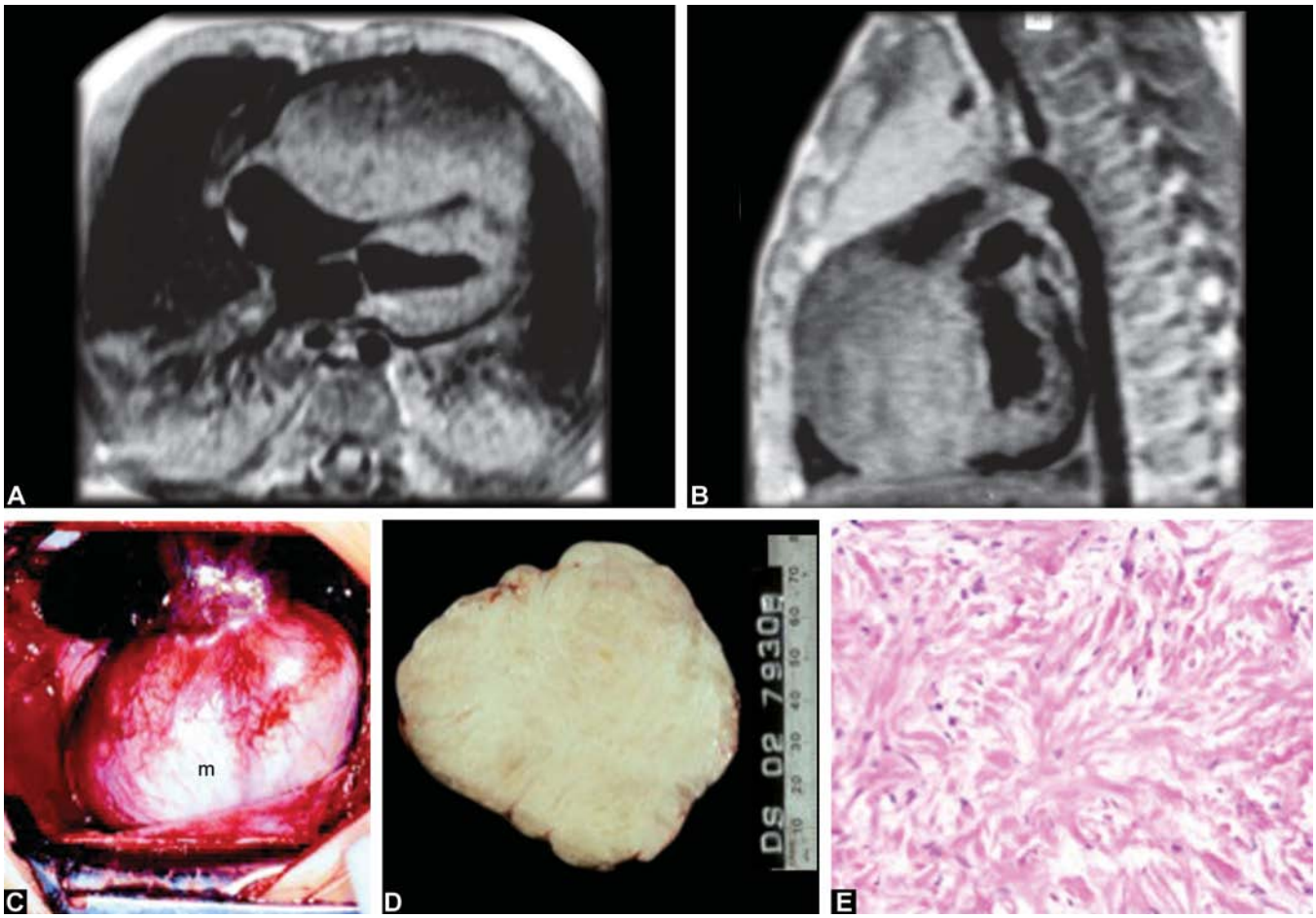
HEMANGIOMA

Hemangiomas are exceedingly rare benign vascular tumors that represent less than 5% of heart tumors. They may occur in any location in the heart. A recent case report describes ventricular tachycardia associated with cardiac hemangioma.[39] Of 45 cases, 15 were located in the atria, 12 in the left ventricle or ventricular septum, 11 in the right ventricle, 6 in the pericardium and 1 on the mitral valve.[40-42] The majority are mural lesions and the remainder are endocardial lesions that project into the atrial or ventricular cavity. They range in size from 1 cm to 8 cm or larger. Histologically, they are similar to extracardiac hemangioma and show a variety of histologic patterns (Figs 9A to D).

LIPOMAS AND LIPOMATOUS HYPERTROPHY

Lipomatous hypertrophy of the atrial septum is a rare benign condition characterized by a proliferation of mature fat, multivacuolated fat and atypical myocytes in the interatrial septum. An association between lipomatous hypertrophy of the interatrial septum and supraventricular arrhythmias has long been recognized. In fact, there have been several reports of sudden cardiac death without pathologic findings at autopsy other than the presence of lipomatous hypertrophy. Microscopically, there is an admixture of fat cells (adipocytes) and bizarre appearing cardiac myocytes with some of the fat cells demonstrating vacuolization typical of brown fat.

Lipomas constitute 8–12% of primary tumors of the heart and pericardium. Most are extramyocardial or subepicardial, but they also have been reported on the mitral valve. They consist of encapsulated masses of fat and are similar to benign lipomas of soft tissue. Histologically, they contain mature fat and may be quite vascular (Figs 10A to D).



FIGURES 8A TO E: Cardiac fibroma in a newborn girl in whom anterior myocardial thickening had been noted at prenatal ultrasound. (A) Axial T1 weighted and (B) sagittal T1 weighted MR images demonstrate a large homogeneous mural mass of the anterior wall of the right ventricular cavity. (C) Intraoperative photograph shows the large right ventricular mural mass. (*Source:* Grebenc ML, Rosado de Christenson ML, Burke AP, et al. Primary cardiac and pericardial neoplasms: radiologic-pathologic correlation. Radiographics. 2000;20:1073-103). (D) Cardiac fibroma cut section showing prominent whorled surface. (E) Microscopically, the tumor is composed of spindle shape cells with pale cytoplasm and interspersed collagen bundles, forming intersecting bundles. The cellularity decreases with age

CARDIAC PARAGANGLIOMA

Cardiac paragangliomas are rare neoplasms of neural crest origin arising in the chromaffin and chemoreceptor tissues. Most are located in or adjacent to the left atrium. Affected patients are young adults with an age range at diagnosis from 15 years to 60 years. About half of patients present with hypertension and symptoms of pheochromocytoma, indicating that these tumors are functional.

Grossly, they are large, poorly circumscribed masses ranging 5–15 cm in greatest dimension. Most are located on the epicardial surface of the base of the heart or atria. Histologically, they are unencapsulated and tumor cells form cell nests (zellballen) surrounded by sustentacular cells. Their histologic appearance and immunohistochemical profile are identical to extracardiac paragangliomas (Figs 11A and B).

ATRIOVENTRICULAR NODE TUMORS

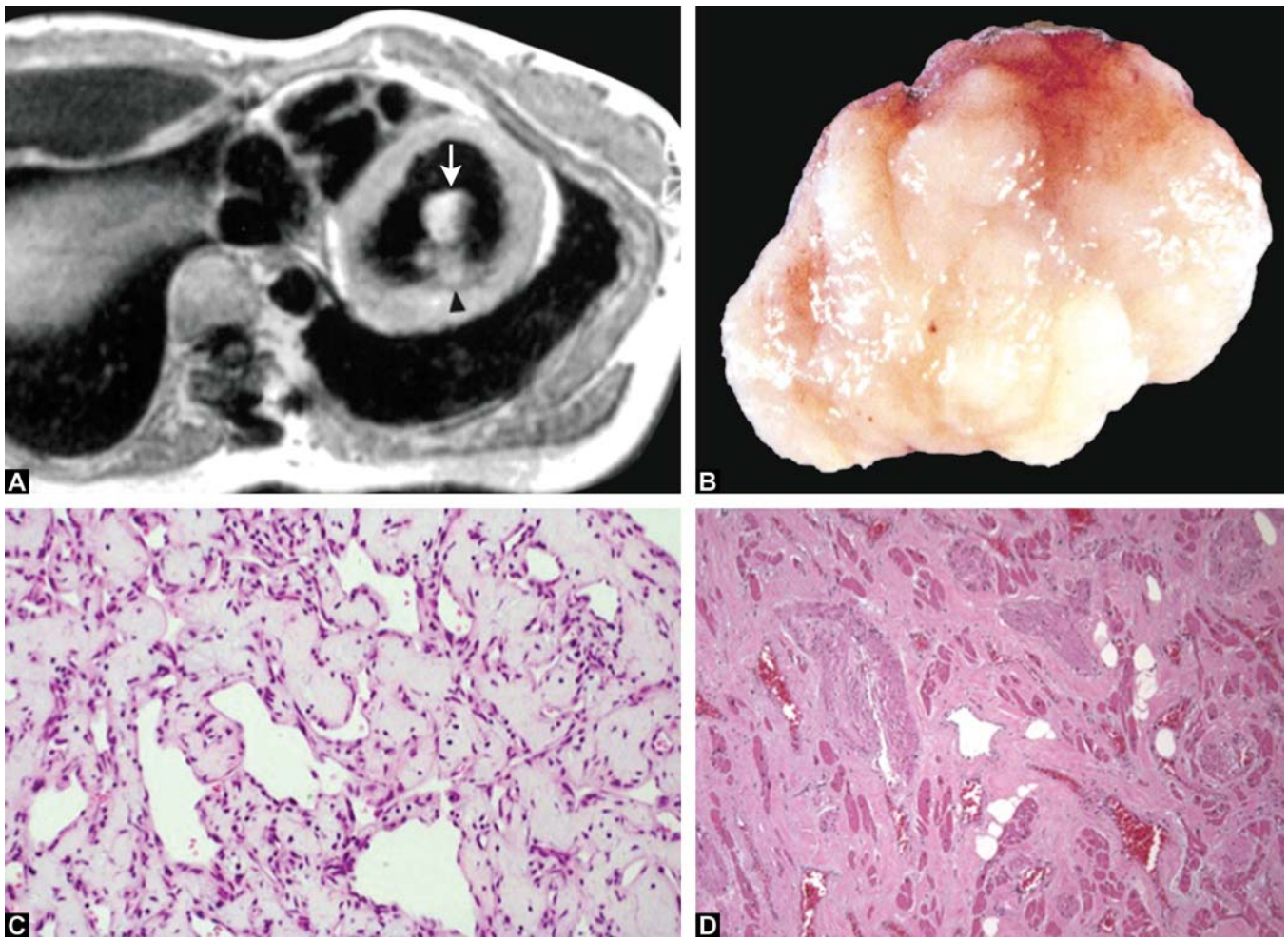
The cystic tumor of the AV node is a rare congenital cystic mass located at the base of the atrial septum in the region of the AV node. The majority of patients with cystic tumors of the AV node present with complete heart block. The diagnosis is usually made at autopsy and has a female predominance. The tumors range in size from 2 mm to 20 mm. Histologically, they are composed of nests of cells that often form cysts of various sizes. The cell nests can replace myofibers within the inferior interatrial septum and are composed of cuboidal, transitional or squamous cells. Often there is dense fibrosis surrounding the cysts or cell nests. Immunohistochemical marker indicate an endodermal derivation for the cells of cystic AV nodal tumors.[43]

MALIGNANT TUMORS

Primary malignant tumors are seen even less frequently than benign forms and account for approximately 10–15% of all cardiac tumors.[1] Almost all cardiac malignancies are sarcomas and they are classified similarly to sarcomas of extracardiac soft tissue. Primary malignant tumors, including sarcomas, occur on either side of the heart and may also involve the pericardium. The prognosis of patients with sarcomas remains very poor with a mean survival of less than 1 year.

PRIMARY CARDIAC SARCOMAS

Although rare, primary sarcomas are the second most common primary cardiac tumor and comprise the vast majority of



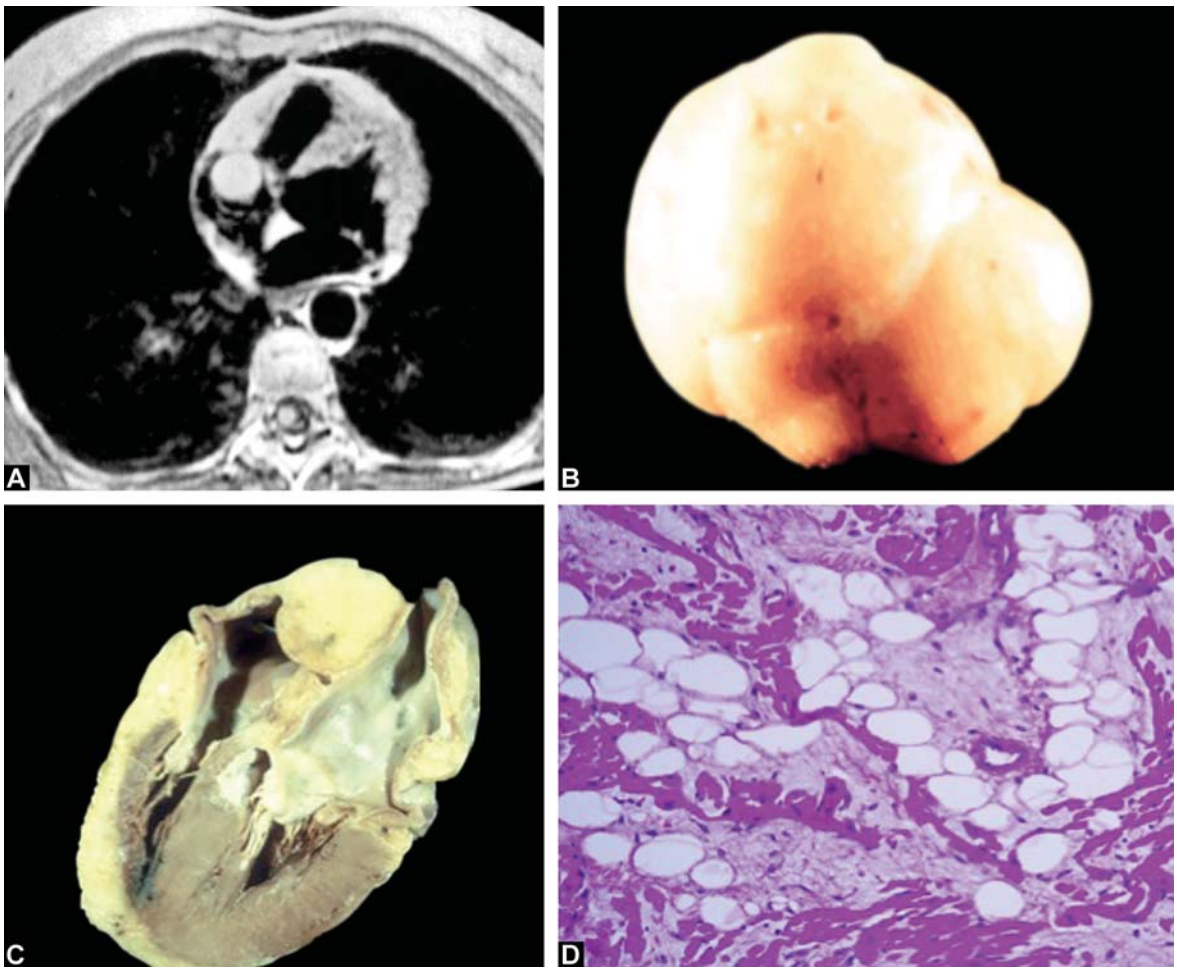
FIGURES 9A TO D: Cardiac hemangioma in a 24-year-old pregnant woman with Marfan syndrome and mild aortic root dilatation, who was found to have a left ventricular mass at surveillance echocardiography. (A) Axial T1-weighted MR image demonstrates a lobular, pedunculated, intracavitry left ventricular mass (arrow) arising from the posterior papillary muscle (arrowhead). (B) Photograph shows the tan, bosselated mass that was excised at surgery. (*Source:* Grebenc ML, Rosado de Christenson ML, Burke AP, et al. Primary cardiac and pericardial neoplasms: radiologic-pathologic correlation. Radiographics. 2000;20:1073-103) (C) Hemangioma showing relatively uniform population of capillary type vessels with variable degree of dilatation. The myxoid matrix may suggest a myxoma, but other features of myxoma are absent. (D) Some hemangiomas may show more fibrosis as seen in this case with interspersed myocytes, dilated capillaries and focal thickened arterioles

malignant tumors. In a series of cardiac sarcomas seen as referrals at AFIP between 1976 and 1993, unclassifiable sarcomas were as frequent as angiosarcomas.[44] The AFIP series (1976–1993) is the largest surgical series to date; the most common forms include angiosarcoma (33% of cases), unclassified or undifferentiated sarcoma (33% of cases), MFH (16%), leiomyosarcoma (12%) and osteosarcomas (13%)[38] (Table 5). Our review of surgically resected cardiac sarcomas from 12 institutional series showed that the incidence of unclassified sarcomas and angiosarcomas was 26% and 25% respectively (Table 6). It is interesting to note that in several recent pathological studies of primary cardiac tumors, cardiac sarcomas were often difficult to classify, even with the use of additional immunohistochemical stains.[45,46]

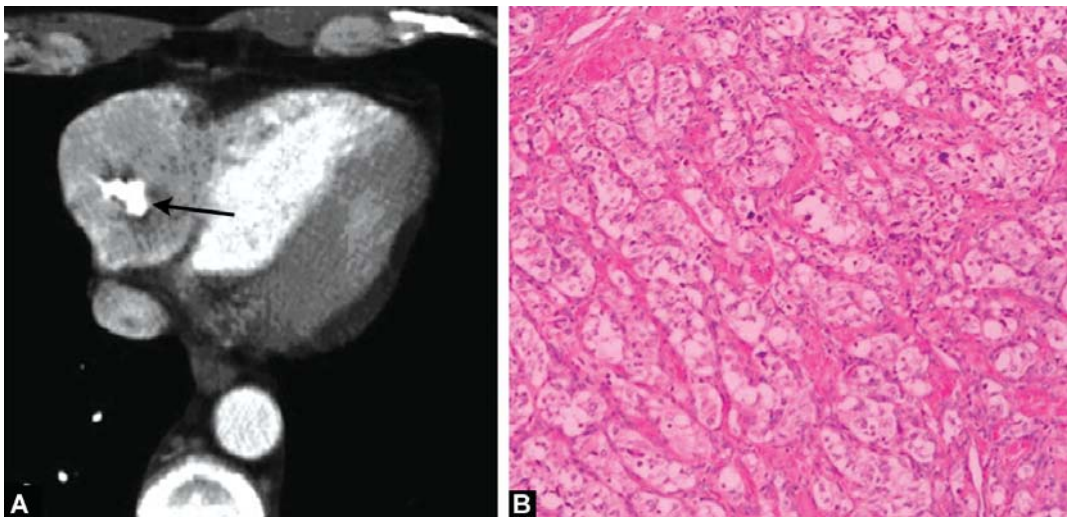
In the current classification of primary cardiac tumors established by the World Health Organization (WHO), primary cardiac sarcomas are classified under the same schema as that used in the categorization of extra-cardiac soft tissue sarcomas. However, there has been less consensus on the establishment of a universally accepted grading system for this rare group of neoplasms. Two widely used systems include the Federation des Centres de Lutte Contre le Cancer (FNCLCC)[47] and the National Cancer Institute (NCI)[48] systems, both of which are three-tier grading schemes. While the NCI system is based on evaluation of the tumor histologic type, location and amount of tumor necrosis, the FNCLCC is based on tumor differentiation, tumor necrosis and mitosis count. Previous studies have suggested a slight advantage of the FNCLCC system to predict tumor mortality and distinct metastasis over the NCI scheme.[49]

Imaging

The most common radiographic abnormality observed in cardiac sarcomas is cardiomegaly. Transthoracic 2D-echocardiography is used for initial screening; however, TEE is more useful. On TEE the lesion appears as an intramyocardial mass and when located in the right atrium invasion of the vena cava can be detected when present. CT, however, is more helpful in cardiac sarcomas as it shows the characteristic broad based tumor infiltration into the myocardium as well as pericardial and mediastinal invasion or a mass protruding into the cardiac



FIGURES 10A TO D: (A) Intracardiac lipoma in a 45-year-old woman with palpitations. Axial proton density weighted MR image demonstrating a smooth, round intracavitary right atrial mass with a signal intensity characteristic of fat. (B) Photograph of the specimen demonstrates a well-circumscribed, spherical, yellow mass that was excised from the right atrium. (*Source:* Reproduced with permission from Grebenc ML, Rosado de Christenson ML, Burke AP, et al. Primary cardiac and pericardial neoplasms: radiologic-pathologic correlation. Radiographics. 2000;20:1073-103) (C) Gross photograph of lipomatous hypertrophy of atrial septum note spherical fatty mass projecting into the right atrium limited inferiorly by the fossa ovalis. (*Source:* Shirani J, Roberts WC. Clinical, electrocardiographic and morphologic features of massive fat deposits ("lipomatous hypertrophy") in the atrial septum. J Am Coll Cardiol. 1993;22:226-38) (D) Lipomatous hypertrophy of atrial septum note multivacuolated adipocytes which represent brown fat along with mature fat



FIGURES 11A AND B: Paraganglioma. (A) ECG gated 64-detector dual-source CT with intravenous contrast in a 60-year-old male demonstrating a well-circumscribed heterogenous mass with a broad base of attachment and areas of central calcification (arrow) representing a paraganglioma at the base of the heart related to anterior and posterior aspect of the right ventricle. (*Source:* Anavekar NS, et al. Radiology Clin N Am. 2010;48:799-816). (B) Paraganglioma, microscopic features demonstrate classic nesting (zell-ballen) appearance of the paraganglion cells

TABLE 6

Clinical and morphologic characterization of surgically resected cardiac sarcomas: results of 12 institutional series

Histologic type	*Mean age, range (yrs)*	*M:F :Unknown*	*LA (%)*	*RA (%)*	*Vent, Diff*	*Pericardium*	*Survival until death, mean (mos)*	*Survival until last follow-up mean (mos)*
Unclassified (n = 49) (26%)	45(1–88)	19:18:12	49	13	32%	6%	3 (n = 14)	12 (n = 2)
Angiosarcoma (n = 48) (25%)	42(14–70)	31:10: 7	5	68	16%	11%	3 (n = 19)	22 (n = 2)
MFH (n = 19) (10%)	43(12–86)	5:12:2	86	10	4%	0	5 (n = 9)	8 (n = 2)
Leiomyosarcoma (n = 17) (9%)	32(1–62)	8:9	77	17	6%	0	9 (n = 3)	0
Osteosarcoma (n = 14) (7%)	35(16–67)	6:7:1	100	0	0	0	6 (n = 11)	8 (n = 2)
Rhabdomyosarcoma (n = 12) (6%)	17(0–42)	3:4:5	40	15	45%	0	3 (n = 4)	0
Fibrosarcoma (n = 11) (6%)	40(2–68)	4:7	46	36	18%	0	7(n = 4)	5 (n = 1)
Myxosarcoma (n = 8) (4%)	42(2–66)	3:5	76	12	12%	0	50 (n = 1)	6 (n = 3)
Synovial sarcoma (n = 6) (3%)	37(13–48)	5:1	33	0	50%	17%	56(n = 2)	8 (n = 1)
Liposarcoma (n = 4) (2%)	45(8–70)	2:2	0	0	75%*	25%	9 (n = 2)	No data
MPNST (n = 2) (1%)	52(48–55)	2:0	0	0	50%	50%	No data	No data
Total (n = 190)	40(0–88)	88:75:27	46	16	28%	10%	6.5 (n = 69)	10 (n = 13)

Data derived from the following series: Putnam et al. (21 tumors), Murphy et al. (13 tumors), Bear et al. (8 tumors), Tazelaar et al. (7 tumors), Miralles et al. (7 tumors), Dein et al. (7 tumors), Reece et al. (5 tumors). Data were not available for all cases.

*One patient had intracardiac mass involving LA, LV and mitral valve

(Abbreviations: M: Male; F: Female; MFH: Malignant fibrous histiocytoma; LA: Left atrium; RA: Right atrium; mos: Months; yrs: Years)

(*Source:* Virmani R, Burke AP, Farb A, et al. (Eds). "Cardiovascular Pathology" Major Problems in Pathology, 2nd edition. Philadelphia: WB Saunder; 2001. p. 425.

chamber. CT will also illustrate any contiguous invasion of other cardiac chambers such as the right ventricle and pericardial thickening and hemorrhage, especially in angiosarcomas.

ANGIOSARCOMA

As the most frequently reported primary malignant cardiac neoplasm, angiosarcomas occur with equal frequency in both men and women.[50] In one series of 24 cases of primary cardiac sarcomas diagnosed between 1994 and 2006, angiosarcoma accounted for 42% of all sarcoma cases.[51] In the AFIP series, angiosarcoma accounted for 25% of all sarcomas. For most of the primary cardiac sarcomas, the peak in diagnosis is in fourth decade. Eighty percent arise in the right atrium adjacent to atrioventricular groove, with smaller numbers found in other three chambers and pericardium.[52] Patients may present with chest pain, symptoms of right-sided heart failure, supraventricular arrhythmia,[53] shortness of breath, malaise and fever.[54] Right atrial lesions also have shown a propensity for pericardial involvement causing hemopericardium and pericardial constriction;[54] however, the majority of angiosarcoma cases are silent. Pseudoaneurysm of the (right) coronary arteries is rare complication with very few case reports in the literature.[55]

Imaging

Typically angiosarcomas show a heterogeneous signal by MRI, as there are areas of hemorrhage as well as necrosis.[12,38,56] T1WI images of the tumor show a low signal whereas T2WI show increased signal and a central area of hyperintensity because of hemorrhage and necrosis. In the peripheral regions of the tumor the signals are of moderate intensity; with gadolinium there is strong signal enhancement because of high vascularity.[12]

Gross Pathology

Angiosarcomas are typically bulky, lobulated, masses extending from the right atrial wall into the chamber, ranging from 2.0 cm[53] to 17 cm (mean 7.2 cm) in greatest dimension.[51] In a typical case, the cut surface varies from variegated tan solid areas with red-brown hemorrhagic foci to frank necrosis, or can present as dark brown or black masses resembling a melanoma.[1]

Histologic Findings

Approximately two-thirds of primary cardiac angiosarcomas can be considered well to moderately differentiated and are characterized by well formed, anastomosing vascular channels or papillary structures lined by pleomorphic malignant endothelial cells with varying amounts of atypia and mitoses.[14,51] The remaining one-third of cases are considered poorly differentiated and are composed of highly atypical spindle cells (Figs 12A to E). Most angiosarcomas express endothelial markers such as CD31 and CD34 in the cells lining the vascular channels or papillary structures. In addition, laminin or type IV collagen can highlight vascular channels,[4] and in areas of endothelial differentiation, cytokeratins can be diffusely positive.[57]

MALIGNANT FIBROUS HISTIOCYTOMA

In one review of 47 reported cases the age range for presentation with malignant fibrous histiocytoma (MFH) was between 14 years and 77 years of age, with a female predominance (mean age for presentation of 50.1 years in women). Patients present with symptoms similar to those seen with other sarcomas, such as dyspnea, heart palpitations and chest discomfort. The classic "tumor plop", often auscultated in cases of myxoma, can be appreciated in instances of an MFH obstructing the mitral valve orifice.[1,58] Metastasis of cardiac MFH have been reported in the brain, lung, bone and adrenal glands.[58]

Gross Pathology

Malignant fibrous histiocytomas primarily arise from the posterior wall of the left atrium, with gross infiltration into the left atrial wall. Often these tumors are large, multiple (with up to 10 tumors identified in a single case) and lobulated, described either as soft or creamy in texture,[1,59] or as white to gray firm masses with cystic cavities on the cut surface (Figs 13A and B).[1,60]

Histologic Findings

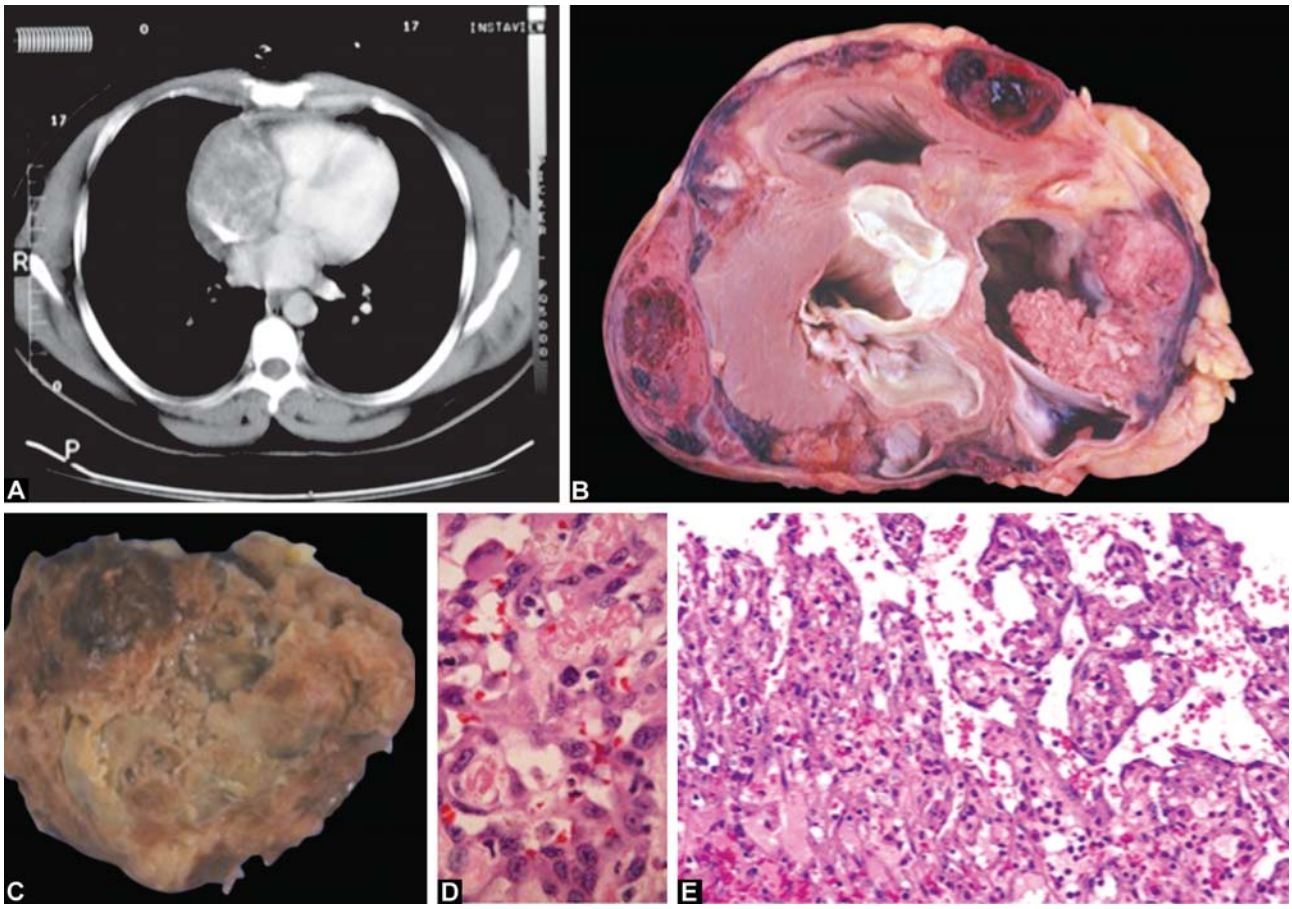
The primary cardiac MFH is a highly cellular neoplasm, much like its soft tissue counterpart. Despite the recognition of multiple histologic patterns seen in soft tissue MFH, only two basic patterns have been reported in the heart including the characteristic pleomorphic histiocytoid and fibroblastic cells arranged in a storiform pattern or a myxoid variant.[58,60] Positivity with immunohistochemical stains for vimentin, CD68 (focal), smooth muscle actin (focal), α-antitrypsin and α-antichymotrypsin have been reported. Usually, MFH is negative for cytokeratin, desmin, myoglobin, S-100 and factor VIII-related antigen.[1,58,60]

OSTEOSARCOMA

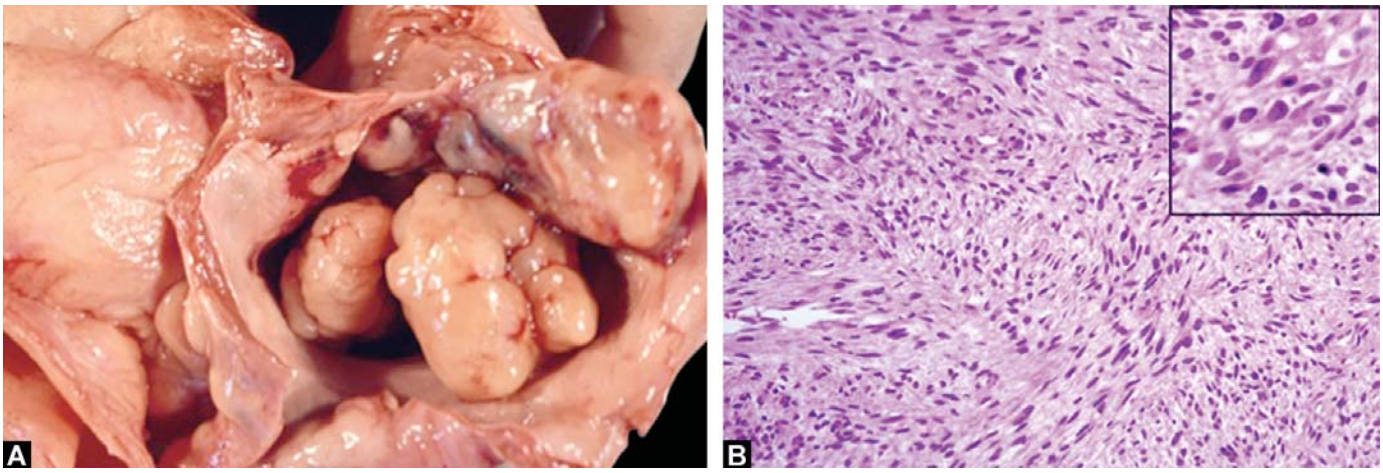
Primary cardiac osteosarcomas are aggressive neoplasms, with a high rate of reoccurrence and metastasis to sites such as bone, brain, skin, lung, liver and adrenal glands even after a treatment regimen of surgical resection followed by chemotherapy and radiation therapy.[61] When the mass is located in the left atrium, patients may present with respiratory symptoms such as dyspnea, orthopnea and nocturnal paroxysmal dyspnea. Ventricular masses may present with recurrent ventricular tachyarrhythmia.[54] Case studies report left atrial enlargement on non-contrast chest CT, sometimes with no evidence of calcification.[61]

Gross Pathology

Osteosarcomas of the heart are bulky, sessile growths attached to the wall of the left atrium, ranging from 4 cm to 10 cm in diameter[1] with a mucoid or gelatinous gross appearance. Often, these tumors have a broad base of attachment to the LA wall without a discernable stalk or frank invasion, in contrast to the short, broad-based stalk of the myxoma.[62] Invasion through the left atrial wall or into the mitral valve is seen in approximately 20% of cases of cardiac osteosarcoma. Similar to its soft tissue counterpart, upon sectioning the cut surface of this neoplasm demonstrates gritty or hard areas.



FIGURES 12A TO E: Cardiac angiosarcoma. (A) CT section at the level of the aortic valve demonstrates a soft tissue mass completely filling the right atrium. (B) Cardiac angiosarcoma arising in atrioventricular groove, forming a papillary mass. Note extensive pericardial involvement. (*Source:* Dr William D Edwards). (*Source:* Burke A, Tazelaar H, Veinot JP, et al. Cardiac sarcomas. In: Travis W, Brambilla E, Muller-Hermelink HK, Harris C (Eds). World Health Organization Classification of Tumours. Lyon: IARC Press; 2004) (C) Gross photograph of a surgically removed angiosarcoma note brown appearance with areas of hemorrhage and necrosis. (D) The cells are large with prominent eosinophilic cytoplasm with cytoplasmic vacuoles containing red cells. Nuclei were large and hyperchromatic and had prominent eosinophilic nucleoli. (E) Cardiac angiosarcoma showing papillary features with irregular anastomosing sinusoidal structures lined by hyperchromatic plump nuclei. Both mitosis and atypia are noted in such tumors



FIGURES 13A AND B: Malignant fibrous histiocytoma. (A) Gross appearance of the lesion which is located in the left atrium, note polypoid appearance. (*Source:* Burke A, Tazelaar H, Veinot JP, et al. Cardiac sarcomas. In: Travis W, Brambilla E, Muller-Hermelink HK, Harris C (Eds). World Health Organization classification of tumours. Lyon: IARC Press; 2004). (B) Histologic appearance is variable but this tumor showed spindle cells arranged in a storiform pattern with marked pleomorphism and fibrohistiocytic appearance. Mitotic figures were easy to find. Inset shows pleomorphic nature of the tumor

Histological Findings

Cardiac osteosarcomas are a histologically heterogeneous group of neoplasms, reflected in the numerous names applied to this tumor in the past. Most exhibit malignant bone forming cells embedded in a background of a spindle cell or pleomorphic cardiac sarcoma. Some case studies report focal immature osteoid deposition.[1,61] These spindle cells are focally actin positive and diffusely vimentin positive.[1] The term chondrosarcoma denotes tumors in which S-100 positive chondroid cells are present in the absence of osteoid. Osteoclastoma, as a label is applied when the presence of numerous osteoclast-like giant cells is noted; in the past this variant is also classified as the giant cell MFH. It is important to note that osteosarcoma can be misidentified as a myxoma in the heart, given that both may exhibit calcified or ossified areas.[1,61]

LEIOMYOSARCOMA

As for other primary cardiac sarcomas, the mean age for presentation with this rare neoplasm is in the fourth decade, with little difference in the distribution among the sexes. The majority are localized to the left atrium (75–80%) and present with pulmonary symptoms of dyspnea, chest pain and non-productive cough.[1,54] When present in the left ventricle, patients may experience right heart failure, valve stenosis, rhythm alterations, conduction abnormalities, hemopericardium and sudden death as result of left ventricular outflow obstruction.[1,54]

Gross Pathology

Leiomyosarcomas appear as sessile, mucoid or myxoid masses localized to the posterior left atrial wall. Infiltration into the pulmonary veins or mitral valve can occur, and up to 30% of cases demonstrate multiple masses.[1]

Histologic Findings

On microscopic sections, primary cardiac leiomyosarcomas appear as mesenchymal neoplasms composed of spindle cells with blunt edged, hyperchromatic nuclei oriented in well-defined fascicles. Characteristically, the spindle cells show varying amounts of structural and/or immunohistochemical evidence of smooth muscle differentiation. The spindle cells may display characteristic features such as cytoplasmic glycogen, perinuclear vacuoles and intracytoplasmic desmin. Myxoid degeneration in up to 25% of the tumor mass has been reported.[1,63] In one case study, focal rhabdomyoblastic differentiation was identified in a small subset of myogenin-positive, alpha smooth muscle actin-negative polyhedral cells.[63]

RHABDOMYOSARCOMA

Rhabdomyosarcomas are the most common cardiac malignancy in children and usually diffusely infiltrate the myocardium involving either the atrium or the ventricle, which may be the primary site. The rhabdomyosarcomas in the left atrium present often present with "classic" atrial myxoma that lead to pulmonary symptoms. Others may present with palpitations and symptoms related to pericardial effusions.[38] They occur slightly more frequently in males than females (1.4:1), especially in the pediatric and young adult population with a mean age in presentation in the second or third decade.[1,52,64] Patients present with non-specific symptoms, such as pleuropericardial symptoms, distal embolization, arrhythmias and/or obstructive symptoms.[54]

Gross and Histology

Like other primary cardiac sarcomas, rhabdomyosarcomas are large, bulky neoplasms, measuring past 10 cm in diameter, often invasive in the left atrium (and less often into the mitral valve).[1] One distinctive feature is that rhabdomyosarcomas may arise in any of the four cardiac chambers. On histology these are characterized in the same manner as extracardiac rhabdomyosarcoma, embryonal and adult (Figs 14A to D).

SYNOVIAL SARCOMA

Synovial sarcomas, regardless of primary location, are a biphasic tumors composed of a spindle cell and an epithelial cell component. As an entity, it is distinguished by the characteristic X: 18 chromosomal translocation. This neoplasm is encountered in young to middle aged adults with no sex predilection and can be located on the pericardium, right ventricle, right atrium and left atrium.[1]

UNCLASSIFIABLE OR UNDIFFERENTIATED SARCOMAS

This subgroup includes those sarcomas without specific histologic, ultrastructural or immunohistochemical patterns and cannot be further subclassified. Clinical features are similar to those for the sarcoma categories, including a mean age at presentation of 45 years, a predominately left-sided location and presenting symptoms related to congestive heart failure (Figs 15A to D).[1]

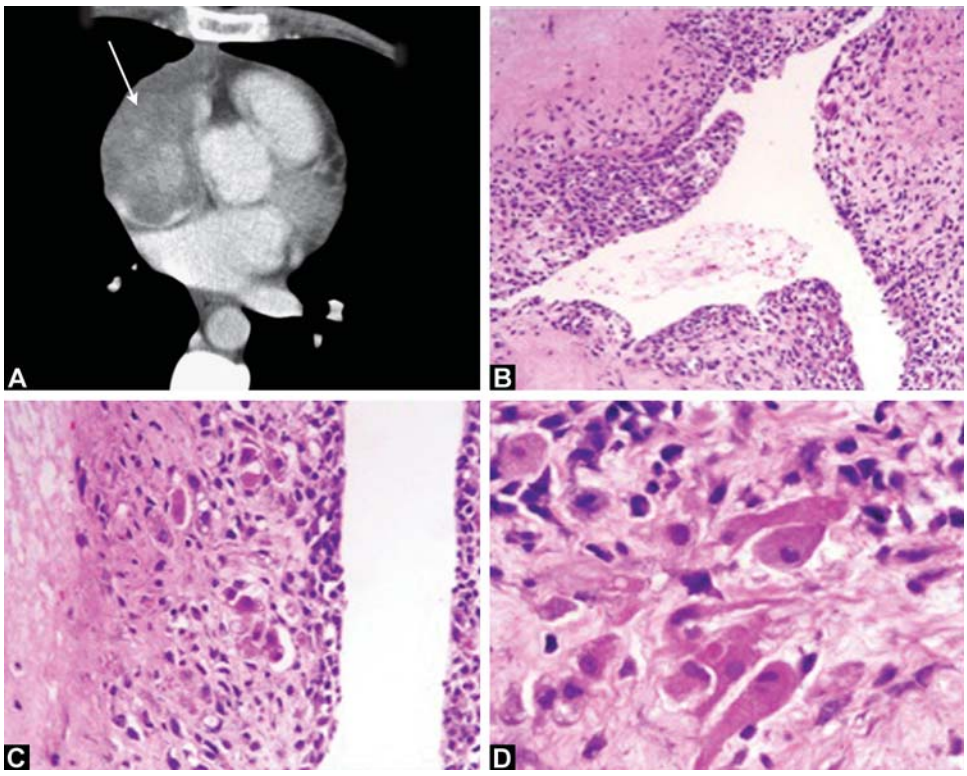
OTHER SARCOMAS

Although rare, additional sarcomatous subtypes include liposarcomas, malignant schwannoma, malignant mesenchymoma (sarcomas with two or more distinct subtypes of cellular differentiation in a background of either fibrosarcoma or MFH), malignant rhabdoid tumors, Kaposi's sarcoma and malignant hemangiopericytoma.

PRIMARY CARDIAC LYMPHOMA

Primary lymphomas of the heart are rare and frequently diagnosed at autopsy. At the time of the last fascicle on cardiac tumors from the Armed Forces Institute of Pathology in 1996 a total of 38 primary lymphomas had been published since then another 50 or so have been added. By far the largest series of 5 cases comes from Brigham and Women's Hospital with 3 patients presenting with chest pain and 3 had dyspnea. One patient had bradycardia but none had constitutional symptoms.[65]

Primary cardiac lymphoma (PCL) is defined as an extranodal non-Hodgkin's lymphoma arising from only the heart and/or pericardium with small secondary lesions present in



FIGURES 14A TO D: Primary cardiac lymphoma. Primary cardiac lymphoma in a 75-year-old woman with progressive dyspnea, superior vena cava syndrome and atrial fibrillation. (A) Coronal T1-weighted MR image shows vena cava invasion (arrow) by a mass. (B) Photomicrograph of the specimen of the heart obtained at autopsy showed a firm, white, multinodular right atrial tumor with plaque-like pericardial infiltration (obstruction of the superior vena cava). (*Source:* Grebenc ML, Rosado de Christenson ML, Burke AP, et al. Primary cardiac and pericardial neoplasms: radiologic-pathologic correlation. Radiographics. 2000;20:1073-103) (C) The tumor shows large neoplastic cells with vesicular chromatin and small amount of pale eosinophilic cytoplasm. (D) Immunohistochemical stain for CD 20 established B-cell lineage

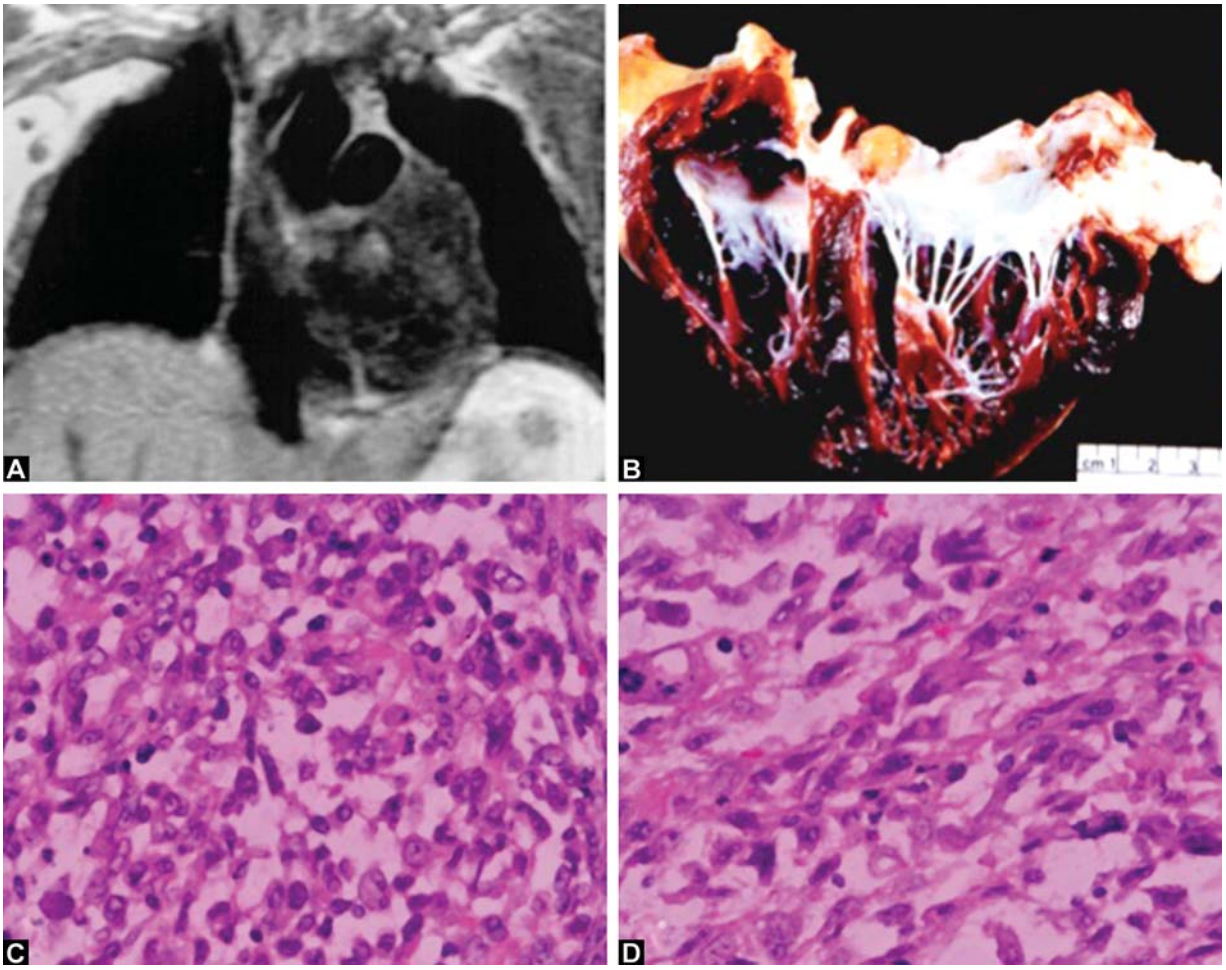
distant sites. PCL accounts for only 1.3% of all primary cardiac malignancies, with a male predominance (male to female ratio 3:1). However, in one population of 197 patients, the male to female ratio was as low as 1.94[66] and in one series of five cases of PCL, all patients were women between the fourth and sixth decades.[65] Patients may present with symptoms of congestive heart failure (47%)[66] including exertional dyspnea (seen in up to 64%),[66] atrial fibrillation and features of right-sided heart obstruction or cardiac tamponade.[54] Additional clinical presentations reported in patients with PCL include superior vena cava obstruction, multiple pulmonary emboli and infarction, hypertrophic cardiomyopathy, pericardial effusion (12.5% of cases) or complete atrioventricular block.[4] Primary lymphomas of the heart also have a tendency to arise from the right side with right atrium being the most frequent site and pericardial involvement with effusion is often present. They rarely show necrosis or valvular involvement unlike the more common malignant sarcomas. In most cases, the bone marrow is not involved and no enlarged superficial lymph nodes are identified.[67] Although most PCL cases arise in immunocompetent patients, there is evidence to suggest that immunodeficiency may play a role in its evolution in immunocompromised solid-organ transplant or HIV-positive patients as component of widespread lymphomatous disease.[4,66] Some argue that the apparent increase in newly diagnosed cases of PCL reflects the longer life span of immunocompromised patients; others claim this increase is secondary only to advances in the diagnostic capability of imaging techniques.[66]

Imaging

Echocardiography, CT and MRI are helpful not only in the diagnosis but also for the monitoring of the chemotherapy. On echocardiography they appear as hypoechoic myocardial masses in the right heart with pericardial effusion. On CT, cardiac lymphomas are hypoattenuated or isoattenuated relative to the myocardium with heterogeneous enhancement after contrast agent administration. On MRI images they appear isointense or hypointense relative to myocardium on both T1 and T2WI and show heterogeneous enhancement after administration of gadolinium.[12,38,56]

Gross Pathology

In two-thirds of patients, the right atrium is involved; however, PCL can arise in any chamber of the heart or the pericardium. PCL is another large, infiltrative cardiac tumor with reports of diameters greater than 7.5 cm. Often, PCL will invade into the myocardium and cavities as multiple polypoid projections obliterating the cavity involved. When the pericardium is involved, it is thickened by white-gray tumor infiltration (Figs 16A to D).[4]



FIGURES 15A TO D: Unclassified sarcoma in a 29-year-old man with cough, fever and weight loss who underwent heart transplantation. (A) Coronal T1-weighted MR image shows a large, invasive mass of intermediate signal intensity involving the left side of the heart. (B) Photograph of the excised heart shows the nodular mass invading the left atrial wall and mitral valve. (C) Photomicrographs of an unclassifiable sarcoma showing small rounded cells in a focally myxoid background. (D) Shows an area of pleomorphic epithelioid appearance of cells

Histological Findings

In the majority of published cases (80%), diffuse large B-cell lymphoma is the predominant histologic pattern (Figs 16A to D) with fewer cases (listed in order of decreasing frequency) including Burkett's lymphoma (in a child in one series),[67] T-cell lymphoma, small lymphocytic lymphoma and plasmacytic lymphoma.[4,66]

PERICARDIAL MESOTHELIOMA

The diagnosis of primary pericardial mesothelioma can only be rendered if, with the exception of lymph node metastasis, no tumor is present outside of the pericardium.[1] Clinical symptoms include chest pain, cough, dyspnea and palpitations.[54] Despite being the most common primary pericardial tumor (50%),[68] it is a vanishingly rare tumor with 1/40 million persons a year diagnosed with primary pericardial mesothelioma (yearly incidence of 0.0025 per 100,000) in Canada (1970) and only 150–200 well established cases reported in literature worldwide.[69] The mean age for presentation is 46 years (range 2–78 years), with a male to female ratio of 2:1, which is lower than the 3.5:1 ratio for pleural mesotheliomas.[1]

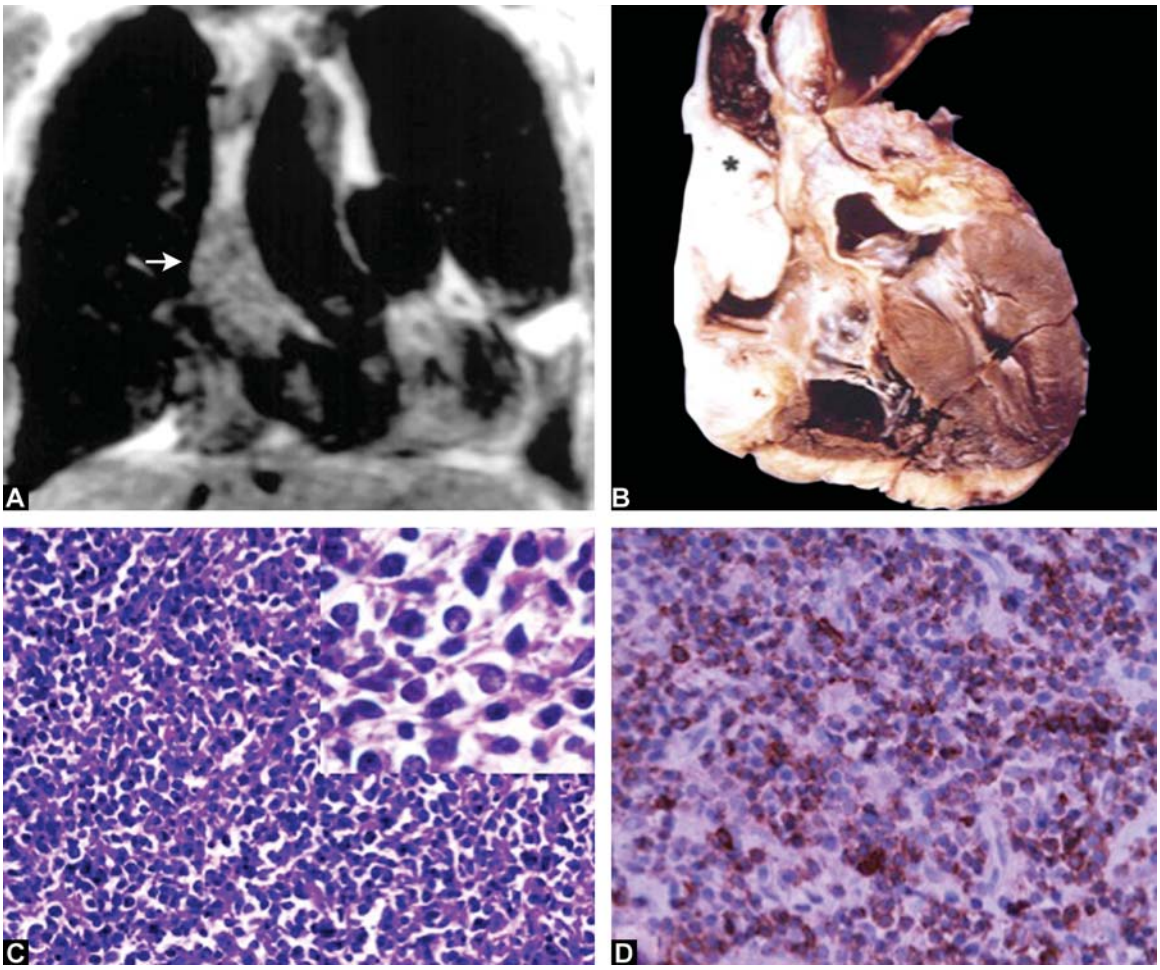
Gross Pathology

Malignant mesotheliomas of the pericardium may demonstrate bulky nodules that fill the pericardial cavity and encase the heart. Rarely is there infiltration of the myocardium. On sectioning, the tumor has a variable cut surface ranging from solid white to hemorrhagic, cystic and necrotic. In addition, there may be secondary nodules on surfaces on diaphragmatic and pleural surfaces.

Histologic Findings

Malignant mesotheliomas are histologically identical to pleural mesotheliomas with three subtypes: (1) epithelial cell; (2) sarcomatoid and (3) mixed (biphasic). The epithelial type demonstrates atypical cells forming cords, nests tubules and papillary structures in a desmoplastic background. In the sarcomatoid subtype, cells characteristically exhibit ample cytoplasm, large oval nuclei and prominent nucleoli.

The immunohistochemical profile is similar to that of pleural mesothelioma. There is expression of pancytokeratin, calretinin, cytokeratin 5/6 and vimentin (preferentially in sarcomatoid areas in pleural mesotheliomas) occasional positivity for EMA (in



FIGURES 16A TO D: Rhabdomyosarcoma. (A) Single-detector single-source CT of the chest with intravenous contrast performed in a 42-year-old woman. CT imaging demonstrates an irregular mass starting at the confluence of the superior vena cava and right atrium extending to completely involve the right atrium (arrow). (*Source:* Anavekar NS, et al. Computed tomography of cardiac pseudotumors and neoplasms. Radiology Clin N Am. 2010;48:799-816) (B) Embryonal rhabdomyosarcoma masquerading as a small cell undifferentiated tumor with cellular areas concentrated toward the surface, which has also been observed in myxomas. (C) Higher magnification showing focal areas of cells with abundant eosinophilic cytoplasm. (D) Rhabdomyoblasts, some tadpole shaped with large eosinophilic cytoplasm

epithelioid mesothelioma of pleura). CEA, Ber-EP4, Leu, Mi1, HMBE1, CD45, CD24, CD20, CD45RO, CA 125, S100 protein, desmin, B72.3 and smooth muscle actin are typically negative.[10,25]

METASTATIC TUMORS

Metastatic tumors to the heart are by far the most common cardiac malignancy and should always be in the differential diagnosis before making the diagnosis of a primary malignancy. They occur at a frequency 100-fold to 1,000-fold greater than those of primary cardiac neoplasms.[54] Carcinomas by definition must always be metastatic and cannot arise from any cell type within the heart; in the case of sarcomas and mesotheliomas, a primary site must first be ruled out. In a recent report by Butany et al. cardiac involvement at autopsy was reported to be 2.3%; however, the incidence of cardiac involvement when there is disseminated metastasis is 10–25%.[54] In addition, cardiac metastases are more frequently carcinomas than sarcomas. Most metastases are to the pericardium and/or epicardium, followed by myocardium and endocardium.[70] Epithelial malignancies tend to spread via lymphatics. Melanomas, sarcomas, leukemias and renal cell carcinomas spread hematogenously which usually results in myocardial involvement.[71] Interestingly, melanomas (and secondarily malignant germ cell tumors and malignant thymoma) have the highest rate of metastasis to the heart, involving the myocardium in more than 50% of cases.[72] However, the most commonly identified tumor types are breast and lung carcinomas followed by esophageal carcinoma and malignant lymphoma/leukemias[1,71] (Table 7). Classically, renal cell carcinoma spreads secondary to intraluminal growth extending into the inferior vena cava. However, direct extension via the inferior vena cava is also seen with hepatocellular carcinoma, leiomyoma of the uterus, nephroblastoma (Wilms tumor), pheochromocytoma and adrenal cortical carcinoma. There can also be extension into the right atrium via the superior vena cava from lung and thyroid carcinomas.[71]

Symptoms depend on the primary tumor as well as myocardial or pericardial involvement.

TABLE 7

Tumors metastatic to the heart at autopsy

Primary tumor	*Total autopsies*	*Heart* involvement*	*Pericardial involvement***	*Total*
Melanoma	69	32 (46%)	2 (3%)	34 (49%)
Malignant germ cell tumor	21	8 (38%)	1 (5%)	9 (34%)
Leukemia	202	66 (33%)	2 (1%)	68 (43%)
Carcinoma of lung	1037	180 (17%)	112 (11%)	292 (28%)
Sarcoma	159	24 (15%)	11 (7%)	35 (22%)
Lymphoma	392	67 (17%)	15 (4%)	82 (21%)
Carcinoma of breast	685	70 (10%)	69 (10%)	139 (20%)
Carcinoma of esophagus	294	37 (13%)	13 (4%)	50 (17%)
Carcinoma of kidney	114	12 (11%)	5 (4%)	17 (15%)
Carcinoma of oral cavity and tongue	235	22 (9%)	2 (1%)	24 (10%)
Carcinoma of larynx	100	9 (9%)	2 (2%)	11 (11%)
Carcinoma of thyroid	97	9 (9%)	3 (3%)	12 (12%)
Carcinoma of uterus	451	36 (8%)	5 (1%)	41 (9%)
Carcinoma of stomach	603	28 (5%)	16 (3%)	44 (7%)
Carcinoma of colon and rectum	440	22 (5%)	3 (1%)	25 (6%)
Carcinoma of pharynx	67	1	2	3 (4.5%)
Carcinoma of urinary bladder	128	8 (6%)	0	8 (6%)
Carcinoma of ovary	188	2 (1%)	6 (3%)	8 (4%)
Carcinoma of prostate	171	6 (4%)	0	6 (4%)
Carcinoma of nasal cavity	32	1	0	1 (3%)
Carcinoma of pancreas	185	6 (3%)	0	6 (3%)
Carcinoma liver and biliary tract	325	7 (2%)	0	7 (2%)
Totals***	6240	654 (10%)	299 (5%)	953 (15%)

*Tumors with pericardial and myocardial involvement
**Bulk of tumor localized to pericardium
***Including uncommon tumors or location not mentioned in the tables
(*Source:* Burke AP, Virmani R. Tumors of the heart and great vessels. In: Rosai J, Sobin L (Eds). Atlas of Tumor Pathology, 3rd series. Armed Forces Institute of Pathology (AFIP); 1995. pp. 1-227)

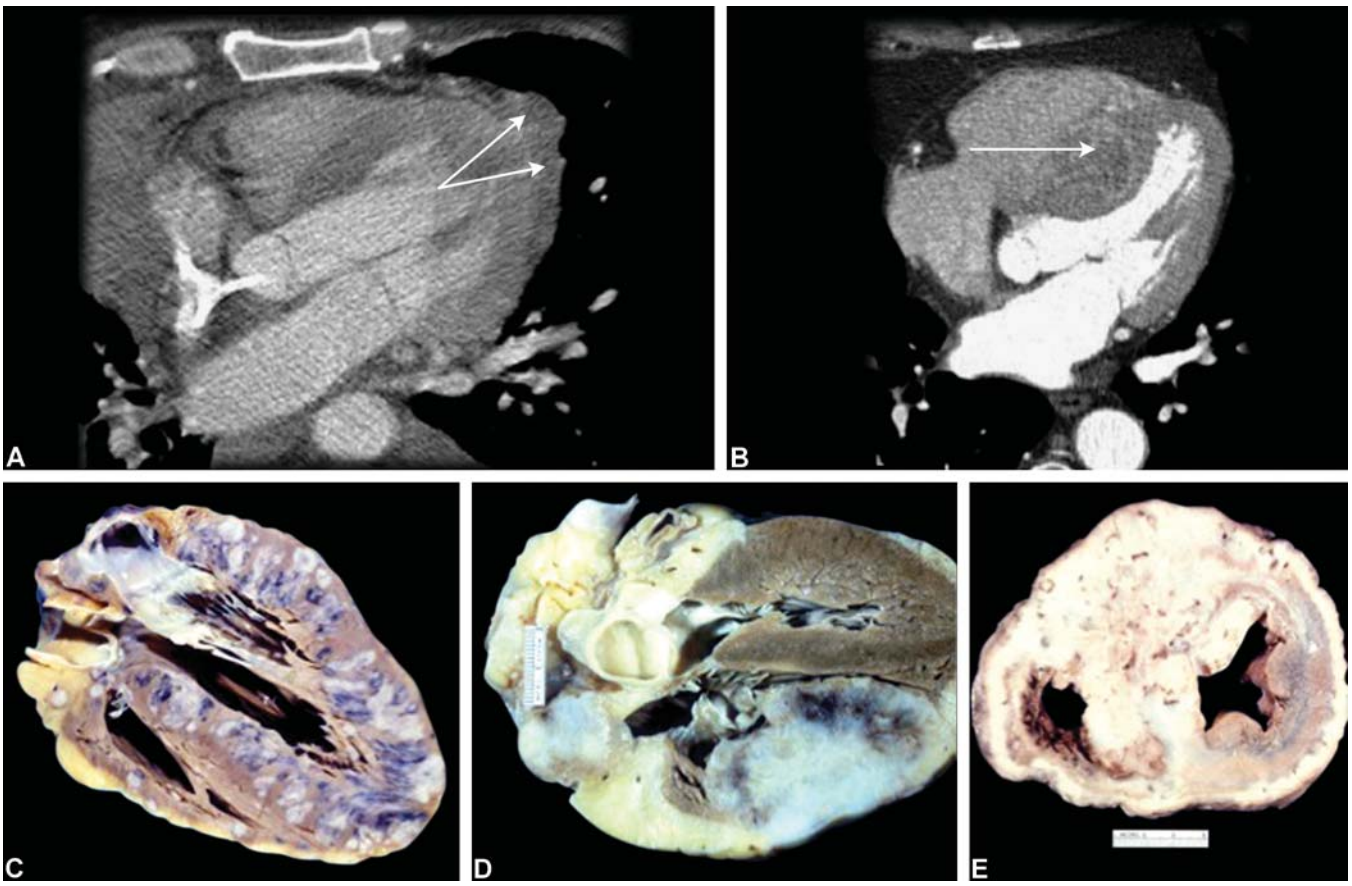
However, most remain silent and are first discovered upon autopsy and often the extent of spread does not correlate with reported symptomatology during the patient's life.[71] Tachycardia, arrhythmias, cardiomegaly or heart failure in a patient with carcinoma should raise suspicion of cardiac metastasis.[54]Rarely, cardiac involvement, such as pericardial effusion or incipient cardiac tamponade, can be the first clinical feature of malignant disease, although 90% are clinically silent.[54] Pericardial effusion is most likely to occur with lung or breast carcinoma.

Imaging

Chest radiography usually reveals an increase in cardiac silhouette, which may be secondary to pericardial effusion or pericardiac and/or paracardiac tumor involvement. Also, bony metastases from osteogenic sarcoma can be visualized.[71] Echocardiography may reveal dense pericardial bands reflecting a pericardium thickened by tumor infiltration and inflammation. Effusions can also be diagnosed, even in the presence of large myocardial metastasis and regional wall motion abnormalities. CT and MRI imaging methods are both useful for establishing myocardial and pericardial involvement as well as mediastinal, pulmonary and thoracic structures.[56] Most metastases show low signal intensity compared to myocardium on T1WI and high signal intensity on T2WI. It has been shown that melanomas appear bright on T1WI because of paramagnetic effects of melanin (Figs 17A to E).[24]

Gross Pathology

Metastatic tumors vary greatly in their pattern of deposition. Carcinomas may diffusely seed or thicken pericardium. In addition, there may be carcinomatous spread to subepicardial lymphatics. Discrete intramyocardial interstitial tumor nodules are seen with melanoma, renal cell carcinoma, lymphoma and sarcomas (Figs 17A to E). Often primary versus secondary (metastatic) sarcomas are indistinguishable from each other grossly.[11]



FIGURES 17A TO E: (A) Four-detector single-source CT with intravenous contrast performed to assess for pulmonary embolism in a 44-year-old man presenting with dyspnea and known history of rectal cancer. CT demonstrates pericardial nodular metastases (arrows) as a result of lymphatic spread of rectal cancer. (B) ECG gated 64-detector dual-source CT with intravenous contrast in a 63-year-old man with metastatic renal cell carcinoma. CT image demonstrated renal cell carcinoma involving the interventricular septum (arrow), which enhances after contrast. (*Source:* Reproduced with permission from Anavekar NS, et al. Computed tomography of cardiac pseudotumors and neoplasms. Radiology Clin N Am. 2010;48:799-816) (C) Gross photograph of the heart from a case of metastatic melanoma note extensive puckering of the left ventricular free wall, ventricular septum and right ventricular myocardium by both pigmented and non-pigmented malignant melanoma metastasis. (D) This elderly man had a primary colonic carcinoma with widespread metastasis. Note massive infiltration of the right ventricle and atrium. (E) Left and right ventricular slice from a patient with primary lung carcinoma. Note anterior surface of the right, left and interventricular septum are replaced by massive metastasis

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Chapter 97

Neurogenic and Stress Cardiomyopathy

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Chapter Outline

- Neurogenic Cardiomyopathy
  - Clinical Features
  - Pathophysiology
  - Diagnosis
  - Treatment
  - Prognosis
- Stress Cardiomyopathy
  - Clinical Features
  - Pathophysiology
  - Diagnosis
  - Treatment
  - Prognosis

INTRODUCTION

The brain is capable of exerting profound influence on the heart through direct effects of innervation and indirect effects of chemical mediators. Due to this relationship, brain injury or psychological stress may result in abnormal autonomic outflow to the heart, causing a diverse spectrum of cardiac injury and dysfunction which may present diagnostic and therapeutic challenges. The purpose of this review is to educate treatment providers about the clinical features, pathophysiology, prognosis and treatment of these unique cardiac conditions.

NEUROGENIC CARDIOMYOPATHY

Myocardial activity is mediated by multiple sites in the central nervous system (CNS). Through systemic release of catecholamines and direct innervation by the autonomic nervous system (ANS), the heart can meet a broad range of metabolic demands. Not surprisingly, brain injury may have numerous effects on the heart, including contractile dysfunction, arrhythmia and even sudden cardiac death. The syndrome of CNS-mediated cardiac injury has also been referred to as stunned neurogenic myocardium, neurogenic heart disease and neurocardiogenic injury. Cardiac abnormalities are observed in a variety of intracranial disturbances including brain trauma, ischemic stroke, brain hemorrhage, seizure disorders, post-electroconvulsive therapy and in brain dead organ donors. The presentations and mechanisms of neurogenic myocardial injury are complex, but the influence of the ANS is of central importance.

CLINICAL FEATURES

Many patients with brain injury are unable to communicate cardiac symptoms. However conscious patients may report symptoms such as chest discomfort, dyspnea, palpitations and presyncope or syncope. Some cases of sudden cardiac deaths have been attributed to neurogenic mechanisms. The demographic and clinical characteristics of the patients are generally determined by the underlying neurological condition. For example, 60–70% of patients with subarachnoid hemorrhage (SAH) are women. In general, women appear more likely to experience many forms of neurogenic heart disease.

ECG Abnormalities

Prominent U waves, prolonged QT interval and inverted T waves (Fig. 1) are common ECG changes after stroke and other forms of brain injury. The most common ECG abnormality is QT prolongation, which is observed most frequently in SAH but also occurs after intraparenchymal hemorrhage and ischemic stroke. The ECG may also reveal ST changes or new Q waves; the latter are not necessarily indicative of myocardial infarction (MI). ECG evidence of left ventricular hypertrophy (LVH) has been observed in SAH patients, even in the absence of a prior history of hypertension.[1] In this setting, as well as in brain dead organ donors, the ECG LVH pattern may reverse over time and might be due to myocardial edema or another acute process.

Arrhythmias

A variety of cardiac arrhythmias can be seen after brain injury and are quite common in some circumstances, occurring in up to 100% of SAH patients and 20% of patients with ischemic stroke. The observed arrhythmias include bradycardia, supra-ventricular tachycardias (SVT) including atrial fibrillation, premature ventricular contractions (PVCs), ventricular fibrillation and torsades de pointes (Fig. 2). The frequency and severity of arrhythmias are most severe during the first 48 hours after presentation.[2] Some arrhythmias are associated with brain injury in specific locations. Sinus bradycardia and SVT are seen in traumatic frontal lobe hemorrhage a third of

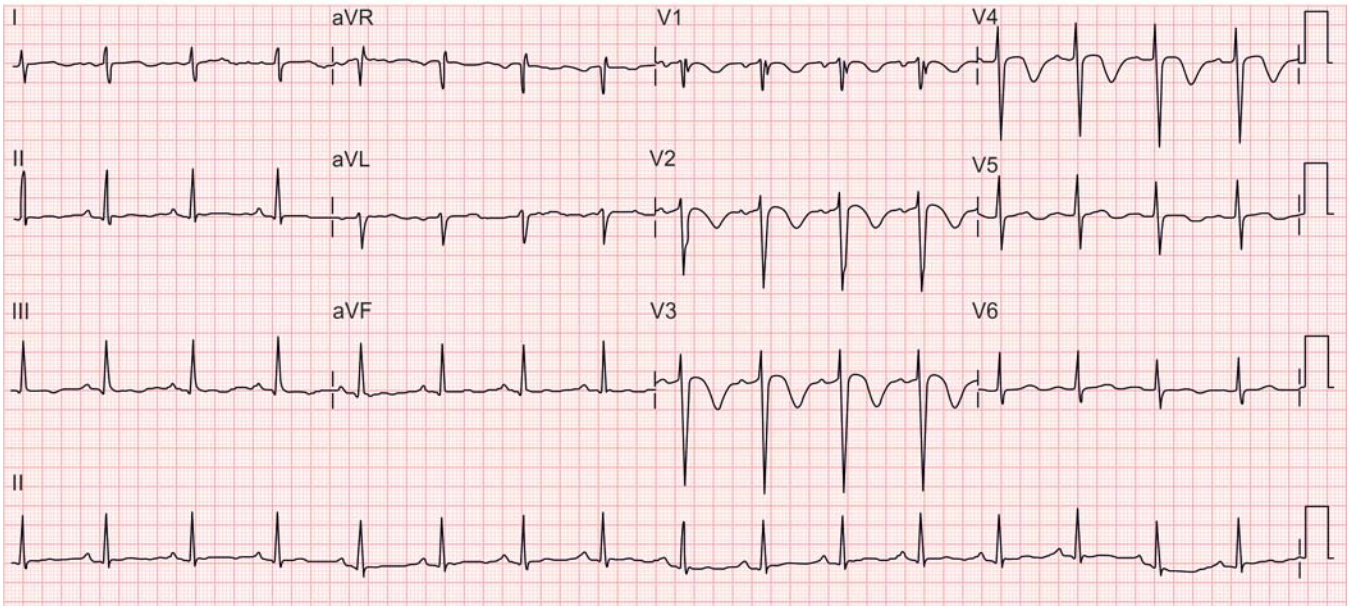


FIGURE 1: QT prolongation and deep anterior T wave inversions in a patient with subarachnoid hemorrhage

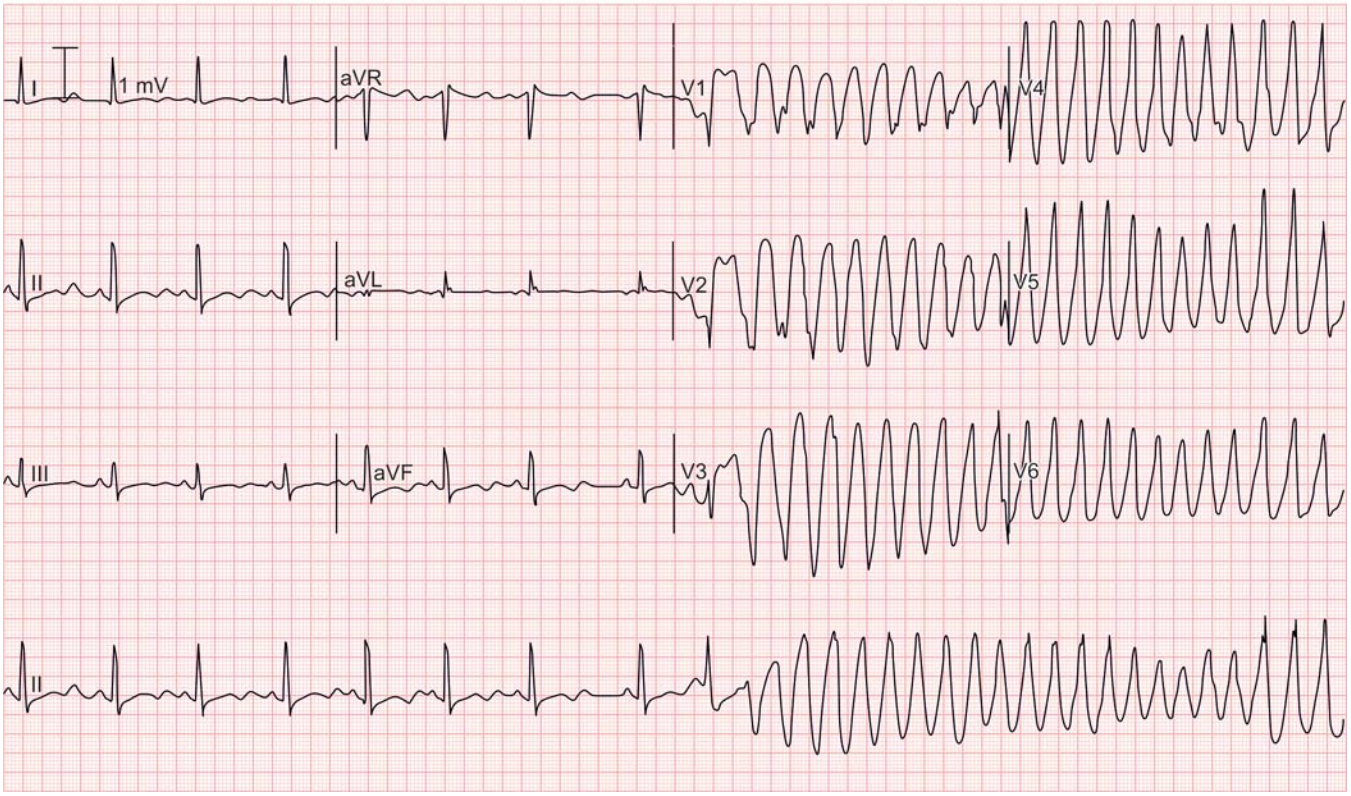


FIGURE 2: Torsades de pointes

the time.[3] Hemorrhage in the temporal-parietal region has been associated with atrial and ventricular ectopic beats. In ischemic strokes, PVCs are the most common arrhythmia.[4] Prolongation of the QT interval is relatively frequent in stroke caused by right middle cerebral artery occlusion. A prolonged QT interval may result in torsades de pointes, which might partially explain the occurrence of fatal arrhythmias after right hemispheric strokes. Patients with a prolonged QT after SAH who also have hypokalemia are more likely to develop torsade de pointes.

Release of Cardiac Biomarkers

Myocardial necrosis can occur in many forms of intracranial insult. Elevation of cardiac biomarkers is common in ischemic and hemorrhagic stroke. Creatine kinase (CK) and CK-MB

isoenzyme can be elevated in 10–45% of stroke patients.[5] Unlike MI from coronary atherosclerosis, however, CK-MB is elevated 4 days after stroke, peaks more slowly and plateaus at a lower value. In approximately a quarter of patients with SAH, cardiac troponin I (cTnI) is elevated and is associated with greater SAH severity and female gender.[6,7] Release of cardiac troponin I after SAH is also associated with adverse sequela, including pulmonary edema, delayed cerebral ischemia, poor functional outcome and death.[8]

Plasma levels of B-type natriuretic peptide (BNP) are frequently elevated to a modest degree after SAH and are more significantly elevated (> 600 pg/ml) in 9% of cases.[9] An elevated level of BNP is associated with myocardial necrosis, pulmonary edema, systolic and diastolic dysfunction.[7] BNP has been shown to be independently associated with adverse neurologic outcomes and can predict mortality after SAH.[9,10]

Left Ventricular Dysfunction

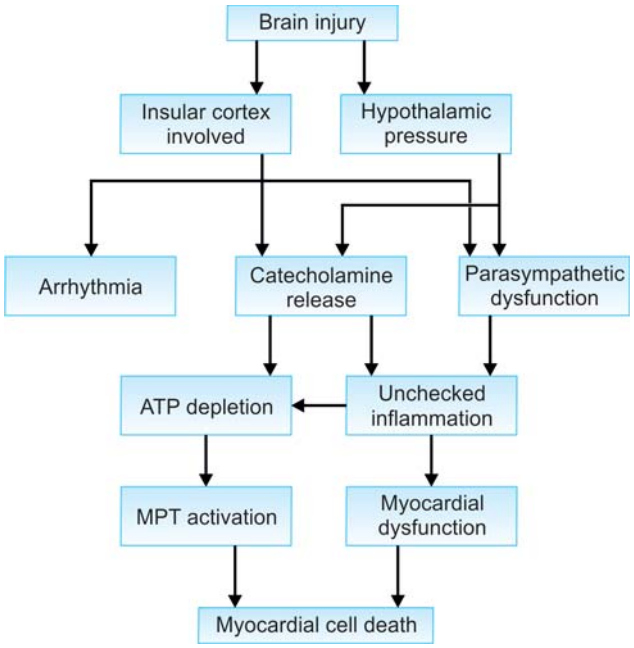
Left ventricular (LV) dysfunction has been observed in many types of brain injury. It is particularly common, however, after SAH, where a reduced left ventricular ejection fraction (LVEF) has been observed in 15–30% of patients. Both global and regional LV systolic dysfunction has been described.[11] Diastolic dysfunction is more common than systolic dysfunction, occurring in 71% of patients after SAH. High grade diastolic dysfunction is strongly associated with pulmonary edema.[12] Many regional wall motion patterns have been observed after SAH. Most typically observed is hypokinesis to akinesis of the basal left ventricle and particularly the basal septum, with preserved or even hyperdynamic systolic function of the LV apex. This pattern is not consistent with a coronary artery distribution but does correlate to some degree with the distribution of the myocardial sympathetic nerve terminals.[13] However, patterns of midventricular and apical ballooning (similar to stress cardiomyopathy) may occur after SAH, along with patterns more typical of MI.

Regional wall motion abnormalities are usually present within the first 2 days after the initial neurologic insult.[11] LV dysfunction is less frequently encountered after 3–8 days. In most cases, SAH-associated LV systolic dysfunction resolves prior to hospital discharge.[11] The presence of LV systolic dysfunction correlates with the severity of neurologic injury and may occasionally escalate to severe congestive heart failure in patients with SAH.[12]

PATHOPHYSIOLOGY

The mechanism of neurogenic myocardial injury involves complex interactions between specific components of the ANS and the heart (Flow chart 1). A systemic rise in circulating catecholamines mediated by an increase in sympathetic tone is probably not the only mechanism behind a neurogenically stunned myocardium. For example, an experimental model of brain injury resulted in a dramatic increase in the myocardial interstitial levels of catecholamines but only a subtle increase in circulating plasma levels of catecholamines.[14] This is supported by observational clinical studies in which serum catecholamines do not correlate with ECG abnormalities. Furthermore, stellate ganglionectomy and C2 spinal cord resection have been shown to prevent cardiovascular damage after experimental brain injury.

FLOW CHART 1: Proposed pathophysiological pathways resulting in neurogenic cardiomyopathy



(*Source:* Mashaly HA, Provencio JJ. Inflammation as a link between brain injury and heart damage. Cleve Clin J Med. 2008;75(Suppl 2):S26-30. Copyright 2008 The Cleveland Clinic Foundation. All rights reserved, with permission)

An increased interstitial level of catecholamines may adversely affect the myocardium by inducing demand ischemia through its inotropic and vasoconstrictive properties. It is more likely, however, that catecholamine toxicity is mediated by free radical formation with membrane perforation and/or an excessive influx of calcium into the cardiomyocytes through the activation of Beta1-adrenergic receptors. Cardiomyocytes then contract due to the surge of intracellular calcium and depleting adenosine triphosphate (ATP) stores. Depletion of ATP results in mitochondrial dysfunction and cell death. This mechanism of cell death results in a unique histological pattern called contraction band necrosis.

In humans, the presence of specific genetic polymorphisms of the adrenoceptors predisposes patients with SAH to myocardial damage demonstrated by cardiac troponin I release and LV systolic dysfunction.[15] LV systolic dysfunction in humans with SAH has also been associated with myocardial sympathetic denervation by radionuclide imaging, suggesting that a surge of catecholamines may damage the myocardium as well as the sympathetic nerve terminals.[16]

The parasympathetic nervous system (PNS) also plays a role in mediating cardiac dysfunction through the vagus nerve, and its ability to modulate the inflammatory response of the myocardium.[17,18] How the PNS modulates inflammation is unclear. Indirect clinical evidence comes from the cardiac transplant patient population. Myocardial samples from brain dead organ donors with LV systolic dysfunction demonstrate uncoupling of the beta-adrenergic receptors and dominance of the vagal/muscarinic receptors and the inhibitory G protein pathway.[19] Patients who receive cardiac transplants from donors who died of intracerebral hemorrhage show signs of inflammation and fibrosis in their coronary arteries.[20] Various experimental models have shown

increased expression of inflammatory markers such as matrix metalloproteinases, angiotensin II type 1 receptors, tumor necrosis factor α (TNFα) and interleukins.[21-27] Due to differential influence of the cerebral hemispheres on cardiac function, the type of arrhythmias may be determined by the type and location of stroke.[28] Animal models have demonstrated that stimulation/inhibition of the right medulla, hypothalamus and cerebral hemisphere result in greater effects on heart rate than the left. This was attributed to right-sided autonomic control of the nervous system on the heart through the innervation of the sinoatrial node. Injury to the right insula more frequently result in bradycardia and hypotension while damage to the left causes tachycardia and hypertension. The imbalance of function between the sympathetic and the PNS is thought to be important in the pathogenesis of arrhythmias. Increased sympathetic tone has been observed to induce supraventricular tachycardia. Conversely, impaired parasympathetic tone caused by right hemispheric injury may also result in arrhythmias.

DIAGNOSIS

Diagnosing neurogenic cardiac injury may be challenging. As patients who have cerebrovascular disease may also have pre-existing coronary artery disease, differentiating between an acute coronary syndrome (ACS) and a neurogenic process can be particularly problematic. Additionally, many patients with severe SAH, ischemic stroke or other significant brain injuries have altered mentation and are unable to describe symptoms such as chest pain. Although diagnosis presents a dilemma, it remains of particular importance because neurogenic myocardial dysfunction is transient but, if left untreated, primary ischemic cardiovascular disease can lead to significant morbidity and mortality.

Cardiac enzyme elevation, electrocardiographic changes, echocardiographic changes including regional wall motion abnormalities can occur in both populations. Thus the most important clue in diagnosing neurogenic stunned myocardium is an appropriate clinical setting. A relatively young patient with no previous cardiac history, who suffers an acute brain injury that is not associated with vascular atherosclerosis and has elevated cardiac enzymes and global hypokinesis, should prompt a physician to think about neurologic associated myocardial damage. Similarly, an LV wall motion pattern of basal hypokinesis of the septum is atypical of MI. In general, cardiac catheterization should be preserved for patients with specific features suggestive of ACS, such as chest discomfort, ST elevation on ECG, an echo wall motion pattern that fits a coronary distribution, a troponin level that continues to rise beyond 2–3 days after brain injury and hypotension that could be due to cardiogenic shock.

TREATMENT

All patients with significant acute brain injury should get an electrocardiogram and measurement of troponin and BNP. Additionally, patients with right middle cerebral artery ischemic stroke, SAH and hypertensive diencephalic hemorrhages should be kept on a cardiac monitor for at least 72 hours due to the high risk for arrhythmias in these populations.

Treatment of neurogenic cardiac injury and dysfunction should focus on treating the underlying cause. Cerebral function and outcomes should be given clinical priority and neuro-interventional and neurosurgical interventions should not be withheld due to cardiac concerns. For example, SAH patients require securing of the aneurysm by endovascular or surgical treatment. Additionally, SAH patients at the risk of cerebral vasospasm should be treated using "triple-H therapy" (HHH—hypertension, hypervolemia and hemodilution). Nimodipine, a cerebral vasodilator is also useful in prevention of vasospasm. In cases of relative hypotension, vasoactive medications, such as phenylephrine, are commonly used to maintain cerebral perfusion pressure and prevent vasospasm. However in the setting of poor systolic function even a potent peripheral vasoconstrictor may not provide adequate blood pressure support (Fig. 3). In such cases, addition of an inotrope to a peripheral vasoconstrictor may assist in providing adequate cerebral perfusion pressure.[8,9] In severe cases of neurocardiogenic injury, intra-aortic balloon counterpulsation can be used to maintain cerebral perfusion pressure until LV systolic function improves.

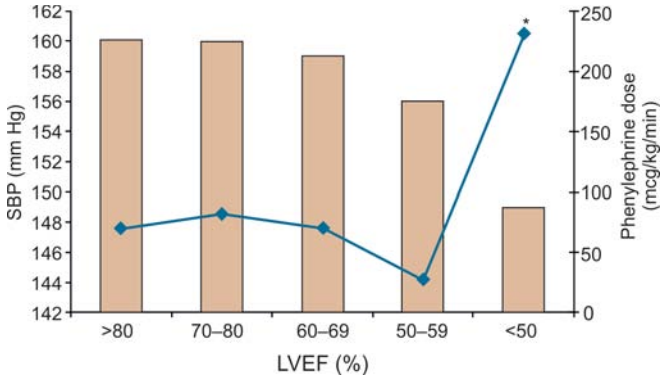


FIGURE 3: Relationship between left ventricular ejection fraction (LVEF), systolic blood pressure (SBP) and phenylephrine dose used to treat cerebral vasospasm after subarachnoid hemorrhage. High dose phenylephrine was ineffective in raising SBP when LVEF was low[9]

Although HHH therapy is a commonly accepted strategy for managing SAH, it has the potential to worsen cardiac toxicity. For instance, permissive hypertension increases afterload which can lead to greater myocardial oxygen demand and depress LV function. Hemodilution may prevent vasospasm, but it can also compromise oxygen delivery to the myocardium. Finally, hypervolemia increases LV filling pressures and can worsen pulmonary edema. Despite these risks, most patients tolerate this therapy well and thus it should not be withheld in cases of neurogenic stunned myocardium from SAH. In the setting of neurogenic stunned myocardium, intracerebral pathology is always prioritized.

Since excessive catecholamine release is thought to be a central cause of neurogenic cardiac injury, adrenergic-blocker therapy makes theoretical sense. A very small randomized double-blind placebo-controlled trial of 12 patients compared combined propranolol/phentolamine treatment to placebo. Results showed necrotic myocardial lesions in all placebo-treated patients which were not observed in the active treatment group.[29] In a randomized trial of 224 patients, 3 weeks of propranolol was shown to reduce the risk of neurological deficits ($p = 0.003$) and death ($p = 0.02$) in comparison to both placebo and phentolamine.[30] The 28-day mortality rate was 11.7% in the

beta-blocker group versus 22.6% in the controls. This study had design problems such as an early discontinuation of the phentolamine arm and unequal randomization. However the most likely reason that prolonged treatment with beta-blockers was not widely adopted was the establishment of HHH therapy and treatment with nimodipine.[31] Due to blood pressure lowering effects, clinicians may believe that beta-blockers are contraindicated in the window of cerebral vasospasm after SAH. In some SAH treatment centers, beta-blockers are used transiently when systolic blood pressure (SBP) is being lowered prior to clipping or coiling. Van der Bilt and colleagues in a recent meta-analysis reported an association between bradycardia and decreased risk of death in SAH.[32] It remains to be seen if this was due to a slow heart rate or a direct antiandrenergic effects of beta-blockers.

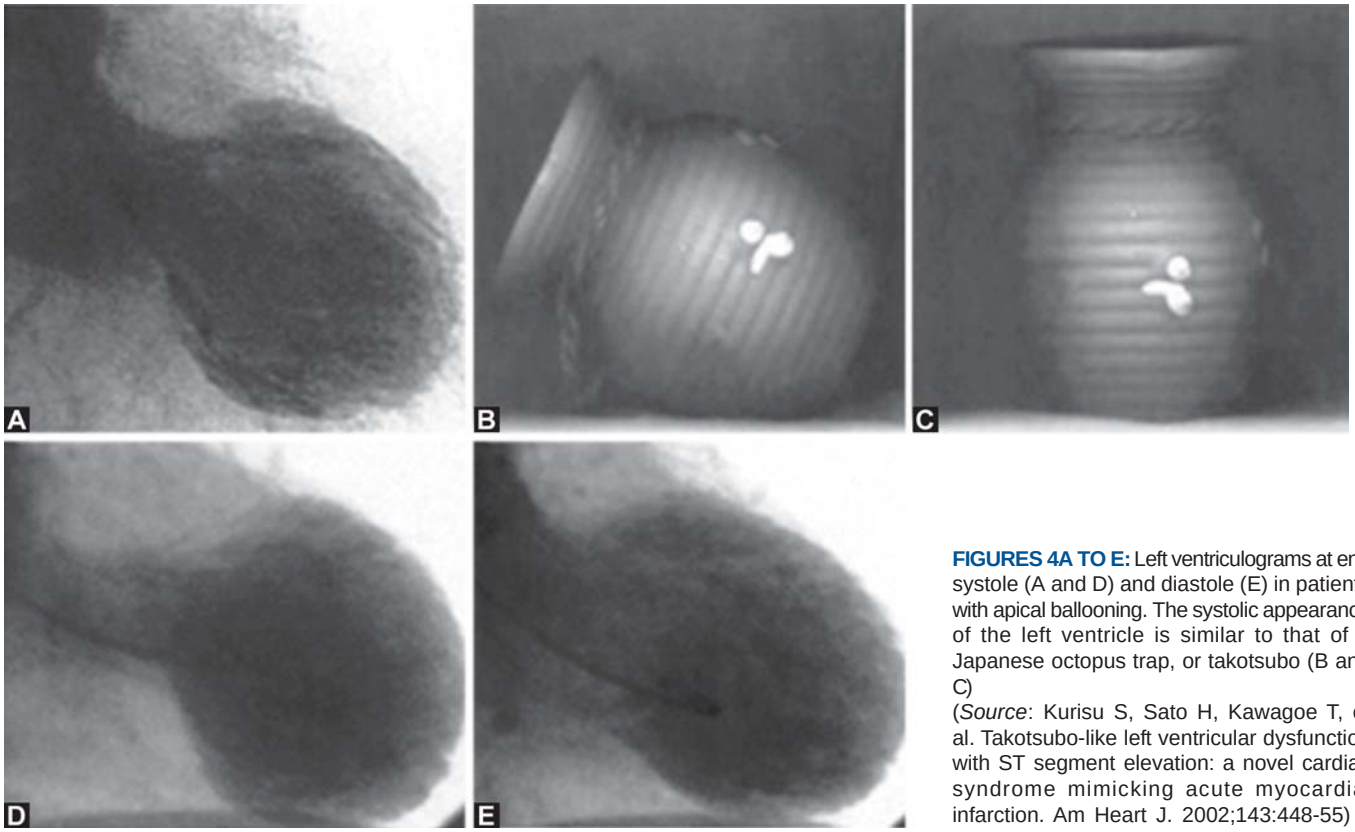
Pulmonary edema occurs frequently after brain injury and in many cases may be due to LV systolic and/or diastolic dysfunction, or volume overload. However direct pulmonary catecholamine toxicity may occur and results in neurogenic pulmonary edema. Several experimental models have shown that alpha-blockers can prevent pulmonary edema associated with neurologic injury. Similarly, the use of phentolamine may be beneficial in patients with myocardial dysfunction as long as hypotension does not occur and cerebral perfusion is not compromised. No clinical trials currently exist that explore this possibility. Further research is needed to elucidate the benefit of alpha and beta-blockers after neurogenic cardiac injury.

PROGNOSIS

Neurogenic cardiac injury is not necessarily benign and has been associated with morbidity and mortality. Studies have suggested that the presence of LV dysfunction, elevated cardiac biomarkers, Q waves, ST depression and T wave abnormalities observed during the initial insult are all associated with poor outcomes, mortality and delayed cerebral ischemia up to 6 months after hospital discharge in patients with SAH.[32] Ventricular arrhythmias have occurred up to 3 months after SAH.[33] Brady arrhythmias are also associated with increased mortality. Over time, LV dysfunction typically returns to normal. Complete or partial recovery usually occurs by the time of hospital discharge. Cardiac outcomes do not seem to be affected by procedures such as aneurysm clipping or coiling.[34] Although the presence of ECG abnormalities can be alarming, various studies have inconsistently linked ECG changes to mortality and adverse outcomes.[32,35,36]

STRESS CARDIOMYOPATHY

Although carrying a different name, stress cardiomyopathy, originally known as takotsubo cardiomyopathy, can be considered a variant of neurogenic cardiac injury. Stress-induced cardiomyopathy was first described in the early 1990s in Japan.[37] Later, cases were reported in the United States and Europe.[38-41] The condition has also been called stress-induced cardiomyopathy, transient apical ballooning syndrome and the broken heart syndrome. The original name stems from the pattern of ventricular systolic dysfunction recognized on left ventriculogram, resembling the shape of a Japanese octopus trap, or takotsubo (Figs 4A to E).[38,40] The hallmark of the condition is transient LV systolic dysfunction with characteristic LV apical and midventricular regional wall motion abnormalities in the absence of significant coronary artery disease.[38,40] Stress cardiomyopathy is an increasingly recognized condition, although the exact incidence remains



FIGURES 4A TO E: Left ventriculograms at end systole (A and D) and diastole (E) in patients with apical ballooning. The systolic appearance of the left ventricle is similar to that of a Japanese octopus trap, or takotsubo (B and C)
(*Source*: Kurisu S, Sato H, Kawagoe T, et al. Takotsubo-like left ventricular dysfunction with ST segment elevation: a novel cardiac syndrome mimicking acute myocardial infarction. Am Heart J. 2002;143:448-55)

unknown at this point.[38,42] At this point in time, it appears that approximately 2% of patients with suspected ACS on initial presentation are subsequently diagnosed with stress cardiomyopathy.

CLINICAL FEATURES

Patients with stress cardiomyopathy have typically experienced some sort of acute emotional or physical stress. Emotional triggers may include heated arguments, severe anxiety and the death of a friend or family member. Reported physical stressors have included exacerbations of chronic obstructive pulmonary disease, advanced cancer, severe infection (sepsis), trauma, gastrointestinal bleeding and various surgical procedures. Potential pharmacologic triggers include high doses of beta-agonist bronchodilator drugs. Rare cases without a specific trigger have also been reported.[38,42,43]

Postmenopausal women are most commonly affected by stress cardiomyopathy, representing 82–100% of the cases and the mean age has ranged 62–75 years in different studies. Only a minority of patients are younger or male.[38,40,44,45]

Classic coronary risk factors, such as hypertension, diabetes mellitus, hyperlipidemia, a positive family history of MI and tobacco use, have been found to have a lower incidence in the patient population presenting with stress cardiomyopathy compared to patients with MI.[46]

The most commonly reported symptom is substernal chest pain.[38,40,43] In a minority of cases, the presenting symptom has been dyspnea or syncope.[38,44,47,48] Sudden cardiac death and cardiac arrest upon presentation have been reported rarely.[38,42] However fatal outcomes are very rare. There have been cases of recurrence of stress cardiomyopathy after complete recovery from the initial episode. The trigger events for repeated episodes described were similar or identical.[38,42]

ECG Abnormalities

The 12 lead ECG of stress cardiomyopathy classically demonstrates QT prolongation and deep, symmetric T wave inversions, similar to ECGs observed in patients with SAH.[38] However other ECG abnormalities may also occur including anterior ST elevation, anterior Q waves, nonspecific ST and T wave abnormalities, left bundle branch block and right bundle branch block.

Arrhythmias

Diverse arrhythmias, including atrial fibrillation, can occur in patients with stress cardiomyopathy.[38,42] In rare cases, life-threatening ventricular arrhythmias, such as torsades de pointes, have occurred on initial presentation or later during the course. Since torsades occur in other settings where a prolonged QT interval is present, it is unknown whether the underlying stress cardiomyopathy creates a myocardial substrate for arrhythmias, beyond the repolarization abnormality.[49] Finally, there are case reports of atrioventricular block occurring in the setting of stress cardiomyopathy.

Release of Cardiac Biomarkers

Serum levels of cardiac troponin are mildly elevated in most cases. A systematic review determined that levels of cardiac troponins or the CK-MB fraction were elevated in 86% and 74% of patients respectively. The severity of presentation is not well correlated with troponin release.[38,45]

Left Ventricular Dysfunction

The main complication of stress cardiomyopathy is left-sided heart failure. In the acute setting, this has been reported in 3–46% of patients.[38] The typical mechanism of heart failure is LV systolic dysfunction and this can be demonstrated with a variety of imaging techniques, including left ventriculography, echocardiography and magnetic resonance imaging of the heart. Most commonly, midventricular and apical akinesis or dyskinesis are described. Midventricular dysfunction with sparing of the apical region has also been reported.[38,40] Right ventricular systolic dysfunction has also been reported in patients with stress cardiomyopathy.[50,51] In some cases, left heart failure may be caused by LV outflow tract obstruction which is related to hyperdynamic systolic function of the basal LV segments. Mitral regurgitation may accompany this finding secondary to systolic anterior motion of the mitral valve leaflets.[38] An isolated case of LV rupture has been reported.[38,52] Finally, in the setting of decreased LV systolic function, LV apical thrombi may develop and cardioembolic events may occur.[38,42,53]

PATHOPHYSIOLOGY

No single pathophysiologic process can explain all cases of stress cardiomyopathy. Excessive release of catecholamines is probably an important mechanism, similar to cases of neurogenic cardiac injury. Studies have shown that patients with stress cardiomyopathy may have abnormalities of myocardial sympathetic innervation.[54,55] The typical apical pattern of ventricular dysfunction is thought to be mediated by increased density of adrenergic receptors in affected areas.[38] The wall motion abnormalities described in stress cardiomyopathy are similar to findings in catecholamine-induced cardiomyopathy.[38] It is possible that excessive myocardial catecholamines result in direct myocardial injury or microvascular spasm. Microvascular function has been found to be abnormal during invasive measurements of myocardial perfusion and coronary flow reserve.[38,40,56]

Another possible mechanism is epicardial coronary spasm, which has been demonstrated in some stress cardiomyopathy patients. Incidence of provocable multivessel epicardial spasm ranged from 0% to 43% in different series.[38] Plaque rupture of the left anterior descending artery has been demonstrated by intravascular ultrasound, which might have caused transient thrombosis or vasospasm, in some cases.[57]

Some researchers have suggested myocarditis as an underlying process, although myocardial biopsies taken from stress cardiomyopathy patients did not support this theory.[40,44,47,48] Finally, one study has suggested that apical ballooning occurs secondary to dynamic LV outflow tract obstruction causing a profound increase in apical wall stress.[58] It is possible that a combination of the outlined pathophysiologic processes or one process leading to another is more likely than an isolated process.[38] It is also possible that the observed apical wall motion abnormalities may be due to a different mechanism in different patients.

Thus the exact pathophysiology of stress cardiomyopathy remains uncertain. It remains unclear at this point why the postmenopausal female population is affected to a greater extent than the younger or male population. It is also puzzling that some patients will experience recurrent events and others will not. Future studies will need to focus on identification of further risk factors, risk stratification and potential preventive measures.

DIAGNOSIS

Prior to making the diagnosis of stress cardiomyopathy, significant underlying coronary artery disease must be excluded. The following diagnostic criteria have been proposed by the Mayo Clinic:[38]

- Transient akinesis or dyskinesis of the LV apical and midventricular segments with regional wall motion abnormalities extending beyond a single epicardial vascular distribution
- Absence of obstructive coronary disease or angiographic evidence of acute plaque rupture
- New electrocardiographic abnormalities (either ST segment elevation or T wave inversion)
- Absence of:
  - recent significant head trauma
  - intracranial bleeding
  - pheochromocytoma
  - obstructive epicardial coronary artery disease
  - myocarditis
  - hypertrophic cardiomyopathy

In clinical practice, the regional wall motion abnormalities are most often demonstrated by left ventriculography or echocardiography, although cardiac CT or magnetic resonance imaging may also be used for this purpose.

TREATMENT

Most stress cardiomyopathy patients presenting to an emergency department will initially be suspected of having an ACS, ultimately resulting in coronary angiography.[38,40] After flow-limiting coronary disease has been excluded and the diagnosis of stress cardiomyopathy has been made, treatment should focus on relief of chest pain and treatment of LV dysfunction and heart failure symptoms. Appropriate medical therapies may include beta-blockers (such as carvedilol), angiotensin-converting enzyme inhibitors and diuretics.[38,40] If transient coronary thrombosis or vasospasm are suspected as possible mechanisms, aspirin, clopidogrel, calcium channel blockers and nitrates may also be considered. If LV systolic function is not improving rapidly (over a few days), anticoagulation with warfarin needs to be considered in order to prevent thrombus formation and cardioembolus. Warfarin can be discontinued when LV apical systolic function has normalized. Long-term treatment with beta-blockers may have a protective effect and should be used in patients with more than one episode.[38]

PROGNOSIS

In general, full recovery of LV function occurs prior to hospital discharge or shortly thereafter and the prognosis is very good.[38,40] In rare cases, recovery of function takes up to 2.5–12 months. In some patients, a further episode occurs after symptoms have resolved. The recurrence rate is thought to be up to 8% taking a number of different case series into account. In most cases, the recurrence was triggered by identical or similar events that brought on the initial episode.[38] Compared to age and gender-matched controls, patients with stress cardiomyopathy do have higher mortality rates, beyond the initial episode.[38]

CONCLUSION

Neurogenic and stress cardiomyopathy share common mechanisms and clinical manifestations. Optimal treatment of both disorders remains uncertain, although the cardiac prognosis is generally favorable. Further research is required to enhance existing knowledge regarding the pathophysiology and management of cardiac injury in the setting of brain injury and psychological stress.

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Chapter 98

Kidney and the Heart

Mony Fraer

Chapter Outline

- Epidemiology
- Pathophysiology
- Cardiovascular Risk Factors in Chronic Kidney Disease
  - Hypertension
  - Hyperlipidemia
  - Smoking
  - Diabetes Mellitus
  - Left Ventricular Hypertrophy
  - Anemia
  - Hypoalbuminemia
  - Increased Extracellular Volume
  - Arteriovenous Fistulae
  - Arteriosclerosis
  - Hyperhomocysteinemia
  - Oxidative Stress and Inflammation
  - Abnormal Divalent Ion Metabolism and Vascular Calcifications
  - Prothrombotic Factors
- Spectrum of Cardiovascular Disease in Chronic Kidney Disease
  - Ischemic Heart Disease
  - Congestive Heart Failure
  - Pericardial Disease
  - Infective Endocarditis
  - Valvular Heart Disease
  - Arrhythmias
- Diagnostic Tests
  - Cardiac Markers
  - Electrocardiography
  - Echocardiography
  - Stress Tests
  - Computerized Tomography Scans
  - Coronary Angiography
- Principles of Treatment of Cardiovascular Disease
- Kidney Transplant Recipients

DEFINITION

Chronic kidney disease (CKD) is defined as the persistence for 3 or more months of structural and/or functional abnormalities of the kidneys.[1] These abnormalities can be any of the following: microalbuminuria (or proteinuria), an abnormal urinalysis or imaging studies or an estimated glomerular filtration rate (eGFR) that is less than 60 ml/min per 1.73 m^2.

EPIDEMIOLOGY

Among patients with CKD, cardiovascular disease (CVD) is 2–4 times more prevalent[2,3] and advances at twice the rate,[4] resulting in a 5–10 times greater likelihood of dying from CVD than reaching end-stage renal disease (ESRD).[5-8] This appears to be a graded association between reduced eGFR and the risk of death and cardiovascular (CV) events.[5,7,9,10] The effect is amplified among individuals of low socioeconomic status.[11] The incidences of de novo coronary events, stroke and peripheral vascular disease in hemodialysis (HD) patients, 2 years from starting dialysis, a 10.2%, 2.2% and 14% respectively.[12] Besides the decreased GFR, albuminuria and proteinuria have emerged as independent risk factor for myocardial infarction, stroke and death.[13-15] In 2006, the annual mortality rate for dialysis patients was 221 deaths/1,000 patients per year (about 20% per year). The CV mortality rate in ESRD patients on dialysis is 41–50% of all-cause mortality, 10–20 times higher (100 times in patients younger than age 45) than in the general population.[5,16-20] Coronary artery disease (CAD), arrhythmias and sudden cardiac death (SCD) are responsible for 20%, 27% and 27% respectively of all-cause mortality in dialysis patients.[18,21-23] Overall, CAD is the major cause of morbidity and mortality in ESRD patients.[24] The prevalence of angiographically significant CAD ranges from 25% in young, nondiabetic HD patients to 85% in older ESRD patients with long-standing DM.[16] For example, one-third of the type 1 diabetics and half of the type 2 asymptomatic diabetic transplant candidates have clinically silent CHD (significant coronary artery stenosis by cardiac catheterization). CAD is also the underlying cause of heart failure in most cases in patients treated with renal replacement therapy. The risk of cardiac arrest is related to duration of renal replacement therapy[21] and there is a poor survival rate after cardiopulmonary resuscitation: 92–100% in-hospital death and 97% 6-month mortality rate.[25] The CKD-CVD interaction goes both ways since there is also a risk of CKD among patients with CVD. Regarding the interaction between the kidneys and the heart, the information presented in this chapter complements the chapter on “Cardiorenal Syndrome”.

PATHOPHYSIOLOGY

Patients with CKD have a high prevalence of arteriosclerosis which may occur in the presence or absence of significant atherosclerosis; this is a result of the calcification of the intimal and medial layers of blood vessels. Abnormalities of bone mineral metabolism, including elevations in serum phosphorus, calcium and calcium-phosphorus product, are involved in promoting vascular calcification. These vessels become stiff, leading to an increase in systolic blood pressure (BP), a decrease in diastolic BP, a widened pulse pressure and an increased pulse wave velocity. A higher systolic BP increases left ventricular (LV) afterload and contributes to the development of left ventricular hypertrophy (LVH), while the reduced diastolic pressure compromises coronary artery perfusion leading to myocardial ischemia.

The traditional CV risk factors—advanced age, diabetes mellitus (DM), hypertension (HTN), low high-density lipoprotein (HDL), smoking and LVH—are more prevalent in subjects with CKD.[26] Most patients have more than one of these risk factors, resulting in an even higher risk of adverse outcomes. More unusual is the fact that ESRD patients have a "reverse epidemiology" and a "U-shaped" mortality curve: patients with low cholesterol, not obese and with low BP paradoxically have an increased mortality. To explain this "reverse epidemiology" the so-called nontraditional risk factors (anemia, abnormalities of calcium and phosphate metabolism, inflammation, oxidative stress, prothrombotic factors, hyperhomocysteinemia, hypoalbuminemia and elevated apolipoprotein B) have been invoked;[27] although these factors have been linked to the increased CVD in CKD, a causal relationship has not been proven. Alos, the increased in mortality is thought to reflect underlying malnutrition, inflammation and advanced cardiac disease. Besides the known risk factors for CVD there is a yet not understood predisposition for CVD related to the kidney disease itself.

CARDIOVASCULAR RISK FACTORS IN CHRONIC KIDNEY DISEASE

HYPERTENSION

The Seventh Report of the Joint National Committee on Hypertension and American Diabetic Association recommends a therapeutic BP target of 130/80 mm Hg.[28,29] BP goals are: less than 130/85 mm Hg for individuals with renal parenchymal disease, DM or with less than 1 g/day of proteinuria.[30-32] Achieving this degree of BP reduction in individuals with CKD typically entails the use of two to three antihypertensive agents including a renin angiotensin aldosterone system (RAAS) blocker and a diuretic.[30,33]

Inhibiting RAAS is effective even in advanced CKD,[34] is cardioprotective,[35] reduces risk of CKD progression and it works even in African-Americans (particularly if they have proteinuria).[36-38] Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blocker (ARB) usage results in regression of LVH among dialysis patients.[39-42] The BP-lowering effect of ACEIs is generally less in volume-expanded forms of HTN (as is often the case in CKD), compared with other forms of HTN; however, addition of a diuretic to an ACEI (or ARB) typically improves the BP-lowering response.[43] The kidney/disease outcomes quality initiative (K/DOQI) guidelines published in 2006 suggest that these agents are preferred in dialysis patients with HTN and significant residual renal function since they may preserve kidney function. A frequent concern is whether ACEI and ARB should be started in patients who have advanced CKD and, when or whether they should be stopped in those who are already on such treatments. In one study, benazepril reduced the risk for doubling of serum creatinine, ESRD or death by 19% in the group with more advanced CKD and, also reduced proteinuria by 52% and the rate of decline in GFR by 23% compared with placebo.[34] No specific adverse effect has been identified from ACEI accumulation and usually ACEI are titrated to effect. An attempt should be made to use ACEI or ARB in patients down to an eGFR of 15 ml/min per 1.73 m^2. Below this level, case reports suggest a high rate of hyperkalemia and the concern of accelerating the course to ESRD and dialysis. ARB and ACEI have similar issues in terms of adverse effects, including hyperkalemia and possible decreased erythropoiesis.[44] ACEI should also be used to prevent HF in asymptomatic patients whose LV ejection fraction is less than 35% and in postmyocardial infarction patients with an ejection fraction of 40% or less.[45,46] A retrospective analysis supports the use of ACEI in patients with ESRD admitted with HF.[47] ARBs are probably as effective as ACEIs for cardiac failure in the case of LV dysfunction. For example, losartan has reduced hospitalization for HF in diabetics with overt nephropathy.[38] As with diabetic nephropathy, the addition of an ARB to an ACEI, reduced proteinuria in CKD[48] and also slowed CKD progression, for the similar degree of BP control.[49] A meta-analysis that compared combined ACEI and ARB therapy with ACEI treatment alone found a substantial increase in adverse effects with combination therapy, including worsening renal function, hyperkalemia and hypotension.[50]

Control of volume status can either normalize the BP or make the HTN easier to control. Diuretics should be used with a goal to reach BP target or until the patient develops symptoms and signs of hypovolemia. Loop diuretics are important to achieve euvolemia in heart failure. Thiazide diuretics usually become ineffective with a GFR below 30 ml/min. The synergistic diuretic effect of loop diuretics and thiazides persists even at relatively advanced stages of renal insufficiency. Avoidance of large weight gains in the interdialytic period and removing fluid with dialysis until a stable weight is achieved and also is associated with normotension, regression of LVH and improved survival.[51-54] The patients should be on a restricted salt diet (750–1,000 mg of sodium/day), which also helps decrease thirst.[55-57]

The third antihypertensive drug could be a calcium channel blocker; the available data is only for amlodipine which, compared to placebo, improves overall survival among hypertensive dialysis patients.[58] An aldosterone antagonist (spironolactone and eplerenone) is an effective fourth-line agent for the treatment of resistant HTN in general and in patients with CKD; hydralazine and labetalol are also good option, particularly if hyperkalemia is a concern. Minoxidil is reserved for refractory HTN, with sodium retention, worsening edema and hirsutism being the major side effects.[59] Selection of

antihypertensive agents is guided by the presence of associated comorbidities.[60] The HTN in acute glomerular disease with edema typically improves with volume removal with diuretics (or dialysis). In patients with vasculitis or scleroderma, RAAS blockade is the treatment of choice.[61] Therapy with antihypertensive drugs is primarily indicated in the 25–30% of dialysis patients in whom HTN persists despite seemingly adequate volume control. Factors to be considered in the setting of refractory HTN are concurrent use of a medication that can raise the BP (such as nonsteroidal anti-inflammatory drugs), renovascular HTN, noncompliance to medical regimen and expanding cyst size in polycystic kidney disease. The difficult task in the ESRD patient is to achieve BP goals without having hypotension during dialysis sessions. Dialysis related hypotension can worsen clinical and subclinical cardiac ischemia.[62]

Sympathetic nervous system activity is increased in CKD and contributes to the CV risk.[63] In a post hoc analysis of the Bezafibrate Infarction Prevention (BIP) study, β-blockers were found to reduce cardiac risk in patients with coronary heart disease (CHD) to a similar magnitude as in patients without CKD.[64] Large relative risk reductions in all-cause mortality have been reported for patients who receive β-blockers with ESRD after CAD events.[65] Carvedilol was shown to improve LV function and the number of deaths and hospitalizations in patients with dilated cardiomyopathy receiving HD.[66] Accumulation of a renally cleared β-blocker, such as atenolol, in a patient with CKD does not typically improve BP control but can be associated with more frequent concentration-dependent adverse effects.[67] Metoprolol and nebivolol are the two β-blockers that do not accumulate in CKD and have no active metabolites.

HYPERLIPIDEMIA

Lipid abnormalities are more prevalent in patients with CKD than in the general population.[68] Fifty percent of HD patients and 70% of peritoneal dialysis patients demonstrate dyslipidemia.[69] Patients with CKD have increased serum triglyceride (TG), very low-density lipoprotein (VLDL) and low-density lipoprotein (LDL) with unchanged total cholesterol (TC) and low HDL. HD patients usually have normal TC and LDL levels but higher HDL and serum TG levels. However, in patients with nephrotic syndrome, LDL, TG and TC are markedly elevated whereas HDL decreases.[70] A meta-analysis of studies of statin use in CKD showed that compared with placebo, statins significantly reduced TC, LDL cholesterol, urinary protein excretion and both fatal and nonfatal CV events. There was however no improvement in GFR and no effect on all-cause mortality with statin treatment.[30,71-75] Regarding the combination of ezetimibe and simvastatin in CKD, this regimen led to an incremental 21% reduction in LDL cholesterol compared with simvastatin alone.[76] Studies in dialysis patients have found a 'U'-shaped curve either with CV events or with overall mortality: one study in Japanese HD patients demonstrated that patients with a serum cholesterol between 200 mg/dL and 220 mg/dL had the best outcome.[77] In patients with ESRD, two large randomized trials, 4-D and AURORA, have attempted to assess the efficacy of lipid-lowering. These trials found no difference between HMG CoA reductase inhibitors (statins) therapy and placebo with respect to CV death, nonfatal myocardial infarction and stroke despite a reduction of LDL and of progression of coronary artery calcifications (CAC).[22,78] It is likely that confounding factors, such as concurrent malnutrition or inflammation, explain these findings.[79,80] Fewer than 60% of dialysis patients have their lipids measured during the course of a year.[81-83] Only 8–18% of nondiabetic patients take lipid-lowering drugs prior to dialysis and 4–10% of dialysis patients use statins. If statin therapy is administered to dialysis patients, the guidelines recommend: a serum LDL cholesterol of lesser than 100 mg/dL and a non-HDL cholesterol of lesser than 130 mg/dL in patients who have already achieved the target LDL cholesterol level but have TG greater than or equal to 200 mg/dL.[68,84]

SMOKING

Smoking has been independently associated with *de novo* HF, peripheral vascular disease and death in CKD patients.[85] However, there are no studies demonstrating that cessation of smoking improves the outcome of CKD.

DIABETES MELLITUS

The presence of DM in patients with moderate to severe CKD predicts CV deterioration in patients with or without CVD at baseline.[86] Diabetic patients are more prone to CAD, impaired LV function and LVH.[87,88] Only 11% of diabetic patients had normal echocardiographic dimensions compared with 25% of nondiabetic patients, predominantly due to severe LVH (34% vs 18%).[89] Only limited data are available regarding potential benefits of tight glycemic control.

LEFT VENTRICULAR HYPERTROPHY

Left ventricular hypertrophy increases in prevalence with declining renal function and is already evident in 30–45% of patients with moderate CKD[90] and in up to 75% of those commencing dialysis.[91-94] In dialysis patients, LVH is a strong predictor for the subsequent development of congestive heaft failure (HF), CAD and SCD.[93,95] LVH occurs in response to pressure or volume overload. HTN, arteriosclerosis and aortic stenosis contribute to pressure overload, while volume overload occurs as a result of anemia, hypervolemia and arteriovenous fistulas.[96] The hypertrophied ventricle becomes stiff, causing diastolic dysfunction and an increased risk for death and cardiac events.[97]

ANEMIA

One of the causes of anemia in patients with CKD is a relative deficiency of erythropoietin, an erythrocyte stimulating protein that is normally produced by renal parenchyma in response to blood partial pressure of oxygen. It contributes to adverse outcomes due to decreased tissue oxygen delivery and utilization.[98] Among patients with CHF, for each 1 g/dL decrement in Hb, there is a 13% increase in risk for all-cause mortality.[98] Anemia is an independent risk factor for the development and progression of LVH, CHF, CAD, stroke and increased mortality in patients with CKD.[90,99-106] There is an inverse relationship between hemoglobin (Hb) and LV mass index.[107] LV mass is a strong and independent predictor for

survival and CV events in dialysis patients.[108] Correction of anemia with erythropoietin stimulating agents improves oxygen delivery and cardiac output resulting in a 10-30% reduction in LV mass index. Partial regression of LVH has been associated with reduced mortality in observational studies. Randomized trials in CKD showed that correction of anemia to higher Hb targets (> 12 g/dL) results in worsened CVD outcomes.[109,110] The best outcomes were associated with Hb values between 10 g/dL and 12 g/dL, with a significant reduction in LV mass index.[111]

HYPOALBUMINEMIA

Hypoalbuminemia has been shown to be a predictor of outcome in dialysis patients. It is associated with LV dilatation and predisposes to both de novo heart failure and CHD.[112]

INCREASED EXTRACELLULAR VOLUME

At all stages of CKD, sodium and water retention may cause plasma volume expansion, LV dilatation and LVH. Greater interdialytic weight gain is independently associated with higher BP which is a risk factor for cardiac events.[113]

ARTERIOVENOUS FISTULAE

Blood flow in arteriovenous fistulae and grafts predisposes to LV volume overload.[114,115]

ARTERIOSCLEROSIS

The consequences of arteriosclerosis are: raised pulse pressure, increased carotid wall thickness and elevated pulse wave velocity; these have been associated with an increased mortality.[116-118] Increased pulse pressure and systolic BP are correlated with LVH.[119,120]

HYPERHOMOCYSTEINEMIA

Hyperhomocysteinemia is an adverse prognostic factor for CVD outcomes in dialysis patients.[121,122] Treatment with B vitamins lowers homocysteine levels in CKD patients but does not reduce CV risk.[123]

OXIDATIVE STRESS AND INFLAMMATION

Oxidative stress, through lipid peroxidation, contributes to the formation of atheroma.[124] High sensitivity CRP was found to be associated with the risk of SCD.[23] Statin therapy lead to a reduction in C-reactive protein (CRP) in HD patients.[125]

ABNORMAL DIVALENT ION METABOLISM AND VASCULAR CALCIFICATIONS

In CKD patients CAC are prevalent (40–69%) and calcification scores are higher.[126] This seems to be related more to coronary risk factors and also to the time on dialysis[127,128] than to the level of renal function[129,130] In stages 1–2 CKD, CAC has been explained by African American race and traditional CV risk factors; however, in stages 3–5 CKD, traditional risk factors did not completely explain the association of CKD with CAC.[131,132] The presence of arterial calcification is associated with myocardial infarction, congestive heart failure, endocarditis, valvular heart disease and death.[117,119,133-140] Factors contributing to hypercalcemia and/or hyperphosphatemia, potentially worsening the soft-tissue and vascular calcification are: alterations in phosphorus metabolism, the use of oral calcium salts as phosphate-binding agents and the administration of large doses of vitamin D sterols to treat secondary hyperparathyroidism.[141,142] Animal and observational studies point to an improved CV risk profile and improved survival for individuals who receive vitamin D analogs. The extent of arterial calcifications increased with the use of calcium-based phosphate binders;[143] however, there is no statistically significant difference in CV mortality in patients receiving calcium-based phosphate binders compared to non-calcium-based phosphate binders.[144]

PROTHROMBOTIC FACTORS

Elevated levels of procoagulant factors are observed in CKD and hyperfibrinogenemia has been linked to increased coronary events.[27]

SPECTRUM OF CARDIOVASCULAR DISEASE IN CHRONIC KIDNEY DISEASE

ISCHEMIC HEART DISEASE

Coronary Heart Disease in Chronic Kidney Disease

The increased risk for CHD differs with race but the data is conflicting on this subject.[147,148] Ischemic heart disease develops early, and is present in 40% of incident dialysis patients. Its prevalence rates are 5–20 times greater in ESRD patients than those for the general population. Chronic kidney disease and/or albuminuria alone are independent risk factors for the development and progression of CHD.[17,145,146] The risk of CHD is lower in young, nonobese and nonsmoking patients.[147] The risk of acute myocardial infarction (AMI) is related to the high prevalence of HTN, inflammation, ECV overload, anemia, hypotension and hypoxia during HD, and increased blood flow through the arteriovenous fistula.[149] Even mild renal disease is considered a major risk for mortality after an acute coronary event[150,151] and the risk increases with declining GFR.[152-154] The probability of having a myocardial infarction or angina requiring hospitalization in HD patients is 10% per year.[155] Case fatality rates after AMI are several fold greater in dialysis patients than in the general population, and mortality rates are nearly 60% in the year following a first AMI[5] with a 2-year survival rate of 25%.[156,157] Given the frequent episodes of hypotension during HD, angina during dialysis is perhaps the most common clinical manifestation of CAD in dialysis patients. Renal insufficiency is an independent risk factor for in-hospital and post-discharge mortalities[158-160] and the impact of CKD on mortality is greater than baseline demographics, associated medical conditions or therapies received.[153,156] The risk for death was lower in African Americans compared with Caucasian patients.[161] The more proximal location of culprit coronary atherosclerotic lesions (relative to the coronary ostia) in patients with stages 3 and 4 CKD has been associated with higher risk for AMI and the disproportionately high rates of death after an AMI.[162] Lower creatinine clearances were associated with a greater likelihood

of three-vessel disease. When, comparing the patients who undergo evaluation for CAD, those with ESRD have substantially more numerous and severe coronary artery lesions, as well as more severe LV dysfunction.[16] Other contributing factors to the higher mortality are older age, presence of comorbidities and receiving fewer effective therapies (less reperfusion, glycoprotein IIb/IIIa (GPIIb/IIIa) receptor inhibitors, early angiography and less aggressive medical therapies).[163,164] For all these reasons, the National Kidney Foundation and the American College of Cardiology/American Heart Association to recommend that CKD be considered a CHD risk equivalent.[165,166]

Usually ESRD patients have more numerous and severe coronary artery lesions. Also, 25–30% of ESRD patients will have abnormalities on ECG or perfusion scans indicating CAD, even in the absence of significant narrowing of a major coronary artery.[167,168] Asymptomatic severe CAD is not an uncommon finding due to uremic or diabetic autonomic neuropathy and a sedentary lifestyle.[169]

Coronary Heart Disease as a Risk Factor for Chronic Kidney Disease

The presence of CVD increases the risk of developing ESRD.[170] CKD is prevalent among patients with incident CAD (30%) and is associated with an increased mortality,[152,171] particularly after an acute coronary syndrome.[151,172,173] Patients undergoing coronary angiography, those treated with percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG), and those with atherosclerotic disease are at increased risk of CKD.[17]

In the context of an AMI, a high proportion of CKD patients have atypical presentations (dyspnea only) and episodes of silent cardiac ischemia (presumably due to autonomic disease associated with uremia or diabetes) which may delay diagnosis and adversely affect outcomes.[174] The patients with CKD presenting to the hospital with chest discomfort represent a high-risk group, having a 40% cardiac event rate at 30 days.[173] An indication for hospital admission is chest discomfort in patients with a GFR of less than 60 ml/min per 1.73 m^2 or on dialysis.[175]

Medical Therapy

To avoid a significant decrease in BP, the administration of CV medications must be avoided when the preload is low, such as the end of an HD session; these medications may be dosed nocturnally.[60] Unlike unfractionated heparin, the clearance of low molecular weight heparins (LMWH) is primarily renal; therefore, elimination is slower and less predictable and bleeding complications may be increased. LMWH should only be used with dose adjustments and close monitoring of factor Xa activity.[176] Thus unfractionated heparin is generally preferred. Fondaparinux is a factor Xa inhibitor that may be safer (fewer bleeding complications) and noninferior to enoxaparin for use in acute coronary syndromes.[177] The use of fibrinolytic agents and platelet GPIIb/IIIa inhibitors for acute coronary syndrome is less clear due to the markedly increased risk of bleeding in dialysis patients. Bivalirudin, a direct thrombin inhibitor, when used with PCI in patients with CKD, resulted in lower death rate, lower AMI rate or need for urgent revascularization, as well as lower risk of bleeding compared with heparin.[178] There are reports of an increased risk of bleeding with the use of GPIIb/IIIa antagonists; however, their use is still generally recommended in appropriate individuals after dose adjustment. Abciximab and tirofiban (GPIIb/IIIa inhibitors) do not require dose changes in dialysis patients.[60] In a retrospective study of thrombolysis in AMI, the finding was that reduced renal function resulted in delays in thrombolytic treatment, proportionally to the magnitude of renal impairment. There was no increase in risk for excessive bleeding after thrombolysis among these patients.[161] There are few studies regarding the efficacy of clopidogrel in CKD. Regarding the combination of aspirin and clopidogrel, it is known that it is associated with increased bleeding when it was used for the prevention of arteriovenous graft stenosis.[179]

Interventional Therapy

Patients with ESRD and CAD who receive only conservative medical management tend to fare the worst.[16,180-183] There are no prospective randomized studies guiding the choice of revascularization method in CKD; however, the long-term risk of cardiac events and/or death in dialysis patients are higher following PCI than after CABG, particularly in those with DM.[181,184-189] In view of the propensity for restenosis after PCI, there is a consensus in favor of CABG for left main or extensive three-vessel disease and in favor of PCI for single-vessel disease. In the remaining cases of multivessel disease with culprit lesions, it appears that PCI with stenting had similar clinical outcomes to CABG, but repeated revascularization procedures had to be done.[181,190] In general, PCI provides excellent angiographic success (90% in most published series), but (with or without stenting) is associated with increased restenosis (over 80% in some series) and the need for revascularization[191] as well as an increased mortality which is proportional with the degree of renal dysfunction.[159,192-199] The risk for both coronary restenosis (at 1 and 6 months) and death at 1 year are increased in proportion to reduction in renal function.[192,199] The clinical detection of restenosis may be more difficult in the dialysis patient because symptoms induced by increased fluid volume, particularly increased LV preload, can mimic those resulting from recurrent ischemic disease.[200] Therefore, provocative stress imaging should be considered to detect clinically silent restenosis 12–16 weeks after a PCI[200] procedure.[60] For nondiabetic ESRD patients who underwent PCI with stent, the risk of all-cause death was 10% lower, compared with those who had PCI without stent.[189] In dialysis patients, drug-eluting stents, compared with bare metal stents, are associated with reduced restenosis rates and a decreased requirement for repeat revascularization[201-205] but their role, or that of brachytherapy is not clear yet.[206] CKD and dialysis patients undergoing CABG face 4.4 times greater in-hospital mortality, 3.1 times greater risk of mediastinitis and 2.6 times greater risk of stroke compared to patients without renal disease.[184,200,207,208]

In patients with CKD and acute coronary syndrome requiring acute coronary revascularization, PCI with stenting has improved the 2-year survival rate over medical therapy alone, and results were comparable to those who underwent CABG.[182] There was a significant increase in risk for bleeding complications among patients with CKD who underwent PCI and were treated with intensive antiplatelet therapy, with the

risk increasing progressively with declining level of renal function. The frequency of bleeding complications and in-hospital mortality appear to be inversely related to the level of kidney function.[193,199] In-hospital complication rates and in-hospital as well as long-term mortality are higher among CKD patients with diabetes or peripheral vascular disease, and are highest among patients on dialysis.[209-212]

CONGESTIVE HEART FAILURE

There is a high incidence of HF in CKD,[6] a high prevalence of HF when starting dialysis (35%),[213,214] a high incidence of de novo HF in HD patients[85,105] as well as a higher rate of de novo symptomatic HF in renal transplant recipients than in the general population.[215] Observational studies suggest that the prevalence of heart failure is 10–30-fold higher among dialysis patients than in the general population.[155,216,217] The pathogenesis of heart failure is multifactorial with contributions from LVH, CHD, valvular heart disease, chronic extracellular fluid volume expansion, disturbances in divalent ion metabolism, anemia and the presence of arteriovenous fistulas. Patients may have systolic dysfunction, diastolic dysfunction or both. Endomyocardial biopsies done in ESRD patients with CHF but without CAD showed severe myocyte hypertrophy and extensive fibrosis, resembling findings from the dilated phase of hypertrophic cardiomyopathy.[218] The presence of HF independently predicts early mortality in ESRD as it does in nonuremic patients.[105,219-222] Increasing clinical severity of CHF, as determined by the New York Heart Association classification, is also associated with increased mortality.[221] Patients with LV dysfunction often tolerate dialysis treatments poorly and episodes of intradialytic hypotension may occur. As a consequence, these patients experience repeated ischemic events leading to chronic reduction in LV function with its associated adverse prognosis. This condition appears to be common (64% of patients in one study) and is called HD-induced myocardial stunning.[223] The K/DOQI guidelines recommend that, at initiation of dialysis, all patients should undergo baseline echocardiography and electrocardiography. Heart failure has not been well studied in CKD patients. Thus studies in the general population are the only basis upon which to guide treatment in CKD.

PERICARDIAL DISEASE

Pericarditis, uremic or dialysis related is encountered in 5–20% of patients requiring chronic dialysis.[224] Uremic pericarditis is less frequently encountered and, as opposed to dialysis pericarditis, it responds to intensive dialysis. Due to hypervolemia from inadequate dialysis, pericardial effusions are frequent but they rarely lead to cardiac tamponade. Pericardial contents are usually sterile. A clue to the presence of impending cardiac tamponade is the occurrence of repeated and/or severe hypotension episodes during dialysis. Pericardiocentesis with or without catheter drainage should be reserved for cases of circulatory collapse associated with cardiac tamponade. In most other cases, there is sufficient time for more effective surgical options for pericardial sac drainage.[225]

INFECTIVE ENDOCARDITIS

Bacteremia in patients receiving HD is often the result of access site infections, access manipulation and procedures such as dental work.[226] The incidence of bacteremia is 0.7–1.2 episodes per 100 patients per month, and about 10% of these bacteremic episodes are complicated by infective endocarditis (IE).[227] *Staphylococcus aureus* is the causative organism in 60–80% cases of IE in HD patients. Methicillin-resistant *S. aureus* is more common than methicillin-susceptible *S. aureus* (67% vs 33%).[228] Other causative organisms are *Staphylococcus epidermidis*, *Streptococcus viridans*, enterococci and gram-negative organisms.[229] IE with these pathogens is associated with a mortality rate greater than 50% in this setting.[226] In the HD population, the mitral valve is more often infected than the aortic valve, and, together, both are more often affected than the right-sided valves.[229,230] Treatment guidelines recommend a minimum of 4 weeks of antimicrobial therapy after a diagnosis of IE is made in an HD patient.[229] Surgical indications and contraindications for acute IE in ESRD patients are similar to those for general population.[231] Unfortunately, surgical mortality associated with valve replacement in ESRD related to endocarditis is quite high. In the setting of ESRD, there has been no difference in survival among those who received tissue or mechanical valve prostheses. Thus tissue valves are a reasonable choice given the complicating issue of chronic anticoagulation and bleeding with dialysis vascular access.

VALVULAR HEART DISEASE

Impaired renal function has been linked to dystrophic calcifications of the valvular annulus and leaflets, particularly the aortic and mitral valves.[232,233] The prevalence of aortic valve calcification in dialysis patients is up to 55%, similar to that in the elderly general population, although it occurs 10–20 years earlier.[233-235] Aortic stenosis is associated with an increased CV mortality[236] and its prevalence in dialysis patients is 3–13%.[237] Age, duration of dialysis, hyperphosphatemia and an elevated calcium phosphate product appear to be important risk factors for the development of aortic stenosis;[233,238] additional factors include specific involvement of the posterior cusp, left atrial dilatation, duration of dialysis and duration of predialysis systolic HTN. Mitral valve calcification was found in 39–45% and 18% in HD and peritoneal dialysis patients respectively,16% in predialysis patients and 10% in the general population.[233,239,240] Valve calcification has been associated with rhythm abnormalities and cardiac conduction defects, valvular insufficiency and peripheral vascular calcification. Factors associated with a decreased survival in these patients include the severity of calcifications, presence of mitral regurgitation and reduced LV function.[233,235,239,240]

ARRHYTHMIAS

Uremia, LVH, LV dilation, CHF, ischemic and valvular heart disease, calcification of the conduction system from secondary hyperparathyroidism, pericarditis, dialysis-associated hypotension, acid-base and electrolyte disturbances and hypoxemia are all potential causes for the various types of arrhythmias

encountered in CKD.[241,242] The prevalence of arrhythmias is 68–88% for atrial arrhythmias, 56–76% for ventricular arrhythmias and premature ventricular complexes were found in 14–21%.[243,244] Serious arrhythmias are uncommon except in patients with underlying heart disease, those receiving digitalis or those with severe hyperkalemia.[245] The majority of the premature ventricular contractions are unifocal and number less than 30 per hour; however, high-grade ventricular arrhythmias were found in 27% of patients with 24-hour Holter monitoring.[246] Dialysis-associated hypotension seems to be an important factor in precipitating high-grade ventricular arrhythmias, irrespective of the type of dialysis.[247] The finding of high-grade ventricular arrhythmias in the presence of CAD has been associated with an increased risk of cardiac mortality and SCD.[247] CKD and ESRD patients have elevated defibrillation thresholds and a high failure rate of implantable cardioverter defibrillators (ICDs).[248] CKD and ESRD in particular, may cause elevated defibrillation thresholds and failure of ICD.[248] Patients receiving ICD should have close surveillance and be considered for noninvasive programmed stimulation for appropriate antitachycardia and defibrillation therapy. Patients with atrial fibrillation (AF) have a markedly higher incidence of thromboembolism[249] and overall morbidity and mortality[250] compared to those in normal sinus rhythm. An increased risk of ischemic stroke of tenfold with AF was observed. Observational studies found that low and full intensity anticoagulation with warfarin in dialysis patients was associated with twice the number of major bleeding episodes as those observed in dialysis patients either receiving subcutaneous heparin or not receiving warfarin.[251] Many antiarrhythmic medications (digoxin, sotalol and procainamide) require dose adjustments in renal insufficiency. The risk for arrhythmias in dialysis patients receiving digitalis increases sharply during dialysis due to rapid shifts of potassium. Therefore, digitalis should be prescribed with the lowest therapeutic dosage and the potassium concentration in the dialysate can be increased. Considering the high rates of sudden death in patients with ESRD, clinical trials of prophylactic ICDs in this population are under consideration.

DIAGNOSTIC TESTS

CARDIAC MARKERS

Creatine kinase and troponin elevations are frequently observed in asymptomatic ESRD patients (more often with troponin T than with troponin I). For this reason, obtaining serial levels of troponin I is a good approach for diagnosing acute ischemic events. Cardiac troponin T is a predictor of asymptomatic multiple vessel coronary artery stenoses[252,253] and all-cause mortality.[254,255] B-type natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP) increase by 20.6% and 37.7% respectively for every 10 ml/min per 1.73 m^2 reduction in eGFR.[256] In euvolemic CKD patients, plasma BNP concentration was predicted by LV mass index and β-blocker usage. The NT-proBNP levels were associated with the same parameters and also GFR and Hb.[257] Between the two markers, it appears that BNP level is less dependent of GFR. In dialysis patients, increased NT-proBNP levels are significantly associated with increased mortality and LV systolic dysfunction.[92] Independent of renal function, these markers are a predictor of coronary events.[258] However their exact role of these markers in assessing CV prognosis is unclear.[259]

ELECTROCARDIOGRAPHY

Hemodialysis induces or changes in serum electrolytes and volume status. These, coupled with the presence of LVH and the effect of medications contribute to the changes seen in the resting electrocardiogram. There are changes in the ST-T segment morphology (in the absence of ischemia)[260-262] as well as an increase in: QT interval and dispersion, P wave duration, amplitude of the QRS complex (especially with LVH). For these reasons, the ST segment depression on resting ECG is considered an unreliable marker of coronary ischemia in the dialysis patient. Ectopy and tachyarrhythmias are more common in patients with advanced renal disease, transplant recipients and in patients with uremic cardiomyopathy, explaining the higher risk of sudden death.[92]

ECHOCARDIOGRAPHY

By the time of starting dialysis, only a minority of patients have a normal echocardiogram (15% in one study).[91] LV disease is common in dialysis patients and manifests as LVH, dilated cardiomyopathy and systolic dysfunction.[95] Although echocardiography overestimates LV mass in HD patients,[263] the echocardiogram is most accurate when performed at the patient's "dry weight" and there is a true increase in LV mass in patients on HD compared with predialysis patients.

STRESS TESTS

In patients with CKD and stable CAD, an increased prevalence of exercise-induced ischemia was noted.[145] Exercise ECG and thallium scintigraphy stress tests are of limited utility in renal failure because patients are unable to attain their target heart rate (poor exercise tolerance, autonomic neuropathy, use of medications that impair the chronotropic response to exercise) and because of abnormalities of the resting ECG.[264] In patients with markedly impaired kidney function, baseline levels of adenosine are increased; this would lead to a reduced vasodilatory response to dipyridamole. Symmetrical coronary disease and/or a blunted tachycardic response due to autonomic neuropathy can mask significant pathology.[265,266] Also, BP may be too high or too low to permit safe administration of a vasodilatory agent, coronary flow reserve may be reduced (due to LVH and small vessel disease). This may be the reasons that the dipyridamole-thallium nuclear stress test has a low sensitivity (37–86%), specificity (75%) and positive predictive value (70%).[267] A meta-analysis looked at thallium scintigraphy and dobutamine stress echocardiogram studies for risk stratification among patients with ESRD who were candidates for kidney transplantation. Compared to patients with negative test results, those with positive tests had a relative risk of myocardial infarction of 2.73 and of cardiac death of 2.92 following transplantation. Dobutamine echocardiography reportedly has a sensitivity of 69–95% and a specificity of approximately 95% in patients with CKD, making this test a better choice for detecting CAD.[265,268] However, there is a 2–4% risk of transient

AF in dialysis patients with this method, compared to only 0.5% in general population.[269] The National Kidney Foundation recommends noninvasive stress testing in the following dialysis patients:[60]

- Kidney transplant waitlist patients who have diabetes, have a high Framingham risk score, have known CHD (but not revascularized) or, prior to 1 year ago, underwent angioplasty or stent placement
- Selected dialysis patients with a high risk of an adverse CV event and that are not kidney transplant candidates
- History of complete coronary revascularization with coronary artery bypass surgery that occurred at least 3 years ago
- History of incomplete coronary revascularization with coronary artery bypass surgery that occurred at least 1 year ago
- LV systolic ejection fraction less than 40%
- Change in symptoms related to ischemic heart disease or change in clinical status.

COMPUTERIZED TOMOGRAPHY SCANS

Electron beam computerized tomography and helical computer tomography scanning can be used to assess the degree of CAC. The CAC scores of ESRD patients are several times greater than those found in the general population. There is data to suggest that an increased calcium content is a poor prognostic sign.[136,234,270] However it is unclear whether there is a correlation between CAC scores, atherosclerotic plaque burden and CV events or mortality.

CORONARY ANGIOGRAPHY

This is the "gold standard" test. In predialysis patients, the procedure may worsen renal function by causing contrast nephropathy or cholesterol embolization. The K/DOQI guidelines suggest that a limited amount of iso-osmolar radiocontrast media should be administered to patients with residual renal function who have been treated with prophylactic N-acetylcysteine, to help decrease the risk of contrast nephropathy and volume overload. For patients who have had an AMI, angiography is indicated when there are symptoms of myocardial ischemia at rest or after minimal exertion or if there is early, severe ischemia during a stress test. Otherwise, coronary angiography should be limited to those with symptoms refractory to medical therapy and for patients in whom revascularization would be undertaken if critical CAD were to be identified.

PRINCIPLES OF TREATMENT OF CARDIOVASCULAR DISEASE

There is a paucity of data on treatment because patients with kidney disease were excluded in 56% of the major CV intervention trials and only 10% of studies reported information on baseline renal function.[271] CV medications are less frequently used in patients with renal dysfunction and this is associated with significantly increased risk for subsequent mortality.[272] It is likely that underutilization of effective therapies occurs in patients with CKD and that optimal targets for treatment are not achieved.[273,274] However there is enough data to support the idea that patients with concurrent CKD and CVD likely benefit from many of the interventions implemented in individuals with CVD alone (or at the highest risk for development of CVD), incuding the same secondary prevention measures employed in the general population; observational studies indicate that heart failure patients may derive a mortality benefit from ACEIs and β-blockers. Efforts to improve CV outcomes by single risk factor intervention have been unsuccessful and the approach should be global, multifaceted, multidisciplinary. There have been few randomized controlled trials conducted in the CKD population addressing primary prevention of ischemic heart disease. The data related to the effectiveness and safety of aspirin in patients with CKD, particularly those with ESRD is scarce and conflicting; although individuals with CKD have a propensity for bleeding, only minor bleeding episodes were increased with the use of low-dose aspirin.[275] In patients with CKD with mitral or aortic valve disease primary control of potentiating factors and frequent monitoring once valve surface area decreases are the mainstay of treatment.

Peritoneal dialysis is less efficient at removing drugs than HD and is most effective for smaller molecular weight drugs that are not extensively bound to serum proteins. Drug clearance in dialysis patient is affected by their water solubility, protein binding, distribution volume and diffusion across the dialysis membrane. In patients with ESRD but without pre-existing CVD, different renal replacement modalities lead to similar CV outcomes.[276] Exercise training during HD significantly improves both interdialytic and treatment-related BP.[277] There is evidence that tight glycemic control in DM, reduction of BP to below 130/80 mm Hg, with either ACEIs or ARBs, weight loss in obese patients and dietary protein restriction to the recommended daily allowance of 0.8 g/kg per day reduce the risk of progressive kidney disease and risk of CVD. Close follow-up is required for potentially dangerous complications that may be more common in CKD such as hyperkalemia with the use of ACEIs, ARBs or aldosterone antagonists. Correction of anemia to a target of 10–12 g/dL is currently recommended.

KIDNEY TRANSPLANT RECIPIENTS

After renal transplantation, systolic dysfunction, LV dilatation, LVH and risk of hospitalization for HF improve despite levels of BP that are similar with those found prior to grafting.[95,278,279] Although mortality rates are lower in transplant recipients compared with dialysis patients, they are still substantially higher than in the general population. It is not clear yet what is it about transplantation (and improved renal function) that provides protection against CVD despite the fact that immunosuppression can exaggerate known CVD risk factors such as hyperlipidemia, HTN, anemia and DM.

Despite these positive results, there is significant progression of CAC and atherosclerotic CVD is one of the most frequent causes of morbidity and mortality after transplantation.[280] The CVD rates peak during the first 3 months following transplantation and decrease subsequently compared to those patients who are listed for transplantation but remain on dialysis.[281] It is uncertain if transplant patients are at an increased risk of death from myocardial ischemia.[282] Even young adults who received pediatric kidney transplants had CAC

detected by electron beam computed tomography (EBCT) with the quantity of CAC comparable to asymptomatic individuals from the community between 10 years and 40 years older.[283] Pre-transplant CVD is a major risk factor for developing post-transplant CVD.[281,284] Other risk factors associated with CV complications are: male gender, age, HTN before transplantation, smoking, high CRP, abnormal Hb, cytomegalovirus seropositivity, longer pre-transplantation dialysis, post-transplantation diabetes, increased pulse pressure after transplantation, use of corticosteroids, lower serum albumin, higher serum TG levels after transplantation and metabolic syndrome.[285-288] Attention has been focused in recent years on so-called nontraditional risk factors, including inflammation and oxidative stress, which are prevalent in patients with CKD and are not effectively controlled by dialysis. CAD progression is most likely to occur in white patients and is associated with clinical factors such as BP, body mass index, renal function and baseline CAC score.[289]

HTN is common in transplant patients with an estimated prevalence of 50–90%. Both cyclosporine and tacrolimus have adverse effects on determinants of CV risk with discrete differences between the drugs.[290,291] The vasoconstrictive effects of calcineurin inhibitors in particular worsen HTN after transplantation.[292] Calcium channel blockers are widely used because they are well tolerated and due to their effects in counter-acting calcineurin-mediated vasoconstriction.

In transplant patients, levels of TC, LDL and TG are usually higher than in the general population but HDL is usually normal.[68] Fewer than 40% of transplant patients have their lipids measured during the course of a year.[81-83] For kidney transplant patients, there is data on fluvastatin which was found to decrease the incidence of cardiac death and myocardial infarction.[293] Clinical practice guidelines for managing dyslipidemia in transplant patients suggest that changes in the immunosuppressive protocol (reduction in prednisone dose, reduction in cyclosporine dose or switching from cyclosporine to tacrolimus, and discontinuation or replacement of sirolimus) be considered when LDL levels remain elevated ($\geq$ 100 mg/dL) despite optimal medical management.[294] The risk of CVD, cerebrovascular disease and death is increased with smoking.[80,295-297] DM has also been found to be an independent risk factor for ischemic heart disease and for cardiac failure in renal transplant recipients.[80,81,297] Hypoalbuminemia is an independent risk factor for the development of both *de novo* cardiac failure and ischemic heart disease.[106,282] Anemia is an independent risk factor for the development of electrocardiographically diagnosed LV hypertrophy and of symptomatic heart failure;[215,282,298,299] anemia correction leads to improvements in LVH, LV dilatation and systolic dysfunction.[278] The presence of LVH during the first year is also an independent predictor for the development of heart failure and death.[299]

Patients at high risk for post-transplant cardiac ischemic events are screened with a pharmacologic stress echocardiography or nuclear imaging testing. Patients with symptomatic CAD or positive stress tests should have a coronary angiography if an intervention (CABG or PCI) is contemplated.[300] For patients who have negative initial evaluations but remain on the transplant waiting list, repeat evaluation for CAD is recommended every 12 or 24 months depending on their risk for CAD (K/DOQI clinical practice guidelines). Special attention is required for the 40% of the renal transplants which are performed in patients with DM; one-third of those have clinically silent CAD and they have the lowest 5-year survival on dialysis.[24] However noninvasive tests are not accurate enough to sufficiently exclude significant CAD in high-risk candidates, and that they may engender a false sense of security.[301,302]

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Chapter 99

Endocrine Heart Disease

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Chapter Outline

- Diabetes Mellitus
  - Coronary Artery Disease
  - Metabolic Syndrome
  - Congestive Heart Failure
  - Sudden Death
- Thyroid Disease
  - Hyperthyroidism
  - Hypothyroidism
  - Amiodarone-induced Thyroid Disease
- Pituitary Disorders
  - Growth Hormone Excess
  - Hypopituitarism
- Adrenal Disorders
  - Pheochromocytoma and Paraganglioma
  - Primary Aldosteronism
  - Cushing's Syndrome
  - Adrenal Insufficiency
- Parathyroid Disorders
  - Primary Hyperparathyroidism
  - Hypoparathyroidism
- Carcinoid Syndrome

INTRODUCTION

Endocrine disorders which include diabetes mellitus commonly affect the heart. In this chapter the authors review the cardiovascular manifestations of a number of endocrine disorders and the impact of treatment on ameliorating the cardiovascular manifestations.

DIABETES MELLITUS

People with diabetes mellitus are at increased risk for angina, myocardial infarction (MI), congestive heart failure (CHF) and sudden death.

CORONARY ARTERY DISEASE

It is well established that diabetes is a major risk factor for cardiovascular disease. In the Framingham cohort, diabetic men had a twofold increase and women a threefold increase in the risk for cardiovascular disease.[1] Also the gender protection afforded to women was lost if they had diabetes—the cardiovascular mortality in women with diabetes matched that of men with diabetes. In some studies individuals who had diabetes but not coronary artery disease (CAD) had the same high risk for major coronary events as individuals with established CAD—in other words, diabetes was coronary heart disease risk equivalent.[2-4] Other studies, however, have not confirmed this observation and find that patients with diabetes have lower risk of cardiovascular outcomes than those with established coronary heart disease.[5-8] Nevertheless, it is true that the combination of diabetes and prior heart disease identifies particularly high-risk individuals.[6-8] Having diabetes also worsen outcomes with cardiac events. Diabetes patients with unstable angina are more likely have in-hospital MI and mortality.[9] During a 2 year follow-up of patients who had been hospitalized with unstable angina or non-Q-wave MI, those with diabetes had higher rates of cardiovascular death, new MI, stroke and new CHF.[10]

There are a number of explanations for this increased risk for heart disease with diabetes. The majority of people with diabetes have type 2 diabetes (~ 95% of the 25.8 million people with diabetes in the United States); and type 2 patients in addition to hyperglycemia typically also have additional risk factors for heart disease including hypertension, dyslipidemia, hypercoagulability and hyperuricemia. These various risk factors act in concert on the vascular wall to increase the risk for atherosclerosis (Fig. 1).

The prevalence of hypertension in patients with type 2 diabetes is approximately twofold higher than age matched subjects without diabetes.[11] Thirty-nine percent of the newly diagnosed type 2 diabetes patients recruited for the United Kingdom Prospective Study had a systolic pressure of 160 mm Hg or greater and/or diastolic pressure of 90 mm Hg or greater.[12] Data from the Framingham cohort suggests that for every 10 mm Hg increase in blood pressure increases cardiovascular risk by about 30%.[13] Experimental and epidemiological evidence suggests that the increased blood pressure affects both the arterial media and the endothelium. In the media the elevated pressure increases the total smooth muscle mass and connective tissue content. Endothelial changes include an increase in number and change in shape of endothelial cells; increased endothelial permeability to macromolecules (including lipoproteins); impaired nitric oxide (NO) induced relaxation and

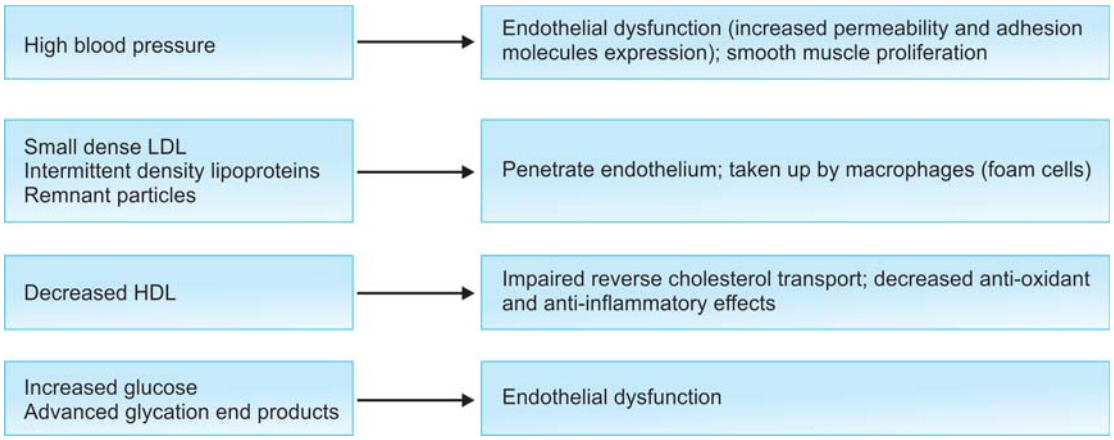


FIGURE 1: Principle mechanisms by which hypertension, dyslipidemia and hyperglycemia in type 2 diabetes promote atherosclerosis

increased cell surface adhesion molecules such as the selectins and vascular adhesion molecule 1 (VCAM 1).[14] These molecules in turn mediate recruitment of inflammatory cells such as monocytes and T cells. When there are other atherogenic factors, such as dyslipidemia, these hypertensive changes promote the development of atherosclerosis.

The lipid abnormalities that are typically present in type 2 diabetes patients—increased triglycerides, low HDL cholesterol levels and increased small dense LDL particles—are also those that in experimental systems promote atherosclerosis.[15] The prevalence of low HDL cholesterol levels in people with diabetes is almost twice as high as the prevalence in nondiabetic individuals (21% vs 12% in men and 25% vs 10% in women).[16] The contribution of triglycerides to cardiovascular risk can be explained by the presence of triglyceride-rich intermediate density lipoproteins and remnant particles that can penetrate the vascular endothelium and be preferentially trapped in the sub-endothelial space. HDL functions in cellular cholesterol efflux and has direct antioxidative as well as anti-inflammatory properties and low HDL cholesterol is an independent risk factor for CAD. Even though the concentration of LDL cholesterol in type 2 diabetes is not significantly different from nondiabetic individuals, the diabetic patients tend to have higher levels of dense LDL particles. These particles have a greater atherogenic potential by their reduced LDL receptor affinity, greater propensity for transport into the sub-endothelial space, increased binding to arterial wall proteoglycans and susceptibility to oxidative modifications.[17]

The increased adipose tissue that is present in many patients with type 2 diabetes, especially visceral fat, is a source of a number of factors including free fatty acids, plasminogen activator inhibitor-1 (PAI-1), tumor necrosis alpha (TNF-α) that negatively affect endothelial function.[15,18,19] TNF-α, for example, has been shown to increase leukocyte adhesion to the endothelium;[20] activate nuclear factor κB (NF-κB) dependent proinflammatory pathways; and induce endothelial cell expression of the VCAM-1 and endothelin 1. It can also induce expression of matrix metalloproteinases in smooth muscle thus contributing to plaque destabilization.[21]

The role of hyperglycemia as an independent risk factor for cardiovascular disease remains a controversial issue.[22] Several studies have reported fasting plasma glucose level as a univariate predictor of cardiovascular event and mortality.[23-25] Other studies, however, have not found a strong association with hyperglycemia.[26-28] It may be that there are subpopulations of people with diabetes who are susceptible to the cardiovascular consequences of hyperglycemia. Only a proportion of people with diabetes develop significant microvascular complications; and microvascular disease, particularly nephropathy predicts cardiovascular disease. The Steno group, for example, showed that the development of proteinuria caused an eightfold increase in the cumulative incidence of CAD over the next 6 years.[29] The link between microvascular and macrovascular disease in some instances may therefore reflect the susceptibility of the individual to both conditions, and, in other instances, the macrovascular disease may be secondary to the microvascular condition. Hypertension and acquired lipid abnormalities in diabetic nephropathy may play an important pathological role in the development of atherosclerosis.[30,31] Experimental evidence also provides mechanistic explanations as to how hyperglycemia can promote atherosclerosis. Both high glucose levels and advanced glycation end products which are formed by sustained exposure of proteins and lipids to high concentrations of glucose, increase endothelial cell oxidative stress; inhibit NO production and increase expression of inflammatory cytokines.[15]

Type 2 diabetes is also associated with changes in homeostatic mechanisms in the direction promoting atherosclerosis.[32] In particular, type 2 diabetes has been associated with increased levels of PAI-1 which suppresses fibrinolysis.[33] PAI-1 is a risk factor for coronary events in patients with angina[34] and for re-infarction post-MI.[35] The vascular endothelium and possibly visceral adipose tissue are the likely sources of the increased PAI-1 levels.

Elevations of factor VII coagulant activity (FVII:c); von Willebrand factor, fibrinogen and activated factor XII (XIIa) have been inconsistently reported in patients with diabetes.[32] Many studies, but not all, have also reported that platelets from patients with type 2 diabetes aggregate more readily than in healthy subjects.[36,37] It may be that some of these changes are secondary to other metabolic abnormalities or complications present in patients with diabetes. For example, lipid particles

may have a role in activation of factor VII.[38] Hyperglycemia, hypertriglyceridemia and endothelial dysfunction (lower NO and prostacyclin production) all have been shown to increase platelet reactivity.[39]

Gout is more common in patients with type 2 diabetes, and hyperuricemia is associated with increased risk of cardiovascular disease. It is unclear, however, if it is an independent risk factor for heart disease.[40,41] For example, a recent study from Italy was unable to observe with significant relationship between uric acid and the prevalence or severity of CAD after correcting for baseline confounding factors of gender, age, renal insufficiency, hypertension and previous CAD.[42] There is, however, substantial evidence that hyperuricemia predicts the development of hypertension.[40] There is also evidence that uric acid has a pro-inflammatory effect on the vascular smooth muscle cells.[43-45]

METABOLIC SYNDROME

The conditions of central obesity, dyslipidemia (elevated triglycerides and/or low HDL cholesterol), glucose intolerance and hypertension co-occur in individuals more often than might be expected by chance. The term "metabolic syndrome", "syndrome X" or the "insulin resistance syndrome" has been used to describe this cluster, and individuals who have this cluster of abnormalities are at higher risk of cardiovascular disease.[46-49] The term "syndrome" is usually used because there is a cluster of signs or symptoms that suggest a unique disease or condition; or because a specific therapy is dictated; or a particular prognosis is predicted.[50] There is considerable debate as to whether "metabolic syndrome" meets these criteria.[51-53] First, since not all the risk factors have to be present to have the diagnosis of metabolic syndrome, patients can be categorized into 16 distinct groups using the National Cholesterol Education Program Treatment Panel III (ATP III) definition[46] and 11 different groups using the International Diabetes Federation definition.[49] As a result the risk for cardiovascular disease is not equivalent across the different risk factor combinations. Second, the risk for cardiovascular disease in those with the syndrome does not appear to be greater than that conferred by constituent components.[54] Third, the treatment of the syndrome as a whole is no different from that of each of its components. Fourth, since type 2 diabetes identifies individuals who have central obesity, dyslipidemia and hypertension, including glucose intolerance in the definition of metabolic syndrome is questionable. Fifth, the hypothesis that insulin resistance is the mechanism that underlies the metabolic abnormalities remains controversial. Sixth, the definition does not include other important risk factors for cardiovascular disease such as age, sex, family history, smoking history, previous cardiovascular events and LDL cholesterol. There are other risk prediction algorithms for cardiovascular disease including the Framingham risk score and the Heart score that outperform the metabolic syndrome in predicting cardiovascular events.[55,56] A recent WHO report concluded that the metabolic syndrome concept is of limited practical utility as a diagnostic or disease management tool.[52] The main value of using this term is to remind clinicians to evaluate for and treat other risk factors when one or more are present.

CONGESTIVE HEART FAILURE

Diabetes is a well established risk factor for CHF.[57] In the Framingham cohort, the frequency of heart failure was increased twofold in diabetic men and fivefold in diabetic women compared with age-matched control subjects.[1] About 30% of patients with heart failure have diabetes. Much of the excess risk for heart failure is thought to be due to ischemic heart disease and its complications.[58] Data, however, from autopsies and animal experiments also support the existence of a distinct diabetic cardiomyopathy unrelated to atherosclerosis.[59] A number of etiologic mechanisms have been implicated.[60,61] Hyperglycemia may increase glycation of interstitial proteins such as collagen resulting in myocardial stiffness and impaired contractility.[62,63] Hyperglycemia may also increase intracellular generation of superoxide leading to cellular injury. In experimental systems, strategies that enhance mitochondrial reactive oxygen species (ROS) scavenging systems have been shown to reverse diabetes-induced cardiac dysfunction. Lipid accumulation within the cardiac myocytes may also be important. In animal models of obesity, such as the Zucker diabetic fatty rat, abnormalities in cardiac structure and function, were accompanied by increases in myocardial triglycerides and ceramides, and an increased rate of apoptosis.[64]

SUDDEN DEATH

Sudden cardiac death in people with diabetes is most often due to atherosclerotic heart disease.[65] The risk for sudden death may be increased if cardiac autonomic neuropathy is present—the hypothesized mechanisms include silent myocardial ischemia and infarction, impaired central control of respiration and predisposition to cardiac arrhythmias because of alterations in the QTc intervals.[66-68] Scintigraphic studies suggest that left ventricular denervation in patients with severe diabetic autonomic neuropathy is heterogeneous.[69,70] Activation of "islands of sympathetic innervation" may paradoxically cause local vasoconstriction and ischemia. This in turn may lead to MI and precipitate cardiac arrhythmias.[71,72] Arrhythmias may be an important cause of death in young people with type 1 diabetes. Typically these patients are in good health and are found "dead in bed".[73] Severe nocturnal hypoglycemia triggering a fatal cardiac arrhythmia is the likely cause for the sudden deaths.[74] Hypoglycemia can be shown to cause QTc prolongation.[68,75,76] QTc prolongation and cardiac rate or rhythm disturbances to episodes of nocturnal hypoglycemia in ambulant patients with type 1 diabetes have been documented.[77]

Prospective intervention studies confirm that treating hypertension, dyslipidemia and hyperglycemia reduce the risk for cardiovascular events in people with type 2 diabetes. In the United Kingdom Prospective Diabetes Study (UKPDS) of type 2 diabetes, a policy of tight blood pressure control (median value 144/82 vs 154/87) substantially reduces the risk of microvascular disease and stroke but not MI.[78] An epidemiological analysis of the UKPDS data however showed that every 10 mm Hg decrease in updated mean systolic blood pressure was associated with an 11% reduction in risk for MI.[79]

Trials of lipid lowering drug studies which include patients with diabetes show that these drugs reduce both primary and

secondary cardiac events.[80-84] In the Heart Protection Study, diabetic patients who did not have pre-existing cardiac disease, taking simvastatin reduced first major vascular event by 33% compared to placebo.[80] In the Scandinavian Simvastatin Survival Study (4S), a secondary prevention study, simvastatin reduced the risk of total mortality by 43% in patients with diabetes versus 29% in nondiabetic patients, and reduced the risk of MI by 55% in diabetic patients versus 32% in nondiabetic patients.[83] In the Veterans Affairs HDL Intervention Trial (VAHIT) study, lowering triglycerides (and increasing HDL cholesterol) using gemfibrozil reduced risk of MI in people with diabetes and coronary heart disease by 24%, a rate comparable to that observed in nondiabetic patients.[84]

There has been debate about the impact of glucose lowering on cardiac events. Long-term follow-up of the Diabetes Control and Complications Trial (DCCT) and UKPDS cohorts provide support that early aggressive management of hyperglycemia in individuals with recent history of diabetes and low rates of pre-existing cardiac disease translates into decreased cardiovascular event rates.[85-88] The Action to Control Cardiovascular Risk in Diabetes (ACCORD), Veteran Administration Diabetes Trial (VADT) and Action in diabetes and Vascular disease (ADVANCE) trials examined the effect of intensive glycemic control in older individuals with long standing diabetes and established cardiovascular disease.[89-91] These studies failed to demonstrate reduction in cardiac events. In the ACCORD study, the intensive arm was discontinued after 3.5 years because of more unexpected deaths in the intensive arm. It is important, however, not to overinterpret the results of these three studies and conclude that tight glucose control will not affect cardiac outcomes. It is possible that the benefits of tight glycemic control on cardiac events were attenuated in patients with longer duration of diabetes or with established vascular disease. Specific therapies used to lower glucose may also have affected cardiovascular event rate or mortality. Severe hypoglycemia occurred more frequently in the intensively treated groups of the ACCORD, ADVANCE and VADT studies. A formal meta-analysis performed of the raw data from the ACCORD, ADVANCE, VADT and UKPDS studies found that allocation to more intensive glucose control reduced the risk of MI by 15%. This benefit occurred in patients who did not have pre-existing macrovascular disease.[92]

As might be expected, multifactorial interventions targeting hyperglycemia, blood pressure and dyslipidemia can substantially reduce risk for cardiovascular events in people with diabetes. The Steno-2 study[93] randomized 160 patients with type 2 diabetes with microalbuminuria to usual or intensive care. The intensively treated group had stepwise introduction of lifestyle and pharmacologic interventions aimed at keeping glycated hemoglobin less than 6.5%, blood pressure less than 130/80 mm Hg; total cholesterol less than 175 mg/dL and triglycerides less than 150 mg/dL. All the intensively treated group received angiotensin-converting enzyme (ACE) inhibitors and if intolerant, an angiotensin II-receptor blocker. The lifestyle component of intensive intervention included reduction in dietary fat intake to less than 30% of total calories, smoking cessation program, light to moderate exercise, daily vitamin-mineral supplement of vitamin C, E and chromium picolinate. Initially, aspirin was only given as secondary prevention to patients with a history of ischemic cardiovascular disease; later, all patients received aspirin. After a mean follow-up of 7.8 years, cardiovascular events (e.g. MI, angioplasties, coronary bypass grafts, strokes, amputations, vascular surgical interventions) developed in 44% of patients in the conventional arm and only in 24% in the intensive multifactorial arm—about a 50% reduction. Rates of nephropathy, retinopathy and autonomic neuropathy were also lower in the multifactorial intervention arm by 62% and 63% respectively. The subjects who participated in this trial were subsequently enrolled in an observational follow-up study for an average of 5.5 years.[94] Even though the significant differences in glycemic control and levels of risk factors of cardiovascular disease between the groups had disappeared by the end of the follow-up period, the interventional group continued to have a lower risk of retinal photocoagulation, renal failure, cardiovascular endpoints and cardiovascular mortality.

In conclusion, diabetes is a major cause for cardiovascular disease. As the prevalence of diabetes increases, the associated cardiovascular prevalence is also expected to increase. Treatment of hyperglycemia and other risk factors early in the course of the disease can substantially reduce the cardiovascular disease. Ultimately public health measures to reduce population rates of obesity are likely to be the most effective way of reducing prevalence of diabetes and associated cardiovascular disease.

THYROID DISEASE

Thyroid disease is common—hyperthyroidism affects 0.5% and hypothyroidism 3.7% of the general US population.[95] Both hyperthyroidism and hypothyroidism are associated with cardiac complications.

HYPERTHYROIDISM

The common cardiac physiologic manifestations of hyperthyroidism include increases in resting heart rate, left ventricular contractility and blood volume and decreased systemic vascular resistance. Cardiac output may be increased by about 50–300%,[96,97] and the increased oxygen demand and reduced cardiac reserve leads to decreased exercise tolerance. With appropriate treatment of hyperthyroidism, these physiologic changes completely reverse and match euthyroid controls. Hyperthyroidism is also associated with several pathophysiologic cardiac complications including atrial fibrillation (AF), cardiomyopathy and pulmonary hypertension.

Atrial fibrillation is usually persistent rather than paroxysmal and develops in about 9–22% of patients with hyperthyroidism.[98] The frequency increases with advancing age, affecting about 15% of patients over the age of 70 years.[96] Hyperthyroidism shortens the duration of the action potential in cardiac myocytes and it is thought that this facilitates the genesis of re-entrant currents.[99] The risk factors for fibrillation in hyperthyroid patients include being male, older, having a history of ischemic heart disease, valvular disease and CHF.[100] Subclinical hyperthyroidism (a suppressed or below normal thyroid-stimulating hormone (TSH) with normal T4 and T3 levels) is also associated with increased risk of AF. Data from the Framingham cohort showed that among people 60 years

or older, subclinical hyperthyroidism with a suppressed TSH was associated with a threefold higher risk for development of AF in the next decade after adjustment for other risk factors.[101] Those with slightly suppressed TSH (> 0.1–0.4 mU/L) had a 1.6 fold increased risk. What about the reverse? What is the risk of having hyperthyroidism if you have AF? Recent studies using the more sensitive TSH assay suggest that approximately 1–1.5% of patients with AF have hyperthyroidism.[102,103]

These patients with hyperthyroidism and AF are at high risk for thromboembolic events but not higher than AF from other causes.[104] Elderly patients with thyrotoxicosis and AF and who have other risk factors for thromboembolism (such as left atrial enlargement) should be anticoagulated. In younger patients with thyrotoxicosis and AF who do not have other heart disease, hypertension or other risk factors for embolism, the risk of anticoagulant therapy probably outweighs the benefits. For these patients aspirin therapy may suffice.

Treatment of AF initially includes beta blockade to control the ventricular rate but successful conversion to sinus rhythm depends upon return to a euthyroid state. In a study of 163 patients with thyrotoxicosis and AF, 62% were in sinus rhythm with 8–10 weeks after achieving euthyroid state.[105] After 3 months of euthyroid state, only a few will revert spontaneously to sinus rhythm. Predictors for successful reversion to sinus rhythm were lower blood pressure measurements at baseline, age, absence of underlying heart disease and a hypothyroid state induced by therapy.[106] Electrical or pharmacologic cardioversion, with anticoagulant treatment for at least 3 weeks before and continued for at least 4 weeks after cardioversion, should be considered for patients who have persistent AF for 4 months or more after returning to a euthyroid state.[105] Hyperthyroid patients need lower doses of warfarin as they have increased clearance of clotting factors and reduced binding proteins.[107]

Rate related cardiomyopathy can occur in hyperthyroidism due to persistent tachycardia, and rate control improves left ventricular dysfunction even before the euthyroid state is restored.[108] In a study of 591 consecutive patients with hyperthyroidism, about 6% had heart failure. In this study the risk factors for heart failure were: being older than 60 years; being male; smoker; having diabetes and being hypertensive. Atrial fibrillation was an independent predictor for CHF.[109] Occasionally, patients with hyperthyroidism can develop a dilated cardiomyopathy. Most of the reported cases had Graves' disease and the cardiomyopathy can be either reversible[110] or irreversible.[109,111,112] The most consistent pathological finding is of excessive separation of myocardial fibers from each other suggesting "myocardial edema". Interstitial and perivascular fibrosis, cellular infiltration and myocyte necrosis occurs in some cases.[113]

Pulmonary hypertension is quite frequent in patients with hyperthyroidism.[114,115] In a study of 75 consecutive patients with hyperthyroidism, 47% had pulmonary hypertension with a pulmonary artery systolic pressure of at least 35 mm Hg.[115] These patients also had increased cardiac output with elevated left ventricular filling pressures. Usually the patients are asymptomatic and the pulmonary pressures normalize on return to a euthyroid state.

HYPOTHYROIDISM

The common cardiac physiologic manifestations of hypothyroidism are diametrically opposed to those described for hyperthyroidism and include bradycardia, decreased myocardial contractility and increased peripheral vascular resistance.[96] Usually patients have elevated blood pressure and treatment reverses these physiological changes. Hypothyroidism can also result in several pathophysiological cardiac conditions.

Severe hypothyroidism can cause a prolongation of QTc interval predisposing the patient to ventricular irritability. Rarely, torsade de pointes may result. Cardiac enlargement most often due to pericardial effusion can occur but cardiac tamponade however is unusual. Hypothyroidism is also associated with increased risk for coronary atherosclerosis. An increase in LDL cholesterol and diastolic hypertension are two factors that may contribute to this increased risk. Levothyroxine replacement should be performed cautiously in elderly patients with longstanding and severe hypothyroidism because too rapid replacement can precipitate or worsen myocardial ischemia.

AMIODARONE-INDUCED THYROID DISEASE

Amiodarone therapy causes thyroid dysfunction in about 15–20% of patients. The drug affects thyroid function in two ways—first, by its inherent effects on the thyroid follicles and on deiodinase activity, and second, by its high iodine content.[116-121]

Amiodarone, a benzofuran derivative, structurally resembles thyroid hormone and it inhibits deiodinase activity. As a result, the drug initially causes a fall in T3 and an increase in T4 and TSH. The TSH levels may transiently rise as high as 20 mU/L. A new steady state is reached after about 3 months with T4 at the upper limit of normal, T3 at the lower limit of normal and TSH in the normal range. These normal alterations in thyroid hormone economy with therapy should be considered first before embarking on studies for amiodarone associated thyroid disorders described in the next few paragraphs.

Amiodarone contains about 37% of organic iodine by weight. Ten percent of this iodine is deiodinated to yield free iodide and so a 200 mg maintenance dose releases 7 mg of iodide into the circulation. This is 70 fold in excess of the daily iodine requirements of 100–150 µg. This excess iodine can cause both hypothyroidism and hyperthyroidism—which condition develops depends on the sufficiency of iodine intake of the population and the underlying thyroid disorder.

Amiodarone induced hypothyroidism is more common in areas of sufficient iodine intake such as the United States and Japan where there is a high prevalence of autoimmune thyroid disease. The presence of a positive thyroid peroxidase antibody increases the likelihood of hypothyroidism by sevenfold to eightfold. Sometimes amiodarone induced hypothyroidism occurs in patients who do not have an obvious thyroid abnormality and have negative thyroid autoantibodies. These patients probably have subtle defects in iodine organification and thyroid hormone synthesis. Almost all the cases of amiodarone induced hypothyroidism occur in the first year of therapy and are treated with levothyroxine. The hypothyroidism is permanent in the majority of patients with positive antibodies

but may resolve in patients who appear to have a normal gland and negative antibodies within 2–4 months of discontinuing the amiodarone.

Areas of insufficient iodine intake, such as Italy, have a higher prevalence of nodular goiter and amiodarone induced thyrotoxicosis occurs twice as frequently as amiodarone induced hypothyroidism. In patients with autonomously functioning nodular goiters (or those patients with latent Graves' disease), the increased iodine availability leads to excessive synthesis and release of thyroid hormone (type 1 amiodarone induced thyrotoxicosis). The thyrotoxicosis can occur early after initiation of amiodarone therapy and may be heralded by worsening of the underlying cardiac disorder and heart failure. Treatment includes methimazole therapy or surgery. Potassium perchlorate depletes intrathyroidal iodine stores and can be used in conjunction with methimazole therapy. It has, however, severe side effects including agranulocytosis and aplastic anemia and is no longer available in the United States. Amiodarone withdrawal usually results in slow remission because the drug is highly lipid soluble and has a long elimination half-life (~ 40–60 days). The decision to withdraw depends on the availability of other therapeutic options to treat the cardiac arrhythmia.

Both amiodarone and the excess iodine can occasionally cause an acute, sometimes painful, destructive inflammatory thyroiditis. Pathological changes include follicular damage, histiocytic infiltration, fibrosis, swelling of follicular cells and vacuolization of the cytoplasm. It occurs in apparently normal glands at any time during treatment. The thyroiditis leads to an initial thyrotoxic phase with release of preformed hormones (type 2 amiodarone induced thyrotoxicosis). This may be followed by hypothyroidism which may be permanent. Glucocorticoids (prednisone 30–40 mg daily) tapered over 2–3 months can be used to treat the destructive inflammatory thyroiditis.

Distinguishing between amiodarone induced thyrotoxicosis type 1 and type 2 at presentation can be challenging. Also, sometimes both types may coexist in a patient. Doppler ultrasound can be helpful—the individuals who have inflammatory thyroiditis will have absent vascularity whereas those individuals with type 1 disease show normal or increased vascularity. Radioactive iodine scans are not that helpful because of the expanded body iodine pool. Some studies but not others have reported that interleukin 6 levels are normal in type 1 but markedly elevated in type 2. If it is not possible to determine whether a patient has type 1 or type 2 amiodarone induced thyrotoxicosis, it is reasonable to start both methimazole and prednisone at the same time—a rapid response with lowering of T3 by at least 50% after 2 weeks would support a diagnosis of type 2 disease, and treatment can be continued with prednisone alone with slow tapering. If the response is modest, however, and T3 levels remain unchanged after 2 weeks, then type 1 disease is likely and the prednisone can be stopped and methimazole continued.

In terms of screening for amiodarone induced thyroid disease, patients should undergo a baseline clinical assessment for thyroid disease and measurements of thyroid autoantibodies and thyroid hormone levels. Patients without any thyroid pathology can then be followed with 3–6 monthly measurements of T4 and TSH.

Finally, dronedarone, also a benzofuran derivative, does not contain iodine, and may be an option for patients who are at risk for amiodarone induced thyroid dysfunction. The drug, however, has been reported to cause severe liver injury.

In conclusion, because thyroid disease is common, thyroid associated cardiac disease is also fairly common. Normalization of thyroid hormones is essential for the successful management of the cardiac complications of hyperthyroidism such as AF and cardiomyopathy. Some of the mortality in severe hypothyroidism and myxedema can be attributed to cardiac rhythm problems. Amiodarone therapy can cause both hypothyroidism and hyperthyroidism, and managing the latter can be particularly challenging. With the availability of new treatments for cardiac rhythm problems including benzofuran derivatives that do not contain iodine, amiodarone associated disease may become a less important clinical issue in the future.

PITUITARY DISORDERS

GROWTH HORMONE EXCESS

Acromegaly due to growth hormone excess, if untreated, reduces life expectancy by approximately 10 years.[122] Predictors of overall mortality include the degree of growth hormone excess and the duration of exposure to elevated levels. In a long-term follow-up study of 151 patients with acromegaly in New Zealand, the excess mortality was principally due to vascular causes—the observed to expected mortality ratios were 3:1 for cardiovascular disease, and 3.3:1 for cerebrovascular disease.[122]

Cardiomegaly is a prominent feature of acromegaly with reported ranges of between 70% and 90% in autopsy studies.[123] The enlargement of heart is generally proportionate to that of other visceral organs and so is unlikely to be only due to the hypertension. A direct effect of growth hormone and IgF-1 is likely. Growth hormone and IgF-1 receptors are present on cardiac myocytes, and in cultured rat cardiomyocytes, IgF-1 induces hypertrophy.[124] Growth hormone also stimulates matrix metalloproteinases which may be involved in the remodeling process of the extracellular matrix that occurs with cardiac hypertrophy.[125] Hypertension, however, is important in exacerbating the hypertrophy—in a multistep regression analysis, diastolic blood pressure was the best predictor of cardiac hypertrophy.[126] Histopathological studies show varying degrees of myocardial hypertrophy and interstitial fibrosis affecting the myocardium of both ventricles. Less frequently, mild interstitial cellular infiltrate to a true myocarditis may be present.

Echocardiography in patients with acromegaly confirms biventricular involvement with increase in left ventricular mass index and right free wall thickness. The chambers are not dilated. Impairment in left and right ventricular diastolic filling is present but the overall ejection phase indices are normal.[127] The ejection fraction, however, is impaired with exercise. About 10% of patients with acromegaly develop heart failure.

The presence of myocardial interstitial fibrosis may affect the conduction system leading to cardiac arrhythmias. In a study of 32 patients with acromegaly, stress electrocardiography and Holter monitoring revealed more frequent complex and repetitive ventricular arrhythmias at rest and during exercise. The severity of ventricular arrhythmias correlated with left

ventricular mass and with severity of acromegalic symptoms and signs. The frequency of ventricular premature beats correlated with duration of disease.[128] The frequency of ventricular arrhythmias tends to remain even after the treatment of acromegaly probably reflecting incomplete reversal of myocardial fibrosis.

Valvular heart disease occurs in patients with acromegaly. In an autopsy study, aortic and mitral valvular disease was present in 4 of 27 cases (15%)—2 had aortic regurgitation, and 2 had mitral stenosis and regurgitation. There was no historical or morphological evidence to suggest rheumatic or luetic origin.[123] In an echocardiographic study of 40 consecutive patients with acromegaly and 120 controls (matched for age, sex, hypertension and left systolic function); regurgitant valvular disease was more common in patients with acromegaly. Mild aortic regurgitation was present in 7 patients (17.5%) and 5 controls (4%), and severe in 1 patient (2.5%) and none in controls. Pathological mitral regurgitation (moderate or severe according to FDA criteria) was present in 2 patients (5%) and none in controls. None of the patients had pathological tricuspid valve regurgitation. The presence of valvular disease increases with increased duration of disease affecting up to 40% after 16 years.[129] Even patients who are cured of their acromegaly have been reported to have higher rates of both mitral and aortic regurgitation.[130] The persistence of the valvular abnormalities indicates the need for careful cardiac follow-up even after cure. In a surgical report of 5 patients who underwent valvular surgery, the causes of aortic valvular regurgitation were aortic valvular degeneration and aortic annular dilatation, and the causes of mitral regurgitation were chordal rupture and mitral valvular degeneration. Histopathological examination of the excised valves showed mucopolysaccharide deposits and myxomatous degeneration of the leaflets.[131]

There is an increase in prevalence of risk factors for CAD (hypertension, diabetes, insulin resistance and dyslipidemia) in patients with acromegaly. In an autopsy study of 27 patients, 3 (11%) had significant CAD; 4 (15%) had evidence of old MI and 6 (24%) had atherosclerosis of the abdominal aorta.[123] There is, however, no evidence that the CAD risk in patients with acromegaly is greater than in people with similar cardiac risk factors but no acromegaly. In a study of 21 acromegalic patients, carotid intima-media thickness was found to be equivalent to controls when matched for cardiovascular risk factors.[132] In another study of 52 patients with acromegaly, 24 controlled or in remission and 28 untreated or not controlled, there was no difference in the Framingham risk score or distribution of coronary calcium score. Seventy-one percent of the patients had a low Framingham risk score, and there were no coronary events over the 5 years of follow-up. In a 5 year prospective study of 52 consecutive patients with controlled and uncontrolled acromegaly, the level of coronary heart disease risk was unrelated to IgF-1 levels or duration of disease and no patient developed ischemic heart disease during follow-up.[133] Given these findings it is reasonable to treat cardiac risk factors in patients with acromegaly similar to patients without acromegaly.

Normalization of serum IgF-1 and growth hormone levels (< 1 ug/L) by surgery or using somatostatin analogs reduces overall mortality to normal.[134-137] Successful treatment also improves cardiovascular parameters with reduction in cardiac mass and improvement in diastolic filling. Patients with shorter duration of disease were more likely to have reversal of cardiomyopathy.[138] Treatment with the growth hormone antagonist—pegvisomant—has been shown to significantly improve blood pressure and fasting blood glucose levels in those patients who normalized their IgF-1 levels.[139]

In conclusion, acromegaly due to growth hormone excess is associated with approximately 10 year reduction in life expectancy mostly due to cerebrovascular and cardiovascular disease. Curing the disease reverses this increased mortality. The cardiac hypertrophy and risk of arrhythmia reverses with treatment especially if the duration of the acromegalic state is short. Longer duration of disease may limit the reversibility. The valvular changes seem to persist in a significant proportion of cases. There is clustering of the standard cardiovascular risk factors in patients with acromegaly and the CAD risk is commensurate to the risk factors. The disease is rare so these conclusions are based on data from relatively small cohorts, and also include data from patients who were managed in an era of less sensitive growth hormone and IgF-1 assays, and different surgical and medical options.

HYPOPITUITARISM

Hypopituitarism, a deficiency of one or more hormones of the anterior or posterior pituitary gland, is associated with an increase in all cause mortality. In a recent meta-analysis, the standard mortality ratio in hypopituitary patients was 2.06 (95% CI 1.94–2.20) in men and 2.80 (95% CI 2.59–3.02) in women.[140] In most studies but not all vascular mortality (cardiovascular or cerebrovascular) was increased.[141] The mechanisms underlying this increased propensity to vascular disease are not known. Hypopituitary patients have a reduction in lean mass and increase in central obesity and are significantly insulin resistant compared to normal matched controls.[142,143] Increases in triglycerides and PAI-1 levels and decrease in Low HDL cholesterol have also been reported. Growth hormone deficiency may play a role in the development of these abnormalities. Indeed growth hormone replacement reverses the body composition abnormalities and improves the lipid profile. Sustained improvement in carotid intimal media thickening has also been reported.[144] Growth hormone replacement however does not uniformly improve cardiovascular risk factors;it increases plasma glucose and also lipoprotein (a)—an independent risk factor for cardiovascular disease. There are currently no data showing that growth hormone replacement effects on cardiovascular risk profile translate into improved cardiovascular outcomes.

Other hormone deficiencies present in hypopituitarism could also potentially play a role in the increased mortality with this disease. Traditionally the daily hydrocortisone dose for adrenal insufficiency was 30 mg daily. Recent studies, however, suggest that this is higher than the cortisol production in normal subjects (~ 10 mg/day).[145] It is possible that the subtle increased glucocorticoid exposure with the traditional 30 mg dose might contribute to the increased morbidity and mortality. Similarly, the adequacy of thyroid hormone replacement in central hypothyroidism is difficult to assess because TSH levels cannot be used to titrate the T4 dose. Both over-replacement and under-

replacement with T4 could have negative cardiovascular effects. There is little information on the role of estrogen and testosterone replacement on morbidity and mortality in hypopituitarism. An increase in mortality in gonadotropin deficient patients not receiving sex steroids has been reported.[146]

The increased cerebrovascular risk in hypopituitary patient may be a reflection of treatment rather than any particular hormone deficiency. Stereotactic radiosurgery is a relatively new therapy and most of the mortality data in hypopituitary patients dates from the era of conventional radiotherapy. A number of studies have reported that conventional radiotherapy is associated with increased risk for cerebrovascular disease.[147]

In conclusion, hypopituitarism is associated with increased mortality principally to vascular disease. This may reflect suboptimal replacement of pituitary hormones—not replacing growth hormone or sex steroids, too much hydrocortisone and too much or too little T4. Pituitary radiotherapy may be an additional cause in cerebrovascular mortality.

ADRENAL DISORDERS

PHEOCHROMOCYTOMA AND PARAGANGLIOMA

Pheochromocytomas arise from the adrenal medulla and paragangliomas arise from the non-adrenal chromaffin tissue. Most of these tumors secrete catecholamines in excess—sometimes as much as 27 times the usual amount. The increased levels of epinephrine and norepinephrine lead to activation of alpha 1 and beta 1 adrenergic receptors with resulting increases in heart rate, contractility and vasoconstriction. Pheochromocytomas can also secrete other peptide hormones that have vascular effects such as neuropeptide Y, a very potent noradrenergic vasoconstrictor. The clinical picture is of hypertension, left ventricular hypertrophy, dilated cardiomyopathy and arrhythmias.[148]

Hypertension is present in approximately 90% of patients. The blood pressure patterns vary among patients. Most commonly the patients have sustained hypertension with paroxysms of severe hypertension during symptomatic episodes which typically consist of headache, palpitations and diaphoresis. Some patients may be normotensive between paroxysms. Despite being hypertensive, patient may have orthostatic drops in blood pressure from lying to standing. Sometimes epinephrine secretion from a pheochromocytoma can cause episodic hypotension and even syncope.[149,150] Individuals with hypertension should be screened for pheochromocytoma if there are any red flags such as young age, labile blood pressure, and paroxysmal symptoms of headaches, palpitations and sweats. When screening for secondary causes of hypertension, the prevalence of pheochromocytoma is approximately 0.1–0.6%.[151,152]

Left ventricular hypertrophy commonly develops probably secondary to the hypertension. The high levels of catecholamines can also cause myocarditis and cardiomyopathy and patients can present with pulmonary edema.[153] In most cases the cardiomyopathy resolves after removal of the tumor. In an autopsy study of 26 patients with pheochromocytoma, 15 (58%) had evidence for myocarditis—histology showed focal necrosis with infiltration of inflammatory cells, perivascular inflammation and contraction band fibrosis.[154,155] In some patients the myocardial scarring and fibrosis leads to irreversible cardiomyopathy and heart failure. The pathogenesis of the catecholamine induced cardiomyopathy is probably multifactorial. Norepinephrine may induce changes in sarcolemmal membrane resulting in increase intracellular calcium influx and apoptosis. The norepinephrine could also cause myocardial injury by both increasing cardiac oxygen demand and decreasing coronary blood flow.

Cases of myocardial stunning have also been reported—presumably the release of catecholamines cause marked cardiac ischemia and myocardial contractile dysfunction that reverses with recovery of coronary perfusion.[156,157] Echocardiographic findings analogous to myocardial stunning due to sudden emotional stress (Takotsubo cardiomyopathy) can also occur.[158,159]

Electrocardiographic abnormalities in patients with pheochromocytoma commonly include left ventricular hypertrophy and T wave inversion. Patients can also present with electrocardiographic evidence of ischemia due to coronary artery vasoconstriction and increased oxygen demand. Sinus tachycardia, paroxysmal supraventricular tachycardia and supraventricular ectopic activity occur from direct chronotropic effects of the catecholamines. Marked prolongation of QT interval and widened deep T waves may predispose to ventricular arrhythmias.

Surgical resection of the pheochromocytoma or paraganglioma usually reverses the abnormalities although in some patients with longer duration of disease, cardiovascular remodeling and organ damage can lead to persistence of complications especially hypertension.[160] Those patients with hypertension without recurrence of tumor should be managed as if they have essential hypertension.[161]

In conclusion, cardiovascular complications predominate in the clinical presentation of pheochromocytoma and paraganglioma, and surgical cure is associated with survival rates similar to that of the normal population.

PRIMARY ALDOSTERONISM

Aldosterone increases the number of open epithelial sodium channels in the renal cortical collecting tubule, increasing sodium and water absorption and potassium excretion. The hypertension may be a consequence of volume expansion or possibly due to direct actions of sodium itself. Early studies suggested that only 2% of patients with hypertension have primary aldosteronism.[162] More recent epidemiological studies suggest a higher prevalence in the 10–15% range.[163,164] These later studies however may have a referral bias or included patients in whom the diagnosis was not confirmed by additional testing. In a study of over 1,000 patients with resistant hypertension (blood pressure > 140/90 despite being on a three drug regimen), 11.3% had primary aldosteronism, suggesting that the prevalence is lower in the general hypertensive population.[165] The etiology of the primary aldosteronism may modulate the severity of hypertension—patients with adrenal adenomas have been reported to have higher pressures (181/112 mm Hg) compared to patients with adrenal hyperplasia (161/105 mm Hg).[166]

The hypertension may explain some of the cardiovascular morbidity and mortality but it appears that aldosteronism *per se* has additional cardiovascular and renal sequelae. The mineralocorticoid receptor is expressed on cardiomyocytes, endothelial cells, vascular smooth muscles and on renal cells other than the collecting tubules and in experimental systems aldosterone induces inflammation, oxidative stress, endothelial dysfunction and fibrosis. In rat models, chronic aldosterone infusions with a high salt diet induce coronary and myocardial inflammation that progresses to myocardial fibrosis. There is also aortic fibrosis and, in the kidney, evidence for glomerular injury and tubulointerstitial fibrosis.[167] Patients with primary aldosteronism have greater left ventricular wall thickness (posterior and septal wall), concentric remodeling and impaired diastolic filling when compared to controls matched for age, sex, body mass index, blood pressure and duration of blood pressure.[168,169] In longitudinal and cross-sectional studies, primary aldosteronism is associated with increased risk of AF, MI, heart failure and stroke. For example in one study of 124 patient with aldosteronism, the rate of AF were 7.3% versus 0.6%, MI 4.0% versus 0.6% and stroke 12.9% versus 3.4% when compared to patients with essential hypertension.[170] The incidence and degree of proteinuria has been reported to greater than in patients with essential hypertension.[171,172]

Surgery is the preferred treatment for primary aldosteronism due to adenoma (30–60% of cases) and the occasional patient with unilateral hyperplasia (~ 3% of cases). Medical therapy with mineralocorticoid receptor antagonists is used for nonsurgical candidates or those with bilateral hyperplasia. Salt restriction can also lower blood pressure since sodium retention is the primary mechanism for hypertension.[173] The surgical cure for hypertension with adenoma is excellent—more than 70% in some series with improvement in the rest.[166] Good prognostic factors for cure after surgery include younger age, lower pretreatment renin activity and preoperative urinary aldosterone as well as lateralization in patients with hyperplasia.

Echocardiographic studies show normalization of left ventricular mass, and left ventricular filling patterns improve after surgery or medical therapy. The recovery with surgery tends to be more rapid (within 1 year) than with medical therapy. A long-term follow-up of patients with primary aldosteronism treated with surgery or medical therapy observed the same incidence of cardiovascular events (MI, stroke, revascularization procedure, sustained arrhythmia) as patients with essential hypertension, suggesting that the excess morbidity and mortality associated with primary aldosteronism reverses with treatment.[174]

Even in patients without primary hyperaldosteronism, mineralocorticoid receptor blockade by spironolactone or eplerenone improves symptoms of heart failure and reduces mortality.[175,176] In addition to their effects on salt and water retention, the drugs also appear to reduce myocardial and vascular fibrosis and prevent vascular remodeling.

In conclusion, primary aldosteronism is associated with increased risk of AF, MI, heart failure and stroke. Hypertension explains some of the morbidity and mortality but elevated aldosterone levels per se, especially when combined with a high salt diet, induces cardiac, vascular and renal injury. Both surgical and medical therapy reduces the excess morbidity and mortality.

The mortality of untreated Cushing's syndrome is very high. In the older literature, infection was the major cause of death (46%) but cardiovascular causes (heart failure, stroke, renal failure) were close second at 40%.[177] This greatly increased risk of cardiovascular disease is due to the presence of multiple risk factors for atherosclerosis including hypertension, dyslipidemia, hyperglycemia and coagulopathy. In one study, 80% of Cushing's patients had hypertension, and the prevalence of diabetes and dyslipidemia was 47% and 37.5% respectively.[178] Active Cushing's patients have been documented to have premature development of carotid atherosclerotic plaques.[179] Even in subclinical Cushing's, the prevalence of these risk factors is substantially increased. In one study of 20 patients with subclinical disease, the prevalence of hypertension was 45%, glucose tolerance 65% and dyslipidemia 65%.[180]

Glucocorticoid excess is associated with increased visceral fat deposition. The mechanisms underlying this effect are not fully elucidated, but it has been reported that glucocorticoids have a tissue specific effect on AMP-activated protein kinase (AMPK)—inhibiting its activity in the heart and visceral adipose cells and stimulating it in the liver and hypothalamus. A fall in AMPK levels in visceral adipose tissue could lead to an increase in lipid storage in association with increased lipolysis and release of free fatty acids.[181] The release of cytokines and free fatty acids from visceral fat in turn can induce insulin resistance, and those patients who have limited beta cell reserve become glucose intolerant. Saturation of the 11β-hydroxysteroid dehydrogenase in the kidney especially in patients with ectopic adrenocorticotropic hormone (ACTH) syndrome in whom the hypercortisolism is severe, leads to activation of the mineralocorticoid receptor by cortisol. This results in salt and water retention and the development of hypertension. Additional factors thought to contribute the development of hypertension in hypercortisolemia include vascular hyper-reactivity to adrenergic agonists, inhibition of peripheral catabolism of catecholamines, inhibition of the vasodilatory system (including NO synthase, prostacyclin and kinin-kallikrein) and increased activity of the renin-angiotensin system.[182,183] An increase in plasma clotting factors, especially Factor VIII and von Willebrand factor complex, as well as impaired fibrinolysis due to elevated PAI-1 levels also occur and may contribute to the increased risk of thromboembolic events in this population.[184-186]

Cushing's patients have normal left ventricular dimension but increased left ventricular hypertrophy and impaired left ventricle diastolic function when compared to controls matched for age, sex, body surface area, blood pressure and left ventricular ejection fraction. With biochemical normalization of cortisol levels, these changes in cardiac structure and function appear to reverse independent of changes in blood pressure.[187,188]

Surgical cure of the Cushing's syndrome significantly reduces cardiovascular risk but some risk factors may persist. An assessment of cardiovascular risk factors in 15 patients whose Cushing's was in remission for 5 years noted higher levels of systolic and diastolic pressure, lipids, blood glucose, waist hip ratio and intima-media thickening when compared to

sex and age matched controls.[189] There is only limited long-term mortality data in patients with Cushing's disease who have persistent disease or are in remission. The follow-up in the published studies is relatively short (median 10–12 years), the criteria for remission of hypercortisolism and persistent disease variable and the number of deaths during follow-up is small. Nevertheless for patients deemed to be in remission, the standard mortality ratio was not different from relevant normal population.[190] The standard mortality ratio however was worse for those patients with persistent disease with hypertension and diabetes as contributing factors.[191,192]

In conclusion, the increased cardiovascular mortality in Cushing's syndrome is due to the presence of multiple risk factors for atherosclerosis including hypertension, dyslipidemia, hyperglycemia and coagulopathy. Surgical cure substantially ameliorates these risk factors and data from patients in remission suggests that the mortality rate is then the same as the normal population.

ADRENAL INSUFFICIENCY

Arterial hypotension is the most common cardiovascular finding in patients with adrenal insufficiency. In adrenal crisis, recumbent hypotension or shock is almost always present. Rarely cardiomyopathy and heart failure have been reported as the presenting manifestation of adrenal insufficiency.[193] The cardiomyopathy reverses with glucocorticoid replacement. The mechanisms resulting in the cardiomyopathy are not well understood. Excess catecholamine effect without the protective effect of glucocorticoids may be important.[194] Glucocorticoid deficiency could also affect membrane calcium transport function and impair excitation contraction coupling.[195]

PARATHYROID DISORDERS

PRIMARY HYPERPARATHYROIDISM

Both mild and severe primary hyperparathyroidism is associated with increased mortality mostly from cardiovascular events.[196-199] In one study the relative risk of acute MI was 2.5 (95% CI 1.5–4.2) in the 10 years prior to parathyroid surgery.[200]

Several mechanisms may operate to increase cardiovascular risk in these patients. There are parathyroid hormone (PTH) receptors on the vascular endothelium and on vascular smooth muscle cells,[201] and hyperparathyroid patients have evidence for endothelial dysfunction compared to controls.[202]

Hypertension is nearly twice more common in patients with primary hyperparathyroidism than in the general population.[203] Acute administration of PTH in normal subjects induces vasodilatation and lowers blood pressure but chronic continuous infusions on the other hand caused persistent hypercalcemia and hypertension.[204]

Left ventricular hypertrophy and impaired left ventricular filling are common in patients with primary hyperparathyroidism, and the degree of hypertrophy is disproportionate to the blood pressure elevation. Basic studies suggest that both calcium and PTH exert a hypertrophic effect of cardiac myocytes.[205] In a case control study, 28 of 43 (65%) patients with primary hyperparathyroidism had left ventricular hypertrophy compared to 15 of 43 (35%) patients with age, sex and blood pressure matched controls (35%). The degree of PTH elevation was the strongest predictor of left ventricular hypertrophy.[206]

An increase in calcification of cardiac valve annuli, valvular cusps, coronary arteries (media and intima) and myocardial fibers occurs with hyperparathyroidism.[207] An echocardiographic study in primary hyperparathyroidism reported that aortic valve calcification is present in 63% of patients and 12% controls, and mitral valve calcification in 49% of patients and 15% of controls. There were also calcific deposits in the myocardium in 69% of patients and 17% of controls.[208] Myocardial calcifications could potentially predispose patients to complete heart block or severe arrhythmias—this has been observed in dialysis patients with secondary hyperparathyroidism.

In earlier studies, surgery reduced but did not eliminate the excess mortality associated with primary hyperparathyroidism.[198] The risk of increased long-term postsurgical mortality was greatest in patients with advanced disease, with the highest calcium levels and largest burden of pathologic parathyroid tissue.[209-211] More recent studies have not reported persistence of excess mortality after surgical treatment.[212,213] This may be explained by the more extensive screening in the modern era leading to shorter duration of disease and milder hypercalcemia. Surgery partly reverses the changes in cardiac structure—a reduction in mean left ventricular mass index in the 6 months following surgery has reported. The regression seems to occur in normotensive and not hypertensive patients. Cardiac calcification persists but does not appear to progress post-surgery.[214] In most studies hypertension does not appear to be reversible with surgical cure.[215-218] A recent study could not demonstrate improvement in blood pressure, glucose, HOMA-IR, lipid levels, inflammatory markers such as high-sensitivity C-reactive protein (hsCRP) and interleukin-1 receptor antagonist (IL-1 Ra) with surgical treatment over a 2 year period.[219]

In conclusion, primary hyperparathyroidism is associated with hypertension, left ventricular hypertrophy, and valvular, myocardial and coronary calcification. Mortality is increased mostly due to cardiovascular events and more recent series suggest that surgical cure reverses the excess mortality.

HYPOPARATHYROIDISM

The hypocalcemia of hypoparathyroidism can occasionally result in cardiac complications. Calcium plays two pivotal roles in the heart. First, it plays a central role in the excitation-contraction process of the myocardium and second, it regulates and carries ionic currents that are responsible for normal electrical rhythm.[220] Hypocalcemia characteristically causes lengthening of the QTc interval, and this can result in early after depolarizations and trigger dysrhythmias including supraventricular tachycardia, ventricular fibrillation and torsades de pointes.[221-224] In neonates hypocalcemia has been reported to induce atrioventricular block.[225,226]

Long standing poorly controlled hypoparathyroidism has been associated with dilated cardiomyopathy and CHF.[227] The patients tend to have a long history of hypocalcemia and insidious development of signs and symptoms of CHF that are improved with vitamin D and calcium replacement.

CARCINOID SYNDROME

Carcinoid tumors secrete a number of vasoactive amino acids and peptides. 5-hydroxytryptamine (5-HT) is the most prominent secretory product. Other molecules include 5-hydroxytryptophan, bradykinin, histamine, substance P, prostaglandins and calcitonin gene related peptides.[228,229] The first pass hepatic inactivation of the secretory products means that the symptoms tend only to occur when patients have metastatic disease, mainly liver metastases. Bronchial and ovarian carcinoids may present with a carcinoid syndrome without recognized metastases presumably by release of peptides in the systemic circulation.[230] A small proportion of patients with midgut carcinoid tumors also have symptoms without obvious liver metastases presumably via metastases in the retroperitoneal space.

The clinical presentation of the syndrome includes abdominal pain, diarrhea and flushes. Some patients get bronchospasm. The flushing is due to vasodilatation and hypotension can occur. Carcinoid crisis is a rare complication following surgery, chemotherapy or tumor devascularization and is due to massive release of the vasoactive molecules into the circulation. Patients experience fever, severe flush, low blood pressure, tachycardia and bronchoconstriction.

Carcinoid heart disease occurs in about 70% of patients.[231] The typical findings are white plaques or diffuse pearl gray endocardial thickening on the right side of the heart affecting the tricuspid and pulmonary valves. The tricuspid valve leaflets and the pulmonary cusps are thickened and retracted by the fibrotic process. Papillary muscles and chordae tendineae of the tricuspid valves are shortened impairing the mobility of the valves. Histologically the lesions are composed of myofibroblasts embedded in an elastin deficient stroma which is rich in glycosaminoglycans.[232] It is likely that 5-HT is responsible for these pathological changes. The weight loss drugs fenfluramine or phentermine are serotonin reuptake inhibitors and have been associated with valvular changes similar to the kind seen in the carcinoid syndrome.[233] Patients develop symptoms and signs of tricuspid and pulmonary valve regurgitation. Pulmonary outflow obstruction due to pulmonary annular constriction can also occur. Left sided carcinoid syndrome can occur if the liver tumor burden is very high or if there is a patent foramen ovale.[234,235]

Treatment is directed at removing tumor by surgery, chemoembolization, radiofrequency ablation. Octreotide can be used to control symptoms. Valvular disease is a major cause of morbidity and mortality and valve replacement even in the presence of significant tumor burden improves outcomes. Valve replacement (usually tricuspid and/or pulmonary) should therefore be considered in those patients who have progressive decline with ventricular function and whose metastatic disease is well controlled.[234,236,237] When liver metastases are present, the 5 year survival rate is about 18–38%.[238] About 40% of deaths can be attributed to cardiac causes.[239]

SUMMARY

Endocrine disorders as noted in this review frequently have cardiovascular manifestations. Approximately 8.3% of the population in the United States has diabetes and about 4% have thyroid disease and as a result cardiac complications due to these diseases are frequently encountered in clinical practice. Treatment of the underlying endocrine disorder can frequently reverse or arrest the progression of cardiovascular complications. This has been observed in acromegaly, Cushing's disease, primary hyperparathyroidism, thyroid diseases, pheochromocytoma and primary aldosteronism. In Type 2 diabetes, aggressive multifactorial interventions targeting hyperglycemia, blood pressure and dyslipidemia substantially reduces the risk for cardiovascular events. Also not infrequently, it is the cardiovascular complication that prompts the patient to seek medical attention and in such cases recognizing the underlying endocrine disorder is important in the management of the cardiovascular complication. Thus patients with pheochromocytoma and primary aldosteronism present with hypertension. AF may be the presenting complaint in hyperthyroidism and cardioversion should be delayed until a euthyroid state is achieved. The cardiomyopathies associated with thyrotoxicosis, adrenal insufficiency, hypoparathyroidism and pheochromocytoma reverse with treatment of these conditions.

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Chapter 100

Cardiovascular Trauma as Seen by the Cardiologist

Arthur Hill, Melvin D Cheitlin

Chapter Outline

- Classification and Physics of Traumatic Injury to the Cardiovascular System
  - — Penetrating Injury
  - — Non-penetrating Injury (Blunt Injury)
- Classifying the Pathology of Cardiac Trauma
- Management of the Acutely Injured Patient with Thoracoabdominal Injury
  - — Cardiovascular Injuries
  - — Penetrating Cardiac Injury and Cardiac Tamponade
  - — Pericardial Injury
  - — Cardiac Laceration
  - — Myocardial Contusion—Blunt Cardiac Injury
- Intracardiac Injuries from Both Penetrating Wounds and Blunt Cardiac Injury
  - — Septal Defects
  - — Valvular Injuries
  - — Non-ventricular Septal Defect and Non-atrial Septal Defect Intracardiac Fistulas
  - — Coronary Artery Laceration and Thrombosis
  - — Aortic and Arterial Trauma
  - — Retained Foreign Bodies
  - — Iatrogenic Cardiovascular Injuries

HISTORY

Descriptions of cardiac trauma date back to ancient times and until the beginning of the 20th century were believed to be almost universally fatal. In 1888, surgical standards of care existed such that surgical repair of cardiac injuries was considered infeasible. As indicated by the famous German-Austrian physician Theodor Billroth who wrote, "The surgeon who attempts heart surgery loses the respect of his colleagues".[1] The first report of successfully suturing a stab wound of the right ventricle of a 22-year-old man was in 1896 by Ludwig Rehn from Frankfort, Germany.[2] In 1897, Doctor DH. Williams in Chicago reported on a 24-year-old man with a thoracic stab wound which he had treated in 1893 by suture repair of the pericardium but not the right ventricular laceration since it was not bleeding.[3] Further advances were made by Alexis Carrel who won the Nobel Prize in Medicine and Physiology in 1912 for his work in vascular repair and vascular anastomosis (nobelprize.org; Carrel A. The operative technique of vascular anastomoses and the transplantation of viscera. Medicine de Lyon. 1902;98:859).

The development of blood typing, endotracheal intubation, mechanical ventilation, antibiotics, anticoagulation and cardio-pulmonary bypass surgery, as well as the rapid resuscitation of the injured patient have made possible the significant advances in the treatment of patients with cardiovascular injury. If the acute trauma patient does not succumb to the acute physiologic sequelae of their injuries in the prehospital or emergency room (ER) setting, then the possibility exists for successful surgical treatment of almost any cardiac or vascular injury. As has been the case in the past, advances in the diagnosis and treatment of patients with vascular and cardiac injuries were first made by military surgeons during wartime. Until World War II, a penetrating thoracic or abdominal injury was most frequently fatal. In the Korean War and war in Vietnam, application of vascular repair techniques was done for repair of extremity artery lacerations markedly decreased the incidence of amputations. Also in those conflicts, rapid evacuation by helicopter of the seriously injured to a treatment facility where definitive surgery could be performed dramatically reduced the mortality of battle casualties.

Lessons learned in war have been applied to civilian life. Penetrating urban trauma is epidemic in certain areas of the United States, where gunshot wound and stab wound incidence and severity can approximate that seen in war. Emergency departments (EDs) in certain urban hospitals have adopted methodologies developed by Mobile Army Surgical Hospitals (MASH units) during the Korean War. The other source of mayhem and mortality in civilian life is motor vehicle accidents, frequently precipitated by drivers under the influence of alcohol and lately by other attention-diverting activities such as talking and texting on cell phones while driving. The province of rapid resuscitation and the acute evaluation of the injured patient belongs to emergency medical technicians (EMTs), ED physicians and trauma surgeons. Guidelines for the management of the acutely injured patient are published, taught and certified by the American College of Surgeons (ACS) (American College of Surgery. Advanced Trauma Life Support for Doctors. Student

Course Manual, 8th edition. Chicago:American College of Surgery 2008). Involvement of internists and cardiologists in cardiovascular trauma occurs when the resuscitated patient, usually now stable, and during the secondary examination, is recognized to have an abnormal physical examination findings (such as a murmur or arrhythmia), abnormal laboratory findings (such as on ECG or chest X-ray) or develops hemodynamic instability not associated with evident hemorrhage.

CLASSIFICATION AND PHYSICS OF TRAUMATIC INJURY TO THE CARDIOVASCULAR SYSTEM

Conventionally, cardiovascular trauma is divided into penetrating and non-penetrating injuries;[4] these categories encompass essentially all types of cardiovascular injuries described. A variety of forces are involved in producing cardiovascular trauma.

Penetrating injuries:

- Low-velocity injuries (e.g. stab wounds, shrapnel, flying objects and spent bullets)
- High-velocity injuries (e.g. gunshot wounds)

Non-penetrating injuries:

- Deceleration and acceleration injuries (e.g. vehicular accidents and falls from a height)
- Chest compression and crush injuries (e.g. steering wheel impacts and heavy objects falling on bodies)
- Blast and concussion injuries [e.g. explosions, improvised explosive device (IEDs)]
- Lower body compression (e.g. sand-pit collapse while digging a hole)
- Electrical injury (e.g. shocks from a power line and lightning strikes)
- Environmental injury (e.g. excessive cold or heat exposure).

PENETRATING INJURY

The body's tissues are injured by direct trauma, tearing and crushing from the penetrating object and by transfer of energy to the tissues during deceleration of the penetrating object, or by the force of compression by non-penetrating trauma. With missile penetration, damage is related to the velocity, mass and shape of the object, its tumbling characteristics (such as dynamic yaw tendency) and its tendency to fragmentation.[5] A low-velocity missile, such as a knife or spent bullet, usually causes little damage remote from its path of penetration. Shrapnel and low-velocity bullets decelerate as they pass through the body and release little energy and may come to rest within body cavities or as foreign bodies in the heart or vessels. Since this type of penetrating trauma has low velocity, these objects can be deflected off bones or even tissue planes and thereby can undergo radical direction change as penetration occurs through tissue. For this reason it may not be possible by examining the point of entry to predict the missile's path and, therefore, the structures injured or where the missile finally came to rest. If a penetrating object enters and remains within one of the cardiac chambers, large arteries, or veins, it can embolize to some part of the body distant from its point of entry.

A penetrating missile releases energy along its path through the body according to the following equation:[6]

$$KE = \frac{m\,(V_1\text{-}V_2)}{2\,g}$$

where KE = kinetic energy
m = mass of the missile
V_1 = entrance velocity
V_2 = exit velocity
g = gravity constant

When a missile strikes the body, two types of pressure waves are produced. The first is a sonic pressure wave simply the sound of the projectile striking the surface of the body. It travels at the speed of sound, generates pressures of up to 60 atmospheres, has a short duration of action (a few microseconds) and, therefore, usually produces little damage. The second pressure wave occurs as the missile penetrates tissue and the direction of the secondary pressure wave is perpendicularly radial to the direction of the missile. The secondary pressure wave follows the penetration of the missile and produces a temporary cavity, pushing tissue aside or destroying tissue along the missile tract, but with larger diameter than the missile diameter and obeying Newton's laws of motion. The cavity pulsates a few times, each pulsation lasting 4–5 milliseconds. The tissue then collapses back to form the permanent cavity or missile track. Tissue damage due to the second radially directed pressure wave is far greater than the sonic pressure wave. Tissue damage is related to the energy carried by the missile, missile mass, missile size and tissue characteristics (inelastic tissues, such as liver and brain, are far more susceptible to damage than the more flexible body tissues, such as lung and muscle).

There has been a great deal of controversy concerning the relative contribution of the variables which cause tissue damage; variables include: crushing and tearing due to the high energy transfer (velocity and mass), missile fragmentation, tumbling/yaw characteristics of the missile, permanent cavity versus temporary cavity surrounding the missile track and tissue characteristics. Current evidence suggests that tissue damage is mostly related to direct crushing and tearing caused by the missile and the elasticity of the tissue through which it passes. Lesser damage is related to the temporary cavity. Therefore, in soft tissues, such as the muscle of the extremities, even with high velocity bullets, the damage is mostly along the missile path.[5] Bullets that deform, fragment or expand on striking the body, such as lead bullets or the Dum-Dum bullets (where the hard metal jacket of the bullet is ground off the tip), cause extensive tissue damage and are prohibited in military conflicts by the Hague Peace Conference of 1899.[6]

NON-PENETRATING INJURY (BLUNT INJURY)

With non-penetrating injury, the trauma is produced by crushing or by the heart's violent collisions with the anterior chest wall or spine. Deceleration injury results from the sudden and marked deceleration of the body at the time of impact, whereas the heart continues at the pre-impact velocity, striking the rib cage and sternum or the spine, resulting in myocardial contusion or laceration. The vascular structures, including the aorta, great vessels and veins, are subject to lacerating force that can partially or completely severe the vessel. Differential movement of the aorta occurs when part of the aorta is relatively restricted in its

movement by the intercostal arteries compared to the more mobile aortic arch,[6] or the ascending aorta as it arises from the heart. The most common site of aortic injury from deceleration trauma is at the aortic isthmus related to localized immobility of the aorta at that site compared to the surrounding aorta. Another site of injury is the junction of inferior vena cava as it enters the right atrium.

The exact mechanism of the laceration of the aorta in vehicular accidents with deceleration injury or massive compression by the steering wheel is noncontroversial. The most common site of aortic rupture, just distal to the ligamentum arteriosus, has been shown to be due to differential aortic motion with the heart continuing to move placing stress on the relatively immobile descending aorta. Experiments with primates and human cadavers subject to sudden sternal compression simulating steering wheel injury using high-speed aortography show marked displacement of the heart out of the middle mediastinum laterally or superiorly placing marked stress on the most frequent places of aortic rupture.[7]

Another type of non-penetrating injury consists of sudden compression injuries to the chest, abdomen and/or lower extremities. An example of this type of injury occurs when an individual who is digging a hole, suddenly gets buried when the sides of the hole cave in, burying the person up to or including the chest. This can cause sudden marked arterial and venous compression; simultaneously, a massive return of venous blood to the heart, with abrupt preload increase, combined with markedly increased systemic vascular resistance (with abrupt afterload increase) and impeded left ventricular ejection. Together these combined forces can result in atrial, ventricular or valvular rupture.

Another factor important in myocardial contusion and rupture is the exact location at which acute blunt force occurs with respect to the cardiac cycle. Animal experiments show that myocardial contusion and laceration are far more likely to occur if the injury is delivered during diastole at which ventricular mass is maximal and wall elasticity and firmness are minimal.[8] During systole ventricular volume and mass is the minimized and the heart muscle is resilient and firm thereby, theoretically, capable of moving away from the force, limiting the distortion of the wall for any given force.

CLASSIFYING THE PATHOLOGY OF CARDIAC TRAUMA

Although any cardiac structure has the potential to undergo injury in penetrating and non-penetrating trauma, there is a pattern to injury related to the mechanism of injury, anatomic relationships and tissue characteristics. It makes sense that cardiac tamponade is more frequent with penetrating than non-penetrating injury. As shown in a study by Parmley, Manion and Mattingly from the Armed Forces Institute of Pathology (AFIP) with non-penetrating cardiovascular trauma in 1958 and more recently from other civilian sources,[9-12] any cardiac structure, including pericardium, all cardiac chambers, atrial and ventricular septae, papillary muscles, valves and arteries and veins, can be contused or lacerated by non-penetrating injuries. In any series of cardiovascular trauma reported from an autopsy population, the types of trauma seen are weighted to the most serious injuries. For this reason, in these autopsy series the most common injuries are laceration of a cardiac chamber and myocardial contusion, with smaller numbers of other injuries such as valvular and ventricular septal trauma. In clinical practice, most patients with injuries severe enough to rupture a cardiac chamber have multiple organ damage and do not survive. To be counted in a clinically selected series of cardiovascular trauma patients, the individual must live long enough to reach the hospital and for this reason, clinical series have greater numbers of patients with suspected potentially survivable myocardial contusion, valvular injuries, coronary artery and great vessel injuries.

MANAGEMENT OF THE ACUTELY INJURED PATIENT WITH THORACOABDOMINAL INJURY

The first responders to trauma victims are the EMTs. These trained professionals follow strict protocols and they are responsible for initiating resuscitation and basic first aid to keep the patient alive until during rapid transfer to a hospital for definitive care. EMTs are trained in various methods of airway control (including endotracheal intubation) and they can start IVs in the field (and initiate volume administration). Further assessment and treatment is done in the ER. With trauma sufficient to cause cardiac injury, the patient often has multiple other injuries. A rapid assessment is made in order of priority: airway control, ventilation/respiration, bleeding, signs of circulatory adequacy (pulse rate, blood pressure and indicators of tissue perfusion). Rapidly fatal injury needs to be ruled out immediately. Rapidly fatal injuries include asphyxiation, cardiac tamponade, tension pneumothorax and exsanguinating blood loss. Airway assessment and treatment is always done first. Signs of airway problems include stridor, mental status alteration, cyanosis and asymmetric or absent breath sounds. Once airway is controlled, adequacy of ventilation/respiration is done. Once proper control of airway and ventilation has been established, circulation is assessed and treated. Signs of circulatory failure include tachycardia, hypotension, jugular venous distention (cardiac tamponade and/or tension pneumothorax) and indicators of poor tissue perfusion (diaphoresis, abnormal mental status, cyanosis, poor capillary refill, acidosis, anuria, etc.). External hemorrhage can be treated immediately while airway and ventilation management is ongoing (external hemorrhage is initially controlled by application of pressure at the bleeding site). A team approach is carried out in Level I trauma centers where multitasking can be effectively carried out in a systematic and professional way. Trained trauma personnel are accustomed to the ABCDE (A = Airway; B = Breathing; C = Circulation; D = Disability; E = Exposure) algorithm of trauma management which is advocated and taught in advanced trauma life support (ATLS). Violation of this priority scheme is considered to be a deviation from standard of care.

Management of all critically injured patients, especially with circulatory compromise, requires intravascular access for rapid volume resuscitation. Initial management includes insertion of large-bore intravenous access with at least two 16-gauge catheters followed by crystalloid fluid administration (1-2 liters in adults and 20 ml/kg for children). Blood transfusion should be started in the ER for critically injured trauma patients. In the

absence of a palpable pulse or blood pressure, cardiopulmonary resuscitation should be initiated and consideration should be made for emergency operative therapy. All patients with thoracic trauma require involvement of a trauma surgeon early in the course of treatment.

A rapid assessment of central venous pressure (CVP) should be made, either by examining the neck veins or by measuring the venous pressure by catheter. If the CVP is elevated and the patient's injuries are capable of producing cardiac tamponade, a presumptive diagnosis should be made and pericardiocentesis or open pericardial drainage immediately performed. If time allows, cardiac tamponade can be rapidly assessed using ultrasound in the ER (FAST examination: Focused Assessment by Sonography in Trauma). If the patient has cardiac tamponade the patient will require definitive operative therapy and should be taken to the operating room immediately. If the patient is too unstable to get to the operating room in time, a thoracotomy should be performed in the ER to relieve cardiac tamponade, followed by definitive repair in the operating room.

Arrhythmias are not uncommon in this setting. Life-threatening arrhythmias, such as ventricular tachycardia/fibrillation, require immediate cardioversion/defibrillation. Atrial fibrillation or flutter can be treated with 200–400 watt-second shocks or rate-controlled with calcium-channel blockers or beta-blockers. In the presence of asystole or high degrees of atrioventricular block, atropine followed by isoproterenol can be used to increase the ventricular rate and, if necessary, transvenous pacing is preferred over external pacing in situations where pacing is necessary.

After the initial resuscitation and the patients become stable, a rapid history can be obtained. Details of the traumatic incident from patients or witnesses should include a description of mechanism of injury and an assessment of the magnitude of forces involve in the injury. Additional information should include place and type of accident; the type of weapon used. Caliber, type of gun and number of bullets fired can provide information. A description of the weapon used in a stab wound (knife vs other instrument; length, width, serrations, etc.) can be useful in determining magnitude of injury. In non-penetrating blunt injury, important factors include: passenger versus driver, motorcycle versus automobile, high-speed versus low-speed, bicycle versus pedestrian, the position of the patient in the vehicle, etc. Whether seat belts or shoulder restraints were used and the type of accident, e.g. whether a head-on or a rear-end collision. A past medical history, especially of cardiovascular disease is very important. A list of all the medications the patient was taking and whether there is a history of alcohol or illicit drugs should be obtained, since these may explain the presence of arrhythmias, diminished consciousness or ECG changes. A history of a past myocardial infarction (MI), angina, or the presence of a known heart murmur might explain abnormalities found and therefore avoid unnecessary diagnostic studies. A history of use of anti-platelet agents or anticoagulation agents is of critical importance in trauma patients.

After a rapid initial examination to rule out rapidly fatal injuries, a thorough secondary examination should be done. A physical examination assessing the presence and site of contusions, lacerations, entrance and exit wounds of a missile injury are important. The facial color, presence of cyanosis or pallor of face and extremities can give clues to the adequacy of gas exchange and recognition of venous or arterial injury. Examination of the head and neck for cranial or cervical injury is especially important before moving the patient. Palpation over a cranial contusion for depressed skull fractures should be done as well as inspection of nose and ear canals for cerebrospinal fluid (CSF) or blood. The height of the CVP by inspection may give clues to the severity of blood loss or the presence of cardiac tamponade. The position of the point of maximal impulse (PMI), palpable precordial lifts or thrills, a pericardial friction rub, the quality of the heart tones, the presence of murmurs, gallops or rales, the presence of pulsus alternans or pulsus paradoxus should all be noted. Abdominal and extremity injury and the presence or absence of peripheral pulses recorded. A rapid neurologic examination for the state of consciousness, cranial nerve abnormalities, pupillary and extra-ocular eye movements, strength and mobility of all extremities and the presence and quality of deep tendon reflexes should be rapidly made.

Laboratory examinations should include hemoglobin and hematocrit, serum electrolytes, a urinalysis and arterial blood gases. A chest X-ray looking for fractured ribs, sternum or clavicles pleural effusion, pneumomediastinum or pneumothorax, pulmonary edema or lung contusion, position and size of the cardiac silhouette, the width of the superior mediastinum, the sharpness of the aortic knob, evidence of abdominal contents above the diaphragm and air or fluid in the peritoneal cavity. If head injury is present or suspected, computed tomography (CT) of the head and neck should be done. If the mediastinum is wide, an emergency CT angiography of thorax should be done to rule out aortic injury.

CARDIOVASCULAR INJURIES

Cardiac injury is unusual, occurring in about 3% of patients with thoracoabdominal wounds.[13] The mortality of patients with penetrating wounds depends on the mechanism of injury, the characteristics of the bullet, knife or penetrating object, the type of cardiac injury, as well as the other organs injured. Mortality in patients with penetrating cardiac wounds varies from 65% to 80% with gunshot wounds being the most lethal.[14,15] In patients entering the ED after chest injury who were in extremis or in cardiopulmonary arrest, in those too unstable to transport to the operating room, ED thoracotomy can be lifesaving. Factors that influence the outcome were the mechanism of injury (gunshot vs stab wound), location of the major injury and signs of life, including the presence of one or more of the following: cardiac electrical activity, respiratory effort and pupillary response. In one study[15] survival rates from ER thoracotomy for penetrating injuries were 8.8% and 1.4% for non-penetrating injuries. For stab wounds, the survival rate was 16.8% and for gunshot wounds 4.3%. For thoracic injuries the survival rate was 10.7%, for abdominal injuries 4.5% and for multiple injuries 0.7% (Table 1).

PENETRATING CARDIAC INJURY AND CARDIAC TAMPONADE

Cardiac tamponade is mostly seen with penetrating injuries of the chest and upper abdomen, although it can occur with non-penetrating trauma with cardiac laceration, coronary artery or

TABLE 1

Penetrating thoracic trauma

Distribution of organ injury	
• Chest wall	100%
• Lung	65–90%
• Heart	49%
• Diaphragm	30%
• Intra-abdominal injury	
— Liver	20%
— Stomach	8%
— Small intestine	7%
— Colon	6%
— Kidney	5%

vein laceration, and especially with rupture of the ascending aorta. The development of cardiac tamponade depends on blood accumulating within a relatively intact pericardial sac so that it is less often seen with extensive laceration of the pericardium than with a stab wound with a limited tear. With a large tear of the pericardium, the blood accumulates in the left pleural cavity and the patient presents with a left-sided hemothorax and exsanguination. Laceration of the right atrium or right ventricle results in relatively slow bleeding into the pericardium from the low-pressure chamber, with cardiac tamponade occurring more gradually, allowing maintenance of the circulation and time for the patient to reach the hospital for definitive therapy. Laceration of the left ventricle is more likely to result in rapid bleeding from the high-pressure chamber, rapid increase in intrapericardial pressure and severe, usually fatal cardiac tamponade.

The first consideration in any trauma patient with an elevated CVP by examination should be cardiac tamponade. The differential diagnosis includes tension pneumothorax, tension hemothorax and right heart failure as a result of extensive right ventricular contusion or prior heart disease, with or without tricuspid regurgitation and rupture of the tricuspid valve. In any patient with penetrating injury that could cause cardiac tamponade, if the patient is pulseless, in shock or pulseless with a low blood pressure, an immediate thoracotomy should be performed in the ED in order to have any hope of saving the patient.[15-18]

Under these circumstances the delay for transportation to the operating room dooms the patient. If the patient is hemodynamically stable with an elevated CVP after a penetrating injury that could have caused cardiac tamponade, a FAST examination can be done or pericardiocentesis with a large bore needle can be performed. If the trauma was caused by a low-velocity injury with a narrow-bladed weapon where slow bleeding and gradual tamponade occurred, the wound has a reasonable chance of clotting and pericardiocentesis can be diagnostic and provide temporary relief of tamponade. With rapid bleeding, intrapericardial blood can clot and no blood can be extracted from the pericardium. Even if the initial pericardiocentesis is successful, tamponade can recur. In a series of 459 cases of penetrating wounds of the heart, unsuccessful pericardiocentesis occurred 25% of the time.[19] For this reason, initially stable patients are usually taken to the operating room for thoracotomy for exploration of their pericardial and cardiac injuries and suture of the lacerations and ligation or repair of bleeding arteries or veins.[20] FAST examination is considered state of the art for pericardial tamponade diagnosis and has largely replaced pericardiocentesis in most trauma centers. The accuracy of FAST diagnosis of cardiac tamponade in a hypotensive trauma patient approaches 100% and can gain further refinement if diastolic RA and/or RV collapse is present [Menaker J, Cushman J, Vermillion JM, et al. Ultrasound-diagnosed cardiac tamponade after blunt abdominal trauma-treated with emergent thoracotomy. Emergency Medicine. 2007;32:99-103].

In cardiac tamponade the filling of the right ventricle is maintained by the higher pressure developed in the veins and right atrium compared to the right ventricle in diastole. The high venous pressure is the result of vasoconstriction due to increased sympathetic nervous system activity and later by expansion of the intravascular volume. Under these circumstances, if the patient is anesthetized and sympathetic tone withdrawn, cardiovascular collapse could occur.[21] For this reason, the patient's chest should be shaved, prepped and draped, the surgical team set for immediate thoracotomy before the patient is anesthetized. Unlike the patient where cardiac tamponade occurs gradually where an elevated CVP is the first sign, in the acutely injured patient where intravascular volume may be low because of hemorrhage, cardiac tamponade may be present with a normal or low venous pressure and be manifest only by a marked decrease in cardiac output and shock. Therefore, in thoracoabdominal injury where cardiac tamponade is possible, rapid blood replacement should be given and if the blood pressure does not return toward normal after estimated blood loss is replaced, thoracotomy should be considered since cardiac tamponade is often the cause. In most instances where adequate blood replacement is given, the CVP will become elevated even with the blood pressure remaining low in the presence of cardiac tamponade.[22,23]

Another possible explanation for an increased CVP after a traumatic episode is massive over replacement of fluid and/or blood during resuscitation. In a patient with pre-existing heart disease, right ventricular infarction or myocardial contusion, the CVP may become elevated without pericardial effusion. A clue to the problem of overhydration in the patient with a normal heart by echocardiography would be the development of rales, a third heart sound, evidence of pulmonary congestion on chest X-ray, or a murmur of tricuspid or mitral regurgitation. The cardiac output and stroke volume would be higher than normal if measured, and the pulse bounding. With heart failure, the pulse is likely to be thready and small, with other signs of heart failure such as rales, pulmonary congestion of chest X-ray, pulsus alternans and an S_3 gallop. Obviously these problems can be sorted out by an echocardiogram that in cardiac tamponade demonstrates pericardial fluid and signs of tamponade such as right atrial and/or ventricular diastolic collapse and good left ventricular contraction.

PERICARDIAL INJURY

The pericardium can be lacerated or ruptured without the development of cardiac tamponade. With non-penetrating injury, such as chest compression or rapid deceleration, the pericardium can rupture and the heart may herniate into the left pleural cavity. With severe trauma, there is usually massive cardiac injury or laceration with fatal consequences.[24] With penetrating chest

injury it is not unusual at thoracotomy to find pericardial laceration without cardiac herniation. From 1937 to 1982 there were 142 cases of traumatic pericardial rupture found in the literature usually discovered during surgical exploration for other indications with 99 survivors.[25] Pericardial rupture is most frequent in the left pleuropericardium and next most common in diaphragmatic portion of the pericardium.[26] Pericardial rupture with some degree of cardiac herniation can be suspected on chest X-ray by a shift of the heart into the left chest with little cardiac mass to the right of the spine.[27] With gross cardiac herniation the PMI is displaced to the left and on chest X-ray the heart is markedly moved to the left. If cardiac herniation is found, thoracotomy and repair of the pericardial laceration is indicated.[28] In the absence of cardiac tamponade or displacement, a pericardial laceration usually goes unsuspected.

Occasionally, a small pericardial tear allows the left atrial appendage or even a greater part of the heart to herniate and become strangulated.[29] This can be suspected on chest X-ray by an abnormal bulge just under the main pulmonary artery segment on the left cardiac border. If found repair is imperative since a major part of the heart can herniate through the tight tear and become incarcerated.[30]

After injury, the clinical occurrence of acute pericarditis is not uncommon. The patient develops a pleuritic-type chest pain with or without a pericardial friction rub. An echocardiogram may show pericardial fluid without tamponade. Pain relief with aspirin or other anti-inflammatory drugs, such as indomethacin and nonsteroidal anti-inflammatory agents, are usually effective. The late development from a week to a few months after thoracic trauma of post-traumatic pericarditis is probably related to an autoimmune response to traumatic pericardial and myocardial cell damage with the development of antigen-antibody complement fixation with resultant pericardial inflammation.[31] Large pericardial effusions and even cardiac tamponade can occur and the symptoms can be recurrent.

After cardiac injury, blood in the pericardium may be quickly resorbed without residual damage. Occasionally with bleeding and extensive tissue necrosis, a thickened, constrictive pericarditis can result with the clinical picture presenting months or years later. If the patient is found to have constrictive pericarditis, with its hemodynamic consequences, pericardiectomy is indicated.

CARDIAC LACERATION

When laceration of the walls of the cardiac chambers occurs, it is usually the result of penetrating injury, although non-penetrating trauma, such as high-velocity deceleration trauma, chest compression, or even blast injury, can cause cardiac laceration or rupture.[32,33] Due to their location, the chambers most vulnerable to laceration with penetrating injury are the right ventricle and intrapericardial portion of the great vessels in 40–60% of cases, left ventricle and right atrium. The left atrium, being posterior, is least often lacerated.[20,22,23,34]

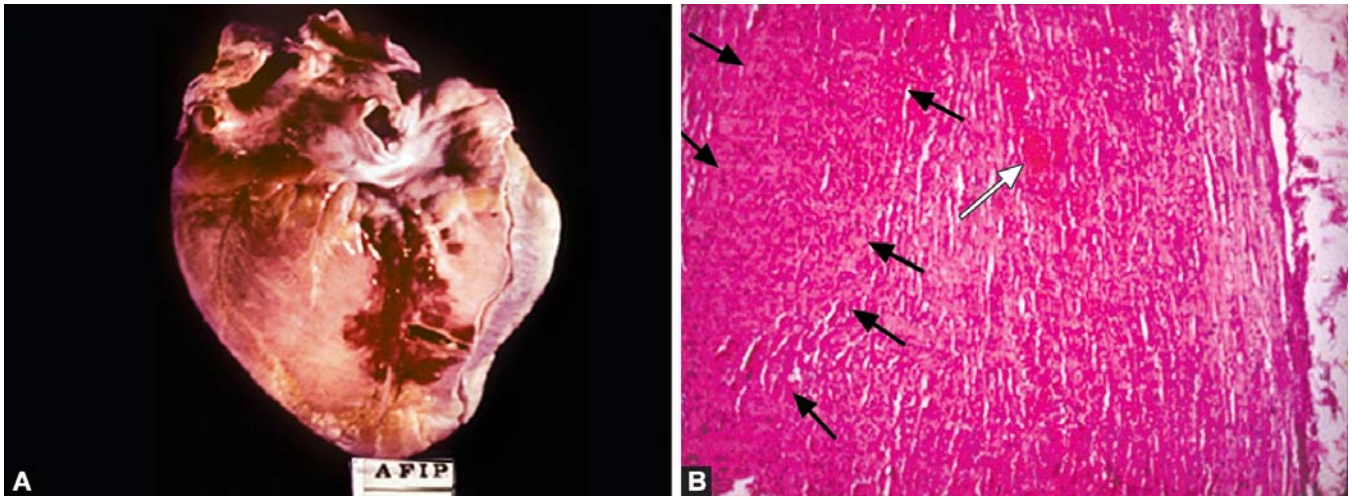
With penetrating injury to the thin-walled, low-pressure right atrium and right ventricle with subsequent cardiac tamponade, there is often slowing and cessation of bleeding resulting in longer survival and greater opportunity for definitive treatment. If the perforation is with a narrow blade and the laceration is small, pericardiocentesis may be sufficient. With needle aspiration and reduction in the intrapericardial pressure, there is danger of the bleeding restarting and recurrence of tamponade. Most often, thoracotomy is necessary to suture the laceration. Suture of a laceration in the ventricle leaves a scar which if small enough will not interfere with ventricular function. If the injury is extensive or if there was coronary artery injury, a true aneurysm can form at the site of the laceration repair. If there is continued bleeding from the ventricle contained by an epicardial thrombus, a false aneurysm results. Both true and false aneurysms are usually discovered because of the distortion they cause of the cardiac silhouette on chest X-ray. When false aneurysms are found, repair is necessary since late rupture can occur.

MYOCARDIAL CONTUSION—BLUNT CARDIAC INJURY

Myocardial contusion is most often seen in civilian life as a result of vehicular accidents and represents the greatest cause of cardiac trauma at present. Since almost any type of cardiac injury including chamber rupture, coronary artery laceration or thrombosis, atrial and ventricular septal rupture and valvular disruption can occur, a better, more inclusive term describing the results of non-penetrating injury is blunt cardiac trauma (BCI).[35] The term myocardial contusion implies myocardial necrosis with or without intramural bleeding. In addition to motor vehicle accidents, BCI can result from falls, chest compression from heavy objects and collapse on the person of a hole being dug. A condition known as commotio cordis results from a sudden blow to the precordium as with a punch, a baseball or steering wheel that precipitates a fatal ventricular arrhythmia. At autopsy, there are no signs of visible or microscopic myocardial injury and the arrhythmia results from energy imparted to the heart at a vulnerable time just before the peak of the T wave (peak of repolarization) causing ventricular tachycardia/fibrillation.[36] Madias and colleagues have shown that at the moment of impact, the left ventricular pressure rapidly rises transiently, activating ion channels via mechano-electric coupling. This generates an inward current and can likely result in augmentation of repolarization and non-uniform myocardial activation, precipitating premature ventricular depolarizations that trigger the malignant ventricular arrhythmias. When commotio cordis occurs, unless there are people who react rapidly with cardiopulmonary resuscitation and external defibrillation, mortality is extremely high.[37,38]

Incidence of Myocardial Contusion

Although the incidence of myocardial contusion following BCI is stated to be 5–50% in the literature,[39,40] the true incidence is not known since many patients after trauma have other injuries requiring immediate attention and if the cardiac trauma remains asymptomatic, it is never discovered. In those patients dying after thoracoabdominal trauma, the incidence of myocardial contusion at autopsy is about 15%. In other series the incidence reported varies from 9% to 76%.[41-43] After a vehicular accident, myocardial contusion is undoubtedly more common than we suspect, since there is no “gold standard” for the diagnosis in the surviving patient.



FIGURES 1A AND B: (A) Heart dorsal aspect of a woman who died in an automobile accident. Note the large hemorrhagic area with section removed for microscopic examination. (B) Low-powered microscopic view of sectioned myocardium. Black arrows outline area of myocardial necrosis with round cell infiltration. White arrow indicates area of intramural hemorrhage. (Abbreviation: AFIP: Armed Forces Institute of Pathology)

Clinical Picture of Myocardial Contusion

If the heart is examined pathologically after BCI, myocardial necrosis, edema and intramural hemorrhage can be seen. The degree of injury depends on the mechanism of trauma and the magnitude of the force of BCI.[23,30] Necrosis of myocardium releases potassium, myocardial enzymes and other intracellular contents into the interstitial space and initiates the inflammatory response, all similar to that which occurs after an acute MI caused by coronary artery disease (Figs 1A and B). The complications seen are also comparable: arrhythmias, myocardial rupture, ventricular dysfunction with congestive heart failure and both true and false aneurysms.

A common cause of myocardial contusion is the severe compressive or crushing injury caused by the steering wheel or by impact of the heart on the sternum, anterior chest wall or vertebral column in acceleration and deceleration accidents.[44,45] With crushing injuries there is frequently accompanying fractures of the ribs, sternum and clavicles as well as multisystem trauma.[46] Some, but not all, studies have reported that patients with fractured sternum or first or second ribs are most likely to have BCI.[47] The use of seat belts and chest restraints has markedly reduced the incidence of severe BCI.[45]

As indicated above, other types of trauma, such as being crushed by a heavy object or against a wall, blast injury suffered in an explosion all can cause BCI. Commonly there is evidence of chest injury by contusions, abrasions or lacerations, but it is not uncommon for cardiac contusion to be present without external signs of injury to the chest.[48] This is especially true in acceleration and deceleration trauma where speed as low as 20 mph can cause BCI without external chest wall trauma.[49]

Diagnosis of Myocardial Contusion

Chest discomfort is frequently present, but difficult to differentiate from pain related to the chest wall trauma, so its presence or absence is not helpful to the diagnosis of myocardial contusion. Frequently the diagnosis is suspected from the presence of atrial or ventricular arrhythmias, the presence of a pericardial friction rub, or signs of congestive heart failure including pulmonary rales, a small thready pulse consistent with a low stroke volume, pulsus alternans, an S_3 gallop or especially with right ventricular contusion, an elevated CVP. BCI is also suspected with the development of a new systolic or diastolic murmur. The problem is in differentiating these findings that may be due to BCI from pre-existing cardiac disease such as coronary artery disease, valvular disease or other diseases causing heart failure. Other confounders of the clinical picture are drugs, both for pre-existing diseases or illegal drugs and increased sympathetic and catecholamine responses to injury that cause ECG abnormalities, blood pressure and heart rate changes and arrhythmias. A good history can help in suspecting pre-existing heart disease as an explanation for the post-traumatic cardiac abnormalities.

Imaging Techniques

A variety of imaging techniques are of great help in the diagnosis of BCI. The chest X-ray can reveal rib, sternal and clavicular fractures, pleural effusion, pneumothorax, pulmonary edema or contusion, displacement of the heart and abnormalities of the cardiac aortic silhouette as seen with pericardial effusion, ventricular aneurysm and aortic rupture.[50] Trauma surgeons and ER physicians are using ultrasound technology in the ER to rapidly assess pericardial tamponade, hemothorax and intra-abdominal hemorrhage. As mentioned in a previous section, the method is referred to as the FAST examination. Echocardiography, both transthoracic echocardiogram (TTE) and transesophageal echocardiography (TEE) have been of immense importance in diagnosing BCI, including the presence of pericardial fluid, the presence of right and left ventricular all motion abnormalities and valvular disruption. Other non-invasive imaging techniques are equally valuable, although frequently less readily available such as CT with contrast and magnetic resonance imaging (MRI) and angiocardiography. These techniques are most useful in the evaluation of patients with stable chronic cardiac trauma or in specific acute situations such as suspected aortic rupture.

Electrocardiogram: When BCI is suspected, an electrocardiogram (ECG) and chest X-ray are essential.[51] In diagnosing arrhythmias and suspecting cardiac contusion, the ECG is the most important test. Foil and colleagues [52] reviewed 524 suspected BCI cases and found that 85% who developed cardiac complications, mostly arrhythmias, had an abnormal ECG, sinus tachycardia excepted, on admission. Maenza and colleagues in a meta-analysis of 43 studies involving 4,681 patients suspected of having a BCI,[53] and Biffl and colleagues [54] reviewing 359 patients at high risk for BCI found that an abnormal ECG, excluding sinus tachycardia, was the most significant independent predictor of cardiac complications, defined as arrhythmia requiring therapy, cardiogenic shock, traumatic valvular regurgitation or cardiac tamponade.

The ECG, although frequently abnormal in patients with chest trauma, shows no changes highly predictive of BCI. The most common findings are sinus tachycardia, not otherwise explained, followed by premature atrial and ventricular extrasystoles. Other less frequent findings are non-specific T wave changes, atrial fibrillation/flutter, ST segment elevation or depression, conduction abnormalities including all degrees of atrioventricular block, fascicular block and bundle branch block. Less commonly seen are serious ventricular arrhythmias, including non-sustained and sustained ventricular tachycardia, prolonged QT interval and new Q waves.[41-43,55,56] Unfortunately, after trauma, arrhythmias can result for other reasons than BCI caused by heightened autonomic nervous system (ANS) tone, catecholamines, electrolyte shifts, blood gas alterations with hypoxia, respiratory and metabolic acidosis, drugs and alcohol, hypotension and pre-existing heart disease. Central nervous system (CNS) injury can also be responsible for arrhythmias and ECG changes independent of BCI.

Echocardiography: The echocardiogram, both transthoracic and transesophageal, are of paramount importance in the ED setting in diagnosing BCI, including the presence of pericardial effusion and cardiac tamponade, ventricular dysfunction and valvular disruption. Having the echocardiographic equipment when the patient first is seen, with ER personnel properly trained to do a rapid assessment for pericardial and peritoneal fluid and left ventricular function, has been called the bedside focused assessment with sonography for trauma (FST) examination.[57,58] In 1–2 minutes four windows can be examined, subcostal, right and left upper quadrant and suprapubic. In a study by Mandavia and colleagues[57] the FAST examination was 97% accurate for myocardial injury and Rozycki and colleagues[59] reported 100% sensitivity and specificity for FAST in detecting hemopericardium in patients with penetrating injuries.

There is not universal agreement on the value of routine use of sonography in diagnosing cardiac contusion. In a meta-analysis of 18 studies by Christensen and Sutton[60] in patients suspected of having myocardial contusion, they found no support for the routine use of echocardiography as a screening test for diagnosing clinically significant myocardial contusion. Karalis and colleagues[61] in a prospective series of 105 cases of non-penetrating injury found that myocardial contusion was common, present in 30% of the patients, but rarely required treatment and was associated with a favorable prognosis. They concluded that routine echocardiography was not useful, but should be reserved for patients who develop cardiac complications. Nagy and colleagues[62] analyzed 315 patients with blunt chest trauma and concluded that echocardiography added little to the diagnosis for patients with a normal ECG and blood pressure on admission. Finally, the eastern association for the surgery of trauma (EAST) recommends that echocardiography should be reserved for patients with hemodynamic instability or who develop cardiac complications.[51] TEE is needed when the TTE is inadequate or when aortic disruption is suspected.

Multidetector computed tomography and magnetic resonance imaging: In many hospitals multidetector computed tomography (MDCT) is available in or near the ED 24 hours per day, 7 days a week, and is the fastest way to rule out rupture of the aorta. It is also excellent in detecting pericardial effusion and evaluating myocardial function and valvular regurgitation. It detects the presence of air, bone, blood and metal fragments along the wound track of a penetrating missile.[63] MRI can also visualize the same problems, but has the disadvantage of being less readily available and isolating the patient for longer periods of time. It is therefore rarely used in the immediate workup of acutely injured patient suspected of having BCI. However, MRI with gadolinium contrast is helpful in differentiating contused stunned, but viable myocardium from non-viable myocardium. This delayed enhancement is seen whenever myocardium is infarcted whether from trauma or from coronary artery disease.[64,65]

Although radioisotope imaging can identify viable versus nonviable myocardium in areas of myocardial contusion, because it can visualize relatively large transmural defects and miss smaller areas of injury as well as injury to the thinner right ventricle, it has a relatively little role to play in the diagnosis of BCI.[53,66]

Cardiac enzymes: Serum glutamic oxaloacetic transaminase (SGOT), lactate dehydrogenase (LDH) and creatine kinase (CK) are all frequently elevated after acute trauma from a variety of tissues including myocardium. The isoenzyme of CK, creatine kinase myocardial bound (CKMB), is the most specific of these enzymes for myocardial necrosis. In a series of 78 patients with blunt chest trauma, 24% had a serum CKMB greater than or equal to 6% of total CK activity, 36% had less than 6% CKMB and 40% had no CKMB activity.[67] Pathologic ECG changes were seen in 89% of patients with CKMB greater than or equal to 6% and in 32% of the patients without CKMB activity. Eleven patients died, five with macroscopic myocardial injury all of whom had elevated CKMB levels. However, an elevated CKMB level is not pathognomonic of cardiac injury since other tissues, especially bladder, small bowel and liver, have CKMB activity. Even skeletal muscle has small amounts of CKMB, so with extensive skeletal muscle trauma, CKMB can be elevated.

The introduction of myocardial-specific enzymes, troponins I and T has made the detection of myocardial necrosis possible with a high degree of certainty. Collins and colleagues [68] prospectively evaluated 68 consecutive patients with blunt chest trauma and possible BCI. They found that in hemodynamically stable patients, a normal troponin 4–6 hours after injury excludes clinically significant BCI, with or without ECG abnormalities.

An elevated troponin does not definitely diagnose clinically significant BCI, but these patients need at least 24 hours' monitoring in the hospital.

Rajan and Zellwger[69] examined troponin as a predictor of the risk of developing an arrhythmia or left ventricular dysfunction in 187 multiply injured patients after blunt chest trauma. They found that 34% had myocardial contusion with elevated troponin I levels within 6 hours of injury of whom 25% were symptomatic and 9% showed no abnormalities. The remaining 124 patients (66%) had negative troponin I levels and remained asymptomatic. The level of the troponin I correlated positively with the severity of the arrhythmia developed and the depression of the left ventricular ejection fraction (LVEF). Velmahos and colleagues[70] followed 333 consecutive patients with significant blunt thoracic trauma prospectively. Serial ECGs and troponin I levels were performed routinely and echocardiograms done selectively. Clinically significant BCI was defined as cardiogenic shock, arrhythmias needing treatment or post-traumatic structural defects. Significant BCI was diagnosed in 44 (13%) of patients. Of 80 patients with an abnormal ECG and troponin I levels, 27 (34%) developed significant BCI. Of 131 patients with normal ECGs and troponin I levels, none developed significant BCI. The positive predictive value was 29% and the negative predictive value 98% for the ECG, 21% and 94% for troponin I and 34% and 100% for the combination of ECG and troponin I. On admission, either the ECG or the troponin I level was abnormal in 43 of the 44 patients with significant BCI. In the absence of other reasons for hospitalization, patients with normal ECG and troponin I levels at 6 hours after injury can be safely discharged. On review of the literature, Foot[71] also concludes that patients with normal serial ECGs and troponin I levels over 8 hours excludes the diagnosis of significant BCI.

Management of the Patient with Myocardial Contusion

Myocardial contusion should be considered in any patient who has suffered a severe traumatic incident, not only those with injury to the chest. Especially suspicious for BCI are those with rib or sternal fractures. When myocardial contusion is suspected, an ECG should be obtained looking for ST-T wave changes, arrhythmias or Q waves, followed by ECG monitoring for arrhythmias. Troponin I or T should be drawn on admission and again at 6–8 hours after injury. If both the ECG and troponin levels are normal and there are no arrhythmias requiring treatment, the patient can be safely discharged providing hospitalization is not required for treating other, non-cardiac injuries. If the troponin is elevated or there is ST segment elevation, a TTE should be done and the patient monitored in the intensive care unit for 24–48 hours.

If the patient has myocardial contusion and has pulmonary congestion on chest X-ray, a Swan-Ganz catheter should be placed in the pulmonary artery since the pulmonary capillary wedge pressure can help differentiate between left ventricular congestive heart failure and pulmonary contusion where the wedge pressure is normal or low. If heart failure is present, conventional therapy with hemodynamic support, diuretics, angiotensin converting enzyme inhibitors and possibly low-dose beta-blockers should be instituted and their effects monitored hemodynamically. Treatment is indicated for symptomatic atrial fibrillation/flutter, ventricular arrhythmias, high degree atrioventricular block, or arrhythmias causing hemodynamic instability.



FIGURE 2: Patient was a 20-year-old man who was stabbed in the left chest. A 2 cm laceration of the left ventricle was repaired. This is a frame from a cineangiogram. Right anterior oblique position with injection in the left ventricle. The ventricle is in diastole. Note the contrast-filled protruding aneurysm near the apex. The wall of the aneurysm consists of thrombus contained by epicardium and adhered pericardium

Prognosis and Development of Late Complications

Most patients with myocardial contusion that does not cause malignant arrhythmias, heart failure or hemodynamic instability do very well, usually healing to form a myocardial scar. If the contusion is extensive, chronic congestive heart failure can result, but this is distinctly unusual since most patients with such extensive myocardial contusion do not survive hospitalization. Contusion or lacerations can result in extensive myocardial fibrosis or small ventricular lacerations that bleed but form epicardial thrombus, the genesis of either a true or false ventricular aneurysm (Fig. 2). Complications of ventricular aneurysms are similar to those of aneurysms seen after acute MI: arrhythmias, thrombus and embolization, heart failure and late rupture. Since the majority of patients with myocardial contusion are younger than the majority of those with coronary disease causing the acute MI and since coronary disease puts the patient at future risk of progression, the myocardial contusion patient with the same extent of damage as the coronary patient has a better prognosis. At San Francisco General Hospital, our experience is that once a patient has survived the first 48 hours after definite myocardial contusion, there have been very few late, functionally significant sequelae. Whether the myocardial scar will form the substrate for future ventricular arrhythmias, although possible, is not really known.

INTRACARDIAC INJURIES FROM BOTH PENETRATING WOUNDS AND BLUNT CARDIAC INJURY

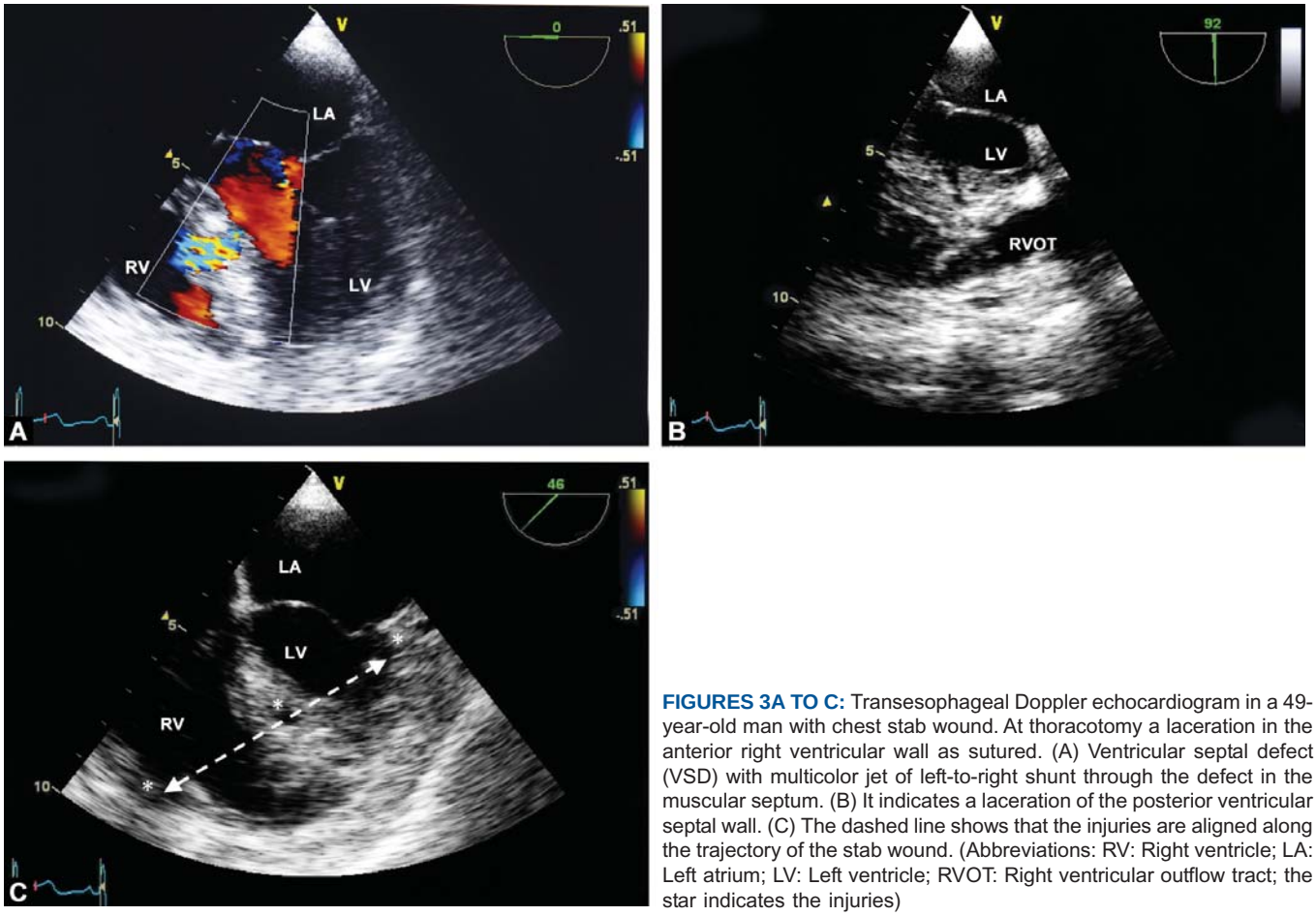
Intracardiac injuries can be limited in extent or can be extensive with involvement of many cardiac structures. For instance, a

penetrating injury which results in aortic regurgitation is likely to have traversed additional cardiac structures on the way to the aorta; thereby, additional injuries may include aorta-to-right ventricular fistula, ventricular septal defect (VSD), tricuspid regurgitation and/or mitral regurgitation. A suspicion of complex and multiple lesions is needed to properly secure a definitive and complete diagnosis in these patients. Echocardiography is an excellent method for obtaining this kind of complex diagnosis; however, echocardiography is highly operator dependent and an active search for suspected lesions is the only way to rule-in or rule-out an additional unexpected findings. A combination of lesions as opposed to a single lesion results in a complicated clinical picture, including complex variation in physical examination findings, hemodynamic response and therapeutic strategy. Not infrequently, the presence of one lesion, for instance, mitral regurgitation, results in a loud murmur that obscures signs of other cardiac trauma, such as coronary artery injury or the presence of a traumatic VSD. For this reason, with any cardiac injury, a careful echocardiographic or other imaging study should be performed and often a right and left heart catheterization is necessary to obtain a complete diagnosis and before definitive surgical treatment is carried out.

SEPTAL DEFECTS

Both penetrating injuries and BCI can result in atrial septal defects (ASDs) or VSDs.[72-74] The ventricular septum is more vulnerable to laceration in penetrating injuries than the atrial septum, because of its more anterior location and larger target area. Also, because the signs of ASD are so subtle, the defect escapes early detection and a small defect may remain undetected. With a significant laceration of the atrial septum, a large left-to-right shunt develops producing right ventricular volume overload, right ventricular precordial hyperactivity, grade II-III/VI systolic ejection murmur at the base due to increased right ventricular stroke volume and possibly a widely split second heart sound (although this is not a constant finding in traumatic ASDs). Since in congenital ASD the widely split second sound is possibly related to the capacious pulmonary arteries and delay in the "hang-out" time to close the pulmonic valve, the wide split may not be present shortly after the acute laceration of the septum. Over time, as the pulmonary arteries remodel and enlarge, the second sound may become widely split.

With penetrating injuries, the VSD can occur at any location in the septum (the muscular portion of the venticular septum has a larger surface area and is more likely to be penetrated at that site) (Figs 3A to C). With non-penetrating injuries, usually the result of crushing or deceleration accidents,[75] the injured septal tissue may rupture immediately or septal rupture may be delayed as contused necrotic muscle liquefies and the shunt enlarges with clinical manifestation occurring over one to two weeks after the initial injury.[76] With ventricular septal rupture there is usually a loud, pansystolic murmur along the left sternal border due to the left-to-right shunt, loudest along the left sternal border due to the left-to-right shunt, the magnitude of which depends on the size of the defect and the relative resistance of the systemic and pulmonic vascular beds. With a small defect,



FIGURES 3A TO C: Transesophageal Doppler echocardiogram in a 49-year-old man with chest stab wound. At thoracotomy a laceration in the anterior right ventricular wall as sutured. (A) Ventricular septal defect (VSD) with multicolor jet of left-to-right shunt through the defect in the muscular septum. (B) It indicates a laceration of the posterior ventricular septal wall. (C) The dashed line shows that the injuries are aligned along the trajectory of the stab wound. (Abbreviations: RV: Right ventricle; LA: Left atrium; LV: Left ventricle; RVOT: Right ventricular outflow tract; the star indicates the injuries)

the shunt can be small to moderate, the left ventricle can accommodate to this increased volume load and the patient can remain asymptomatic. Since the patient was usually normal before the trauma, the pulmonary vascular resistance is low and, depending on the size of the defect, the shunt can be extremely large and the patient can rapidly develop congestive heart failure. With a large shunt, the pulmonary blood flow is markedly increased, thereby placing a preload volume overload on the left ventricle. If the septal tear is large enough, the pressure in the right ventricle increases even to the level of the systemic pressure placing an afterload burden on the right ventricle. These pathophysiologic changes explain the rapid development of left heart failure, pulmonary edema and usually rapid death.

The clue to considering the possibility of a traumatic VSD is the development of a pansystolic murmur usually along the left sternal border, although the murmur can be loudest at the apex depending on the location of the septal defect. The loudness of the pulmonic second sound depends on the presence of pulmonary hypertension. With a large left-to-right shunt, there will be both right and left ventricular overactivity. The chest X-ray in a patient with a large shunt may show increased pulmonary hypervascularity or pulmonary edema. Serial chest X-rays may show progression of these findings. The ECG is usually non-diagnostic and the diagnosis can be made by TTE with Doppler, where there is increased left ventricular volume and a left-to-right jet through the septal defect. Echocardiographic bubble-contrast injection may be useful, where the jet of unopacified blood from the left ventricle can be seen to wash away the bubbles in the right ventricle at the site of the VSD. Treatment of traumatic ASD or VSDs depends on their size and hemodynamic consequences. With small defects and small left-to-right shunts, the heart chambers remain normal in size and function and the patient may have no symptoms. In this case, the patient should be followed and defect closure may not be necessary or, if progressive pathophysiologic changes are documented, then recommend defect closure. When the shunt is large and the pulmonary/systemic flow ratio is greater than or equal to 2.0 or the patient is symptomatic, closure of the defect should be considered. For patients who are not in heart failure, it is wise to delay closure, since traumatic defects, especially VSDs, tend to close or at least become smaller spontaneously.[74,75,77] If the shunt has flooded the lungs and the patient is in congestive heart failure, immediate closure is indicated. If the patient is hemodynamically unstable, an intra-aortic balloon pump can reduce the left ventricular systolic impedance and decrease the left-to-right shunt and increase effective forward flow before surgical closure. Percutaneous transcatheter closure has been used an alternative to open heart surgery using a device, like the Amplatzer VSD occluder,[78] but the expertise needed to perform these procedures may not be available [Dehghani P, Ibrahim R, Collins N, et al. Post-traumatic ventricular septal defects—review of the literature and a novel technique for percutaneous closure. J Invasive Cardiol. 2009;21:483-7].

VALVULAR INJURIES

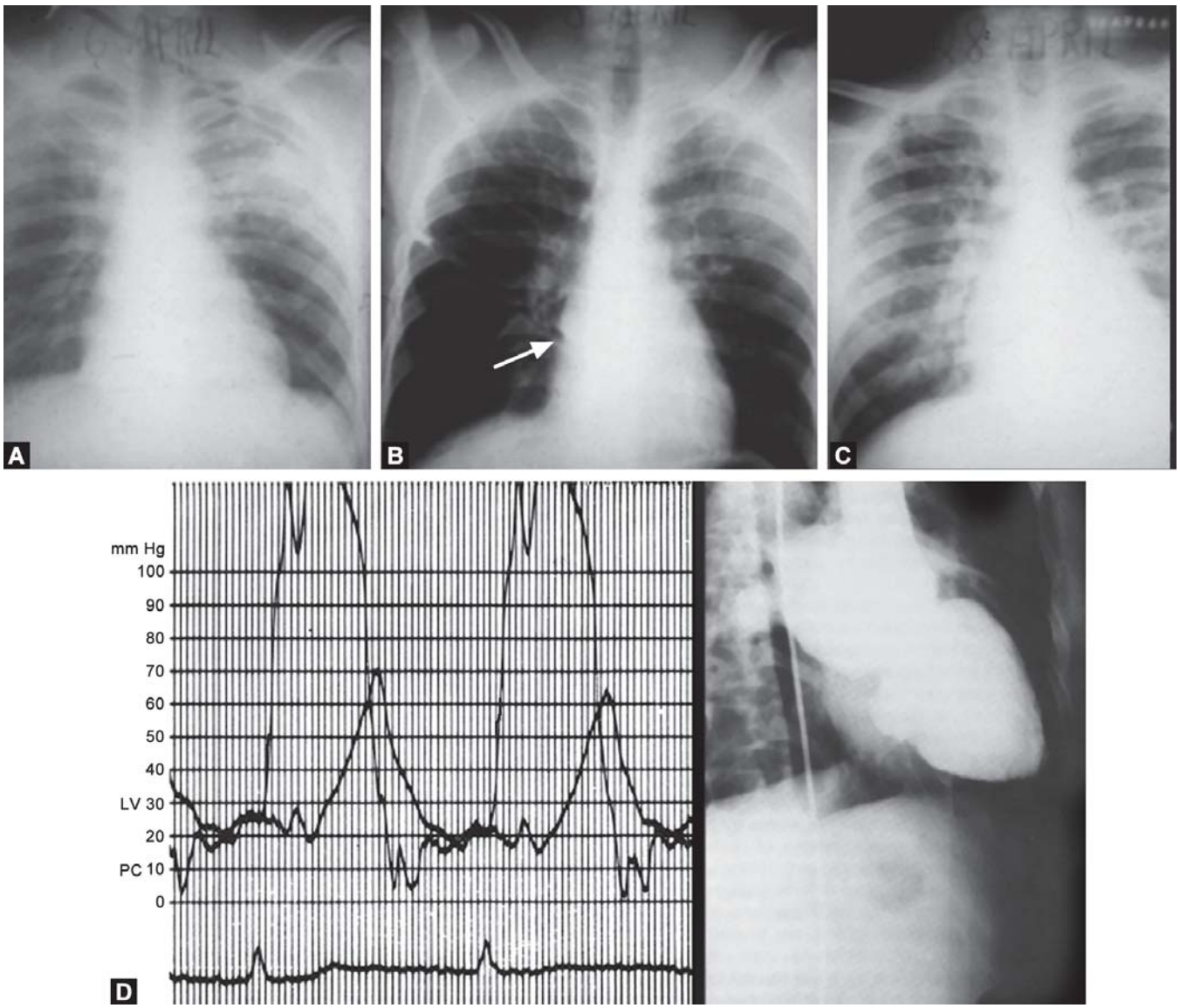
All cardiac valves can be damaged to a greater or lesser extent by either penetrating injury or BCI.[79,80] Penetrating injury can lacerate any valve causing valvular regurgitation. BCI can cause mitral or tricuspid valve regurgitation by rupturing the valve leaflet, one or more chordae, tearing a papillary muscle or by extensive ventricular wall contusion. With BCI due to crush injury, there may be marked distention of the left and/or right ventricle caused by an extremely high increase in peripheral vascular resistance with a marked increase in aortic systolic pressure. In addition, there may be lower body compression with a marked increase in venous return to the heart, all of which can put enormous force on all the cardiac valves resulting in valvular rupture and regurgitation. In our experience, with BCI caused mitral regurgitation, the chordae and papillary muscles are torn more often than the valve leaflets are ruptured. In aortic valve injury, the leaflet itself is torn, either at or behind the leading edge of the cusp, most frequently near the commissures.

The injury to the valve can be of varying severity causing minimal to severe regurgitation. The hemodynamic consequences depend on the severity of the regurgitation and the valve involved. With acute rupture of the aortic or mitral valve, the resulting large regurgitant volume increases the diastolic left ventricular volume suddenly and without time for the ventricle to gradually increase its volume and for eccentric hypertrophy to occur. This results in a marked increase in left ventricular diastolic filling pressure, left atrial and pulmonary capillary pressure and pulmonary edema. Since the absolute increase in left atrial and ventricular volume is relatively small, the heart may not appear to be enlarged on chest X-ray.

Tricuspid Regurgitation

Tricuspid regurgitation can occur either because of laceration of the valve cusps, rupture of the chordae tendineae or rupture of papillary muscle heads.[81] The degree of tricuspid regurgitation varies from minimal to severe. With severe tricuspid regurgitation the degree of elevation in the CVP and the height of the "v" wave depends on the compliance of the right atrium and systemic veins. Although the "v" wave may be characteristically elevated, the "y" descent may remain normal if the right ventricle has not failed and the mean right atrial pressure may not be equally dramatically high. If the right ventricle fails with compliance loss, then the "a" wave and the mean CVP become elevated. On palpation over the precordium, with severe tricuspid regurgitation there may be a parasternal precordial lift. The murmur of tricuspid regurgitation can be a typical pansystolic parasternal murmur that increases with inspiration, an atypical systolic ejection left sternal border murmur, or be totally absent. Tricuspid regurgitation is easily demonstrated by Doppler echocardiography with an enlarged right atrium and ventricle and a systolic regurgitant jet. The mechanism of the tricuspid regurgitation can also be defined.

Repair of the tricuspid valve is necessary only if the patient has evidence of hemodynamic compromise such as markedly elevated CVP, hepatomegaly with or without liver function abnormalities, ascites, intractable peripheral edema or a decrease in cardiac output. If there is any left heart disease or increase in pulmonary vascular resistance, effective forward flow may be impaired and cardiac output decreased. If these problems persist after medical management, the tricuspid valve can usually be repaired but, if necessary, replaced.[82,83]



FIGURES 4A TO D: Chest X-rays of a 26-year-old man involved in a head-on vehicular collision. (A) Taken on arrival to the ER. There are infiltrates in the superior portions of both lungs. The heart size is normal (posteroanterior view). (B) Taken 2 days later. There is a grads III/IV pansystolic murmur at the apex. Patient is having increased dyspnea on minimal exertion. The infiltrates have decreased in both lungs, more in the right upper lung field. The heart size is still normal. The white arrow indicates the left atrium as it protrudes beyond the right cardiac border (posteroanterior view). (C) The patient now has pulmonary edema with increased upper lobe vascularity. The heart size has increased and the systolic murmur has decreased in duration but not loudness and radiates to the left chest posteriorly. At surgery, the left anterolateral papillary muscle was nearly totally ruptured. The mitral valve was excised and a prosthetic valve placed. (D) (Left) Left ventricular pressure with pulmonary capillary wedge pressure simultaneously recorded. The mean wedge pressure is markedly elevated with a giant "v" wave of severe mitral regurgitation. (Right) Angiocardiogram from right anterior oblique position. Injection in the left ventricle with instantaneous severe regurgitation into the left atrium and into the pulmonary veins

Mitral Regurgitation

Penetrating trauma can cause mitral regurgitation by injuring any of the elements of the mitral apparatus. With BCI, mitral regurgitation is often a consequence of left ventricular wall, papillary muscle injury or ruptured chordae[84,85] (Figs 4A to D). After a traumatic incident, mitral regurgitation is suspected by the development of an apical pansystolic murmur not known to have been present before the trauma. If a papillary muscle is ruptured or chordae torn, the murmur may appear immediately, but if there is myocardial wall contusion and necrosis of the ventricular wall or papillary muscle, the murmur may appear later.[86] The signs of severe mitral regurgitation are a hyperactive, volume overloaded left ventricle. With sudden severe mitral regurgitation, the marked increase in diastolic volume in the unprepared left ventricle results in a large increase in left ventricular filling pressure and a similar increase in left atrial and pulmonary capillary pressure resulting in pulmonary edema, with or without the ability to increase forward effective stroke volume.[87] Doppler echocardiography establishes the diagnosis and can identify the mechanism of the developed mitral regurgitation. If the mitral regurgitation is minimal, then only the murmur is present and no immediate therapy is necessary. If the mitral regurgitation is severe, medical management with diuretics, angiotensin blocking agents and preload and afterload reduction with nitroprusside to diminish

the regurgitant volume and preload and improve the effective forward stroke volume is indicated. An aortic balloon pump can be effective in increasing the effective forward stroke volume and reducing the degree of mitral regurgitation. If the patient is hemodynamically unstable or does not respond rapidly to medical management rapidly, then surgical repair or replacement of the mitral valve is necessary.[84,87]

Aortic Regurgitation

Unlike the atrioventricular valves, aortic valve injury either by penetrating trauma or BCI results almost exclusively from a laceration of one or more of the aortic cusps.[88] The severity of the aortic regurgitation can be minimal, but is usually severe. The typical physical findings of acute aortic regurgitation result from a collapse of the aortic diastolic pressure and sudden severe volume overload of the unprepared left ventricle. If the regurgitation is minimal to moderate in degree, the left ventricle gradually remodels with enlargement of its cavity and eccentric hypertrophy, and the diastolic compliance of the ventricle remains normal.[89] The patient may be asymptomatic and the diagnosis depends on finding a new (not previously present) typical diastolic, blowing murmur along the left sternal border. With severe acute aortic regurgitation, because of the high left ventricular diastolic pressure, the driving pressure of the high-volume regurgitant jet is smaller and the murmur is lower pitched and shorter, even may be absent. The systolic pressure may not be high as in severe, chronic aortic regurgitation and the diastolic pressure not as low. Therefore the pulse pressure may not be high, eliminating many of the peripheral signs of chronic, severe aortic regurgitation. However, the carotid pulse usually maintains its collapsing quality (Corrigan's pulse) and the to-and-fro bruit created by compressing the femoral artery with the stethoscope (Duroziez's sign) will usually be present. Another characteristic finding in acute aortic regurgitation is the soft or absent first sound due to the high left ventricular diastolic pressure prematurely closing the mitral valve.[89] Since there is a marked elevation in the left ventricular filling pressure, the left atrial and pulmonary capillary pressures also rise resulting in pulmonary congestion and pulmonary edema. With a high left atrial pressure, there is an increase in pulmonary artery pressure and a loud P_2. Sinus tachycardia is an important compensation for the severe aortic regurgitation since with tachycardia there is a decrease in the diastolic filling time/minute, shortening the time for aortic regurgitation. With tachycardia, a loud pulmonic second sound, the short low-pitched diastolic murmur may be mistaken for a systolic ejection murmur. Therefore, it is most helpful to feel the carotid pulse while listening to the heart to avoid missing the fact that the murmur is diastolic.

The diagnosis can be verified using Doppler echocardiography where the jet of aortic regurgitation, the enlarged left ventricle and the early closure of the mitral valve are seen.[90] With severe aortic regurgitation, diastolic reversal of flow in the descending aorta is also observed using echocardiography. The site and nature of the injury can often be characterized by a skilled echocardiographer—although this is highly operator dependent. As the process becomes subacute or chronic, secondary changes associated with congestive heart failure arise including depressed LV systolic function, left atrial enlargement and elevation of estimated pulmonary systolic pressure. Cardiac catheterization is occasionally used to further verify the diagnosis and to rule-in or rule-out coexisting injury or disease.

The treatment depends on the severity of the aortic regurgitation. If mild to moderate, the patient can be managed medically, possibly with preload and afterload reduction. Very severe aortic regurgitation with congestive heart failure requires urgent cardiac surgery. If the aortic cusp tear is small without marked disruption of the valve tissue, repair or patching of the valve laceration is possible. Otherwise aortic valve replacement is necessary.[88,91,92] TEE is an important adjunct in the operating room (pre- and post-repair) to assure that the injury repair is complete and that there no other injuries are missed.

Pulmonic Valvular Regurgitation

The pulmonic valve is rarely injured in BCI, but is vulnerable to penetrating trauma. Laceration of the pulmonic valve results in pulmonic valvular regurgitation, which, if severe, causes right ventricular volume overload. The murmur created is diastolic, along the left sternal border and begins distinctly after the aortic component of the second sound, perceptively separated from it. The diastolic pressure gradient from pulmonary artery to right ventricle is small, and, with rapid regurgitation, the murmur is low-pitched and can be very short or even absent. With severe pulmonic regurgitation, a right precordial lift is not uncommon as well as a right-sided S_4 and S_3, and when the right ventricle dilation occurs, development of functional tricuspid regurgitation may occur. If the pulmonic valve disruption is the only traumatic problem, it rarely requires immediate surgery. If after a time, the right ventricle dilates, especially if it demonstrates reduced contractility, or the patient develops right heart failure, then pulmonic valve replacement will be required. The percutaneous transcatheter approach has not been used for traumatic pulmonary valve disease (its use has largely been for congenital cardiac disease), and it is conceivable that this approach may in the future have application in the treatment of pulmonic valve traumatic injury.

NON-VENTRICULAR SEPTAL DEFECT AND NON-ATRIAL SEPTAL DEFECT INTRACARDIAC FISTULAS

Trauma, usually penetrating, but also BCI can result in fistulous connections between high-pressure and low-pressure chambers.[93-97] The usual traumatic intracardiac fistulas are between the aorta and the right atrium and/or right ventricle and occasionally, the pulmonary artery.

The fistulous shunt between the aorta and the low-pressure chambers is frequently manifested by a continuous murmur. Depending on the chamber into which the fistula empties, the murmur can be along the upper left sternal border in an aortic-to-right ventricle or pulmonary artery fistula or the lower left sternal border if into the right atrium. Depending on the size of the shunt, the continuum of symptoms can extend from asymptomatic to acute congestive heart failure.[98] If the shunt is large, the aortic pulse pressure may be increased similar to the wide pulse pressure seen in severe aortic regurgitation and there

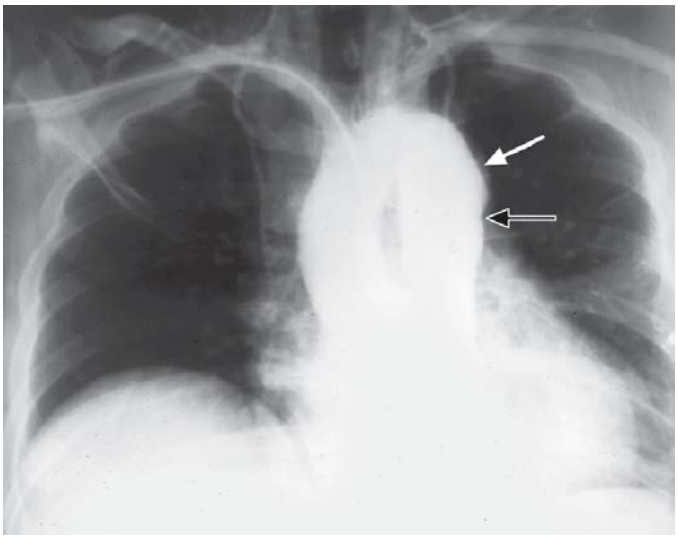


FIGURE 5: Aortogram (Anteroposterior position) of 45-year-old man in a head-on collision with another car. White arrow indicates the distorted contrast-filled flattened lumen and the black arrow indicates the distal indentation which marks the site of the aortic tear. There is also widening of the mediastinum

may be signs of right ventricular volume overload with increased pulmonary blood flow. In patients with large shunts, surgical correction is indicated. At present, with catheter techniques to plug small sized orifices, it is possible to close some intracardiac traumatic fistulas relatively noninvasively.

CORONARY ARTERY LACERATION AND THROMBOSIS

Coronary artery injury is mostly seen in penetrating trauma, but can occur in BCI.[99,100] The coronary artery injury spectrum includes coronary artery laceration, coronary artery pseudo-aneurysm, coronary dissection, coronary artery thrombosis, coronary arterio-venous fistula and/or coronary-cameral fistula (most often to right atrium or right ventricle).[101-103] Coronary artery embolization can occur as a result of embolization which originates from a left ventricular thrombus adjacent to an area of myocardial contusion (Fig. 5).

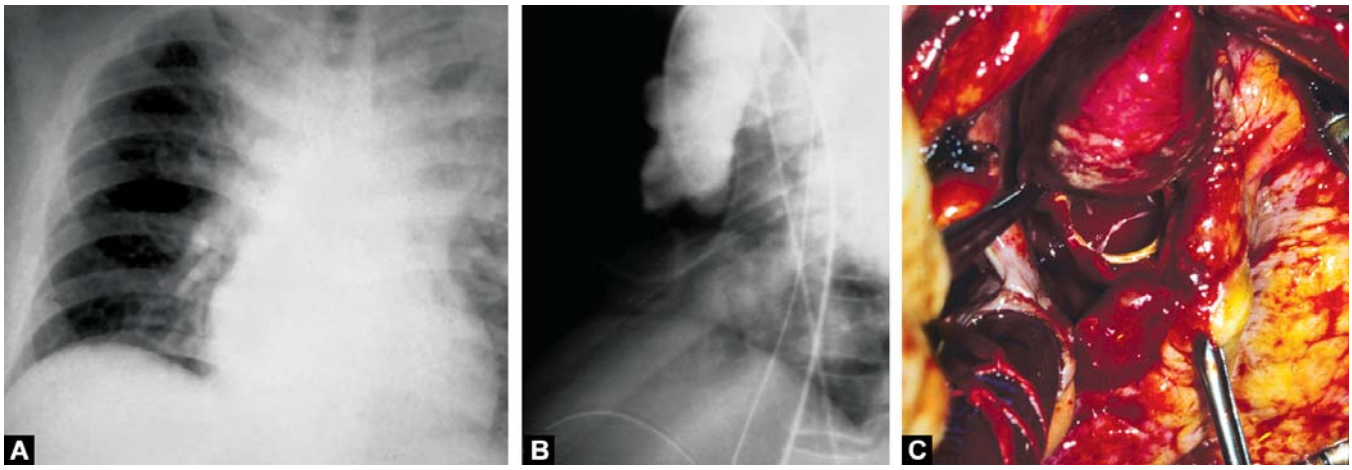
With laceration, there is frequently hemorrhage into the pericardial space with subsequent cardiac tamponade. The ECG may show anything from ST segment elevation MI, non-MI related ST-T wave changes, or even remain normal.[104,105] In many cases the lacerated coronary artery is discovered after emergency surgical evacuation of pericardial blood and suturing of a ventricular laceration. If surgery is done early after injury, an attempt can be made to either repair or perform bypass grafting to the injured artery. Since most of these injuries occur at odd hours and pump bypass may not readily be available, the lacerated bleeding artery is often ligated—this may result in MI. Most often, if coronary ligation is required, the patient is young and otherwise has normal coronary arteries, and, if the infarction is small and does not decrease left ventricular function, the patient's prognosis is good.[106] The development of a traumatic coronary arterio-venous or coronary-cameral fistula is suspected, a continuous murmur frequently is found with diastolic accentuation.[100,107] Coronary-cameral fistulas usually occur between the coronary artery and the right atrium or ventricle, but occasionally they can develop between the left coronary artery and the left ventricle or rarely the left atrium.

The volume of the shunt is usually not large initially, but can either increase or decrease over time. If the shunt gradually increases and the coronary blood flow into the fistulous artery increases proportionally, there will be no myocardial ischemia as a result of the "steal" phenomenon. However, if the runoff is into a low resistance chamber and the coronary blood flow proximal to the fistula cannot increase sufficiently, there will be a drop in coronary arterial pressure distal to the shunt and the development of myocardial ischemia, especially as myocardial oxygen demand increases with activity.[108] The patient may develop angina or even an MI. Any patient with a coronary artery fistula with evidence of myocardial ischemia (which can manifest either as angina, or when stable, with exercise stress testing), should have the fistula closed. If the shunt is small, there is no associated false aneurysm and the patient is asymptomatic with no evidence of ischemia after an exercise test, the patient should do well without intervention and the patient should be followed medically to detect an increase in the size of the shunt and the development of myocardial ischemia. Bravo and colleagues reported a patient with a coronary arteriovenous fistula followed for 20 years without a change in shunt size or in angiographic anatomy.[109]

Coronary thrombosis can occur with BCI, usually resulting from chest compression or blast injury. With high velocity missile penetrating injury, the coronary arterial injury with thrombosis can occur without laceration can occur even if the path of the missile is near to, but not in contact with, the artery.[105,110] The fact that coronary artery thrombosis has been described at postmortem in young people, even children, after crush injuries to the chest proves that BCI can cause coronary artery thrombosis. When this occurs, the patient develops an acute MI similar to that seen from coronary occlusion due to atherosclerosis. The fact that in the AFIP report of 546 cases of non-penetrating cardiovascular trauma cases weighted to the more severe injuries, there were no instances of traumatic coronary thrombosis. This is evidence that traumatic coronary occlusion is a rare event. In fact, when an acute MI is seen after an accident, it is far more common that the MI was caused by coronary atherosclerosis and the MI precipitated the accident.

AORTIC AND ARTERIAL TRAUMA

Trauma, both penetrating and BCI, can result in vascular laceration with hemorrhage, arteriovenous and other types of fistulas, thrombosis, and aneurysm formation.[12,49,93-95,111-114] Laceration of the aorta commonly leads to exsanguination and rapid death. Eighty-five percent of patients with traumatic aortic injury from deceleration trauma do not make it to the hospital alive. In deceleration trauma, common in vehicular accidents and falls from heights, the differential movement of sections of the aorta or marked displacement of the heart from the middle mediastinum either laterally or superiorly places enormous stress on the root of the ascending aorta and on the proximal descending aorta just beyond the takeoff of the left subclavian artery. Laceration and complete disruption of the aorta is almost always fatal within minutes at the scene of the accident. If the



FIGURES 6A TO C: (A): Chest X-ray (AP supine) of a 50-year-old man involved in a high speed boating accident. The patient had multiple injuries including rupture of his ascending aorta. The cardiac silhouette is normal size and there is an infiltrate obscuring the aortic knob, the medial portion of the right lung, widening the mediastinum and opacifying the upper two-thirds of the left lung. (B) Aortogram (left anterior oblique position) with injection at the aortic root showing aneurysmal bulge anteriorly just above the sinotubular junction. (C) Picture taken at operation showing the almost severed ascending aorta. Forceps is retracting the right atrial appendage (if we use this we will have to mark certain landmarks and define them in the legend). The patient had an aortic graft placed and survived to leave the hospital

ascending aorta is lacerated, with its position within the pericardial sac, there is little resistance to adventitial tear and 200–300 ml of blood results in rapid cardiac tamponade. For this reason, although the ascending aorta is one of the two most frequent sites of rupture along with the proximal descending aorta, it is most unusual to see survivors with complete rupture of the ascending aorta [Shkrum MJ, McClafferty KJ, Green RN, et al. Mechanisms of aortic injury in fatalities occurring in motor vehicle collisions. J Forensic Sci. 1999;44:44-56] (Figs 6A to C).

In the proximal descending aorta, with pleura and mediastinal tissues abutting the aorta, there is more resistance to adventitial tear. When the intima-medial tear occurs, the bleeding into the adventitial tissues can be contained and a false aneurysm can develop (Fig. 7).[115] If the intima-medial rupture is circumferential, the two ends of the ruptured aorta can retract and the aortic blood flow contained by the walls of the false aneurysm.

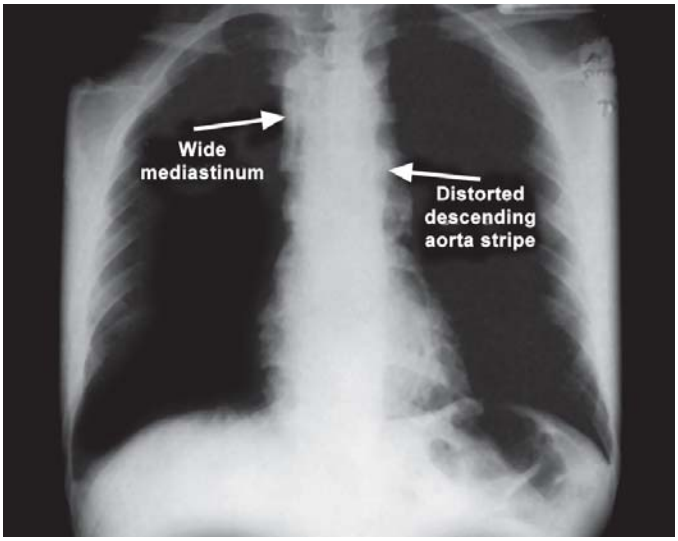


FIGURE 7: Chest X-ray of a 24-year-old man who was involved in a vehicular accident 5 years before taken because of a chronic cough. The widened mediastinum and distorted descending aorta is indicated by the arrows. A small false aortic aneurysm in the proximal descending aorta was repaired

In the AFIP experience, 15% of patients with aortic rupture from BCI lived long enough to reach the hospital.[116] The false aneurysm can last many years after the accident only to be discovered serendipitously by a chest X-ray taken for an unrelated problem. On the chest X-ray there may be distortion of the aortic silhouette with or without calcification in the aneurysmal wall. The diagnosis of ruptured aorta should be suspected in any deceleration or chest compression accident, especially those where there is also steering wheel chest impact.

In the acute stage, a good posteroanterior projection chest X-ray is most helpful in recognizing the widened superior mediastinum due to aortic bleeding, the loss of the paraspinal aortic stripe of the descending aorta and the blurring of the superior margin of the aortic arch with bleeding over the cap of the left lung. If bleeding has occurred into the left pleural space, a left-sided pleural effusion can be present. With superior mediastinal bleeding a shift to the right of the trachea can occur.[117]

Physical examination, with the exception of the tracheal shift and left-sided pleural effusion mentioned above, offers little help in making the diagnosis of ruptured aorta. If the adventitial hematoma compresses the true aortic lumen, a systolic bruit may be heard in the back similar to that heard in patients with coarctation of the aorta. There may also be a decrease in the femoral pulses, or compression of branches of the aorta, such as the left subclavian artery, resulting in a loss or diminution of pulses, but these findings are very unusual.

If aortic rupture is suspected, in the past aortography was done to establish the diagnosis. At present, where possible, a 64-slice rapid CT scan is performed and only where the CT scan is not available is TEE or aortography utilized.[114,115,118] Thoracic CT angiography is the most reliable and accurate method for diagnosis of traumatic aortic injury. If the patient is stable hemodynamically, repair can be delayed with relatively

low mortality until the medical management is optimized. Prior to surgery, the blood pressure should be lowered and myocardial contractility (dP/dT) decreased by a combination of beta-blockers and nitroprusside. If the patient is hemodynamically unstable, then immediate repair is necessary, albeit at a higher perioperative mortality.[113,119] Until recently, surgical repair was the only option.[111,119,120] Over the last decade, percutaneously placed endovascular stent grafts have been used to repair aortic aneurysms, including traumatic aortic rupture with success that is equal to or better than open surgical repair. Results have shown lower operative mortality, lower perioperative stroke rate and possibly lower rate of spinal cord injury.[114,121] The placement of endovascular stent grafts requires personnel skilled in the technique and there is a steep learning curve. Therefore only certain institutions with sufficient experience should consider this a viable alternative to surgical repair. In addition, patients who have undergone endovascular stent grafting require periodic follow-up to detect persistent endo-leak and aneurysm development. Long-term data is not yet available, and, although the short-term success of the percutaneous methods is promising, concern exists regarding the long-term consequences of these new devices.[115,122,123]

When the chronic traumatic aortic aneurysm is discovered weeks to years after the trauma, usually by finding distortion of the aortic silhouette in a patient with a past history of trauma, a decision must be made as to whether it should be repaired (Fig 7). There are studies indicating that late rupture of chronic traumatic aortic aneurysms is not unusual and that late symptoms of aneurysmal expansion can occur. Surgical correction or, possible, endovascular stent grafting is usually required. Finkelmeier and colleagues[124] reported 413 cases of chronic traumatic thoracic aneurysms reported in the literature over 30 years. Symptoms of aneurysmal expansion developed in 42% of the patients within 5 years, 85% within 20 years of injury. Chest pain followed by increase in size of the aneurysm on chest X-ray (or other imaging modalities) were the most frequent signs precipitating surgical correction. Of 60 patients followed medically, 20 died of their aortic lesions. The combined risk of dying or developing symptoms was 41% at 5 years. Over 300 patients underwent operative repair with a perioperative mortality of 4.6%. Survival probability was greater with surgical repair than with those treated medically. For these reasons, it is generally recommended that, when found, traumatic aortic aneurysms should be repaired[124] unless there are comorbidities that make surgical repair more hazardous. If a calcified pseudoaneurysm is detected more than 2 years after injury, some authorities have recommended medical management with beta-blockers and blood pressure control. The patient must be followed radiologically at 6–12 month intervals to detect evidence of aneurysmal enlargement. The presence of pain, enlargement or compression of surrounding organs is indications for prompt intervention.[125]

Aortovenous fistulas involving the inferior vena cava, innominate vein or iliac veins occur with penetrating injury and much less frequently with BCI. Iatrogenic arteriovenous fistula as a complication of lumbar disc surgery resulting in severe high-output heart failure is well described.[126] This catastrophic complication should be suspected if, after lumbar disc surgery, the patient develops congestive heart failure and has a continuous murmur over the abdomen and/or back. Smaller arteries can be involved in arteriovenous fistulas, such as the renal artery and vein, after renal biopsy (Fig. 8).

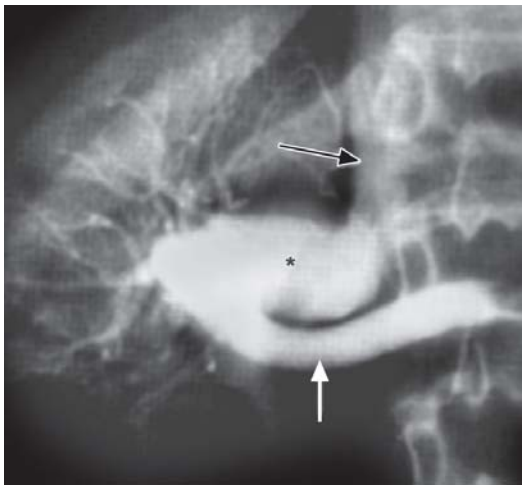


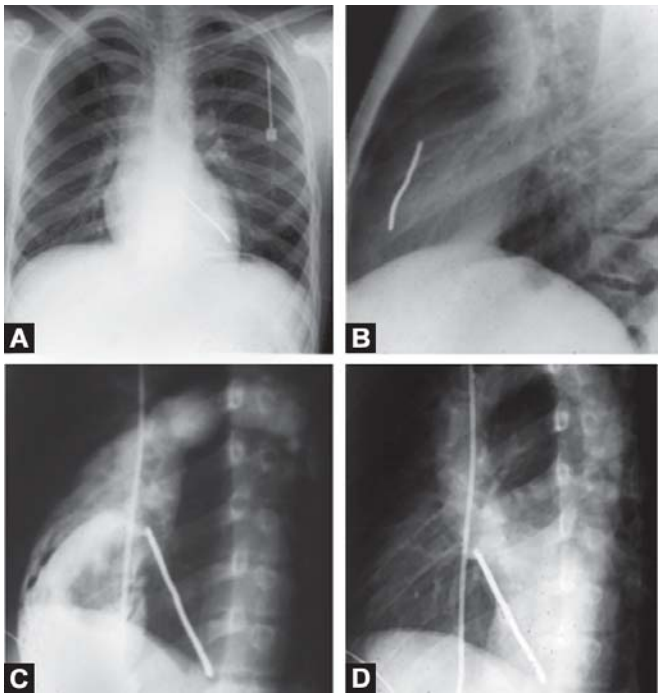
FIGURE 8: Renal arteriogram in an 18-year-old woman with nephritic syndrome who has had multiple renal biopsies. A continuous bruit heard over the right flank

False aneurysms of the aortic branches and extremity arteries usually result from penetrating injury. Since false aneurysms tend to enlarge and rupture, they should be repaired when discovered. Thrombosis of arteries as a result of either penetrating injury or BCI leads to immediate ischemia of the organ in the territory of the involved artery.[126] If a limb is involved, the extremity suddenly becomes cold, pale and pulseless. Surgical removal of the clot and repair or bypass is necessary to revascularize the affected limb. If there are no symptoms of the vascular occlusion, it is usually not found near the time of the injury and vascular repair is usually not necessary.

RETAINED FOREIGN BODIES

Penetrating missiles, especially those entering the body at low velocity, can come to rest within the pericardial sac, the cardiac muscle, any of the cardiac chambers, or in arteries or veins. If a bullet enters a cardiac or vasculature chamber, the foreign body is likely to embolize and lodge at sites distant from their entrance point (Figs 9A to D).[127-131] With foreign bodies in right-sided cardiac chambers, the object can embolize downstream into the pulmonary arteries and lung,[132] or retrograde into the inferior vena cava and systemic veins. With objects in left-sided cardiac chambers, embolization into the aorta and arterial branches can occur—often with severe consequences. With objects that penetrate the lung and lodge in a pulmonary vein, the foreign body can embolize into the left heart and beyond into the arterial tree.[133]

Immediately after penetrating cardiovascular trauma, physiologic abnormalities may manifest immediately including hemorrhage, cardiac tamponade and fistula formation. Low-velocity missiles passing through contaminated areas can carry foreign material and bacteria into the body and result in infection and abscess formation anywhere in the body including the heart. Lodged in the pericardial sac, foreign bodies can cause infection, pericarditis and pericardial effusion that resolve only with removal of the foreign body.[134] Lodged in the myocardial



FIGURES 9A TO D: (A and B) Posteroanterior and left lateral chest X-ray of a 15-year-old boy who felt a bee-sting I his anterior chest while mowing the lawn. Note the wire-like foreign body within the cardiac silhouette. (C and D) Angiocardiogram in the left anterior oblique position. Figure C shows right ventricle and pulmonary artery opacified and Figure D the left ventricle and aorta. Note the foreign body lies acutely across the position of the ventricular septum, mostly over the left ventricle. At operation, the wire was imbedded superficially in the muscle of the left ventricle and was beneath the left anterior descending coronary artery. The wire was removed and the patient made a full recovery

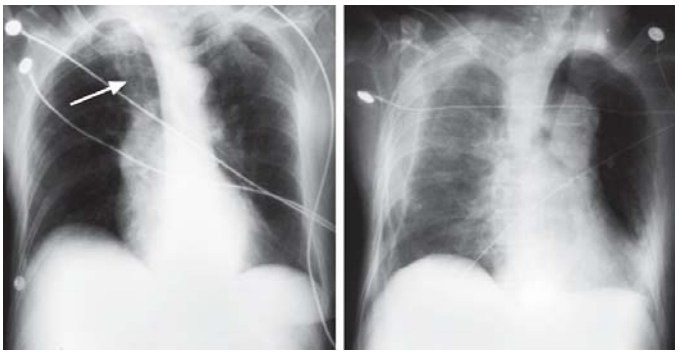


FIGURE 10A: Legend for chest X-rays attempted subclavian vein stick chest X-rays of a 25-year-old man with an attempted percutaneous insertion of a central line into the right subclavian vein. The patient shortly after the procedure had a profound drop in blood pressure and became short of breath. (Left) Chest X-ray (supine, anteroposterior position). First film after drop in blood pressure. The white arrow indicates infiltration in the right superior lung field. (Right) Right anterior oblique position. Infiltrates have spread over the entire right hemithorax

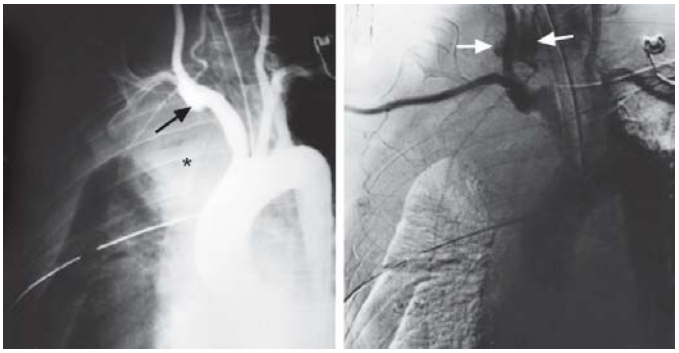


FIGURE 10B: (Left) Retrograde aortogram (anteroposterior position). Left panel black arrow indicates a bulge at the bifurcation of the innominate artery. The star indicates an area of opacification in the superior medial right lung field. (Right) Subtraction film of the same aortogram. The white arrows point to the extravascular contrast from the punctured innominate artery

muscle, the object can become encapsulated with fibrous tissue and remain inert for many years. Occasionally, the object can erode into adjacent structures such as a coronary artery and cause occlusion or aneurysm formation. A foreign body present in the cardiac chamber can precipitate fibrin deposits with subsequent embolization.

Whether these foreign bodies should be removed depends on how soon after the injury the foreign body is discovered, the location of injury and whether it has caused symptoms. Frequently, the penetrating object has caused bleeding or cardiac tamponade and the object is removed during repair of the acute damage. In the absence of acute complications occurring from the acute injury, surgical removal of the foreign body may still be required. Patients with symptoms caused by the foreign body (such as infection, arrhythmias or neurotic anxiety) should have surgical removal of the foreign body. In patients shortly after injury with a known retained foreign body and with associated infection, embolization or erosion, the foreign body should be removed. Asymptomatic foreign bodies without associated risks or with a diagnosis made late after the injury may be treated conservatively, particularly if imbedded in the myocardium, pericardium or pericardial sac.[128,131] Removal of the intracardiac foreign body requires accurate identification of its position in the heart by echocardiography or CT scan and the usually method of extraction is surgical. Extraction can, under certain circumstances, be accomplished by retrieval catheters or snares to extract lost wires, catheter fragments and other small objects that are intracavitary and freely moveable in the right atrium or ventricle.[129,131,135-138]

IATROGENIC CARDIOVASCULAR INJURIES

With the increasing number of cardiovascular diagnostic and therapeutic techniques and devices, the incidence of iatrogenic cardiovascular trauma is also increasing. With percutaneous introduction of catheters into the subclavian or internal jugular veins there are increasing reports of subclavian and carotid arterial lacerations with bleeding into the mediastinum and pleural cavity, with occasional fatal results. Pneumothorax, arterial and venous thrombosis, arteriovenous fistulas, and "lost" leads and catheter fragments have all been reported accidents (Figs 10A and B).[139-141] Percutaneous needle renal biopsy is the most common cause of acquired renal arteriovenous fistulas, occurring in between 10% and 16% of biopsies (Fig. 8).[142,143] With transseptal techniques of left heart catheterization, there is danger of puncturing the root of the aorta producing an aortic or coronary-right atrial fistula, or into the pericardial space, resulting in cardiac tamponade.[144,145] Removal of pacemaker

leads can result in tricuspid valve trauma and tricuspid regurgitation.[146] Transvenous cardiac biopsy has been reported as a cause of tricuspid valve injury and RV perforation [Huddleston CB, Rosenbloom M, Goldstein JA, et al. Biopsy-induced tricuspid regurgitation after cardiac transplantation. Ann Thorac Surg. 1994;57:832-6; discussion 836-7]. Percutaneous coronary intervention has been reported as a cause of coronary artery rupture with consequent tamponade and need for emergency surgery [Witzke CF, Martin-Herrero F, Clarke SC, et al. The changing pattern of coronary perforation during percutaneous coronary intervention in the new device era. J Invasive Cardiol. 2004;16:257-301].

Electrophysiological studies with multiple stiff catheters run the risk of right and left atrial, right and left ventricular and coronary sinus perforation. With heat and radiofrequency ablation techniques, aortic valve damage and cardiac-esophageal fistulas have been reported.[147,148] With mitral balloon valvuloplasty, tearing of the mitral valve resulting in severe mitral regurgitation and left-to-right shunting through a catheter-induced atrial septal tear are complications. With coil and device closure of a patent ductus arteriosus or paravalvular leaks around a prosthetic valve, these devices can cause valvular injury and device embolization.[138] In the future, there will be a great variety of ways that diagnostic and therapeutic interventions can cause cardiovascular trauma.

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Chapter 101

Venous Thromboembolism and Cor Pulmonale

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Chapter Outline

- Venous Thromboembolism
  - Epidemiology
  - Etiology
  - Pathophysiology
  - Outcomes
  - Clinical Manifestations
  - Symptoms
  - Signs
  - Diagnostic Testing
  - Diagnostic Approach
  - Optional Pathways
  - Acute Management
  - Mortality Risk Assessment
  - Management of Patients at High Risk of Death
  - Thrombolysis
  - Surgical and Catheter-based Thrombectomy
  - Intermediate Risk Populations
  - Low Risk Populations
  - Anticoagulation Therapy
- Cor Pulmonale
  - Signs and Symptoms
  - Studies
  - Pulmonary Function Testing
  - Echocardiography
  - Therapy

INTRODUCTION

This chapter reviews the disorders associated with pulmonary vascular disease, focusing on venous thromboembolism and pulmonary heart disease (cor pulmonale).

VENOUS THROMBOEMBOLISM

Venous thromboembolism (VTE), most commonly originating from deep venous thrombosis (DVT) of the legs, ranges from asymptomatic pulmonary emboli, incidentally discovered emboli to massive embolism causing immediate death. Acute pulmonary embolism (PE) may occur rapidly and unpredictably and may be difficult to diagnose. Treatment can reduce the risk of death, and appropriate primary prophylaxis is usually effective.[1] The interaction of an extensive pulmonary artery obstruction and the presence of cardiopulmonary comorbidity may lead to right ventricular dysfunction. The result is hemodynamic instability and, in severe cases, death.[2]

Mortality in untreated VTE is approximately 30%, but with adequate anticoagulation, this can be reduced to 2–8%.[3] Unfortunately, overall cumulative mortality remains at 15.3% as described in the International Cooperative Pulmonary Embolism Registry (ICOPER) study.[4] A major reduction of the morbidity and mortality will occur only through the widespread use of prophylactic measures in populations at risk and through a heightened clinical suspicion and awareness of the often subtle and nonspecific presentation of the disease.

EPIDEMIOLOGY

Few health care providers realize that the case fatality rate for PE exceeds the mortality rate for acute myocardial infarction (MI).[5] In spite of this considerable clinical burden, VTE remains a disorder for which we have incomplete epidemiological knowledge.

Deep venous thrombosis of the lower extremity has an estimated incidence of 1 per 1,000 persons per year. Around 19.2% of these cases will be complicated by PE,[6] accounting for 200,000 to 300,000 hospitalizations per year.[7] Forty to fifty percent of patients with symptomatic proximal DVT without symptoms of PE will have ventilation-perfusion lung scan findings associated with a high probability of embolism.[8]

The reported annual incidence of VTE varies widely ranging from 20.8 to 65.8 per 100,000 (published rates were age-adjusted and sex-adjusted to the 1980 United States white population). It was reported to be as high as 69 per 100,000 in a 25 year retrospective population base study from Olmsted County, Minnesota.[9] It is estimated that 50,000 to 100,000 die of VTE annually in the United States.[7] Ten percent of patients with symptomatic VTE will die within one hour of onset. Of patients diagnosed with VTE before death, 5–10% have shock at presentation. These individuals suffer a mortality rate of 25–50%. Those patients with VTE who do not die acutely often have nonspecific symptoms.[8] In addition, patients diagnosed with VTE will have 12% mortality within one month[10] and 14.7% at 6 months. Increased mortality risk was associated with

systolic arterial hypotension, congestive heart failure, cancer, tachypnea, right ventricular hypokinesis on echocardiogram, chronic obstructive pulmonary disease and age older than 70 years.[4,10] The mortality rate at 1 year is approximately 25%. Out of those, 20% are caused by VTE (usually recurrence). Most late deaths are due to underlying malignancy or less commonly cardiopulmonary disease.[8,11]

Venous thromboembolism is a common clinical problem that is predominantly a disease of older age with the higher number of deaths in the 75- to 84-year group.[12,13] The age-adjusted mortality rates are consistently higher among black compared to white patients. Mortality rates are also consistently higher among men than among women. However overall morbidity and mortality have decreased in the past 20 years.[7,14-17] The incidence is higher during winter months, possibly owing to a decrease in physical activity.[8] First episode of VTE carries association with the following processes: (1) 18% of patients suffer malignancy; (2) 23% have undergone surgery within 2 months; (3) 15% develop thromboembolism during hospitalization for medical illness; (4) 2% have major trauma and (5) 41% are idiopathic.[18]

Recurrent VTE occurs despite anticoagulation and is most frequent in the first 3 weeks after diagnosis. Fatal events are more likely in the first week post diagnosis. In patients with VTE treated with anticoagulation, recurrent VTE is more likely to occur if the patients have been immobilized for more than 3 days.[19]

Conditions that increase risk of VTE are well-described in the literature, including trauma, fractures, postoperative state and obesity. These conditions are over-represented in persons who died with VTE.[7] The highest risk period for postoperative fatal VTE appears to be 3–7 days after surgery.[8]

The overall incidence of subsequent cancer is 6% in all patients with PE. The most frequent sites of cancer are gastrointestinal malignancies, but pulmonary and genitourinary malignancies are also represented. Time elapsed from the diagnosis of VTE to that of cancer in these individuals averages 30.7 months. The mean survival from the diagnosis of cancer is 14.6 months.[6,12,20]

Autopsy studies have reported that patients with cancers involving organs of the abdominal cavity (ovarian, biliary, stomach) have a high prevalence of VTE at the time of death.[20] The risk among patients with malignancy is increased fourfold.[21,22] It has been shown that tumor cells interact with thrombin and plasmin generating systems and can directly influence thrombus formation.[23] The highest 1 year incidence rate of thromboembolic disease is associated with prior diagnosis of metastatic lung, uterine, bladder, pancreatic, gastric and renal cell carcinoma. In addition, women with breast cancer who undergo chemotherapy in association with surgery had three times the risk of VTE compared with women that undergo surgery alone,[24] perhaps associated with hormonal modification.

VTE is also a women's health issue as pregnancy, hormonal contraception and postmenopausal hormonal therapy each contribute to increased risk.[25] The risk of thromboembolism is five times greater in a pregnant woman than in a nonpregnant woman of similar age. The risk for thromboembolic events is increased fourfold with oral contraceptive use alone,[26] and twofold to fourfold with hormone replacement therapy.[21]

TABLE 1

Risk factors for venous thromboembolism

Hereditary factors	
Antithrombin deficiency	Protein C deficiency
Congenital dysfibrinogenemia	Factor V Leiden (G1691A mutation)
Thrombomodulin	Plasminogen deficiency
Hyperhomocysteinemia	Dysplasminogenemia
Anticardiolipin antibodies	Protein S deficiency
Excessive plasminogen activator inhibitor	Factor XII deficiency
Prothrombin G20210A mutation	Homozygous C677T mutation
Acquired factors	
Trauma/fractures	Surgery
Stroke	Immobilization
Advanced age	Malignancy (chemotherapy)
Central venous catheters	Obesity
Chronic venous insufficiency	Heart failure
Smoking	Long distance travel
Pregnancy/puerperium	Oral contraceptives or hormone replacement therapy
Crohn's disease	Antiphospholipid syndrome
Nephrotic syndrome	Prosthetic surfaces
Hyperviscosity (polycythemia, Waldenstrom's macroglobulinemia)	Acute medical illness
Platelet abnormalities	Spinal cord injury

ETIOLOGY

In 1856, Virchow defined a triad of primary risk factors for thromboembolism: (1) local trauma to the vessel wall; (2) hypercoagulability and (3) venous stasis. VTE is a multifactorial disease with genetic and genetic-environmental interaction. The risk factors responsible are summarized in Table 1.

The majority of cases of secondary thrombosis have more than one underlying condition, with the combination of surgery and malignancy occurring with highest frequency.[27] The role of combined risk factors in thromboembolic disease hints at a probable multi-hit pathophysiology underlying VTE.

The incidence of VTE increases dramatically with advancing age, ranging from about 1 case per 1 million person-years for children less than 15 years of age to nearly 1 case per 100 person-years for adult more than 85 years old.[21]

Immobility is a risk factor as well. Fifteen percent of patients on bed rest for less than a week before death had VTE at autopsy, whereas the incidence rose to 80% in patients in bed for a longer period.[24]

The highest risk for VTE is associated with surgery at 6–22 times background rate.[21] Thrombosis may even begin intraoperatively. Thrombosis may start days, weeks or even months after surgery.[8] High-risk surgical procedures include neurosurgery, major orthopedic procedures involving the leg, as well as thoracic, abdominal or pelvic surgery for malignancy. Renal transplantation and cardiovascular surgery also demonstrate high risk for VTE.[21] Three quarters of proximal DVTs that occur after major orthopedic surgery are in the operated leg, and pelvic surgery is associated with isolated pelvic

vein thrombosis.[8,24,28] Recent trauma increases risk for thromboembolism 13 fold, especially among patients with head trauma, spinal injury, and fractures of the pelvis, femur and tibia.[21]

Hypercoagulability can be inherited or acquired. The inherited disorders should be suspected in patients with recurrent or life-threatening VTE. This is particularly true if there is a family history of venous thrombosis, if the patient is younger than 45 years of age or if there are no apparent acquired risk factors. Women who have a history of multiple spontaneous abortions or still births should also be considered at risk.[29]

Factor V Leiden is produced by a mutation involving a G/A substitution at nucleotide position 1691 of the factor V gene. The mutation causes resistance to the anticoagulant effect of activated protein C.[30,31] The risk for VTE is increased sevenfold in heterozygous individuals and 80 fold in those who are homozygous.[32] A prospective study of 22,071 subjects showed increased risk of primary venous thrombosis associated with the mutation. It was also shown that the mean age at the time of the first VTE was 63.2 years in those patients.[33] In addition, there was a higher risk for recurrent thromboembolism in patients with the mutation.[34] The combination of oral contraceptive use and factor V Leiden mutation strongly increases the risk of VTE;[30,34] a population-based case-control study estimated a cumulative 30-fold increase for those who are heterozygous and more than a 100-fold increase for homozygous individuals.[30]

Other inherited hypercoagulable disorders include prothrombin gene mutation (G20210A). Most patients with this mutation will have an episode of thrombosis by age 50.[35] Antithrombin III deficiency presents as a familial coagulopathy. Affected individuals may present with childhood thrombosis and frequently have recurrent events. They usually will have an accompanying risk factor and often develop thrombus at unusual anatomical locations.[23] Persons with heterozygous deficiencies of protein C and protein S systems are prone to develop thromboembolism in their sixties.[23,29,35] Disorders of plasmin generation are rare causes of recurrent familial thromboembolic disease associated with impaired fibrinolysis.[23] Hyperhomocysteinemia can be caused by genetic disorders affecting the trans-sulfuration or remethylation pathway of homocysteine metabolism. It can also be caused by folic acid deficiency, vitamin B12 deficiency and vitamin B6 deficiency. This disorder may be particularly important in the development of VTE in younger adults.[23,36,37] VTE is the most common initial clinical manifestation of antiphospholipid antibody syndrome, occurring in up to 32% of these patients.[38]

Pulmonary embolism is the leading cause of maternal death in the developed world.[39,40] VTE is estimated at 0.76 to 1.72 per 1,000 pregnancies.[40] Pregnancy is classically thought to be a hypercoagulable state, due to major changes in all aspects of hemostasis—increasing concentrations of clotting factors, decreasing concentrations of some of the natural anticoagulants and reducing fibrinolytic activity.[41] In addition, there is a reduction in venous flow velocity of approximately 50% in the legs by 25–29 weeks of gestation. The risks of recurrent VTE during pregnancy or the puerperium for women with a past history of VTE who forego anticoagulation is not known.[41] Almost 90% of DVTs in pregnancy occur in the left leg, possibly due to compression of the left iliac vein by the uterus.[40,42] The major risk factors for VTE in this population are increasing maternal age (particularly over 35), black race, heart disease, sickle cell disease, diabetes, lupus, smoking, multiple pregnancies, obesity, previous VTE, thrombophilia and cesarean delivery (especially emergency cesarean section during labor).[40,42]

Upper extremity DVT can occur spontaneously, or sometimes as a complication of an intravascular device such as a pacemaker or long-term use of a central venous catheter. Cancer is also associated with upper extremity DVT.[21,43] PE may complicate up to 3% of upper extremity DVT based on a cohort of 5,388 patients. In the same population, the most powerful independent predictor of upper extremity DVT was the presence of an indwelling central venous catheter.[44]

Obesity is also associated with VTE, especially in patients less than 40 years old. It seems to be a stronger risk factor in women.[45] Air travel has also been considered a risk factor for VTE, even though hypobaric hypoxia was not associated with prothrombotic alterations in the hemostatic system in healthy individuals.[46] Low atmospheric pressure was shown, however, to increase thrombin in individuals with the factor V Leiden mutation who also took oral contraceptives.[2] People who travel for more than 8 hours are estimated to have an eightfold increased risk of fatal PE. Despite the increased risk, events are rarely associated with air travel, with an incidence of roughly 0.4 case per million passengers.[47,48]

A large observational study in France of symptomatic superficial venous thrombosis (SVT) of lower extremities showed that DVT occurred in 25% of the patients and 3.9% had symptomatic PE; the risk factors associated with development of VTE in patients with symptomatic SVT were history of VTE, cancer, male sex and the absence of varicose veins.[49] Risk associated with varicose veins varies by age. The 45-year-old patients have a fourfold increase risk of VTE compared with a twofold increased risk for 60-year-old-patients. No increased risk is seen for 75-year-old patients.[43]

PATHOPHYSIOLOGY

Acute PE causes major pulmonary physiologic derangements. Acute right-sided heart failure due to increased pulmonary vascular resistance (PVR) is the prime cause of death in VTE.[50,51] Although life-threatening PE has been equated with anatomically massive PE (> 50% obstruction of pulmonary vasculature, or the occlusion of two or more lobar arteries), the outcome of PE is most likely a function of both the size of the embolus and the underlying cardiopulmonary function.[52] In addition, there is also a pulmonary vasoconstrictive response that may play an important role in the increase of PVR after acute PE.[50] PE results in abnormal hemodynamics, abnormal gas exchange, alterations of ventilatory control and increased airway resistance and compliance.[51]

Pulmonary embolism acutely increases PVR with mean pulmonary artery pressures increasing in proportion to the degree of vascular obstruction in patients without pre-existent pulmonary vascular disease. In an animal model, a mean pulmonary pressure of 30–40 mm Hg representing severe pulmonary hypertension was demonstrated. An additional doubling of pulmonary artery pressure may occur in patients

with prior pulmonary hypertension.[51,53] In contrast to the muscular left ventricle (LV), the thin-walled right ventricle (RV) is poorly suited to compensate for acute increases in afterload produced by PE. The impact of VTE on the pulmonary outflow tract precipitates an increase in right ventricular impedance, increasing the pressure load on the RV producing stroke volume reduction, which will later depress cardiac output resulting in right ventricular dilatation. As a consequence, left ventricular preload will decrease along with an additional leftward shift of the interventricular septum related to right ventricular dilation that will further impair left sided function. The additional decrease of left ventricular flow results in systemic hypotension, which associated with increasing right ventricular end diastolic pressure and increased oxygen demands, will precipitate right ventricular ischemia, which may lead to right ventricular failure.[50,52-54]

Vasoactive mediators may also contribute to an increase in right ventricular impedance. There is strong evidence that thromboxane A2 produces systemic and pulmonary vasoconstriction. Platelet derived serotonin is the most powerful known pulmonary vasoconstrictor. Other vasoconstrictive mediators include endothelin, prostaglandin F2 alpha, histamine, platelet activating factor and thrombin.[50,52]

Gas exchange abnormalities in patients with PE are complex. Factors include the size and character of the embolic material, extent of occlusion, underlying cardiopulmonary status and the length of time since embolization. Decreased arterial partial pressure of oxygen (hypoxemia) and an increase in alveolar-arterial oxygen tension gradient are the most common gas exchange abnormalities.[51,53] Arterial hypoxemia is caused by decreased O_2 diffusing capacity across the pulmonary membrane, ventilation-perfusion mismatching and shunting of blood at either the intracardiac or the intrapulmonary level.[55] VTE causes redistribution of blood flow so that some lung gas exchange units have low ratios of ventilation to perfusion, whereas others have high ratios. Arterial hypoxemia mainly occurs when venous blood flows through lung gas exchange units with a low ratio of ventilation to capillary blood flow[53] increasing alveolar dead space.[51] Right to left shunting of mixed venous blood may occur in patients with more than 50% of the pulmonary vascular bed obstructed.[51] Shunt becomes a significant contributor to hypoxemia only if atelectasis or other causes of volume loss develop.[55] Atelectasis may arise from loss of surfactant and alveolar hemorrhage.[52] Another source of shunt physiology is pulmonary edema resulting from alteration of pulmonary alveolar-capillary permeability or from increased blood flow to the still-perfused lung.[55] Flow through a patent foramen ovale induced by high right atrial pressures is an additional cause.[52]

Although PE impairs efficient pulmonary elimination of CO_2 as a result of increased dead space, hypercapnia and respiratory acidosis rarely accompany PE. This is the result of compensatory hyperventilation.[51] Medullary chemoreceptors sense any increase in arterial PCO_2 and increase the total minute ventilation. As a result many patients with PE have lower than normal arterial PCO_2 and respiratory alkalosis.[53] Hypercapnia reflects a massive embolism due to marked increase in both anatomic and physiologic dead space,[53] except in subjects with fixed minute ventilation such as those with severe chronic obstructive pulmonary disease and patients intubated and sedated in the intensive care unit. The diffusing lung capacity for carbon monoxide (DLCO) is usually decreased in VTE.[51,53]

The lungs have a certain capacity to dispose of thromboemboli by endogenous thrombolysis making pathological investigation difficult. Large emboli obstructing the pulmonary trunk or main pulmonary arteries can be detected during autopsy, but lobar and segmental pulmonary arteries are not regularly evaluated. As a result, thrombosis in those vessels may escape detection.[56,57] Autopsy specimens demonstrate a prevalence of multiple over single lesions. There is also a very marked increased incidence of disease in the right lung and in the lower lobes. This is thought to be related to a higher distribution of blood flow to those areas.[56,58] Large thrombi present in major elastic pulmonary arteries are thought to be embolic in nature in the absence of underlying disease of the vascular wall. Usefulness of this description decreases rapidly with the caliber of the pulmonary arteries involved. A large thromboembolus does not differ microscopically from a minute embolus.[56]

A fresh thrombus is particularly susceptible to fragmentation in transit; however, older organized thrombus is more likely to pass intact into the pulmonary circulation and to lodge on bifurcations.[58] If a patient survives the initial PE, the thrombus undergoes endogenous thrombolysis. The remaining thrombus then undergoes organization into vascularized connective tissue. The final step is recanalization.[56] Residual thrombosis, however, is common after anticoagulation. Complete resolution of thrombus is not achieved in more than 50% of patients at 6 months after diagnosis.[59] Approximately 4–5% of first-time symptomatic VTE patients acquire chronic thromboembolic pulmonary hypertension within 2 years.[59,60]

Autopsies reveal that less than 10% of PE causes pulmonary infarction.[61] Pulmonary infarction is the death of lung tissue distal to embolic obstruction and is usually associated with an obstruction of a medium-sized pulmonary artery. This is uncommon sequelae of PE because lung tissue has three sources of oxygen: (1) pulmonary arteries; (2) airways and (3) bronchial arteries. Pulmonary infarction is unlikely to occur unless there is impaired circulation, particularly involving inadequate bronchial circulation or an impediment to the pulmonary venous outflow.[51,56]

OUTCOMES

The short-term prognosis of PE depends on hemodynamic status and underlying disease. The hemodynamic status and underlying disease states, mainly malignancy, were the main prognostic factors for major adverse events at 30 days.[62] There are other factors associated with poor outcomes, for example, right ventricular dysfunction assessed by echocardiography or spiral CT as well as increased levels of brain natriuretic peptide (BNP), pro-BNP and troponin T.

Patients with acute symptomatic PE and concomitant DVT have a higher short-term risk for all-cause mortality, PE-related death and recurrent VTE than patients solely diagnosed with VTE over a 3 month follow-up. The risk of death in patients with concomitant DVT was about two times higher and the risk of recurrent VTE and PE-specific death was about four times higher than in patients without DVT.[63]

Despite these data more than 90% of survivors of submassive PE had resolution of right ventricular dilatation and hypokinesis at the 6 month follow-up.[64]

The Worcester VTE study gathered data from 12 hospitals over a period of 4 years in the Massachusetts area and demonstrated that patients presenting with PE had similar rates of PE recurrence compared to patients with DVT only.[65] In another long-term outcome study in patients after acute PE, at 1 year follow-up only 70% of patients were free of adverse outcomes, and after a period of 4 years 50% of the patients developed serious clinical complications. In addition, there was no difference in the pooled risk for adverse outcomes for patients with unprovoked and provoked VTE.[66]

In patients with acute PE and increased pulmonary artery systolic pressure of more than 50 mm Hg by echocardiography, the risk for persistent pulmonary hypertension or RV dysfunction increases threefold. This effect is more pronounced if it is associated in patients with advanced age and the diagnosis of malignancy.[22,67,68]

A 14,426 patient population-based study in 186 acute care hospitals in Pennsylvania showed that a substantial proportion of patients (14.3%) with PE were readmitted within 30 days. Recurrent PE or bleeding was the reason for readmission in 26.9% of those cases. Some of the risk factors that were significant predictors of readmission were African American race, severity of illness and lack of private health insurance. This is probably related to suboptimal anticoagulation practices, as well as sicker patients in these groups.[69] Additional risk factors for postdischarge mortality were both a short hospital length of stay (< 4 days) and a longer duration of hospitalization (> 8 days).[70]

CLINICAL MANIFESTATIONS

Deep venous thrombosis usually starts in the calf veins; it may extend to the proximal veins, and subsequently break free to cause PE. Each of these stages of thromboembolism may or may not be associated with symptoms. The development of symptoms depends on the extent of thrombosis, the adequacy of collateral vessels and the severity of associated vascular occlusion and inflammation. An additional factor is the capacity of the patient to tolerate thrombosis. Therefore, maintenance of a high level of suspicion is critical for the identification of patients who may benefit from diagnostic testing.

Prospective investigation of pulmonary embolism diagnosis (PIOPED) II was a prospective multicenter study that defined clinical syndromes in patients with PE: the syndrome of hemoptysis or pleuritic pain (previously defined as syndrome of pulmonary infarction in PIOPED), uncomplicated dyspnea syndrome and the circulatory collapse syndrome. These syndromes occurred in 44% of patients, 36% of patients and 8% of patients respectively. Fourteen percent of patients presented with a combination of syndromes.[71]

SYMPTOMS

New dyspnea at rest or with exertion was the most frequent symptom (73%). Orthopnea was associated with dyspnea in 38% of patients. The onset of dyspnea was rapid in 67% of patients. Pleuritic chest pain was more frequently reported than hemoptysis. Description of hemoptysis varied from pinkish to blood streaked to grossly bloody sputum.[71] Most patients with VTE are afebrile but fever may occur in 14% of patients.[72] Commonly reported symptoms in patients with suspected DVT including leg pain and swelling are neither sensitive nor specific for this condition.[73]

SIGNS

Tachypnea was present in 57% of patients, and tachycardia was present in 26% of cases. Abnormal cardiac examination with increased P2, right ventricular lift or jugular venous distention occurred in 22% of patients. Lung examination was abnormal in 37% of patients. Crackles and decreased breath sounds were reported frequently, while ronchi and wheezes were uncommon.[71] Hepatomegaly is infrequently seen and may herald right ventricular compromise.[74] Abnormal lung examination correlates with other medical conditions as well. A recent report demonstrated a 25.5% incidence of PE in patients hospitalized with exacerbation of chronic obstructive pulmonary disease. This was particularly true in patients with increased dyspnea in absence of increased cough or sputum production.[75]

Signs of suspected DVT include pitting edema, warmth, dilated superficial veins and erythema. Homans sign, pain in the calf or popliteal region on forceful and abrupt dorsiflexion of the ankle with the knee in flexed position, may be demonstrated in these patients.[73] A majority of patients with DVT do not have symptoms suggesting PE; however, 51% of these patients will have a high probability lung scan at presentation.[76] This is a compelling argument to evaluate any patient who presents with DVT for the presence of PE.[77]

Arterial blood gas analysis commonly demonstrates hypoxia and hypocapnia;[74] however, a PaO_2 higher than 80 mm Hg is not uncommon in patients with the hemoptysis or pleuritic pain syndrome. Hypoxemia was common among patients with uncomplicated dyspnea syndrome.[78] A normal A-a gradient did not distinguish patients with acute PE from patients with no PE.[79,80] Arterial blood gas, therefore, should not be ordered to either rule in or rule out VTE.[81] A modest leukocytosis (< 15,000/mm^3) may accompany and possibly be caused by VTE.[82]

Chest radiographs are nonspecific in PE. Common findings include elevated hemidiaphragm, unilateral pleural effusion and plate-like atelectasis.[74] The hemoptysis or pleuritic pain syndrome group tended to have a higher prevalence of abnormal radiological findings, while the circulatory collapse syndrome group tended to have a higher prevalence of cardiomegaly.[78] Hampton's hump is the eponym given to the pleural based defect noted on chest radiograph that is associated with a large segmental PE (Fig. 1).

Electrocardiography is also nonspecific and may show a normal pattern, sinus tachycardia, T wave inversion in V1 to V3 leads, the S1Q3/S1Q3T3 pattern (Fig. 2) or a right bundle branch block.[74] A normal ECG was found in 46% of patients with hemoptysis or pleuritic pain syndrome compared to 10% of patients with uncomplicated dyspnea. A right bundle branch block was more prevalent among patients with the circulatory collapse syndrome (67%).[78,83] T wave inversion in leads V1 to V3 had the greatest diagnostic accuracy of right ventricular dysfunction at 81%;[84] however, in other series Qr in V1 was

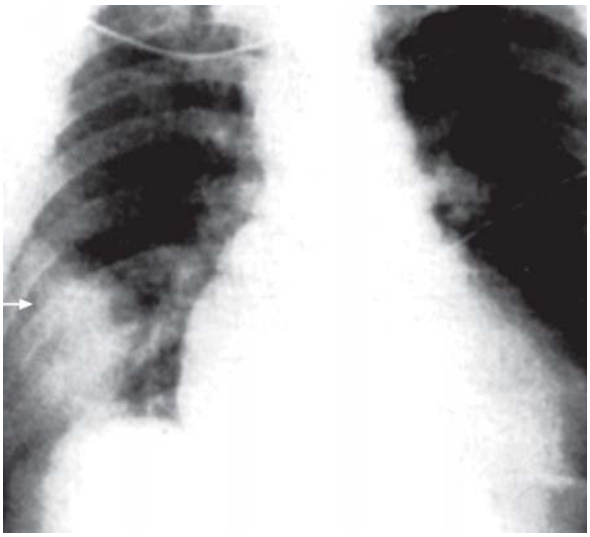


FIGURE 1: Hampton's hump is a classic finding caused by a pleural-based abnormality due to pulmonary infarction. (*Source:* Reprinted with permission from Stein PD, Woodard PK, Weg JG, et al. Diagnostic pathways in acute pulmonary embolism: recommendations of the PIOPED II investigators. Am J Med. © 2008 with permission from Elsevier)

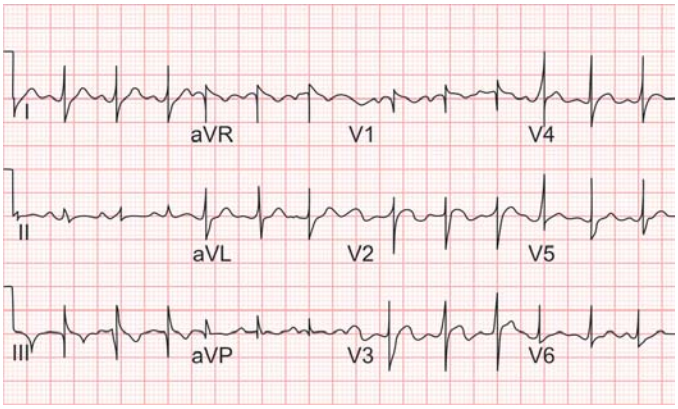


FIGURE 2: The S1Q3T3 pattern. (*Source:* Reprinted with permission from Stein PD, Woodard PK, Weg JG, et al. Diagnostic pathways in acute pulmonary embolism: recommendations of the PIOPED II investigators. Am J Med. © 2008 with permission from Elsevier)

very specific for PE, and was the strongest predictor of right ventricular dysfunction.[85] Atrial arrhythmias (mostly atrial fibrillation or flutter) are also frequently present in VTE patients.[86]

Pleural effusions are rarely massive in VTE patients. A pleural effusion occurred in 48% of patients with VTE in the PIOPED study; however, only blunting of the costophrenic angle was seen in 86% of this group.[87] Sixty-five percent are sanguineous and usually associated with infiltrates on the chest radiograph; 50% of the effusions are exudates, even in the absence of an infiltrate. Twenty-seven percent of patients with VTE and pleural effusions are grossly bloody.[61]

DIAGNOSTIC TESTING

In patients with suspected VTE, a careful assessment is in order to obtain the diagnosis. Adequate history, physical examination and known risk factors, as well as studies, like electrocardiography, chest radiography and arterial blood gas analysis, may not be enough to achieve that goal; therefore, additional investigations are frequently needed.

Plasma D-dimer is a marker of endogenous fibrinolysis and should therefore be detectable in patients with thromboembolic disease. D-dimers have a half-life of 8 hours with plasma clearance via urinary excretion and the action of reticuloendothelial system. Levels are elevated by any condition in which fibrin is formed and degraded by plasmin. ELISA based assays are statistically superior to those latex agglutinations based tests.[88] After a thrombotic event, D-dimer levels may normalize within 15–20 days. Levels of D-dimer are rarely elevated in healthy individuals, and are usually elevated in infections, cancer, surgery, cardiac or renal failure, acute coronary syndromes, acute nonlacunar stroke, pregnancy and sickle cell crises.[89]

The D-dimer assay has a high negative predictive value, and it is a sensitive but nonspecific marker of thromboembolism. Incorporating D-dimer testing into a diagnostic strategy with clinical estimation of pretest probability simplifies the diagnosis processes.[90] The finding of a normal plasma concentration of D-dimer was shown to exclude VTE accurately in most patients presenting with low clinical probability.[91-94] Moreover, diagnostic strategies combining clinical probability assessment, D-dimer measurement, venous ultrasonography and helical computed tomography or lung scan are safe and effective in the diagnosis of suspected VTE.[95,96] A negative D-dimer should never prevent further investigation of VTE if the clinical suspicion is high.[97,98]

Contrast venography is the diagnostic gold standard for patients with suspected lower extremity DVT. Noninvasive testing with compression ultrasonography has largely replaced venography to diagnose proximal DVT.[99,100] Thus management strategies that use venous ultrasonography, which detect proximal DVT at presentation, have been developed.[101,102] It should be emphasized that compression ultrasonography needs to be repeated over the course of a week, since 6% of the cases of DVT were detected during serial testing.[103,104] The reason for serial compression ultrasound studies 5–7 days after the initial negative result is based on questionable accuracy of sonography to detect distal vein DVT (below the knee),[105] conversely a meta-analysis has shown that whole-leg compression ultrasonography has a low failure rate to exclude DVT in symptomatic patients. The efficiency and convenience of whole-leg compression ultrasonography as a single study is superior to that of repeated compression ultrasonography evaluations.[99] Other alternative studies are available like magnetic resonance venography; however, clinical utility is to be determined.[106]

PIOPED was a multicenter prospective study performed from January 1985 through September 1986 to estimate the sensitivity and specificity of the ventilation/perfusion scan or V/Q scan for the diagnosis of PE. Almost all patients (98%) with clinically important PE had lung scans that fell into one of the three abnormal categories (high, intermediate or low probability) making V/Q scans sensitive enough to serve as a screening test for PE, but the specificity was limited. Combining a lung scan interpretation with a strong clinical suspicion of PE is a sound diagnostic strategy. The negative predictive value of

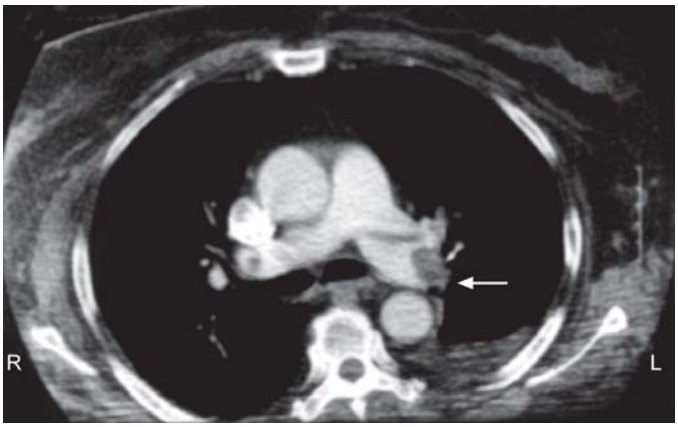


FIGURE 3: Spiral computerized tomographic pulmonary arteriography. (*Source:* Reprinted with permission from Stein PD, Woodard PK, Weg JG, et al. Diagnostic pathways in acute pulmonary embolism: recommendations of the PIOPED II investigators. Am J Med. © 2008 with permission from Elsevier)

the low-probability scan rose to 96% when accompanied by a clinical assessment of low likelihood. The positive predictive value of a high-probability scan increased to 96% if supported by a high-likelihood clinical assessment.[107]

V/Q scan is frequently used to investigate potential PE; however, its use has been plagued by a nondiagnostic rate as high as 30%,[108,109] particularly if PE is limited to subsegmental pulmonary arteries.[110] Diagnostic uncertainty occurs whenever scans are either low or intermediate probability. The actual incidence of PE ranges between 10% and 40% in this group.[111] Options after a nondiagnostic V/Q scan include pulmonary angiography, serial noninvasive leg studies for DVT and computed tomographic pulmonary angiography.[112]

Computed tomographic pulmonary angiography (Fig. 3) is an alternative that provides a clear result (either positive or negative) and may detect alternative nonthrombotic causes of symptoms.[113] A randomized controlled investigator-blinded noninferiority study has shown that a diagnostic management strategy, using computed tomographic pulmonary angiography in combination with consideration of clinical probability, D-dimer testing and leg venous ultrasonography, was not inferior to one using V/Q scanning in excluding the diagnosis of VTE.[111] Thus computed tomographic pulmonary angiography is safe as the primary diagnostic test in patients with suspected VTE.[114] Additional utility may be provided by simultaneous CT venography of the pelvic and lower extremity veins, which may reduce false negative rates.[115,116]

CT investigations also allows assessment of right ventricular enlargement, which has been shown to predict early death (30-day) as well as in-hospital complications in patients with a right ventricular diameter/left ventricular diameter (RVD/LVD) ratio higher than 0.9.[117]

Pulmonary angiography is thought to be the most definitive of the techniques used for the diagnosis of PE; however, it is not ideal because it is invasive, expensive, and has a 6% risk of morbidity and 0.5% risk of mortality.[118,119] In patients with VTE in the main, lobar or segmental pulmonary arteries, the diagnostic accuracy of computed tomographic pulmonary angiography compares favorably with that of pulmonary angiography.[120,121] Therefore, pulmonary angiography is generally reserved for patients in whom the clinical suspicion of PE remains high despite negative computed tomographic pulmonary angiography and bilateral lower extremity venous evaluations (by computed tomographic venography or ultrasonography), or for those with contraindications to computed tomographic pulmonary angiography and an indeterminate V/Q scan.[120,122] Based on the PIOPED study the risks of pulmonary angiography are sufficiently low to justify this test as a diagnostic tool in the appropriate clinical setting.[123]

Magnetic resonance imagings (MRI) of pulmonary and deep venous system remain as second-line diagnostic tools due to higher costs, technical limitations, limited availability and logistical constraints.[120,124] The most recent PIOPED III was designed to assess sensitivity and specificity of magnetic resonance angiography, alone or with magnetic resonance venography, for diagnosis of VTE, and VTE showing that MR pulmonary angiography often resulted in technically inadequate images that varied considerably among centers. MRI, therefore, should be consider only at centers that routinely perform it well and only for patients for whom standard test are contra-indicated.[125]

Magnetic resonance direct thrombus imaging (MRDTI) is a technique that has demonstrated accuracy and reproducibility for DVT diagnosis in limited studies.[126] It detects the presence of methemoglobin in clots, allowing visualization of thrombus without using intravenous contrast and making it useful for detection of subacute thrombosis.[127] The potential major advantages of MRDTI over conventional modalities include: (1) early data suggesting that it is highly accurate for the detection of both DVT and PE, providing a single imaging modality for the detection of VTE;[127,128] (2) direct visualization of thrombus, avoiding the pitfalls of conventional techniques that have either identified thrombus as a filling defect or in terms of surrogates and (3) simultaneous imaging of the legs and chest, allowing a comprehensive assessment of thrombus load, minimizing the importance of overlooked subsegmental PE and potentially facilitating more titrated treatment.

Echocardiography is a convenient and safe imaging technique that may provide critical insight into the pathophysiologic effect of VTE on right ventricular function. Among patients with large PE, abnormalities are seen on transthoracic echocardiography, which include right ventricular dilation and hypokinesis, abnormal motion of the interventricular septum, tricuspid regurgitation and lack of collapse of the inferior vena cava (IVC) during inspiration. The McConnell sign—hypokinesis of the right ventricular free wall with sparing of the apex—has a sensitivity of 77%, specificity of 94%, positive predictive value of 71% and negative predictive value of 96% in patients with VTE.[129] Right-sided intracardiac thrombi were identified in 4% of patients in the ICOPER study.[130]

Right ventricular dysfunction is defined as a right ventricular to left ventricular end diastolic diameter ratio greater than 1, a right ventricular end diastolic diameter greater than 30 mm or paradoxical right ventricular septal systolic motion.[129] The prevalence of right ventricular dysfunction ranges from 40% in normotensive patients to 70% in patients with large VTE.[131] Echocardiographic right ventricular hypokinesis independently predicts early death among patients with VTE who present with a systemic arterial pressure of 90 mm Hg or higher.[129,132]

TABLE 2

The revised Geneva rule is compared with the Wells score

Revised Geneva score		*Wells score*	
Variable	*Points*	*Variable*	*Points*
Predisposing factors		*Predisposing factors*	
Age > 65 years	+1		
Previous DVT or PE	+3	Previous DVT or PE	+15
Surgery of fracture within 1 month	+2	Recent surgery or immobilization	+1.5
Active malignancy	+2	Cancer	+1
Symptoms		*Symptoms*	
Unilateral lower limb pain	+3		
Hemoptysis	+2	Hemoptysis	+1
Clinical signs		*Clinical signs*	
Heart rate		Heart rate	
75–94 beats/min	+3	> 100 beats/min	+1.5
> 95 beats/min	+5	Clinical signs of DVT	+3
Pain on lower limb deep vein at palpitation and unilateral edema	+4		
		Clinical judgment	+3
		Alternative diagnosis less likely than PE	
Clinical probability	*Total*	*Clinical probability (3 levels)*	*Total*
Low	0–3	Low	0–1
Intermediate	4–10	Intermediate	2–6
High	> 11	High	≥ 7
		Clinical probability (2 levels)	
		PE unlikely	0–4
		PE likely	> 4

(*Source:* Torbicki A, Perrier A, Konstantinides SU, et al. Guidelines on diagnosis and management of acute pulmonary embolism. Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC). Eur Heart J. 2008;29:2276-315)

RV/LV ratio of more than or equal to 0.9 has also shown to be an independent predictive factor for hospital mortality.[133] Transesophageal echocardiography is also a very useful bedside diagnostic tool in the setting of unexplained shock with distended jugular veins. Detection of central thromboemboli, aortic dissection, segmental akinesis and pericardial tamponade are possible with the aid of this test.[134]

DIAGNOSTIC APPROACH

The clinical presentation and routinely available tests are not enough to confirm or rule out PE. The result of large-scale prospective studies of the diagnosis of VTE lend support to the concept that clinical assessment is a fundamental step in the diagnostic work-up of these patients.[135,136] The main limitations of implicit judgment are lack of standardization. Therefore, several sets of standardized prediction rules have been evaluated and validated.[137-140] A clinical decision rule is an instrument containing variables obtained from history, physical examination and simple diagnostic tests quantifying the likelihood of a diagnosis, which correct implementation will decrease the need for expensive, time-consuming and invasive diagnostic imaging testing.[141,142] The choice of diagnostic tests depends on the clinical probability of PE, condition of the patient, availability of diagnostic tests, risks of ionizing radiation exposure and cost; thus a clinical assessment should be made before imaging and by an objective method.[139] In order for a test, or combination of test, to be considered accurate enough to diagnose the presence of PE, it should have a positive predictive value of 85%. To exclude the presence of VTE, such a test should have a negative predictive value of 95%.[143]

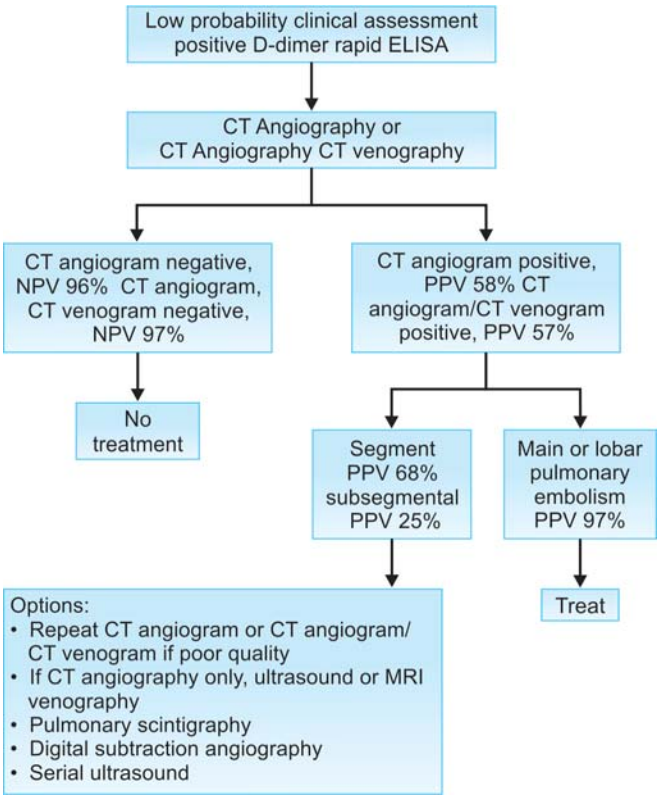
The most frequently used clinical prediction rule, the Wells score, uses both a three-category scheme (low, moderate or high clinical probability) and a two-category scheme (PE likely or PE unlikely); however, the interobserver reproducibility is variable.[137,144] The revised Geneva rule is also widely used; it comprises four variables not included in the Wells score: (1) age; (2) unilateral lower limb pain; (3) heart rate and (4) signs of DVT; this rule has also been extensively validated[141] (Table 2). The pulmonary embolism rule-out criteria (PERC) is an eight-factor decision rule designed to support the decision not to order a diagnostic test for VTE in patients with low clinical suspicion for disease.[145-147]

The use of assessment of probability allows patients to be classified into three groups on the basis of the approximate prevalence of PE: (1) low clinical probability (a prevalence of 10% or less); (2) intermediate clinical probability (a prevalence of approximately 30%) and (3) high clinical probability (a prevalence of 70% or higher).[138]

Patients with a Low Probability Clinical Assessment

Twenty-five to sixty-five percent of patients with suspected VTE are categorized as having a low clinical probability of embolism.

FLOW CHART 1: Pathway for diagnosis with CT angiography or CT angiography/CT venography following testing with D-dimer in combination with low probability clinical assessment



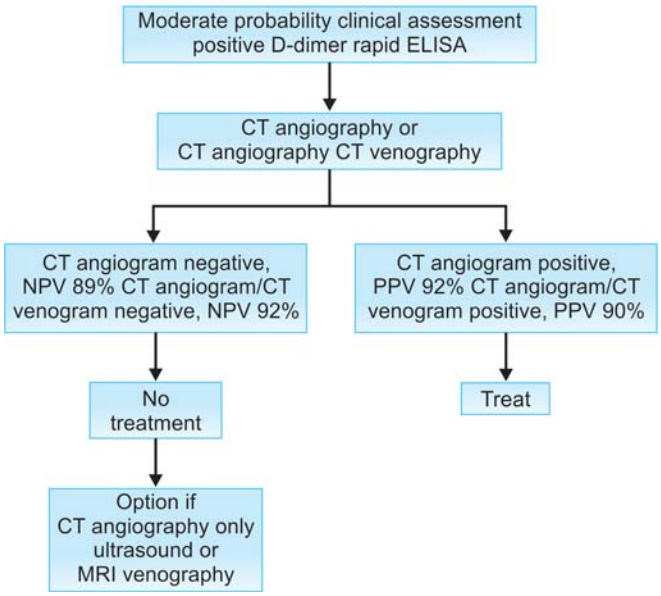
(Abbreviations: CT angiography: Contrast-enhanced multidetector computed tomographic pulmonary angiography; CT venography: Contrast-enhanced multidetector computed tomographic venous phase imaging of the veins of the lower extremities; NPV: Negative predictive value; PPV: Positive predictive value). (*Source:* Stein PD, Woodard PK, Weg JG, et al. Diagnostic pathways in acute pulmonary embolism: recommendations of the PIOPED II investigators. Am J Med. ©2008 p. 1052 with permission from Elsevier)

VTE can be ruled out in outpatients on the basis of negative results on a validated, standardized, highly sensitive D-dimer assay,[138] the post-test probability of VTE ranges from 0.7% to 2% with a normal D-dimer, and no further testing is required.[139] An abnormal D-dimer indicates the need for further testing such as CT pulmonary angiography with or without CT venography of lower extremities. If CT studies are negative there is no need for treatment; however, if positive results with main or lobar PE treatment is indicated. With segmental or subsegmental PE the certainty of diagnosis should be reassessed.[139] PE can also be clinically ruled out on the basis of a normal, low or intermediate probability ventilation-perfusion scan coupled with a negative result on compression ultrasonography[138,148] (Flow chart 1).

Patients with a Moderate Probability Clinical Assessment

Another 25–65% of patients are categorized as having an intermediate clinical probability of PE.[138] The post-test probability of PE with a 30% clinical probability is 5% with a normal D-dimer assay. If D-dimer is negative, no further testing is necessary, but a venous ultrasound or magnetic resonance

FLOW CHART 2: Pathway for diagnosis with CT angiography or CT angiography/CT venography following testing with D-dimer in combination with moderate probability clinical assessment



(Abbreviations: CT angiography: Contrast-enhanced multidetector computed tomographic pulmonary angiography; CT venography: Contrast-enhanced multidetector computed tomographic venous phase imaging of the veins of the lower extremities; NPV: Negative predictive value; PPV: Positive predictive value). (*Source:* Reprinted with permission from Stein PD, Woodard PK, Weg JG, et al. Diagnostic pathways in acute pulmonary embolism: recommendations of the PIOPED II investigators. Am J Med. © 2008 with permission from Elsevier)

venography should be considered.[139,149] If CT pulmonary angiography or CT pulmonary angiography/CT venography is negative, no treatment is necessary, but a venous ultrasound is recommended for those with a negative CT pulmonary angiography alone.[139] If CT pulmonary angiography or CT pulmonary angiography/CT venography is positive, or a high probability ventilation-perfusion scan, treatment is recommended[138,139] (Flow chart 2).

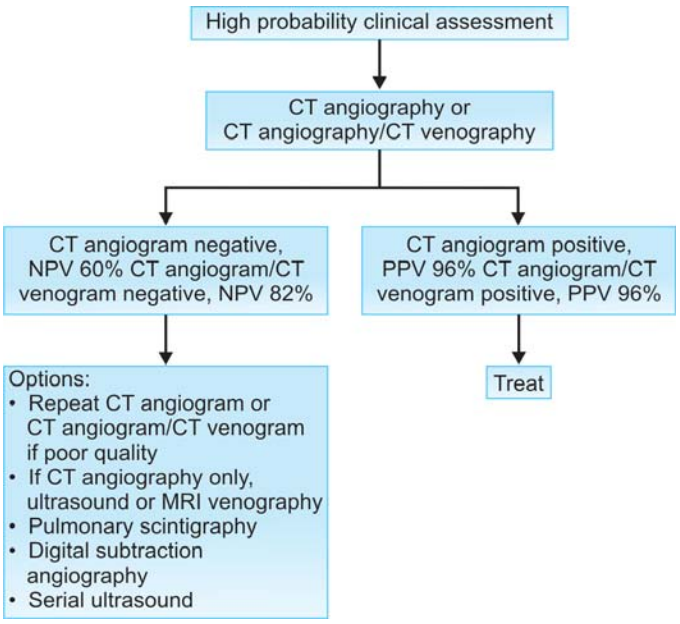
Patients with a High Probability Clinical Assessment

Approximately 10–30% of patients with suspected PE are categorized as having a high clinical probability of embolism.[138] A D-dimer is not helpful because a negative test does not exclude PE in more than 15% of patients with high probability clinical assessment.[139] Patients should be treated while awaiting the outcome of diagnostic tests. If CT pulmonary angiography or CT pulmonary angiography/CT venography is negative, other options include serial venous ultrasound examinations, pulmonary digital subtraction angiography and pulmonary scintigraphy. If CT pulmonary angiography or CT pulmonary angiography/CT venography is positive, treatment is recommended[139] (Flow chart 3).

OPTIONAL PATHWAYS

Venous compression ultrasound detects DVT in 13–15% of patients with suspected PE and in 29% of patients with proven PE, following this a venous ultrasound before imaging with CT pulmonary angiography or CT pulmonary angiography/

FLOW CHART 3: Pathway for diagnosis with CT angiography or CT angiography/CT venography following testing with D-dimer in combination with high probability clinical assessment



(Abbreviations: CT angiography: Contrast-enhanced multidetector computed tomographic pulmonary angiography; CT venography: Contrast-enhanced multidetector computed tomographic venous phase imaging of the veins of the lower extremities; NPV: Negative predictive value; PPV: Positive predictive value). (*Source:* Reprinted with permission from Stein PD, Woodard PK, Weg JG, et al. Diagnostic pathways in acute pulmonary embolism: recommendations of the PIOPED II investigators. Am J Med. © 2008 with permission from Elsevier)

CT venography is optional and may guide treatment if positive.[139] Patients with mild to moderate iodine allergy may be pretreated with steroids and then obtain CT. With severe iodine allergy, ventilation-perfusion scanning coupled with venous compression ultrasound will then be indicated. Serial venous ultrasound and gadolinium-enhanced CT angiography is an option.[139]

In patients with severe pre-existing pulmonary parenchymal or airway disease, ventilation-perfusion scanning is of limited usefulness;[150,151] in such cases, CT pulmonary angiography as the initial diagnostic study would be appropriate.

Patients with impaired renal functions will benefit from testing with venous ultrasound and ventilation-perfusion scanning, followed by selective conventional CT pulmonary angiography if the diagnosis remains unclear and patients have been given prophylactic hydration with sodium bicarbonate.[138,139]

ACUTE MANAGEMENT

The acute management of VTE begins during work-up. Patients judged to be moderate or high clinical probability for PE should be started on anticoagulation therapy as arrangements are being made for confirmatory testing. The role of anticoagulation in the treatment of PE was established over 40 years ago showing a significant survival benefit over no treatment.[152] The morbidity and mortality of undiagnosed PE outweighs the risk inherent in anticoagulation.

MORTALITY RISK ASSESSMENT

In parallel with the assessment of clinical probability, the patient should be assessed for mortality risk. Unlike the complex evaluation inherent in diagnosis, this task is accomplished at the bedside. Two clinical findings identify patients at high risk of mortality associated with PE: the presence of shock or hypotension defined by systemic systolic blood pressure less than 90 mm Hg, or a drop from baseline of greater than or equal to 40 mm Hg for greater than 15 minutes with no other identifiable cause. Subset analysis of the ICOPER study demonstrated a 52.4% all-cause mortality rate at 90 days for patients with systolic pressures less than 90 mm Hg compared to 14.7% in patients with normal pressure.[153] The management and prognosis in pulmonary embolism trial (MAPPET) registry demonstrated a 24.5% all-cause in hospital mortality for shock and 15.2% for hypotension as defined above.[154]

Attempts to classify pulmonary emboli as massive, submassive and nonmassive may result in attention being paid to the actual size, shape or location of the clot burden instead of the clinical picture. The simple presence or absence of shock or hypotension easily discriminates between a population with a mortality rate greater than 15% and a population with less risk. Table 3 provides a scheme for stratification of patients on the basis of mortality risk.

MANAGEMENT OF PATIENTS AT HIGH RISK OF DEATH

Shock or hypotension in a patient with PE is a medical emergency and rapid therapy should be initiated to prevent death. Fluid resuscitation is the cornerstone of therapy in many forms of shock. In one study, a 500 ml fluid challenge with

TABLE 3

Risk stratification—expected pulmonary embolism-related mortality

PE-related early mortality risk	*Clinical (shock/ hypotension)*	*RV dysfunction*	*Myocardial injury*	*Treatment implications*
High > 15%	+	Na	Na	Thrombolysis (consider embolectomy)
Intermediate (3–15%)	–	+	+	Hospital Admission
		+	–	
		–	+	
Low	–	–	–	Early discharge

(*Source:* Torbicki A, Perrier A, Konstantinides SV, et al. Guidelines on the diagnosis and management of acute pulmonary embolism: the Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC). Eur Heart J. 2008;29:2276-315)

dextran improved the cardiac index of normotensive patients with PE from 1.6 l/min/m^2 to 2.0 l/min/m^2.[155] Extreme caution is advised in this patient population; however, as an animal model has demonstrated worsening RV function in response to aggressive resuscitation.[156]

Although no prospective clinical trials have been performed, vasopressors and inotropes may provide temporary benefit though they do not address or correct the cause of shock in this clinical scenario. No clinical trials have assessed the benefit of supplemental oxygen in the treatment of hypoxemic patients with PE; however, this therapy is logical given the vasoconstrictive effect of hypoxemia on the pulmonary vascular bed. Mechanical ventilation may be required in extreme cases but should be initiated with caution given the unstable nature of these patients.

THROMBOLYSIS

Subset analysis from the ICOPER study demonstrated a tenfold increased risk of intracranial bleeding (3% vs 0.3%) in patients receiving thrombolysis versus patients without thrombolysis. Additionally, no survival benefit was demonstrated with this intervention, even among patients with shock.[157] There is, however, data to support improvement in hemodynamic parameters (30% reduction in mean arterial pressure with 15% increase in cardiac index) and vascular obstruction (12% reduction) acutely when patients with VTE are treated with this therapy.[158] For this reason, current guidelines support treating patients presenting with shock or hypotension associated with PE with thrombolytic therapy.[159,160] Resolution of obstruction and prevention of end organ damage associated with shock are postulated as possible benefits.

Catheter delivery of thrombolytic agents directly into the pulmonary artery did not show improved efficacy over systemic therapy, and was associated with bleeding at the introducer site.[161] Contraindications to thrombolytic therapy include recent major trauma or surgery, intracranial disease and uncontrolled hypertension at presentation.[162]

SURGICAL AND CATHETER-BASED THROMBECTOMY

In patients judged to have high-mortality risk due to shock or hypotension who have contraindications to thrombolytic therapy, other options for acutely managing pulmonary vascular obstruction should be considered. In this clinical scenario, surgical thrombectomy may be a good choice. Surgery may also be necessary in patients who fail a trial of systemic thrombolysis. In one study of 47 consecutive patients undergoing embolectomy at a single center, the survival rate over the 4-year period of the study was 96%.[163]

A second option for patients with contraindication to or failure of thrombolysis is catheter thrombectomy. Multiple devices and techniques have been described but no randomized controlled trials have been performed. In one case series of 20 patients, a rotational pigtail catheter was used to fragment pulmonary emboli associated with hemodynamic compromise. Mortality was 20% and 15 patients received thrombolysis post procedure. The study measured hemodynamic parameters and physical clot characteristics and did not measure long-term outcomes.[164] Given the available data, in high-risk patients who have contraindications to thrombolysis, surgical thrombectomy is the preferred alternative and more data are needed before catheter directed therapies can be recommended.

INTERMEDIATE RISK POPULATIONS

The patient with PE that presents without evidence of shock or hypotension may benefit from additional risk assessment. Several markers of poor outcome have been identified. Broadly, they include markers of right ventricular dysfunction and markers of myocardial injury (Table 3).

Use of markers of right ventricular strain and myocardial injury assist in the identification of patients who, although they may not demonstrate hemodynamic instability, may be at increased (intermediate) risk for mortality. The current American College of Chest Physicians guidelines recommend a case by case assessment of these intermediate risk patients in order to identify those who may benefit from thrombolysis despite absence of shock or hypotension.[159] Regardless, this population represents a group of patients that warrant close attention.

LOW RISK POPULATIONS

Patients found to have PE who lack evidence of shock, hypotension, right ventricular dysfunction or myocardial injury represent a population at low risk for mortality. These patients may be candidates for early discharge or possibly even home therapy as long as appropriate anticoagulation strategies are employed.

ANTICOAGULATION THERAPY

Introduction

The main aim of VTE therapy is to prevent extension of thrombosis and embolization to the lungs. Other long-term goals include reduction in the incidence of recurrent VTE, prevention of post-thrombotic syndrome and avoidance of pulmonary hypertension.[165] Anticoagulants have been the mainstay of VTE therapy since Barritt and Jordan demonstrated the efficacy of heparin and warfarin in reducing morbidity and mortality in patients with acute PE.[152] Since then, a vast array of drugs have emerged, including low molecular weight heparin (LMWH), direct thrombin inhibitors and factor Xa inhibitors.

When looking at agents for anticoagulation an understanding of the coagulation cascade needs to be achieved. There are two pathways of the coagulation cascade: (1) the contact activation pathway (intrinsic pathway) and (2) the tissue factor pathway (extrinsic pathway).[166] These two pathways meet to form the final common pathway.

Parenteral Anticoagulants

Heparins: First discovered in 1916, unfractionated heparin (UFH) exerts its anticoagulant effect by binding to antithrombin.[167] The resulting heparin-antithrombin complex inhibits the activity of factor Xa and thrombin. Only one-third of the molecules of UFH have the required sequence for binding to antithrombin.[168] UFH also contains molecules that bind to other plasma proteins that are present in variable amounts in each individual. Thus UFH has an unpredictable effect in different people.[165] UFH is metabolized by the liver and has side effects of bleeding, heparin-induced thrombocytopenia (HIT) and

TABLE 4

Unfractionated heparin. Different routes and dosing administration

Route	*Weight-based*	*Non-weight-based*
IV	80 units/kg bolus + 18 units/kg per hour infusion	5,000 units bolus + 32,000 units/day infusion
SQ	333 units/kg bolus + 250 units/kg twice daily	5,000 units bolus + the weight based daily dose

osteoporosis.[165] When used to treat VTE, for example, different routes and dosing administration can be used (Table 4).[169-172] Frequent monitoring of the activated partial thromboplastin time (aPTT) to ensure that a steady therapeutic level of anticoagulation is achieved.[169-171]

To date, there have been no randomized clinical trials comparing the effectiveness of these two regimens; however, the literature is clear that the goal for dosing UFH is either to use a weight-based nomogram or non-weight-based approach with an appropriate infusion rate in order to achieve a therapeutic aPTT within 24 hours. These approaches have reduced the incidence of recurrent venous thromboembolic disease.[173]

The activity of heparin is measured by the degree of inhibition of activated factor X (Xa) which can be monitored using the aPTT with a therapeutic range being 1.5–2.5 times the normal (or 0.3–0.7 antifactor Xa units/ml).[174,175] As with warfarin, the dose of heparin is adjusted based on the institution's nomogram or dose adjustment protocol. The therapeutic aPTT is dependent on the reagent used during testing as they do vary.[176]

Fractionated heparin, also known as LMWH, is formed by enzymatic cleavage of UFH. LMWH retains the ability to inhibit factor Xa and thrombin, but its smaller size decreases nonspecific binding to other plasma proteins. Compared to UFH, LMWH has increased bioavailability, longer half-life and a more predictable dose response. In addition, LMWH is associated with a lower incidence of HIT, potentially lower risk of bleeding and lower risk of osteoporosis.[165] It has a dose dependent renal clearance, which needs to be taken into consideration in patients with renal insufficiency. Other considerations include dosing difficulties in obese patients and problems with reversibility in cases of bleeding. There are currently eight LMWH available in the market worldwide, each with its own molecular weight and dosing regimen. There is insufficient evidence to differentiate amongst these LMWHs based on efficacy and safety.[165] LMWHs do not require monitoring to ensure therapeutic anticoagulation. The utility of antifactor Xa assay is controversial since its correlation with anticoagulant effect and bleeding risk is unclear.[177]

Early studies demonstrated that LMWH had better efficacy and safety when compared to UFH, particularly for reducing mortality at 3–6 month follow-up.[178] The more recent evidence has shown a lower magnitude of benefit of LMWH over UFH.[179] The majority of the evidence is with respect to therapy of DVT rather than PE. However a recent meta-analysis provided evidence that LMWH is safe and efficacious in patients with non-critical PE.[180] Cost-effectiveness analyses have shown a benefit or at least equivalency for LMWH in comparison to UFH regardless of treatment setting.[181]

The low molecular weight heparins available in the United States are enoxaparin (Lovenox®), dalteparin (Fragmin®) and tinzaparin (Innohep®). Since their Food and Drug Administration (FDA) indications vary, they will be listed separately. Enoxaparin is indicated in the prophylaxis of VTE, as well as in the treatment of VTE and ST segment elevation MI. The medication is also used in patients with unstable angina and non-ST elevation MI for prevention of ischemic embolisms during treatment of these disease states.[182] Dalteparin is not indicated in the treatment of VTE unless the patient has cancer and a history of blood clots;[183] however, it can be used for prophylaxis similar to enoxaparin.[184] Tinzaparin is only indicated for therapy in patients with VTE.[185]

Contraindications to using LMWHs as a class include hemorrhage, HIT, when regional anesthesia is needed, and allergies to the drug, heparin or pork.[182,184,185] If a patient is allergic to sulfites or benzyl alcohol, tinzaparin therapy is contraindicated.[185]

Enoxaparin is used most often in the hospital setting, and dosing is listed below. For specific dosing on dalteparin and tinzaparin, please refer to their package insert.[184,185] Treatment dosing for enoxaparin is 1 mg/kg twice daily or 1.5 mg/kg daily. In patients with creatinine clearance (CrCl) of less than or equal to 30 ml/min, dosing is decreased to 1 mg/kg daily. Prophylactic dosing for surgeries is normally 40 mg daily or 30 mg twice daily. In renal dysfunction, the dose is decreased to 30 mg daily.[182]

The low molecular weight heparin monitoring is usually not performed; however, high-risk patients can be monitored using antifactor Xa levels. High-risk patients include those who have received heparin within the past 6 months and women who are pregnant.[174]

Fondaparinux is an indirect factor Xa inhibitor. It has a linear pharmacokinetic profile, allowing for weight based daily dosing, negating the need for continuous monitoring.[186] It does not bind to platelet factor 4 and theoretically does not cause thrombocytopenia and it has renal clearance. In two large, multicenter clinical trials, fondaparinux was as effective and safe as UFH for the treatment of PE, and as effective and safe as enoxaparin for the treatment of DVT.[187,188] The drug is also used for prophylaxis of VTE and is contraindicated in patients with CrCl less than 30 ml/min, hemorrhage, bacterial endocarditis, thrombocytopenia, allergy to the drug itself and for prophylaxis in patients weighing less than 50 kg.[189] Fondaparinux is dosed based on body weight for treatment and at a fixed dose for prophylaxis (Table 5).

As with LMWHs, Fondaparinux is customarily not monitored.[174]

Direct thrombin inhibitors: Direct thrombin inhibitors also have the advantages of predictable dose response and reduced

TABLE 5

Fondaparinux. Dosing administration

	Weight	*Dose*
Prophylaxis	2.5 mg	2.5 mg
Treatment	< 50 kg 50–100 kg > 100 kg	5 mg 7.5 mg 10 mg

incidence of thrombocytopenia. However they do not have an antidote for cases of severe bleeding. Argatroban and lepirudin are two intravenous direct thrombin inhibitors that are FDA approved for the prevention and/or treatment of VTE in patients with HIT.[190]

Ximelagatran is an oral direct thrombin inhibitor that has been withdrawn from the market due to an increased risk of hepatic toxicity.

These medications bind directly to thrombin to inhibit the activation of fibrin. Lepirudin and argatroban are indicated for patients with HIT.[190-192] Bivalirudin is indicated for patients undergoing percutaneous transluminal coronary angioplasty (PTCA) who have unstable angina.[193] Contraindications to the direct thrombin inhibitors include hypersensitivity to the products[191-193] and major bleeding. Antidotes are not available for the direct thrombin inhibitors.[194]

Lepirudin is dosed 0.4 mg/kg body weight (up to 110 kg) IV as a bolus dose, then 0.15 mg/kg body weight/hour IV continuous infusion for 2–10 days.[191] If a patient's body weight exceeds 110 kg, the maximum initial dose should be 44 mg, and the maximum infusion dose should be 16.5 mg/h. The dose of lepirudin does need to be renally adjusted starting at a CrCl of 60 ml/min. Monitoring of lepirudin is done with the aPTT. A baseline value should be obtained, and lepirudin should not be started if the baseline aPTT is more than 2.5 times the normal aPTT control. Target range for aPTT during lepirudin treatment should be 1.5–2.5 times the normal aPTT control, with the value taken 4 hours after the initial dose of lepirudin.[191]

Argatroban is dosed initially at 2 mcg/kg/min as a continuous infusion. The dose may be adjusted up to 10 mcg/kg/min to an aPTT of 1.5–3 times the baseline.[192] The aPTT levels need to be drawn 1–3 hours after the dose is given. No dosage adjustment is necessary in renal impairment. However adjustments are needed in hepatic impairment to 0.5 mcg/kg/min as an initial dose, and then adjust according to the aPTT.[192]

Initial dose of bivalirudin is an IV bolus of 0.75 mg/kg, followed with an infusion of 1.75 mg/kg/h during the PTCA.[193] An activated clotting time (ACT) should be drawn 5 minutes after the bolus, and an extra 0.3 mg/kg should be given to achieve the target ACT of 300–350 seconds if needed. Dose adjustments are necessary in renal impairment. In patients with CrCl of 30–59 ml/min, the infusion rate should be 1.75 mg/kg/h, CrCl less than 30 ml/min, reduce rate to 1 mg/kg/h.[193]

Oral agents—vitamin K antagonists-warfarin: While there are many ongoing studies to find a new anticoagulant medication, warfarin remains the only oral anticoagulant available on the market in the United States. Indications for warfarin include VTE, atrial fibrillation, mechanical and bioprosthetic heart valve replacement, MI and hypercoagulable conditions.[194,195]

Vitamin K antagonists (VKAs) exert their anticoagulation effect by inhibiting the enzyme vitamin K oxide reductase blocking the conversion of vitamin K epoxide to vitamin K. This inhibits the carboxylation and activation of the vitamin K dependent coagulation factors II, VII, IX, X and protein C and S.[196] Warfarin is a racemic mixture of two active isomers—the R and S enantiomers. Of the two enantiomers, the S enantiomer is 2.7–3.8 times more potent than the R enantiomer. The S enantiomer is metabolized by the CYP2C9 enzyme of the cytochrome P450 system whereas the R enantiomer is metabolized by CYP 1A2 and 3A4.[196] Therefore, medications that are metabolized through the CYP2C9 enzyme are more likely to affect the metabolism of warfarin, including amiodarone, azole antifungals, metronidazole and sulfamethoxazole-trimethoprim.

TABLE 6

Warfarin initial dosing protocol

INR	*Day 1*	*Day 2*	*Day 3*	*Day 4*	*Day 5*
< 1.5	5 mg	5 mg	7.5 mg	10 mg	10 mg
1.5–1.99	2.5 mg	2.5 mg	5 mg	7.5 mg	7.5 mg
2–2.49		1 mg	2.5 mg	5 mg	5 mg
2.5–2.9		0 mg	1 mg	2.5 mg	2.5 mg
3–3.5		0 mg	0 mg	1 mg	1 mg
> 3.5		0 mg	0 mg	0 mg	0 mg

Patients should be advised to monitor their diet when initiating warfarin due to the adverse effect it can have on the patient's therapy.[197]

Warfarin dosing is highly individualized and must take into account comorbid disease states. The recommended initiation dose for warfarin is 5 mg, which was shown to achieve therapeutic international normalized ratio (INR) as fast as the 10 mg loading dose.[198] This was contested in a recent outpatient study which demonstrated faster achievement of target INR with a 10 mg loading dose;[199] however, an increased rates of bleeding associated with the higher loading dose was found. A lower starting dose of 2–3 mg daily may be used in patients with disease states or illnesses causing an increased response to warfarin, including the elderly population.[196-200] Table 6 is an example of a warfarin dose adjustment protocol used in our facility for initiation of warfarin.[197]

In patients at high risk for developing another event and in need of immediate anticoagulation, heparin/LMWH is used alongside warfarin for at least 4–5 days and pending two therapeutic INR levels. The therapeutic INR range for most indications continues to be 2–3 (target 2.5).[194,196,201]

All the above mentioned potential complications that can be seen with the long-term use of warfarin can be significantly reduced when monitoring and management is performed by an anticoagulation clinic staffed with certified anticoagulation providers.[202-206]

Inferior Vena Cava Filters

Inferior vena cava filters are indicated for patients for whom anticoagulation is contraindicated, those who experience recurrent PE despite adequate anticoagulation, and possibly those with patients with PE who have poor cardiopulmonary reserve.[207] Vena cava interruption has been used in the treatment of DVT to prevent PE since the early 1970s. However there has been only one randomized clinical trial evaluating the efficacy of IVC filters to prevent recurrent VTE.[208] Patients in the IVC filter group had significantly fewer total PE after 12 days and fewer symptomatic pulmonary emboli at 8 years. However the IVC filter group also had significantly higher rates of DVT. There was no difference in mortality between the groups. Both groups received early anticoagulation, so the study

did not provide information about effectiveness of filters in patients in whom anticoagulation is contraindicated. Retrievable IVC filters are approved as an alternative for patients with temporary contraindication to anticoagulation, but data for these are limited.[209]

New Anticoagulants

Current medications on the market for anticoagulation have many drawbacks. VKAs require intensive monitoring and have multiple drug interactions. Heparin usually requires admission to the hospital, it is administered parenterally, and there is the possibility for the development of HIT. LMWHs are also parenterally administered, have the potential for developing HIT, and cost considerably more than the other alternatives. Several new medications are being studied to attempt to alleviate some of the current drawbacks.

As mentioned earlier, there are two pathways of the coagulation cascade: (1) the contact activation pathway and (2) the tissue factor pathway.[166] These two pathways meet to form the final common pathway. The first step in this pathway to initiate coagulation is the binding of tissue factor to factor VII which activates factor VIIa/tissue factor complex. New agents that are being studied target this step to inhibit the initiation of coagulation, including tifacogin and nematode anticoagulant protein c2 (NAPc2) which are both parenteral medications.[174] The propagation step of the coagulation cascade is where the final common pathway begins at factor Xa.[166] With inhibition of factor Xa, propagation is terminated. This can be done indirectly by binding to the plasma cofactors (antithrombin) or directly by binding to the enzyme. This can also be achieved by inhibiting factor IXa, thus preventing the activation of X to Xa. The indirect factor Xa inhibitors in development include idraparinux, SSR12517E and SR123781A, all of which are parenteral.[174] The direct factor Xa inhibitors still under development are otamixaban, apixaban, rivaroxaban, LY517717, YM150, DU176b and PRT054021.[194] Of these, otamixaban is parenteral, and the rest are oral medications. The only factor IXa inhibitor under development is RB006, which is IV administration. Another target in the coagulation cascade is the final step, the formation of fibrin. Thrombin converts fibrinogen to fibrin and activates platelets.[166] By inhibiting thrombin, the final step of the coagulation cascade is terminated. Again, this inhibition can be done indirectly or directly. The indirect thrombin inhibitors act on the heparin cofactor II. There was an oral indirect thrombin inhibitor in development, odiparcil.[194] However its development was stopped at phase II. Of the direct thrombin inhibitors being developed, two are parenteral, flovagatran and pegmusirudin.[194] The other is oral, dabigatran etexilate.[194] Factor Va is activated by thrombin which then helps to convert more prothrombin into thrombin. Activated protein C degrades factor Va to act as a natural anticoagulant.[166] Two of the new medications being developed act on factor Va. Drotrecogin alfa is a recombinant form of activated protein C which will degrade factor Va, and ART 123 converts thrombin into an activator of protein C.[194]

COR PULMONALE

Cor pulmonale or "pulmonary heart disease" is characterized by right heart dysfunction secondary to underlying lung disease. It may manifest as right ventricular hypertrophy or overt dilation and systolic failure.[210] All forms of cor pulmonale share the unifying feature of pulmonary hypertension and are classified in group 3 of the revised classification of pulmonary hypertension—pulmonary hypertension owing to lung disease and/or hypoxia.[211] Disease entities included in this group include such diverse states as chronic obstructive pulmonary disease (COPD), interstitial lung disease, sleep disordered breathing and diseases of alveolar hypoventilation.

The increased load on the RV is driven by hypoxic vasoconstriction, acidemia,[212] hypercarbia,[213] structural changes to the vascular bed including scarring and destruction, elevated cardiac output and elevated blood viscosity. Prolonged hypoxia also mediates vascular remodeling by interacting with the nitric oxide and endothelin pathways.[214] The PVR rises and the RV, which is a low pressure pump, develops pressure overload.

SIGNS AND SYMPTOMS

The initial symptom of cor pulmonale is dyspnea. If untreated the process progresses to overt right heart failure resulting in bilateral lower extremity edema, chest pain, presyncope and syncope. Advanced COPD has been associated with edema in the absence of right heart failure, so further investigation should be considered in the clinically stable COPD patient with leg swelling.[215]

STUDIES

Multiple classic electrocardiographic findings have been described, including a rightward p wave axis, the $S_1S_2S_3$ pattern, the S_1Q_3 pattern, right bundle branch block and evidence of RV hypertrophy.[216] These findings are helpful when present, but are often absent. Frequently, in patients with cor pulmonale associated with COPD, the hyperinflated lungs will actually attenuate the ECG, resulting in a low voltage pattern.

The chest film in cor pulmonale will demonstrate large central pulmonary arteries, obliteration of the retrosternal air space and right-sided chamber enlargement. Depending on the underlying process, lung fields may show stigmata of lung disease, including the hyper-expansion noted in COPD and interstitial changes characteristic of interstitial lung disease. Another important feature to be mindful in patients with cor pulmonale is the absence of evidence of left-sided heart failure, including diffuse vascular congestion, cephalization, Kerley B lines, significant pleural effusions and left ventricular enlargement.

PULMONARY FUNCTION TESTING

Any patient suspected of having cor pulmonale should undergo pulmonary function testing to assess the severity of the underlying lung disease. It has been demonstrated that as many as 40% of patients with COPD who have an forced expiratory volume in one second (FEV1) of less than 1 liter have evidence of cor pulmonale.[217] Patients with interstitial lung disease who have reduction of the forced vital capacity (FVC) to less than 50% of predicted may also be at significant risk. Conversely, patients suspected of having cor pulmonale secondary to obstructive or restrictive disease that have normal pulmonary function testing should be assessed for other causes of their pulmonary hypertension.

The combination of echocardiographic evidence of right ventricular hypertrophy or dysfunction and severe COPD or interstitial lung disease is consistent with cor pulmonale. The echo can also be used to estimate the right ventricular systolic pressure and thus the severity of the pulmonary hypertension. Caution is advised, however. In a study pairing echocardiographic assessment of pulmonary hypertension with invasive assessment within 1 hour, wide variation was documented.[218] In another study, comparing echocardiogram to right heart catheterization within 72 hours in a cohort of patients being assessed for lung transplantation, normal pressures were measured in almost 50% of cases where echocardiogram was consistent with pulmonary hypertension.[219] This information is helpful in the light of multiple available directed therapies for pulmonary arterial hypertension.

THERAPY

Direct pulmonary vasodilator therapy includes the prostacyclin analogs epoprostenol, iloprost and treprostinil; the endothelin receptor antagonists bosentan and ambrisentan and the phosphodiesterase-5 inhibitors sildenafil and tadalafil. Their efficacy in the treatment of pulmonary arterial hypertension has been proven by well-designed clinical trials and they have been approved by the FDA for use in patients with Group 1 pulmonary hypertension.[220] They have not, however, been approved for patients with Group 3 PH.[220] Multiple clinical trials are under way in this patient population. Unfortunately, preliminary data are contradictory at best.

The first study looking at these medications in patients with cor pulmonale was an open label study looking at the effect of sildenafil on walk distance in patients with idiopathic pulmonary fibrosis. The mean improvement in 6-minute walk test was 49 m.[221] Unfortunately, another randomized placebo-controlled trial failed to demonstrate significant difference in 6-minute walk when compared to placebo.[222] In a recent randomized placebo-controlled trial of bosentan in patients with interstitial lung disease secondary to systemic sclerosis, no improvement in exercise tolerance was found in the treatment verses placebo arm.[223] In one study of the calcium channel blocker nifedipine, PVR was reduced at the cost of ventilation and perfusion inequalities that resulted in hypoxemia.[224] This is a theoretical risk associated with treatment with vasodilators in patients with structural lung disease.

The issue is further complicated by the fact that a small proportion of patients with obstructive or restrictive lung disease demonstrate evidence of severe pulmonary hypertension in the face of mild abnormalities in spirometry. These patients frequently demonstrate severely reduced diffusion capacity as well.[225] As stated, echocardiography can be misleading in this population. If concern exists for pulmonary hypertension "out of proportion" to underlying disease, right heart catheterization is required to accurately measure pressures. This is also required to rule out a contribution of left-sided dysfunction and provides clearer prognostic information. The available data do not support treatment of these patients with the therapies outlined above. If therapy is pursued, it should be in the context of a clinical trial at a pulmonary hypertension center.[226]

Oxygen Therapy

Oxygen is the only therapy that has been proven to treat cor pulmonale in patients suffering from COPD. The nocturnal oxygen therapy trial (NOTT) and the British Medical Council long-term domicillary oxygen treatment trial actually demonstrated hemodynamic benefit of therapy. The NOTT trial demonstrated reductions in resting PVR in patients treated with 2 liters of oxygen for at least 15 hours a day. An improvement in survival was also noted, but the mechanism is unclear.[227] The British study demonstrated slower rise in the PVR in patients treated with oxygen.[228] Patients with interstitial lung disease who demonstrate oxygen desaturation with activity have a poor prognosis.[229] Unfortunately no current evidence supports a survival benefit in patients with ILD receiving supplemental oxygen.[230]

Therapy for Acute Decompensation

As the only vasodilator shown to have benefit in patients with cor pulmonale, oxygen is the cornerstone of therapy for acute decompensation. Maintenance of oxygen saturation at 90% promotes pulmonary vasodilation, reducing right ventricular afterload, thus improving cardiac output and inducing a diuretic effect. Care must be taken to monitor for worsening of coexisting hypercapnia. If elevated PCO_2 is detected, ventilatory support may be indicated.

Diuretic therapy should be utilized with care and close monitoring of fluid and electrolyte status. Treatment of bronchospasm with beta 2 agonists and anticholinergics in combination with noninvasive ventilation may help alleviate airflow obstruction.[231] Antimicrobial therapy should also be considered in patients in acute exacerbation of COPD with cor pulmonale.[231] Additionally, corticosteroid therapy is recommended for this patient population.[231]

Long-Term Therapy

Continuous oxygen therapy treats the persistent alveolar hypoxia that is thought to be the triggering mechanism in cor pulmonale. Therapy may reduce chronic elevation of pulmonary pressures despite progression of airflow limitation resulting in improvement in right ventricular function, quality of life and mortality. Patients with evidence of cor pulmonale and oxygen saturation less than 89% or PO_2 less than 59 mm Hg qualify for supplementation, but improvement with therapy to at least 90% (60 mm Hg) must be documented.[231]

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Section 12

RELEVANT ISSUES IN CLINICAL CARDIOLOGY

Chapter 102

Noncardiac Surgery in Cardiac Patients

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Chapter Outline

- Preoperative Cardiac Risk Assessment
  - General Risk Stratification
  - Ischemic Heart Disease
  - Hypertension
  - Heart Failure
  - Valvular Heart Disease
  - Congenital Heart Disease
  - Arrhythmias
- Preoperative Diagnostic Testing
  - 12-Lead Resting Electrocardiography
  - Ambulatory Electrocardiography
  - Heart Rate Variability
  - Assessment of Left Ventricular Function
  - Noninvasive Studies for Myocardial Ischemia
  - Coronary Angiography
  - Cardiac Biomarkers
- Preoperative Risk Mitigation Strategies
  - Pharmacologic Interventions
  - Nonpharmacologic and Other Interventions
- Intraoperative Management
  - Choice of Anesthesia
  - Hemodynamic Monitoring
- Management of Patients with Implanted Electronic Devices
- Postoperative Management
  - Pulmonary Artery Catheters
  - Surveillance for Ischemia
  - Postoperative Arrhythmias
  - Pain Management
- Appendix

INTRODUCTION

Patients with cardiovascular disease or major risk factors incur a significant risk of adverse cardiac events during major noncardiac surgery. Almost 32 million noncardiac, nonobstetric surgical procedures are performed annually in the United States and most of these procedures are performed on patients aged 65 or older.[1] The elderly population in the United States is expected to double in the coming years[2] and the number of major operative procedures performed on older persons could potentially increase from the current 6 million to almost 12 million per year.[3] Since the prevalence of cardiovascular disease, especially coronary heart disease (CHD), increases with age, the development of perioperative cardiac complications may also increase substantially. Adverse perioperative cardiac events, mainly nonfatal myocardial infarction (MI) and cardiac death, usually occur in patients with known or occult CHD, left ventricular (LV) dysfunction or severe valvular heart disease (VHD) who are undergoing surgical procedures that produce prolonged hemodynamic aberrations and cardiac stress response. Perioperative cardiac complications have implications not only for the immediate postoperative period but also influence long-term patient outcomes. Therefore the identification of patients at the highest risk for perioperative adverse cardiac events and the development of strategies to reduce such events are important public health issues. Over the past 30 years a large number of studies have been conducted addressing these issues and the knowledge base has been summarized in a series of papers and clinical guidelines, which also provide recommendations for the perioperative management of cardiac patients. In this chapter, the authors have summarized the available information with emphasis placed on evidence derived from randomized controlled studies and discussed the current best practices. The most important concept that has become evident in this discussion is that current evidence shows that preoperative interventions, designed simply to reduce perioperative risk, are rarely necessary or useful unless they are indicated irrespective of the preoperative status. Relevant American College of Cardiology/American Heart Association (ACC/AHA)[4] and, in some instances, European Society of Cardiology (ESC)[5] guideline recommendations have been discussed. The latest ACC/AHA guideline recommendations have also been listed in tabular form in the Appendix.

PREOPERATIVE CARDIAC RISK ASSESSMENT

The key element of perioperative management of patients with cardiac disease undergoing noncardiac surgery is a thorough preoperative assessment of the risk of cardiac events. This process involves two equally important elements: (1) factors related to the patient and (2) factors related to the specific surgery being performed.

Although patient related factors are an important tool in assessing risk, a practitioner seeing a patient prior to surgery must first assess the urgency of the surgery. It is important to remember that emergency surgery should not be delayed for preoperative risk stratification. Once it is clear that surgery can be delayed, the patient should be examined closely to evaluate the perioperative risk, beginning with a thorough history and physical examination. Patient related risk factors—those elements in the medical history of a patient that predict adverse cardiac events—have been the focus of close study for almost forty years. During this time, much has been learned about the specific conditions that predispose a particular patient to perioperative adverse cardiac events.

The first widely accepted clinical risk score was proposed by Goldman et al. in 1977[6] and modified by Detsky et al. in 1986.[7] These landmark studies were the first to identify specific clinical factors that predicted perioperative risk. Since then, the original risk index has been modified and validated several times. In 1999, the Revised Cardiac Risk Index (RCRI) was published by Lee and coworkers who further modified the clinical risk predictors.[8] The RCRI has been widely accepted, and is used in the current ACC/AHA guidelines[4] as the basis for the preoperative clinical assessment of cardiac risk.

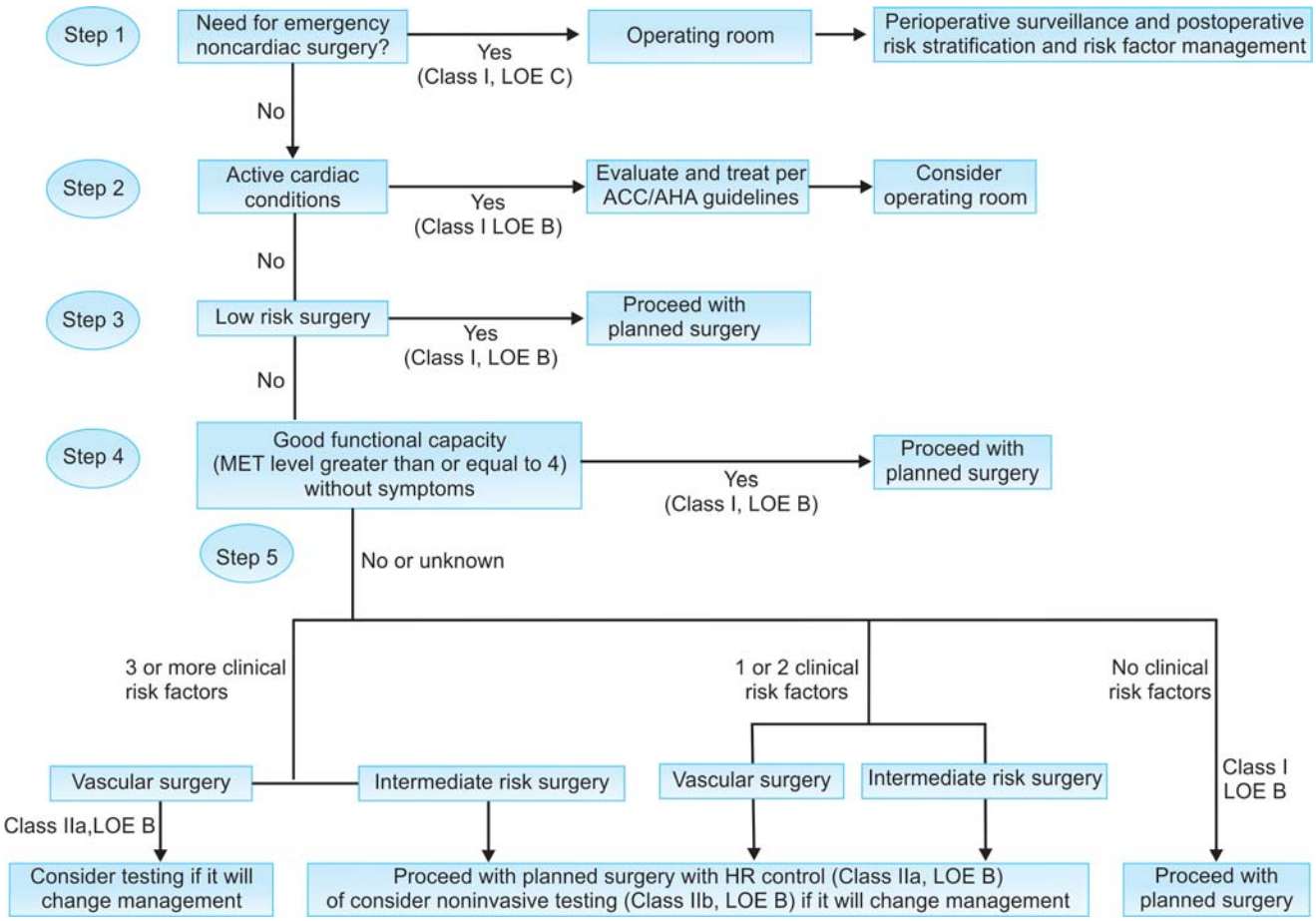
GENERAL RISK STRATIFICATION

For the practitioner who is asked to see a patient prior to surgery, the ACC/AHA guidelines provide a useful framework. By following a simple, stepwise approach to the patient based mainly on history and physical examination, one can quickly assess the risk of adverse cardiac events during the perioperative period (Flow chart 1).

The first step in this process is to decide whether the patient is in the midst of an "active cardiac condition" which places him or her in the highest perioperative risk category (Table 1). It is extremely important to identify such patients, as their risk for further ischemic injury with the stress of surgery is prohibitive. Strong consideration should be given to delaying any nonemergent noncardiac surgery until all such active cardiac conditions are thoroughly evaluated and treated.

The next step is to evaluate the medical history to identify those factors that increase risk and to ascertain the patient's functional status. For this task the RCRI, which is based on a multivariate analysis and has been validated by several studies,[8,9] is commonly used. The six RCRI variables are important risk predictors and are listed in Table 1 as intermediate risk predictors. By assigning one point to each of these variables, a

FLOW CHART 1: Cardiac evaluation and care algorithm for noncardiac surgery-based on active clinical conditions (high-risk predictors), known cardiovascular disease, or cardiac risk factors for patients aged more than or equal to 50 years



(Abbreviations: HR: Heart rate; LOE: Level of evidence; MET: Metabolic equivalent. (*Source:* Fleisher LA, Beckman JA, Brown KA, et al. 2009 ACCF/AHA Focused Update on Perioperative Beta Blockade Incorporated into the ACC/AHA 2007 Guidelines on Perioperative Cardiovascular Evaluation and Care for Noncardiac Surgery, J Am Coll Cardiol. 2009;54:e13-118; originally published online Nov 2, 2009. With permission from the American College of Cardiology)

TABLE 1

Perioperative risk predictors

- *High risk predictors (active cardiac conditions)*
  Acute coronary syndromes*
  Decompensated heart failure
  Significant arrhythmias**
  Severe valvular disease
- *Intermediate risk predictors (RCRI variables)*
  History of ischemic heart disease
  History of compensated or prior heart failure
  History of cerebrovascular disease
  Diabetes mellitus
  Renal insufficiency (serum creatinine > 2 mg/dL)
- *Minor risk predictors (low risk)*
  Age less than or equal to 70 years
  Abnormal ECG
  Rhythm other than sinus
  Uncontrolled hypertension

*Documented myocardial infarction (MI) within 7 days, any MI within 30 days with evidence of residual ischemic risk by a noninvasive study, high-risk unstable angina
**High-grade AV block, sustained ventricular tachyarrhythmias
(*Source:* ACC/AHA Guideline text (4) and reproduced from Gregoratos G. Current guideline-based preoperative evaluation provides the best management of patients undergoing noncardiac surgery. Circulation. 2008;117:3134-44)

risk score is created. Patients with no risk factors are considered low risk. Patients with 1–2 risk factors are at intermediate risk and those with 3 or more risk factors are considered at high risk. Stratifying patients according to the RCRI score provides a simple way to estimate an individual's perioperative risk and is used extensively in the ACC/AHA and other guidelines. The type of surgery is addressed independently of the other risk variables in the ACC/AHA risk assessment and management algorithm (Flow chart 1).

An important determinant of overall perioperative risk is the patient's functional capacity as estimated by Metabolic Equivalents (METs). The MET is a standardized unit of function that defines the energy cost of physical activities as multiples of the resting metabolic rate based on the resting oxygen consumption of a 40-year-old 70 kg man in one minute (3.5 ml/kg/min). For example, 2 METs are expended in walking very slowly (1–2 mph) on a level surface whereas walking very briskly at 4 miles an hour is equivalent to 5 METs. The patient's self-reported exercise tolerance has been used as a guide to determine their functional status using any one of several scales. Patients who can walk up one flight of stairs or briskly two blocks without stopping or symptoms have a functional status of at least 4 METs. One study has shown that the ability to perform physical activity equivalent to 4 METs is associated with a decreased risk of perioperative MI. In this study, the ability to walk up 2 flights of stairs and 4 blocks without symptoms was associated with an approximately 50% reduction in perioperative cardiovascular complications[10] compared to patients with a lesser exercise capacity. At times, a more detailed assessment of function is required and for this a validated estimation of activity, such as the Duke Activity Scale Index, can be used.

Once a patient is assigned to a clinical risk category, the type of surgery should be considered. All surgical procedures elicit a stress response to a greater or lesser degree. The stress response is initiated by tissue injury and mediated by neuroendocrine factors that may induce tachycardia and hypertension which in turn lead to increased myocardial oxygen requirements. Adding to the stress of surgery are the large fluid shifts that are generated during major surgical procedures. Major surgery also causes changes in the balance between prothrombotic and fibrinolytic factors which may produce a hypercoagulable state and promote coronary thrombosis. Preoperative risk assessment should therefore include a rough estimate of the severity of the stress response that the anticipated surgery will produce. Surgical procedures can be divided into high risk, intermediate-risk or low-risk surgery according to the reported incidence of perioperative cardiac complications (Table 2). As noted in the table, low-risk surgical procedures do not generally require extensive preoperative testing and evaluation. However, there are exceptions. Laparoscopic surgery is currently being performed with increasing frequency, in preference to open abdominal surgery, in patients with heart disease. It has the advantage of producing less tissue injury, less postoperative pain and less fluid shifts due to postoperative ileus. However, the required pneumoperitoneum and increased intra-abdominal pressure may cause decreased cardiac output and increased systemic vascular resistance which impose a significant load on the heart especially in patients with impaired LV systolic function. Therefore, laparoscopic surgery should be considered an intermediate risk surgery and patients should be evaluated accordingly. This is especially true for patients undergoing such surgery for morbid obesity.[4]

Thus, initial risk stratification prior to noncardiac surgery is based upon the stepwise integration of all elements mentioned above: urgency and type of surgery; presence or absence of an active cardiac condition; the patient's functional status and the number of the patient's clinical risk predictors. These simple steps will provide adequate initial clinical risk stratification for the majority of patients undergoing surgery and point toward further steps to be taken to minimize perioperative risk. Specific

TABLE 2

Cardiac risk* of noncardiac surgical procedures

Risk stratification	*Procedure examples*
Vascular (reported cardiac risk > 5%)	Aortic and other major vascular surgery Peripheral vascular surgery
Intermediate (reported cardiac risk 1–5%)	Intraperitoneal and intrathoracic surgery Carotid endarterectomy Head and neck surgery Orthopedic surgery Prostate surgery
Low (reported cardiac risk < 1%)†	Endoscopic procedures Superficial procedures Cataract surgery Breast surgery Ambulatory surgery

*Combined risk of cardiac death and nonfatal MI.
†These procedures do not generally require further preoperative cardiac testing.
(*Source:* Fleisher et al.[5])

cardiac pathologies that add to the complexity of risk assessment and require additional evaluation prior to surgery are discussed below.

ISCHEMIC HEART DISEASE

Patients with known ischemic heart disease are at considerable risk for developing an adverse cardiac event in the perioperative period. Evaluation of these patients should include an assessment of symptoms, the patient's ischemic threshold, amount of myocardium at jeopardy (if known), LV function and whether the patient is on optimal medical therapy. Even in asymptomatic patients with CHD, the metabolic demands of surgery can increase myocardial oxygen demand and induce ischemia. Although absolute prediction of how much a particular ischemic burden affects the risk of a perioperative event is difficult, there is good evidence to suggest that the magnitude of the risk is dependent on several clinical factors, including any recent MI, current or recent ischemic symptoms, and functional status. Estimation of functional status is especially important in patients with CHD because if their functional capacity is limited to less than four METs, either due to angina, dyspnea or noncardiac limitation of activity, consideration should be given to further testing.

Several studies, including Goldman's original analysis in 1977, have shown that increasing age is associated with increased risk.[6,11,12] Although age is not an independent risk variable in the RCRI, the relation of advancing age to CHD must be kept in mind even if symptoms of CHD are absent.

HYPERTENSION

There is some controversy regarding whether isolated hypertension is an independent risk factor of perioperative complications. The earliest studies that examined this question in the 1970s suggested that hypertension (defined as a diastolic BP >120 mm Hg) was associated with increased intraoperative arrhythmias and perioperative ischemia.[13] Other more recent studies have suggested that pre-existing hypertension independently predicts 30 days cardiovascular death after surgery.[14] Still, the two largest studies to date that have examined risk factors for cardiac events during noncardiac surgery have not found hypertension to be an independent predictor of cardiovascular events in the perioperative setting.[6,8] What is known from the general literature on hypertension is that it does increase the risk of ischemic disease (both CHD and stroke).[15,16] Additionally, it can worsen the ischemic burden in the setting of stress situations such as surgery. If patients have Stage I or II hypertension that is well controlled on medications, their risk is not significantly elevated compared to those without hypertension, and these patients can proceed to surgery. On the other hand, patients with Stage III hypertension (SBP >180) and those who have evidence of end-organ damage have an increased risk of intraoperative blood pressure lability and possibly of perioperative complications. Therefore, it is advisable that in these cases, hypertension be thoroughly evaluated and treated prior to elective noncardiac surgery. Occasionally, a new diagnosis of hypertension is made during preoperative assessment. If so, the usual evaluation for secondary causes of hypertension and standard treatment guidelines should be applied. However, the decision to delay surgery for new hypertension should be taken cautiously; since a "new diagnosis" may be simply preoperative "white-coat hypertension".[15]

HEART FAILURE

Clinical evidence of heart failure (HF) has been identified as a predictor of poor clinical outcomes in the surgical setting in every analysis that has examined the question. Goldman et al. included clinical signs of HF and the presence of an S3 as predictors of poor outcomes.[6] The RCRI includes HF as an independent predictor of perioperative complications.[8] Additionally, decompensated HF is considered an "active cardiac condition" that requires treatment prior to surgery.[4] As a result, any patient that carries a diagnosis of HF, even compensated, is thought to be at increased risk for perioperative complications. Due to the clear link between HF and surgical risk, a careful history and physical examination should be undertaken prior to surgery in any patient for whom HF is a potential diagnosis. Decreased exercise tolerance due to shortness of breath, paroxysmal nocturnal dyspnea or new orthopnea, elevation of the jugular venous pressure (JVP), peripheral edema, or the presence of an S3 should prompt further evaluation prior to surgery to either confirm or rule out a diagnosis of HF. For patients with documented HF, every effort should be made to optimize their medical regimen preoperatively and continue it with as little interruption as possible.

VALVULAR HEART DISEASE

Valvular disease includes a broad and varied set of pathologies, and each disease process affects surgical risk in different ways. Murmurs and valve-related symptoms must be identified during the initial patient assessment. Transthoracic echocardiography (TTE) will be frequently required to assess the severity of the valvular lesion. In general, severe valvular obstructive lesions carry the highest risk of perioperative cardiac complications whereas regurgitant lesions are better tolerated.

Aortic Stenosis

Stenosis of the aortic valve is the most common and most concerning of all valvular lesions for adults in the perioperative setting. Severe symptomatic aortic stenosis (AS), defined as a valve area less than 1 cm^2 with valve related symptoms, is considered an active cardiac condition that carries significant risks of cardiovascular morbidity and mortality and warrants medical optimization and surgical correction, if possible, prior to surgery. Even in asymptomatic patients with severe AS, the surgical risk of adverse cardiovascular events is as high as 31% in some studies.[17,18] For most operations, this risk is prohibitive and as such, attention should be given to surgical repair of the valve prior to noncardiac surgery. For patients that refuse or are not candidates for valve surgery, the mortality risk of noncardiac surgery is approximately 10%,[17] and this should be carefully discussed with the patient prior to proceeding. Patients with asymptomatic moderate AS can safely undergo even major

noncardiac surgery with careful control of ventricular preload and afterload.

Aortic Regurgitation

When aortic regurgitation (AR) is identified, it is important to quantify the amount of regurgitation prior to surgery. For patients with mild AR, noncardiac surgery can proceed without delay. In the case of moderate to severe AR, medical therapy should be initiated to reduce afterload and optimize volume control. Bradycardia is detrimental in patients with AR because it prolongs diastole and increases the regurgitant volume. Therefore, the use of beta blockade in this setting should be undertaken with caution if at all. It is also important to make clear to all that intra-aortic balloon counterpulsation is detrimental and contraindicated in patients with AR.

Mitral Stenosis

Patients with mild mitral stenosis (MS) tolerate surgery well. With moderate to severe MS, careful attention needs to be paid to reducing the heart rate as patients are dependent on diastolic filling time to maintain cardiac output. Beta blockers are used effectively to achieve heart rate control and may reduce the incidence of perioperative atrial fibrillation. Even asymptomatic patients with moderate to severe MS are at an increased risk of pulmonary edema and therefore volume control is essential. As always, a careful physical examination must be done to look for signs of HF prior to proceeding to surgery. Patients with MS have also an increased risk of venous thromboembolic complications—appropriate perioperative prophylaxis is necessary.

Mitral Regurgitation

For patients with mitral regurgitation (MR), the LV ejection fraction (EF) is the key factor in determining risk of perioperative events. Since the regurgitant volume is reflected in the calculated EF, even mild reductions of EF indicate decreased forward cardiac output and this should be taken into account when assessing perioperative risk. Mild to moderate MR is often well tolerated even during major high-risk surgery. However, patients with severe MR are at increased risk and may benefit from afterload reduction and diuretics preoperatively to achieve optimal hemodynamic stability. Patients with MR and depressed LVEF are more sensitive to vasodilatation that can occur during induction of anesthesia and should be watched closely. These patients should be monitored for volume overload intraoperatively to avoid development of HF.

Prosthetic Valves

Although there is no specific increase in risk associated with a well-functioning prosthetic valve, meticulous perioperative management of chronic anticoagulation is required. Transition of warfarin anticoagulation to unfractionated or low-molecular weight heparin should be carefully planned and instituted preoperatively. Additionally, antibiotic prophylaxis should be prescribed as is recommended by the AHA guidelines on endocarditis prophylaxis.[19]

CONGENITAL HEART DISEASE

It is estimated that there are more than 800,000 adults in the United States with corrected or palliated congenital defects and this number is increasing annually given improvements in diagnostic techniques and surgical procedures.[20,21] In these patients, it is the physiology of the underlying defect and the consequences of the repair that drive risk. Consequently, the risk of a particular patient with a congenital cardiac defect is difficult to generalize. However, there is general consensus that patients with pulmonary hypertension including those with Eisenmenger's physiology, those with cyanotic congenital defects those in New York Heart Association Functional Class III or IV and those with severe left sided obstructive lesions (aortic stenosis, coarctation of the aorta) or severe systemic ventricular dysfunction (EF < 35%) are at highest risk.[20,22] Patients with Eisenmenger's physiology are at significantly higher risk of complications during and after surgery, likely due to baseline shunt-related hypoxemia. The right to left shunt can increase due to increased intrathoracic pressure from ventilation during surgery and from the systemic vasodilatation induced by anesthesia. In one small study, the perioperative mortality of such patients was approximately 10%[22] and was not altered by the type of anesthesia. Patients with congenital heart disease often have decreased exercise capacity due to depressed ventricular function,[23] even after repair, and this contributes to the increased perioperative risk of adverse cardiac events. It is recommended that adult patients with complex congenital defects and those thought to be at high risk during noncardiac surgery be managed at specialized centers.[20]

ARRHYTHMIAS

Many cardiac dysrhythmias discovered preoperatively are benign, especially if they are asymptomatic and incidentally found on ECG monitoring. Occasional premature atrial or ventricular beats and even short runs of nonsustained ventricular tachycardia (VT) in the preoperative setting have not been associated with increased perioperative cardiac events.[24] In many cases, these dysrhythmias are associated with metabolic derangements or drug toxicity. Identifying the underlying cause is important, but should not delay surgery. There are some arrhythmias, however, that portend a worse prognosis during surgery.

Sustained atrial arrythmias, such as atrial fibrillation, found during preoperative evaluation frequently indicate the presence of underlying structural heart disease and have been identified as independent risk factors for perioperative cardiac complications. Especially in the elderly, atrial fibrillation may indicate the presence of underlying ischemic or structural heart disease or sinus node dysfunction. Atrial fibrillation with rapid ventricular response increases myocardial oxygen demand and may therefore increase the risk of perioperative myocardial ischemia in patients with CHD. Control of these arrhythmias, either via rate or rhythm control agents, should be attempted prior to surgery.

Sustained VT found in the preoperative setting significantly increases the risk of intraoperative arrhythmias and is suggestive of serious structural or ischemic heart disease. Therefore, sustained VT episodes should be fully evaluated for an underlying cause and potential treatment prior to surgery.

Supplemental tests are frequently used to help risk stratify patients prior to noncardiac surgery and arrive at a decision whether a preoperative intervention is warranted. Although the role of preoperative testing has been deemphasized to some extent in the most recent iteration of the ACC/AHA guidelines,[4] their role will be discussed in order to review their appropriate use and their limitations.

12-LEAD RESTING ELECTROCARDIOGRAPHY

A resting 12-lead electrocardiogram (ECG) is performed commonly as part of preoperative cardiovascular risk-assessment in patients with established CHD undergoing noncardiac surgery. The preoperative ECG contains important prognostic information and is predictive of long-term morbidity and mortality independent of clinical findings and the presence of perioperative myocardial ischemia.[25] The magnitude and extent of Q-waves in an abnormal ECG provide a rough estimate of the LVEF and are predictors of long-term mortality.[26] Similarly, ischemic segment depression greater than 0.5 mm, left ventricular hypertrophy (LVH) with the so-called "strain" pattern and left bundle branch block (LBBB) in patients with CHD are all associated with increased long-term mortality.[27-29] However, the ECG may be normal or show only nonspecific abnormalities in patients with either ischemia or infarction. For this reason, the routine performance of an ECG prior to all types of surgery is the subject of considerable debate.

In a recent retrospective study, investigators reviewed the outcomes of 23,036 patients scheduled for 28,457 surgical procedures. Patients with abnormal ECG findings had a higher incidence of cardiovascular death than those with normal ECGs (1.8% vs 0.3%). However, among patients who underwent low-risk or low- to intermediate-risk surgery the absolute difference in the incidence of cardiovascular death, between those with or without ECG abnormalities, was only 0.5%.[30] Current ACC/AHA guidelines recommend preoperative electrocardiography for patients with known atherosclerotic vascular disease or at least one clinical risk factor who are to undergo vascular or intermediate-risk surgery (see Appendix). The optimal time interval between obtaining a preoperative ECG and elective surgery has not been studied, but it is thought that for patients with stable disease, an ECG within 30 days prior to surgery is adequate.[4]

AMBULATORY ELECTROCARDIOGRAPHY

Several studies have evaluated the positive and negative predictive value of ambulatory electrocardiography for perioperative cardiac complications. The frequency of ST-segment abnormalities consistent with silent myocardial ischemia has ranged from 9% to 39% and the positive predictive value for perioperative MI and cardiac death from 4% to 15%, whereas the negative predictive value ranged from 3% to 16%. Therefore, although this test can be predictive of cardiac complications during noncardiac surgery, its low positive predictive value suggests that it cannot be used to further stratify high-risk patients in order to identify those requiring preoperative intervention.[4,31,32]

HEART RATE VARIABILITY

Many studies of cardiac patients have shown that decreased heart rate variability (HRV) is a more powerful predictor for cardiovascular mortality including sudden cardiac death than other established clinical predictors.[33] Decreased HRV in the preoperative period is also thought to be an independent predictor for postoperative cardiac death or MI after major surgery or trauma. A recent study that evaluated predictors of long-term outcomes in patients with documented or suspected CHD who survived major noncardiac surgery showed that depressed HRV measured a few minutes before induction of anesthesia was an independent and powerful predictor of one year mortality. However, robust prospective data regarding the role of decreased HRV as a preoperative risk predictor are sparse and further studies are needed to establish its possible predictive value for short- and long-term outcomes after noncardiac surgery.[34] No guideline recommendations regarding preoperative HRV determination have been published.

ASSESSMENT OF LEFT VENTRICULAR FUNCTION

Studies that have evaluated the role of left ventricular (LV) function in relation to perioperative risk have generally concluded that LV dysfunction has poor sensitivity and a low positive predictive value for perioperative cardiac events. In a meta-analysis of eight studies, LV ejection fraction less than 35% under resting conditions had a sensitivity of 50% and specificity of 91% in predicting major perioperative cardiac events.[35] Impaired LV function also did not reliably predict perioperative ischemic events. Therefore, the current ACC/AHA guidelines do not recommend routine preoperative evaluation of LV function and suggest that such assessment might be useful only for patients with dyspnea of unknown origin and for patients with HF and worsening symptoms (see Appendix).

NONINVASIVE STUDIES FOR MYOCARDIAL ISCHEMIA

Several noninvasive diagnostic tests have been proposed to assess the presence and extent of CHD before noncardiac surgery. Exercise electrocardiography has traditionally been used to evaluate individuals for the presence of CHD and myocardial ischemia. However, a substantial number of high-risk patients are either unable to exercise or have contraindications to exercise. This is especially true for patients who are to undergo vascular surgery and are limited by intermittent claudication or have an abdominal aortic aneurysm, conditions associated with a significant incidence of perioperative adverse cardiac events. Therefore, pharmacologic stress testing with imaging has been employed commonly as a preoperative test in patients undergoing high risk and especially vascular surgery. A large body of knowledge has accumulated showing that the presence of a distribution defect on dipyridamole perfusion scintigraphy (DPS) or extensive wall motion abnormalities on a dobutamine stress echocardiographic (DSE) study predict perioperative adverse cardiac events[36] with high sensitivity, but overall low positive predictive value. A recent meta-analysis of 25 stress echocardiographic and 50 nuclear perfusion pharmacologic stress studies preoperatively concluded that the likelihood of a

perioperative MI or death in patients with a positive stress echocardiogram was more than twice that for patients with a positive stress nuclear perfusion study.[37] The finding of a moderate to large stress-induced defect by either technique was highly predictive of perioperative MI or death with a likelihood ratio (sensitivity/1-specficity) of 8.35. Other studies have also quantified stress-induced redistribution defects in nuclear perfusion tests or the extent of wall motion abnormalities in DSE studies and related the extent and severity of such defects to the risk of perioperative cardiac events.[38,39]

Recently, the role of preoperative noninvasive testing for myocardial ischemia has been questioned with current ACC/AHA guidelines recommending such testing only if it will change patient management. The rationale for limiting the role of preoperative ischemia testing relates to several issues:

- Many studies of preoperative ischemia testing have been retrospective and conducted primarily on vascular surgery patients thus excluding a large number of other potential candidates.
- In many studies, the endpoint was related to the finding of ischemia with unclear clinical outcomes.
- Preoperative noninvasive ischemia testing leading to preoperative coronary revascularization does not appear to materially improve long-term clinical outcomes in patients with stable CHD.
- Approximately one half of perioperative MIs are due to plaque rupture or disruption in nonstenotic lesions and consequent coronary thrombosis[40,41] and are not the result of stress induced myocardial ischemia. It is for these reasons that the current guidelines recommend preoperative ischemia testing only if the clinician anticipates that the results of such testing will change patient management.

Although this position has been criticized as "circular reasoning", the current ACC/AHA guideline recommendations (see Appendix) suggest to the authors that the following patient groups may benefit from preoperative stress testing:[42]

- Patients with symptomatic CHD who require vascular or intermediate-risk surgery. Many of these patients will have required stress testing under circumstances other than preoperative assessment.
- Asymptomatic patients with known CHD and poor functional capacity or diabetes mellitus who require vascular or intermediate-risk surgery because clinical assessment alone cannot usually provide adequate risk prediction.
- Patients with poor or unknown functional capacity and 3 or more clinical risk factors require vascular surgery. Many of these patients will have significant unsuspected CHD and may be candidates for revascularization irrespective of preoperative status.

Conversely, the following patient groups will not likely benefit from preoperative stress testing for myocardial ischemia:

- Most patients with only 1 or 2 clinical risk factors and either poor functional capacity undergoing intermediate-risk surgery or good functional capacity undergoing vascular surgery are unlikely to benefit from preoperative revascularization. Preoperative stress testing for these patients may be considered only if unusual individual circumstances exist.
- Most patients with known or suspected CHD who are clearly not candidates for revascularization will also not benefit from preoperative stress testing. However, in some such patients, preoperative stress testing may help the clinician better define the extent of myocardial ischemia and arrive at a decision to proceed with or cancel elective surgery or substitute a procedure of lesser magnitude.*

The reduced emphasis on preoperative noninvasive testing for myocardial ischemia will likely result in a significant reduction of preoperative evaluation costs and reduce delays in the performance of the elective noncardiac surgery by eliminating unnecessary testing.[39,43]

CORONARY ANGIOGRAPHY

Invasive coronary angiography is a well-established diagnostic technique which is infrequently indicated preoperatively to assess the risk of noncardiac surgery since randomized clinical trials have not demonstrated much benefit in perioperative risk assessment, and there is little information derived from such trials on its usefulness in this setting. Additionally, a preoperative invasive coronary angiogram will frequently result in an unnecessary and unpredictable delay in the planned noncardiac surgical intervention as it will often lead to coronary revascularization procedures which have not been shown to improve long-term clinical outcomes. For these reasons, the accepted indications for preoperative coronary angiography and revascularization in patients with known CHD are similar to the established indications in the non-preoperative setting: acute or unstable coronary syndromes, unacceptable level of angina or high-risk results of noninvasive studies.[4,44,45] As previously noted for noninvasive testing, for some patients who do not meet standard indications, preoperative coronary angiography may help better define the extent of coronary artery disease and thus help the clinician arrive at a decision to proceed with or cancel elective surgery or substitute a procedure of lesser magnitude.

In two recent small, randomized, controlled trials from Italy, investigators examined the value of a systematic strategy of prophylactic coronary angiography prior to major vascular surgery and carotid endarterectomy (CEA) in medium- to high-risk patients. In these two studies, patients with an RCRI score of two or more who were scheduled to undergo vascular surgery or CEA were randomly assigned to either a selective strategy group or to a systematic strategy group. Patients in the selective strategy group underwent coronary angiography based on the results of noninvasive tests whereas patients in the systematic strategy group underwent preoperative coronary angiography without a prior noninvasive test. Preoperative coronary revascularization was undertaken depending upon the findings of angiography. Both studies showed that patients in the systematic coronary angiography group, who subsequently underwent selective coronary revascularization

*Reprinted from Gregoratos G. Current guideline-based preoperative evaluation provides the best management of patients undergoing noncardiac surgery. Circulation. 2008;117:3134-44 with permission of Wolters Kluwer Herald.

preoperatively, had better long-term survival and cardiac event-free survival at follow-up of 58 ± 17 months.[46,47] There was also a trend toward improved perioperative outcomes although this was not statistically significant. These relatively small trials should be considered as "hypothesis generating" and must be corroborated by additional and preferably larger randomized studies before the current criteria for preoperative coronary angiography can be changed.

The advent of noninvasive CT angiography may introduce changes in current practice. However, the role of CT coronary angiography for preoperative risk assessment has not been rigorously studied so far.

CARDIAC BIOMARKERS

Cardiac biomarkers have been found to have major prognostic significance in the nonoperative setting and also provide important prognostic information in cardiac patients about to undergo noncardiac surgery.

Cardiac troponin T and I (cTnT and cTnI) have superior sensitivity and tissue specificity for myocardial injury compared to other markers.[48] The prognostic information provided by these markers is independent of other important cardiac predictors of risk such as electrocardiographic ST-segment deviation and abnormal LV function. Evidence available suggests that even small increases in cTnT in the perioperative period reflect clinically important myocardial injury and poor cardiac prognosis and outcomes.[49]

Brain Natriuretic Peptide (BNP) and N-terminal pro-BNP (NT pro-BNP) are produced by cardiac myocytes in response to increased myocardial wall stress independent of the presence or absence of myocardial ischemia and have emerged as important prognostic indicators in patients with HF in non-surgical settings.[50,51] Recent studies have also found that elevated preoperative natriuretic peptide levels are powerful independent predictors of major adverse cardiovascular events in patients undergoing noncardiac surgery.[52,53]

Inflammatory markers, such as C-reactive protein (CRP), are thought to be associated with unstable coronary artery disease in population studies.[54] More recently, an elevated preoperative CRP was found to be a strong and independent predictor of perioperative major cardiovascular events in noncardiac surgery patients.[53] The authors of this study suggest that the sensitivity of predicting perioperative adverse cardiovascular events could be increased from 59% to 77% by adding CRP and NT pro-BNP levels to the clinical risk prediction system.

Despite these and other recent studies that suggest that cardiac biomarkers may be valuable additions in the preoperative risk assessment process, data, particularly from prospective controlled trials, are sparse. For this reason, routine assessment of cardiac biomarkers for patients undergoing noncardiac surgery is not generally recommended or utilized. However, the recently published ESC perioperative guidelines do recommend consideration of NT pro-BNP and BNP measurements in high-risk patients about to undergo non-cardiac surgery to obtain independent prognostic information for perioperative and late cardiac events.[5]

PREOPERATIVE RISK MITIGATION STRATEGIES

PHARMACOLOGIC INTERVENTIONS

Beta-Adrenergic Blockade

Beta-blocking agents are the mainstay of anti-ischemic therapy in many clinical settings. In the perioperative period, a significant catecholamine surge takes place resulting in increased heart rate and myocardial contractility thereby increasing myocardial oxygen consumption. These changes frequently trigger myocardial ischemia through an imbalance between myocardial oxygen demand and supply. Beta-blocking agents are used perioperatively to decrease myocardial oxygen consumption by reducing heart rate and decreasing myocardial contractility.[55] Additional cardio-protective benefits may include redistribution of coronary blood flow to the sub-endocardium, increased threshold of ventricular fibrillation and possibly plaque stabilization. Several studies have shown that beta-blockers and other drugs that lower heart rate can reduce perioperative myocardial ischemia.[41,56] It is therefore theorized that beta-blockers may also decrease the incidence of peri-operative MI since approximately one half of such events are due to myocardial oxygen supply-demand imbalance and not to plaque disruption.[57] Whether these theoretical beneficial effects of beta-blockade translate into clinical benefit has been the focus of numerous studies. Both prospective randomized and retrospective cohort studies have been used to analyze the incidence of adverse perioperative cardiovascular events in patients treated with these agents.

Seven major randomized trials evaluating the effect of perioperative beta-blockade on clinical outcomes have been published.[57-63] Three of these trials included patients at high risk for perioperative adverse cardiac events because of high-risk surgery, the presence of CHD, or the presence of major risk factors for perioperative cardiac complications. Three other trials did not require the presence of clinical risk factors except for diabetes. One trial included patients with a wide spectrum of risk for perioperative complications.

In all these randomized trials, the incidence of peri-operative MI and other ischemic events was significantly lowered by the use of beta-blockade. However, the results on perioperative mortality were quite variable, with a recent meta-analysis finding that the overall mortality was higher in patients receiving beta-blockers than in the placebo group.[64] The principal driver for this unexpected result was the large POISE trial in which 8,351 patients undergoing noncardiac surgery were randomized to extended release metoprolol or placebo.[58] The incidence of cardiovascular death, MI or cardiac arrest was reduced by an absolute 1.1% in the metoprolol treated group compared to placebo (5.8% vs 6.9%, P = 0.04). However, total mortality was paradoxically higher in the metoprolol group (3.1% vs 2.3%, P = 0.03). This increased all-cause mortality was driven primarily by increased rates of hypotension, significant bradycardia, and stroke in the metoprolol treated group.

Several issues have been raised regarding the applicability of the results of POISE across the board in the perioperative setting: The initial dose of metoprolol (100 mg) had double the

adrenergic blocking potency of the initial dose of bisoprolol or atenolol used in other studies. The drug was not titrated—the initial dose of 100 mg was given 2–4 hours preoperatively and the second 100 mg dose administered within 6 hours after surgery and withheld only for systolic blood pressure less than 100 mm Hg. An additional 200 mg may have been administered to some patients 12 hours later, so these patients received a total of 400 mg of metoprolol in the first 24 hours. This aggressive acute treatment regimen, particularly for elderly patients and those with pre-existing cerebrovascular disease probably accounts for the higher rates of stroke and total mortality.[42] Nevertheless, the results of POISE strongly suggest that routine prophylactic beta-blockade therapy in the perioperative period may not be safe, particularly if appropriate dose titration is not carried out.

A large retrospective study from a quality of care database of 329 hospitals analyzed outcomes of 663,635 patients undergoing noncardiac surgery; of these 30% were high risk.[65] In this study, 121,338 patients received perioperative beta-blockade prior to noncardiac surgery while 541,297 patients did not. Patients receiving beta-blockers had an RCRI ranging from 0 to 4. The investigators found that the relationship between perioperative beta-blocker treatment and the risk of death varied directly with degree of cardiac risk. Among patients with an RCRI score of 0 or 1, beta-blocker therapy was associated with no benefit and possibly harm with an adjusted odds ratio of 1.43 and 1.13 respectively. Conversely, among patients with an RCRI score of 2, 3 or 4 the adjusted odds ratio for in-hospital death was 0.88, 0.71 and 0.58 respectively. The investigators concluded that perioperative beta-blockade therapy was associated with a reduced risk of in-hospital death among high-risk patients and therefore enhanced patient safety in this group, whereas there was no beneficial effect and possibly harm among low-risk patients undergoing major noncardiac surgery.

Discrepancies in the results of the various trials can be explained by differences in type of noncardiac surgery, patient characteristics, and such attributes of beta-blockade as drug dose, type, timing and onset of therapy and, importantly, heart rate response. Several recent studies have concluded that achieving a heart rate response below the ischemic threshold is an important factor in realizing the benefits of perioperative beta-blockade. The term "tight heart rate control" has been coined to describe resting heart rates between 60 and 65 per minute and considerable evidence exists suggesting that clinicians should strive to achieve this preoperatively[39,66] provided patients can tolerate this degree of beta-blockade with no hypotension or other adverse effects.

Integrating the results of randomized and observational studies we can conclude that careful preoperative administration of beta-blockers with appropriate gradual dose titration to achieve tight heart rate control is beneficial for high-risk patients who are undergoing noncardiac surgery. The ACC/AHA focused update of the perioperative guidelines dealing specifically with beta-blockade[67] recommends that beta-blockers be continued in patients undergoing surgery if they are receiving these agents for the treatment of pre-existing conditions and that it is reasonable to administer beta-blockers titrated to appropriate heart rate and blood pressure to high-risk patients undergoing vascular surgery (see Appendix for details). Especially important is the additional recommendation that routine preoperative administration of high-dose beta-blockers in the absence of dose titration is not useful and may be harmful to patients not currently taking beta-blockers.

Statin Therapy

In addition to their lipid lowering effects, statins (3-hydroxy-3-methylglutaryl co-enzyme A reductase inhibitors) improve endothelial function, stabilize atherosclerotic plaques, and reduce vascular inflammation. By these mechanisms statins may reduce perioperative cardiac events. Early observational studies suggested a definite beneficial role for the preoperative use of these agents[68,69] and subsequent prospective, randomized controlled trials have confirmed these observations.[70,71] In the randomized Dutch Echocardiographic Risk Evaluation Applying Stress Echocardiography (DECREASE-III) study, a total of 497 vascular surgery patients were allocated to either Fluvastatin 80 mg daily or placebo starting an average 37 days before the planned vascular surgery. Compared to the placebo group, patients on Fluvastatin experienced a lower incidence of postoperative ischemic events (10.8% vs 19.0%) and cardiac death or MI (4.8% vs 10.2%). In both instances the difference in events was highly statistically significant.[71] Due to these studies, recent guidelines recommend the initiation of statin therapy in high-risk surgery patients starting ideally between 30 days and one week before surgery and continuation of statin therapy perioperatively for patients taking these agents chronically (see Appendix).

A potential limitation of perioperative statin use is the lack of parenteral formulations as there are concerns that discontinuation of the drug perioperatively may cause a rebound effect with detrimental consequences.[68] Therefore, it is preferable to prescribe in this setting a statin with long half-life or an extended release formulation.

Calcium Channel Blockers

The pharmacologic effects of calcium channel blockers on myocardial oxygen supply/demand balance make them theoretically useful for perioperative risk reduction. However, this applies primarily to calcium channel blockers that lower heart rate such as diltiazem and verapamil, and not to dihydropyridines. A meta-analysis of perioperative calcium channel blockade in noncardiac surgery was published in 2003 and included 11 studies with a total of 1,007 patients.[72] In this meta-analysis calcium channel blockers significantly reduced ischemic events and episodes of supraventricular tachycardia and were associated with trends toward reduced death and MI. The majority of these benefits were seen with the use of diltiazem. Verapamil decreased the incidence of supraventricular tachycardias but neither verapamil nor dihydropyridines reduced the incidence of ischemic events. Another study of 1,000 patients undergoing urgent or elective aortic aneurysm surgery showed that dihydropyridines were independently associated with increased perioperative mortality.[73]

The ACC/AHA perioperative guidelines offer no recommendations regarding the perioperative use of calcium channel blockers. The ESC guidelines[5] recommend that calcium channel blockers be continued during noncardiac surgery in patients

taking them for Prinzmetal angina and suggest that diltiazem may be considered before noncardiac surgery (for risk reduction) only for patients who have contraindications to beta-blockade. These guidelines emphasize that routine use of calcium channel blockers to reduce the risk of perioperative cardiovascular complications is not recommended.

Alpha-2 Adrenergic Receptor Agonists

The role of alpha-2 receptor agonists in the perioperative period is still evolving. These agents reduce postganglionic norepinephrine output and theoretically may reduce the catecholamine surge that develops during anesthesia and surgery. Several studies have examined the role of clonidine and mivazerol for perioperative cardiac protection. The European Mivazerol Trial randomized 1,897 patients with ischemic heart disease who underwent intermediate or high-risk noncardiac surgery. Overall, mivazerol did not decrease mortality or MI but there was a reduction of postoperative death and MI in a subgroup of 904 vascular surgery patients.[74] A more recent prospective randomized double-blind clinical trial of patients with CHD or at risk for CHD investigated whether prophylactic clonidine reduced perioperative myocardial ischemia and long-term mortality in patients undergoing noncardiac surgery.[75] Clonidine 0.2 mg orally and by patch, or placebo, was administered the night before surgery and again the morning of surgery. In this small trial prophylactic clonidine administration significantly reduced episodes of myocardial ischemia during the intraoperative and postoperative periods and reduced postoperative mortality for up to 2 years to a statistically significant degree compared to placebo. Of relevance is the fact that in this trial, clonidine resulted in minimal hemodynamic effects intraoperativly. Current ACC/AHA guidelines provide a weak Class IIb recommendation stating that these agents may be considered for perioperative control of hypertension in patients with known CHD or with at least one clinical risk factor who are undergoing surgery (see Appendix). The ESC guidelines[5] provide also a Class IIb recommendation stating that alpha-2 agonists may be considered to reduce the risk of perioperative cardiovascular complications in vascular surgery patients.

Nitrates

Nitrates, especially nitroglycerine, have been used for many years to effect coronary vasodilatation and reverse myocardial ischemia in patients with chronic stable angina. Nitroglycerin administration during surgery has been proposed as a way to ensure good coronary flow and maintain myocardial oxygenation in the setting of surgical stress. Countering this theoretical beneficial effects are its complex hemodynamic effects of arterial and venous dilatation. This makes the use of nitroglycerin in the perioperative setting highly debatable. Currently, there are insufficient data regarding the prophylactic use of nitrates in high-risk patients during noncardiac surgery. One small controlled study demonstrated decreased perioperative myocardial ischemic events in patients with stable angina who were given intravenous nitroglycerine during noncardiac surgery, but there was no effect on the incidence of MI or cardiac death.[76] Similar results were obtained in another study which showed no effect on ischemic events, MI or cardiac death.[77] Because the intraoperative use of nitroglycerine may decrease preload excessively which in turn may lead to tachycardia and hypotension, and because there is little convincing evidence to support its use, both the ACC/AHA and the ESC guidelines offer only a weak Class IIb recommendation for the use of nitroglycerin during noncardiac surgery, stating that prophylactic nitroglycerin intraoperatively is of uncertain usefulness even in patients on chronic nitrate therapy for angina control (see Appendix).

Antiarrhythmic Agents

In contrast to a large body of literature covering the use of antiarrhythmic agents to prevent perioperative arrhythmias in patients undergoing cardiac surgery, there is limited evidence available regarding their prophylactic use in noncardiac surgery; most of the evidence available is derived primarily from studies of patients undergoing pulmonary resection. Several small studies have demonstrated that beta-blockade therapy can reduce the incidence of arrhythmias in the perioperative period[78,79] in the setting of thoracic noncardiac surgery. In an extensive literature review reported in 2004, Shrivastava and co-workers concluded that there is also adequate evidence to support the use of diltiazem and magnesium supplements for prophylaxis against atrial fibrillation in patients undergoing noncardiac thoracic surgery.[80] Interestingly, they also reported that in a randomized trial comparing digoxin to placebo in patients undergoing extensive noncardiac thoracic surgery, the incidence of atrial fibrillation was higher in the group receiving digoxin than in the control group and concluded that digoxin has no role for prevention of atrial fibrillation in patients undergoing lung surgery. In another meta-analysis reported in 2005, Sedrakyan and co-workers reviewed the results of 11 trials that included 1,294 patients and concluded that both calcium channel blockers and beta blockers reduced the risk of atrial tachyarrhythmias in patients undergoing noncardiac thoracic surgery.[81]

Amiodarone has also been shown to reduce the risk of perioperative atrial fibrillation, primarily in patients undergoing lung surgery. In a prospective randomized study, amiodarone was shown to significantly reduce the incidence of atrial fibrillation after pulmonary resection and was associated with a significant reduction in length of intensive care unit stay.[82] In another prospective observational study diltiazem and amiodarone were evaluated in patients undergoing lung resection with postoperative atrial fibrillation. Both restored sinus rhythm in 70% and 67% respectively in the first 24 hours, but atrial fibrillation recurred in 37% of patients.[83]

Due to the well-known side effects of antiarrhythmic agents, current practice does not include their preventive use perioperatively despite the above reported studies. It is noteworthy that both the ACC/AHA and the ESC guidelines do not provide specific recommendations regarding the prophylactic use of antiarrhythmic agents for cardiac patients undergoing noncardiac surgery. However, it is explicitly stated in the discussion of beta-blockers that these agents reduce the incidence of new-onset perioperative atrial fibrillation along with their overall beneficial effects. We must therefore conlude that, with the exception of beta-blockade, the strictly prophylactic use of antiarrhythmic drugs to prevent the development of perioperative arrhythmias is not warranted.

Aspirin

Aspirin is widely prescribed to patients with CHD both prior to and after coronary revascularization, whether by surgery or percutaneous intervention. However, evidence of beneficial actions of aspirin in the noncardiac perioperative setting is limited. In a randomized trial of patients undergoing CEA, aspirin was found to be effective in preventing intraoperative and postoperative stroke, but there was no effect detected on mortality or perioperative MI.[84] A subsequent meta-analysis of 10 trials found that antiplatelet agents, including aspirin, reduced serious vascular events and vascular death in patients undergoing vascular surgery.[85] However, the benefit of antiplatelet therapy did not reach statistical significance for the combined endpoint of vascular events in this population.

In the past, concerns regarding operative bleeding often led to the discontinuation of aspirin in the perioperative period. However, a systematic review of patients with CHD or at risk for CHD demonstrated that aspirin non-adherence or withdrawal was associated with a significant risk of major cardiac events.[86] Consequently, there is general consensus that in patients taking aspirin this agent should be continued perioperatively and should be discontinued only if the bleeding risk outweighs the potential cardiac benefits. The ESC guidelines recommend that aspirin discontinuation in patients previously treated with this agent should be considered only in those in whom hemostasis is difficult to control during noncardiac surgery.[5] The ACC/AHA perioperative guidelines do not provide a general recommendation regarding aspirin therapy in this setting. However, they do provide a Class IIa recommendation to continue aspirin, if at all possible, in patients who have previously received a drug eluting stent (see Appendix). Given this complex framework, the decision to continue or discontinue aspirin preoperatively should depend on the specific patient situation and the type of noncardiac surgery to be undertaken and should be reached in consultation with the responsible surgeon.

NONPHARMACOLOGIC AND OTHER INTERVENTIONS

Coronary Revascularization

Preoperative myocardial revascularization has been advocated as means of preventing perioperative fatal and nonfatal MIs. However, it has become abundantly clear that whereas revascularization is quite effective in treating high-grade coronary stenosis and relieving stress-induced myocardial ischemia, it does not prevent coronary thrombosis due to disruption of a vulnerable plaque during the stress of surgery. Since approximately one half of perioperative infarcts are due to plaque disruption and coronary thrombosis[40,41] the efficacy of coronary revascularization in preventing a perioperative MI has been called to question.

Older evidence from observational studies suggests that prior successful revascularization might decrease perioperative cardiac risk in patients undergoing elective vascular surgery. A sub-analysis of the CASS Registry data[87] found a small but significant improvement in outcomes of noncardiac surgery in patients who had undergone prior coronary revascularization. Furthermore, in patients undergoing major vascular surgery, mortality after noncardiac surgery was reduced by two-thirds if they had had prior coronary bypass. However, the recent publication of three prospective randomized controlled trials has defined better the role of preoperative coronary revascularization. The results of all three trials indicate that in most instances coronary revascularization preoperatively does not improve perioperative and, especially, long-term outcomes.

In the first prospective trial (CARP), published in 2004, 510 patients with significant coronary artery stenosis were randomly assigned to either coronary revascularization or no revascularization before major vascular surgery.[88] Patients with significant left main coronary artery stenosis, LV ejection fraction less than 20%, severe AS or unstable coronary syndromes were excluded. Among the 225 patients who received preoperative coronary artery revascularization before going on to vascular surgery, 59% had a percutaneous coronary intervention (PCI) and 41% had coronary bypass surgery (CABG) at the discretion of the local investigators. At 30 days, mortality was not significantly different between the patients who received preoperative revascularization and those who did not. Similarly, there was no significant difference in survival at 3 years between the two groups. It was the conclusion of the investigators that routine coronary revascularization in patients with stable cardiac symptoms before elective vascular surgery did not alter the long-term outcomes or short-term risk of death or MI. A sub-analysis of the CARP trial published subsequently found that, as a result of coronary revascularization, the necessary vascular surgery was delayed for over 60 days in 25% of patients who had revascularization by PCI and in 37% of patients who had CABG. They also found that the incidence of MI increased with longer delays between coronary revascularization and vascular surgery.[89]

The Dutch Echocardiographic Risk Evaluation Applying Stress Echocardiography (DECREASE-II) study was designed to evaluate the utility of preoperative ischemia testing in patients with intermediate cardiac risk prior to undergoing major vascular surgery; all patients were on adequate beta-blocker therapy. Seven hundred and seventy patients were randomly assigned to preoperative ischemia testing (DSE or DPS) or no testing. Patients with extensive myocardial ischemia, whose vascular surgery could be delayed, underwent coronary angiography and subsequent coronary revascularization depending on the angiographic results. The composite endpoint of death and nonfatal MI was evaluated at 30 days postoperatively and was similar in the two groups (2.3% vs 1.8%). The investigators concluded that in this intermediate-risk patient group with extensive myocardial ischemia, revascularization did not improve 30 days outcomes although the number of patients was too small to definitively state so.[39]

The DECREASE-V pilot study screened 1,818 patients scheduled for major vascular surgery and identified a high-risk cohort of 101 patients by the presence of three or more clinical risk factors and the presence of extensive myocardial ischemia on DSE or DPS; 43% of these patients had an LVEF of 35% or less. These patients were randomized to best medical therapy and revascularization or best medical therapy alone before undergoing the required vascular surgery. At 30 days, all-cause mortality and nonfatal MI rates were similar between the revascularization and medical therapy groups at 43% versus

33% respectively with P = 0.3. At one year, the incidence of all cause mortality or MI was similar in both groups as was survival at 5 years after surgery.[90,91]

As a result of these and other studies, we can conclude that the role of prophylactic preoperative coronary revascularization in reducing perioperative cardiac complications is limited to two general categories of patients with CHD:

- Patients who are found to have prognostically high-risk coronary anatomy and in whom long-term outcomes would likely be improved by coronary revascularization under all circumstances (e.g. stable angina with significant left main coronary artery disease, or stable angina and 3-vessel disease with depressed LV ejection fraction)
- Patients with unstable coronary syndromes such as acute ST-segment elevation MI, high-risk unstable angina or non ST-segment elevation MI.

These are the Class I recommendations for preoperative coronary revascularization listed in the current ACC/AHA perioperative management guidelines.[4] Additionally, the guidelines provide an important Class III recommendation that routine prophylactic coronary revascularization is not recommended for patients with stable coronary artery disease before noncardiac surgery (see Appendix).

Some clinicians believe that in addition to the above indications, selected high-risk patients with extensive myocardial ischemic burden on preoperative testing who are scheduled to undergo high-risk surgery may also benefit from preoperative revascularization; especially as considerable evidence from cohort studies has accumulated over the past 20 years confirming that the risk of perioperative adverse cardiac events increases as the extent of myocardial ischemia increases.[92-94]

The decision to proceed with preoperative revascularization must take into account several important issues. Whether to recommend CABG or PCI must be addressed first. There are, of course, generally accepted indications for CABG such as severe left main disease or multi-vessel coronary disease and for PCI such as single vessel disease or to recanalize the culprit lesion in an acute coronary syndrome (ACS). However, the available evidence does not suggest that one revascularization method is superior to the other in the perioperative setting, even in patients with multivessel CHD (see below). Other important issues that must be examined carefully include: the delay that coronary revascularization will introduce prior to proceeding with the planned noncardiac surgery and the attendant risk of such delay; the type and duration of antiplatelet therapy that will be required after revascularization and the risk of associated bleeding which must be discussed with the patient and the attending surgeon.

In general, noncardiac surgery is deferred for 4–8 weeks after CABG depending on the rate of the patient's recovery, the comorbidities of the patient and the urgency of the noncardiac surgery planned. Limited evidence available provides some guidance: In one reported study of a cohort of 2,452 patients who had abdominal aortic aneurysm surgery, 100 patients required perioperative revascularization. CABG was performed in 86 and PTCA in 14. The median delay of aneurysm repair was 68 days after CABG and 10 days after PTCA and there were no deaths in either group. The perioperative mortality in the entire 2,452 patients cohort was 2.9%.[95]

Limited data are available comparing outcomes of prophylactic revascularization with CABG and PCI (with or without stenting) before noncardiac surgery. In the Bypass Angioplasty Revascularization Investigation (BARI) patients with multi-vessel CHD were randomly assigned to undergo balloon angioplasty or CABG.[96] A subset of 501 patients underwent noncardiac surgery after revascularization. Of these 250 had undergone CABG and 251 PTCA. The mortality rate and the incidence of MI was 1.6% in both groups and no difference in length of hospitalization or cost was found. The risk of death or MI was lower when noncardiac surgery was performed within 4 years after coronary revascularization.[97] These data suggest that the risk of perioperative MI or death during noncardiac surgery is approximately equal in patients who undergo balloon angioplasty or CABG preoperatively. Evidence from primarily retrospective studies suggests that PTCA performed within 2 months prior to noncardiac surgery is safe.[98] However, there is a significant risk of acute vessel closure if noncardiac surgery is performed too soon after PTCA. Conversely, delaying noncardiac surgery for more than 8 weeks after PTCA increases the risk of restenosis at the angioplasty site and theoretically at least increases the risk of perioperative ischemia or MI. Therefore, there is a general consensus that noncardiac surgery should be delayed for at least 2 weeks after balloon angioplasty, but should be performed within a period of 2 months after PTCA. Daily aspirin therapy should be continued in these cases without interruption perioperatively, unless major bleeding complications are anticipated. The ACC/AHA guidelines recommend that noncardiac surgery be performed 14–29 days following PTCA and that elective or non-urgent surgery be delayed if balloon angioplasty was performed less than 14 days prior (see Appendix).

The issue of performing noncardiac surgery after PCI utilizing stents is far more complex. Some studies reported high mortality rates of up to 20% due to acute stent thrombosis at the time of noncardiac surgery if it was performed within weeks after the insertion of a coronary stent and antiplatelet therapy was discontinued.[99,100] Bare metal stent (BMS) thrombosis is most common in the first 2 weeks after stent placement and is rare more than 4 weeks after the procedure.[101,102] Since BMS endothelialization usually takes 4–6 weeks, general consensus is that elective and nonurgent noncardiac surgery should be deferred for 4–6 weeks to allow for at least partial endothelialization of the stent, but not for more than 12 weeks when the incidence of restenosis begins to increase. In this respect, the ACC/AHA guidelines recommend a window of 30–45 days after BMS insertion for the performance of noncardiac surgery.[4] Dual antiplatelet therapy of aspirin and clopidogrel is the rule for the first 4 weeks after BMS insertion, although many clinicians believe that optimal dual antiplatelet therapy should be continued up to 3 months. After 3 months, clopidogrel may be discontinued and patients can undergo noncardiac surgery on aspirin therapy alone.[100]

Currently, the majority of stents inserted during PCI are drug eluting stents (DES). These stents represent a major advance in reducing in-stent restenosis, but have a major drawback in the

need for prolonged dual antiplatelet therapy with aspirin and clopidogrel for at least 12 months. Several reports of stent thrombosis after discontinuation of antiplatelet therapy for noncardiac surgery have been published and raise concerns regarding the timing of such procedures. In one study of 2,229 patients, 1.3% had stent thrombosis after DES implantation with a case fatality rate of 45%.[101] It is generally accepted that after DES implantation, elective surgery should not take place until after at least 12 months of continuous dual antiplatelet therapy.[102] After that period of time, clopidogrel may be discontinued but daily aspirin therapy should be continued perioperatively during noncardiac surgery. If there is a contraindication to 12 months of combined aspirin-clopidogrel therapy because of the urgency of noncardiac surgery, then a DES should not be implanted and other revascularization options should be considered. This position is supported by the ACC/AHA and the ESC perioperative guidelines, and the Science Advisory promulgated by several professional societies.[4,5,103]

Interventions for Valvular Lesions

Patients with severe VHD have a high risk of adverse cardiac complications during noncardiac surgery. Severe AS in particular, the most common form of VHD in elderly patients, has been found to be a major risk factor for perioperative mortality and MI.[18,104] There is little information available from controlled trials regarding optimal preoperative management of the patient with severe AS who is about to undergo noncardiac surgery. Clinical experience suggests that if the AS is symptomatic, elective noncardiac surgery should be deferred and aortic valve replacement should be undertaken prior to noncardiac surgery. Patients who are not candidates for aortic valve replacement and those who require urgent high-risk noncardiac surgery may benefit from a temporizing aortic balloon valvuloplasty to bridge patients through the noncardiac surgical period.[105-107] The development of transcatheter aortic valve replacement techniques may alter practice eventually. Unfortunately, there is little information available from controlled studies regarding the appropriateness of valvular repair or replacement before noncardiac surgery. The above statements are based on clinical experience. As a result, the ACC/AHA guidelines do not offer concrete recommendations regarding the preoperative management of adults with severe AS.

Similar considerations can be applied to MS, which has become relatively rare in the United States today. Patients with moderate severity MS (valve area > 1.5 cm^2) and no significant pulmonary hypertension (systolic pulmonary artery (PA) pressure < 50 mm Hg) can usually undergo even high-risk noncardiac surgery safely. Preoperative surgical correction of MS in these patients is not necessary. Special considerations to be observed in patients with MS undergoing noncardiac surgery are avoidance of fluid overload and control of heart rate, since severe tachycardia may cause pulmonary edema. MS patients are at considerable risk of developing perioperative atrial fibrillation, which may cause significant clinical deterioration.[107] These patients are also at risk for development of thromboembolic complications and consideration should be given to perioperative anticoagulation. Patients with severe symptomatic MS (valve area < 1.0 cm^2) and significant pulmonary hypertension are at high risk of cardiac complications during noncardiac surgery and clinical experience suggests that these patients may benefit from open mitral valve repair if the surgery is not urgent or percutaneous mitral balloon valvotomy if it is urgent.[4,106]

Even less information is available regarding preoperative interventions for aortic or MR. In general, it is thought that regurgitant valvular legions are better tolerated than stenotic lesions. Asymptomatic patients with preserved LV function and moderate aortic or MR may undergo even high-risk noncardiac surgery with no significant increase in perioperative cardiac complications.[106] Symptomatic patients with a regurgitant lesion and those with severely impaired LV ejection fraction (LVEF < 30%) are at high risk for perioperative complications and noncardiac surgery should be deferred if possible or alternative lower risk noncardiac surgery should be considered. All patients with aortic or MR should have their medical therapy optimized in accordance with best clinical practice and the ACC/AHA valvular heart disease guidelines.[107] The role of percutaneous mitral valve repair prior to noncardiac surgery is at this time investigational.

Arrhythmias and Conduction Abnormalities

The presence of sustained ventricular or supraventricular arrhythmias in the preoperative period requires thorough evaluation for underlying structural heart disease and institution of appropriate therapy according to relevant guidelines.[108-110] Nonsustained ventricular arrhythmias including complex ventricular ectopy and nonsustained VT do not usually require specific therapy unless they are associated with hemodynamic compromise, myocardial ischemia or severe LV dysfunction. The incidence of such arrhythmias among high-risk patients undergoing noncardiac surgery can be as high as 50%. However the presence of these arrhythmias has not been found to be associated with increased risk or perioperative MI or cardiovascular death.[24,111]

In general, preoperative use of antiarrhythmic agents to reduce perioperative arrhythmias has not been found to be beneficial or free of potential complications. One exception is the use of beta-blockade. Several studies have reported that beta-blockers reduce the incidence of arrhythmias during the perioperative period and provide better control of heart rate in chronic atrial fibrillation than non-dihydropyridine calcium channel blockers or digoxin.[78,79] Digoxin may be used as a first line drug for rate control only in patients with HF since it cannot effectively block atrioventricular conduction in high adrenergic tone situations such as surgery. Rate control therapy in patients with chronic AF should be continued with minimal interruptions perioperatively.

Patients with chronic atrial fibrillation are usually on chronic anticoagulant therapy. In most instances, it will be necessary to discontinue anticoagulation for a few days before surgery. It is customary to bridge warfarin anticoagulation with either low-molecular weight or unfractionated heparin if the risk of embolic complications is significant as in patients with a mechanical prosthetic valve. For urgent surgeries, warfarin anticoagulation may be reversed with parenteral vitamin K or fresh frozen plasma.[112]

Significant perioperative brady-arrhythmias requiring therapy have been reported to occur in 0.4% of patients.[113] They are usually the result of anesthesia-induced changes in sympathetic/parasympathetic tone balance independent of type of volatile anesthetic used.[113] In general, perioperative bradycardia can be effectively treated with short-term pharmacologic therapy (atropine or beta-1 agonists), or transcutaneous pacing.[24,113] It is rarely necessary to initiate temporary transvenous pacing preoperatively, even in the presence of bifascicular block or left bundle-branch block.[114,115] It should be noted that asymptomatic bifascicular block even with associated first-degree atrioventricular block is not an indication for temporary transvenous pacing since the progression of these conduction defects to high-grade atrioventricular block is slow. Thus, the indications for temporary transvenous pacing during the perioperative period are generally the same as those for permanent pacing.[115,116]

Hemodynamic Optimization

Preoperative optimization of hemodynamics, oxygen delivery and volume status may reduce perioperative complications of high-risk patients undergoing noncardiac surgery. In addition to optimizing standard medical therapy consisting of ACE inhibitors or angiotensin receptor blockers (ARBs), beta-blockers and statins, a variety of other interventions have been recommended including the insertion of an intra-aortic balloon (IABP) counter pulsation device and preoperative intensive care unit management with an indwelling PA catheter for monitoring the hemodynamic consequences of intensive medical therapy. Limited data are available to support this concept with much evidence derived from case reports or observational studies. Even reported randomized controlled trials suffer from significant heterogeneity and have arrived at different conclusions regarding the benefit of intensive care unit monitoring and therapeutic optimization before noncardiac surgery.[117,118] A meta-analysis of 30 randomized trials showed that hemodynamic optimization resulted in decreased mortality rate (relative risk ratio 0.75).[119] This meta-analysis, however, has been criticized because the mortality results were affected by significant heterogeneity. In a more recent meta-analysis of 20 trials, mortality was reduced in the treatment group,[120] but significant statistical heterogeneity was again observed. Furthermore, this meta-analysis included studies primarily designed to ascertain whether preoperative optimization was effective in reducing renal injury and mortality was a secondary endpoint. Because of the inconsistency of results and the absence of robust randomized controlled studies demonstrating a benefit of preoperative hemodynamic optimization, the ACC/AHA guidelines provide only a weak Class IIb recommendation regarding the use of PA catheter-based monitoring preoperatively for this purpose (see Appendix). What is clear from all the studies available is that if preoperative monitoring with a PA catheter is undertaken to improve hemodynamics, such monitoring should be continued throughout the entire perioperative period.

Patients with stable severe obstructive CHD or an active cardiac condition could theoretically benefit from improved coronary artery perfusion and reduced LV afterload that insertion of an IABP device provides. Several small nonrandomized series and case reports have reported the results of IABP use perioperatively in patients with ACSs or severe CHD undergoing noncardiac surgery.[121-123] In general, these studies have documented a lower rate of cardiac complications with the use of IABP compared with other series of patients at similar high risk as well as low rates of IABP-related complications. However there is no robust evidence available regarding the preoperative insertion of an IABP device as a means of reducing perioperative myocardial ischemic events. Although no guideline recommendations are available for the use of IABP prophylactically given the absence of robust randomized controlled trials, an answer may be available soon as a randomized trial is currently underway to examine the role of IABP in this setting. For now, the decision to insert an IABP device for prevention of perioperative cardiac events must be made on strictly clinical and empirical grounds.

INTRAOPERATIVE MANAGEMENT

Intraoperative management of a cardiac patient undergoing noncardiac surgery involves both an understanding of the physiologic implications of anesthesia for a particular patient and an integration of all aspects of patient status and the type of surgery. This is the role of the anesthesiologist and beyond the scope of the consulting cardiologist. However the consultant can offer advice as to the hemodynamic consequences of anesthetic agents, mechanisms to protect the myocardium during surgery, and options for intraoperative hemodynamic monitoring.

CHOICE OF ANESTHESIA

In general, the choice of anesthesia should be made by the anesthetist. The consultant cardiologist can be helpful by providing some general principles as they apply to a particular patient. In patients with Eisenmenger's physiology, for example, it will be important to recommend that systemic vasodilatation should be avoided as much as possible since it can increase the right to left shunt and the hypoxemia. Apart from such individual patient clinical and hemodynamic considerations, there are also some general guiding principles to promote cardiac protection during surgery.

Volatile Agents versus Opiates

Historically, high dose opioid anesthetic agents have been preferred for cardiac patients because it was thought that volatile anesthetics induced more myocardial depression and afterload reduction.[4] Over the last twenty years, however, several randomized controlled trials in the setting of cardiac surgery have shown volatile anesthetics to be at least equal to opioids in terms of cardiac protection. One such study randomized 1,012 patients undergoing coronary artery bypass grafting to either an inhaled agent (ethoflurane, haloflurane or isoflurane) or high dose sufentanil[124] and found no difference in the rate of intraoperative or postoperative myocardial ischemia or death between the two groups. Multiple other randomized trials using a variety of agents have confirmed these findings.[125,126] Further studies in cardiac surgery have demonstrated reduction in

troponin I levels and better preservation of contractile function of the ventricle with inhaled agents,[127-132] suggesting that these anesthetic agents may be preferable to opioids in patients where the ischemic risk is high.

It is important to note that all of these studies have been in the setting of on-pump cardiac surgery. Although some believe that these data can be extrapolated to noncardiac surgery,[4] there has been a paucity of data examining this question.[133,134] At this time, as there are no data suggesting harm with inhaled agents in noncardiac surgery, it is reasonable to conclude that inhaled agents may provide improved cardiac protection in high-risk patients undergoing noncardiac surgery (see Appendix).

General, Neuraxial and Monitored Anesthesia Care

General anesthesia has long been thought to be the most physiologically demanding of anesthetic modalities. Therefore, other techniques, such as monitored anesthesia care (MAC) or spinal/epidural anesthesia, have been proposed to reduce the physiologic burden and therefore provide better cardiac protection.

Neuraxial blocks (spinal or epidural), when performed for lower extremity or abdominal surgery, have the advantage of minimal changes in cardiac loading conditions and therefore theoretically provide some degree of cardiac protection. A substudy of one trial that examined general versus neuraxial anesthesia for lower extremity vascular surgery did show a decreased incidence of MI from 7.9% to 2.7%, but did not control for factors such as the use of beta-blockers.[135] Additionally, there have been at least five randomized trials in a variety of cardiac, vascular and intra-abdominal surgeries that examined the differences between general and spinal or epidural anesthesia.[135-139] In all of these studies, there was no difference in mortality or major cardiac complications, suggesting that the theoretical benefit to the myocardium may not be as clinically significant as once thought.

Monitored Anesthetic Care—essentially deep sedation with local anesthesia in the awake patient—can safely be used for minor surgeries. However, for major surgery in patients with known cardiac disease, MAC incompletely blunts the stress response and may allow a significant catecholamine surge, which in turn may increase the risk of cardiac events. In one observational study, there was an increase in 30 days mortality with MAC when compared to general anesthesia,[140] but this may have been due to selection bias.

HEMODYNAMIC MONITORING

Intraoperative monitoring of hemodynamics with either a PA catheter or transesophageal echocardiogram is not routinely recommended. However, there are specific clinical situations when their use is helpful in managing a high-risk patient during surgery.

In patients with cardiac pathologies such as pulmonary hypertension or severe AS, when hemodynamics must be kept within a very narrow window, a PA catheter may be helpful in maintaining an optimal hemodynamic state. Since misinterpretation of data or misplacement of a PA catheter can result in significant harm, it is imperative to use PA catheters for hemodynamic monitoring only when warranted by a specific clinical situation, and when the anesthetist has experience in the placement of the PA catheter and interpretation of the data obtained.[4]

Recently, transesophageal echocardiographic (TEE) monitoring of volume status has gained favor and can be used to emergently assess volume and cardiac output during the intraoperative period.[141] Additionally, monitoring for elevated left ventricular end diastolic pressure (EDP) using E/e' ratios on TEE can be helpful; elevated EDP has been shown to predict postoperative morbidity in patients undergoing cardiac surgery.[142] Another potential use for intraoperative TEE is the identification of wall motion abnormalities suggestive of active ischemia. This is an appealing idea, and in the small studies that have examined its use in noncardiac surgery, the presence of wall motion abnormalities on TEE increased the likelihood of subsequent myocardial ischemic events by 2.6 times.[143] Based on these findings, the 2007 ACC/AHA guidelines state that the emergency use of intraoperative or perioperative TEE is reasonable for determining the cause of an acute, persistent and life-threatening hemodynamic change (see Appendix). Since little evidence is available regarding the cost-effectiveness of intraoperative TEE monitoring, the routine use of TEE during noncardiac surgery does not appear to be warranted unless it is believed that the TEE could help with diagnosis and management of a severe, acute hemodynamic abnormality or help determine the results of a surgical procedure, such as mitral valve repair, before the patient leaves the operating room. As with other technologies the key component of the effectiveness of TEE for enhanced monitoring is that an experienced operator is involved in its use.

MANAGEMENT OF PATIENTS WITH IMPLANTED ELECTRONIC DEVICES

It is estimated that more than half a million persons in the United States have permanent pacemakers or implantable cardioverter defibrillators (ICDs), and more than 100,000 devices are being placed annually. When a patient with an existing device is scheduled for noncardiac surgery, the consulting cardiologist will frequently be asked to assist in intraoperative management of the device. Careful preoperative planning is key to making this process as smooth as possible. It is imperative that the device type (ICD or pacemaker) and mode of operation are clearly identified. Routine device maintenance, including interrogation and battery assessment, if necessary, should be done prior to surgery. Finally, pacemaker dependence—the percentage of time the patient is pacer dependent—should be assessed.

Intraoperatively, the two main elements of management are to create redundant systems and reduce the risk of electromagnetic interference (EMI). Redundant systems usually include external pacing pads on the patient for transcutaneous pacing or defibrillation, if necessary. Sources of EMI during surgery include electrocautery and radiofrequency ablation. Once potential sources of EMI are identified, they should be minimized as much as possible. Bipolar electrocautery devices produce less EMI and should be used preferentially in patients with implanted electronic devices. If EMI is unavoidable during surgery, a magnet should be placed over an ICD to reduce

inappropriate defibrillation during surgery. Additionally, close monitoring of rhythm and pulse during the procedure will help to identify dangerous changes in rhythm if they occur. After surgery is completed, a 12 lead ECG will help confirm that pacemaker settings have been restored. If there is concern about device functionality after surgery, re-interrogation should be undertaken.[144]

POSTOPERATIVE MANAGEMENT

The postoperative period is a particularly risky period for cardiac events after noncardiac surgery, especially in the first 48 hours for patients that are at increased risk for cardiac events.[145] In selected populations, the risk warrants close monitoring of hemodynamics and electrocardiographic ischemic markers. Although the routine use of serial ECGs or PA catheters is not indicated, specific patients may benefit from their use.

PULMONARY ARTERY CATHETERS

There have been a series of studies that have evaluated the routine use of PA catheters in the postoperative setting. None of the larger studies have shown any significant benefit to routine placement[118,146,147] and in some cases, there has been a propensity toward harm—increased mortality, more pulmonary emboli and increased incidence of HF exacerbations.[148,149] However, in selected patients, the hemodynamic information gained from a PA catheter can guide an elegant approach to the management of fluids and hemodynamic support. For example, in patients with clinical signs of HF prior to surgery, intraoperative fluid shifts may significantly worsen loading conditions and create severe hypervolemia. In this case, using a PA catheter to appropriately titrate inotropic therapy, diuresis and management of systemic vascular resistance can restore euvolemia and cardiopulmonary hemodynamics to a compensated state quickly and safely.

In patients with severe AS and other cardiac diseases where fine titration of loading conditions is required to prevent decompensation, a PA catheter can help the clinician maintain correct fluid balance and continuously keep loading conditions optimized. Clinicians should be aware that, even in the appropriate clinical setting, an ever present risk of patient management with PA catheter hemodynamic data is the misinterpretation of the data. Clinical management based on hemodynamics should, therefore, be guided by clinicians with a thorough understanding of cardiac and postoperative physiology and experience with insertion and management of PA catheters.

SURVEILLANCE FOR ISCHEMIA

Patients with risk factors for perioperative cardiac events should be monitored closely in the postoperative setting. Close observation for symptoms of chest pain, shortness of breath, palpitations and other signs of an acute cardiac event is important. When these symptoms are noted, evaluation with serial ECGs, cardiac biomarkers and, where warranted, transthoracic echocardiograms or stress tests are appropriate. If a patient is deemed low risk for perioperative cardiac events during preoperative evaluation, there is no utility in routine surveillance ECGs or biomarker assays, as the false positive rate in these patients is prohibitively high. Symptom-based management in these patients should still involve the appropriate testing.

For patients who fall into the intermediate or high-risk groups, the question of routine surveillance in the absence of symptoms has been the focus of much investigation. In one study, 232 patients with some risk factors for heart disease—mostly hypertension or diabetes—who underwent intermediate risk gynecologic surgery were screened with serial ECGs and CK-MB assays for up to 6 days postoperatively.[150] The most sensitive method of surveillance was via serial ECGs on the first two postoperative days which captured 88% of postoperative MIs. Since then at least two large observational studies have examined and confirmed the diagnostic value of routine postoperative ECGs.[151,152] In one study by Rinfret et al. screening ECG changes, including ST-segment elevation or depression and T-wave changes immediately after surgery was completed were associated with a 2.2 fold increase in the risk of having postoperative cardiac ischemia.

The data on routine measurement of biomarkers in the postoperative setting, including CK-MB, troponin I and troponin T are much less clear. The relationship between increased levels of CK-MB and increased mortality in the short and long term has been shown[153,154] and the advent of Troponin T and Troponin I has only strengthened that relationship.[151] The issue, however, is that the routine use of surveillance CK-MB or troponin without regard to symptoms postoperatively appears to reduce the specificity of the test without improving sensitivity.[155,156]

Based on these data, we can conclude that cardiac biomarker assays in the absence of symptoms are unlikely to be helpful in diagnosing perioperative ischemia, although negative markers, especially Troponin I, have fairly strong negative predictive value. Overall, ECG abnormalities on surveillance tracings may be more helpful in predicting postoperative infarction and can be considered in patients at elevated risk. Of course, when clinical symptoms associated with MIs are included in the assessment, the predictive value of both ECG tracings and biomarker assays increase significantly.[151] Specific recommendations regarding postoperative surveillance for perioperative infarction are listed in the Appendix.

POSTOPERATIVE ARRHYTHMIAS

Benign arrhythmias are very common in the postoperative setting and most ectopic rhythms do not predict cardiac disease outside the perioperative period. Isolated PACs and PVCs are often the result of electrolyte imbalance, pain, volume shifts or a response to increased adrenergic tone after surgery. These rhythms should be monitored and treated by addressing the underlying cause of the arrhythmia. In most cases, these rhythms disappear when the underlying stimuli are removed. If there is a high burden of ventricular ectopy and the patient is symptomatic, beta-blockade can be considered as first line therapy.

Postoperative atrial flutter and atrial fibrillation are also very common after surgery, with rates reported as high as 40% in some studies.[156-159] Certain demographic factors, including

prior history of atrial fibrillation, COPD and advanced age, increase the risk of postoperative atrial fibrillation significantly. In one study that examined patients after cardiac surgery, for each 10 years of advancing age the odds of postoperative atrial fibrillation increased by a factor of 1.75.[159] It is also clear that the onset of these rhythms is not without consequence—they have been associated with adverse renal, neurologic and infectious outcomes, and can create discomfort for the patient. Since the frequency and morbidity associated with postoperative atrial fibrillation, several prophylactic strategies have been proposed to reduce its incidence, especially in patients undergoing cardiac surgery. A detailed discussion on these strategies is available in the section on preoperative risk mitigation.

For the treatment of atrial tachyarrythmias that arise in the postoperative setting, beta-blockade is the recommended first line therapy for rate control. The use of intravenous metoprolol followed by oral maintenance therapy is a robust treatment strategy. Alternatively, agents, such as diltiazem or digoxin, can be used as adjuncts, as can amiodarone in the appropriate clinical setting. Electrical cardioversion is not recommended as postoperative atrial fibrillation is likely to recur until the stimulus for the arrhythmia is corrected. If the patient is hemodynamically unstable, however, electrical cardioversion should be used as emergent therapy. Isolated atrial fibrillation after surgery is not an indication for anticoagulation, but patients with paroxysmal or persistent fibrillation should be considered for long-term anticoagulation using the CHADS2 risk stratification score and relevant guidelines.[160]

Sustained ventricular arrhythmias can be seen after surgery, and may reflect profound electrolyte disturbances, underlying ischemia or structural heart disease. Evaluation and treatment of these rhythms should follow generally accepted principles and management is not affected by the postoperative state.[109] Postoperative bradycardias are most often related to a cardiac effect of noncardiac stimuli. Medications, electrolyte abnormalities and increased vagal tone are the most common agents associated with bradycardia. If the patient is symptomatic or hypotensive, acute intervention may be necessary. In such cases, 0.5–1.0 mg of atropine administered intravenously will usually reverse the bradycardia. Occasionally, transcutaneous or transvenous temporary pacing may be required to support cardiac output in patients who are severely symptomatic or hemodynamically unstable. In the rare case that sinus node dysfunction or AV nodal disease is first discovered in the postsurgical setting, evaluation and treatment should proceed as it would for any patient with similar conduction system dysfunction.

PAIN MANAGEMENT

Aggressive pain control in the perioperative setting is important for patient comfort, increased early mobilization and decreased length of hospitalization. It has the additional effect of blunting the stress response and reduces the metabolic demands on myocardium in the postoperative setting. Although no study has examined this question specifically, adequate pain control is important for patients with known cardiac disease to reduce the risk of perioperative cardiac events.

APPENDIX

Relevant recommendations from the ACC/AHA guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery

(Reproduced from Fleisher LA, Beckman JA, Brown KA, et al. 2009 ACCF/AHA Focused Update on Perioperative Beta Blockade Incorporated into the ACC/AHA 2007 Guidelines on Perioperative Cardiovascular Evaluation and Care for Noncardiac Surgery. J Am Coll Cardiol. 2009;54:e13-118; originally published online Nov 2, 2009. With permission of the American College of Cardiology)

The American College of Cardiology and the American Heart Association have been publishing guidelines on the evaluation and care of cardiac patients undergoing noncardiac surgery since 1996. The latest iteration of the guidelines was published in 2007 with a focused update on perioperative beta-blockade published in 2009. The selected recommendations given below are taken from the combined document referenced.

Guideline recommendations are reported in one of four classes according to the criteria listed below:

- **Class I:** Procedure/treatment is recommended/indicated; general agreement that procedure/treatment is useful and effective; benefit far outweighs risk.
- **Class IIa:** Procedure/treatment probably recommended/indicated is reasonable to apply; some conflicting evidence regarding usefulness/efficacy, but weight of evidence/opinion is in favor of usefulness/efficacy; benefit outweighs risk.
- **Class IIb:** Procedure/treatment may be considered; usefulness/efficacy less well established because of greater conflicting evidence; benefit equals or slightly outweighs risk.
- **Class III:** Procedure/treatment not recommended; not useful/effective; may be harmful; should not be performed; risk may outweigh benefit.

In addition, each recommendation is assigned a level of evidence (LOE) according to the strength of evidence supporting the recommendation:

Level of Evidence A: There is sufficient evidence from multiple randomized trials or meta-analyses with general consistency of direction and magnitude of effect.

Level of Evidence B: There is limited evidence from a single randomized trial or non-randomized studies.

Level of Evidence C: Recommendation based only on expert opinion, case studies, or standard of care.

TABLE A-1

Recommendations for preoperative diagnostic testing

Indication	*Class I*	*Class IIa*	*Class IIb*	*Class III*
Noninvasive evaluation of LV function	None	It is reasonable for patients with dyspnea of unknown origin to undergo preoperative evaluation of left ventricular (LV) function. (LOE: C) It is reasonable for patients with current or prior HF with worsening dyspnea or other change in clinical status to undergo preoperative evaluation of LV function if not performed within 12 months. (LOE: C)	Reassessment of LV function in clinically stable patients with previously documented cardiomyopathy is not well established.(LOE: C)	Routine perioperative evaluation of LV function in patients is not recommended. (LOE: B)
12-lead resting ECG	1. Preoperative resting 12-lead ECG is recommended for patients with at least 1 clinical risk factor* who are undergoing vascular surgical procedures (LOE: B) 2. Preoperative resting 12-lead ECG is recommended for patients with known coronary heart disease, peripheral arterial disease, or cerebrovascular disease who are undergoing intermediate-risk surgical procedures (LOE: C)	Preoperative resting 12-lead ECG is reasonable in persons with no clinical risk factors who are undergoing vascular surgical procedures. (LOE: B)	Preoperative resting 12-lead ECG may be reasonable in patients with at least 1 clinical risk factor who are undergoing intermediate-risk operative procedures. (LOE: B)	Preoperative and postoperative resting 12-lead ECGs are not indicated in asymptomatic persons undergoing low-risk surgical procedures. (LOE: B)
Noninvasive stress testing before noncardiac surgery	Patients with active cardiac conditions (Table A-2) in whom noncardiac surgery is planned should be evaluated and treated per ACC/AHA guidelines† before noncardiac surgery. (LOE: B)	Noninvasive stress testing of patients with 3 or more clinical risk factors and poor functional capacity [< 4 metabolic equivalents (METs)] who require vascular surgery is reasonable if it will change management. (LOE: B)	1. Noninvasive stress testing may be considered for patients with at least 1 to 2 clinical risk factors and poor functional capacity (< 4 METs) who require intermediate-risk noncardiac surgery if it will change management. (LOE: B) 2. Noninvasive stress testing may be considered for patients with at least 1 to 2 clinical risk factors and good functional capacity (≥ 4 METs) who are undergoing vascular surgery. (LOE: B)	1. Noninvasive testing is not useful for patients with no clinical risk factors undergoing intermediate-risk noncardiac surgery. (LOE: C) 2. Noninvasive testing is not useful for patients undergoing low-risk noncardiac surgery. (LOE: C)

*Clinical risk factors include history of ischemic heart disease, history of compensated or prior heart failure, history of cerebrovascular disease, diabetes mellitus and renal insufficiency.
†Vascular surgery is defined as aortic and other major vascular surgery and peripheral vascular surgery (see Table A-2).

TABLE A-2

Risk mitigation: pharmacologic interventions

Intervention	*Class I*	*Class IIa*	*Class IIb*	*Class III*
Beta-blocker therapy	Beta-blockers should be continued in patients undergoing surgery who are receiving beta-blockers for treatment of conditions with ACC/AHA Class I indications for the drugs. (LOE: C)	1. Beta-blockers titrated to heart rate and blood pressure are probably recommended for patients undergoing vascular surgery who are at high cardiac risk owing to coronary artery disease or the finding of cardiac ischemia on preoperative testing. (LOE: B) 2. Beta-blockers titrated to heart rate and blood pressure are reasonable for patients in whom preoperative assessment for vascular surgery identifies high cardiac risk, as defined by the presence of more than 1 clinical risk factor. (LOE: C) 3. Beta-blockers titrated to heart rate and blood pressure are reasonable for patients in whom preoperative assessment identifies coronary artery disease or high cardiac risk, as defined by the presence of more than 1 clinical risk factor, who are undergoing intermediate risk surgery. (LOE: B)	1. The usefulness of beta-blockers is uncertain for patients who are undergoing either intermediate risk procedures or vascular surgery in whom preoperative assessment identifies a single clinical risk factor in the absence of coronary artery disease. (LOE: C) 2. The usefulness of beta-blockers is uncertain in patients undergoing vascular surgery with no clinical risk factors who are not currently taking beta-blockers. (LOE: B)	1. Beta-blockers should not be given to patients undergoing surgery who have absolute contraindications to beta blockade. (LOE: C) 2. Routine administration of high-dose beta-blockers in the absence of dose titration is not useful and may be harmful to patients not currently taking beta-blockers who are undergoing noncardiac surgery. (LOE: B)
Statin therapy	*Class I*	*Class IIa*	*Class IIb*	*Class III*
	For patients currently taking statins and scheduled for noncardiac surgery, statins should be continued. (LOE: B)	For patients undergoing vascular surgery with or without clinical risk factors, statin use is reasonable. (LOE: B)	For patients with at least 1 clinical risk factor who are undergoing intermediate-risk procedures, statins may be considered. (LOE: C)	None
Alpha-2 agonists	*Class I*	*Class IIa*	*Class IIb*	*Class III*
	None	None	Alpha-2 agonists for perioperative control of hypertension may be considered for patients with known CAD or at least 1 clinical risk factor who are undergoing surgery. (LOE: B)	Alpha-2 agonists should not be given to patients undergoing surgery who have contraindications to this medication. (LOE: C)
Intraoperative nitroglycerin	*Class I*	*Class IIa*	*Class IIb*	*Class III*
	None	None	The usefulness of intraoperative nitroglycerin as a prophylactic agent to prevent myocardial ischemia and cardiac morbidity is unclear for high-risk patients undergoing noncardiac surgery, particularly those who have required nitrate therapy to control angina. The recommendation for prophylactic use of nitroglycerin must take into account the anesthetic plan and patient hemodynamics and must recognize that vasodilation and hypovolemia can readily occur during anesthesia and surgery. (LOE: C)	None

TABLE A-3

Risk mitigation: other interventions

Coronary revascularization	*Class I**	*Class IIa*	*Class IIb*	*Class III*
	1. Coronary revascularization before noncardiac surgery is useful in patients with stable angina who have significant left main coronary artery stenosis. (LOE: A) 2. Coronary revascularization before noncardiac surgery is useful in patients with stable angina who have 3-vessel disease. (Survival benefit is greater when left ventricular ejection fraction is less than 0.50.) (LOE: A) 3. Coronary revascularization before noncardiac surgery is useful in patients with stable angina who have 2-vessel disease with significant proximal left anterior descending stenosis and either ejection fraction less than 0.50 or demonstrable ischemia on noninvasive testing. (LOE: A) 4. Coronary revascularization before noncardiac surgery is recommended for patients with high-risk unstable angina‡ or non-ST segment elevation myocardial infarction (LOE: A) 5. Coronary revascularization before noncardiac surgery is recommended in patients with acute ST-elevation MI. (LOE: A)	1. In patients in whom coronary revascularization with percutaneous coronary intervention (PCI) is appropriate for mitigation of cardiac symptoms and who need elective noncardiac surgery in the subsequent 12 months, a strategy of balloon angioplasty or bare-metal stent placement followed by 4 to 6 weeks of dual antiplatelet therapy is probably indicated. (LOE: B) 2. In patients who have received drug-eluting coronary stents and who must undergo urgent surgical procedures that mandate the discontinuation of thienopyridine therapy, it is reasonable to continue aspirin if at all possible and restart the thienopyridine as soon as possible. (LOE: C)	1. The usefulness of preoperative coronary revascularization is not well established in high-risk ischemic patients (e.g. abnormal dobutamine stress echocardiogram with at least 5 segments of wall-motion abnormalities). (LOE: C) 2. The usefulness of preoperative coronary revascularization is not well established for low-risk ischemic patients with an abnormal dobutamine stress echocardiogram (segments 1-4). (LOE: B)	1. It is not recommended that routine prophylactic coronary revascularization be performed in patients with stable coronary artery disease (CAD) before noncardiac surgery. (LOE: B) 2. Elective noncardiac surgery is not recommended within 4 to 6 weeks of bare-metal coronary stent implantation or within 12 months of drug-eluting coronary stent implantation in patients in whom thienopyridine therapy or aspirin and thienopyridine therapy will need to be discontinued perioperatively. (LOE: B) 3. Elective noncardiac surgery is not recommended within 4 weeks of coronary revascularization with balloon angioplasty. (LOE: B)
Preoperative ICU monitoring	*Class I*	*Class IIa*	*Class IIb*	*Class III*
	None	None	Preoperative intensive care monitoring with a pulmonary artery catheter for optimization of hemodynamic status might be considered; however, it is rarely required and should be restricted to a very small number of highly selected patients whose presentation is unstable and who have multiple comorbid conditions. (LOE: B)	None

*All of the Class I indications below are consistent with the ACC/AHA 2004 Guideline Update for Coronary Artery Bypass Graft Surgery.
‡High-risk unstable angina/non-ST elevation MI patients were identified as those with age greater than 75 years, accelerating tempo of ischemic symptoms in the preceding 48 hours, ongoing rest pain greater than 20 minutes in duration, pulmonary edema, angina with S3 gallop or rales, new or worsening mitral regurgitation murmur, hypotension, bradycardia, tachycardia, dynamic ST-segment changes greater than or equal to 1 mm, new or presumed new bundle-branch block on ECG or elevated cardiac biomarkers, such as troponin.

TABLE A-4

Perioperative management

Use of volatile anesthetics	*Class I*	*Class IIa*	*Class IIb*	*Class III*
Perioperative use of pulmonary artery catheters		It can be beneficial to use volatile anesthetic agents during noncardiac surgery for the maintenance of general anesthesia in hemodynamically stable patients at risk for myocardial ischemia. (LOE: B) Use of a pulmonary artery catheter may be reasonable in patients at risk for major hemodynamic disturbances that are easily detected by a pulmonary artery catheter; however, the decision must be based on 3 parameters: patient disease, surgical procedure (i.e. intraoperative and postoperative fluid shifts), and practice setting (experience in pulmonary artery catheter use and interpretation of results), because incorrect interpretation of the data from a pulmonary artery catheter may cause harm. (LOE: B)		
Transesophageal echocardiography	*Class I*	*Class IIa*	*Class IIb*	*Class III*
	None	The emergency use of intraoperative or perioperative transesophageal echocardiography is reasonable to determine the cause of an acute, persistent, and life-threatening hemodynamic abnormality. (LOE:C)	None	None
Intraoperative and postoperative ST- segment monitoring	*Class I*	*Class IIa*	*Class IIb*	*Class III*
	None	Intraoperative and postoperative ST-segment monitoring can be useful to monitor patients with known CAD or those undergoing vascular surgery, with computerized ST-segment analysis, when available, used to detect myocardial ischemia during the perioperative period. (LOE: B)	Intraoperative and postoperative ST-segment monitoring may be considered in patients with single or multiple risk factors for CAD who are undergoing noncardiac surgery. (LOE: B)	None
Surveillance for perioperative MI	*Class I*	*Class IIa*	*Class IIb*	*Class III*
	Postoperative troponin measurement is recommended in patients with ECG changes or chest pain typical of acute coronary syndrome. (LOE: C)	None	The use of postoperative troponin measurement is not well established in patients who are clinically stable and have undergone vascular and intermediate-risk surgery. (LOE: C)	Postoperative troponin measurement is not recommended in asymptomatic stable patients who have undergone low-risk surgery. (LOE: C)

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Chapter 103

Gender and Cardiovascular Disease

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Chapter Outline

- Prevalence of IHD in Women
- Identification and Management of IHD Risk Factors in Women
- Assessment of Symptoms and Myocardial Ischemia in Women
  - Symptom Assessment
  - Approaches for Diagnosing IHD in Women
- Management of IHD in Women
  - Acute Ischemic Syndromes: Differences in Presentation and Treatment in Women
  - Treatment Strategies for Women with Stable Coronary Artery Disease
  - Medical Therapy and Risk Factor Management for Stable CAD
  - Coronary Angiography and Revascularization for Stable CAD
- Heart Failure in Women
- Sex and Cardiac Arrhythmias
- Call for more Sex-specific Research

INTRODUCTION

Cardiovascular disease (CVD)—including ischemic heart disease (IHD), stroke and other heart diseases such as hypertension (HTN) and heart failure is the leading cause of mortality and disability for women in the United States. Nearly 37% of all female deaths in America occur from CVD. Although there has been a reduction in the death rate from CVD since 1980, reduction in mortality for women lags behind those realized for men,[1] and mortality has increased among women of younger age.[2]

The incidence and severity of CVD among premenopausal women is lower than among men of comparable age, even after correction for various risk factors.[3] The causes of these differences are unclear. Cardiovascular factors strongly associated with sex include vascular function (endothelium-dependent flow-mediated dilation and aortic compliance are greater in females) and a left ventricular (LV) mass index that is greater in males. Cardiovascular risk then increases with age in both sexes. However, this increase is sharper in women, so that in old age women have similar rates of CVD. In other words, there is a gradual, but striking loss of the "protective effect" of female gender, and once affected by IHD, females may actually have a worse prognosis than their male counterparts. The mechanisms underlying this differential age effect are not well understood. Changes in serum total cholesterol level, body mass index (BMI) and diabetes prevalence explain only 50% of the age-related increase in cardiovascular morbidity and mortality among women.[4]

PREVALENCE OF IHD IN WOMEN

Most cardiovascular events in women are caused by IHD. IHD, which includes coronary atherosclerotic disease, myocardial infarction, acute coronary syndromes and angina, is the largest subset of CVD mortality, with more than 240,000 women dying annually from the disease.[5] Given the aging population and epidemics of obesity and diabetes, the total number of women dying of IHD is projected to continue to rise. In addition to an absolute greater number of women dying from IHD than man (455,000 vs 410,000 annually),[6] a greater proportion of women die of sudden cardiac death before hospital arrival (52%) contrasted with 42% of men.[7]

During the past several decades, an evolving appreciation regarding sex differences in IHD has emerged. Significant differences exist between men and women in the epidemiology, diagnosis, treatment and prognosis of IHD that should be taken into consideration in the care of women with known or suspected disease. In general, women tend to get heart disease 10 years later in life than men, and they are more likely to have coexisting chronic conditions at the time of presentation or diagnosis. Paradoxical sex differences are observed where women have less anatomical obstructive coronary artery disease (CAD) and relatively preserved LV function yet greater rates of myocardial ischemia and mortality compared with similarly aged males.[8] Accordingly, it is proposed that the term IHD be used rather than CAD and coronary heart disease (CHD) for discussion specific to women. IHD in women presents a unique and complex challenge to clinicians as a result of larger symptom

burden, higher rate of functional impairment, a lower prevalence of obstructive CAD by coronary angiography, greater cost to the healthcare system and poorer outcomes as compared with men.[9] This societal burden of the disease is further intensified by a lack of public awareness on the part of patients and clinicians alike. Despite being the leading killer of women at all ages, the prevalence of obstructive CAD in women is relatively low before menopause (average age 51 years), only approaching equal prevalence rates for men and women in their seventh decade of life. This has over the years been misinterpreted that IHD is a disease of older women and those with significant other risk factors. Although awareness of CVD as the leading cause of death has increased significantly since national educational programs, such as the Heart Truth and Red Dress campaigns, have been targeted to women, awareness continues to lag among racial and ethnic minorities.[10] Work is needed to continue to improve awareness of the problem of CV health among both women and their healthcare providers, especially because awareness of CVD risks has been linked to implementation of preventative measures. Studies [such as those by the Women's Ischemic Syndrome Evaluation (WISE) study investigators] are also underway to address what is missing in our understanding of the gender gap and ultimately improve the care and outcomes in women with CVD and, in particular, IHD.

IDENTIFICATION AND MANAGEMENT OF IHD RISK FACTORS IN WOMEN

The incidence of IHD is very low among premenopausal women. Stroke incidence is higher than myocardial infarction,[11] whereas more than 80% of midlife women have one or more traditional cardiac risk factors. IHD mortality increases with the number of traditional cardiac risk factors, with 30-year death rate (per 10,000 person-years) ranging from 1.5 to 9.1 for women with 0 to greater than or equal to 2 risk factors.[12] Clustering of multiple risk factors is common after menopause, notably with the development of obesity, HTN and dyslipidemia, which is potentially related to hormonally mediated metabolic disturbances. Specifically, women have, on average, greater blood cholesterol levels than men after their 5th decade of life, and reveal mild decreases in high density lipoprotein (HDL) cholesterol after menopause. Low blood levels of HDL appear to be a stronger predictor of heart disease death in women than in men in the over-65 age group; Hypertriglyceridemia is a more potent independent risk factor for women than men.[13] Obesity is present in one-third of women, including 7% with BMI greater than or equal to 40 kg/m^2 with associated increased mortality.[14] Diabetic women have significantly increased IHD mortality rate compared with diabetic men. Most notably, 30-year trends reveal marked CVD mortality reduction for diabetic men but not for diabetic women.[15]

In addition to the traditional risk factors, it has been recognized that novel risk factors such as hormonal disturbances and inflammation due to autoimmune diseases may play prominent roles for IHD sex differences. Disruption of ovulatory cycling indicated by estrogen deficiency and hypothalamic dysfunction or irregular menstrual cycling in premenopausal women is associated with an increased risk of coronary atherosclerosis and adverse CVD events.[8] Polycystic ovary syndrome is prevalent in 10–13% of women and is linked with a clustering of risk factors and adverse IHD events postmenopausally.[16] Women who had premature menopause and/or oopherectomy may have accelerated atherosclerosis and possibly increased risk for IHD, although the causative link between low estrogen level and premature IHD may be confounded by other comorbid conditions.

Chronic inflammation-induced endothelial dysfunction due to underlying systemic autoimmune disorders is increasingly recognized as a nontraditional IHD risk factor. In the general population, individuals with elevated inflammatory biomarkers [e.g. C-reactive protein (CRP)] have increased CV events.[17] Patients with Rheumatoid Arthritis (RA) have chronically elevated CRP and other inflammatory markers and increased CV mortality not explained by established cardiac risk factors. Premenopausal women with a history of lupus have 5–10 times the risk of IHD-related events compared with the background population. The reason for this increased risk of IHD is likely to be multifactorial. Additional metabolic, inflammatory and immunological factors as well as therapy with agents such as corticosteroids are likely to have an adverse effect on cardiovascular risk in this population. The new drugs, such as TNF-alpha receptor blockers or IL-6 blockers, provide an interesting opportunity to test the hypothesis that the specific reduction of inflammation will reduce IHD incidence.

Use of traditional risk factors and scoring system such as the Framingham risk score (FRS) has been recognized to underestimate IHD risk in women. The FRS, calculated by summing point scores given to age, blood pressure, cholesterol, diabetes and cigarette smoking, is used to classify patients' 10-year risk of CAD death or MI to determine the appropriate level of therapeutic intervention for both low-density lipoprotein cholesterol and HTN. However, the FRS classifies more than 90% of women as low risk with very few assigned a high-risk status before the age of 70.[18] The Reynold's risk score is a sex-specific tool recently devised from large derivation (n = 24,588) and validation (n = 8,158) cohorts of women.[19] It incorporates high-sensitivity CRP (hsCRP) into the equation. When compared with the FRS, use of the Reynold's score resulted in risk reclassification in more than 40% of intermediate FRS women. The use of multiple novel biomarkers has also been reported by other authors to improve IHD risk assessment in women.[20-22] As we gain more in-depth understanding of the sex-specific pathophysiology of IHD in women, further investigation into the optimal utilization of novel risk factors for IHD risk stratification in women is needed.

Two-thirds of women who die suddenly from CHD had no previous symptoms (compared with half of men). This suggests that the primary prevention—risk factor modifications in patients who do not have clinical evidence of IHD–must be a key strategy to reduce the burden of IHD in women. There are a number of published guidelines from the American Heart Association (AHA), American College of Cardiology (ACC) and National Institutes of Health-National Heart, Lung, and Blood Institute (NIH-NHLBI, e.g. NCEP III-ATP) that detail management strategies for primary prevention risk-reducing

methods for men and women.[23] Risk-reducing strategies, including control of major cardiac risk factors (e.g. weight, blood pressure, smoking and regular exercise), can be extremely effective in reducing cardiac risk and preventing heart disease in women.

Tobacco use is the leading preventable cause of IHD in women, especially in those who have 50 years of age or younger. Aggressive public health campaigns put forth over the last decades have resulted in declining smoking rates for both women and men. Based on the 2008 National Health Interview Survey, smoking prevalence was 18.3% in the adult women population in the United States, whereas 33.9% of women were smokers in 1965.[24] There appears to be a dose-dependent relationship between total tar consumption per day and risk of myocardial infarction. As few as 1–4 cigarettes per day increases a patient's risk of fatal or nonfatal MI by as much as twofold to threefold. There is also a well-established synergistic relative risk for women who smoke and also use oral-contraceptives, including an elevated risk of thrombosis and cardiovascular complications. Clinicians should counsel female smokers to quit as smoking cessation decreases CVD morbidity and mortality. One year after cessation, risk of MI decreases by 50%, and in 10 years, the CVD rate approaches that of nonsmokers.[25]

Ischemic heart disease prevalence increases for women in their postmenopausal years. Studies have suggested that the determinants of a woman's risk for IHD at older age are largely determined by her levels of risk factors at premenopausal to early postmenopause.[26] Risk factors measured premenopause therefore could be key determinants of postmenopausal IHD and prevention of such risk factors premenopausal may be instrumental in successful reduction of the risk of IHD for postmenopausal women. The role of estrogen supplementation in postmenopausal women has been the focus of most research aimed at both primary and secondary prevention of CVD risk. In a woman's premenopausal years, estrogen levels are approximately 10 times higher than that of an older-aged woman, which is accounted for primarily by the ovarian production of estrogen. Endogenous estrogen may serve to protect a woman's risk of IHD through higher levels of high-density lipoprotein (HDL) cholesterol, improved arterial compliance and coronary flow reserve, as well as improvements in global myocardial function responses to stress.[25] The net benefit of estrogen or combined estrogen-progestin replacement therapy in postmenopausal women is still uncertain. Extensive observational data suggest that estrogen may be cardioprotective. Recent results from clinical trials have shown that estrogen therapy alone or in combination with progestin does not protect from heart disease or stroke and may even be harmful.[27-29] Most of them now agree that the estrogen is still a reasonable therapy when used short-term for menopausal symptoms, but it should not be prescribed for either primary or secondary prevention of IHD or stroke.

In numerous population-based studies, diabetic women have a threefold to severe fold increase in IHD death when compared to a twofold to threefold increase in death for diabetic men.[25] A key to effective blood glucose control is the maintenance of a diet low in saturated fats and cholesterol along with optimal weight control. Patients are also recommended to adopt a regular exercise regimen as the risk of diabetes increases with increased weight and BMI. For women, a BMI greater than 30 is associated with an increased risk for diabetes, HTN, heart failure as well as other major adverse cardiac events. Optimal risk reduction strategies can be effective at reducing the risk of heart disease and its associated adverse sequelae.

Nearly one in three adults has HTN, which is defined as systolic blood pressure (SBP) greater than 140 mm Hg and/or diastolic number greater than 90 mm Hg. HTN is a major risk factor for IHD. A higher percentage of men than women have HTN until age 45. From ages 45–54, the percentage of women is slightly higher. After that a much higher percentage of women have HTN than men do. In addition to traditional risk factors such as dyslipidemia, obesity and diabetes, other factors, such as autonomic mechanisms as well as hemodynamic and metabolic influences, are also implicated in the high prevalence of HTN and CVD in older women.[30] For women, HTN leading to diastolic dysfunction is a major cause of congestive heart failure, noted as the primary cause in 60% of cases of heart failure in women. Elevation in blood pressure also increases a patient's risk of stroke as well as IHD. Furthermore, prognostic implications of LV hypertrophy caused by HTN may be more profound in women than in men.[31] Although genetics do play a strong role in developing HTN, modifiable and environmental factors can aid in blood pressure control. Initial steps to control HTN include weight control and dietary changes. Particularly, dietary modifications as part of a primary prevention program should include lowering of sodium intake and reduction of alcohol consumption. There is evidence that hypertensive females, in comparison to male patients, are more likely to benefit from salt reduction and aggressive blood pressure lowering. Diets high in fruits and vegetables have also been reported to lower blood pressure. Following initial care for weight control and dietary changes, some hypertensives may require drug therapy [e.g. beta blockers, diuretics, angiotensin-converting enzyme (ACE) inhibitors] to provide adequate blood pressure control. The issue of optimal blood pressure target in patients at high risk for IHD such as those with diabetes remains unresolved. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood pressure[32] recommended a blood pressure goal below 130/80 mm Hg in patients with diabetes, but this recommendation was not based on evidence from randomized, controlled trials. Recent studies[33,34] revealed that the tight control of SBP to less than 120 mm Hg among patients with diabetes was not associated with the improved cardiovascular outcomes compared with usual control to a SBP target of less than 140 mm Hg, whereas serious adverse events that were attributable to blood pressure medication were more frequent in the intensive therapy group.

The rational for treating hypercholesterolemia as primary preventative measure is based upon epidemiologic data documenting a continuous graded relationship between the total plasma cholesterol concentration and CHD events and mortality.[35,36] In premenopausal women, genetic disorders of lipid metabolism [i.e. elevated low-density lipoprotein (LDL) or apolipoprotein B (ApoB)] are probably the most important determinants of premature IHD. Current cholesterol manage-

ment has been published by the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III).[37]

In high-risk patients, defined as those with known CHD or equivalents with 10-year risk greater than 20%, the NCEP updated guideline calls for drug therapy in those with LDL cholesterol levels between 100 and 129 mg/dL. Instead of explicitly recommending clinicians lower LDL cholesterol in high-risk patients to levels less than 70 mg/dL, the ATP III report left the door open for future evidence. In these very high-risk patients, lowering LDL cholesterol levels to less than 70 mg/dL remains a "therapeutic option", while the definitive recommendation is to lower LDL cholesterol levels to a target of less than 100 mg/dL.

In moderate-risk patients, those with two or more risk factors for CHD (10–20% risk of CHD within 10 years), the NCEP target remains LDL cholesterol less than 130 mg/dL but gives clinicians a new therapeutic option to treat to less than 100 mg/dL.

In low-risk patients, those with 0–1 risk factor, the target LDL cholesterol is less than 160 mg/dL with option to implement lipid lowering therapy if not meeting this target despite adequate therapeutic lifestyle changes.

Statins (3-hydroxy-3-methyl-glutaryl coenzyme A reductase inhibitors) were shown to be effective in lowering cholesterol and have been extensively studied. The absence of women in the earlier statin trials led to questions about extrapolating to women. A meta-analysis of data later indeed demonstrated the efficacy of statins in women.[38] A large-scale trial (JUPITER) showed that for primary prevention benefits from statins are similar in women 60 years or older and men 50 years or older.[39] However, the number needed to treat and side effects might be higher in women than in men.[40] Further research is needed to define the risk-benefit ratio of statins for primary prevention in diverse populations of women with varying risks of CVD. In the meantime, aggressive lipid-lowering should be integrated within a well-rounded primary prevention program to further reduce IHD risk in women.

In several studies, HDL-C concentration was found to be the best predictor of IHD in women.[41] The Framingham heart study showed women in the lowest quintile of HDL-C to have a relative risk of IHD three times higher than those in the highest quintile.[42] In ATP III, the definition for low HDL was revised to less than 50 mg/dL (1.29 mmol/L) for women; low HDL for men was changed to below 40 mg/dL (1.04 mmol/L), up from less than 35 mg/dL (0.91 mmol/L) used in the first two ATP reports. ATP III does not explicitly specify a goal for raising HDL. The current body of literature, however, is limited with regard to HDL-C-raising therapies specifically for women. Among drug therapies, niacin continues to be the most effective, especially when combined with fibrate or statin therapy. Currently, no role exists for the use of estrogen replacement therapy to raise HDL-C or to reduce cardiovascular risk in post-menopausal women. Lifestyle alterations that include dietary changes, smoking cessation and aerobic exercise must be employed concomitantly with pharmacotherapy to achieve the best clinical results. New modalities currently being investigated to further increase HDL-C levels include CETP inhibitors, exogenous HDL mimetics, and ABCA1 upregulators.

Elevated triglyceride levels appear to be a stronger risk factor for IHD in women than in men.[13,41] Framingham study data reveal that individuals with triglyceride levels exceeding 150 mg/dL have an increased IHD risk greater than 1.5.[43] Triglyceride values that exceed 350 mg/dL are associated with a twofold increased IHD risk. ATP III defines triglycerides of 150–199 mg/dL (1.70–2.25 mmol/L) as borderline high, 200–499 mg/dL (2.26–5.64 mmol/L) as high and greater than or equal to 500 mg/dL (5.65 mmol/L) as very high. Although the exact role and mechanism that triglycerides play in the development of CAD is not yet completely understood, for women with elevated levels, it is important to reduce fat intake and restrict the intake of simple carbohydrates to reduce triglyceride levels. The Action to Control Cardiovascular Risk in Diabetics (ACCORD) lipid[44] trial demonstrated that addition of fenofibrate to statin therapy did not further reduce the rate of major cardiovascular events in the majority of patients with type 2 diabetes mellitus who were at high risk for CVD. Prespecified subgroup analyses suggested heterogeneity in treatment effect according to sex, with a benefit for men and possible harm for women (P = 0.01 for interaction) and a possible interaction according to lipid subgroups, with a possible benefit for patients with high baseline triglyceride and low baseline HDL cholesterol levels (P = 0.057 for interaction). Interestingly, the treatment interaction according to sex for the entire ACCORD lipid cohort was not observed in the sub-subgroup of female patients with dyslipidemic profile as defined by the study (triglyceride level 204 mg/dL or more and HDL cholesterol of 34 mg/dL or less). Results from this trial and others support the view that combination lipid lowering therapy should be limited to those high-risk patients with substantial dyslipidemia.

In terms of other pharmacological therapy targeting the primary prevention population, aspirin is recommended for men with a 10-year IHD risk of 10% or more and for women with 10-year IHD risk of 20% or more, given different thresholds of risk and benefit. Published data available from six large-scale primary prevention trials and their meta-analyses[45,46] demonstrate that aspirin conclusively reduces the risk of a first MI by about one-quarter to one-third, but the available data on stroke and cardiovascular death are inconclusive. The totality of randomized evidence suggests that there are no differences in response to aspirin between men and women. The decision to prescribe aspirin for primary prevention should be an individual clinical judgment that weighs the benefit in reducing the first MI against the established risk of major bleeding with long-term administrations.

In summary, a large number of differences in risk-factor prevalence and outcome exist between men and women. Generally, women have a greater degree of comorbidity, an older age of presentation and a larger risk-factor burden, which play important roles in clinical outcomes. A compilation of evidence suggests that there is sex-related variation in the interplay of risk factors; hormonal factors, and disease burden that further impact on outcome. For optimal prevention, the aim of a healthy lifestyle is to prevent the future evolution of cardiac risk factors. Optimal utilization of risk scores, identification and management of risk factors, provides the platform for reducing a large

percentage of the population attributable risk for IHD in women.[25]

ASSESSMENT OF SYMPTOMS AND MYOCARDIAL ISCHEMIA IN WOMEN

SYMPTOM ASSESSMENT

There are substantial differences between women and men in the type, frequency and quality of symptoms noted during chest pain presentations.

A careful medical history and physical exam can provide the key elements to determine IHD likelihood. As presented in Figure 1, the likelihood of significant obstructive coronary disease is variable by the type of chest pain symptoms, including noncardiac chest pain, atypical angina or typical angina.

Typical angina is defined as having all three of the following characteristics: (1) substernal chest discomfort (almost never a sharp or stabbing pain) with a *quality* characterized by patients as "squeezing", "grip-like", "pressure-like", "suffocating" and "heavy", unchanging with position or respiration and a *duration* of angina episodes that typically last minutes (a fleeting discomfort or a dull ache lasting for hours is unlikely to be angina); (2) provoked by exertion or emotional stress and (3) relieved by rest or nitroglycerin. Atypical angina meets two of the previous characteristics, whereas noncardiac chest pain meets one or none of the typical angina characteristics. However, attempts to apply the "typical" angina definition derived predominantly from male population to female cohorts frequently hamper the clinical evaluation of women patients. The symptoms, that women experience, often differ from the "classic" symptoms (substernal crushing chest pain radiating to the left arm) typically perceived by men. In women, the pain may be: (1) centered in the chest with or without radiation down one or both arms; (2) located in the ear, jaw or neck region or (3) located in the back or shoulder region.[48] Other reported symptoms are diaphoresis, light-headedness, shortness of breath, nausea and vomiting; these symptoms may or may not accompany chest pain or discomfort. As women present later in life and are more often functionally impaired, their frequency of nonexertional symptoms is higher than that of their male counterparts. Additionally, for elderly women, shortness of breath is more often the initial presenting symptoms for acute MI. As such, the differential presentation of an acute MI in at risk symptomatic women provides a unique diagnostic challenge.

Despite the reported gender differences, when women do present with typical symptoms acutely, defined as chest pain or discomfort, dyspnea, diaphoresis and arm or shoulder pain, they are significantly associated with acute coronary syndrome.[49] It is also noted that older women often present similarly to men with typical angina symptoms, whereas younger women are also less likely to present with ST-segment elevations, a factor that may protract their time to diagnosis, the ensuing intensity of management, and result in worsening outcomes. When evaluated for symptoms suggestive of myocardial ischemia, women have lower rates of obstructive CAD at angiography.

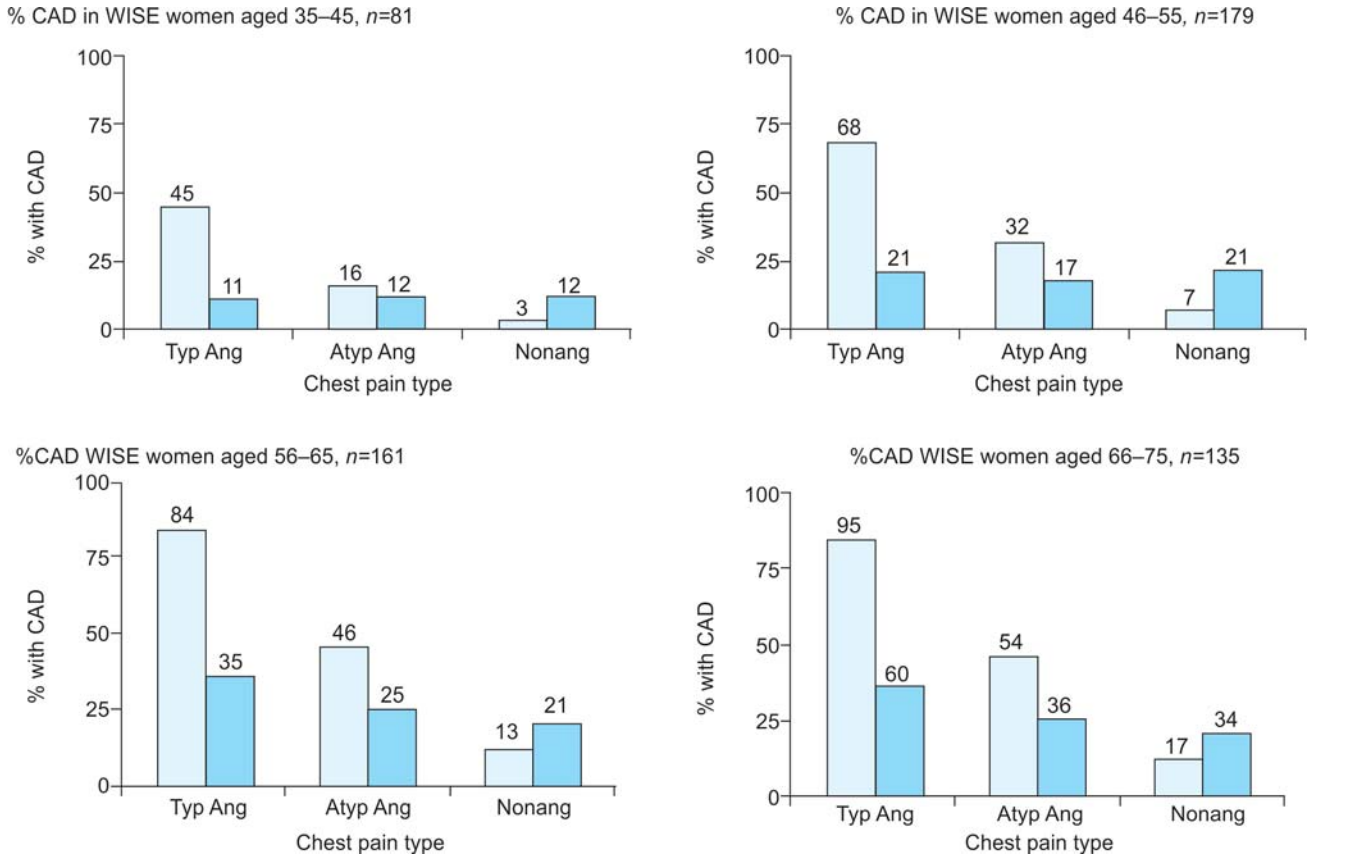


FIGURE 1: From the women's ischemia syndrome evaluation (WISE), the diamond probability of coronary artery disease (CAD) as compared with observed CAD prevalence in symptomatic women ages 35–45, 46–55, 56–65 and 66–75 years[47] (Notes: *Solid bars* = WISE prevalence; *Open bars* = diamond probability)

A majority of women without obstructive CAD at coronary angiography continue to have symptoms that contribute to a poor quality of life and consumption of large amounts of healthcare resources due to repeated evaluations and hospitalization. Moreover, the Coronary Artery Surgical Study (CASS) Registry most clearly demonstrated that for a given extent of CAD (single, double or triple vessel) measured by angiography, women were more symptomatic, had more functional (Canadian Cardiovascular Society) impairment, and more unstable symptoms than men.[50] Data from the Women's Health Initiative document that women with nonspecific chest pain have a twofold greater risk for nonfatal MI,[51] whereas WISE data demonstrate increased rates of mortality in women with chest pain and no obstructive CAD,[52] underscoring that prognosis in these women is not benign.

Initial skepticism about altered pain threshold and psychologic factors operative in women has gained credence, although Cardiac Syndrome X (angina-like chest pain despite normal coronary angiograms, especially those with ischemic-appearing ST-segment depression during exercise) is also increasingly recognized and appreciated based on the finding of abnormal coronary flow velocity reserve suggestive of microvascular dysfunction in these women.[53] Recently, Han et al.[54] studied patients with obstructive CAD who also underwent simultaneous intravascular ultrasound and coronary reactivity assessment and demonstrated that men have a greater atheroma burden and more diffuse epicardial endothelial dysfunction while women have more disease of the microcirculation. These factors may influence the higher rates of angina, ischemia and acute coronary syndrome (ACS) in the absence of obstructive CAD in women supporting coronary microvascular dysfunction as a prominent disorder in women compared to men.

Accumulating evidence over the years also supports the crucial role endothelium plays in vascular homeostasis. Endothelial dysfunction is characterized by impairment of endothelium-dependent vasodilation as well as emergence of proinflammatory and prothrombotic endothelial phenotypes that promotes atherosclerosis, plaque progression and occurrence of clinical events.[55] Almost all known cardiovascular risk factors, including hypercholesterolemia, HTN, hyperglycemia, smoking and aging, are associated with endothelial dysfunction. Indeed, studies have shown that endothelial dysfunction is present in patients with risk factors, but without angiographic or ultrasound evidence of obstructive disease. There is also considerable evidence that endothelial dysfunction contributes to clinical events.[56]

The relative importance of endothelial and microvascular dysfunction has only recently been recognized and as yet insufficiently explored. An integrated understanding of mechanisms and manifestations of ischemia impacting IHD risks in women has been summarized in Figure 2.[8] It is hypothesize that coronary microvascular dysfunction is more prevalent in women than in man as the result of risk factor clustering, vascular inflammation and remodeling, and hormonal alterations and is etiologic for the observed paradoxical frequent yet atypical symptoms, evidence of ischemia and adverse outcomes. This model, although in need of validation by more studies, provides a rational for incorporating nonobstructive atheroma into the risk stratification tool in diagnosing IHD in women.

APPROACHES FOR DIAGNOSING IHD IN WOMEN

Recommendations for the workup of women presenting with stable angina are summarized in Flow chart 1.[47]

For woman presenting with symptoms of chest pain and suspected IHD, the preferred management approach is to perform a noninvasive stress testing to assess the severity of the residual ischemia. Although specific exceptions were allowed, the guidelines recommended that standard exercise testing be used in the initial female evaluation. Interpretation of the exercise test includes symptomatic response, exercise capacity, hemodynamic response as well as ECG response. Abnormalities in exercise capacity, SBP response to exercise,

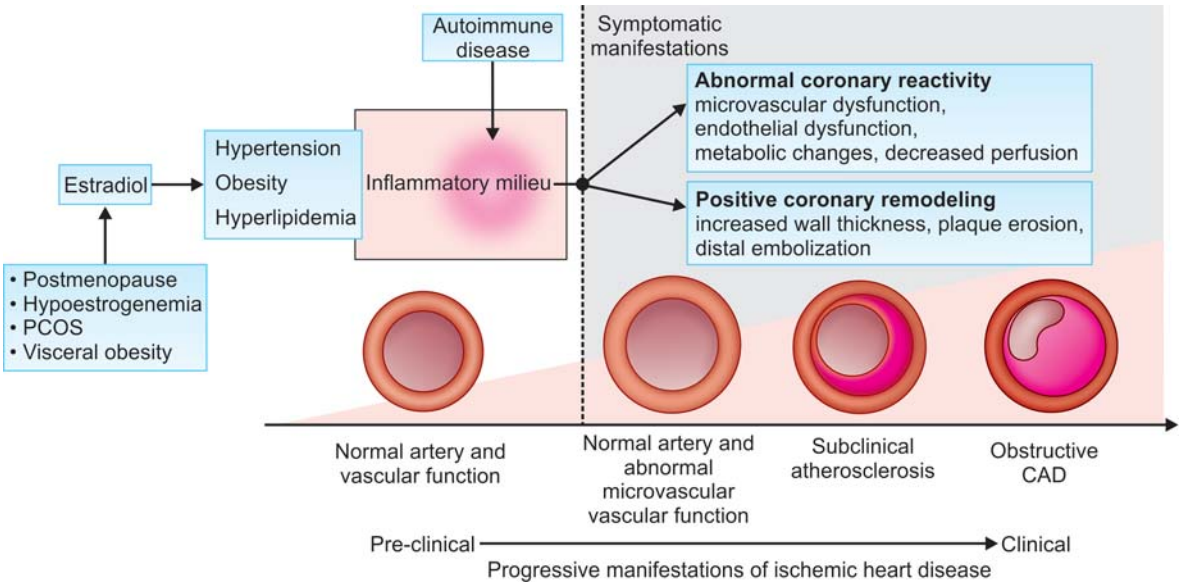
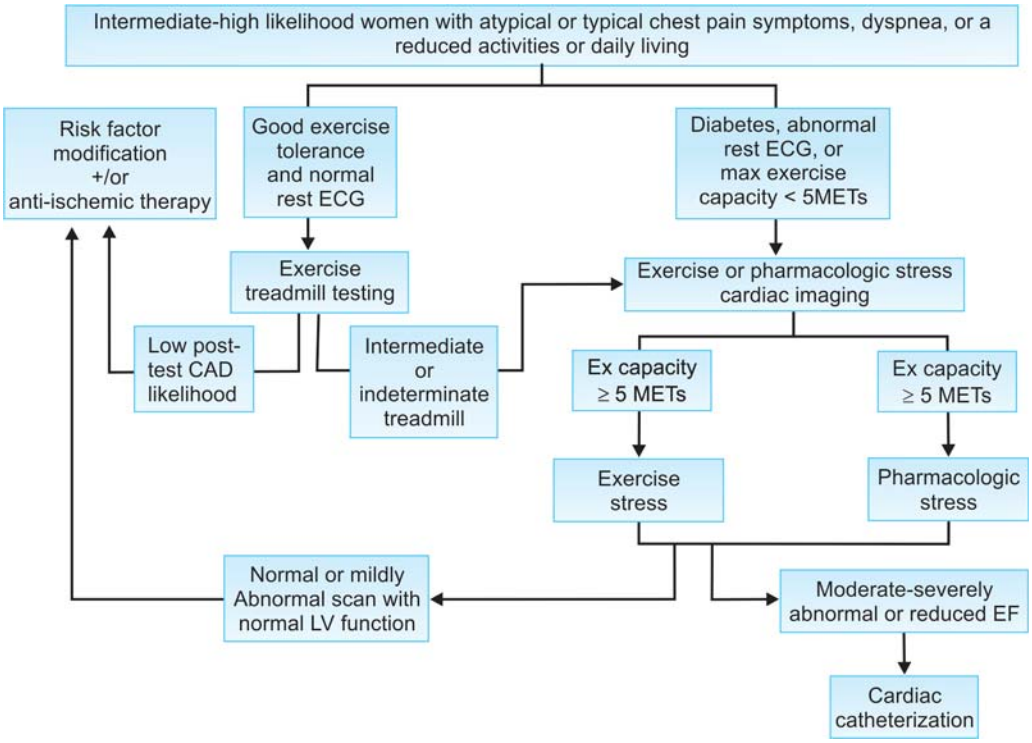


FIGURE 2: Overarching working model of ischemic heart disease pathophysiology in women[8]
(Abbreviations: CAD: Coronary artery disease; PCOS: Polycystic ovary syndrome)

FLOW CHART 1: A revision of consensus statement from the American Society of Nuclear Cardiology (ASNC) workup algorithm for noninvasive testing in women[57]



(Abbreviations: CAD: Coronary artery disease; ECG: Electrocardiogram; EF: Ejection fraction; Ex: Exercise; LV: Left ventricle/ventricular; METs: Metabolic equivalents)

heart rate response to exercise and occurrence of ischemic chest pain during exercise are all important findings that carry diagnostic as well as prognostic significance above and beyond ECG interpretations.[58] Therefore, exercise-based test is the preferred diagnostic modality of choice over pharmacological test in those patients who are able to exercise.

The different noninvasive and invasive modalities as they are applied in women patients are discussed separately below.

Exercise Electrocardiographic Evaluation

The exercise ECG is the most frequently performed diagnostic test. Using a threshold for abnormality of greater than or equal to 1.0 mm of ST-segment depression, it has a lower diagnostic accuracy (sensitivity and specificity for significant coronary artery obstruction at approximately 60–70%). Multiple factors contribute to the decreased diagnostic accuracy of exercise ECG in women, such as lower CAD prevalence as well as greater comorbidity and functional impairment that preclude women from achieving maximal levels of exercise. In sedentary women, an early hyper-exaggerated heart rate response, excessive dyspnea and premature fatigue can be seen in the early stages of exercise protocol. Women who could not achieve maximal level of exercise with no inducible ischemia remain without a diagnostic confirmation for the symptoms. The other problem more frequently encountered in exercise ECG in women is the relatively high false positive rate.[59] A digoxin-like effect of endogenous estrogen can possibly promote false positive rates in premenopausal women. For the premenopausal women, chest pain and the inducibility of ST-segment abnormalities can vary by the menstrual cycle with lower mid-cycle estradiol levels being associated with a greater frequency, intensity and severity of ECG-based ischemia.[47] These findings reveal that relying on the exercise ECG alone for IHD diagnosis may be less accurate in women than in men. However, exercise stress test risk scores (e.g. Duke treadmill score) have been shown to improve prognostic performance of exercise ECG test in women but, of all the factors noted during testing, the strongest predictive parameter from the treadmill test is exercise duration. Peak and recovery heart rate measures have also been shown to improve risk assessment and diagnostic accuracy for IHD in women. The measurement of heart rate recovery may be particularly important for deconditioned women who have a rapid heart rate increase early into the test and remains elevated during recovery.

Stress-induced Perfusion Abnormality Assessment

In the progression of the ischemic cascade, reductions in myocardial perfusion occur earlier than either ECG changes or ventricular wall motion abnormalities and may provide a more sensitive measure for estimating IHD risk. Myocardial perfusion single-photon emission computed tomography (SPECT) is a nuclear-based technique that is most commonly used in the evaluation of women presenting with chest pain symptoms. Generally, the literature supports SPECT imaging as a highly sensitive test for the detection of CAD in both women and men. A recent study of 3,213 women and 5,458 men who underwent exercise treadmill stress testing with myocardial perfusion imaging demonstrated that more women than men had a false-

positive test, whereas the false-negative rate was significantly lower in women than in men. In fact, women who underwent stress testing with imaging had a lower test sensitivity and positive predictive value, but higher test specificity, negative predictive value and accuracy in comparison to men.[60]

The accuracy of SPECT techniques is subject to the same limitations of exercise ECG when it is performed in conjunction with an exercise program. Specifically, women with a limited exercise tolerance enjoy the diminished diagnostic accuracy with SPECT testing as well. For those patients who are unable to adequately exercise, pharmacologic stress testing (commonly performed with adenosine or dipyridamole or the newly developed selective A2A adenosine receptor agonist—Regadenoson) is recommended by the American College of Cardiology/American Heart Association and American Society of Nuclear Cardiology Guidelines as a reasonable alternative. Diagnostic specificity can be affected by both breast tissue and obesity that degrade image quality and cause false positive test results, especially in the anterior and lateral aspects of the heart. For this reason, the higher energy Tc-99 m radioisotopes are preferred in women due to a reduction in soft tissue attenuation artifacts. Further reduction in false positives can be achieved by attenuation corrections or prone imaging techniques as well as integrating global or regional LV wall motion, function and wall thickness as a guide to discerning true positive reductions in regional myocardial perfusion.

For SPECT perfusion techniques, deficits are identified based upon variations in the regional distribution of blood flow that is comparatively assessed across the myocardium. It is therefore possible that in the setting of global coronary vascular dysfunction (endothelial or microvascular dysfunction), the SPECT study could show no regional differences in the distribution of flow and appear normal. Additionally, global reduction in flow or impaired vasodilatory response to stress may reflect balanced reduction in flow in the setting of severe, multi-vessel CAD. A study by Hansen et al. reported that SPECT detects CAD in fewer women than in men, and they found a significant statistical correlation of their results to the smaller heart sizes in women and the limited spatial resolution of SPECT cameras.[61] This raises the possibility that the smaller myocardial areas of reduced perfusion in women may be missed. Although these small abnormalities may not be prognostically significant, they may explain persistent anginal symptoms in women, particularly for those without obstructive CAD. Contemporary techniques that use Tc-99 m agents, prone imaging and/or attenuation correction algorithms diminish the frequency of artifacts.

Cardiac positron emission tomography (PET) has over time ascended to the "gold standard" status for noninvasive assessment of myocardial perfusion and viability, due to its inherently quantitative nature, its superior detection sensitivity, and its advantageous spatial and temporal resolution over conventional SPECT techniques. Use of FDA-approved ^{82}Rb and ^{13}N-ammonia as PET perfusion tracers allow for short imaging protocols due to their short half-lives. In recent years, technical innovations such as new detector material and reconstruction algorithms have contributed to a steady improvement in the performance of clinical cardiac PET systems.[62] A recent review reports a weighted sensitivity of 90% and specificity of 89% for the detection of significant CAD.[63] The use of ^{82}Rb PET has several advantages in women, including quantification of absolute values of regional and global blood flow to assess microvascular disease (flow reserve) and integrated attenuation correction along with improved image quality compared with SPECT. The use of PET has notable advantage for obese women; however, there is limited prognostic data with no sex-specific reports.

Stress-induced Wall Motion Abnormality Assessment

As wall motion abnormalities appear after perfusion abnormalities, identification of this marker has been associated with a higher diagnostic specificity and prognostic significance. Stress echocardiography, the most commonly applied test for wall motion assessment, has advantages due to its low cost, absent radiation exposure and ability to image both cardiac structures as well as ventricular function. Despite these advantages, stress echocardiography can become a suboptimal option due to obesity or lung disease with poor acoustic windows and reducing exercise tolerance. Variable operator experience and local expertise also reduce the general applicability of stress echocardiography in many centers. Women with poor exercise tolerance are commonly referred to dobutamine stress echocardiography. Table 1 summarizes the diagnostic accuracy of the modalities.

Cardiovascular MR Assessment

Stress CMR imaging uniquely allows the measurement of subendocardial perfusion. In a report of 19 symptomatic women with abnormal stress tests and normal coronary angiograms, subendocardial ischemia frequently was observed.[64] This finding was later confirmed in a larger cohort reporting a strong correlation between subendocardial ischemia and abnormal

TABLE 1

Summary of published meta-analyses on the diagnostic accuracy of exercise electrocardiography, stress echocardiography and stress SPECT imaging in women[47]

	Exercise electrocardiography		*Stress echocardiography*		*Stress SPECT**	
Author, Year (Ref.)	*Sensitivity*	*Specificity*	*Sensitivity*	*Specificity*	*Sensitivity*	*Specificity*
Fleischmann et al., 1998	—	—	85%	77%	87%	64%
Kwok et al., 1999[59]	61%	70%	86%	79%	78%	64%
Beattie et al., 2003	—	—	81%	73%	77%	69%
Average	61%	70%	84%	76%	81%	66%

*SPECT: Single photon emission computed tomography

coronary reactivity testing,[65] although population heterogeneity has resulted in varying results.[66] Further investigation into the prognostic implications of CMR subendocardial ischemia in women with regard to IHD events and its association with future angina burden is needed.

Coronary Computed Tomographic Angiography

Coronary computed tomographic angiography (CCTA) is a noninvasive anatomic technique with a reported high diagnostic accuracy for obstructive CAD. In a series of 51 women and 52 men, diagnostic sensitivity and specificity were similar by sex at 85% and 99%;[67] although a recent larger controlled trial reported a lower specificity of 90%.[68] An inherent limitation of CCTA is that it should be used cautiously in younger women given a heightened lifetime cancer risk with ionizing radiation exposure. Test protocols emphasizing reductions in radiation exposure, including ECG-controlled tube current modulation, prospective gating, minimization of scan length and optimization of tube current and voltage, should be emphasized in women.

In summary, it is important to recognize that women with angina and confirmatory ischemia have an elevated IHD mortality.[69] Abnormalities in functional capacity and noninvasive imaging are valuable IHD risk predictors in symptomatic women. Further work is needed to integrate the use of existing and emerging strategies to optimize IHD risk detection in women.

Coronary Angiography

Coronary angiography use as a diagnostic tool may be indicated if a patient's risk factors, medical history and clinical presentation are consistent with an intermediate-to-high IHD probability. If a patient's symptoms are definitive, a diagnostic angiogram would help to define the patient's coronary anatomy and the amount of myocardium at risk. However, if more information is needed before a diagnosis can be made, it is preferable to proceed with noninvasive testing first, starting with an ECG (despite the limitations previously noted), proceeding to an exercise imaging study (myocardial perfusion imaging or echocardiography) if ECG is ambiguous. Pharmacological stress should be used if the patient is unable to exercise. If the patient is not at high risk for a cardiac event, and if noninvasive testing has provided sufficient information for diagnosis, an angiogram can be postponed until its need becomes evident in the future. For high-risk women, with either a high coronary disease probability or with unstable symptoms (e.g. increasing chest pain frequency in the proceeding 6 weeks of evaluation, rest angina, etc.), the decision to perform diagnostic angiography is supported by an abundance of evidence. However, angiography may not be an option for women who are not good candidates for revascularization, especially elderly women. For those patients and symptomatic women with an intermediate risk of coronary disease, the decision to perform diagnostic testing, including exercise echocardiography or myocardial perfusion imaging, is part of the standard workup. Subsequent management ensues for women who undergo noninvasive testing based on the extent and severity of abnormalities detected during testing.

Among women referred for coronary angiography, the magnitude and frequency of angina-type chest pain classified as an ACS, yet occurs in the absence of coronary artery stenosis, is of practical importance but remains largely unexplained. It has been shown that women are five times as likely as men to have normal coronary angiograms at catheterization.[70,71] Although this may suggest that women were referred inappropriately for catheterization, a number of studies have also documented sex-based differences in utilization rates of coronary angiography and revascularization, even among those with positive exercise tests for subsequent chest pain,[72] contributing to a poorer outcome. In one report, for example, women with a positive exercise test were more likely to have no further cardiac evaluation than men (62% vs 38%), a difference that, at three year follow-up, was associated with a higher incidence of MI or death in women (14.3% vs 6% year in men).[73] Other studies, however, have not found a difference in catheterization rates between men and women. In a review of over 3,000 patients (33% women) who underwent exercise radionuclide imaging, referral rates for men and women were comparable when stratified by the amount of abnormally perfused myocardium detected,[74] yet the subsequent cardiac event rate was higher for women than men (17.5% vs 6.3%), suggesting that women were being under-referred for comparable degree of risk. The possible bias against performing coronary revascularization in women has been acknowledged in the past decade. Women with abnormal noninvasive tests are currently more likely to be referred to coronary angiography as compared with a decade ago.[75] Furthermore, a recent report from the Study of Myocardial Perfusion and Coronary Anatomy Imaging Roles in CAD (SPARC) Registry[76] reveals that women were approximately twice as likely as men to be referred to cardiac catheterization after cardiac imaging, irrespective of the modalities used. Whether this finding reflects excessive referral in women versus underutilization in men requires further investigation; however, this finding possibly reflects the increased recognition of IHD in women over the past decade or so.

MANAGEMENT OF IHD IN WOMEN

ACUTE ISCHEMIC SYNDROMES: DIFFERENCES IN PRESENTATION AND TREATMENT IN WOMEN

Women with ACS often present for evaluation with symptom patterns that differ from their male counterparts and are more likely than men to report differences in chest pain quality and frequency. Women were more likely than men to present with mid-back pain, nausea and/or vomiting, dyspnea, palpitations and indigestion. Additionally, women were more likely than men to report chest pain during daily activities, but not during physical activity, and when challenged with mental stressors. Women who present with ACS, including unstable angina, non-ST-segment elevation MI and ST-segment elevation MI, are often older than their male counterparts with a higher rate of HTN, diabetes, hypercholesterolemia, tobacco use, obesity and a prior history of CHF.[77-79] The GUSTO-II ACS study showed that fewer women than men presented with ST-segment elevation MI (27% vs 37%) and for the remainder of patients

with NSTEMI or unstable angina, approximately 37% of women had an infarction when compared to 48% in men.[80] Among women with ACS like chest pain syndromes, more have no obstructive coronary disease at catheterization than men. Numerous clinical syndromes have been implicated in this phenomenon, including mitral valve prolapsed, vasospastic angina, microvascular endothelial dysfunction as well as hypothyroidism, neuromuscular disorders and tachyarrhythmias. Women who are found to have significant or multivessel epicardial CAD by angiography present with the same degree of disease as men pertaining to lesion severity and distribution, including the prevalence of left-main and three-vessel disease.[81]

Women who are offered percutaneous coronary revascularization procedures as a therapeutic modality often have clinical characteristics that are associated with an increased risk of major adverse events. For example, women tend to be older and have a higher prevalence of comorbidities in comparison to men. For this reason, women are also more likely to be considered suboptimal candidates for surgical revascularization.

At catheterization, women have smaller diameter coronary arteries, yet coronary lesion morphology and distribution is similar to that in men. Women also tend to have more ostial lesions and calcified lesions, which significantly influence device utilization including the more frequent use of balloon angioplasty and rotational atherectomy with an increase in major adverse cardiac events.[82] Other studies, however, have demonstrated a similar angiographic outcome, incidence of periprocedural MI, and need for emergent CABG in women compared to men.[83,84] In the New Approaches to Coronary Intervention (NACI) Registry, women undergoing percutaneous revascularization with new devices had a higher risk clinical profile, yet, when compared to men, a similar procedural success rate was observed. However, women did experience a higher percentage of periprocedural complications, including coronary artery dissection, need for vascular access repair, hypotension and transfusion. There was no significant sex-based difference in the rate of in-hospital death, ST-elevation MI and emergent CABG and sex was not found to be an independent predictor of major adverse cardiac events. At 1-year follow-up, more women than men reported an improvement in their angina symptoms (70% vs 62%) and fewer women than men required repeat revascularization (32% vs 36%).[85]

Advances in surgical techniques and myocardial protection have increased the availability of surgical revascularization procedures for women with ACS found to have coronary anatomy that warrants surgical intervention. In spite of these advances, in-hospital mortality rates for women are often two to three times higher than for men. This discrepancy in outcomes in only partially explained by older age and higher risk profiles, and indeed, has been attributed to greater technical difficulty associated with female operation as well as the increased frequency of urgent or emergent female procedures.[86-88] In women, surgical myocardial revascularization has increasingly been performed using an off-pump (without cardiopulmonary bypass) technique. In a series of patients considered appropriate for off-pump revascularization procedures, the mortality for women was lower in comparison to men who underwent traditional surgical revascularization procedures. However, these favorable outcomes in women may reflect patient selection and require further study.[89]

Historically, several studies have found a worse prognosis for women post-MI than men in both the pre- and post-reperfusion era. This observed difference in outcome may reflect differences in utilization of percutaneous revascularization procedures in women in comparison with men. It has also been shown that women took longer to seek medical attention, and, once evaluated, were less likely to receive immediate aspirin therapy and had longer time to reperfusion.[90] It has also been suggested that women tend to have a poor outcome even when anticoagulant or antiplatelet agents are used in conjunction with percutaneous revascularization. Moreover, increased age was found to be associated with a higher mortality rate and independent predictor of mortality and repeat infarction at 30 days.[91]

One serious complication post-acute MI is cardiogenic shock, occurring in 5–15% of patients and is recognized clinically as systemic hypotension, accompanied by end-organ hypoperfusion and elevated cardiac filling pressures. Patients who present with or develop cardiogenic shock tend to be older have more IHD risk factors and more likely to have and a prior MI and pre-existing LV dysfunction, CABG surgery, and, importantly, are more likely to be women.[92] To determine the role of mechanical reperfusion therapies in the treatment of cardiogenic shock, the SHOCK (should we emergently revascularize Occluded Coronary arteries for cardiogenic shock) trial was conducted.[93] This multicenter trial randomized 302 patients with AMI and LV dysfunction and assigned 37% of women to revascularization and 27% to medical therapy. There was no significant difference in 30-day mortality between treatment groups, yet by 6 months, there was a survival benefit for patients who underwent revascularization. Of note, patients 75 years of age or older had a worse outcome if they underwent any revascularization procedure. As women who present with acute ST-elevation MI accompanied by cardiogenic shock are often older, these findings suggest that revascularization may not improve mortality and, in fact, may predict a worse outcome in this subset of women.

Importantly, a total of 1,107 patients ineligible for the SHOCK trial were entered into the SHOCK Registry, in which women were found to have similar cardiogenic shock rate owing to LV dysfunction, but higher rate due to mechanical complications such as acute severe mitral regurgitation, ventricular septal rupture or isolated right ventricular shock than men.[94]

In conclusion, for patients with ACS, several sex-based differences in clinical presentation, evaluation, treatment strategies and outcome have been well-documented. Women have consistently been shown to be older, with more high-risk clinical features and comorbid disease than their male counterparts. Additionally, noninvasive and invasive tests often poorly diagnose the etiology of chest pain owing to the high chest pain prevalence in the absence of a fixed epicardial coronary artery stenosis. Women who are found to have obstructive CAD often have more high-risk angiographic features than men. Based on these observations, women with ACS undergo coronary revascularization with a higher risk for adverse outcomes; however, recent advances in device application, adjunctive therapies and surgical techniques suggest that

coronary revascularization strategies are safe and effective to treat women in the setting of ACS.[25]

TREATMENT STRATEGIES FOR WOMEN WITH STABLE CORONARY ARTERY DISEASE

While revascularization by PCI or CABG has been shown by many studies to be superior to medical management alone in outcomes in ACS and severely symptomatic patients with complex CAD, in chronic stable angina of mild or moderate severity and in patients with silent ischemia only, there is ongoing debate as to which treatment strategy should be offered to patients: optimized intense medical drug therapy combined with revascularization if medical therapy fails, or direct coronary angiography, both combined with strict risk factor control and secondary prevention.[95] This debate has been further stimulated by the findings of two large randomized controlled trials, COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive drug Evaluation).[96] and BARI 2D (Bypass Angioplasty Revascularization Investigation type 2 Diabetes),[97] which showed that in selected patients with mild to moderate angina and documented CAD by coronary angiography suitable for revascularization, there was no difference in death or MI between the two strategies. It remains unclear, however, how these findings can be generalized to patients with unknown coronary anatomy and to female patients, which only represented 15% of the total COURAGE cohort.

MEDICAL THERAPY AND RISK FACTOR MANAGEMENT FOR STABLE CAD

Optimized medical therapy is the cornerstone of each treatment strategy in patients with chronic CAD, even in patients undergoing revascularization. It includes aggressive risk factor modification with diet, exercise training, treatment of diabetes, HTN and hyperlipidemia as well as smoking cessation and overweight reduction. Medical therapy has well-documented effects, that is it reduces angina, improves prognosis, is less risky, and less costly than revascularization but is underused in daily practice. Current medical therapy and risk factor modification strategies should conform to updated ACC/AHA treatment guidelines as summarized in Tables 2 and 3.

Optimal management is both aggressive and multifaceted, targeted to achieve stabilization of existing atherosclerotic plaque and reduce future risk of ischemic events. The guidelines provide a consistent therapeutic approach with the understanding that a particular drug (or drugs) may be administered for more than one purpose. The therapy goals are, of course, to keep patients as symptom-free as possible within their individual tolerance for medication and to configure cardiac risk factors.

All patients with coronary disease and chest pain syndromes should receive antithrombotic therapy with aspirin. Aspirin acts via irreversible inhibition of platelet COX-1 and thus thromboxane production, which is normally complete with chronic dose of 50–75 mg/day. Since there is a dose-dependent gastrointestinal toxicity of aspirin, the lowest dose of aspirin that has been shown to be effective in a particular clinical setting should be used. The available evidence supports daily use of aspirin in the range of 75–100 mg for long-term prevention of vascular events.[95] Clopidogrel 75 mg/day may serve as an alternative in the case of aspirin allergy or intolerance.[98] In addition, it may be added to aspirin in patients after stent implantation or after MI. However, there are no trial data on a possible advantage of such a more aggressive antiplatelet regimen in patients with chronic stable CAD in which the downside of a more intense antiplatelet therapy, that is bleeding, may become more relevant.[95]

Lipid-lowering drugs and particularly statins improve survival in patients with acute as well as chronic CAD. Statins lower cholesterol effectively, but mechanisms other than cholesterol synthesis inhibition, such as anti-inflammatory and antithrombotic effects, may contribute to cardiovascular risk

TABLE 2

Drugs used to treat patients with chronic stable CAD[95]

Medication	*Indicated in all patients*	*Symptomatically useful*	*Prognostically useful*
Antithrombotic drugs (e.g. Aspirin)	Yes	No	Yes
Lipid lowering drugs (e.g. statins)	Yes	No	Yes
Beta-blocking agents	Yes	Yes	Yes (chronic stable CAD?)
Calcium channel blockers	No	Yes	No
Nitrates	No	Yes	No
ACE inhibitors	No	No	Yes (chronic stable CAD?)
Nicorandil	No	Yes	Yes
Ivabradine	No	Yes	No
Chronic stable CAD → limitations see text			

TABLE 3

Goals for risk factor management in symptomatic women[25]

Risk factor	*Goal*	
Smoking	Cessation	
Total dietary fat	< 30% calories	
Saturated fat	< 7% calories	
Dietary cholesterol	< 200 mg/day	
LDL cholesterol (primary goal)	60-85 mg/dL (1.56–2.21 mmol/L)	
HDL cholesterol (secondary goal)	≥ 40 mg/dL (1.04 mmol/L)	
Triglycerides (TG) (secondary goal)	< 150 mg/dL (1.69 mmol/L)	
Physical activity	30–45 minutes of moderate intensity activity 5 times/week supplemented by an increase in daily lifestyle activities	
Body weight by body mass index (BMI)	Initial BMI	Weight loss goal
Desirable < 25	25–27.5	BMI < 25
Overweight 25.0–29.9	27.5	10% relative weight loss
Obese > 30.0	27.5	10% relative weight loss
Blood pressure	< 130/85 mm Hg	
Diabetes	HbA1c < 7.0%	

reduction. Current guidelines recommend a goal LDL-C of less than 100 mg/dL in patients with stable CAD. A more stringent goal of less than 70 mg/dL is left to the discretion of treating clinicians.

Beta-blockers have powerful anti-ischemic, antihypertensive, and antiarrhythmic properties. In patients with chronic CAD, their main indication is treatment of (exercise-induced) angina. They are the treatment of choice in patients with concomitant HTN or suffering from arrhythmias. Despite their beneficial prognostic effects in patients of post-MI or with congestive heart failure, there is no trial data documenting a similar beneficial effect on mortality in patient with chronic stable CAD.

Calcium antagonists have anti-ischemic, antihypertensive and in part antiarrhythmic effects similar to beta-blocking agents; however, the mechanism of action is different: they mainly reduce systemic and coronary resistance by dilating peripheral and coronary arteries. Therefore, they may be added to beta-blockers to enhance therapy with the exception that calcium antagonists with heart rate lowering properties (verapamil or diltiazem) may cause excess heart rate slowing or high-grade AV block in some patients when used in combination with beta-blockers. Due to their vasodilatory effects, calcium antagonists are particularly useful in relieving angina at rest and coronary vasospasm.[95]

Nitrates provide effective and rapid symptom relief during attacks of angina. However, nitrates have no prognostic benefits in patients with chronic CAD. Since nitrate tolerance may develop when they are used continuously, patients on long-acting nitrates should have a "nitrate-free" interval each day or night to preserve therapeutic effectiveness of these drugs.[99]

For patients with refractory angina symptoms despite optimal medical therapy and revascularization, other newer anti-ischemic drugs may provide additional symptomatic relief. Ranolazine is a drug with a novel mechanism of action that has been shown in several large trials to be an efficacious adjunctive agent in reducing symptoms of chronic stable angina. It is thought to work by inhibiting the late sodium current in cardiac myocytes, thereby reducing sodium and calcium overload that follows ischemia. This improves myocardial relaxation and reduces LV diastolic stiffness, which in turn enhances myocardial contractility and perfusion. The drug is generally well tolerated and the evidence so far is encouraging.[100] Nicorandil, a potassium channel opener, has anti-ischemic effects similar to long-acting nitrates and may be used in combination with other anti-ischemic drugs to treat chronic angina. One study revealed prognostic efficacy of nicorandil.[101] Ivabradine also has anti-ischemic effects. It reduces heart rate at rest and during exercise by inhibiting sinus node activity. Thus, it may be an alternative drug for patients not tolerating beta-blocking agents.[102]

CORONARY ANGIOGRAPHY AND REVASCULARIZATION FOR STABLE CAD

In all randomized trials comparing invasive versus conservation strategies for chronic CAD, revascularization has been shown to reduce angina severity more effectively and more rapidly than medical therapy. The same was true for quality of life improvement in those studies in which this was measured.[95] Recent subgroup analyses of COURAGE[103] and BARI-2D[104] confirmed findings from previous studies that higher risk patients or those with complex CAD derived the most benefit from revascularization. PCI is recommended for a proximal coronary artery stenosis that jeopardizes a large myocardium area, which may result in severe inducible ischemia and also angina refractory to medical therapy. Drug-eluting stents and maturation of other catheter-based techniques have improved the procedural success rate and further reduced restenosis rate. In a report in 118,548 patients undergoing PCI, women who underwent coronary stenting had higher rates of same-admission mortality and urgent CABG when compared with men.[105] Upon event-free survival through hospitalization, the overall therapeutic PCI benefit for women is equivalent to that of men.

CABG surgery is considered the treatment of choice for patients with significant obstruction of the left-main coronary artery, as well as for those with triple-vessel CAD and LV systolic dysfunction. Women who undergo CABG generally have less symptomatic relief than men. This has been related to smaller-diameter vessels and more incomplete revascularization. In conjunction with older age and greater comorbidity, women tender to have higher in-hospital mortality following CABG.[106] Despite differences in near-term outcomes, female sex is not associated with late morbidity and mortality post CABG.[107]

HEART FAILURE IN WOMEN

Heart failure affects 5 million Americans, and nearly 50% of these are women. Compelling sex differences have been noted regarding the underlying etiology, prognosis, the response to treatment and how the disease impacts the quality of life. While HTN and valvular disease are more likely the culprits for heart failure in women, men are more likely to have CAD as the underlying cause.[108]

Women often present at an older age with better systolic function than men. The higher prevalence of congestive heart failure despite a lower prevalence of LV systolic dysfunction (consistent with fewer previous myocardial infarctions) in women contrasted with men undergoing both CABG and PCI has been attributed to heart failure with preserved ejection fraction (HFpEF),[109] a condition variously known as "diastolic heart failure" or "heart failure with normal ejection fraction". It is essentially defined as heart failure in the absence of obvious depression of LV systolic function (EF $\geq$ 45%). Recent reviews and guidelines estimate the incidence of HFpEF to be present in 20–60% of patients with CHF, the patients' population under the study are obviously of great importance in making this estimate. The older the patients' population is, the higher the incidence of HFpEF. Women constitute a significant majority of this elderly population and hence disproportionally affected by HFpEF in that two-thirds of those with HEPEF are women.[25] HTN is the most common comorbidity (approximately 75%) and CAD less prevalent (approximately 35%). Studies have shown that mortality of patients with HFpEF was at least as high as, if not exceeding, that of heart failure with demonstrable systolic dysfunction.[110]

For both sexes, heart failure contributes to significant morbidity and mortality, but age-adjusted data reveal that women

have a better survival. The reasons why survival is better for women remain unclear, but it may be due to differences in the underlying disease. However, women tend to have lower quality of life than men due to greater physical limitations with exercise, more heart failure related hospital stays and depression.

Although difficult to study because women are often underrepresented in heart failure trials, owing to lower enrollment rate as well as older age and preserved LV systolic function frequently serving as exclusions for enrollment, several observations have increased our understanding of issues specific to heart failure in women. In elderly patients hospitalized with (all-cause) heart failure, female gender is an independent predictor of preserved LV systolic function. Among postmenopausal women with established coronary disease, diabetes with elevated BMI or depressed creatinine clearance imparts the highest risk for developing heart failure, with annual incidence rates of 7% and 13% respectively, while myocardial infarction appears to have a lower risk of heart failure in women than men.[111] Indeed, experimental studies and postmortem and observational clinical studies suggest the presence of important differences in myocardial remodeling between females and males in response to different types of injuries including aging, pressure overload, volume overload and myocardial infarction. Interestingly, the remodeling process appears to be more favorable in women versus men in that there appears to be reduced ventricular dilation during the remodeling, resulting in women being more likely to present heart failure with preserved systolic function chronically and low output syndrome acutely. Various factors influencing differential myocardial responses to stress in women and men were recently reviewed[112] and summarized in Table 4. These differences between men and women are widely held to be related to sex hormones such as estrogen, although the molecular effects of estrogen on ventricular cardiomyocytes are incompletely understood. A better understanding of the processes leading toward the differences in remodeling in women will likely lead to novel treatment modalities and ultimately benefit the patients of both sexes.

Despite these known sex differences, medical management recommendations are the same for women and men, because prospective sex-specific clinical trials have not been performed. However, concerns exist that women might respond differently to therapy. A recent study[108] examined the many aspects in which we lack data for heart failure in women. Some of the available medications may not be as effective in women, while other therapies, for example beta blockers, aldosterone antagonists and pacemakers, may be very beneficial.

The advent of device therapy including implantable cardioverter-defibrillators (ICDs) and Cardiac Resynchronization therapy for heart failure further highlights the sex-specific response to novel heart failure management strategies. Implantation of ICDs has expanded to include primary prevention for sudden cardiac death following the publication of randomized clinical trials establishing their efficacy.[113,114] Approximately 30% of ICD recipients are women.[115] However, data supporting the efficacy of ICDs for primary prevention in women is sparse. A meta-analysis of pooled data from five trials (934 women) revealed no statistically significant decrease in mortality in women with heart failure who received ICDs (hazard ratio, 1.01).[116] Meanwhile, recent analysis of the National Cardiovascular Data Registry found that women have a 70% higher risk of major adverse events following ICD implantation than do men.[117]

CRT has become a significant part of the management of patients with advanced CHF. Several large-scale studies demonstrated the significant improvement in multiple endpoints, including survival in patients with advanced CHF.[118,119] Sex-specific results are similarly lacking for the use of CRT devices. Studies have shown that women have received significantly fewer CRT devices, despite the facts that more women have left bundle branch block at baseline and the prevalence of heart failure with preserved systolic function is only slightly higher in women.[120]

For advanced heart failure patients, Thoratec HeartMate II (Thoratec Corporation, Pleasanton, California) is a ventricular assist device that is recently approved based on data from only 44 women, who constituted 23% of the overall study population. Among the women participants, there was a threefold higher incidence of stroke (18% vs 6% in men) and trends toward a higher incidence of bleeding and infection events.[121]

Part of the reason for the lack of sex-specific data for devices may be related to the lack of Food and Drug Administration (FDA) guidance in this area. There is reason to be optimistic that this deficit will start to be corrected in the near future. The FDA center for Devices and Radiological Health held workshops that addressed underrepresentation of women in cardiovascular trials, barriers to enrolling women and improperly designed trials that fail to account for the unique characteristics of women. Current FDA guidelines already suggest that sex-specific data should be reviewed with every new drug application.[122]

Our knowledge of how to treat heart failure with preserved ejection fraction (HFpEF) is limited. Common treatment approaches incorporate therapy applied to other forms of HF. In particular, diuretics are the mainstay of therapy, although the necessity of maintaining filling pressure for optimal cardiac output frequently results in a narrow window between congestion and overdiuresis, resulting in potentiation of the cardiorenal syndrome. Treatments designed to ameliorate HTN have been shown to be efficacious and controlling blood pressure is a Class I recommendation of the ACC/AHA Heart Failure Guidelines.[123]

The renin-angiotensin-aldosterone system is involved in many of the processes associated with HFpEF. Inhibitors of this system have been of particular interest as therapeutic interventions, although multiple large-scale, randomized control trials failed to demonstrate effectiveness of this class of drugs in reducing mortality and cardiovascular events among patients who had heart failure with preserved EF.[124-126] The effect of aldosterone antagonists is being tested in the ongoing Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial (NCT00094302) conducted by the National Heart, Lung and Blood Institute. The cornerstone of therapy for HFpEF remains to be treatment of the underlying disease process. This is outlined in the revised ACC/AHA guidelines for the Evaluation and Management of Chronic Heart Failure in the Adults.[123] Treatment of ischemia and adequate blood pressure control are paramount. The maintenance of fluid balance is stressed, as is the control of ventricular rate in patients with atrial fibrillation (AF).

TABLE 4

Factors influencing cardiovascular prognosis in men and women[112]

Women	*Men*
	Ageing cardiomyopathy
Preservation of cardiac weight	Reduction in cardiac weight (1 g/yr)
Preservation of myocyte number	Reduction in myocyte number (64 million/yr)
Preservation of myocyte volume	Increase in myocyte cell volume
Constant mononucleate/binucleate myocytes ratio	Decreased mononucleate/binucleate myocytes ratio
Low apoptotic index	Apoptotic index 3-fold higher than women
Increased apoptotic rate	Decreased apoptotic rate
	Myocardial response to pressure overload
Earlier improvement in EF after aortic valve replacement	Later improvement in EF after aortic valve replacement
Greater degree of LVH	Lower degree of LVH
Increased LV mass	
Increased relative wall thickness	
Smaller end-diastolic and-systolic dimensions	
Preserved LV function	Impaired LV function
Later onset of impaired systolic pump performance	Earlier onset of impaired systolic pump performance
Greater EF	
Greater cardiac index	
Smaller end-diastolic and systolic volumes	
Higher expression of β-myosin heavy chain	Lower expression of β-myosin heavy chain
Higher expression of ANF mRNA	Higher expression of ANF mRNA
	Myocardial response to volume overload
Smaller end-diastolic and-systolic volumes	Larger end-diastolic and-systolic volumes
Greater LV mass/volume ratio	Lower LV mass/volume ratio
Concentric hypertrophy	No concentric hypertrophy
No impairment of cardiac function	Impairment of cardiac function
Minimal ventricular dilation	Significant ventricular dilation
No changes in myocardial compliance	Decreased ventricular compliance
	Myocardial response to acute myocardial ischemia
Lower apoptotic role in peri-infarct region	10-fold higher apoptotic rate in peri-infarct region
Lower bax expression in peri-infarct region	Greater bax expression in peri-infarct region
Longer duration of the cardiomyopathy	Shorter duration of the cardiomyopathy
Later onset of cardiac decompensation	Earlier onset of cardiac decompensation
Longer interval between heart failure and transplantation	Shorter interval between heart failure and transplantation
Earlier myocardial healing	Delayed myocardial healing
Lower infarct expansion index	Higher infarct expansion index
Three times lower mortality	Greater incidence in cardiac rupture
Better cardiac function	Worse cardiac function
Better remodeling	Maladaptive remodeling
	Significantly greater dilatation
	Myocyte hypertrophy
	Premature extracellular matrix degradation
	Higher number of neutrophils
	Increased activity of metalloproteinases
	Cardiogenic shock
Significantly lower cardiac index	Higher cardiac index
More frequent adverse clinical events	Less frequent adverse clinical events
More frequent mechanical complications	Less frequent mechanical complications
More common low cardiac output syndrome	Less common low cardiac output syndrome
	Heart failure
Preserved LV EF	Impaired LV EF
Smaller LV end-diastolic volume	Greater LV end-diastolic volume
Smaller stroke volumes	Greater stroke volumes
Higher LV end-diastolic pressure	Lower LV end-diastolic pressure
More frequent congestive symptoms	Less frequent congestive symptoms
Greater impairment in diastolic filling	Lower impairment in diastolic filling

(Abbreviations: ANF: Atrial natriuretic factor; EF: Ejection fraction; LV: Left ventricle/ventricular; LVH: Left ventricular hypertrophy; mRNA: Messenger ribonucleic acid)

TABLE 5

Sex-related frequency in clinical arrhythmias[127,128]

Arrhythmia type	*Male predominance*	*Female predominance*
Bradyarrhythmia	Atrioventricular block Carotid sinus syndrome	Sinus node disease
Supraventricular tachyarrhythmias	Premature atrial contraction Atrial fibrillation AVRT WPW syndrome	Inappropriate sinus tachycardia AVNRT
Ventricular tachyarrhythmias	Premature ventricular contraction Ventricular tachycardia Sudden cardiac deah SUDS Brugada syndrome	Congenital LQTS Acquired LQTS

(Abbreviations: AVNRT: Arterioventricular node re-entrant tachycardia; AVRT: Arterioventricular reentrant tachycardia; LQTS: Long QT syndrome' SUDS: Sudden unexplained death syndrome; WPW: Wolff-Parkinson-White

SEX AND CARDIAC ARRHYTHMIAS

Reports have noted differences in the incidence of certain clinical arrhythmias according to the sex of those studied (Table 5).[127] Some of these differences are related to known variations in the frequency of underlying organic heart disease, such as CAD and associated ventricular arrhythmias. However, clinical and experimental observations also suggest that true differences in electrophysiological properties exist between men and women. These differences have important clinical implications and raise special therapeutic considerations in the management of arrhythmias in women.

It is long recognized that women have a longer corrected QT interval compared with that of men, and the difference becomes more pronounced at lower heart rate. Indeed, the high incidence of torsade de pointes (TdP) in women has been described in connection with both congenital and acquired long QT syndromes.[127] Results from the International Long QT Registry showed that 70% of the probands and 58% of the affected members were women.[129] In a pooled analysis of 322 patients with drug-induced TdP, 70% of those affected were women.[130] This predominance was irrespective of underlying LV function, electrolyte abnormalities, and baseline QT intervals. Female sex and advanced age are both among the risk factors for developing TdP in hospitalized patients.[131] A possible protective effect of androgen has been proposed to explain longer corrected QT interval and higher incidence of TdP in women as it has been shown that corrected QT interval drops in males after puberty (when androgen levels are highest).[132]

Atrial fibrillation is the most common supraventricular tachycardia, affecting approximately 2.2 million people in the United States. Its incidence increases dramatically with age, and the development of AF is associated not only with increased morbidity rates but also with an approximate doubling of all-cause mortality. Men are at greater risk of AF than are women in all age groups. However, because there are almost twice as many women as men who are older than 75 years in the general population, the absolute number of women with AF in older age groups exceeds that of men. Women affected by AF are more likely to experience symptomatic attacks, a higher frequency of recurrences and significantly higher heart rates during AF, which increases the risk of stroke.[133] Additionally, although the incidence of AF is higher in men, the risks of stroke and mortality from AF are significantly higher in women.[134] The exact mechanism responsible for gender related symptomatic differences in AF is unclear. Several mechanisms have been proposed. It is generally believed that women have faster baseline sinus rate than do men. Electrophysiologic differences may exist throughout the atria, instead of being restricted to the sinus node. Faster ventricular rates could be related to variable atrial input to the atrioventricular (AV) node. AF in women may also be influenced by menstrual cycle phase and age-related differences in atrial effective refractory period (AERP).

The benefits of the various strategies aimed at the control of heart rate, the prevention of thromboembolic complications and the conversion to and maintenance of sinus rhythm are also affected by the sex of the patient. The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study reported no significant sex differences in response to either rate control or rhythm control strategy in high-risk AF patients. Both sexes had an increased risk of death that was not significant in the rhythm-control arm compared with the rate-control arm.[135] The Rate Control versus Electrical Cardioversion (RACE) study, however, revealed that women randomly assigned to rhythm control had three times the risk of cardiac events. The significantly increased risk in women was mainly due to the higher incidence of CHF, thromboembolic complications, and severe adverse antiarrhythmic drug events (including proarrhythmia and bradycardia necessitating pacemaker implantation.[136,137] Therefore, caution must be used in the administration of antiarrhythmic agents to women, because of their propensity for developing QT prolongation and TdP. Whether rate or rhythm control is used, anticoagulation is pivotal to avoid AF-related thromboembolism. Anticoagulation therapy is frequently interrupted for various reasons. This may have contributed to the significantly higher rate of thromboembolism observed in the Stroke Prevention using an Oral Thrombin Inhibitor (SPORTIF) trial.[138] The reluctance of physicians and patients to use warfarin may be due to an increased risk of bleeding in women. The Canadian Registry of Atrial Fibrillation (CARAF) database reported that women taking warfarin were 3.35 times more likely to experience major bleeding.[139] Dabigatran, a new oral direct thrombin inhibitor, has recently been shown to be noninferior to warfarin in terms of thromboembolism prevention and risk for bleeding.[140] In patients with AF for whom vitamin warfarin therapy was considered unsuitable, the addition of clopidogrel to aspirin may serve as a reasonable alternative.[141]

Significant sex-related differences in the origins of ventricular tachycardia and sudden cardiac death/arrest (SCD/SCA) were also noted in the Framingham study.[142] Over a 26-year follow-up period, the incidence of SCD increased with the age of the subjects, with a male predominance in all age groups. Although this difference was partly explained by the epidemiology of CAD—women present 10–20 years later than men. Women were significantly less likely than men to have a

diagnosis of structural heart disease (LV dysfunction or CAD) before SCA.[143] Kudenchuk and co-authors[144] reported that women were younger, had better ejection fractions, had lower defibrillation thresholds, were less likely to have organic heart disease and more likely to present with ventricular fibrillation. On a 2-year follow-up, the incidence of ventricular events necessitating device therapy was lower in women than in men (37% vs 52%). These observations carry important clinical implications. If SCA tends to occur more unexpectedly in women, fewer women may be eligible for prophylactic ICD placement based on current guidelines and therefore may not have equal opportunity for prevention. Enhancement of SCA risk stratification may have even higher importance for women. Nevertheless, the same therapeutic considerations should be applied equally to all who present with malignant ventricular tachyarrhythmias. Even if women have less structural heart disease, fewer arrhythmic events, and less inducibility during electrophysiologic testing, these factors should not preclude the use of implantable devices, especially in survivors of sudden death.

In summary, there are clear sex-related differences in the incidence and prevalence of certain cardiac arrhythmias. The exact mechanisms responsible for these differences are as yet unknown. The scant evidence available suggests two general mechanisms: (1) sex steroid hormone effects on ion channels and (2) modulation of autonomic tone. Better understanding of the basic mechanisms of these differences will facilitate the development of more effective sex-specific methods of diagnosis and treatment.

CALL FOR MORE SEX-SPECIFIC RESEARCH

Sex-specific research has uncovered important differences in the causes, symptoms and treatment of heart disease. The rate of public awareness of CVD as the leading cause of death in women has nearly doubled between 1997 and 2005 (from 30% to 55%).[145] Despite better understanding of the mechanisms and growing awareness of sex-specific differences, several issues remain to be solved. For example, much of the evidence supporting current recommendations for noninvasive diagnostic studies in women is extrapolated from studies conducted predominantly in cohorts of middle-aged men. Furthermore, women are still underrepresented in clinical trials.

In an analysis of 156 randomized clinical trials cited by the American Heart Association's 2007 guidelines for CVD prevention in women, females were substantially underrepresented compared with how frequently they are affected by various cardiovascular conditions.[146] Overall, women made up just 30% of the patient population in the clinical trials used to support the 2007 guidelines. Also, only about one-third of the 156 trials reported sex-specific results, whereas women accounted for at least half the deaths in the affected patient populations studied. These findings underscore the importance and urgency of having adequate representation of women in clinical trials to solidify the evidence based practice guidelines. Further study in sex-specific areas of cardiovascular research holds great promise in the development, prevention and treatment of CVD in the aging female population.

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Chapter 104

Overview of the Athlete's Heart

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Chapter Outline

- Historical Perspective
- Exercise Physiology and the Athlete's Heart: Overview
- Exercise-induced Cardiac Remodeling
  - The Left Ventricle
  - The Right Ventricle
  - The Aorta
  - The Left Atrium
- Issues Relevant to the Cardiovascular Care of Athletes
  - Overview of the Clinical Approach to the Trained Athlete
  - Etiology of Left Ventricular Hypertrophy
  - Arrhythmia
  - Syncope
  - Steroids and Sport Performance Supplements
  - Sudden Death and Preparticipation Disease Screening

INTRODUCTION

The association between cardiac "abnormalities" and participation in athletic activity has been appreciated for more than a century. Initial descriptions of cardiac enlargement in healthy trained athletes, later characterized as global chamber dilation and myocardial hypertrophy, lead to the concept of the athlete's heart. Our understanding of how repetitive exercise affects heart structure and function has advanced considerably since the initial descriptions in the 1890s. This chapter provides an overview of the physiology and clinical relevance of myocardial remodeling in athletic individuals.

HISTORICAL PERSPECTIVE

Initial reports describing cardiac enlargement in athletes date back to the late 1890s. In the United States, Eugene Darling of Harvard University used the rudimentary, yet elegant physical examination skills of auscultation and percussion to demonstrate increased cardiac dimensions in university rowers.[1] Similar observations were made during the same year by the Swedish clinician Henschen in elite Nordic skiers.[2] In the early 1900s, Paul Dudley White studied the radial pulse contour among Boston Marathon competitors[3] and was the first to report marked resting sinus bradycardia in long distance runners.[4] Further advances in our understanding of the relationship between athletic activity and cardiac morphology have paralleled developments in diagnostic technology. Early use of chest radiography confirmed the physical examination finding of global cardiac enlargement in trained athletes.[5-7] The development of electrocardiography enabled widespread study of the electrical activity in the heart of the trained athlete.[8-14] In addition to the morphologic patterns of cardiac hypertrophy, early ECG work documented bradyarrhythmias[15] and tachyarrhythmias[16] in exercise trained individuals. The development and rapid dissemination of two-dimensional echocardiography lead to important further advances in our understanding of the athlete's heart. Descriptions of biventricular chamber enlargement, myocardial hypertrophy and atrial dilation lead to a more comprehensive understanding of the typical cardiac findings in the trained athlete. Most recently, advanced echocardiography and magnetic resonance imaging have begun to clarify important functional adaptations that accompany previously reported changes in structure.

EXERCISE PHYSIOLOGY AND THE ATHLETE'S HEART: OVERVIEW

Successful performance of physical exercise relies on coordinated activity of the lungs and pulmonary vasculature (oxygen uptake), the heart and systemic vasculature (oxygen transport) and the skeletal muscle (oxygen utilization and force generation). Numerous superb reviews of clinically relevant exercise physiology are available.[17-19] Only key aspects relevant to exercise-induced cardiac remodeling (EICR) will be reviewed here.

There is a direct relationship between exercise intensity (external work) and the body's demand for oxygen. This oxygen demand is met by increasing pulmonary oxygen uptake (VO_2). The cardiovascular system is responsible for transporting oxygen rich blood from the lungs to the skeletal muscles, a process quantified as cardiac output (L/min). The Fick equation (Cardiac Output = VO_2 x Arterial-Venous O_2 D) can be used to quantify the relationship between cardiac output and VO_2. In the healthy human, there is a direct and inviolate relationship between VO_2 and cardiac output.

Cardiac output, the product of stroke volume and heart rate, may increase 5–6 fold during a maximal exercise effort. Coordinated autonomic nervous system functions, characterized by rapid and sustained parasympathetic withdrawal coupled with sympathetic activation, are required for this to occur. Heart rate in the athlete may range from less than 40 beats per minute at rest to greater than 200 beats per minute in a young maximally exercising patient. Maximal heart rate varies innately among individuals and decreases with age.[20] Heart rate increase is responsible for the majority of cardiac output augmentation during exercise. Importantly, maximal heart rate does not increase with exercise training.[21]

In contrast, stroke volume both at rest and during exercise characteristically increases significantly with prolonged exercise training. Cardiac chamber enlargement and the accompanying ability to generate a large stroke volume is a direct result of EICR and is one of the cardiovascular hallmarks of the endurance-trained athlete. Stroke volume rises during exercise due to increases in ventricular end diastolic volume and to a lesser degree, due to sympathetically mediated reduction in end systolic volume (particularly during upright exercise).[18] Left ventricular (LV) end diastolic volume is determined by diastolic filling, a complex process that is affected by a variety of variables including heart rate, intrinsic myocardial relaxation, ventricular compliance, ventricular filling pressures, atrial contraction and extracardiac mechanical factors including pericardial and pulmonary constraints. At the present time, to what degree each of these factors contributes to stroke volume augmentation during exercise remains uncertain.

Hemodynamic conditions, specifically changes in cardiac output and peripheral vascular resistance, vary widely across sporting disciplines. Although some overlap exists, exercise activity can be segregated into two forms with defining hemodynamic differences. (1) Isotonic exercise, also referred to as endurance exercise, involves sustained elevations in cardiac output with normal or reduced peripheral vascular resistance. Such activity represents primarily a volume challenge for the heart, which affects all four chambers. This form of exercise underlies activities including long distance running, cycling, rowing and swimming. (2) Isometric exercise, in contrast, also referred to as strength training, involves activity characterized by increased peripheral vascular resistance and normal or only slightly elevated cardiac output. This increase in peripheral vascular resistance causes transient, but potentially marked systolic hypertension and LV afterload. Strength training is the dominant form of exercise in activities such as weightlifting, track and field throwing events and American style football. Many sports, including popular team-based activities, such as soccer, lacrosse, basketball, hockey and field hockey, involve significant elements of both endurance and strength exercise. As have been discussed, sport-specific hemodynamic conditions may play an important role in EICR.

EXERCISE-INDUCED CARDIAC REMODELING

THE LEFT VENTRICLE

The impact of exercise training on LV structure has been the topic of extensive study. Early studies utilizing electrocardiography in trained athletes demonstrated a high prevalence of increased cardiac voltage suggestive of LV enlargement.[9,22] Subsequent work with two-dimensional echocardiography confirmed underlying LV hypertrophy and dilation.[23] Most of these early studies utilized a cross-sectional design comparing small groups of endurance-trained athletes to sedentary controls. More recently, newer noninvasive cardiovascular imaging techniques have been used to examine LV structure and function in a wide variety of athletes including cyclists,[24] triathletes,[25] runners,[26] canoeists,[27] weight lifters,[28,29] orienteers,[30] tennis players,[31] tumblers,[32] football players,[33] soccer players,[34] baseball players,[35] hockey players,[36] skiers[37] and swimmers.[38]

Italian physician-scientists have contributed a great deal to our understanding of LV structure in athletes using data derived from their long-standing preparticipation screening program. Pelliccia et al. reported echocardiographically derived LV end diastolic cavity dimensions in a large group (n = 1,309) of Italian elite athletes.[39] This cohort was comprised predominantly of male athletes (73%) and included individuals from 38 different sports. LV end diastolic diameters varied widely from 38 mm to 66 mm in women (mean = 48 mm) and from 43 mm to 70 mm in men (mean = 55 mm). Importantly, LV end diastolic diameters were greater than or equal to 54 mm in 45% and greater than 60 mm in 14% of the cohort. Markedly, dilated LV chambers (> 60 mm) were most common in athletes with higher body mass and those participating in endurance sports (cycling, cross-country skiing and canoeing).

Pelliccia et al. similarly reported echocardiographic measurements of LV wall thicknesses among 947 elite athletes. Within this cohort, a small but significant percentage of athletes (1.7%) had LV wall thicknesses greater than or equal to 13 mm and all of these individuals had concomitant LV cavity dilation.[40] Sharma et al. also reported a low incidence of LV wall thickness greater than 13 mm among 720 elite junior athletes and confirmed that increased LV wall thickness was associated with increased chamber size consistent with adaptive remodeling even in these young athletes.[41] Although studies such as these demonstrate a low incidence of increased wall thickness measurements among athletes, a small but significant number of trained individuals do have wall thickness values in the 13–15 mm range. This finding may be particularly common among elite athletes and those that engage in exercise training with both significant isometric and isotonic physiologic stress such as rowers.[42] It has been consistently shown the most marked LV hypertrophy which occurs in athletes with relatively large body size. As such, careful interpretation of LV hypertrophy in athletes, particularly with respect to differentiating adaptive from pathologic hypertrophy, requires consideration of their sporting activity and correction or normalization for body size.

Copious data confirm the suggestion that sporting discipline impacts the LV response exercise. The notion that endurance-based exercise and strength-based exercise lead to distinctly different changes in LV structure was first proposed by Morganroth et al. in 1975.[43] These authors compared echocardiographically derived LV measurements in wrestlers (isometric training), swimmers (isotonic training) and sedentary controls and found significant differences with different forms of exercise training. Athletes exposed to isometric hemodynamic

stress demonstrated concentric LV hypertrophy whereas individuals exposed to isotonic hemodynamic stress demonstrated eccentric LV enlargement. This study led to the concept of sport-specific cardiac remodeling, often referred to as the "Morganroth hypothesis". Although some data have been presented which refute the concept of sport-specific LV remodeling,[44-46] the majority of cross-sectional data and, more recently, carefully designed longitudinal work support the Morganroth hypothesis.[47] The interested reader is referred to a comprehensive review of this topic by Naylor and colleagues.[48]

Exercise-induced adaptations in LV function have also been studied. Numerous investigators have examined resting LV systolic function in athletes using cross-sectional, sedentary control study designs.[25,49-51] These studies and a large meta-analysis show that LV ejection fraction is generally normal among athletes,[52] although at least one study of 147 cyclists participating in the Tour de France found that 17 (11%) had a calculated LV ejection fraction less than or equal to 52%.[53] Such results suggest that endurance athletes may occasionally demonstrate borderline LV function at rest. Recent advances in functional myocardial imaging, including tissue Doppler echocardiography and strain echocardiography, have also suggested that exercise training may lead to changes in LV systolic function that are not detected by assessment of a global index like LV ejection fraction.[54-56] The importance of these findings with respect to our understanding of exercise physiology and for differentiating athletic from pathologic remodeling is an area of active investigation.

LV diastolic function has also been extensively evaluated in trained athletes. Most studies of diastolic function in athletes have utilized conventional two-dimensional (transmitral) and tissue Doppler echocardiography. It is now well-recognized that endurance exercise training leads to enhanced early diastolic LV filling as assessed by E-wave velocity and mitral annular/LV tissue velocities.[34,42,57-59] It is likely that improved LV diastolic function, particularly the ability of the LV to relax briskly at high heart rates, is an essential mechanism for stroke volume preservation during exercise. There are sparse data examining diastolic function in strength-trained athletes, but one longitudinal study suggested that the concentric LV hypertrophy associated with strength training is accompanied by impaired relaxation.[47]

THE RIGHT VENTRICLE

Exercise training induced cardiac remodeling is not confined to the LV. Endurance exercise requires both the LV and right ventricle (RV) to accept and eject relatively large quantities of blood. In the absence of significant shunting, both chambers must augment function to accomplish this task. Recent advances in noninvasive imaging have begun to clarify how the RV responds to the repeated challenges of exercise.

Henriksen et al. examined RV and LV cavity and wall measurements using M-mode and two-dimensional echocardiography in 127 male elite endurance athletes.[60] Compared to historical controls, endurance-trained athletes demonstrated significantly larger RV cavities and a trend toward thicker RV free walls. In an elegant MRI-based study, Scharhag et al. confirmed that RV enlargement is common among endurance athletes.[61] Data from this study suggest that RV enlargement (predominantly dilation) parallels LV enlargement leading to the concept of balanced, biventricular enlargement.

The impact of strength training on the RV remains unclear as the limited available data are inconsistent. Perseghin et al. compared RV and LV structure in endurance athletes (marathon runners), strength athletes (sprinters), and sedentary controls and found the largest right ventricular volumes among the strength athletes. However, there were no significant difference between the RV dimensions in strength and endurance athletes after adjustment for body surface area.[62] One of us recently compared right ventricular structure in collegiate endurance-trained (rowers) and strength-trained (American-style football players) athletes before and after 90 days of team-based exercise training.[47] There was statistically significant RV dilation in the endurance athletes but no changes in right ventricular architecture in the strength athletes. Further elucidation of how the RV responds to different forms of exercise and its contribution to exercise capacity is an important area for future work.

THE AORTA

The aorta experiences a significant hemodynamic load during exercise. The nature of this load is dependent on sport-type with endurance activity causing high-volume aortic flow with modest systemic hypertension and strength activity resulting in normal volume aortic flow with potentially profound systemic hypertension. It is logical to assume that such conditions may result in variable aortic remodeling along athletic individuals. This premise has been the topic of numerous studies, but no definitive conclusions. For example, Babaee and colleagues compared aortic dimensions in 100 elite strength-trained athletes to those in 128 age matched controls.[63] They reported significantly larger aortic dimensions at the valve annulus, sinuses of Valsalva, sinotubular junction and proximal root in the strength-trained athletes. Further the largest dimensions were observed in those with the longest duration of exercise training. Similarly, D'Andrea et al. used transthoracic echocardiography to measure aortic dimensions in 615 elite athletes (370 endurance-trained athletes and 245 strength-trained athletes; 410 men; mean age 28.4 ± 10.2 years, range 18–40). These authors found that aortic root diameter was significantly higher among strength-trained athletes.[64] Vascular remodeling may also take in place in the descending abdominal aorta.[65] In contrast, Pelliccia et al. reported aortic root dimensions in a heterogeneous group of 2,317 Italian athletes and found the largest aortic root measurements in endurance-trained athletes, specifically swimmers and cyclists. Such contradictory data make definitive conclusions about the impact of exercise training on aortic dimensions impossible. Of note, these and other studies[66] have found that the ascending aortic root rarely exceeds the clinically accepted upper limits of normal (40 mm). As such, it seems reasonable to conclude that athletic training is not a common cause of marked aortic dilation.

THE LEFT ATRIUM

Numerous authors have examined left atrial structure in trained athletes. Hauser et al. presented an early echocardiographic

study demonstrating larger left atria in 12 endurance athletes than in 12 sedentary controls.[67] A similar early study documented relative left atrial enlargement in older individuals with a history of exercise training.[68] Hoogsteen et al. compared atrial dimensions in young competitive cyclists (17 ± 0.2 years, n = 66) to those in older, presumably more experienced cyclists (29 ± 2.6 years, n = 35) and found larger dimensions in the older athletes.[69] Pelliccia et al. presented the largest data set of atrial measurements in athletes (n = 1,777) and demonstrated that left atrial enlargement (> 40 mm in an anterior/posterior transthoracic echocardiographic view) was present in 20% of the athletes.[70] Of note, few of the athletes with left atrial dilation had clinical evidence of supraventricular arrhythmias.[70] D'Andrea et al. recently confirmed a high prevalence of left atrial enlargement in trained athletes and demonstrated an association with endurance sports training.

ISSUES RELEVANT TO THE CARDIOVASCULAR CARE OF ATHLETES

OVERVIEW OF THE CLINICAL APPROACH TO THE TRAINED ATHLETE

The trained athlete is typically regarded as the paradigm of excellent health and there are copious data showing that regular vigorous exercise reduces the incidence of atherosclerotic cardiovascular disease. Nevertheless, trained athletes are frequently referred to general practitioners, internists and cardiovascular disease specialists. Athletic patients may be directed to medical attention due to abnormal findings during preparticipation screening or they may seek medical attention due to symptoms related to their sport participation. Although the fundamentals of general patient care apply when dealing with the athletic patient, additional considerations may facilitate optimal management of this special patient population.

Certain aspects of the medical history may prove particularly valuable in the assessment of the athletic patient. First, a detailed athletic training and participation history must be elicited. This should include characterization of prior athletic achievements (useful for determining the competitive caliber of the athlete), current fitness level, recent training endeavors and future goals. The cardiac adaptations that occur with exercise training do not happen immediately upon starting an exercise program nor do they occur in individuals who are infrequent exercisers or whose exercise training volume is low. Consequently, an exercise training history is extremely important in evaluating an athlete. In the symptomatic athlete, it is imperative to determine if changes in training technique, volume or intensity correlate with the onset of symptoms. Second, a detailed family history is important as many conditions that predispose athletic patients to sport-related sudden death are heritable. The comprehensive family history in the athlete should include specific inquiry about the incidence of sudden unexplained death or collapse, syncope or pacemaker/defibrillator placement in immediate and extended family members. Finally, athletes of all ages should be questioned about the use of illicit substances. As discussed in more detail below, we recommend asking specifically about traditional drugs of abuse (cocaine, marijuana, tobacco, alcohol) and about sport-specific performance enhancing agents (PEAs).

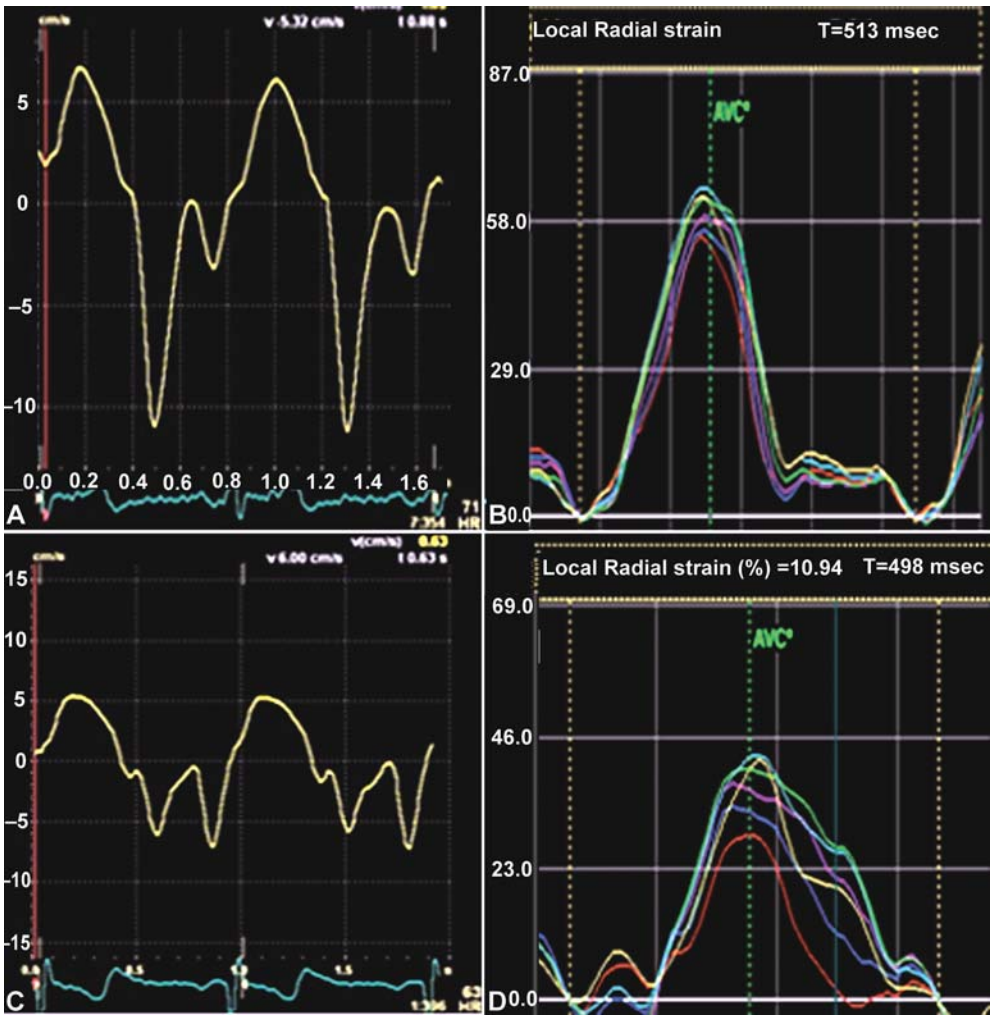
The phenotypic overlap between EICR and pathologic structural heart disease is widely appreciated. The extreme cases of exercise-induced LV hypertrophy and RV dilation may be difficult to differentiate from mild forms of hypertrophic cardiomyopathy and arrhythmogenic right ventricular cardiomyopathy respectively. The overlap between features of the athlete's heart and characteristics of common cardiomyopathic conditions that affect young athletes has been coined "Maron's gray zone".[71] The concept of the gray zone emerged during a time period in which noninvasive cardiovascular imaging was in its infancy and for the most part, restricted to basic two-dimensional echocardiography.

The clinical task of differentiating marked EICR from important forms of cardiomyopathy remains an important task for the clinician charged with the care of athletes. Cardiac structural abnormalities of unclear significance may be detected during preparticipation cardiovascular disease screening or during evaluation of the athlete with symptoms. Differentiating adaptive remodeling from pathologic structure has important implications for sports eligibility and risk modification treatments including medication and placement of an implantable cardiac defibrillator.

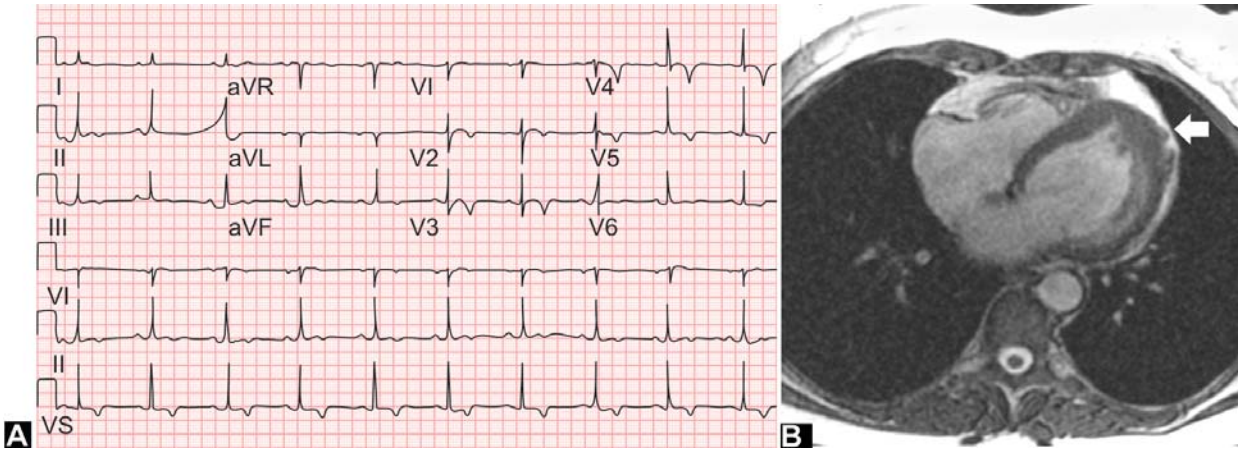
At the present time, there is no single diagnostic test with adequate accuracy for differentiating adaptive remodeling from pathologic cardiomyopathy. Consequently, clinician's faced with this diagnostic dilemma are encouraged to begin the assessment with an integrated consideration of personal and family medical history, 12-lead electrocardiography and echocardiography.[72] In many cases, this relatively basic, but informative triad will provide sufficient information for informed diagnostic decision-making. In cases that remain unclear after this initial evaluation, advanced imaging techniques including tissue Doppler echocardiography, speckled tracking echocardiography, magnetic resonance imaging, cardiopulmonary exercise testing and disease specific genetic testing may be considered. The presence of a previously identified genetic abnormality associated with structural cardiac disease can increase the conviction that a borderline cardiac abnormality in an athlete represents early disease and not exercise-induced adaptation. Examples illustrating the utility of advanced echocardiographic techniques (Figs 1A to D) and magnetic resonance imaging (Figs 2A and B) for the assessment of athletes with suspected myocardial pathology are shown.

ARRHYTHMIA

Arrhythmia and conduction alterations are common in the trained athlete. Bradyarrhythmias including sinus bradycardia, junctional bradycardia, first-degree AV block and Mobitz type I AV block are commonly observed.[73] Athletic patients with these bradyarrhythmias are almost always asymptomatic and profound bradycardia in the context of rest or sleep does not appear to portend a poor prognosis. It has been suggested that heightened parasympathetic tone, specifically increased efferent vagus nerve activity, is responsible for these bradyarrhythmias. However, there are some experimental data suggesting that repeated exercise training may also lead to intrinsic sinoatrial



FIGURES 1A TO D: Echocardiographic tissue Doppler imaging (A and C) and speckle-tracking radial strain analysis (B and D) in two different athletic patients presenting with left ventricular hypertrophy. Figures A and B demonstrate normal tissue velocity (A) and radial strain (B) in a 23-year-old male elite rower with marked eccentric LV hypertrophy (interventricular septal thickness = 15 mm, posterior wall thickness = 15 mm, LV end diastolic dimension of 64 mm by echocardiography). Figures C and D demonstrate pathologic tissue velocities (C) and reduced, heterogeneous radial strain (D) in a 20-year-old male collegiate football player with concentric LV hypertrophy (interventricular septal thickness = 15 mm, posterior wall thickness = 15 mm, LV end diastolic dimension of 42 mm by echocardiography) who was subsequently diagnosed with hypertrophic cardiomyopathy after minimal regression during prescribed detraining and a genetic test identifying a pathologic mutation in the cardiac beta-myosin heavy chain gene



FIGURES 2A AND B: (A) Electrocardiogram from a 46-year-old male triathlete who presented following long-standing palpitations and a recent episode of syncope. The findings of diffuse T wave inversions prompted an echocardiogram which revealed normal LV dimensions and function. (B) A subsequent magnetic resonance imaging study confirmed the present of focal, asymmetric LV hypertrophy consistent with a variant form of apical hypertrophic cardiomyopathy

node slowing.[74] In the asymptomatic athlete with any of these common bradyarrhythmias, reassurance and documentation of an appropriate chronotropic response to exercise is typically sufficient to exclude a pathologic process.[75] More advanced forms of heart block including Mobitz type II second-degree and third-degree heart block, that is either prolonged or occurs during awake time, are unusual in athletes and should be considered pathologic.[76]

Premature beats (both atrial and ventricular) and nonsustained burst of ventricular tachycardia may be observed in trained athletes. Since, athletes tend to "know their bodies well" and, thus may be particularly sensitive to rhythm disturbances, palpitations caused by premature beats are a common reason for athletes to seek medical attention. In such instances, it is important to exclude structural and valvular heart disease and to assess the impact of exercise on the frequency of the premature beats. In the absence of structural heart disease and when suppressed by exercise, premature atrial and ventricular beasts are usually benign and without long-term implications.[77,78] Similarly, reassuring data have been published regarding the benign nature of nonsustained ventricular tachycardia in athletes without structural heart disease.[79]

Tachyarrhythmias, specifically atrial fibrillation may particularly be problematic in the trained athlete. There are several studies suggesting that atrial fibrillation is more common among presently or previously trained athletes than in their sedentary counterparts.[80-83] This appears to be particularly true of the older athletic patient. The mechanism(s) producing atrial fibrillation in athletes are speculative, but a combination of exercise-induced left atrial remodeling and inflammation,[70,84] increased sympathetic activity during exercise,[80] and parasympathetically mediated slow resting heart rates potentiating atrial escape[74] have been suggested as potential contributors.

Initial evaluation of the athlete with supraventricular tachyarrhythmias including atrial fibrillation should include exclusion of metabolic derangements, especially hyperthyroidism, detailed nutritional and supplement intake history (i.e. caffeine, other stimulants) and an assessment for structural and valvular heart disease. Careful attention to the physiologic conditions during which an individual athletes develops arrhythmia, specifically differentiating fast heart rate conditions (i.e. exercise) arrhythmia from slow heart rate conditions (i.e. sleep, exercise recovery) arrhythmia, may be useful for individualizing management. Rate control agents including beta-blockers and calcium channel blockers do not reduce the frequency of atrial fibrillation but may minimize symptoms in the athlete. Class IC antiarrhythmic agents, including flecainide and propafenone, may be effective ways of maintaining sinus rhythm, but both increase atrioventricular conduction and generally require an additional agent to prevent an accelerated ventricular response if atrial flutter should occur. Both flecainide and propafenone can be used with the "pill in the pocket" approach to atrial fibrillation,[85] which may be attractive in some athletes. Although data documenting the success of catheter-based ablation for atrial fibrillation in athletes are sparse,[86,87] this may be an appropriate strategy for certain individuals.

SYNCOPE

Syncope, defined as a transient loss of consciousness accompanied by loss of postural tone, is common in trained athletes. In a large cohort of Italian athletes, roughly 6% reported syncope in the prior 5 years.[88] In this important study, the vast majority of syncope was unrelated to exercise (86.7%) or occurred in the post-exertional period (12%). In the small minority with true exertional syncope (1.3%), explanatory structural heart disease was common.

The vast majority of athletes have syncopal episodes that are attributable to neurocardiogenic mechanisms. Typically, neurocardiogenic syncope in the athlete occurs immediately after exercise and is due to transient cerebral hypoperfusion produced by residual peripheral arterial vasodilatation and a sudden reduction in venous return produced by the cessation of skeletal muscle contraction. The athlete with neurocardiogenic syncope will typically report presyncopal feelings of warmth, diaphoresis or lightheadedness which culminate in a loss of consciousness ranging from several seconds to a minute. Syncope during exercise is almost never due to neurocardiogenic mechanisms and should alert the practitioner to the possibility of arrhythmia, structural/valvular heart disease or coronary artery anomalies.

The approach to the athletic patient with syncope begins with a detailed history, physical examination and 12-lead electrocardiogram. Care should be taken to characterize potential triggers, the timing and duration of the event, and the risk associated with similar future loss of consciousness. The 12-lead electrocardiogram should be inspected for abnormalities of conduction (QT prolongation, pre-excitation, right bundle branch block with early precordial ST-elevation suggestive of Brugada syndrome) and structural heart disease (complete bundle branch block, LV hypertrophy with repolarization abnormalities, diffuse T-wave inversions). Transthoracic echocardiography is recommended to exclude structural and valvular heart disease in individuals with syncope, especially if anything abnormal is detected during physical examination or ECG interpretation. Syncope that occurs during exercise requires diagnostic assessment with exercise stress testing. This stress testing should be designed to approximate the exercise conditions in which the syncope occurred and careful attention should be placed on the exercise electrocardiogram for the detection of explanatory arrhythmias. Exercise testing is frequently normal in individuals with coronary artery anomalies; however, so coronary imaging may be required in athletes with syncope and this clinical possibility.[89] Ambulatory monitoring with a loop or an event recorder may prove useful in patients with symptoms that are not reproduced during a laboratory-based exercise assessment.

Management of the athlete with syncope is dictated by etiology. Individuals with structural or valvular heart disease should be managed based on their specific abnormality with some combination of sport restriction, medication, electrophysiologic study with or without ablation or implantable defibrillator placement or surgery. Neurocardiogenic syncope can often be avoided by always including an active cool-down period after vigorous exertion and by attention to hydration and supplemental salt intake. In athletes with recurrent neurocardiogenic syncope despite these first line treatments, postural training

TABLE 1

Summary of recent studies examining the impact of long-term androgenic anabolic steroid use on myocardial function in athletes

Reference	*Year*	*No. of athletes*	*Study design*	*Athlete description*	*Reported prior to steroid exposure*[a]	*Findings compared to controls*
Nottin et al.[93]	2006	6	Cross-sectional comparison with AAS-free weight lifters	Recreational weight lifters	> 2 years	No difference in systolic function ↓ diastolic function (transmitral and tissue velocities)
D'Andrea et al.[92]	2007	20	Cross-sectional comparison with AAS-free weight lifters	Top-level competitive body builders	524 ± 91 mg/ week (31 ± 6 weeks/year over 8.9 ± 3.8 years)	↓ systolic function (strain, strain rate) ↓ diastolic function (transmitral and tissue velocities)
Krieg et al.[95]	2007	14	Cross-sectional comparison with AAS-free weight lifters	Recreational weight lifters	817 ± 619 mg/ week (27 ± 11 weeks/year over 8.4 ± 4.8 years)	No difference in systolic function ↓ diastolic function (transmitral and tissue velocities)
Baggish et al.[94]	2010	12	Cross-sectional comparison with AAS-free weight lifters	Recreational weight lifters	675 [513,950] mg/week (468 [169,520] lifetime weeks)	↓ systolic function (LVEF, strain) ↓ diastolic function (transmitral and tissue velocities)

[a]= numbers represent testosterone equivalences dose, ± = mean, [ ] = interquartile range
(Abbreviations: AAS: Androgenic anabolic steroid; LVEF: Left ventricular ejection fraction)

or pharmacologic therapy with either selective serotonin uptake inhibitors or midodrine may be reasonable next steps. Permanent pacemaker therapy is rarely necessary in athletes with neurocardiogenic syncope.

STEROIDS AND SPORT PERFORMANCE SUPPLEMENTS

Advances in the science of human performance coupled with increasing societal and financial pressure for athletes to perform has led to increasing the use of PEAs. Although a detailed review of commonly used PEAs is beyond the scope of this review, several principles are clinically relevant. The most widely known forms of PEAs are androgenic anabolic steroids. These agents became available for widespread use by professional and recreational athletes in the early 1980s and their popularity continues to grow. Numerous small studies have documented deleterious cardiovascular effects of androgenic anabolic steroids including dyslipidemia,[90] exaggerated exercise blood pressure response[91] and myocardial dysfunction[92-94] (Table 1). Definitive data documenting the impact of antigenic anabolic steroid use on cardiovascular health, particularly in older individuals who used these agents for prolonged periods, remains uncertain and constitutes an important area of future work.

Nonsteroidal muscle mass growth stimulators including injectable insulin, human growth hormone and creatine are also popular drugs of abuse in athletes. Cases of cardiovascular toxicity attributable to these agents have been reported. There has been increasing interestingly use of stimulants among competitive athletes. Numerous compounds are available including prescription medications (i.e. methylphenidate) and over-the-counter preparations (high-dose caffeine). Although the long-term toxicity of stimulant use remains controversial, these agents are well recognized precipitants of common complaints in the athlete including palpitations. Finally, erythropoietic stimulants including human recombinant erythropoietin are reportedly widespread use among endurance athletes. The increase in oxygen carrying capacity that is afforded by augmented red cell mass leads to improved endurance capacity. Potential complications of erythropoietic stimulant use are related to increased red cell mass and including microvascular sludging and infarction.

SUDDEN DEATH AND PREPARTICIPATION DISEASE SCREENING

Sudden death in young athletic individuals is a rare but tragic event. Studies examining sudden death in athletes report a wide range of prevalence. United States data from a single state registry suggest a sudden death prevalence of 1:200,000/year[20] while data from the Italian preparticipation screening program suggest a significantly higher rate.[96,97] The variability in sudden death prevalence statistics may be attributed to multiple factors including geographic variability in the prevalence of causal diseases, characteristics of the populations studied, and case ascertainment techniques. Although there appears to be some regional difference in the causes of sudden death in athletes, hypertrophic cardiomyopathy is the most common cause in the United States. Sudden death has been documented in most types of competitive sport but may be more common during participation in physically intense sports such as basketball, soccer and American style football. In addition to sport-type, gender and ethnicity appear to contribute to sudden death risk with males and individuals of Afro-Caribbean descent more likely to succumb to sport-related sudden death.

Most cases of sudden, sport-related death in young athletes are attributable to underlying cardiovascular pathology (Table 2). Both the American Heart Association and the American College of Cardiology (AHA/ACC)[98] and European

TABLE 2

Common cardiovascular conditions associated with sudden death in athletes

Disorders of the myocardium:
- Hypertrophic cardiomyopathy
- Arrhythmogenic right ventricular cardiomyopathy
- Familiar/idiopathic dilated cardiomyopathy
- Acute and subacute myocarditis

Disorders of myocardial electrical activity and conduction:
- Congenital and acquired long QT syndrome
- Short QT syndrome
- Wolff-Parkinson-White syndrome
- Brugada syndrome
- Catecholaminergic polymorphic ventricular tachycardia
- Commotio cordis

Disorders of the coronary circulation:
- Congenital anomalies of coronary arterial origin and course
- Acquired atherosclerotic disease

Disorders of the heart valves:
- Bicuspid aortic valve disease associated with any of the following:
  - Significant aortic root dilation
  - Marfan syndrome
  - ≥ Moderate stenosis of regurgitation
- Mitral valve prolapse
- Pulmonic stenosis

TABLE 3

Criteria for abnormality during preparticipation medical history and physical examination screening*

Medical history

Personal history:
1. Exertional chest pain/discomfort
2. Unexplained syncope/near-syncope not clearly attributable to neurocardiogenic/vasovagal mechanism
3. Excessive and unexplained dyspnea/fatigue, associated with exercise
4. Prior recognition of a heart murmur
5. Elevated systemic blood pressure

Family history:
6. Premature death (sudden and unexpected) before age 50 years in ≥ 1 relative
7. Disability from heart disease in a close relative ≤ 50 years of age
8. Knowledge of hypertrophic or dilated cardiomyopathy, long-QT syndrome, Marfan syndrome or clinically important arrhythmias in any family member

Physical examination

9. Heart murmur
10. Diminished or asymmetric femoral pulses (to exclude aortic coarctation)
11. Physical stigmata of Marfan syndrome
12. Asymmetric or elevated (> 140/90 mm Hg) brachial artery blood pressure

*Criteria adopted from current recommendations from the American Heart Association regarding preparticipation screening of competitive athletes. Circulation. 2007;115:1643-55

Society of Cardiology (ESC)[99] have established sport eligibility criteria for individuals diagnosed with these conditions. Guidelines endorsed by these two groups are largely similar aside from a few notable situations including the management of athletes with asymptomatic Wolff-Parkinson-White syndrome and the approach to athletes with genotype positive/phenotype negative myocardial or electrical heart disease.[100]

The tragic nature of sudden death in young, previously asymptomatic athletes has led to considerable efforts at prevention. The logic that the detection and management of cardiovascular disease prior to sport participation may reduce the incidence of sudden cardiac death has led to recommendations for preparticipation screening. The AHA/ACC and the ESC[101,102] have published consensus committee-based recommendations for preparticipation athlete screening (Table 3). Both governing bodies recommend a focused medical history and physical examination. The ESC recommends the addition of a 12-lead electrocardiogram. This addition of 12-lead ECG to medical history and physical remains an area of intense debate. Observational data from the Italian national experience and recent prospective trial data from the United States suggest that ECG may improve the sensitivity of preparticipation cardiovascular screening.[103,104] However, a number of issues including: (1) the financial and "man-power" costs of the mandated ECG, (2) the high rate of false positive ECG findings, (3) the cost of follow-up testing for those with abnormal results, (4) the logistics of ECG acquisition and interpretation and (5) considerations about future insurability for athletes with detected disease represent considerable obstacles to implementing a mandatory 12-lead ECG as part of preparticipation screening in the United States. Although additional observational data from organizations or nations utilizing ECG are welcomed, this issue will almost certainly remain controversial until a prospective, randomized, multinational trial is conducted to provide a definitive answer. In absence of such data, priority should be placed on widespread dissemination and implication of current history and physical examination recommendations with consideration of ECG only in localities with sufficient resources and expertise for this technique.

CONCLUSION

Our understanding of the athlete's heart has progressed considerably since Darling and Henschen first observed cardiac enlargement in athletes in 1899. Today, the findings of global chamber enlargement coupled to normal or enhanced cardiac function are well-established markers of the athlete's heart. As participation in organized sport and individualized vigorous physical exercise continue to grow, the practicing clinician will likely see an increase in the number of patients with possible exercise-induced cardiac adaptations. A basic understanding of the athlete's heart and a familiarity with clinical issues common in athletic patients are essential for effective management of this specific patient population.

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Chapter 105

Cardiovascular Aging

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Chapter Outline

- Age-related Changes
  - Cellular Aging
  - Vascular Changes
  - Myocardial Changes
  - Electrophysiologic Changes
  - Exercise-related Changes
  - Attenuating Age-related Changes
- Clinical Syndromes
  - Heart Failure
  - Vascular Disease—Isolated Systolic Hypertension
  - Ischemic Heart Disease
  - Conduction Disease
  - Valvular Disease
- Special Issues
  - Prevention
  - End-of-Life Care

INTRODUCTION

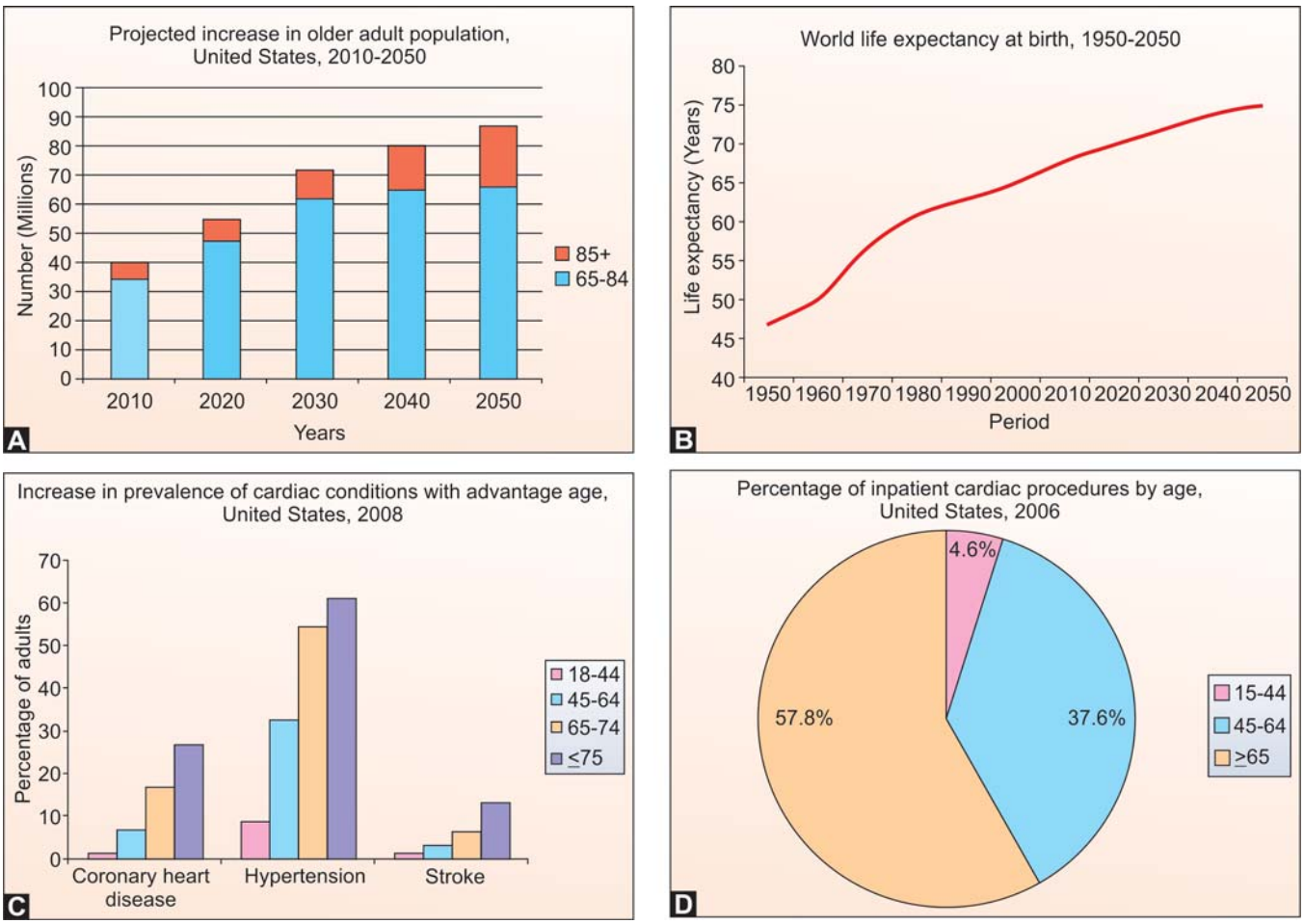
The world population has been aging over the past century, a trend which is expected to continue into the foreseeable future, especially among the oldest-old (Fig. 1A).[1] Although definitions vary,[2] the term "older adults" in the developed world generally refers to people older than 65 years of age, and within this group the population can be subdivided into the young old (65–74 years), old old (75–84 years) and oldest old (≥ 85 years).

In the United States, the number of older adults increased from 12 million in 1950 to 37 million in 2006, which was a faster rate of increase than the population as a whole. Individuals older than or equal to 75 years of age represented the fastest-growing segment, with an annual growth rate of 2.8% per year (compared to 1.2% per year for the general population).[3] The percentage of the population older than or equal to 75 years old, estimated at 6% of total US residents in 2006, is expected to double to 12% by the year 2050.[3] Such a trend is also projected for other developed countries.[2] Contributing to the aging of the U.S. population has been the nearly uninterrupted decline in the age-adjusted death rate over past 50 years, which as per most recent estimates is 43% lower now than it was in 1960. Life expectancy in the year 2010 was 78 years in the United States, which is the highest on record, and world life expectancy is projected to increase through the year 2050 (Fig. 1B).[3]

Cardiovascular disease (CVD) is the leading cause of mortality overall in the United States, accounting for approximately one in three deaths in 2006.[4] Advancing age is the most powerful risk factor for development of CVD, and the prevalence of cardiovascular conditions such as hypertension and coronary heart disease (CHD) is greatest in older adult patients (Fig. 1C). Of all cardiac procedures including percutaneous coronary intervention (PCI), coronary artery bypass surgery, pacemakers and implantable cardiac defibrillators performed in the United States, more than half are performed on older adult patients (Fig. 1D). Additionally, CVD-related mortality increases markedly in older persons. For example, patients older than 75 years of age account for 60% of acute myocardial-infarction (AMI) related deaths, and the odds for in-hospital mortality after admission for acute coronary syndrome (ACS) increase by 70% for each 10-year increase in age.[5] Aside from absolute mortality, conditions, such as angina pectoris, congestive heart failure (CHF), atrial fibrillation (AF) and stroke, lead to substantial morbidity and impairment in health-related quality of life in older adults.

While the burden of CVD in older adults is substantial, an increasing number of interventions have significantly decreased the morbidity and the mortality associated with certain conditions.[6-9] For example, the in-hospital mortality,[7] one-month mortality[6] and long-term mortality[8] for older adult patients with AMI have all decreased over the past decade, which has been attributed to the improved application of evidence-based therapies including aspirin, clopidogrel, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors and statins, as well as PCI.[6,8] Procedure-related mortality in older adults appears to be declining as well, with a reduction in mortality attributed to urgent or elective PCI seen in patients older than 80 years since the year 2001.[9]

However, many challenges remain. Although AMI-related mortality in older adults appears to be declining, heart failure (HF) incidence is on the rise.[7] Other chronic conditions including AF, stroke and valvular disease are expected to reach epidemic proportions which will place a substantial burden on the health care system.[10,11]



FIGURES 1A TO D: Demographics. (A) Projected rate of increase in US Older Adult Population, 2010–2050 (*Source:* US Census Bureau, 2004); (B) World life expectancy at birth, 1950–2050 (projected) (*Source:* United Nations, 2006); (C) Selected cardiovascular conditions among persons 18 years or older, United States, 2008 (*Source:* NCHS, 2009); (D) Inpatient procedures (including PCI, CABG, ICD, pacemaker, valves) by age, United States, 2006 (*Source:* AHA, 2010)

Older adult patients, especially the oldest old, pose many diagnostic as well as therapeutic challenges. Symptoms such as fatigue and dyspnea, which may be attributable to a single organ system in younger individuals, are more likely to be multifactorial with advancing age.[12] The majority of patients older than or equal to 65 years have two or more chronic medical conditions, and nearly one-third older than or equal to 85 years have four or more chronic conditions[13] (Table 1). This increasing number of comorbidities makes the application of standard evidence-based therapies that have been proven in younger patients difficult,[14] and balancing the potential cardiovascular benefits against competing risks challenging. Examples in daily clinical practice with older adults include performing PCI in the setting of advanced renal insufficiency, prescribing oral anticoagulation in patients with prior falls, and performing valve surgery for individuals who are frail.

The ultimate goals of treatment in older adult patients with CVD may differ as well, with quality rather than duration of life taking on increasing importance.[14,22] Goals of care in patients with advanced disease may include prevention of repeat hospitalizations, relief of symptoms, such as dyspnea and pain, and avoidance of invasive procedures, which may challenge traditional aggressive approaches with proven benefit in younger and healthier patients. As the population continues to age, the field of cardiology will be increasingly challenged with how best to provide high quality, patient-centric and specific care to the growing population of older adults.

In this chapter, authors initially focus on the biology of the aging cardiovascular system, and subsequently address clinical CVDs that are especially relevant to older adult populations. Finally, special concerns in the older adults with CVD including prevention and end-of-life care have been addressed.

AGE-RELATED CHANGES

Aging results in numerous changes in the cardiovascular system that is caused by various cellular mechanisms resulting in an altered phenotype in properties of the heart and vasculature.

CELLULAR AGING

The cellular mechanisms underlying cardiovascular aging are numerous and complex (Table 2). A comprehensive review is beyond the scope of this chapter and for details, authors would refer readers to the following sources.[23-27]

Telomeres, the special chromatin structures containing TTAGGG tandem repeats at the end of mammalian chromosomes, undergo attrition with each division of somatic cells in culture and are hypothesized to contribute to cellular aging by

TABLE 1

Common comorbidities in older adults with cardiovascular disease

Condition	*Prevalence*	*Assessment technique*
Renal dysfunction	16%—GFR ≤ 30 mL/min 40%—GFR 30–59 mL/min[15]	Cockroft-Gault formula MDRD formula
Chronic lung disease	20–32%[16]	Pulmonary function tests
Dementia	8.5%[17]	MMSE Mini-Cog
Delirium	Delirium— • 30–50% of hospitalized patients • 36.8% (range, 0–73.5% in postoperative patients • > 70% in ICU	CAM (Confusion assessment methodology)
Diabetes	30–50%	Blood glucose Glycosylated hemoglobin
Depression	8%[18]	Geriatric depression scale
Falls, mobility difficulties	30–50%	Timed get up and go Tinnetti gait and balance scale Berg balance scale
Postural/Postprandial hypotension	Postural: 10–30% Postprandial: 10–20%	Orthostatic/Postprandial blood pressure measurements Tilt table testing
Anemia	Inpatient: 70% Outpatient: 10–20%	Complete blood count
Urinary incontinence	Women > Men 35% and 22%, respectively[19]	Bladder diary
Sensory impairments	24%—Ocular disorders	Hearing loss screener Snellen eye chart Contrast sensitivity Auditory evaluation
Frailty	30–50%	ADLs IADLs Frailty scale[20]
Fatigue/Anergia	Mild to moderate—70% Severe—20%	Fatigue assessment Anergia scale[21]
Nutritional deficiencies	> 30%	Dietary questionnaires specific vitamin and nutrient levels
Polypharmacy	Almost all	Greater than four medications

TABLE 2

Cellular mechanisms of cardiovascular aging

	Proposed mechanism	*Evidence of clinical correlations*
Telomere shortening	Genomic instability, replicative senescence, and apoptosis	Hypertension[28]
Oxidative stress	Activates intermediate signaling molecules that promote inflammation	Atherosclerosis[29]
Protein misfolding	Abnormal proteins are deposited in tissues (myocardium, aorta)	Cardiac amyloidosis[30]
Autophagy	When inhibited, breakdown of intracellular components is impaired	Response to ischemia CHF[31]
Inflammation	Promotes arterial plaque formation	Atherosclerosis[26,29]
Advanced glycosylation	Added sugar residues alter structural protein function such as collagen, resulting in cross linking	Isolated systolic hypertension[32]

inducing genomic instability, replicative senescence and apoptosis.[33] Several alterations in telomere length have been delineated in the cardiovascular system with aging.[34,35] In the vascular smooth muscle cells of the distal abdominal aorta, telomere length demonstrates a strong inverse correlation with age,[34] and in patients with severe coronary artery disease the lengths of telomeres are significantly shorter than those of controls.[35]

Protein misfolding has been implicated in aging-related diseases as diverse as Alzheimer's disease, type 2 diabetes, in the cardiovascular system and systemic amyloidosis.[23,36] So-called "senile" cardiac amyloidosis (SCA) is seen almost exclusively in older men, and is believed to be caused by the deposition of wild-type transthyretin-related (TTR) amyloid molecules, also known as prealbumin, primarily in the heart.[36] TTR molecules are normally arranged in stable

tetramers, but misfold and aggregate when they dissociate into monomers.[30]

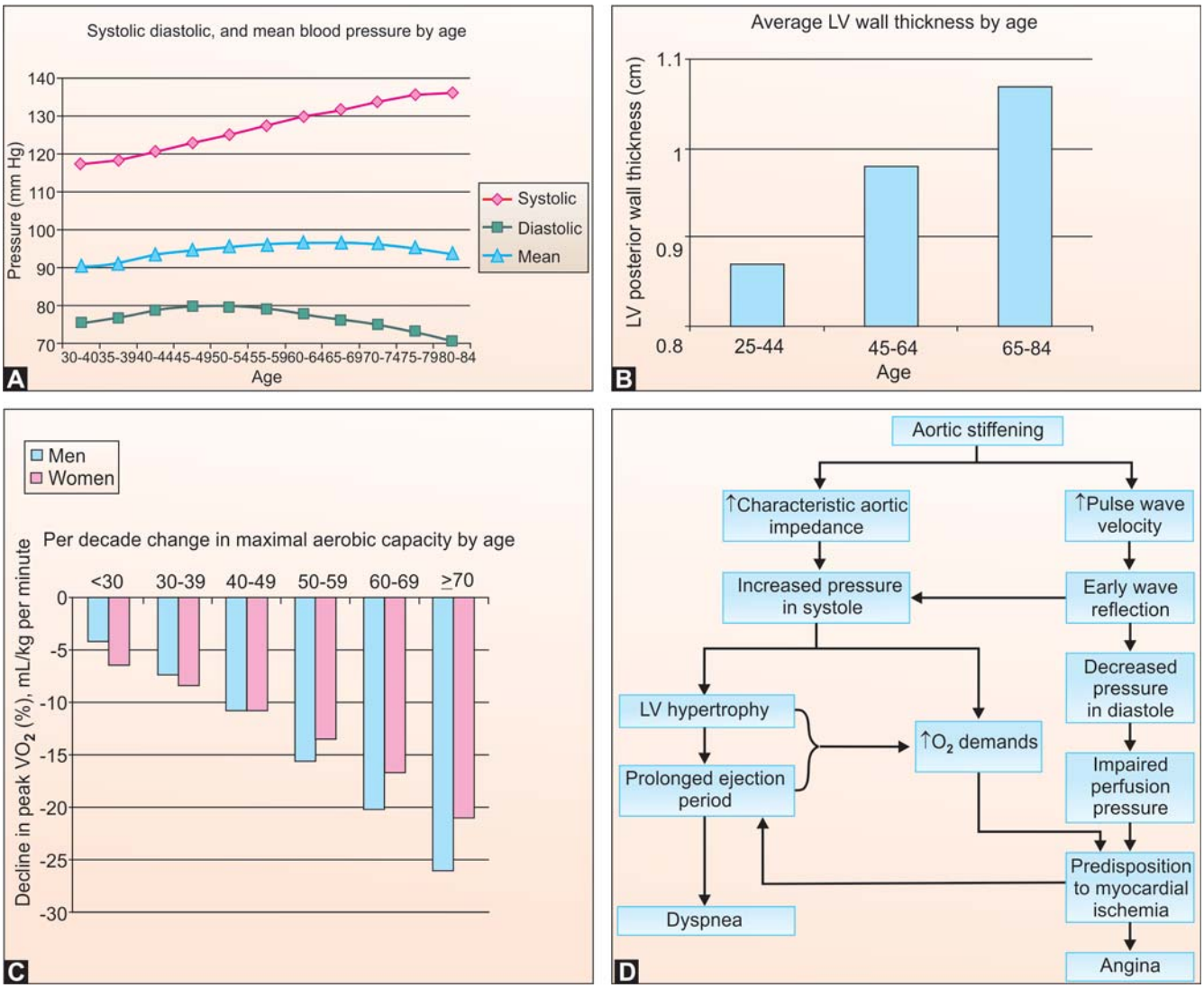
Inflammation plays a central role in the cellular pathogenesis of atherosclerosis, and advancing age has been described as a "proinflammatory" state.[29] The concentration of inflammatory cytokines increases with age and likely represents a combination of chronic antigenic stress and immune dysregulation, combined with lifestyle factors and comorbid disease.[26] The vessels of older adults exhibit inflammatory changes, including clusters of macrophages, mast cells, fetal-like smooth muscle cells, and angiotensin-II signaling molecules, even in the absence of atherosclerosis.[24] Inflammation results, at least in part from oxidative stress and the production of reactive oxygen species (ROS) which influence proinflammatory changes.[29]

Collectively, these cellular mechanisms contribute to an altered cardiovascular phenotype as humans age, with manifest changes in the vasculature and myocardium delineated below.

VASCULAR CHANGES

Endothelial cells, which line the luminal surface of the vasculature, regulate diverse functions including angiogenesis and maintenance of vessel tone, undergo a number of changes with aging.[37,38] Endothelium-dependent vasodilation is impaired in older adults both with and without hypertension.[39] The number of circulating endothelial progenitor cells (EPCs) in patients with coronary artery disease decreases with advancing age, and EPC mobilization after coronary artery bypass grafting (CABG) is impaired in older patients compared to their younger counterparts.[38]

Average systolic blood pressure rises steadily with increasing age in both men and women. However, diastolic blood pressure tends to rise until about age 50 and declines in older adults (Fig. 2A).[40] This trend is thought to be predominantly due to increased large artery stiffness with aging, a phenomenon which is present in persons with or without clinical CVD.[40,41] It is



FIGURES 2A TO D: Age-related changes. (A) Average systolic, diastolic and mean blood pressures by age, Framingham Study (*Source:* Franklin et al. Circulation, 1997); (B) Average left ventricular posterior wall thickness by age in healthy individuals (*Source:* Baltimore Longitudinal Study of Aging, 1977); (C) Per decade change in maximal aerobic capacity by age group (*Source:* Fleg et al. Circulation, 2005); (D) Age-associated cardiovascular changes and their relation to clinical disease (*Source:* Lakatta & Levy, Circulation, 2003)

traditionally thought to result from the process of intimal media (IM) thickening, with collagen deposition, reduced elastin content, elastin fractures and calcification.[32,42] There has been an increasing awareness that other factors such as endothelial dysregulation and neurohormonal alterations may also contribute to this phenotype.[32]

MYOCARDIAL CHANGES

Several studies have described an increase in left ventricular (LV) mass with aging independent of clinical disease.[41,43,44] The Baltimore Longitudinal Study on Aging (BLSA) demonstrated that the age was associated with increased LV wall thickness in healthy individuals without a prior history of hypertension[24,44] (Fig. 2B). In a larger sample of patients from the Framingham Heart Study, the presence of LV hypertrophy increased markedly with age, and was seen in approximately 30% of men and 50% of women over the age of 70.[43] Autopsy studies have demonstrated cardiac myocyte hypertrophy in older adult patients without clinical CVD,[45] as well as an increase in the amount of collagen within the myocardium.[46]

Early echocardiographic studies demonstrated that, in addition to LV wall thickness, left atrial size increases with advancing age.[44] Increased left atrial size is thought to reflect age-related changes in LV filling, and enlargement may worsen with increasing severity of diastolic dysfunction.[47] Left atrial enlargement was associated with an increased risk of new-onset AF in older adults in the Framingham study,[48] a finding that was confirmed by subsequent investigations.[49,50]

The rate of early LV diastolic filling progressively decreases after age of 20, even in individuals without clinical CVD.[46] Concomitantly, more vigorous filling occurs in late diastole due to augmented atrial contraction, which is seen as an exaggerated A-wave on Doppler echocardiography.[51] In contrast, LV systolic function as measured by ejection fraction (EF) is usually preserved at rest in healthy older adults, although the ability to augment EF with vigorous exercise is reduced.[46]

Calcific changes in the cardiovascular system increase with advancing age and include calcification of the mitral annulus, aortic valve, coronary arteries, and aortic root.[52,53] Mitral annular calcification and coronary artery calcification have been associated with an increased risk of cardiovascular events and all-cause mortality.[52,53] The pathophysiology of calcification is incompletely understood but may involve genetic factors,[54] local inflammatory changes[55] and metabolic derangements.[56]

ELECTROPHYSIOLOGIC CHANGES

The maximum heart rate (MHR) during exhaustive exercise decreases with advancing age, with an accelerated rate of decline in the oldest old.[57] The average decrease in MHR is approximately 30% between 20 and 85 years of age.[32] As the MHR decreases, an increasing reliance on stroke volume is necessary to maintain the adequate cardiac output during physical exertion. In addition to MHR, heart rate (HR) variability, or the beat-to-beat fluctuation of HR, declines steadily with age and may be associated with an age-related reduction in parasympathetic function with a concomitant increase in sympathetic activity.[46,58] On a structural level, a decline in the number of pacemaker cells occurs after age of 60, and less than 10% of the number seen in young adults remains after age of 75.[59] Calcification of the central fibrous skeleton and the aortic and mitral annuli is observed, which may interfere with atrioventricular (A-V) conduction and result in conduction delay or block.[59]

EXERCISE-RELATED CHANGES

The maximum oxygen consumption rate (peak VO_2), a measure of aerobic fitness, declines in older adults.[57,60] The rate of decline, rather than being linear, appears to accelerate with advancing age; for example, a study of the BLSA cohort demonstrated a decline of 3–6% per 10 years for people in their 20s and 30s, and more than 20% per 10 years for individuals older than 70 years[57] (Figs 2C and D).

Peak VO_2 is defined by the Fick equation as follows:

$$VO_2 \text{ max} = Q(CaO_2 - CvO_2)$$

Where Q = cardiac output, CaO_2 = arterial oxygen content, CvO_2 = venous oxygen content.

Variables influencing peak VO_2 include muscle mass, cardiac output, hemoglobin level, pulmonary reserve and vascular distribution.[60] Peak VO_2 has been well-established as a prognostic indicator in patients with advanced HF,[61] where low cardiac output (Q) dominates the equation. In normal aging, muscle loss (sarcopenia) accounts for the greatest percentage decline in peak VO_2, since most O_2 consumption during maximal aerobic activity occurs in exercising muscle.[60] There is some evidence that peak VO_2 can be improved through exercise training in older adults.[62] Other interventions to directly address sarcopenia in this population, including dietary modification[63] and hormone supplementation[64] have been shown to increase lean muscle mass but not definitively improve peak VO_2. However, with further study, these therapies may play a future role in improving exercise capacity in older adults.

ATTENUATING AGE-RELATED CHANGES

The interrelation of the various cellular and structural changes in older adults with lifestyle is illustrated in two interventions which may reduce accelerated cardiovascular aging: exercise and caloric restriction.[65-71]

Habitual aerobic exercise is associated with a decreased risk of CVD in older adults, which may be mediated by reductions in large-artery stiffness and improvements in vascular endothelial function.[65] Studies have illustrated both baseline physiologic differences between individuals who exercise and those who are inactive,[66] as well as the potential for exercise interventions to improve hemodynamic parameters and cardiovascular risk profiles in previously sedentary individuals.[25,66,68] For example, a study of middle-aged and older men who underwent an aerobic exercise endurance program for 3 months demonstrated a 25% increase in central arterial compliance as measured by ultrasound and applanation tonometry of the carotid artery.[66] It has been hypothesized that such exercise-mediated changes in large artery stiffness result from a reversal of the accumulation of interstitial collagen in the arterial wall, which reacts with glucose to produce advanced glycation end-products.[68]

Caloric restriction has long been established as a method of prolonging the lifespan of experimental animals ranging from invertebrates to nonhuman primates, when started in early or middle age.[70-72] There is an emerging evidence that caloric restriction may have similar effects in humans, including an improved cardiovascular risk profile, although studies are small and data remain observational.[67,73] For example, one study of 18 adults on a calorie-restricted diet for an average of 6 years found a lower low-density lipoproteins (LDL) cholesterol, lower systolic and diastolic blood pressures, and a 40% reduced carotid intimal medial thickness when compared with 18 controls on a typical American diet.[67] Although a reduction in cardiovascular events with caloric restriction in humans has not been demonstrated definitively, a recent study of caloric-restricted Rhesus monkeys found a lower lifetime incidence of CVD when compared with controls.[72] The cellular mechanisms underlying extended longevity with caloric restriction are still being elucidated, but are likely to include reduction in free radical production and oxidative stress,[71] increased autophagy[74] and modulation of growth factor signaling.[75]

CLINICAL SYNDROMES

Clinical syndromes that disproportionately affect patients older than or equal to 65 years, and particularly patients older than or equal to 80 years of age include HF (especially with a normal or preserved EF), SCA, isolated systolic hypertension, ischemic heart disease (IHD), AF and valve disease [particularly senile calcific aortic stenosis (AS)]. As this segment of the population grows, these disorders will become increasingly prevalent and clinicians will be continued to be challenged by their management.

HEART FAILURE

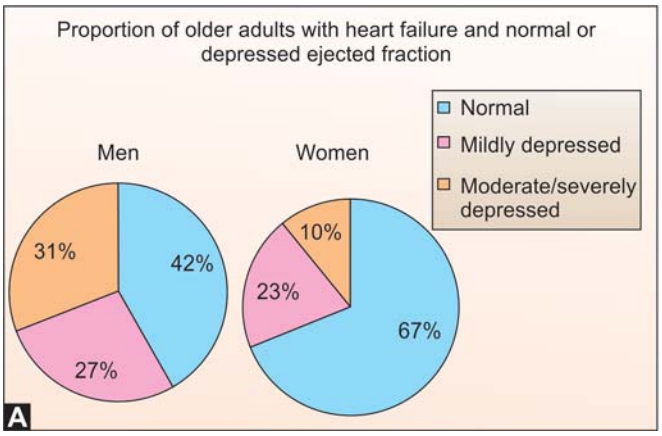
Epidemiology

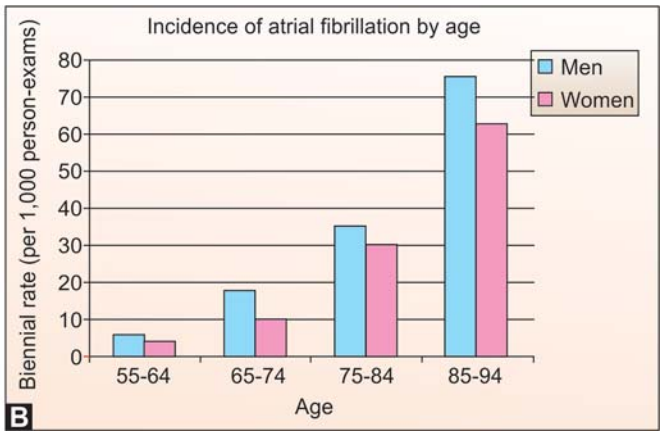
Over 80% of patients with HF are aged 65 years or older, and HF represents the most common reason for hospitalization among medicare beneficiaries.[76] Among older adults, the prevalence of HF continues to increase with advancing age; for example, data from the Cardiovascular Health Study showed a prevalence of 7.8% in men and 4.1% in women aged 70, and 18.4% in men and 14.3% in women aged older than or equal to 85 years.[77] The proportion of HF patients older than or equal to 65 years with preserved EF, the same study was approximately 42% in men and 67% in women, which underscores the importance of this subtype among older adults as well as its disproportionate distribution in female patients[77] (Fig. 3A). HF is increasingly becoming a disease of older adults; for example, the mean age of patients in a community-based sample in Minnesota was 76 years, and nearly half were older than 80 years.[78] However, a considerable knowledge gap exists with older adults, specifically the oldest old, as the majority of studies addressing the diagnosis, prognosis, and treatment of HF have focused on younger individuals.[77]

Heart failure with preserved ejection fraction (HFPEF) represents a particular challenge in older adults, both in diagnosis and therapy. The disorder is heterogeneous with a diverse set of related underlying clinical co-morbidities that can mimic symptoms of HF and cause or contribute to the pathogenesis of this syndrome. There are no uniformly accepted criteria for the diagnosis of HFPEF, although it is agreed that the condition requires signs and symptoms of HF as well as normal LV systolic function (usually estimated by an LVEF > 50%).[79] The 2007 European Society of Cardiology guidelines also included invasive or noninvasive evaluation of LV diastolic dysfunction as additional criteria for diagnosis,[79] although noninvasive methods, particularly Doppler echocardiography, may be influenced by loading conditions rather than intrinsic myocardial properties.[80] The existence of comorbid conditions in the oldest old including respiratory disease, frailty and chronic fatigue of unexplained origin can make clinical diagnosis especially difficult.

Pathogenesis

The exact pathogenesis of HFPEF is unclear and likely secondary to multiple mechanisms, which may vary by patient. These include intrinsic myocardial properties such as active relaxation and passive ventricular filling,[81] as well as extrinsic factors including loading conditions.[80] It is likely that older





FIGURES 3A AND B: Epidemiology of selected conditions. (A) Proportion of older adult patients with heart failure and normal, mild, or moderate/severe depression in ejection fraction (*Source:* Kitzman et al. Am J Cardiol, 2001); (B) Incidence of atrial fibrillation by age based on biennial patient exams in the Framingham study (*Source:* Benjamin et al. JAMA, 1994)

adults are more prone to HFPEF secondary to age-related structural changes including concentric LV hypertrophy[44] and increased arterial stiffness,[41] as well as the presence of comorbid conditions including anemia[82] and renal insufficiency.[83] The specific reason why certain older adults develop HFPEF and others do not (even in the presence of structural changes and comorbidities) has yet to be definitively elucidated.

One etiology of HFPEF that is only seen in older adults is SCA, which is due to deposition of wild-type transthyretin (TTR, also known as prealbumin) that aggregates to form amyloid fibrils primarily in the heart.[84] The disease affects almost exclusively older men,[36] and differs from familial amyloidosis which presents at a younger age and involves mutant TTR deposition at multiple sites.[84] Senile amyloid deposits have been estimated to be present in up to 25% of individuals older than 80 years of age, and the proportion of older adults with asymptomatic deposits is much higher than those with clinically evident disease.[84] It is thought that SSA may be an under-recognized cause of HFPEF in older adults, given the fact that definitive diagnosis requires endomyocardial biopsy.[36] As the disease progresses, deposition of wild-type TTR molecules between individual myocytes interrupts contractile function and electrical conduction, the ventricular wall thickens and becomes stiff, and a restrictive cardiomyopathy develops.[85] Right-sided HF symptoms predominate, including lower extremity edema, elevated jugular venous pressure, and hepatic congestion.[86] The electrocardiogram typically reveals low or normal QRS voltage, while echocardiography demonstrates LV hypertrophy, normal ventricular cavity size, atrial dilatation and a restrictive Doppler filling pattern.[86]

Therapy

For SCA, treatments have typically been limited to symptomatic management of HF and pacemaker therapy when indicated,[86] although new therapies are emerging which are targeted at preventing the protein misfolding and aggregation that occur when normal TTR tetramers dissociate into monomers.[30,87] For example, two nonsteroidal anti-inflammatory drugs (NSAIDs), diflunisal and flufenamic acid, have been found to stabilize TTR tetramers in vitro via binding to the T4 binding sites.[30] Another mechanism under investigation involves the use of RNA interference (RNAi) to silence TTR production in the liver; preclinical studies have shown a targeted RNAi strategy can induce regression of amyloid deposits in mice which overexpress the mutant human V30M TTR gene.[88]

For the broader population with hypertensive HFPEF, all major trials of therapy to date have demonstrated no significant reduction in mortality.[89-93] The CHARM-Preserved trial, which randomized over 3,025 patients with Class II—IV HF and left ventricular ejection fraction (LVEF) more than 40% to receive the angiotensin II receptor blocker (ARB) candesartan versus placebo, demonstrated no difference in the primary endpoint of combined cardiovascular death or hospitalization for HF, although an analysis of HF hospitalizations alone yielded fewer events in the candesartan arm.[89] The PEP-CHF study, which randomized 852 older adult patients (≥ 70 years) with HFPEF to receive the ACE inhibitor perindopril versus placebo, found no difference in all-cause mortality or HF hospitalizations.[90] The randomized I-PRESERVE trial, which utilized the IRB irbesartan versus placebo in over 4,128 patients older than or equal to 60 years of age with LVEF more than or equal to 45%, found a similar negative result.[91]

Beta-blockers, which theoretically may improve diastolic filling time through controlling HR, have been less extensively studied in randomized trials. A small study of older adults (average age 81) with prior MI and HF with EF more than or equal to 40% randomized to placebo versus propranolol demonstrated a 35% mortality reduction in the latter group at 32 months.[94] The SENIORS trial, which randomized 2,135 patients with HF (depressed or preserved EF) older than or equal to 70 years of age to the beta-blocker nebivolol versus placebo, found no reduction in all-cause mortality, including in the subgroup analysis of patients with preserved EF.[93] A large, multicenter, randomized trial of beta-blocker therapy with metoprolol versus placebo in HFPEF is ongoing (β-PRESERVE), and may provide further insights into the efficacy of this therapy.[95]

Interpretation of studies in patients with HFPEF is limited due to heterogeneous enrollment criteria (with differing cutoffs for a "normal" EF) and varied clinical endpoints.[92] Generally, there is no universally accepted therapy for HFPEF, and management strategies remain limited to symptom control as well as modification of coexisting cardiac risk factors such as hypertension. Clinical trials of newer medications, including the phosphodiesterase inhibitor sildenafil (RELAX) and the aldosterone antagonist spironolactone (TOPCAT), are ongoing and may provide novel therapeutic options.[96] In addition, as specific pathophysiologic mechanisms are defined on a cellular level, future treatments may become more tailored to individual patients or pathophysiologic subgroups.

VASCULAR DISEASE—ISOLATED SYSTOLIC HYPERTENSION

Epidemiology

Hypertension increases in prevalence with advancing age, and affects over 50% of individuals aged 65–74 and 60% of individuals aged 75 and older.[3] Data from up to 30 years of patient follow-up in the Framingham Study demonstrated that on average, there is a linear rise in systolic blood pressure with aging, while diastolic pressure begins to decline between ages 50 and 60.[40] As a result, isolated systolic hypertension is overwhelmingly the most common form of hypertension seen in the oldest-old.

Pathogenesis

As discussed earlier, increased large artery stiffness is thought to be the predominant pathophysiologic mechanism underlying isolated systolic hypertension.[41] Pulse-wave velocity, which is a noninvasive index of vascular stiffening, increases steadily with age and is thought to reflect structural alterations of the arterial wall including collagen overproduction, elastin fractures and calcification.[32] Pathologic examination of vessels reveals

TABLE 3

Effect of antihypertensive therapy on cardiovascular events in older adults

Trial	*NR*	*Age range (years)*	*Relative risk reduction (%)*		
			Heart failure	*Stroke*	*MI*
SHEP[100]	4,736	≥ 60	55%*	36%*	33%*
STOP-Hypertension[103]	1,627	70–84	51%*	47%*	13%
STONE[104]	1,632	60–79	68%	57%*	6%
Syst-Eur[101]	4,695	≥ 60	36%	42%*	30%
HYVET[105]	3,645	≥ 80	64%*	30%†	28%

*Achieved statistical significance, $p < 0.05$ NR = Not Reported, †Reduction in fatal stroke (39%) statistically significant, $p = 0.046$

an increase in intimal-medial thickness, disarrayed endothelial cells, increased collagen content and the presence of inflammatory cells.[97] Endothelial dysfunction has been increasingly recognized as a significant factor, in part through regulation of vascular smooth muscle tone.[32] Isolated systolic hypertension has been linked in epidemiologic studies to the development of HF, CHD and decline in renal function.[98,99]

Management

The benefit of treating isolated systolic hypertension in older adults has been well-established by several large trials (Table 3).[100-102] Data from the randomized Systolic Hypertension in the Elderly Program (SHEP) in subjects older than or equal to 60 years of age demonstrated a significant reduction in stroke and a trend toward reduction in cardiovascular events at a mean follow-up of 4.5 years, with a regimen of chlorthalidone and atenolol (if necessary) versus placebo.[100] Another randomized trial in subjects older than or equal to 60 years, the Systolic Hypertension in Europe (Syst-Eur) study, demonstrated a reduction in stroke as well as all fatal and nonfatal cardiac endpoints, with utilization of a calcium channel blocker (versus placebo) as a first-line agent.[101]

Until recently, however, it was unclear if the benefits of treating isolated systolic hypertension extended to the oldest old.[106] This was addressed by the HYVET trial, which included exclusively patients older than or equal to 80 years of age with an average systolic BP of more than or equal to 160 mm Hg.[105] Patients were randomized to placebo versus the diuretic indapamide, with provisional ACE inhibitor (perindopril) in the intervention arm, if necessary to reach target blood pressure of 150/80 mm Hg. The trial found a significant reduction in fatal or nonfatal stroke, as well as a reduction in all-cause mortality, death from cardiovascular causes and HF at a median follow-up of 1.8 years.[105]

The results of HYVET challenged the paradigm that there is an "upper limit" of age for antihypertensive therapy, although it should be noted that enrollees were healthier than normal for their age.[107] Theoretically, overly aggressive antihypertensive therapy may lead to postural hypotension and falls in vulnerable patients, although a consistent adverse effect of such a treatment strategy has not been described to date.[4,108] In fact, on the contrary, data would suggest that older adults with uncontrolled hypertension are at the greatest risk for orthostatic hypotension and subsequent falls, suggesting an additional benefit of treatment.[109,110]

ISCHEMIC HEART DISEASE

Epidemiology

Ischemic heart disease (IHD) is the leading cause of death in older adults, and the prevalence and complications of IHD continue to increase with advancing age.[4] The overall prevalence of CHD based on NHANES data (2003–2006) was approximately 25% and 17% in men and women aged 60–79 respectively, and 37% and 23% in men and women older than or equal to 80 years of age respectively.[4] Rates of chronic stable angina as well as ACSs [unstable angina or myocardial infarction (MI)] increase with age as well.[4,5] Additionally, older adults have increased complications and mortality rates after MI; approximately one-quarter of patients over 75 years of age die within one year of hospitalization,[4] and the population over 75 years of age accounts for 60% of MI-related deaths overall.[5]

Older adults with MI are more likely to present with atypical symptoms (including nausea, vomiting, syncope and confusion) or to be asymptomaic.[111,112] In addition, MI is more likely to occur in the setting of acute illness such as pneumonia, exacerbation of chronic obstructive pulmonary disease, or a fall.[5] The difficulties in recognition of MI in this population may lead to a delay of appropriate treatment including pharmacotherapy or invasive evaluation.[111,112]

Pathogenesis

Age is associated with an increasing likelihood of developing atherosclerosis, which may be secondary to changes in the arterial wall that promote the development of plaque formation.[32,42] Intimal medial thickening has been proposed as an aging-related mechanism which may serve as a foundation for atherosclerotic changes.[32] Changes in the vessel wall including atherosclerosis and endothelial cell dysfunction, as well as hemostatic factors such as increased fibrinogen levels and plasma viscosity, contribute to the "prothrombotic" state seen with aging.[113] This likely interacts with traditional risk factors including hypertension, hyperlipidemia and smoking, as well as cellular and genetic mechanisms that are still being elucidated.[32,114]

Management

A significant body of research demonstrated that older adults with ACSs were less likely to receive evidence-based treatments including antiplatelet therapy, beta-blockers and invasive evaluation, despite their greater potential to benefit.[5] However, this paradigm appears to have shifted in recent years,[6,7] and on average older adults are now receiving more standard medical treatments as well as invasive procedures for ACS.[8,115]

Several issues remain important to address in the management of older adults with ACS.[5] This population has altered pharmacokinetics and is vulnerable to medications with the potential to cause hypotension (beta-blockers, nitrates) as well as bleeding (aspirin, thienopyridines, heparin).[5] Comorbidities including renal or hepatic dysfunction, as well as generalized loss of muscle mass (sarcopenia), are often not taken into account when dosing anticoagulant medications, and observational data demonstrate that older adults are the most vulnerable to excessive dosing of this therapy.[5,116] For example, an analysis of the crusade registry showed that patients older than or equal to 75 years of age received excess doses of heparin (38%), low-molecular weight heparin (17%) and GP IIb/IIIa inhibitors (28%), all of which were more common than in younger individuals.[116]

Even when dosed in controlled clinical trials, anticoagulant therapy carries a higher bleeding risk in older patients, especially the oldest old.[117,118] In the PURSUT study of NSTEMI-ACS patients randomized to GP IIb/IIIa inhibitor (eptifibatide) versus placebo, the rate of moderate to severe bleeding in patients older than 80 years of age with GP IIb/IIIa inhibitor was 17% (versus 10% with placebo), which may have offset the potential benefit of this therapy.[118] Data from patients older than or equal to 75 years of age with NSTEMI-ACS enrolled in the acute catheterization and urgent intervention triage strategy (ACUITY) trial (randomized to heparin plus a GP IIb/IIIa inhibitor, versus bilvarudin plus a GP IIb/IIIa inhibitor, versus bilvarudin alone), demonstrated a 10% rate of major bleeding events in those receiving a heparin plus GP IIb/IIIa strategy. The bleeding rate was lower in patients receiving bilvarudin alone (6%), suggesting a potential advantage of this therapy in the oldest-old.[117]

Observational data have shown an increased risk of bleeding from aspirin and thienopyridine therapy in older adults as well, including gastrointestinal, genitourinary and intracerebral hemorrhage requiring hospitalization.[119-121] The risk of dual antiplatelet therapy (aspirin plus thienopyridine), which may be indicated in the setting of ACS, stent placement, or a neurologic event such as stroke, appears to be additive; in several observational and randomized studies, bleeding complications with this strategy were as high as twice that with aspirin alone.[121-123] This risk is further magnified by the addition of warfarin anticoagulation for cooccurring indications including AF, mechanical heart valves and venous thromboembolism.[119,122]

Most studies assessing the risk of dual antiplatelet therapy analyzed patients taking clopidogrel. Of note, prasugrel, a novel thienopyridine which inhibits platelet aggregation more rapidly and consistently than clopidogrel, was found to have a higher likelihood of causing major bleeding (versus clopidogrel) in patients older than or equal to 75 years of age, and should be used with special caution in older adults.[124]

CONDUCTION DISEASE

Cardiac rhythm disturbances are common in older adults and result in substantial morbidity and mortality.[125-128] One of the most prevalent and important standpoint from a public health is AF.

Epidemiology

Atrial fibrillation (AF) is a common condition in older adults and increases in prevalence with advancing age (Fig. 3B). Data from the Framingham Study demonstrated that for each decade, the odds ratio for developing AF was 2.1 in men and 2.2 in women.[129] In 5,201 men and women aged older than or equal to 65 years in the Cardiovascular Health Study, the overall prevalence of AF was 4.8% in women and 6.2% in men.[130] In the subgroup of patients older than or equal to 80 years, the prevalence was 6.7% and 8.0% in women and men, respectively.[130] AF is associated with increased incidence of HF, stroke and all-cause mortality.[131,132] Data from the original Framingham cohort estimated that AF increased the risk of stroke in all participants approximately fivefold, and over one-third of strokes in patients older than or equal to 80 years were associated with AF (which was significantly higher compared to younger subjects).[126]

Pathogenesis

Advanced age has been well-described as an independent risk factor for the development of AF,[129] but the exact pathophysiological mechanism is unclear. Age-associated structural changes are likely to play a significant role, especially increased left atrial size and elevated LV end-diastolic pressures.[48,50] Studies have shown that each 5 mm increase in left atrial size in older adults is associated with an approximately 50% increased risk of AF.[48,50] In addition, the atria of older adults have been found to have a decline in left and right atrial wavefront propagation velocities and an increase in septal refractoriness, possibly setting up an electroanatomical substrate for AF.[133]

Management

Anticoagulant therapy with warfarin has been demonstrated to reduce the risk of stroke by approximately two-thirds in several well-designed randomized trials,[134] and this treatment remains a mainstay of stroke prevention in at-risk patients. It has been estimated that the oldest-old stands to benefit the most from anticoagulant therapy,[135] although there is evidence that they are prescribed anticoagulant therapy less often than their younger counterparts for both primary prevention[136] and after admission for ischemic stroke.[137] Reasons are multifactorial and may include increased bleeding risk, inability to attend clinic visits, dementia, prior falls and general frailty.[137-139]

Observational studies have found an increased incidence of major bleeding in older adults treated with anticoagulant therapy,[140,141] although this has not been demonstrated reliably

in randomized trials.[134,142] Bleeding risk appears highest in the oldest old; for example, an observational study of 472 patients older than or equal to 65 years of age started on warfarin therapy found that the cumulative incidence of major hemorrhage was 4.7% person-years for individuals less than 80 years and 13.1% for those older than or equal to 80 years of age.[140] Another analysis of 2,376 patients receiving warfarin for several indications found that patients older than or equal to 80 years had a relative risk of 4.6% for life-threatening and fatal complications related to anticoagulation, when compared to those less than 50 years.[141]

There is a relative paucity of randomized trial data for anticoagulation involving exclusively the oldest old. The Birmingham Treatment of Atrial Fibrillation in the Aged Study (BAFTA), which randomized 973 AF patients older than or equal to 75 years of age to warfarin versus aspirin, found a significant reduction in a combined endpoint (stroke, intracranial hemorrhage, systemic embolus) in the warfarin arm after a mean follow-up of 30 months (3.8% vs 1.8%).[142] There was no concomitant increase in extracranial bleeding events in the warfarin arm (1.4% vs 1.6% for aspirin).[142] In addition, an observational study of patients more than 75 years old attending an anticoagulation clinic found no increase in warfarin-related major bleeding events at one year (2.8%) when compared with individuals aged 60–69 years (2.9%).[143]

Such results may not extend to patients at very advanced ages (≥ 85 years of age), especially in the setting of contraindications such as frequent falls or previous gastrointestinal hemorrhage. The decision to proceed with anticoagulation therapy in this population still remains very much an individualized one, based on clinicians' assessment of risk and potential benefit. Of note, newer agents, such as dabigatran, an oral direct thrombin inhibitor which demonstrated a lower rate of major hemorrhage than warfarin (with similar rates of stroke) in one trial,[144] may change this paradigm.

VALVULAR DISEASE

Arguably, the most relevant valvular disease in older adults is calcific AS, which occurs infrequently in younger patients except in the setting of a bicuspid aortic valve.

Epidemiology

Aortic stenosis is characterized by restricted excursion of the aortic valve leaflets, leading to LV outflow obstruction and a compensatory increase in LV systolic pressure. In developed countries, AS is due primarily to either a congenital bicuspid valve or calcific disease of a native trileaflet valve.[145] The prevalence of AS increases with age, although exact population estimates vary.[146,147] In 5,653 randomly selected subjects aged older than or equal to 65 years in the Cardiovascular Health Study, the prevalence of AS was 2%.[147] In the Helsinki Aging Study, a random sample of 501 men and women between 75 and 86 years of age, the prevalence of any degree of AS was over 13%, and severe AS increased from 1% in subjects aged 75–76 years to over 5% in those aged 85–86 years.[146]

The prevalence of calcific aortic valve sclerosis, defined as irregular valve thickening without obstruction to LV outflow, is much greater than AS in older adults.[147,148] In the Cardiovascular Health Study, nearly 30% of participants had evidence of aortic valve sclerosis on baseline echocardiography,[147] and this condition was associated with an approximately 50% increase in risk of cardiovascular death and MI even in the absence of AS.[149]

Pathogenesis

On a pathologic level, calcific AS is characterized by LDL deposition and oxidation,[55] inflammatory cell infiltration,[150] and production of proteins which promote calcification.[151] One study which examined lymphocytic infiltrates in calcified aortic valves demonstrated a mostly clonal T-cell population, suggesting a specific (rather than nonselective) immune response accounting for valvular injury.[152]

Once moderate AS is present, the disease progresses on an average by a decrease in valve area of 0.1 cm^2 per year and an increase in mean pressure gradient of 7 mm Hg per year, although there is marked variability among individual patients.[153]

Increasing age appears to be a risk factor for the progression of aortic valve sclerosis to AS along with the degree of valvular calcification, initial gradient and comorbidities such as smoking and hyperlipidemia.[147,154] Of special note in the oldest old is the phenomenon of low-gradient AS despite severely reduced aortic valve area and preserved LVEF.[155,156] This phenomenon is more common in females and is characterized by small ventricular cavity size, concentric LV hypertrophy and increased afterload.[155] Surgical outcomes in such patients tend to be poorer than in those with high-gradient AS, possibly secondary to cardiac structural abnormalities (e.g. remodeling) that represent a more advanced state of disease.[155]

Symptomatic AS is classically manifested as angina, syncope or HF, although in older adults who are activity-limited secondary to frailty, osteoarthritis, or social isolation, evaluating symptoms at routine follow-up may be difficult.[153] Exercise treadmill testing may have a role in patients without clear symptoms, as the assessment of exercise capacity, exertional dyspnea or angina, and exercise-induced hypotension can all be performed, relatively safely in a monitored setting.[157] Untreated, the average survival for symptomatic AS is 2–3 years, with a high risk of sudden death.[158,159]

Management

Once AS becomes symptomatic, the only definitive therapy is replacement of the aortic valve. Medical therapy has not been shown to slow disease progression; notably, trials of statin therapy, with the goal of inhibiting the inflammatory process in the valve leaflets, have been negative to date.[160,161] Balloon valvulotomy, in which one or more balloons are inserted percutaneously and inflated across a stenotic aortic valve, has not been shown to have any effect on long-term survival despite an immediate post-procedural reduction in the transvalvular gradient.[162] A role may remain as a bridge to surgery in hemodynamically unstable patients, as well as for palliation in severely symptomatic patients who are not operative candidates.[153]

Given the above findings, for nearly all symptomatic patients who are operative candidates, referral for aortic valve replacement (AVR) should be considered.[153] The proportion of older adults undergoing AVR is significant of 67,292 patients in the Society of Thoracic Surgeons (STS) database undergoing isolated AVR between 2002 and 2006, approximately one-third were older than or equal to 75 years of age.[163] The 30-day mortality rate for all patients undergoing AVR in this registry was 3.2%, with increasing age associated with an increased odds ratio for death.[163] Other studies have confirmed an effect of age on early mortality, and comorbidities, such as renal insufficiency, lung disease and AF, appear to be important predictors of adverse outcomes.[164,165]

Despite the trend for an increasing number of operations in older adults, many individuals with symptomatic AS are denied surgical AVR, given its concomitant risks,[166] and treatment in this scenario becomes palliative. The paradigm of treatment for symptomatic AS in older adults may be changing, however, with percutaneous AVR, which theoretically avoids many of the risks associated with open-heart surgery.[167] Currently, two valve models—the Edwards SAPIEN valve (balloon expandable, previous version was the Cribier-Edwards) and the CoreValve ReValving System (self-expandable)—have been studied in humans.[168] In a study of 50 patients (mean age 82 years) with symptomatic severe AS who were considered too high-risk for conventional AVR, implantation of a Cribier-Edwards valve was successful in 86% of patients, and 35 of 43 individuals (81%) who had undergone successful transcatheter AVR were alive at one year.[167] A study of 646 high-risk patients (mean age 81 years) undergoing implantation of a CoreValve system found 97% procedural success rate, and 30-day mortality was 8%.[169] Complications with percutaneous valve replacement have included heart block, stroke and access site bleeding, and operator experience appears to play an important role in procedural success.[170] As this technique becomes further refined and studied, it may become a more routine option for older adults whose surgical risk is deemed excessive.

SPECIAL ISSUES

PREVENTION

Numerous primary and secondary prevention trials have shown benefits to treating hypertension and hyperlipidemia to delay the onset, or slow progression, of CVD.[171-173] Treatment with antihypertensive therapy has been associated with an approximately 25% reduction in cardiovascular events (MI, HF, stroke) in a pooled analysis of randomized trials in patients of all ages.[171] However, most hypertension trials, while incorporating older adults, did not enroll substantial numbers of the oldest old (≥ 80 years). A notable exception is the previously discussed HYVET study, which included only patients older than or equal to 80 years of age, although individuals with HF, elevated serum creatinine, dementia and dependence on nursing care were all excluded.[105]

Treatment for hyperlipidemia, particularly statin therapy, has been studied extensively, and in a meta-analysis of over 30,000 patients was found to reduce the rate of major coronary events by 31% and all-cause mortality by 21%.[172] Data on statin therapy for secondary prevention in older adults have generally shown benefit. The PROSPER study of 5,804 patients aged 70–82 years randomized to pravastatin versus placebo demonstrated a 15% reduction in the primary endpoint of cardiac death, nonfatal MI and stroke at 3 years.[174] A meta-analysis of nine trials including nearly 20,000 patients aged 65–82 years found a reduction in all-cause mortality of 22%, with this effect estimated at 50% in the subgroup of patients older than or equal to 80 years.[175] There are limited data, however, on primary prevention of cardiovascular events in patients of very advanced ages, and treatment in this group remains controversial.[176]

More recently, studies have looked at the application of implantable cardioverter defibrillators (ICDs) in the prevention of sudden cardiac death for patients with symptomatic HF and depressed EF.[177,178] The average age in the two major randomized primary prevention ICD trials was 64 years (MADIT II)[177] and 60 years (SCD-HeFT),[178] and comorbidities common to older adults such as advanced renal disease were explicit exclusion criteria. Despite this, the proportion of older adult ICD recipients is significant, with one recent study finding approximately 40% overage 70 and 10% overage 80.[179] The absolute mortality benefit of primary prevention ICDs in the oldest old is unknown, and further study is required to determine persons who may benefit (and, conversely, others in whom it may be futile).

END-OF-LIFE CARE

The majority of serious and chronic illnesses in developed countries occur in older adults, especially the oldest old, and many are accompanied by a long period of functional decline, disability, and loss of independence. While the field of cardiology has enabled older adults with CVD to live longer with an improved quality of life, conditions may progress to the point of being terminal. The final common pathway for pathologies, such as coronary artery disease, AS, hypertension and AF, is often HF, and most of the research to date has been with this condition.

While prediction of disease trajectory in individual HF patients is difficult, characteristics of end-stage disease include dyspnea at rest, renal dysfunction and frequent hospitalizations.[180] For example, within one year of hospitalization for HF, the mortality rate in older adults may be as high as 36%.[181] Current guidelines recommend end-of-life care (hospice) to be considered in HF patients who, despite maximal therapy, have one of the following:

- Frequent hospitalizations (three or more per year),
- Chronic poor quality of life and inability to perform activities of daily living (ADLs),
- Need for intravenous support inotropic therapy or
- Consideration for destination therapy (ventricular assist device).[182]

Despite the existence of such guidelines, less than 2% of patients admitted with acute decompensated HF are discharged to hospice, and the percentage of hospice patients with a primary diagnosis of advanced cardiac disease is only 12%.[183] This is significantly lower than other terminal conditions, most notably metastatic cancer.[183]

The principal goal of palliation for patients with HF is relief of symptoms including pain, fatigue and dyspnea.[180] Standard HF therapies are continued when possible, and diuretics may be titrated to maintain fluid balance. Opioids may be utilized as well, and may relieve dyspnea as well as pain. Psychological and spiritual needs should be screened for and addressed.[184] For terminal HF patients with ICDs, the option of deactivation should be discussed. Research to date has shown that this issue is not often approached by clinicians; for example, one survey found that less than one-third of ICD recipients with terminal disease had discussed the potential for device deactivation prior to death.[185] Multiple ICD shocks near the end of life can be painful, anxiety-provoking, and may not prolong life at a reasonable quality.

Ultimately, the approach to end-stage cardiac disease must be multifaceted, incorporating the patient's individual beliefs and expectations about the dying process, optimizing medial therapy when possible to relive symptoms, and addressing psychosocial needs. As the population with HF ages, there will be an increased need for experts who can bridge the disciplines of cardiology and palliative care.

CONCLUSION

Cardiovascular disease can be considered a disease of older adults, and changing demographics make it imperative to further understand the aging-related mechanisms underlying various pathologic conditions. Many treatments to date have reduced morbidity and mortality in older patients with heart disease, but the field will continue to be challenged by increasing numbers of patients with very advanced age and multiple medical comorbidities. A multidisciplinary approach in this setting, incorporating the disciplines of cardiology, primary care, geriatrics and palliative care, may be necessary to optimize patients' health outcomes and quality of life.

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Section 13

PREVENTIVE STRATEGIES FOR CORONARY ARTERY DISEASES

Chapter 106

Pathophysiology of Atherothrombosis

PK Shah

Chapter Outline

- Sites of Predilection for Atherosclerosis
  - Endothelial Activation and Inflammation in Initiation and Progression of Atherosclerosis
  - Macrophage Heterogeneity in Atherosclerosis
  - Triggers of Inflammation in Atherosclerosis
  - Innate Immunity, Toll-like Receptors and Atherosclerosis
  - Inflammation, Angiogenesis and Atherosclerosis
  - Inflammation, Plaque Rupture and Thrombosis

INTRODUCTION

Vaso-occlusive disease resulting from atherosclerosis is a leading cause of death and disability throughout industrialized nations and expected to rival other diseases in developing nations as well.[1] This global burden of cardiovascular disease carries with it a heavy financial burden as well.[1] Arterial occlusive disorders include atherosclerosis of native arteries, an accelerated variant of atherosclerosis involving vein grafts, allograft vasculopathy of transplanted organs and restenosis resulting from neointima formation following angioplasty and stenting. An improved understanding of the pathophysiology of atherosclerosis and thrombosis is likely to lead to improved prevention, diagnosis and treatment of this common disorder.

Atherosclerosis is a complex disease process that involves the build-up of a plaque composed of variable amounts of lipoproteins, extracellular matrix (collagen, proteoglycans, glycosaminoglycans), calcium, vascular smooth muscle cells, immuno-inflammatory cells (chiefly monocyte-derived macrophages, T lymphocytes, mast cells, dendritic cells), immunoglobulins and new blood vessels (angiogenesis). A large body of evidence suggests that atherosclerosis represents a chronic immuno-inflammatory response to vascular injury caused by a variety of agents that activate or injure endothelium and promote lipoprotein infiltration, retention, and modification, combined with immuno-inflammatory cell entry, retention and activation.[2-4]

SITES OF PREDILECTION FOR ATHEROSCLEROSIS

Specific arterial sites, such as branch points, bifurcations and curvatures, cause characteristic alterations in the flow of blood, including decreased shear stress and increased turbulence. These sites of predilection for atherosclerosis are thus characterized by low and/or oscillatory shear stress, evidence of endothelial activation with expression of leukocyte adhesion molecules, increased influx and/or prolonged retention of lipoproteins and evidence of proinflammatory priming.[5-11] Changes in flow alter the expression of genes that have elements in their promoter regions that respond to shear stress. For example, the genes for intracellular adhesion molecule 1, platelet-derived growth factor B chain and tissue factor in endothelial cells have these elements, and their expression is increased by reduced shear stress.[5-18] Recent studies have demonstrated that in vitro application of flow patterns observed at sites of predilection for atherosclerosis to endothelial cells activates a broad based proinflammatory gene program whereas application of flow patterns observed at atheroresistant sites inhibits proinflammatory signaling, in part through activation of a master switch, the Kruppel-like factor 2 (KLF2), a novel transcription factor.[19]

Rolling and adherence of inflammatory cells (monocytes and T cells) occur at these sites as a result of the upregulation of proinflammatory adhesion molecules on both the endothelium and the leukocytes. At these sites, specific molecules form on the endothelium that are responsible for the adherence, migration and accumulation of monocytes and T cells. Such adhesion molecules, which act as receptors for glycoconjugates and integrins present on monocytes and T cells, include several selectins, intercellular adhesion molecules and vascular-cell adhesion molecules.[7,8,12-18] Molecules associated with the migration of leukocytes across the endothelium, such as platelet-endothelial-cell adhesion molecules act in conjunction with chemoattractant molecules generated by the endothelium, smooth muscle and monocytes—such as monocyte chemotactic protein-1 (MCP-1), osteopontin and modified low-density lipoprotein (LDL)—to attract monocytes and T cells into the artery.[5,12-18] Chemokines may be involved in the chemotaxis and accumulation of macrophages in fatty streaks.[20,21] Activation of monocytes and T cells leads to upregulation of receptors on their surfaces, such as the mucin-like molecules that bind selectins, integrins that bind adhesion molecules of the immunoglobulin superfamily, and receptors that bind chemoattractant molecules. These ligand-receptor interactions further activate mononuclear cells, induce cell proliferation, and

help define and localize the inflammatory response at the site of lesions.

In genetically modified mice that are deficient in apolipoprotein E (and have hypercholesterolemia), intercellular adhesion molecule-1 (ICAM-1) is constitutively increased at lesion-prone sites long before the lesions develop. In contrast, vascular cell adhesion molecule 1 (VCAM-1) is absent in normal mice but is present at the same sites as ICAM-1 in mice with apolipoprotein E deficiency. Mice that are completely deficient in ICAM-1, P-selectin, CD18 or combinations of these molecules have reduced atherosclerosis in response to lipid feeding. Proteolytic enzymes may cleave adhesion molecules such that in situations of chronic inflammation it may be possible to measure the "shed" molecules in plasma as markers of a sustained inflammatory response to help identify patients at risk for atherosclerosis or other inflammatory diseases.[22-27]

ENDOTHELIAL ACTIVATION AND INFLAMMATION IN INITIATION AND PROGRESSION OF ATHEROSCLEROSIS

Several studies have suggested that one of the earliest steps in atherogenesis is endothelial activation or injury/dysfunction with infiltration and retention and modification of atherogenic lipoproteins (predominantly the apo B100 containing lipoproteins) in the subendothelial space of the vessel wall[28-39] (Tables 1 and 2).

Various factors that may contribute to endothelial activation or the development of endothelial injury/dysfunction predisposing to atherosclerosis, including risk factors such as elevated and modified LDL/VLDL cholesterol; reduced HDL cholesterol; oxidant stress caused by cigarette smoking, hypertension and diabetic mellitus; genetic alterations; infectious microorganisms; estrogen deficiency and advancing age.[31,32,37] Endothelial activation and injury/dysfunction may manifest in (1) increased adhesiveness of the endothelium to inflammatory cells (leukocytes) or platelets, (2) increased vascular permeability, (3) change from an anticoagulant to a procoagulant phenotype, (4) change from a vasodilator to a vasoconstrictor phenotype or (5) change from a growth-inhibiting to a growth-promoting phenotype through elaboration of cytokines. Abnormal vasomotor function has been one of the well-studied manifestations of endothelial dysfunction in subjects with either established atherosclerosis or in those with risk factors for atherosclerosis. Normal healthy endothelium produces nitric oxide from arginine through the action of a family of enzymes known as nitric oxide synthases.[31,32,37] Nitric oxide acts as a local vasodilator by increasing smooth muscle cell cyclic guanosine monophosphate (GMP) levels while at the same time inhibiting platelet aggregation and smooth muscle cell proliferation.[31,32,37] In the presence of risk factors, a reduced vasodilator response to endothelium-dependent vasodilator stimuli or even paradoxical vasoconstrictor response to such stimuli have been observed in large vessels as well as in the microcirculation, even in absence of structural abnormalities in the vessel wall.[31,32,37] These abnormal vasomotor responses have been attributed to reduced bioavailability of endothelium-derived relaxing factor(s), specifically nitric oxide, due to rapid inactivation of nitric oxide by oxidant stress or excess generation of asymmetric dimethylarginine and/or increased production of vasoconstrictors such as endothelin[31,32,37]

One of the major contributors to endothelial injury is LDL cholesterol modified by processes such as oxidation, glycation (in diabetes), aggregation, association with proteoglycans or incorporation into immune complexes.[31-33,36,38-40] Oxidized LDL has been shown to be present in the atherosclerotic lesions of

TABLE 1

Key steps in atherogenesis highlighting role of inflammation at various steps

1. Endothelial activation with increased infiltration of atherogenic lipoproteins at sites of low or oscillating shear stress (branch points and flow dividers)
2. Subendothelial retention and modification of atherogenic lipoproteins (LDL/VLDL)
3. Endothelial activation with increased mononuclear leukocyte (inflammatory cell) adhesion, chemotaxis and subendothelial recruitment
4. Subendothelial inflammatory cell activation with lipid ingestion through monocyte scavenger receptor expression resulting in foam cell formation
5. Intimal migration and proliferation of medial/adventitial smooth muscle cells/myofibroblasts in response to growth factors released by activated monocytes with matrix production and formation of fibrous cap and fibrous plaque
6. Abluminal plaque growth with positive (outward) arterial adventitial remodeling preserving lumen size in early stages; later plaque growth or negative remodeling results in luminal narrowing
7. Angiogenesis due to angiogenic stimuli produced by inflammatory cells (macrophages) and other arterial wall cells (VEGF, IL-8)
8. Death of foam cells by necrosis/apoptosis leading to necrotic lipid-core formation
9. Plaque disruption (rupture of fibrous cap or endothelial erosion) due to inflammatory cell-mediated matrix degradation and death of matrix-synthesizing smooth muscle cells
10. Exposure of thrombogenic substrate (lipid-core containing tissue factor derived from inflammatory cells) following plaque disruption with arterial thrombosis

TABLE 2

Endothelial activation/dysfunction in atherosclerosis

Phenotypic features

1. Reduced vasodilator and increased vasoconstrictor capacity
   - — enhanced oxidant stress with increased inactivation of nitric oxide
   - — increased expression of endothelin
2. Enhanced leukocyte (inflammatory cell) adhesion and recruitment
   - — increased adhesion molecule expression (ICAM, VCAM)
   - — increased chemotactic molecule expression (MCP-1, IL-8)
3. Increased prothrombotic and reduced fibrinolytic phenotype
4. Increased growth-promoting phenotype

Factors contributing to endothelial activation/dysfunction

1. Dyslipidemia and atherogenic lipoprotein modification
   - — elevated LDL, VLDL, LP(a)
   - — LDL modification (oxidation, glycation)
   - — reduced HDL
2. Increased angiotensin II and hypertension
3. Insulin resistance and diabetes
4. Estrogen deficiency
5. Smoking
6. Hyperhomocysteinemia
7. Advancing age
8. Infection

both experimental animals as well as in humans.[41] Subendothelial retention of LDL particles results in progressive oxidation and its subsequent internalization by macrophages through the scavenger receptors.[36,38,39] The internalization leads to the formation of lipid peroxides and facilitates the accumulation of cholesterol esters, eventually resulting in the formation of foam cells. Once modified and taken up by macrophages, LDL activates the foam cells. In addition to its ability to injure these cells, modified LDL is chemotactic for other monocytes and can upregulate the expression of genes for macrophage colony-stimulating factor (M-CSF) and monocyte chemotactic protein derived from endothelial cells.[42-45] Thus, it may help to expand the inflammatory response by stimulating the replication of monocyte-derived macrophages and the entry of new monocytes into lesions. Continued inflammatory response stimulates migration and proliferation of smooth muscle cells that accumulate within the areas of inflammation to form an intermediate fibroproliferative lesion resulting in thickening of the artery wall.

The inflammatory and immune response in atherosclerosis consists of accumulation of monocyte-derived macrophages and specific subtypes of T lymphocytes at every stage of the disease.[3,46-52] The fatty streak, the earliest type lesion, common in infants and young children, consist of monocyte-derived macrophages, macrophage-derived foam cells and T lymphocytes. The critical role of the macrophage in atherogenesis is supported by the virtual absence (or drastic reduction) of atherosclerosis when M-CSF null genotype is introduced in murine models of severe dyslipidemia induced by a diet or genetic manipulation.[53,54]

Continued inflammations result in increased numbers of macrophages and lymphocytes, which both emigrate from the blood and multiply within the lesion. Activation of these cells leads to the release of proteolytic enzymes, cytokines, chemokines and growth factors, which can induce further damage and eventually lead to focal necrosis. Increased necrosis and/or apoptosis of foam cells and/or with reduced ability for epherocytosis (clean clearance of apoptotic bodies) contributes to the formation of the necrotic lipid core in the plaque.[55-58] Thus, cycles of accumulation of mononuclear cells, migration and proliferation of smooth muscle cells, and formation of fibrous tissue lead to further enlargement and restructuring of the lesion, so that it becomes covered by a fibrous cap that overlies a core of lipid and necrotic tissue resulting in the formation of an advanced and complicated atherosclerotic plaque.

The inflammatory response itself can influence lipoprotein transfer within the vessel wall. Proinflammatory cytokines, such as tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1) and M-CSF increase binding of LDL to endothelium and smooth muscle and increase the transcription of the LDL-receptor gene.[59] After binding to scavenger receptors in vitro, modified LDL initiates a series of intracellular events that include the induction of proteases and inflammatory cytokines.[59] Thus, a vicious circle of inflammation, modification of lipoproteins and further inflammation can be maintained in the artery by the presence of these modified lipoproteins. Recent experimental data have suggested that cholesterol crystals can form early in the evolution of experimental hyperlipidemia induced atheroma and increase in size with further progressions of lesions accompanied by increase in plaque inflammation and that cholesterol crystals activate macrophage inflammatory responses through activation of NLRP3 inflammasome.[60] Thus, cholesterol crystal formation may contribute to plaque inflammation and possibly progression and destabilization.[61]

Monocyte-derived macrophages are present in various stages of atherosclerosis and act as scavenging and antigen-presenting cells. They produce cytokines, chemokines, growth-regulating molecules, tissue factor, metalloproteinases and other hydrolytic enzymes. The continuing entry, survival and replication of monocytes/macrophages in lesions depend in part on growth factors, such as M-CSF and granulocyte-macrophage colony-stimulating factor (GM-CSF), whereas IL-2 is involved in a similar manner for T lymphocytes. Recent experimental observations suggest that in and out trafficking of macrophages within the atherosclerotic vascular wall may be regulated by the microenvironment within the lesion with ingress and retention being promoted by a proinflammatory milieu related to oxidized lipids whereas egress via the lumen or via transformation into migratory dendritic cells and subsequent immigration to regional lymph nodes is associated with reduced proinflammatory lipids in the lesion; an environment promoted by high HDL levels favoring lesion regression.[62] Dendritic cells have been identified within the subendothelium and the adventitia of normal blood vessels. An increase in the number and activity of subendothelial dendritic cells has been observed in the atherosclerotic lesion raising the possibility that dendritic cells may be involved in the pathophysiology of atherosclerosis.[63,64]

Activated macrophages as well as lesional smooth muscle cells express class II histocompatibility antigens, such as human leukocyte antigen-DR (HLA-DR), that allows them to present antigens to T lymphocytes.[3,46-52,59] Atherosclerotic lesions contain both CD4 and CD8 T cells implicating the immune system in atherogenesis.[3,46-52] T cell activation, following antigen processing, results in production of various cytokines, such as interferon-γ (INF-γ) and TNF-α and β, which can further enhance the inflammatory response. Antigens presented include those derived from the protein and lipid components of LDL especially oxidized LDL and heat shock protein 60 which may participate in the immune response in atherosclerosis.[3,46-52,65] In contrast to the proatherogenic role of Antigen responsive T-cells, regulatory T-cells (Tregs) appear to play and anti-inflammatory and atheroprotective role in experimental models.[66]

Macrophages, T cells, endothelial and smooth muscle cells in the atherosclerotic lesions express CD40 ligand and its receptor, which may play a role in atherogenesis by regulating the function of inflammatory cells.[67-71] The antiatherogenic effects of CD40 blocking antibodies in the murine model of atherosclerosis suggests that CD40-mediated signaling may play an important role in atherogenesis.[72]

Platelet adhesion and mural thrombosis are ubiquitous in the generation of advanced atherosclerotic lesions in humans and some animals.[59] Platelets can adhere to dysfunctional endothelium, exposed collagen and macrophages. When activated, platelets release their granules, which contain cytokines and growth factors that, together with thrombin, may contribute to the migration and proliferation of smooth muscle

cells and monocytes. Activation of platelets leads to the formation of free arachidonic acid, which can be transformed into prostaglandins such as thromboxane A2, one of the most potent vasoconstricting and platelet-aggregating substances known, or into leukotrienes, which can amplify the inflammatory response.

Angiotensin II, a potent vasoconstrictor, may also contribute to atherogenesis by stimulating the growth of smooth muscle, increasing oxidant stress, inducing LDL oxidation and increased LDL-proteoglycan binding and subendothelial retention, and promoting an inflammatory response.[59,73-75]

Elevated plasma homocysteine concentrations, resulting from enzymatic defects or vitamin deficiency, may facilitate atherothrombosis by inducing endothelial dysfunction with reduction in vasodilator capacity and enhanced prothrombotic phenotype and smooth muscle replication.[76-81] However, although numerous observational studies have found a positive association between hyperhomocysteinemia and increased risk of atherosclerotic cardiovascular disease,[77-81] recent clinical trials failed to reduce the risk of recurrent vascular events in high-risk patients by lowering the homocysteine level with folic acid and B vitamins.[81-83]

MACROPHAGE HETEROGENEITY IN ATHEROSCLEROSIS

Monocyte derived macrophages have generally been considered an important culprit in atherogenesis by turning into foam cells, inciting inflammatory and vascular proliferative response and contributing to vascular matrix remodeling and thrombosis.[84-88] However, functional heterogeneity of monocytes and macrophages has been demonstrated in atherosclerosis suggesting that under certain conditions, macrophages could assume a more beneficial role by adopting an anti-inflammatory phenotype with the ability to enhance healing, clear apoptotic debris and toxic lipoproteins.[84-88] The precise determinants of in vivo macrophage functional heterogeneity and polarization into a proinflammatory or anti-inflammatory role remain to be defined.[84-88]

TRIGGERS OF INFLAMMATION IN ATHEROSCLEROSIS

It is likely that a number of stimuli are responsible for provoking and sustaining a chronic inflammatory response in the vessel wall in atherosclerosis. Among the key potential culprits are the modified lipoproteins and abnormal flow patterns. Oxidatively modified lipoproteins can induce a variety of proinflammatory genes in the vessel wall that are responsible for recruiting and activating inflammatory cells such as ICAM- and VCAM-type adhesion molecules, chemotactic cytokines such as MCP-1, IL-8, and colony-stimulating factors such as M-CSF. In addition to modified lipoproteins, there is now a body of evidence implicating low-shear stress as a proinflammatory primning factor or tigger in vascular inflammation.[5-11] Although indirect evidence suggesting that arterial wall infections with organisms, such as *Chlamydia pneumonia*, CMV/herpes virus, as well as remote infections, such as chronic bronchitis, gingivitis and *Helicobacter pylori* infection, may affect inflammation, thereby contributing to atherogenesis and/or plaque disruption and thrombosis in the presence of pre-existing atherosclerosis[89-101] failure of interventional studies in humans have dampened enthusiasm about the potential role of infectious organisms in atherogenesis.[102-105]

INNATE IMMUNITY, TOLL-LIKE RECEPTORS AND ATHEROSCLEROSIS

Toll-like receptors (TLRs) are a family of transmembrane receptors that serve as signaling receptors in the innate immune system; their ligation by exogenous and possibly endogenous ligands triggers a proinflammatory signaling cascade in various cells linking innate immunity to inflammation.[106-109] Recent studies have shown that TLRs are expressed in murine and human atherosclerotic lesions and that hyperlipidemia induces proinflammatory signaling, in part through these receptors and their downstream adaptor molecules such as MyD88 (myeloid differentiation factor) contributing to vascular inflammation, neointimal hyperplasia and atherosclerosis in murine models.[102-109]

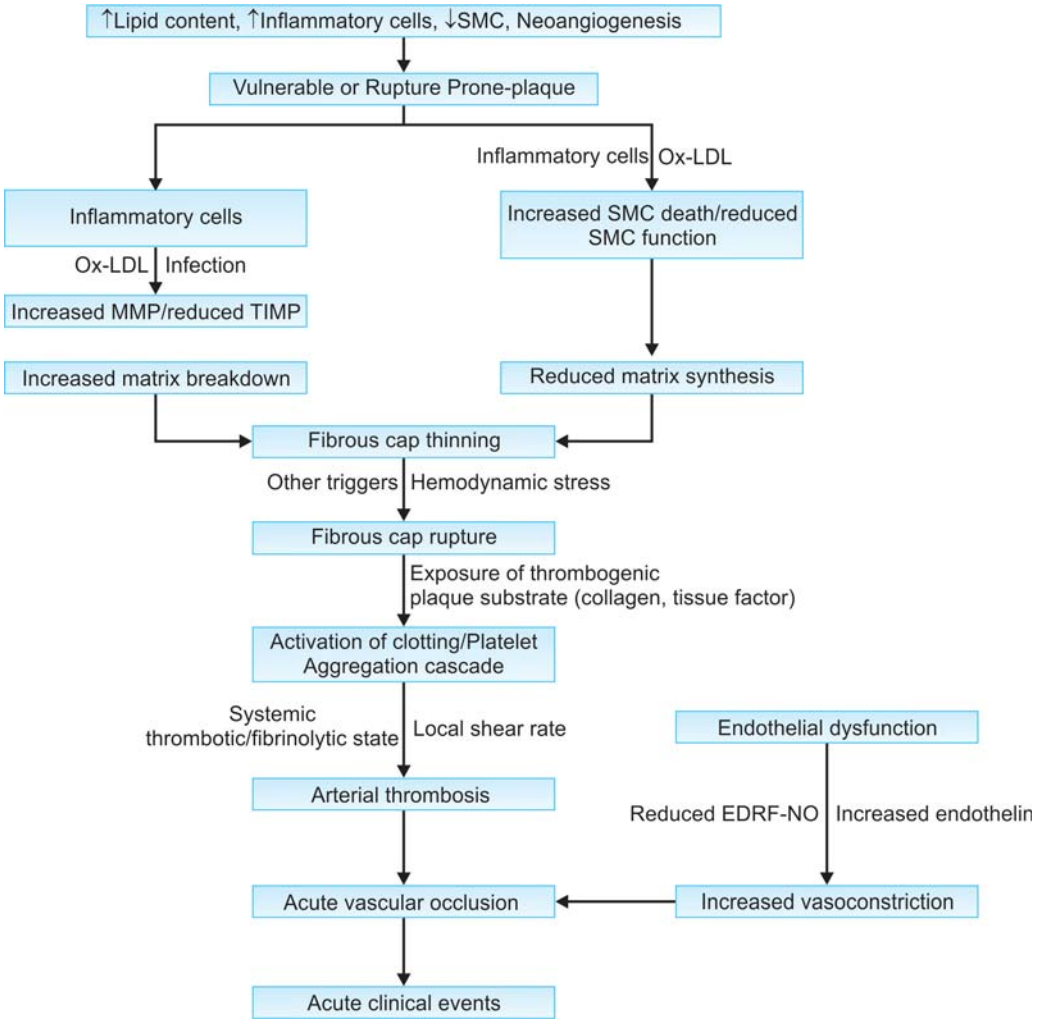
INFLAMMATION, ANGIOGENESIS AND ATHEROSCLEROSIS

Angiogenesis or neovascularization is an essential process that supports chronic inflammation and fibroproliferation, processes that are involved in atherogenesis. Several studies have demonstrated increased adventitial and intimal angiogenesis in atherosclerotic lesions and hypercholesterolemia has been shown to increase adventitial neovascularity in porcine arteries before the development of an atherosclerotic lesion.[110-113] Concomitant development of vasa vasorum with advanced lesion formation in aortas of hypercholesterolemic mice was recently demonstrated after scanning with microcomputed tomography.[114] Proinflammatory chemokines, such as IL-8, and other angiogenic growth factors, such as vascular endothelial growth factor (VEGF), have been demonstrated in atherosclerotic lesions where they could contribute to angiogenesis.[115] Angiogenesis may contribute to plaque progression by providing a source of intraplaque hemorrhage which in turn may provide red cell membrane-derived cholesterol contributing to the expansion of the necrotic lipid core.[116] In addition neovascular channels may also provide a source of inflammatory cells into the vessel wall; thus angiogenesis and inflammation appear to be linked pathophysiologic processes.[116-118] Recently, the ability of macrophages to undergo transdifferentiation into functional endothelial cells has been demonstrated suggesting yet another potential direct link between inflammation and angiogenesis.[119] Recent preliminary data demonstrating an inhibitory effect of angiostatin in murine models of atherosclerosis further supports a potential proatherogenic role for plaque angiogenesis.[120]

INFLAMMATION, PLAQUE RUPTURE AND THROMBOSIS

Thrombosis complicating atherosclerosis is the mechanism by which atherosclerosis leads to acute ischemic syndromes of unstable angina, non-ST-elevation and ST-elevation myocardial infarction and many cases of sudden cardiac death.[121-126] In most cases, coronary thrombosis occurs as a result of uneven thinning

FLOW CHART 1: Schematic describing the pathways and steps involved in disruption of atherosclerotic plaques with consequent thrombosis



(Abbreviations: MMP: Matrix degrading metalloproteinases; TIMP: Tissue inhibitors of metalloproteinases; Ox-LDL: Oxidized low density lipoprotein; EDRF-NO: Endothelium derived relaxation factor-Nitric Oxide)

and rupture of the fibrous cap, often at the shoulders of a lipid-rich lesion where macrophages and T-cells enter, accumulate, and are activated, and where apoptosis may occur.[121-124] Thinning of the fibrous cap may result from elaboration of matrix-degrading metalloproteinases (MMPs), such as collagenases (MMP-1, MMP-13), gelatinases (MMP-2, MMP-9), elastases (MMP-12) and stromelysins (MMP-3), and/or other proteases such as cathepsins, by inflammatory cells, chiefly macrophages.[123,124,127,128] These proteases may be induced or activated by oxidized LDL, cell-to-cell interaction between macrophages and activated T-cells, CD40 ligation, mast cell-derived proteases, oxidant radicals, matrix proteins such as Tenascin-C, and infectious agents.[123,124,127-129] Thinning may also result from increased smooth muscle cell death by apoptosis/necrosis and consequent reduced matrix production.[130-132] Death of vascular smooth muscle cells in the atherosclerotic lesion may be triggered by macrophages as well as subsets of T-cells that are present in atherosclerotic plaques and in the circulating blood of patients with acute coronary syndromes.[133,134] Recent data have also suggested the possibility that cholesterol crystals may contribute to plaque rupture by physically disrupting the fibrous cap and/or by trigerring an inflammatory response.[60,61] Similarly, it has been argued that spotty microcalcification in the vicinity of the fibrous cap may create debonding and contribute to increase stress on the fibrous cap thereby predisposing it to rupture[135] (Flow chart 1).

Inflammatory cells, specifically the macrophages, are also the main source of tissue factor in the atherosclerotic plaque.[136-138] Tissue factor, when exposed to circulating blood, interacts with activated factor VII to generate activated factor X; activated factor X in turn cleaves thrombin from prothrombin. Thrombin is involved in recruiting and activating platelets as well as the clotting cascade, thereby initiating thrombus formation. Tissue factor expression is increased in atherosclerotic plaques, particularly in unstable coronary syndromes.[137,138] The lipid core of the atheromatous lesion is heavily impregnated with tissue factor derived from dead (possibly apoptotic) macrophages and foam cells, accounting for its high thrombogenicity.[139] Macrophage tissue factor expression may be induced by a variety of signals in the atherosclerotic plaque, including various cytokines, infectious agents and oxidized lipoproteins. Furthermore, elevated levels of blood-borne tissue factor may also be detected in patients with acute coronary syndromes.[140] Thrombosis may also occur on a proteoglycan-

rich matrix without a large lipid core, and, in such cases, evidence of superficial endothelial erosion is found.[141] This plaque erosion may account for thrombosis in a relatively higher proportion of young victims of sudden death, particularly in premenopausal women who smoke.[141] The precise molecular basis for these plaque erosions is not clear although endothelial desquamation through activation of basement membrane—degrading MMP may be involved.[128]

Plaques with a large necrotic core, activated inflammatory cell infiltration, and a thinned fibrous cap are therefore considered vulnerable or thrombosis-prone plaques[142] (Flow chart 1). Their identification may be particularly difficult because they may not produce symptoms due to lack of flow-limiting stenoses and may thus escape detection by stress testing and even angiography.[126,143] Plaque rupture is responsible for approximately 75% of fatal coronary thrombi (80% in men and 60% in women).[121] Furthermore, multiple ruptured and inflamed plaques often coexist in the coronary arteries of patients with acute coronary syndromes, indicating that a local culprit lesion-based approach is not enough to eliminate the risk of recurrent events but systemic treatment is (also) necessary.[144-146] Inflammation in atherosclerosis may be accompanied by elevation of circulating proinflammatory markers such as C-reactive protein (CRP), interleukin-6, serum amyloid A and a variety of soluble leukocyte adhesion molecules.[147-152] Elevated CRP levels have been shown to be associated with an increased risk of adverse cardiac events in patients with symptomatic vascular disease as well as in asymptomatic subjects at risk for vascular disease.[147-150,152] However, the predictive value of CRP beyond that provided by conventional risk factors seems to be limited.[153-155]

CONCLUSION

Atherosclerosis is a complex disease process that involves lipoprotein influx, lipoprotein modification, increased pro-oxidant stress, and inflammatory, angiogenic, and fibroproliferative responses intermingled with extracellular matrix and lipid accumulation, resulting in the formation of an atherosclerotic plaque. Endothelial activation/dysfunction is common in atherosclerosis and often manifests as a reduced vasodilator or enhanced vasoconstrictor phenotype that contributes to luminal compromise. Thrombosis resulting from plaque rupture or superficial erosion complicates atherosclerosis, often resulting in abrupt luminal occlusion with resultant acute ischemic syndromes. Infectious agents may contribute to the inflammatory response and thus to destabilization of lesions. An improved understanding of the pathophysiology of atherosclerosis is providing novel directions for its prevention and treatment. In particular, the recognition of the important role of inflammation could lead to novel therapeutic interventions directed at selective inhibition of inflammatory cascade in the vessel wall. Targeting inflammatory triggers, such as lipoproteins, angiotensin II, possible infectious agents and others, are likely to lead to improved outcomes in patients with atherosclerosis.

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Chapter 107

Dyslipidemia

Mary Malloy, John Kane

Chapter Outline

- Lipid Transport and Lipoprotein Metabolism
- Diagnosis of the Dyslipidemias
  - Laboratory Analysis
  - Lipoprotein Treatment Goals
- Hyperlipoproteinemia
  - Pattern 1: Cholesterol Elevated; Triglycerides Usually Normal
  - Pattern 2: Triglycerides Predominantly Increased; Cholesterol may be Moderately Increased
  - Pattern 3: Both Cholesterol and Triglycerides Increased
- Hypoalphalipoproteinemia
- Other Management Considerations
- Annexure: NCEP Evidence Statements

INTRODUCTION

Elevated levels of the lipoproteins that carry apolipoprotein (apo) B-100, and low levels of high density lipoprotein (HDL), are important risk factors for atherosclerotic disease of coronary and peripheral arteries. The lipoproteins that contain apo B-100 are very low density lipoprotein (VLDL), low density lipoprotein (LDL), intermediate density lipoprotein (IDL) and lipoprotein (a) [Lp(a)]. A smaller apolipoprotein—apo B-48—is present in chylomicrons. Their remnants are also atherogenic. Oxidation of the lipoproteins by reactive oxygen species and lipoxygenases stimulates endothelium to secrete monocyte chemoattractant protein-1 and adhesion molecules that recruit monocytes to the developing lesion. Oxidized lipoproteins also cause impaired endothelial vasodilation and are preferentially endocytosed by macrophages and smooth muscle cells, leading to foam cell formation. It is now recognized that a number of inflammatory activities, including mechanisms involved in innate immunity, are prominently involved in plaque biology.[1] HDL mediates the removal of cholesterol from the artery wall and its ultimate removal from the body. It can decrease inflammation, inhibit thrombosis and increase production of nitric oxide. However, it can be dysfunctional under certain conditions and have proinflammatory effects.

Selection of appropriate drug therapy for dyslipidemia rests on determination of the lipoprotein phenotype and knowledge of the primary and secondary disorders of lipoprotein metabolism. It is known that lipid-lowering treatment can result in lack of progression and even regression of plaque, and reduction of new coronary events and the need for invasive procedures.[2]

LIPID TRANSPORT AND LIPOPROTEIN METABOLISM

Free (unesterified) fatty acids (FFA) are carried with albumin from peripheral adipocytes to liver and other tissues. Other lipids are carried in lipoprotein complexes that contain a core of triglycerides and esterified cholesterol surrounded by a monolayer of phospholipids, free cholesterol and apolipoproteins. Unlike the B proteins that do not migrate from one lipoprotein to another, lower molecular weight proteins including apo E, and the several species of the apo C and apo A proteins, equilibrate among the lipoproteins (Table 1). Chylomicrons

TABLE 1

Lipoprotein composition

Lipoprotein class	*Principal apolipoproteins*	*Lipid content*
Chylomicron	B-48 CI, CII, CIII, E	Triglycerides Small amount of phospholipid cholesterol
VLDL	B-100 CI, CII, CIII, E	Triglycerides Small amount of phospholipid cholesterol
IDL	B-100 E	Triglycerides Cholesteryl esters
LDL	B-100	Cholesteryl esters Phospholipid and unesterified cholesterol
Lp(a)	B-100 (a) protein	Cholesteryl esters Phospholipid and unesterified cholesterol
HDL	A-I, A-II CI, CII, CIII, E (many other proteins)	Cholesteryl esters Phospholipid and unesterified cholesterol

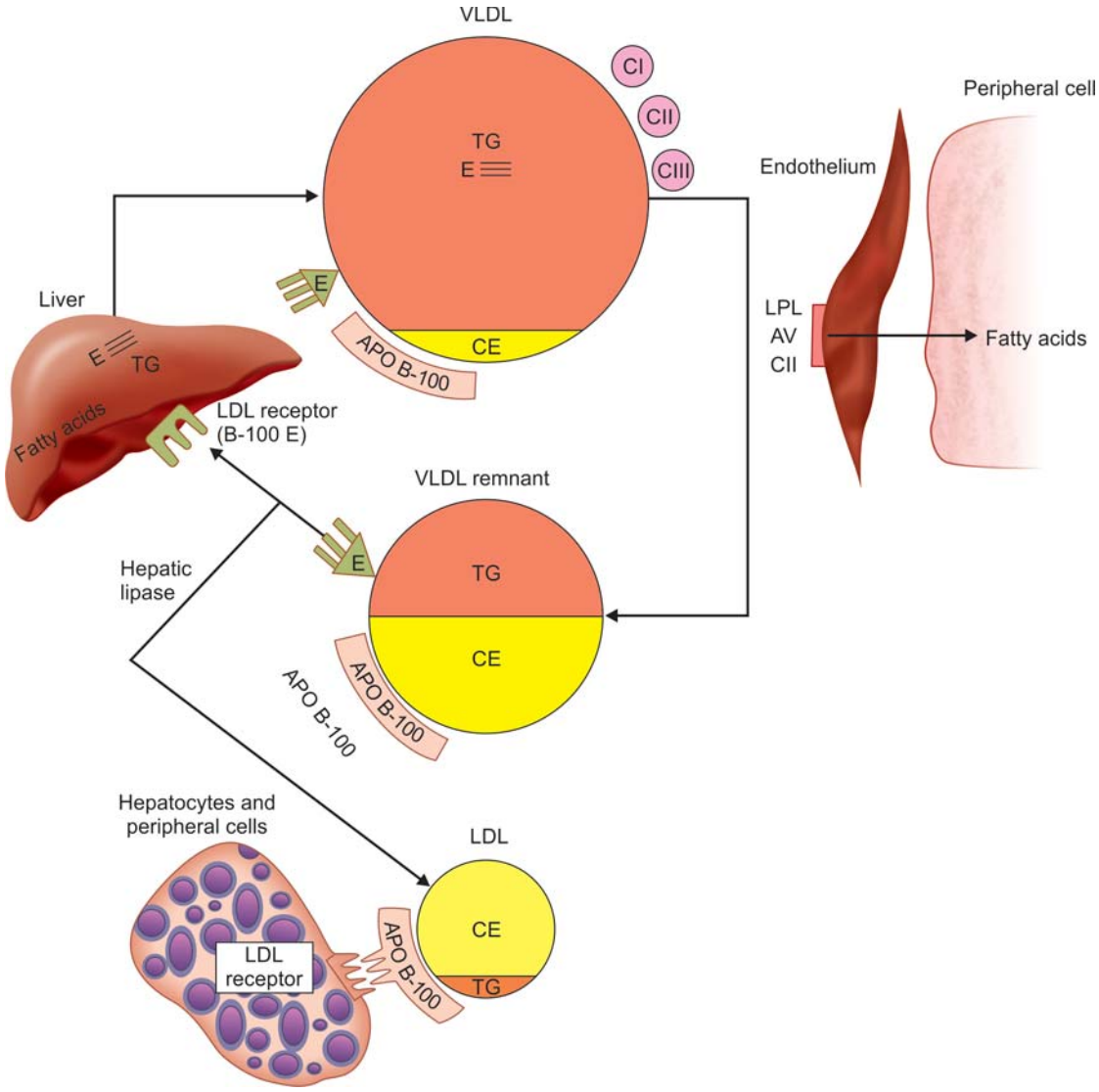


FIGURE 1: VLDL metabolism
Fatty acids derived from plasma and from *de novo* synthesis are esterified to form triglycerides (TG) which are incorporated into precursor particles containing apo B-100 and phospholipids to form very low-density lipoproteins (VLDL), the export vehicles for hepatic triglycerides into plasma. They deliver fatty acids to peripheral cells as the lipoprotein lipase (LPL) complex hydrolyzes their triglycerides. After about 70% of the triglycerides are hydrolyzed, the VLDL remnants, which have acquired cholesteryl esters (CE) from HDL, are partly endocytosed by the liver. The remainder undergoes further hydrolysis of triglycerides mediated by hepatic lipase, forming smaller cholesteryl ester rich particles: low-density lipoproteins (LDL). LDL particles are removed from plasma by endocytosis in many cells, mediated by the LDL receptor

transport triglycerides and some cholesterol from the intestine. VLDL carries triglycerides and some cholesteryl ester from the liver. Factors that increase the delivery of FFA to liver, and hence the formation of VLDL, include abdominal obesity, insulin resistance or insufficiency, ingestion of alcohol, excess caloric intake and estrogens. Cholesteryl esters predominate in the cores of LDL, HDL and Lp(a).

The metabolism of VLDL is depicted in Figure 1. Chylomicrons and VLDL compete for a common pathway that involves the lipoprotein lipase (LPL) system. Insulin transcriptionally upregulates LPL in adipose tissue resulting in storage of fatty acids. In diabetic ketoacidosis and during a prolonged fast, there is a decrease in LPL activity, preventing storage of fatty acids. Heparin and apo C-II are obligatory cofactors. Hydrolysis by LPL results in depletion of triglycerides in the cores of these lipoproteins resulting in smaller, more cholesteryl ester rich particles termed “remnants” or IDL. LPL is saturated at a triglyceride level in the 700–900 mg/dL range so that further entry of triglycerides into plasma from dietary or hepatic sources will exponentially increase the level of triglycerides in plasma. When levels of triglycerides reach 1,000 mg/dL or more, acute restriction of fat in the diet for 48–72 hours will result in significant reduction in triglycerides and is crucial to prevent further increases that could result in pancreatitis.

Chylomicron remnants are endocytosed by the liver via the LDL (B-100: E) and LDL receptor-related protein (LRP1) receptors, and require the participation of at least one copy of apo E-3 or 4 as ligand. The B-48 protein is degraded and the lipids enter hepatic pools. In contrast, VLDL remnants have one of two fates: a minor fraction is removed by B-100: E receptors and is degraded; the major fraction, in normal

individuals, is further metabolized by hepatic lipase to form LDL. Thus increased secretion of VLDL can result in increased production of LDL. This transformation is decreased in the presence of the impaired lipolysis seen in certain hypertriglyceridemic states.

The metabolism of LDL involves high-affinity receptors on essentially all nucleated cells, most importantly in the liver. Apo B-100 is the ligand. The apo B is degraded and the cholesteryl esters from the core are hydrolyzed to free cholesterol which downregulates hydroxymethylglutaryl-CoA reductase and other enzymes that are rate limiting in the synthesis of cholesterol. Excess cholesterol is esterified by acyl cholesterol acyl transferase-2 (ACAT-2) and stored. LDL receptors are downregulated. The PCSK9 protein and ubiquitination of the receptors by Idol enhance the proteolytic degradation of the receptors.

Intestine and liver produce HDL apolipoproteins that organize with lipids to form as many as 20 native species as seen by 2-dimensional separation of plasma HDL. During the hydrolysis of chylomicrons and VLDL, excess free cholesterol and phospholipids are transferred via phospholipid transfer protein (PLTP) to HDL. One of the HDL species, preβ-1 HDL, acquires free cholesterol from cells via the ATP-binding cassette transporter-1 (ABCA1) (Fig. 2). Lecithin-cholesterol acyltransferase (LCAT) esterifies the free cholesterol that is then incorporated in the formation of larger (alpha) HDL particles. Cholesteryl ester transfer protein (CETP) mediates the transfer of the cholesteryl esters to LDL and the triglyceride-rich lipoproteins for return to the liver. HDL also transfers cholesteryl esters to hepatocytes by scavenger receptor, class B, type I receptors (SR-BI). Besides this essential role in reverse cholesterol transport, HDL serves as a carrier for the C apolipoproteins and delivers cholesterol to the adrenal cortex and gonads in support of steroidogenesis. HDL species also play a role supporting fertility in the ovary, promoting the efflux of injurious lipids from the retina, and the binding and neutralization of bacterial endotoxins. In addition to its role in promoting efflux of cholesterol from the artery wall, two other atheroprotective properties include anti-inflammatory and antioxidant activities. The concept is emerging that these qualitative properties of HDL may be more important than the level of total HDL cholesterol. The presence of as many as 80 discreet proteins distributed among the molecular species of HDL is consistent with a large number of biological activities associated with HDL.[3,4] Recent studies have shown that defects in efflux of cholesterol from the artery wall are a major mechanistic element in the development of CAD and myocardial infarction. High levels of preβ-1 HDL in plasma appear to reflect impairment of efflux and are strongly correlated with risk of myocardial infarction and angiographically demonstrable CAD. Measurement of preβ-1 HDL will be expected to provide a facile clinical method of assessing the rate of efflux of cholesterol from the artery wall.[5]

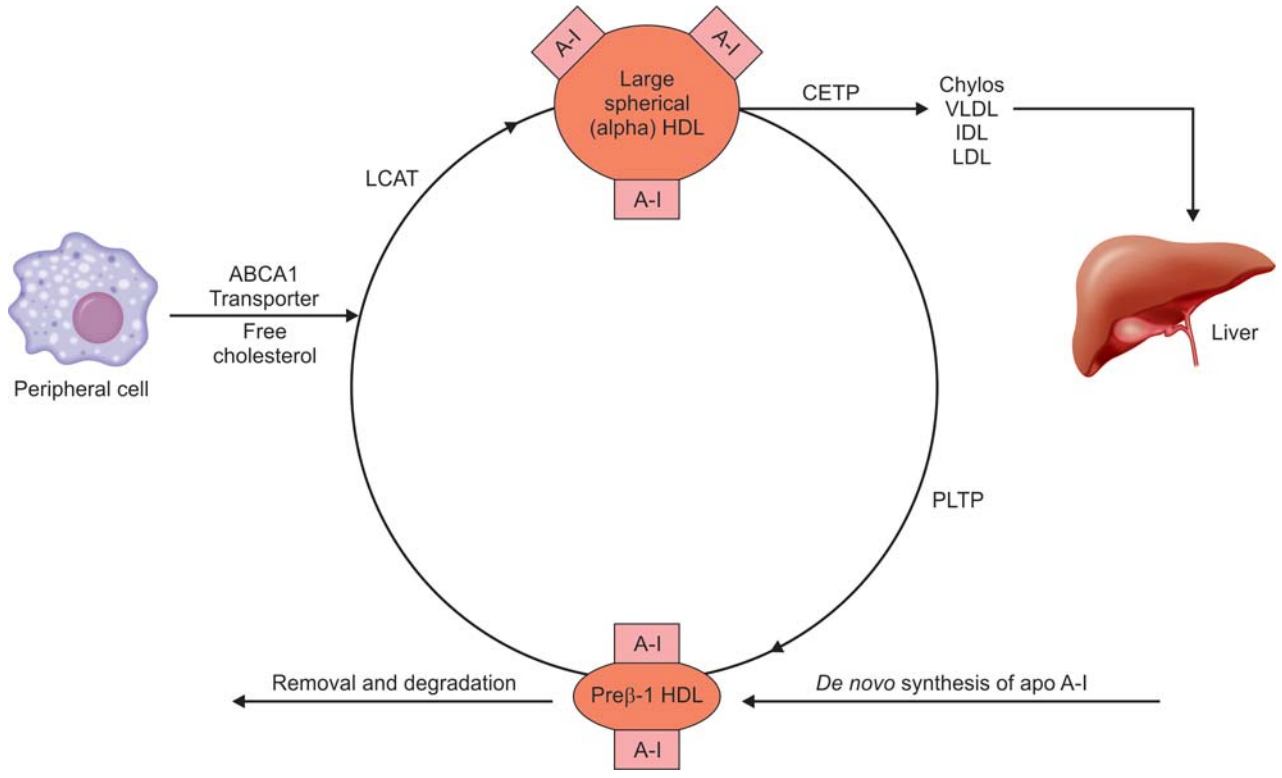


FIGURE 2: Reverse cholesterol transport: the preβ-1 HDL cycle
Preβ-1 HDL is the chief acceptor of unesterified cholesterol effluxed from peripheral cells by the ABCA1 transporter. The cholesterol is esterified by lecithin-cholesterol acyltransferase (LCAT) to form cholesteryl esters. The preβ-1 HDL then accretes to form large spherical HDL particles containing cores of cholesteryl esters. The esters are transferred to accepter lipoproteins (chylomicrons, VLDL, IDL and LDL), by cholesteryl ester transfer protein (CETP). The bulk of the cholesteryl esters are ultimately endocytosed via LDL in the liver where the cholesterol can be secreted into bile or converted to bile acids

DIAGNOSIS OF THE DYSLIPIDEMIAS

LABORATORY ANALYSIS

Lipids and lipoproteins should be measured after a 10-hour fast because chylomicrons, that can contribute as much as 600 mg/dL to the level of triglycerides in plasma in normal individuals, can be present up to 10 hours after a meal, sometimes longer if alcohol was consumed. If triglycerides are not a consideration, levels of LDL and HDL cholesterol are affected minimally in the nonfasting state. Esterified and unesterified cholesterol are usually measured together and are reported as the total cholesterol in serum. A quantitative method, using vertical rotor ultracentrifugation, assesses lipoprotein concentrations and particle diameters. Several techniques for separating and characterizing lipoproteins are available that report LDL particle number, size and subpopulations in addition to measurements of total cholesterol, triglycerides, LDL and HDL cholesterol, VLDL cholesterol, IDL and Lp(a). Many laboratories now report the "non-HDL cholesterol" (easily determined from the other results) which is a very useful measure to assess risk and monitor the treatment because it includes the cholesterol in all the atherogenic lipoproteins. "Small, dense" LDL particles have been associated with the risk of CAD. However, it is unclear whether the increased risk is attributable to properties of these particles or to the metabolic circumstances that lead to their production. LDL particles of large diameter, as occur in familial hypercholesterolemia, are also atherogenic. Small, dense LDL particles are particularly associated with elevated triglycerides. Thus, their measurement in the presence of elevated triglycerides is not informative. Likewise, apo B-100 reflects the levels of all the atherogenic lipoproteins and is not often a factor in the decision to treat with medication.

HDL sub-particles determined by most commercial laboratory methods are not representative of the true speciation of HDL. It is now recognized that the functionality of HDL may be more important than the level, but determinations of this property are not yet available to the practicing physician. Total HDL-cholesterol (HDL-C), then, is currently the best HDL indicator of risk. The amount of triglycerides to which HDL is exposed in plasma is an important determinant of the HDL-C level. There is transfer of cholesteryl esters from HDL into triglyceride-rich lipoproteins that leads to an inverse dependence of HDL-C on triglycerides.

Other tests of lipoprotein composition are of use in certain situations. Enrichment of VLDL by cholesteryl esters is seen in familial dysbetalipoproteinemia. This condition, due to homozygosity of apo E-2 or rarely, the presence of other mutations that vitiate the ligand property of apo E for the LDL receptor, can be suspected by the VLDL-C level and confirmed by analysis of the apo E genotype. Lp(a) can be measured by immunoassay, although some methods are clearly deficient.

When photometric methods are used for other tests, light scattering from high levels of triglyceride-rich lipoproteins can cause erroneous results. Lipemic specimens should be diluted for measurement of amylase activity because it may be inhibited. Core regions of lipoproteins constitute a second phase in plasma because they are not permeable to polar or ionic molecules. When the volume of this phase becomes appreciable, electrolytes and other hydrophilic species are underestimated with respect to their true concentration in the aqueous phase. In the presence of massive hypertriglyceridemia, this can lead to an erroneous diagnosis of hypokalemia, hyponatremia, etc. For each 1,000 mg/dL of triglyceride, the measured concentrations of all hydrophilic molecules and ions should be adjusted upward by 1%.

LIPOPROTEIN TREATMENT GOALS

After the National Cholesterol Education Program published guidelines for treatment of hypercholesterolemia in 2001, reports of major clinical trials suggested that treatment goals should be more aggressive.[6] An LDL-C goal of 70 mg/dL is appropriate for patients at high risk (those with known CAD or risk equivalents). Further investigation of a triglyceride level greater than 150 mg/dL, or a level of HDL-C less than 35 mg/dL for men or less than 45 for women, should be considered. (Acceptable levels of HDL are > 45 and > 55 for men and women respectively). Low levels of HDL-C, and elevated triglycerides, are associated with increased risk of atherosclerosis. The few trials that have specifically addressed these targets have shown at least limited therapeutic benefit. Meta-analysis with a preponderance of statin trials has failed to demonstrate therapeutic benefit from changes in HDL-C and triglycerides, suggesting that interventions with specific impact on these targets are indicated. It must be recognized that the metabolism of the lipoproteins is interrelated, making it very difficult to alter them selectively.

HYPERLIPOPROTEINEMIA

Secondary hyperlipidemias can be the sole cause of a lipoprotein abnormality or can contribute to the severity of a genetic disorder. The genetic and major secondary hyperlipidemias are presented in the context of their clinical phenotypes.

PATTERN 1: CHOLESTEROL ELEVATED; TRIGLYCERIDES USUALLY NORMAL

Secondary Causes

Modest increases in serum cholesterol may be due to high levels of HDL-C that usually do not portend a disease process. However, very high HDL-C levels (> 150 mg/dL) can signal deficiency of CETP or hepatic lipase. Lp-X, the abnormal lipoprotein of cholestasis, can be reported as elevated levels of LDL-C or HDL-C. Hypothyroidism and early nephrosis can elevate LDL-C. LDL is increased when lipemia from any cause resolves, the "beta shift" phenomenon. Monoclonal gammopathy can cause a complex of immunoglobulin and lipoprotein resulting in LDL elevation. In about 40% of patients with anorexia nervosa, cholesterol levels in the 400 mg/dL range or higher probably result from decreased excretion of bile acids and cholesterol in feces. Increased corticosteroids cause elevations in both LDL-C and HDL-C. Lysosomal storage diseases can cause significant elevation in LDL-C. Plant sterols in phytosterolemia, and cholestanol in cerebrotendinous

xanthomatosis, can be reported as cholesterol based on several methods of analysis in use.

Genetic Disorders

Familial hypercholesterolemia (FH): Deficiency of normal LDL receptors, including defects in structure, translation, modification or transport of the protein, underlies this disorder. It rarely occurs in the heterozygous form, which is catastrophic. These patients often have overt coronary and aortic valve disease and extensive xanthomatosis in childhood. Cholesterol levels usually reach 1,000 mg/dL or higher. If even minimal receptor function is present, treatment with a statin plus niacin and ezetimibe may help to postpone more definitive treatment with LDL apheresis or liver transplant. Some patients have combined heterozygosity with some residual receptor activity. Their cholesterol levels are often in the 500–800 mg/dL range and may be somewhat easier to manage with drug therapy.

Heterozygous FH, a codominant trait with high penetrance, occurs with a frequency of about 1 in 500 persons. Cholesterol levels usually vary from about 250 to 400 mg/dL. In the absence of significant hypertriglyceridemia and secondary causes of elevated cholesterol, the diagnosis of heterozygous FH is probable. Xanthomas of the Achilles or other tendons occur frequently (Tendon xanthomas are also seen in ligand-defective apo B and in rare conditions such as phytosterolemia, cholestasis and autosomal recessive hypercholesterolemia). Coronary atherosclerosis tends to occur early, especially if the HDL-C level is low. However, the expression of this disease is occasionally blunted by other genetic determinants.

Treatment includes a low saturated fat (zero trans fat) diet, exercise and drug therapy. A statin alone may bring the LDL-C to goal, but the addition of niacin, a bile acid sequestrant, or ezetimibe, is often required.

Familial ligand-defective apo B-100: The ability of LDL to bind to its receptor can be impaired by mutations that involve the ligand domain in apo B-100. Two of these, at codon 3,500 or 3,531, each occur in about 1 in 1,000 persons. The hypercholesterolemia is usually less severe than in heterozygous FH, but the disease is associated with increased risk of CAD, and tendon xanthomas may be present.

Although statins are the treatment of choice in this disorder, patients may be somewhat resistant to them and the addition of other drugs may be required, as in FH. Statins have some effect because the upregulation of hepatic LDL receptors increases removal of remnant particles for which apo E-3 or 4 serve as ligands. In addition, in heterozygous individuals, the upregulation of LDL receptors increases endocytosis of the population of LDL particles carrying the normal apo B-100 gene product. Diet and exercise are important.

Familial combined hyperlipidemia (FCH): Increased secretion and hyperlipidation of apo B-100 underlies this disorder that may have a codominant mode of transmission. There is also decreased oxidation of fatty acids in the liver. This is the most common form of dyslipidemia, with a frequency of about 1 in 100 individuals. Predominant elevation of VLDL-C or the combined elevation of VLDL-C and LDL-C are common. However, some affected individuals in kindreds with this disorder present with elevations in LDL-C with essentially normal levels of VLDL-C. These individuals are usually younger and not overweight. There are no associated xanthomas and cholesterol levels may be as low as 250 mg/dL. Coronary atherosclerosis is accelerated.

Diet, exercise, and a statin are usually sufficient to reduce the LDL-C to goal. However, because the lipid pattern may shift in an individual over time, marine omega-3 fatty acids, niacin or fenofibrate may be needed to control triglyceride levels should they increase.

Cholesterol 7α hydroxylase deficiency: Decreased catabolism of cholesterol to bile acids, with cholesterol accumulation in hepatocytes, results from the loss of function mutations in this enzyme. LDL receptors are downregulated resulting in elevated levels of LDL-C in plasma. Heterozygous patients have only modest elevation in LDL-C. Homozygosity results in higher levels of both LDL-C and VLDL, premature CAD and cholesterol gallstone disease, and resistance to statins. Preliminary data suggest that at least 100,000 people in the United States are affected.[7]

The elevated lipids in this disorder usually respond when niacin is added to a statin. Low fat diet, avoidance of alcohol and maintenance of appropriate weight are important.

Lp(a) hyperlipoproteinemia: Lp(a) contains apo B-100 and the (a) protein which is a homolog of plasminogen. It can inhibit fibrinolysis and has been demonstrated in atherosclerotic plaque. It is now considered to be an independent risk factor for atherosclerosis of coronary and peripheral arteries.[8] A higher risk of CAD and ischemic stroke are associated with smaller apo (a) isoforms.[9] Certain polymorphisms of the (a) protein are especially associated with risk.[8,10] Levels reflect genetic determinants primarily. Because the (a) gene has an inflammatory response element in the promoter, levels of this lipoprotein also can be greatly elevated in conditions such as nephrosis.

Decreasing levels of LDL-C below 100 mg/dL reduces the risk associated with the elevated Lp(a) to some extent. Niacin is the only currently available agent that can reduce the levels of Lp(a), but not all patients respond. Administration of aspirin mitigates the increased risk of MI associated with the L4399M mutation.[11] Diet and exercise have very limited effect.

Uncommon genetic causes of this pattern include autosomal recessive hypercholesterolemia (ARH), cholesteryl ester storage disease and gain of function mutations in PCSK9 (Loss of function mutations in PCSK9 lead to very low levels of LDL-C and are seen more commonly).[12]

PATTERN 2: TRIGLYCERIDES PREDOMINANTLY INCREASED; CHOLESTEROL MAY BE MODERATELY INCREASED

This pattern reflects a primary increase in VLDL, chylomicrons, or both. The latter is termed “mixed lipemia”. Total cholesterol may be increased because the triglyceride-rich lipoproteins contain a small amount of cholesteryl ester in the core and free cholesterol in the surface monolayer. When triglycerides are greater than 1,000 mg/dL, chylomicrons are usually present

because they compete with VLDL in a common removal pathway.

Levels of LDL-C may be low in the presence of hypertriglyceridemia. This is a useful way to distinguish between conditions that cause impaired removal of VLDL versus overproduction where the LDL is usually normal or elevated.

Levels of triglycerides greater than 150 mg/dL are associated with increased risk of coronary and peripheral vascular disease. There is now abundant epidemiologic evidence that remnants of VLDL and chylomicrons are atherogenic particles, and are present in human plaques.[13,14] Oxidative stress is increased in the presence of hypertriglyceridemia, and endothelial vasomotor dysfunction is frequently present. Adhesion molecules, MCP-1, tissue factor and scavenger receptors are transcriptionally upregulated. Increased bulk blood viscosity, and increased Factor VII and PAI-1 promote coagulation. Hypertriglyceridemia also affects lipoprotein metabolism, increasing the transfer of cholesteryl esters from HDL to VLDL and chylomicrons, resulting in small triglyceride-rich HDL and LDL particles.

Severe hypertriglyceridemia with levels usually greater than 2,000 mg/dL can cause acute pancreatitis. Subsequent attacks might be triggered at lower levels. Light scattering by the large triglyceride-bearing particles causes a whitish cast to the veins in the retina called lipemia retinalis. Eruptive xanthomas can appear. These 2–5 mm diameter, yellowish morbilliform lesions often occur in clusters. They disappear once the triglyceride levels have decreased.

Secondary Causes

These include incomplete fast, physical inactivity, alcohol ingestion within 72 hours of blood sampling, excessive dietary fat, and greater than 60% of energy intake from carbohydrates. Central obesity is associated with elevated levels of FFA in portal blood and elevated triglycerides.

Other causes include exogenous estrogens, corticosteroid excess (Cushing's syndrome or corticosteroid treatment), uremia, severe nephrosis, HIV (infection, per se and treatment with protease inhibitors), glycogen storage disease Type I, myxedema, hypopituitarism and acromegaly, and immunoglobulin-lipoprotein complex disorders. Midline brain tumor, lipodystrophy, infections and collagen vascular disease may also cause hypertriglyceridemia.

Both *type 1 diabetes* (T1D) and *type 2 diabetes* (T2D) can be associated with lipid abnormalities. Marked insulin insufficiency in T1D, with decreased transcription of the LPL gene leading to impeded VLDL catabolism, can cause severe lipemia that usually resolves within a few days with insulin administration. If massive fatty liver is present, however, it can take weeks for the triglycerides to return to normal. As the VLDL decreases, LDL-C will increase and can persist for several weeks. With poor control of T1D, chylomicrons as well as VLDL can be severely elevated and these patients usually have ketoacidosis. However, chronic undertreatment with insulin can result in mobilization of most of the triglyceride from adipose tissue so there is not sufficient substrate for ketogenesis. These patients are emaciated and have striking hepatomegaly and severe lipemia.

With incomplete control of T2D, activity of LPL is decreased and that of hepatic lipase is increased. There is increased flux of FFA to liver causing increased production and secretion of VLDL. LDL can be increased as well. The lipemia usually resolves with management of the diabetes. Increased content of serum amyloid associated proteins, enrichment with triglycerides, and decreased content of paraoxonase 1, all characterize the HDL of patients with T2D. Not only does diabetes have a profound effect on lipoprotein metabolism but also on cholesterol homeostasis in the pancreatic beta cell which affects its insulinogenic capacity. The accumulation of cholesterol associated with elevated LDL depresses insulin secretory capacity, an effect that is mitigated by HDL.[15] Weight loss is essential if the individual is overweight. Pioglitazone increases clearance of VLDL and is the preferred PPAR gamma agonist. Colesevelam, a bile acid binding resin, has been shown to reduce hemoglobin A_{1c} by about 0.5% in diabetics with suboptimal control. Some patients with more marked elevations in VLDL or LDL-C may have another disorder, such as FCH, FH, or other genetic or secondary factor predisposing to lipemia, and require additional treatment for those disorders. In any event, reduction of LDL-C has a significant impact on atherosclerosis among individuals with T2D.[16]

The "*metabolic syndrome*" includes elevated triglycerides and low levels of HDL-C.[17] In most cases, the decreased level of HDL-C is secondary to the elevated triglycerides. The functionality of HDL may be affected. Insulin resistance and visceral obesity are also prominent features along with hypertension and, frequently, proinflammatory and prothrombotic states.[18]

Nonalcoholic fatty liver disease probably involves misdirection of fatty acids from oxidative pathways to triglyceride synthesis. Many of these patients have features of the "metabolic syndrome", including elevated levels of triglycerides and low levels of HDL-C, and are at risk for atherosclerosis. To date, there is no established treatment for this disease. Statins, marine omega-3 fatty acids and fenofibrate used to treat the dyslipidemia do not seem to increase the risk of further liver damage in most patients. Diagnosed early, this condition can often be managed, at least in the short term, with exercise and weight loss. Supplementation with mixed tocopherols is useful.[19]

Genetic Disorders

Lipoprotein lipase deficiency or decreased activity: Activity of this enzyme depends on its cofactor, apo C-II, and other proteins including apo A-V, GPIHBP1 (an endothelial cell-surface glycoprotein that binds LPL) and LMF1.[20-22] Defects in any of these can lead to impaired LPL activity and hypertriglyceridemia, or genetic defects in the LPL gene itself can result in impaired enzyme activity. More than 100 mutations in the LPL gene are known to result in "Familial Chylomicronemia". The LMF1 protein is also essential for secretion of hepatic lipase. Patients with any of these defects can have severe lipemia, hepatosplenomegaly, hypersplenism and bone marrow filled with foam cells. Recurrent epigastric pain and frank pancreatitis are frequent, and eruptive xanthomas may be

present. Chylomicrons predominate in fasting serum and there is often a moderate increase in VLDL. LDL-C is decreased. A precipitous fall in triglycerides when oral fat is restricted to less than10 gm/day makes a presumptive diagnosis of these disorders. Diagnosis can be made in the neonatal period once dietary fat is introduced, or be delayed until lipemic serum is observed in middle age. Patients are usually not obese. If pancreatitis impairs insulin secretion, diabetes can ensue. The risk of pancreatitis is increased during pregnancy, lactation or the administration of estrogens because the hepatic production of VLDL is stimulated by estrogens.

Management is primarily dietary. Most affected adults can maintain triglycerides below 500 mg/dL while eating 15–30 gm of total fat daily. Complex carbohydrates are allowed in moderation and appropriate weight should be maintained. Alcohol and oral estrogens should be avoided and regular aerobic exercise is important. Essential fatty acids, marine omega-3 fatty acids, and fat-soluble vitamins should be supplemented when a patient is consuming less than about 25 gm of fat daily. Women with one of these disorders who become pregnant should be followed by a specialist.

Because the LPL clearance mechanism is saturated when triglycerides reach about 800 mg/dL, an oral "load" of fat or alcohol can exponentially increase the level of triglycerides. If the patient has signs or symptoms of acute or incipient pancreatitis, all dietary intake should be eliminated for 72 hours. Fat emulsions should be excluded from parenteral fluids.

Endogenous and mixed lipemias: Several genetically determined disorders result in elevated levels of VLDL (endogenous lipemia) or elevated levels of both VLDL and chylomicrons (mixed lipemia). Mixed lipemia can be present continuously or can result from increasing severity of endogenous lipemia as high levels of VLDL impede chylomicron removal in competition for the lipolytic pathway. Central obesity, alcohol, insulin resistance, T2D and exogenous estrogens increase the rate of secretion of VLDL. Some patients have impaired removal of triglyceride-rich lipoproteins, often due to heterozygosity for mutations in LPL. Depending on the severity of the hypertriglyceridemia, pancreatitis, lipemia retinalis and eruptive xanthomas can occur. Other features of the metabolic syndrome may be present.

Initial severe restriction of dietary fat can be followed by moderate restriction based on triglyceride levels. Weight reduction, exercise, marine omega-3 fatty acids and avoidance of alcohol usually result in significant reduction of triglycerides. If needed, niacin (in the absence of insulin resistance) or a fibric acid derivative will produce further reduction. The management also includes the factors mentioned above.

Familial combined hyperlipidemia: Patients with this disorder can present with predominant elevation in triglycerides (see below).

PATTERN 3: BOTH CHOLESTEROL AND TRIGLYCERIDES INCREASED

Secondary Causes

Any cause of an increased cholesterol level can coexist with factors that may increase triglycerides, and vice versa. For example, a patient may have FH and one of the endogenous hypertriglyceridemias, or may develop insulin resistance. The beta shift phenomenon can result in this pattern.

Genetic Disorders

Familial combined hyperlipidemia: Both triglycerides and LDL cholesterol are increased in one of the three phenotypes of this disorder. FCH is the most common hyperlipidemia, affecting about 1% of the population, and appears to be inherited as a Mendelian dominant trait involving alternative loci. Overproduction of VLDL underlies the disorder that can variously present as combined hyperlipidemia or with a predominant increase in either LDL or VLDL. The relative efficiency of the lipolytic pathway determines whether VLDL or LDL will predominate. The pattern can change in an individual over time and affected members of a kindred can have any of the three phenotypes. The level of apo B-100 is always increased. The usual factors that increase triglycerides, including overweight and alcohol, do so in this disorder as well. Xanthomas are absent. Coronary disease risk is increased significantly, this disorder accounting for as much as 15% of coronary events in the United States and dictating aggressive management with diet, exercise and drugs.

When the combined pattern is present, many patients will need combination drug therapy. LDL levels tend to increase with fibrate treatment, and resins cause an increase in triglycerides. Therefore a statin is the preferred first drug. Omega-3 fatty acids, niacin or a fibrate can then be added if needed to control triglycerides or to treat a low HDL.

Dysbetalipoproteinemia: About 2% of the US population is homozygous for apo E-2, an isoform of apo E that is a poor ligand for the B-100: E receptors. Definitive diagnosis can be made by an apo E genotype. Other mutations in apo E can also cause dysbetalipoproteinemia, some in the heterozygous state (dominant dysbetalipoproteinemia). Hyperlipidemia may not be expressed unless environmental, and perhaps additional genetic determinants, are present. The former include significant weight gain, alcohol use, hypothyroidism, and diabetes. The hyperlipidemia is characterized by accumulation of remnants of VLDL and chylomicrons. LDL-C levels are low because the transformation of VLDL remnants to LDL is interrupted. The remnant particles are rich in cholesteryl esters, often causing total serum cholesterol to be as high as the level of triglycerides. Hyperlipidemia is usually not present before age 20, although it can occur in young children who develop diabetes, obesity or hypothyroidism. Tuberous or tuberoeruptive xanthomas may develop, commonly on extensor surfaces, especially elbows. Planar xanthomas of the palmar creases, which are also seen in cholestasis, can occur, presenting as orange, sometimes slightly raised deposits. If untreated, the hyperlipidemia can result in premature atherosclerosis of the coronary and peripheral arteries.

Weight reduction, treatment of diabetes or hypothyroidism when present, abstinence from alcohol, and a low fat diet are required. Marine omega-3 fatty acids might be helpful. Drug treatment, if needed, would include a fibrate or niacin (if the patient does not have insulin resistance). A statin sometimes is effective as a single agent, but the addition of niacin is usually needed to normalize the lipid levels.

HYPOALPHALIPOPROTEINEMIA

A low level (usually below 35 in men and below 45 in women) of HDL-C is a significant risk factor for atherosclerosis, especially when it is present with an elevated level of LDL, VLDL, IDL or Lp(a). It remains, however, a strong predictor of risk even when the level of LDL is low.[23,24]

Secondary Causes of Low HDL

When triglycerides are elevated, the transfer of cholesteryl esters from HDL into triglyceride-rich lipoproteins results in lower levels of HDL cholesterol. Central obesity, diabetes, the metabolic syndrome, smoking and extremely low fat diets also are associated with low levels. An unexpected fall in HDL-C can signal the presence of an immunoglobulin disorder associated with myeloma, macroglobulinemia or lymphocytic leukemia.

Genetic Disorders

Uncommon genetic causes of hypoalphalipoproteinemia, include "Tangier Disease" (defects in the ABCA1 lipid transporter) and "LCAT deficiency" (defective esterification of cholesterol prevents formation of larger, mature HDL particles). They are associated with relatively minor risk of CAD. Individuals homozygous for these disorders usually have HDL-C levels below 10–15 mg/dL. Heterozygosity is associated with levels in the 20–30 mg/dL range. Mutations in the principal protein of HDL, apo A-1, can cause major deficiency in HDL. Some of these are amyloidogenic.

Familial hypoalphalipoproteinemia: Many other individuals have significant deficiency of HDL for which specific mechanisms are only beginning to emerge. These are collectively termed familial hypoalphalipoproteinemia. A low level of HDL-C can be the only apparent risk factor in some cases of premature coronary and peripheral vascular disease. Distributions of the low HDL in many kindreds are consistent with autosomal dominance, but other modes of transmission may be involved.

Coronary intervention trials have demonstrated the association of plaque regression with increases in HDL-C. It is not yet known which of the many molecular species of HDL are involved in protection against atherosclerosis or what effects various drugs have on them.

Management of hypoalphalipoproteinemia includes smoking cessation and maintenance of appropriate weight. Strict management of T2D, if present, is crucial and triglycerides should be reduced. Diet and exercise are important, but have little effect in severe cases of hypoalphalipoproteinemia. Niacin is the drug of choice if insulin resistance is not present. It can be used cautiously in patients with T2D and in any diabetic patient managed with insulin or metformin. Although niacin may decrease insulin sensitivity, insulin secretory responsiveness does not appear to decrease. Some patients do not respond, or only partially respond, to niacin or other drugs. In these, the importance of keeping the atherogenic lipoproteins at goal is highlighted. Fibrates often have some ability to increase HDL, largely because of the reduction in triglycerides. The statins tend to have some effect on HDL levels, but it is usually not great enough to increase the very low levels seen in familial hypoalphalipoproteinemia.

OTHER MANAGEMENT CONSIDERATIONS

FREE RADICALS IN DISEASE

A fundamental mechanism linking obesity, dyslipidemia and diabetes to chronic diseases of aging (including atherosclerosis, macular degeneration, cancer and aging per se) is the excess generation of free radicals by the mitochondrion. An increased burden of fatty acyl CoA increases the free radical generation. This can be mitigated by partial uncoupled thermogenesis. The free radical attack is proinflammatory and diffusion limited. Because there are many more free radical targets than antioxidant molecules in the cellular environment, intervention to decrease excess free radical production will have greater impact than free radical scavenging by antioxidants. Nonetheless, antioxidants may be expected to be of benefit.

The *antioxidant defense* includes: antioxidant enzymes (such as superoxide dismutases, glutathione peroxidase, catalase, etc.); tocopherols; vitamin C; carotenoids (lutein, zeaxanthin, etc.); anthocyanins; phenols (resveratrol, etc.) and endogenous antioxidants (such as glutathione, alpha lipoic acid, coenzyme Q, etc.). All the tocopherols are important but too much alpha tocopherol depletes gamma tocopherol, the only form that reduces the peroxynitrite radical. Vitamin C regenerates effective tocopherol by reducing tocopheroxyl radicals. Supplementation of the diet with low dose mixed, natural tocopherols (that include gamma tocopherol) and vitamin C, if the diet is deficient in sources of these vitamins, should be considered. Dietary counseling should also include mention of sources of carotenoids, anthocyanins and phenols.

New derivatives of probucol, that exclude the arrhythmogenic effects, may prove to be useful agents due to their antioxidant and anti-inflammatory activities.[25]

Vitamin D

Higher levels of 25-hydroxy vitamin D in serum are associated with a lower risk of CAD and with larger HDL particles. Supplementation with vitamin D is recommended when the level in serum is low.

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ANNEXURE

NCEP EVIDENCE STATEMENTS

Type of evidence

Category of type of evidence	*Description of type of evidence*
A	Major randomized controlled clinical trials (RCTs)
B	Smaller RCTs and meta-analyses of other clinical trials
C	Observational and metabolic studies
D	Clinical experience

Strength of evidence

Category of type of evidence	*Description of strength of evidence*
1	Very strong evidence
2	Moderately strong evidence
3	Strong trend

Evidence statement: Multiple lines of evidence from experimental animals, laboratory investigations, epidemiology, genetic forms of hypercholesterolemia and controlled clinical trials indicate a strong causal relationship between elevated LDL cholesterol and CHD (A1, B1, C1).

Recommendation: LDL cholesterol should continue to be primary target of cholesterol-lowering therapy.

Evidence statement: Elevated serum triglycerides are associated with increased risk for CHD (C1). In addition, elevated triglycerides are commonly associated with other lipid and nonlipid risk factors (C1).

Recommendation: Greater emphasis should be placed on elevated triglycerides as a marker for increased risk for CHD. First-line therapy for elevated serum triglycerides should be therapeutic lifestyle changes.

Evidence statement: Some species of triglyceride-rich lipoproteins, notably cholesterol-enriched remnant lipoproteins, promote atherosclerosis and predispose to CHD (C1).

Recommendation: In persons with high serum triglycerides, elevated remnant lipoproteins should be reduced in addition to lowering of LDL cholesterol.

Evidence statement: Some species of triglyceride-rich lipoproteins are independently atherogenic; notable among these are cholesterol-enriched remnant lipoproteins (C1). Moreover, VLDL cholesterol is a marker for atherogenic VLDL remnants (C1).

Recommendation: In persons with high triglycerides (≥ 200 mg/dL). VLDL cholesterol should be combined with LDL cholesterol, yielding non-HDL, cholesterol. The latter constitutes “atherogenic cholesterol” and should be a secondary target of therapy.

Evidence statement: A low HDL-cholesterol level is strongly and inversely associated with risk for CHD (C1).

Evidence statement: Population studies show a continuous rise in risk for CHD as HDL-cholesterol levels decline (C1). Higher risk for CHD at lower HDL levels is multifactorial in causation (C1). Although the inverse relationship between HDL cholesterol and CHD shows no inflection points, any reduction in HDL cholesterol from population means is accompanied by increased risk for CHD (C1).

Recommendation: A categorical low HDL cholesterol should be defined as a level of less than 40 mg/dL, in both men and women.

Evidence statement: Clinical trials provide suggestive evidence that raising HDL-cholesterol levels will reduce risk for CHD (A2). However, it remains uncertain whether raising HDL-cholesterol levels per se, independent of other changes in lipid and/or nonlipid risk factors, will reduce risk for CHD.

Recommendation: A specific HDL-cholesterol goal level to reach with HDL raising therapy is not identified. However, nondrug and drug therapies that raise HDL-cholesterol levels and are part of management of other lipid and nonlipid risk factors should be encouraged.

Evidence statement: Atherogenic dyslipidemia commonly occurs in persons with premature CHD (C1). Moreover, atherogenic dyslipidemia strongly associates with abdominal obesity and physical inactivity (C1). Weight reduction and increased physical activity will mitigate atherogenic dyslipidemia (A1).

Recommendation: For management of atherogenic dyslipidemia, emphasis in management should be given to life-habit modification—weight control and increased physical activity.

Evidence statement: Drugs that modify atherogenic dyslipidemia yield a moderate reduction in CHD risk (A2, B2).

Recommendation: Consideration should be given to the treatment of atherogenic dyslipidemia with specific drug therapy, i.e. fibrates or nicotinic acid, in higher risk persons.

Evidence statement: Hypertension is a major, independent risk factor for CHD (A2, B1, C1). Treatment of hypertension does not remove all of the CHD risk accompanying elevated blood pressure (A2, B1).

Recommendation: Elevated blood pressure is a risk factor that should modify goals of LDL-lowering therapy in primary prevention. Treated hypertension should also count as a risk factor for setting goals of LDL cholesterol in primary prevention. Hypertension should be treated in all affected people according to JNC guidelines.

Evidence statement: Cigarette smoking is a strong, independent risk factor for CHD (C1). Smoking cessation is accompanied by a reduction in CHD risk (C1).

Recommendation: Prevention of smoking and smoking cessation should receive prime emphasis in the clinical strategy to reduce CHD risk.

Evidence statement: Diabetes is a major, independent risk factor for CHD and other forms of CVD (B1). Reducing cholesterol levels in people with diabetes reduces risk for CHD.

Recommendation: The presence of diabetes should modify treatment goals for LDL cholesterol. Because of growing evidence that many people with diabetes carry a risk for CHD similar to that of people with established CHD, diabetes should be removed from the list of other risk factors that modify LDL-cholesterol goals. Instead, diabetes should be treated as a separate category of higher risk.

Evidence statement: Obesity is a major, modifiable risk factor for CHD (C1). Nevertheless, the incremental risk imparted by obesity independently of accompanying risk factor is uncertain.

Recommendation: Obesity should be considered a direct target for clinical intervention rather than an indicator for lipid-modifying drug treatment. Because of the association of obesity with other risk factors, obesity should not be included as a factor influencing treatment goals of LDL cholesterol in primary prevention.

Evidence statement: Physical inactivity is a major, modifiable risk factor for CHD (C1). However, a portion of the increased risk for CHD accompanying physical inactivity can be explained by associated major risk factors (C2). Regardless of mechanism, increased physical activity will reduce risk for CHD (B2, C1).

Recommendation: Physical inactivity should be a direct target for clinical intervention. Increased physical activity in accord with a person's overall health status should be encouraged as part of lifestyle therapies to reduce risk for CHD. Patients undergoing clinical cholesterol management should be provided with guidance for safe forms of physical activity that will reduce CHD risk beyond LDL-lowering therapy.

A history of physical inactivity should not be counted as a risk factor for setting goals for LDL cholesterol in primary prevention. However, clinical judgment can be used to decide whether to intensify LDL-lowering therapy in physically inactive persons, or to reduce intensity of therapy in physically active persons.

Evidence statement: An atherogenic diet is a major, modifiable risk factor for CHD (C1). High intakes of saturated fatty acids and cholesterol directly raise LDL-cholesterol concentrations. Further certain dietary patterns appear to modify baseline risk for CHD, independently of effects on LDL cholesterol.

Recommendation: Modification of an atherogenic diet should be employed to reduce CHD risk as part of overall therapeutic lifestyle changes for CHD risk reduction. However, consumption of an atherogenic diet should not be included among risk factors to modify LDL-cholesterol goals in primary prevention.

Evidence statement: Advancing age is a major, independent risk factor for CHD (C1).

Recommendation: Age should count as a risk factor to modify LDL-cholesterol goals in primary prevention.

Evidence statement: Men have a higher baseline risk for CHD than do women at all ages, except perhaps in the oldest age group (> 80 years) (C1).

Recommendation: An age cutpoint at which age becomes a risk factor to modify goals for LDL cholesterol should be set lower in men (≥ 45 years) than in women (≥ 55 years) in primary prevention.

Evidence statement: A positive family history for CHD in a first-degree relative (parent, sibling or offspring) is a major risk factor for CHD. Often a positive family history is associated with a high prevalence of modifiable risk factors (C1); however, a positive family history carries excess risk beyond standard measurements of risk factors (C1). Risk for CHD is higher the younger the age of onset in the affected family member and the greater the number of affected first degree relatives (C1).

Recommendation: The presence and age of onset of CHD in all first-degree relatives should be assessed. The family history should be considered positive for premature CHD if clinical CHD or sudden death can be documented in first degree male relatives younger than 55 years of age and in first degree female relatives younger than 65 years of age. Because a positive family history of premature CHD is immutable but bears information about the risk for CHD and the probability of having modifiable risk factors, it should serve as a factor in making treatment decisions relative to setting and reaching LDL-cholesterol goals in primary prevention.

Evidence statement: The presence of the metabolic syndrome accentuates the risk accompanying elevated LDL cholesterol (C1). This increase in risk appears to be mediated through multiple risk factors—major and emerging risk factors (C1).

Clinical trials show that modifying three major components of the metabolic syndrome—(1) atherogenic dyslipidemia (B2), (2) hypertension (A2, B1) and (3) the prothrombotic state (A2, B1)—will reduce risk for CHD.

Recommendation: Increased emphasis should be placed on therapeutic modification of the metabolic syndrome in persons undergoing LDL-lowering therapy. Primary management of the metabolic syndrome should be to reverse its root causes—overweight/obesity and physical inactivity. In addition, other lipid and nonlipid risk factors associated with the metabolic syndrome should be appropriately treated.

The presence of the metabolic syndrome provides the option to intensify LDL-lowering therapy after LDL-cholesterol goals are set with the major risk factors. Primary emphasis nonetheless should be given to modifying the underlying risk factors (overweight/obesity and physical inactivity) and other risk factors associated with the metabolic syndrome.

Evidence statement: A strong relationship exists between LDL-cholesterol levels and CHD risk (C1). An elevated serum total cholesterol contributes to coronary atherosclerosis throughout life: serum total cholesterol levels measured in young adulthood correlate with CHD rates later in life and over a lifetime (C1). For persons without other CHD risk factors, risk for CHD is relatively low when LDL-cholesterol levels are less than 130 mg/dL (C1). Moreover, for persons with higher LDL-cholesterol levels (≥ 130 mg/dL), clinical trials document the efficacy of LDL, lowering to reduce risk for CHD in primary prevention (A1, B1), particularly when LDL-cholesterol levels are reduce to less than 130 mg/dL (A1).

Recommendation: LDL-lowering therapy should play an important role in primary prevention of CHD in persons at increased risk. For persons at increased risk because of the presence of multiple risk factors, the LDL-cholesterol goal should be less than 130 mg/dL. Therapeutic lifestyle changes should be initiated in all such persons. Persons with multiple risk factors whose short-term (10 year) risk is low to moderate (< 10%) generally should not receive LDL-lowering drugs when LDL-cholesterol concentrations are only borderline high (130–159 mg/dL), but drugs should be considered when LDL levels are high (≥ 160 mg/dL). For higher risk persons with multiple risk factors (10-year risk 10–20%), consideration should be given to drug therapy when the LDL goal (< 130 mg/dL) cannot be achieved by lifestyle therapies. Finally, multiple risk factor persons at highest risk (10-year risk > 20%) need to attain even lower LDL-cholesterol levels (LDL goal < 100 mg/dL), and consideration should be given to starting drug therapy simultaneously with therapeutic lifestyle changes when LDL-cholesterol levels are greater than or equal to 130 mg/dL.

Recommendation: For persons who are otherwise at lower risk (0–1 risk factor), an effort should be made to lower LDL-cholesterol levels to less than 160 mg/dL. In such persons, lifestyle changes should be emphasized when the LDL-cholesterol level is in the range of 130–159 mg/dL to minimize the risk of any marginal (subcategorial) risk factors. Drug therapy at these LDL levels generally should be avoided, because of lack of long-term data on safety and because of relatively low cost-effectiveness ratios. In persons with 0–1 risk factor, if LDL-cholesterol levels cannot be reduced to less than 160 mg/dL by therapeutic lifestyle changes, LDL-lowering drugs can be viewed as optional when levels are in the range of 160–189 mg/dL, and should be strongly considered when levels persist at greater than or equal to 190 mg/dL. Physicians should opt for drug therapy at former levels (160–189 mg/dL) when persons appear to have risk that is greater than that revealed by 0–1 standard risk factor, i.e. because of a severe single-risk factor: a family history of premature CHD, or the presence of life-habit or emerging risk factors.

Recommendation: Routine cholesterol testing should begin in young adulthood (≥ 20 years of age). In young adults, above-optimal LDL-cholesterol levels deserve attention. When LDL-cholesterol concentrations range 100–129 md/dL, young adults should be encouraged to modify life-habits to minimize long-term risk. In those with borderline high LDL cholesterol (130–159 mg/dL), clinical attention through therapeutic lifestyle changes is needed both to lower LDL cholesterol and to minimize other risk factors. If LDL cholesterol is high (160–189 mg/dL), more intensive clinical intervention should be initiated, with emphasis on therapeutic lifestyle changes. However, if LDL cholesterol remains elevated despite therapeutic lifestyle changes, particularly when LDL cholesterol is greater than or equal to 190 mg/dL, consideration should be given to long-term management with LDL-lowering drugs.

Evidence statement: Secondary prevention trials demonstrate that reduction of LDL-cholesterol levels significantly reduces risk for recurrent major coronary events in persons with established CHD (A1). Evidence from endpoint trials with cholesterol-lowering drugs, angiographic trials and epidemiological studies indicates that maximal CHD reduction occurs when LDL cholesterol is less than 100 mg/dL (A2, B1, C1).

Recommendation: Persons with established CHD should receive intensive LDL-lowering therapy. The goal of therapy in persons with established CHD should be LDL cholesterol less than 100 mg/dL.

Evidence statement: Persons with established CHD who have a baseline LDL cholesterol greater than or equal to 130 mg/dL receive benefit from institution of LDL-cholesterol-lowering drugs (A1).

Recommendation: Persons with established CHD who have a baseline LDL cholesterol greater than or equal to 130 mg/dL should be started on a cholesterol-lowering drug simultaneously with therapeutic lifestyle changes and control of nonlipid risk factors (therapeutic lifestyle changes alone are unlikely to achieve the LDL-cholesterol goal of < 100 mg/dL).

Evidence statement: Persons with established CHD who have a baseline LDL cholesterol of 100–129 mg/dL likely with benefit from reducing LDL cholesterol to less than 100 mg/dL (A2, B2, C1). These persons also appear to benefit from therapy that modifies atherogenic dyslipidemia (A2, B2).

Recommendation: Several options should be considered for the treatment of CHD patients with baseline LDL-cholesterol levels of 100–129 mg/dL. These include use of a cholesterol-lowering drug, maximization of therapeutic lifestyle changes, use of a drug to modify atherogenic dyslipidemia and intensified control of nonlipid risk factors.

Evidence statement: In persons with established CHD, LDL-lowering therapy reduces risk for stroke (A1, B1).

Recommendation: For persons with established CHD, LDL-lowering therapy should be carried out to reduce the risk for stroke and for recurrent coronary events.

Evidence statement: Overall benefit of cholesterol lowering on mortality. LDL-lowering therapy reduces total mortality, i.e. extends life by decreasing CHD mortality (A1, B1). This therapeutic benefit was unclear in earlier trials using interventions with limited cholesterol lowering (10%), some of which showed adverse non-CHD effects. However, in trials using statins, in which cholesterol levels were reduced by 20% and non-CHD mortality was not increased, the reduction in mortality is incontrovertible.

Evidence statement: Benefit of cholesterol lowering on mortality in secondary prevention. The benefits of cholesterol lowering on longevity are particularly clear in CHD patients and other high-risk populations due to their high short-term mortality rates when left untreated and to the high proportion of those deaths caused by CHD (A1, B1). In persons with established CHD, a reduction in CHD deaths by effective cholesterol-lowering therapy more than outweighs any side effects of drug therapy.

Evidence statement: Benefits of cholesterol lowering on mortality in primary prevention. Primary prevention trials using statins show a significant reduction in CHD mortality, no increase in non-CHD mortality, and a strong trend towards lower overall mortality (A2). Because of the lower proportion of deaths that are due to CHD in primary prevention trials (relative to secondary prevention), the latter trend is not significant. The statin trials lasted an average of five years; long-term observational studies offer a better indication of the potential lifelong impact of cholesterol reduction on mortality (C1). The lack of overall reduction in mortality in primary prevention trials performed before the advent of the statins can be explained by their modest cholesterol reduction (< 10%) and in some instances by adverse non-CHD effects not seen with the statins.

Evidence statement: In short-term, controlled clinical trials, a 1% reduction in LDL-cholesterol levels on average reduces risk for hard CHD events (myocardial infarction and CHD death) by approximately 1% (A1). Cohort studies suggest that a more prolonged reduction in LDL-cholesterol levels will produce an even greater reduction in CHD risk (C1). In the absence of long-term clinical trials, maximal long-term risk reduction cannot be estimated with certainty.

Evidence statement: Persons with established CHD in the United States have a risk for recurrent myocardial infarction and CHD death (hard CHD) that exceeds 20% per 10 years (C1).

Evidence statement: Clinical forms of non-coronary atherosclerosis carry a risk for clinical CHD approximately equal to that of established CHD and hence constitute a CHD risk equivalent (C1). These conditions include peripheral arterial disease, carotid artery disease (transient ischemic attack or stroke of carotid origin, or greater than 50% stenosis on angiography or ultrasound), and abdominal aortic aneurysm.

Recommendation: Persons with clinical forms of non-coronary atherosclerosis should have the same LDL-cholesterol goal (< 100 mg/dL) as those for persons with established CHD and should be managed similarly.

Evidence statement: Persons with type 2 diabetes have a 10-year risk for major coronary events (myocardial infarction and CHD death) that approximates the risk in CHD patients without diabetes (A2, C1). The high risk can be explained by the combination of hyperglycemia plus lipid and nonlipid risk factors of the metabolic syndrome. In addition, persons with type 2 diabetes have a high incidence of death at the time of acute myocardial infarction as well as a relatively poor prognosis for long-term survival after myocardial infarction (C1). Thus type 2 diabetes constitutes a CHD risk equivalent.

Recommendation: Persons with type 2 diabetes should be managed as a CHD risk equivalent. Treatment for LDL cholesterol should follow ATP III recommendations for persons with established CHD. For younger persons with type 2 diabetes who otherwise are at lower risk, clinical judgment is required as to the intensity of LDL-lowering therapy. However, consideration should be given to using LDL-lowering drugs when LDL-cholesterol levels are greater than or equal to 130 mg/dL.

Evidence statement: Persons with type 1 diabetes have increased risk for coronary heart disease. However, some persons with type 1 diabetes have a 10-year risk for CHD less than 15–20% [i.e. young persons without other risk factors (A2, C1)]. Such

persons will nevertheless have a high long-term risk for CHD (C1). Moreover, there is no reason to believe that the benefits of LDL reduction are different in persons with type 1 and type 2 diabetes (D1).

Recommendation: The intensity of LDL-lowering therapy in persons with type 1 diabetes should depend on clinical judgment. Recent-onset type 1 diabetes need not be designated a CHD risk equivalent; hence reduction of LDL cholesterol to less than 130 mg/dL is sufficient. With increasing duration of disease, a lower goal (< 100 mg/dL) should be considered. Regardless of duration, LDL-lowering drugs should be considered in combination with lifestyle therapies when LDL-cholesterol levels are greater than or equal to 130 mg/dL.

Evidence statement: Some persons with multiple CHD risk factors have an absolute 10-year risk for major coronary events (myocardial infarction and CHD death) of greater than 20% (CHD risk equivalent) (C1).

Recommendation: For persons with CHD risk equivalents, the same recommendations should apply as for persons with established CHD.

Evidence statement: Use of a multidisciplinary team for management of high serum cholesterol improves patient compliance, enlarges the scope of the population served, and improves compliance to treatment guidelines (A2).

Recommendation: Physicians have a primary responsibility for implementing ATP III guidelines. In addition, a multidisciplinary team, potentially including nurses, dietitians, nurse practitioners, pharmacists and health educators, should be utilized whenever possible.

Evidence statement: At current retail drug prices, LDL-lowering drug therapy is highly cost-effective in persons with established CHD (A1).

Evidence statement: LDL-lowering drug therapy is cost-effective for primary prevention in persons with CHD risk equivalents (C1).

Evidence statement: At current retail drug prices, when 10-year risk for hard CHD (myocardial infarction + CHD death) is in the range of 10–20% per year. LDL-lowering drug therapy carries an acceptable cost-effectiveness (by current cost-effectiveness standards in the United States) (B1).

Evidence statement: At current retail drug prices, when 10-year risk for hard CHD (myocardial infarction + CHD death) is less than 10% per year, the cost-effectiveness of LDL-lowering drug therapy exceeds current cost-effectiveness standards in the United States (A2).

Recommendation: When 10-year risk for hard CHD is less than 10% per year, LDL-lowering drugs should be used judiciously. Priority should be given to dietary therapy, which is more cost-effective. However, if LDL-cholesterol levels remain greater than or equal to 160 mg/dL after dietary therapy in persons with 10-year risk less than 10%, LDL-lowering drugs should be considered if long-term risk for CHD is deemed to be high, i.e. if multiple major risk factors are present. When LDL-cholesterol levels are greater than or equal to 190 mg/dL after dietary therapy, long-term risk is considered to be high regardless of other risk factors; thus LDL-lowering drugs should be considered. The need to reduce long-term risk in some circumstances can override the need to stay within currently acceptable cost-effectiveness criteria.

Evidence statement: There is a dose response relationship between saturated fatty acids and LDL cholesterol levels. Diets high in saturated fatty acids raise serum LDL cholesterol levels (A1). Reduction in intakes of saturated fatty acids lowers LDL cholesterol levels (A1, B1).

Evidence statement: Weight reduction of even a few pounds will reduce LDL levels regardless of the nutrient composition of the weight loss diet (A2), but weight reduction achieved through a calorie-controlled diet low in saturated fatty acids and cholesterol will enhance and sustain LDL cholesterol lowering (A2).

Recommendation: Weight loss through reduced caloric intake and increased levels of physical activity should be encouraged in all overweight persons. Prevention of weight gain also should be emphasized for all persons.

Evidence statement: High intakes of saturated fatty acids are associated with high population rates of CHD (C2). Reduction in intake of saturated fatty acids will reduce risk for CHD (A1, B1).

Recommendation: The therapeutic diet to maximize LDL cholesterol lowering should contain less than 7% of total calories as saturated fatty acids.

Evidence statement: *Trans* fatty acids raise serum LDL cholesterol levels (A2). Through this mechanism, higher intakes of *trans* fatty acids should increase risk for CHD. Prospective studies support an association between higher intakes of *trans* fatty acids and CHD incidence (C2). However, *trans* fatty acids are not classified as saturated fatty acids, nor are they included in the quantitative recommendations for saturated fatty acid intake of less than 7% of calories in the TLC Diet.

Recommendation: Intakes of *trans* fatty acids should be kept low. The use of liquid vegetable oil, soft margarine and *trans* fatty acid-free margarine are encouraged instead of butter, stick margarine, and shortening.

Evidence statement: Higher intakes of dietary cholesterol raise serum LDL cholesterol levels in humans (A2, B1). Through this mechanism, higher intakes of dietary cholesterol should raise the risk for CHD. Reducing cholesterol intakes from high to low decreases serum LDL cholesterol in most persons (A2, B1).

Recommendation: Less than 200 mg per day of cholesterol should be consumed in the TLC Diet to maximize the amount of LDL cholesterol lowering that can be achieved through reduction in dietary cholesterol.

Evidence statement: Monounsaturated fatty acids lower LDL cholesterol relative to saturated fatty acids (A2, B2). Monounsaturated fatty acids do not lower HDL cholesterol nor raise triglycerides (A2, B2).

Evidence statement: Dietary patterns that are rich in monounsaturated fatty acids provided by plant sources and rich in fruits, vegetables, and whole grains and low in saturated fatty acids are associated with decreased CHD risk (C1). However, the benefits of replacement of saturated fatty acids with monounsaturated fatty acids have not been adequately tested in controlled clinical trials.

Recommendation: Monounsaturated fatty acids are one form of unsaturated fatty acid that can replace saturated fatty acids. Intake of monounsaturated fatty acids can range up to 20% of total calories. Most monounsaturated fatty acids should be derived from vegetable sources, including plant oils and nuts.

Evidence statement: Linoleic acid, a polyunsaturated fatty acid, reduces LDL cholesterol levels when substituted for saturated fatty acids in the diet (A1, B1). Polyunsaturated fatty acids can also cause small reductions in HDL cholesterol when compared with monounsaturated fatty acids (B2). Controlled clinical trials indicate that substitution of polyunsaturated fatty acids for saturated fatty acids reduces risk for CHD (A2, B2).

Recommendation: Polyunsaturated fatty acids are one form of unsaturated fatty acids that can replace saturated fat. Most polyunsaturated fatty acids should be derived from liquid vegetable oils, semi-liquid margarines and other margarines low in *trans* fatty acids. Intakes of polyunsaturated fat can range up to 10% of total calories.

Evidence statement: Unsaturated fatty acids do not raise LDL cholesterol concentrations when substituted for carbohydrates in the diet (A2, B2).

Recommendation: It is not necessary to restrict total fat intake for the express purpose of reducing LDL cholesterol levels, provided saturated fatty acids are reduced to goal levels.

Evidence statement: The percentage of total fat in the diet, independent of caloric intake, has not been documented to be related to body weight or risk for cancer in the general population. Short-term studies suggest that very high fat intakes (> 35% of calories) modify metabolism in ways that could promote obesity (C2). On the other hand, very high carbohydrate intakes (> 60% of calories) aggravate some of the lipid and nonlipid risk factors common in the metabolic syndrome (A2, B2, C2).

Recommendation: Dietary fat recommendations should emphasize reduction in saturated fatty acids. Further, for persons with lipid disorders or the metabolic syndrome, extremes of total fat intake—either high or low—should be avoided. In such persons, total fat intakes should range 25–35% of calories. For some persons with the metabolic syndrome, a total fat intake of 30–35% may reduce lipid and nonlipid risk factors.

Evidence statement: When carbohydrate is substituted for saturated fatty acids, LDL cholesterol levels fall (A2, B2). However, very high intakes of carbohydrate (> 60% of total calories) are accompanied by a reduction in HDL cholesterol and a rise in triglyceride (B1, C1). These latter responses are sometimes reduced when carbohydrate is consumed with viscous fiber (C2); however, it has not been demonstrated convincingly that viscous fiber can fully negate the trigyceride-raising or HDL-lowering actions of very high intakes of carbohydrates.

Recommendation: Carbohydrate intakes should be limited to 60% of total calories. Lower intakes (e.g. 50% of calories) should be considered for persons with the metabolic syndrome who have elevated triglycerides or low HDL cholesterol. Regardless of intake, most of the carbohydrate intake should come from grain products, especially whole grains, vegetables, fruits, and fat-free and low-fat dairy products.

Evidence statement: Between 5–10 gm of viscous fiber per day reduces LDL cholesterol levels by approximately 5% (A2, B1).

Recommendation: The use of dietary sources of viscous fiber is a therapeutic option to enhance LDL cholesterol lowering.

Evidence statement: Daily intakes of 2–3 gm per day of plant stanol/sterol esters will reduce LDL cholesterol by 6–15% (A2, B1).

Recommendation: Plant stanol/sterol esters (2 gm per day) are a therapeutic option to enhance LDL cholesterol lowering.

Evidence statement: High intakes of soy protein can cause small reductions in LDL cholesterol levels, especially when it replaces animal food products (A2, B2).

Recommendation: Food sources containing soy protein are acceptable as replacements for animal food products containing animal fats.

Evidence statement: The mechanisms whereby n-3 fatty acids might reduce coronary events are unknown and may be multiple. Prospective data and clinical trial evidence in secondary CHD prevention suggest that higher intakes of n-3 fatty acids reduce risk for coronary events or coronary mortality (A2, C2).

Recommendation: Higher dietary intakes of n-3 fatty acids in the form of fatty fish or vegetable oils are an option for reducing risk for CHD. This recommendation is optional because the strength of the evidence is only moderate at present. ATP III support the American Heart Association's recommendation that fish be included as part of a CHD risk-reduction diet. Fish in general is low in saturated fat and may contain some cardioprotective n-3 fatty acids. However, a dietary recommendation for a specific amount of n-3 fatty acids is not being made.

Evidence statement: According to the Institute of Medicine, the RDA for folate for adult is 400 micrograms per day, and the upper limit is 1,000 micrograms per day. There are no published randomized controlled clinical trials to show whether lowering homocysteine levels through dietary intake or supplements of folate and other B vitamins will reduce the risk for CHD.

Recommendation: ATP III endorses the Institute of Medicine's RDA for dietary folate, namely 400 microgram per day. Folate should be consumed largely from dietary sources.

Evidence statement: Oxidative stress and LDL oxidation appear to be involved in atherogenesis. However, clinical trials to date have failed to demonstrate that supplementation of the diet with antioxidants will reduce risk for CHD (A2).

Recommendation: Evidence of CHD risk reduction from dietary antioxidants is not strong enough to justify a recommendation for antioxidant supplementation to reduce CHD risk in clinical practice. ATP III supports current recommendations of the Institute of Medicine's RDAs for dietary antioxidants, i.e. 75 mg and 90 mg per day for women and men respectively, for vitamin C and 15 mg per day for vitamin E.

Evidence statement: Moderate intakes of alcohol in middle-aged and older adult may reduce risk for CHD (C2). However, high intakes of alcohol produce multiple adverse effects (C1).

Recommendation: No more than two drinks per day for men and no more than one drink per day for women should be consumed. A drink is defined as 5 ounces of wine, 12 ounces of beer, or 1 ounce and half of 80 proof whiskey. Persons who do not drink should not be encouraged to initiate regular alcohol consumption.

Evidence statement: JNC VI provides a review of the evidence to support the concept that lower salt intake lowers blood pressure or prevents its rise. One clinical trial further shows that the effects of a dietary pattern high in fruits, vegetables, low-fat dairy products, whole grains, poultry, fish, and nuts and low in fats, red meat, and sweets—foods that are good sources of potassium, calcium and magnesium—to reduce blood pressure are enhanced by a diet low in salt (A2).

Recommendation: The Diet and Health report and JNC VI recommend a sodium intake of less than 2,400 mg per day (no more than 100 mmol per day, 2.4 gm sodium or 6.4 gm sodium chloride). JNC VI further recommends maintaining adequate intakes of dietary potassium (approximately 90 mmol per day) and enough dietary calcium and magnesium for general health. ATP III affirms these recommendations for persons undergoing cholesterol management in clinical practice.

Evidence statement: Despite widespread promotion of several herbal or botanical supplements for prevention of CHD, a paucity of data exists on product standardization, controlled clinical trials for efficacy, and long-term safety and drug interactions. Clinical trial data are not available to support the use of herbal and botanical supplements in the prevention or treatment of heart disease.

Recommendation: ATP III does not recommend use of herbal or botanical dietary supplements to reduce risk for CHD. However, health care professionals should query patients to establish whether such products are being used because of the potential for drug interaction.

Evidence statement: High protein, high total fat and saturated fat weight loss regimens have not been demonstrated in controlled clinical trials to produce long-term weight reduction. In addition, their nutrient composition does not appear to be conducive to long-term health.

Recommendation: High protein, high total fat and saturated fat weight loss regimens are not recommended for weight reduction in clinical practice.

Evidence statement: Nicotinic acid effectively modifies atherogenic dyslipidemia by reducing TGRLP, raising HDL cholesterol, and transforming small LDL into normal-sized LDL (C1). Among lipid-lowering agents, nicotinic acid is the most effective HDL-raising drug (C1). Nicotinic acid usually causes a moderate reduction in LDL-cholesterol levels (C1), and it is the most effective drug for reducing Lp(a) levels (C1).

Evidence statement: Nicotinic acid therapy is commonly accompanied by a variety of side effects, including flushing and itching of the skin, gastrointestinal distress, glucose intolerance, hepatotoxicity, hyperuricemia and other rarer side effects (C1). Hepatotoxicity is more common with sustained-release preparations (D1).

Evidence statement: Nicotinic acid therapy produces a moderate reduction in CHD risk, either when used alone or in combination with other lipid lowering drugs (A2, B2).

Recommendation: Nicotinic acid should be considered as a therapeutic option for higher-risk persons with atherogenic dyslipidemia. It should be considered as a single agent in higher-risk persons with atherogenic dyslipidemia who do not have a substantial increase in LDL-cholesterol levels, and in combination therapy with other cholesterol-lowering drugs in higher-risk persons with atherogenic dyslipidemia combined with elevated LDL-cholesterol levels.

Recommendation: Nicotinic acid should be used with caution in persons with active liver disease, recent peptic ulcer, hyperuricemia and gout, and type 2 diabetes. High doses of nicotinic acid (> 3 gm per day) generally should be avoided in persons with type 2 diabetes, although lower doses may effectively treat diabetic dyslipidemia without significantly worsening hyperglycemia.

Evidence statement: Fibrates are effective for modifying atherogenic dyslipidemia, and particularly for lowering serum triglycerides (C1). They produce moderate elevations of HDL cholesterol (C1). Fibrates also are effective for treatment of dysbetalipoproteinemia (elevated beta-VLDL) (C1). They also can produce some lowering of LDL, the degree of which may vary among different fibrate preparations (C1). Fibrates also can be combined with LDL-lowering drugs in treatment of combined hyperlipidemia to improve the lipoprotein profile, although there is no clinical-trial evidence of efficacy for CHD risk reduction with combined drug therapy (C1, D1).

Evidence statement: Fibrate therapy moderately reduces risk for CHD (A2, B1). It may also reduce risk for stroke in secondary prevention (A2).

Evidence statement: Evidence for an increase in total mortality due to an increased non-CHD mortality, observed in the first large primary prevention trial with clofibrate, has not been substantiated in subsequent primary or secondary prevention trials with other fibrates (gemfibrozil or bezafibrate) (A2, B1). Nonetheless, fibrates have the potential to produce some side effects. Fibrate therapy alone carries an increased risk for cholesterol gallstones (A2), and the combination of fibrate and statin imparts an increased risk for myopathy (B2).

Recommendation: Fibrates can be recommended for persons with very high triglycerides to reduce risk for acute pancreatitis. They also can be recommended for persons with dysbetalipoproteinemia (elevated beta-VLDL). Fibrate therapy should be considered an option for treatment of persons with established CHD who have low levels of LDL cholesterol and atherogenic dyslipidemia. They also should be considered in combination with statin therapy in persons who have elevated LDL cholesterol and atherogenic dyslipidemia.

Evidence statement: Hormone replacement therapy in postmenopausal women does not reduce risk for major CHD events or coronary deaths in secondary prevention (A2). Moreover, hormone replacement therapy carries an increased risk for thromboembolism and gallbladder disease (A2).

Recommendation: Hormonal replacement therapy cannot be recommended for the express purpose of preventing CHD. Instead, control of risk factors should be the primary approach to reducing CHD risk in women. There may be other valid reasons for hormonal replacement therapy, such as for management of perimenopausal and postmenopausal symptoms or for treatment or prevention of osteoporosis.

Chapter 108

Smoking and Air Pollution

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Chapter Outline

- Epidemiology of Smoking and Exposure to Second Hand Smoke
- Active Smoking and Cardiovascular Disease
- Second-hand Smoke and Cardiovascular Disease
- Low-tar (Light) Cigarettes
- Pathophysiology of Tobacco Smoke and Cardiovascular Disease
  - Atherosclerosis
  - Endothelial Dysfunction
  - Platelet Activation and Thrombosis
  - Arterial Stiffness
  - Dyslipidemia
  - Inflammation
  - Oxidative Stress
  - Autonomic Effects and Heart Rate Variability
  - Impaired Oxygen Transport
- Smoking Cessation
  - Nicotine Withdrawal
  - Pharmacotherapy
- Smoke-Free Environments and their Effect on Heart Attack Admissions
- Similar Effects and Mechanisms of Particulate Air Pollution
- Cardiologists as Tobacco Control Advocates

INTRODUCTION

Tobacco smoke, either active or passive, is a leading cause of preventable cardiovascular disease (CVD). Smoking causes coronary heart disease (CHD), ischemic heart disease (IHD) and leads to angina pectoris and acute myocardial infarction (AMI).[1] A third of all smoking-induced deaths are due to CVD,[2] most (60%) from IHD.[3] Active smoking also causes stroke, sudden cardiac death (SCD), abdominal aortic aneurysm, heart failure and peripheral artery disease.[1] Of all cardiovascular deaths, smoking causes more than 20% in North America and 11% worldwide.[4] Active smoking increases the risk of dying from CHD by a factor of 2 to 3.[5] Heavy smokers ($\geq$ 20 cigarettes per day) are at higher risk than light smokers (< 10 cigarettes per day)[1] but even occasional smokers experience substantial increased risk of cardiovascular death compared to nonsmokers [relative risk (RR) 1.5, 95% confidence interval (CI) 1.0–2.3].[6] The dose-response relationship is highly nonlinear with most of the risk appearing at even the lowest levels of cigarette consumption. Therefore light and intermittent (nondaily) smokers—not just heavy smokers—should be advised to quit and assisted in doing so.

Like active smoking, both acute and chronic second-hand smoke (SHS) exposures cause CVD and death from CVD. Passive smoking increases the risk of heart disease by approximately 30% (RR 1.31, 95% CI 1.21–1.41).[7-9] SHS adversely affects many factors that increase CVD over the long-term, in many cases almost as much as active smoking;[9] the acute effects are mediated mainly through increased platelet activation, effects on endothelial function, and increased risk of thrombosis.[8] Despite the much lower dose of tobacco smoke inhaled by passive smokers (1–10% of that of active smokers, depending on the constituent that is being measured), the increased risk of heart disease is 40% of that seen in active smokers (1.78, 95% CI 1.31–2.44).[9-11] Although it is plausible to expect that SHS causes stroke, the evidence is not yet conclusive.[7]

CARDIOVASCULAR BENEFITS OF SMOKING CESSATION

Smoking cessation is an effective primary prevention and treatment for CVD since it not only prevents the increased risk of CVD but also improves the prognosis of smokers with manifest disease. The cardiovascular risks from smoking begin to drop almost immediately when someone stops smoking; the excess risk of suffering an AMI is halfway back to that of a nonsmoker in 1 year.[12] In AMI-free smokers, most risk of AMI disappears after 5 years of quitting.[12,13]

As treatment for someone with heart disease, no other cardiovascular intervention has more profound and rapid benefits than smoking cessation. Quitting reduces total mortality risk by 36%, more than other established and accepted treatments [statins (29%), aspirin (15%), β-blockers (23%) and angiotensin converting enzyme inhibitors (23%)].[14] In patients with CHD, there is a reduction in the risk of progression, complications, hospital readmission and death.[15] Quitting after AMI or cardiac surgery decreases the risk of a subsequent AMI[16] and the risk of death by about a third,[13] rendering long-term survival rates similar to those of never-smokers.[17] Smokers who quit after a coronary artery bypass graft (CABG) have improved

survival and a decreased need for revascularization compared to those who continue smoking.[18]

EPIDEMIOLOGY OF SMOKING AND EXPOSURE TO SECOND-HAND SMOKE

Tobacco use has a long history: more than 1,000 years ago, Mayans recorded tobacco use in a stone carving and 500 years ago Europeans cultivated tobacco in the West Indies for export to Europe. Although tobacco use was widespread by the late 19th century, consumption was low by modern standards and cigarettes—the most efficient way to deliver the addictive drug nicotine—only comprised a small fraction of tobacco use. In 1884, James Bonsack developed the cigarette manufacturing machine, permitting the mass production of low cost cigarettes. In addition, the invention of the safety matches in 1892 and the subsequent development of aggressive cigarette marketing, fueled an increase in cigarette consumption.[19] By the end of the 20th century, tobacco consumption had become the leading cause of preventable deaths in the United States and worldwide.

Worldwide, tobacco-induced disease kills more than 5 million people every year[20] and, absent effective intervention, by 2030 this number will total 8 million, 80% of them in low- and middle-income nations.[21] If current smoking trends continue, tobacco will kill 1 billion people this century.[21] In the United States, cigarette smoking accounts for approximately 440,000 premature deaths each year, including 50,000 nonsmokers exposed to SHS, and costs the economy $193 billion in health care costs and lost productivity.[3]

As of 2008, there were 1 billion smokers in the world, representing about 25% of the adult population.[21] Global consumption of tobacco is shifting from developed to developing countries and from males to females. In the United States and other developed countries, tobacco consumption has decreased dramatically, while China has become the largest consumer of tobacco. In 2008, 21% of US adults (23% of men and 18% of women) were current smokers, less than half the rate in 1950 (44%).[3] The smoking prevalence varies substantially by gender, age, socioeconomic status and racial groups. In the United States, 2009 prevalence was higher among men (23.5%) than women (17.9%).[22] Smoking usually begins in adolescence when the effects of tobacco industry advertising,[19,23] exposure to smoking in the movies[23,24] and a desire to emulate adult behavior are strongest.[15] Smoking prevalence decreases with age, from 19.5% of high school students[25] and 21.8% among 18–24 year olds to 9.5% in those 65 and older[22] (in 2009). Those living below the poverty level are more likely to smoke (31.1%) than others (19.4%), as are those with lower educational level.[22] Americans reporting multiple races (29.5%) and American-Indians/Alaska Natives (23.2%) have the highest smoking prevalence, while Asians (12.0%) and Hispanics (14.5%) have the lowest.[22]

While overall smoking prevalence is declining, light and intermittent smoking patterns are increasing among young, educated people, women and racial minorities.[26-28] The tobacco industry has known since the 1970s that these are stable consumption patterns for many smokers,[29] in contrast to the medical and public health communities that until recently viewed light and intermittent smoking as a transitional phase between experimentation and established heavy smoking or quitting.[30] The lack of consensus on how to define "light smoking" and misclassification of intermittent smokers as nonsmokers poses a challenge to clinicians enquiring about smoking status because many of these people think of themselves as nonsmokers.[29,31] This situation also makes it difficult to estimate the real prevalence and to design research to assess the health effects resulting from these two increasingly important smoking patterns.[31]

Second-hand smoke exposure has substantial effects on disease worldwide accounting for 600,000 deaths every year, most from CVD. An estimated one-third of adults and 40% of children are regularly exposed to SHS.[32] Among 13–15 years old, 44% are exposed at home and 56% in public places.[33] Cotinine, a stable metabolite of nicotine, has been used as a biomarker to assess recent exposure to SHS. Better than questionnaires, it provides complete and objective measure of someone's total recent exposure. In the US exposure (cotinine levels $\geq$ 0.05 ng/ml in nonsmokers) decreased from 88% in the 1988–1991 period to 40% in 2007–2008.[34] White collar and more educated workers are more likely to enjoy a smoke-free workplace than blue collar and less educated workers.[35] Blue collar and manufacturing/construction and service sector nonsmoking workers (including waitresses, waiters and bartenders) have the highest cotinine levels.[36] In 2007–2008, 18.2% of children lived with someone who smoked inside the home compared to 5.3% of nonsmoking adults.[34] Children from low socioeconomic backgrounds and racial minorities have higher odds of exposure.[37] Among nonsmoking adults, SHS exposure decreases with age.[34]

ACTIVE SMOKING AND CARDIOVASCULAR DISEASE

Cardiovascular disease is responsible for a third of all deaths attributed to active smoking.[3] The RR of dying from CHD is higher for younger people because the baseline risk of heart disease increases with aging.[10] The risk of nonfatal AMI progressively increases with daily cigarettes smoked; however, as already discussed, the dose-response relationship is highly nonlinear (Fig. 1).[6,11] Despite the much lower dose of exposure, light smoking (4–7 cigarettes per day) has approximately 70% of the effect of heavy smoking ($\geq$ 23 cigarettes per day).[11] Similarly, the risk of IHD among 35–39 years old men and women who consume 1–4 cigarettes per day is almost three times higher compared to that of a nonsmoker (RR 2.74 in men and 2.94 in women).[6,38]

Smokers have a higher risk of sudden cardiac death (SCD) than nonsmokers. Retrospective analysis of SCD victims revealed that current smoking is more common than hypertension among these subjects, as opposed to the reference population where smoking and hypertension prevalences are similar.[39] Epidemiological studies show that smokers have a higher RR for SCD than for AMI or CHD.[40] These facts suggest that arrhythmogenesis may be a more important mechanism than atherosclerosis in smoking-related SCD. After quitting, the risk of SCD falls rapidly.[41]

Smoking is the third most important risk factor for heart failure (after CHD and diabetes, both of which are caused by smoking),[1,42,43] increasing the direct risk by about 60%

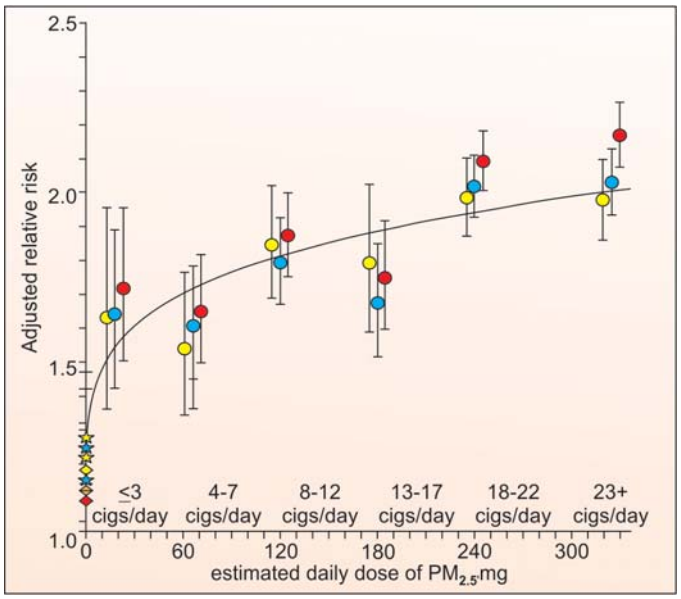


FIGURE 1: Estimated relative risk of ischemic heart disease (light yellow), cardiovascular disease (blue) and cardiopulmonary disease (red) mortality plotted over estimated daily dose of $PM_{2.5}$ (particulate matter 2.5 μm or less in diameter). Circles represent risk from $PM_{2.5}$ from current daily cigarettes (cigs) smoked relative to never smokers, diamonds represent comparable data from air pollution, and stars from SHS exposure. The solid line best explains all data in the graph. (*Source:* Adapted from Reference 11, with permission)

(population attributable risk of 17.1%).[44] Left ventricular dysfunction increases with the numbers of years smoked.[45] Cardiac remodeling and reduced ventricular function, traditional features of heart failure, are also caused by active and passive smoking.[46-48] Patients at high risk of developing heart failure should be strongly advised to quit.[49]

Smoking causes extracardiac vascular diseases including ischemic stroke and subarachnoid hemorrhage, abdominal aortic aneurysm, peripheral artery disease and erectile dysfunction. Smokers face a twofold to fourfold increase in the risk of stroke compared to nonsmokers, an increase that decreases after quitting and disappears over 5–15 years.[7] Smoking causes abdominal aortic aneurysm and increases the rupture risk.[1,50] Screening is recommended for men between 65 years and 75 years of age who have ever smoked (data are not yet conclusive to make such recommendation for women).[51] Smoking causes erectile dysfunction, probably through endothelial dysfunction, atherosclerosis and oxidative stress.[52,53]

Smoking acts synergistically with hormonal contraceptives to increase women's risks of CHD. The combined risk of smoking and using hormonal contraceptives is larger than the sum of the separate risks. Indeed, most of the increased cardiovascular risk of hormonal contraceptives appears to be limited to smokers.[54] Although most studies have shown significant increases of AMI risk with the combination of smoking and hormonal contraceptives,[54] estrogen doses have since decreased[55] and data with currently used doses of estrogens are limited.[56] Nevertheless, current guidelines recommend against using combined hormonal contraceptives (oral, injected, patch or ring) in smokers above age 35, especially smokers of 15 cigarettes per day or more.[56,57]

SECOND-HAND SMOKE AND CARDIOVASCULAR DISEASE

Second-hand smoke is the mixture of sidestream smoke given off by the smoldering cigarette (representing 85% of SHS) and mainstream smoke exhaled by the smoker.[58] Philip Morris tobacco company conducted secret animal toxicology studies that revealed that fresh sidestream smoke is approximately four times more toxic per gram of total particulate matter (PM) than the mainstream cigarette smoke inhaled by the smoker.[58] Moreover, sidestream smoke continues to undergo chemical and physical reactions once it is emitted into a room; smoke "aged" for 30 minutes increases in toxicity by a factor of 2–4, depending on the toxicological endpoint.[59,60] Even though these studies focused on tumorogenesis and respiratory effects, it is likely that there are similar effects in the cardiovascular system.[59]

Passive smokers are at increased risk of fatal and nonfatal CHD: there is no safe level of exposure to SHS.[7] This increased risk of CVD for passive smokers has been found to be almost identical to that of light smokers. Using cotinine as an estimate of exposure, as opposed to self-report, yields higher risk estimates for the effects of SHS, presumably because people underestimate their actual exposure level (which leads to exposure misclassification in epidemiological studies, biasing the risk estimates toward the null). Whincup et al. estimated the risk of CHD with heavy exposure to SHS (serum cotinine levels 2.8–14.0 ng/ml) to be 1.57 (95% CI 1.08–2.28), similar to that found in light active smokers (1.66, 95% CI 1.04–2.68) (Fig. 2).[61] The 14.0 ng/ml cut-off point used in this study is probably too high to separate passive smokers from light smokers because of the decrease in SHS that has occurred in the United States as a result of the spread of smoke-free legislation. A cut-off point of 3 ng/ml cotinine was proposed in 2009 to achieve better sensitivity and distinguish smokers (including light smokers) from nonsmokers.[62]

Similar to the effect seen in light smokers, the increased risk of CVD from SHS exposure is nonlinear. The largest relative effects occur at very low doses (such as those from air pollution and SHS) and a nonlinear dose-response relationship best explains the magnitude of this effect (Fig. 1).[8,11]

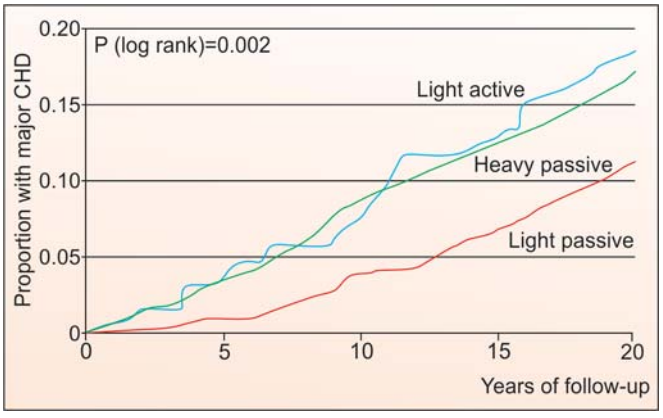


FIGURE 2: Proportion of men with major coronary heart disease (CHD) relative to years of follow-up. "Light active" refers to smokers who report smoking 1–9 cigarettes per day. "Light passive" and "heavy passive" refer to nonsmokers in the lowest quarter (0–0.7 ng/ml) and highest three quarters (0.8–14.0 ng/ml) of cotinine concentrations, respectively. (*Source:* Adapted from Reference 61, with permission)

Passive smoking has been associated with peripheral artery disease[63,64] and erectile dysfunction.[65,66] Furthermore, recipients undergoing a cardiac transplantation should especially be advised to avoid exposure to tobacco smoke because experimental data suggest that either recipient or donor exposure is associated with cardiac allograft rejection and graft loss, possibly mediated through vascular inflammation.[67]

LOW-TAR ("LIGHT") CIGARETTES

Starting in the 1950s cigarette manufacturers re-engineered their product to reduce tar yields as measured by cigarette smoking machines, marketing these cigarettes as a "healthier" alternative to "full flavor". Terms such as "ultra light", "light" and "full flavor" were often used to describe machine tar-yields per cigarette (1–6 mg, 7–15 mg and > 15 mg respectively).[68] The marketing of reduced yield cigarettes using explicit or implied messages that they were healthier was a central element in a successful lawsuit against the major cigarette manufacturers brought by the US Department of Justice under the federal Racketeer Influenced and Corrupt Organizations (RICO) Act alleging fraud. The companies lost this case and, as part of the remedy, allowed to stand by the US Supreme Court in 2010, the judge prohibited the companies from using terms such as "light" and "mild" and making explicit or implied health claims about these products. Congress also made the use of these terms illegal in 2009, when it passed the Family Smoking Prevention and Tobacco Control Act that granted the Food and Drug Administration (FDA) authority to regulate cigarettes and other tobacco products.

In response to these limitations, the companies simply used numbers or color-coded the packages (using red, blue, gold, silver, white and other colors).[69] As of early 2012, it was not clear what, if any, actions either the courts or the FDA would take to limit this practice.

The reason for the fraud is that the reported tar- and nicotine-yields are measured by a machine with fixed smoking patterns, which does not accurately reflect actual smoking by real people, who adjust how they smoke the cigarette to get the amount of nicotine necessary to satisfy their addiction.[70,71] For example, one strategy that the cigarette companies use to produce cigarettes that give lower machine yields is to put microscopic "ventilation" holes in the filter so room air will be pulled in when the machine draws on the cigarette, diluting the smoke and lowering the tar and nicotine measured during a fixed number of puffs. However, these holes are placed strategically so human smokers will block them with their lips or fingers, increasing the smoke concentration and tar and nicotine yields delivered to the human smoker (but not to the machine).[72] In addition, since smokers are addicted to nicotine, they tend to compensate any reduced nicotine delivery per puff by altering their smoking pattern taking deeper puffs, more puffs per cigarette or smoking more cigarettes per day.[68,72] Reported tar- and nicotine-yields are consistently lower than those actually delivered to a smoker and there is little correlation between machine measured yields and actual levels delivered to real smokers.[71,73] Machine measured nicotine yields of cigarettes explain less than 1% of variations among smokers' saliva cotinine levels.[73]

A prospective study found no relation between nicotine yield and tar yield with cardiovascular mortality,[74] but other studies yielded conflicting results.[75] Although evidence regarding different risks between smokers of cigarettes with different yields is still developing, smoking even low-tar cigarettes carries excess risk compared to not smoking. A pooled analysis of three case-control studies revealed that smokers of low-tar (< 10 mg) cigarettes have an odds ratio (OR) of 2.70 (95% CI 2.01–3.63) for AMI compared to nonsmokers.[76]

Low-tar cigarettes should not be recommended as an AMI risk-reduction strategy. The important point for clinicians and patients is that these cigarettes are no safer than "regular" cigarettes, particularly in terms of CVD, where even low levels of smoke exposure confer substantial risks.

PATHOPHYSIOLOGY OF TOBACCO SMOKE AND CARDIOVASCULAR DISEASE

Active and passive smoking affect the cardiovascular system through the same multiple biological mechanisms (Table 1). Rather than isolated mechanisms, these different mechanisms can interact with each other and have a multiplier effect on CVD risk.

The magnitudes of these effects from passive smoking are nearly as large as those from active smoking.[9] Of the more than 4,000 toxic components of tobacco smoke acrolein,[77-80] cadmium,[81] lead,[82-84] particulate matter (PM),[8,85] carbon monoxide,[41] benzo(a)pyrene,[86] crotonaldehyde,[8] 1,3 butadiene[8] and polycylic aromatic hydrocarbons[87] have been identified to induce one or more of these mechanisms.

ATHEROSCLEROSIS

Smoking, active and passive, causes atherosclerosis,[1,7] the underlying pahtophysiologic process in CHD, peripheral vascular disease and stroke. The processes that mediate the appearance of atherosclerotic lesions in smokers include oxidative stress, inflammation, platelet activation, endothelial dysfunction and dyslipidemia [decreased high-density lipoprotein cholesterol (HDL-C) and increased low-density lipoprotein (LDL)].[1] Carotid artery intima-media thickness (a noninvasive quantitative measure of atherosclerosis and predictor of AMI and stroke[88]) and the number of atherosclerotic plaques are increased in current and former smokers compared to never smokers.[89] This increased carotid intima-media thickness correlates with cotinine levels in adolescents and children exposed to SHS, indicating a dose-response relationship.[90]

TABLE 1

Tobacco smoke and cardiovascular disease

Mechanisms
• Endothelial dysfunction
• Platelet activation
• Arterial stiffness
• Dyslipidemia
• Inflammation
• Oxidative stress
• Hemodynamic effects

In addition, smoking causes and interacts with diabetes, leading to more atherosclerotic damage. Among a group of patients with diabetes, carotid intima-media thickness correlates with the duration of diabetes in smokers but not in nonsmokers.[91] Furthermore, diabetics who smoke have more coronary artery calcification than their nonsmoking counterparts.[92]

ENDOTHELIAL DYSFUNCTION

Endothelial dysfunction is strongly and independently associated with cardiovascular events.[93] Under normal conditions, the endothelium is a source of nitric oxide (NO), which is produced by endothelial NO synthase (eNOS) using L-arginine as a primary substrate. Nitric Oxide regulates vasodilation and vasoconstriction to maintain normal coronary (and other) blood flow and inhibit inflammation and platelet aggregation.[94] As blood speeds up through a vessel, the resulting increased shear stress stimulates normal endothelium to secrete NO which, in turns, leads to vasodilation. This so-called flow mediated dilation (FMD) is a clinical marker of endothelial control of the vasomotor tone in arteries.[95] In addition, the healthy endothelium secretes several factors that have antiaggregatory effects on platelets or have anticoagulatory or fibrinolytic properties[96] and prevents platelet interaction with subendothelial connective tissue.[8] Tobacco smoke exposure (both active and passive) interferes with this process and leads to endothelial dysfunction and a decrease in the anticoagulatory potential of the endothelium, an increase in procoagulatory modulators (e.g. tissue factor and plasminogen activator inhibitor)[96] and a reduction of endothelium-dependent vasodilation. These effects result in atherosclerosis, plaque rupture, inflammation, platelet activation and decreased blood flow due to thrombosis and vasospasm.

Tobacco smoke exposure (acute or chronic, active or passive), damages endothelial cells and leads to endothelial dysfunction which is manifest shortly after exposure.[1,8] Smokers show decreased endothelium-dependent and endothelium-independent vasodilation compared to nonsmokers. The ratio of these two measurements, however, is lower in smokers, suggesting that the endothelium-dependent dilation is affected more than the endothelium-independent dilation.[97,98] FMD reduction occurs in a dose-dependent manner shortly after smoking.[97] In a group of smokers, FMD reduction was significant immediately after smoking a cigarette and remained significantly lower after 20 minutes compared to a measurement before smoking.[99] Passive smoking also leads to endothelial dysfunction. After 30 minutes of exposure to SHS in a smoking room, the endothelial function (measured by brachial artery FMD) of nonsmokers was significantly reduced to levels similar to those observed in active smokers.[100] In adolescents, cotinine levels negatively correlate with FMD, indicating that the more smoke they have been exposed to, the more compromised their endothelial function.[101] Similar results have been observed using coronary blood flow velocity reserve, another measure of endothelial function, in the coronary arteries.[102]

Passive smoking exposure does not lead to additional reduction in endothelial function in active smokers,[100] consistent with the other evidence of a nonlinear dose-response, with large effects at low exposures that then tend to saturate.

The harmful effects of tobacco smoke on the endothelium have also been documented at the cellular level. Endothelial cell damage has been documented in smokers just 10–30 minutes after smoking two cigarettes.[103] Healthy nonsmokers exposed to 30 minutes of SHS had a significant increase in endothelial microparticles (circulating damaged endothelial cell remnants), vascular endothelial growth factor (signaling damage to the endothelium) and circulating endothelial progenitor cells (EPC, to repair the damaged endothelium) immediately after exposure, indicating damage to endothelial cells and activation of the repair mechanism.[104] This repair mechanism, however, was compromised; the EPC did not show normal chemotaxis toward vascular endothelial growth factor.[104] Therefore, in addition to damaging the endothelium, SHS compromises the repair system.

The adverse effects of SHS on endothelial dysfunction reverse after exposure ends. Among healthy nonsmokers FMD returns to baseline levels approximately 2.5 hours after a 30-minutes exposure to SHS has ended; however, markers of cellular damage remained elevated for at least 24 hours.[104] The recovery from chronic exposure appears to be more prolonged. A group of former smokers (average 6 years) showed the improved FMD compared to current smokers, but still lower than lifelong nonsmokers.[97] One year after successfully quitting smoking, former smokers that quit had improved brachial artery FMD compared to those that relapsed (mean 6.58% vs 7.20%; $p = 0.05$).[105]

The effect of cigarette smoke on endothelial function is due in part to disruption in the L-arginine-NO pathway. Exposure to cigarette smoke extract reduces endothelial cells uptake of L-arginine, eNOS activity and intracellular NO concentration.[106] In addition, intravenous infusion of L-arginine reverses impaired endothelium-dependent coronary vasodilation in smokers.[107] In hypercholesterolemic and normocholesterolemic, rabbits decreased endothelium-dependent relaxation by SHS could be blocked by L-arginine supplementation.[108,109] In humans, short-term (3 days)[99] but not long-term (6 months)[110] L-arginine supplementation has been associated with some improvement in the endothelial function. A tolerance mechanism may be implicated. The oxidative stress resulting from tobacco smoke exposure is another mechanism by which smoking leads to endothelial dysfunction, possibly by decreasing NO concentrations.[111] A negative correlation between endothelial function and oxidative stress levels has been documented.[100] The decreased level of endothelial NO is similar in smokers of less than one pack per week and those that smoke one pack per week or more[112] consistent with the nonlinear dose-response relationship between smoke exposure and cardiovascular effects, with the largest effect occurring at low levels of exposure.

Cigarette smoke constituents that have been implicated in the detrimental effect on the endothelium include PM[8,85,113] and cadmium.[114] While exposure to fine particle air pollution depresses endothelial function, in contrast to SHS, PM air pollution is associated with depressed levels of EPCs,[113] suggesting that the increased levels of EPCs observed during passive smoking[104] are due to elements other than the PM in SHS. The contribution of nicotine is minor.[8]

Platelet activation and subsequent thrombosis are key factors in the development of CVD[115] and triggering of acute coronary events. The imbalance of prothrombotic and fibrinolytic factors produced by cigarette smoke produces a prothrombotic state, resulting in increased risk of AMI and SCD. This prothrombotic state explains why smokers are generally younger and have less risk factors and CHD than nonsmokers at the time of first AMI. On autopsy, smokers are more likely than nonsmokers to have acute thrombosis rather than stable plaques.[1]

The prothrombotic state is induced through several mechanisms. Platelet factors, fibrinogen and platelet activation are all increased while antithrombotic factors are decreased in smokers. In addition, increased levels of antithrombin III and decreased levels of factor VIII, protein C, factor IX activation peptide, factor X activation peptide and prothrombin fragment 1 + 2 have also been reported.[1]

Platelet activation results from chronic and acute smoking and from exposure to SHS. Baseline platelet activation is higher in smokers than in nonsmokers; however, after exposure to SHS platelet activation rapidly increases and, after repeated SHS exposure, reaches levels undistinguishable from those of a smoker.[116,117] These results suggest that platelets are very sensitive to low levels of tobacco smoke and are already fully activated (at least in terms of the effects of smoke) in chronic smokers. Baseline platelet-dependent thrombin levels in smokers after a 12-hour abstinence were increased compared to nonsmokers; a further increase (threefold) was observed immediately (within 15 minutes) after smoking two cigarettes.[118] Two studies reported that the platelet aggregation in smokers decreases 2–3 weeks after quitting; however, neither study included a nonsmoking control group, so we do not know if levels returned to that of nonsmokers.[119,120] Despite inhaling only 1–10% of the tobacco smoke compared to active smokers, passive smokers experience 96% of the platelet activation seen in active smokers.[9] The increase in platelet aggregation produces an acute increase in the risk of IHD of 43% for active smoking and 34% for passive smoking.[10] Other smoke components than nicotine appear to be the causative agents for these effects on platelets because the smoke extract from low-nicotine to zero-nicotine cigarettes leads to more platelet activation compared to regular ones.[121,122] The fine particles in the smoke probably contribute to the effect of tobacco smoke on platelets; episodes of high levels of fine particle air pollution are associated with increased platelet activation and depressed endothelial function.[113]

In addition to increasing platelet aggregability, smoking interacts with the clinical efficacy of anticoagulation medication, either by potentiating or inhibiting it. On one hand, the platelet inhibitor clopidogrel is converted to its active metabolite via the isoenzyme CYP1A2. Cigarette smoking induces CYP1A2 and smokers taking clopidogrel experience greater relative inhibition of platelet aggregation compared to nonsmokers (46% vs 34%; p = 0.002).[123] It is also possible that because they have more active platelets, smokers will obtain a larger benefit from antiplatelet therapy.[124] On the other hand, smokers are significantly more resistant to the antiplatelet effects of aspirin (RR 11.5; 95% CI 6.7–11.6).[125] While smokers may benefit from clopidogrel therapy after AMI, regardless of which antiplatelet drug smokers with CVD are taking, they should be advised to quit smoking.

ARTERIAL STIFFNESS

Smoking and SHS exposure increase arterial stiffness.[126] For active smoking, the effect is both acute and chronic. Smoking one cigarette increases arterial stiffness within 5 minutes.[127] In a prospective follow-up study of 2,000 healthy Japanese subjects, arterial stiffness was assessed using brachial-ankle pulse wave velocity, which increases in stiffer arteries. After 6 years of follow-up, pulse wave velocity increased in all subjects because aging increases arterial stiffness, but was significantly higher in smokers (mean ± SD 11.0 ± 1.9 cm/s per year) than in never-smokers (5.5 ± 0.6 cm/s per year).[128] In addition, chronic smoking appears to sensitize the arterial response to acute smoking.[129]

Five minutes of SHS exposure produces an increase in arterial stiffness among nonsmokers,[126] a larger effect than when a nonsmoker smokes a single cigarette.[127] Arterial stiffness is positively correlated with cotinine levels in healthy 11-year-old adolescents, indicating a dose-response effect.[130]

Smoking cessation significantly improves arterial stiffness as early as 6 months after quitting,[131] returning to that of nonsmokers after 10 years.[132]

DYSLIPIDEMIA

Both active and passive smoking are associated with a more atherogenic lipid profile. Smokers show significantly lower concentrations of HDL-C and higher triglycerides compared with nonsmokers in a dose-dependent manner.[133,134] Higher total LDL and very-low-density lipoprotein (VLDL) cholesterol levels have also been observed.[1] Smoking increases lipid peroxidation, an important step in the atherosclerosis pathway, and alters lipid metabolism. Higher malondialdehyde in smokers may promote LDL cholesterol uptake by macrophages and decrease cholesterol transport from cell membranes to plasma.[1]

Lower HDL-C levels have been found in female nonsmokers exposed to SHS compared to unexposed nonsmokers. HDL-C levels in passive smokers were similar to those of active smokers.[135] These same effects on HDL-C levels have been found in adolescents exposed to SHS at home.[136]

The presence of metabolic syndrome predicts CVD. Metabolic syndrome is the combination of abdominal obesity with two or more of the following conditions: high triglycerides, low HDL-C levels, hypertension and raised fasting plasma glucose.[137] This syndrome occurs significantly more frequently in smoking adolescents (8.7%) and those exposed to SHS (5.4%) than unexposed nonsmokers (1.2%).[138] In addition to low HDL-C and high triglycerides, other components (glucose intolerance[139] and abdominal obesity[140-142]) are associated with tobacco use.

INFLAMMATION

Active and passive smokers have higher levels of inflammation, a key step in atherosclerotic and CVD pathways.[143] Smokers have higher levels of several markers of inflammation—

leukocyte count, C-reactive protein (CRP), interleukin-6, P-selectin, E-selectin, soluble intercellular adhesion molecule type-1 and fibrinogen—and lower albumin compared to nonsmokers.[1] Levels of inflammatory markers are higher in current than former smokers, which are, in turn, higher than in never smokers.[144] The effect of tobacco smoke on inflammatory markers is similar in active and passive smokers (even at low levels of exposure).[9,145] Inflammatory markers fall shortly after quitting, an effect that grows with time.[146,147]

OXIDATIVE STRESS

Oxidative stress results when the body is unable to detoxify reactive oxygen species (ROS) and free radicals. Oxidizing agents can initiate the inflammatory cascade as well as be produced by an inflammatory process.[85] Cigarette smoke delivers oxides of nitrogen, free radicals and other oxidizing chemicals to active and passive smokers[41] and can increase ROS production directly, thus damaging cardiomyocytes.[111] Smokers are exposed to an estimated 10^5 oxidative free radicals per puff.[143,148] Plasma 8-isoprostane, a surrogate marker of lipid oxidation,[100] and oxidized proteins[149] are increased in smokers compared to nonsmokers. Similar to endothelial dysfunction, oxidative stress increases shortly after SHS exposure. Thirty minutes after exposure to SHS at levels similar to those found in a bar, plasma 8-isoprostane levels increased in nonsmokers to levels undistinguishable to those found in smokers.[100] In chronic smokers, isoprostanes levels rapidly decrease after quitting (within a few days to a few weeks).[8] Although no conclusive statements can be made, components that have been related to increased oxidative stress include PM,[85] heavy metals, particularly lead and cadmium,[8] and possibly nicotine.[150]

Antioxidants (e.g. folate, ascorbic acid, β-carotene) are the physiological barrier that protects blood vessels against oxidative stress. Antioxidants are similarly decreased in active and passive smokers[9] compared to nonsmokers.[1,151] Therefore, the effects of tobacco smoke on oxidative stress are twofold: it is a source of oxidative stress and consumes the physiologic antioxidant barrier.

AUTONOMIC EFFECTS AND HEART RATE VARIABILITY

Smoking and passive smoking affect the autonomic nervous system by increasing sympathetic activity. Nicotine increases catecholamine concentrations and muscle sympathetic nerve activation through direct action on nicotinic receptors, increasing myocardial contractility, heart rate and vasomotor tone.[152] Active and passive smoking increase heart rate;[153,154] quitting reverses the effect.

Decreased heart rate variability (HRV) is a marker of autonomic dysfunction and predictor of CHD, heart failure, CVD death, and death and arrhythmic complications after AMI.[155-157] Compared to nonsmokers, smokers have decreased HRV.[158] Quitting reverses the effect as early as 3–7 days[153,159] and former smokers show no difference from never-smokers, indicating the rapid and sustained benefits from smoking cessation.[160] SHS exposure reduces HRV in animals and humans. Mice exposed for 3 days, 6 hrs/day, to sidestream smoke have decreased HRV after the first 24 hours of exposure and continuing 24 hours after the last day of exposure.[161] Healthy nonsmokers experienced a rapid 12% decrease in HRV during the time spent in an airport smoking lounge. This decrease was rapidly reversed after moving out of the lounge.[162] Chronic (regular exposure at home or work for > 2 hrs/day) and occupational exposure to SHS reduce HRV.[154] Employees working in bars and restaurants where smoking is allowed exhibit a decrease in HRV that employees working in smoke-free venues do not experience. HRV was negatively correlated with $PM_{2.5}$ (particulate matter 2.5 μm or less in diameter) measured in the smoking venues,[163] indicating a dose-response effect.

Even though smoking and passive smoking have been associated with a transient elevation in blood pressure, they have not been associated with hypertension.[8,154]

IMPAIRED OXYGEN TRANSPORT

By binding to hemoglobin, carbon monoxide impairs oxygen transport resulting in a state of relative hypoxemia. Carboxyhemoglobin in smokers persists throughout the day. Levels of carboxyhemoglobin relative to total hemoglobin average 5% but can be as high as 10% in heavy smokers, compared to 0.5–2% in nonsmokers,[41] suggesting impaired ability to transport oxygen.

SMOKING CESSATION

Smoking cessation is the most cost-effective CVD prevention strategy (followed by aspirin in high-risk individuals).[164] Forty-one percent of smokers tried to quit in the year 2000, but only 4.7% maintained abstinence for 3–12 months.[165] In addition, 70% of smokers report wanting to cut down or quit.[166] Young adults, many of whom have not become fully addicted smokers, have the highest spontaneous quit rates[167] and represent a particularly important audience for smoking cessation given that quitting before age 30 results in mortality rates equal to those of never smokers.[168]

Among adults 25 years and older, quit ratios (ratio of former smokers to ever smokers) are lower among smokers of low-educational level (39.9%) and the highest among those with a graduate degree (80.7%).[166] These quit rates can be improved substantially with smoking cessation treatment, including counseling and medications when needed.[169]

Cardiologists should use a systematic approach on all inpatients and outpatients who use tobacco, and (at a minimum) ask every patient for smoking status and advise smokers to quit and nonsmokers to avoid SHS exposure. Asking all adults about tobacco use and providing cessation treatment has been given a Grade A (interventions that have been proven effective in well-designed studies) recommendation by the US Preventive Services Task Force.[170] Doing so is not difficult; clinicians should use the 5 As (*ask*, *advise*, *assess*, *assist* and *arrange*) strategy to identify smokers and get them into treatment:[169]

- *Ask* every patient at every visit for tobacco use.
- *Advise* all tobacco users to quit regardless of age, health status or tobacco product used (e.g. cigarettes, pipe, cigar, chewable, snuff).

- *Assess* willingness to quit and categorize patient as (a) not ready to quit in the next month; (b) ready to quit in the next month; (c) recent quitter, in the past 6 months or (d) former user, having quit more than 6 months ago.
- *Assist* in the quitting process giving counseling and medication if needed, and help the patient design a quit-plan according to assessed status (not ready, ready, recent quitter, former smoker).
- *Arrange* for follow-up contact. Multiple and frequent contacts will increase the probability of success.

If a patient is not ready to make a quit attempt, he or she might respond to a brief intervention where the 5 Rs (*relevance*, *risk*, *rewards*, *roadblocks* and *repetition*) should be addressed:[169]

- *Relevance*: Ask the patient to state why quitting would be relevant to his/her personal situation (e.g. health, living with children, economic reasons, physical well-being or any personal characteristic).
- *Risk*: Mention health risks to the patient and those around him/her (e.g. cancer, respiratory disease, CVD, sudden infant death syndrome, risks of SHS to spouse or children).
- *Rewards*: Mention rewards that will be attained once the patient quits (e.g. improved health, saving money, physical well-being, the improved sense of taste or smell).
- *Roadblocks*: Have the patient list possible reasons why he/she is not ready to quit (e.g. fear of failure, withdrawal symptoms or weight gain, depression). Provide intervention to address these reasons.
- *Repetition*: Repeat intervention at every contact with the patient.

For clinicians who lack the time to go over the 5 As and 5 Rs, they could just do an abbreviated version, and just *A*sk and *A*dvise followed by *R*efer to other resources such as a quitline. (The nationwide quitline is 1-800-QUITNOW and many states have quitlines; the national quitline forwards callers to their state quitline if the state has one).

For light (< 10 cigarettes per day) and intermittent (non-daily) smokers, a different strategy is warranted. They are unlikely to label themselves as smokers and are therefore more difficult to identify.[31] Instead of asking "Are you a smoker?" clinicians should ask "Do you use any tobacco product in a daily, weekly or social basis?"[6] or "Have you used tobacco products in the past month?".[29] In addition, smokers in this group often feel immune to the health risks of smoking and believe that they can quit at anytime but are concerned about the dangers of their smoke on others, requiring a different approach during counseling. They may be more willing to quit when emphasis is given to the harm their smoking poses on others rather than on their own health risk.[29]

Patients with established CVD might be particularly motivated to quit. In the University of Ottawa Heart Institute, an institutional smoking cessation program achieved a 44% quit rate at 6 months among admitted cardiac patients.[171] In a meta-analysis of smoking cessation therapies on cardiac patients, behavioral therapy (OR 1.97, 95% CI 1.37–2.85) and pharmacotherapy (1.72, 1.15–2.57) achieved significantly higher abstinence rates compared to usual care and placebo.[172] In patients admitted for AMI or CABG, receiving intensive counseling (minimal counseling plus 40–60 minutes of bedside counseling, take-home materials and 7 nurse-initiated counseling calls for 2 months after discharge) significantly increased the abstinence rate compared with minimal counseling (advice from physicians and nurses and two pamphlets).[173]

NICOTINE WITHDRAWAL

Smokers smoke due to nicotine addiction, which results from nicotine activating the nicotinic acetylcholine receptors in the neurons of the ventral tegmental area in the brain. These neurons then release dopamine, stimulating neurons in the brain's "reward center", the nucleus accumbens. When a smoker quits and nicotine stimulation of the receptors ends, lower concentrations of dopamine are released leading to craving and nicotine withdrawal symptoms, provoking the urge to smoke.[174]

These physiological and cognitive effects should be addressed to avoid relapse after someone quits smoking. Withdrawal symptoms manifest within the first 1–2 days, peak within the first week, and subside within 2–4 weeks.[175] Withdrawal symptoms include cravings for nicotine and increased appetite, anxiety, lightheadedness, irritability, sleep disturbances, poor concentration, depression and restlessness.[175,176] In addition, moderate weight gain, altered drug metabolism (CYP1A2 enzyme activity decreases back to normal after quitting) and increased blood pressure have been documented.[177] Constipation, cough, dizziness, increased dreaming, nausea, sore throat and mouth ulcers may be related to cessation.[175] Pharmacotherapy can help in reducing withdrawal symptoms, making patients more comfortable while quitting.

PHARMACOTHERAPY

Pharmacotherapy should be offered as an option to all smokers willing to quit, except when contraindicated or for special population where its efficacy has not been proven. The latter include light smokers, smokeless tobacco users, adolescents and pregnant women.[169] Light or intermittent smokers' dependence on nicotine is still controversial. Currently available medications are designed for daily smokers of more than 10 cigarettes per day and they have not been studied in the former group.[31] Table 2 (adapted from Rx for Change) presents the first-line medications approved by the FDA, including adverse effects, dosage, recommended duration of treatment and available presentations.[178] For the complete and updated information, refer to the manufacturer's package inserts.

The FDA has approved five different nicotine delivery formulations (NRT) (nicotine gum, oral inhaler, lozenge, nasal spray and patch) and two non-nicotine drugs that act on the central nervous system [varenicline, a nicotinic acetylcholine receptor partial agonist, and the antidepressant bupropion sustained release (SR)] as first-line treatment for tobacco dependency.[169] They all increase the long-term abstinence rate compared to placebo.[169] Combination therapies can be used, as they increase success rates, and are considered first-line therapy. Recommended combinations include the nicotine patch with either bupropion SR or an acute nicotine delivery formulation (gum, lozenge, nasal spray or oral inhaler).[169,179,180] It is not recommended to use varenicline with NRT or bupropion.[169]

Cessation treatment (either counseling, pharmacological or both) should be initiated in all smoking patients, including all cardiac patients. Stable CVD is not a contraindication to receiving pharmacotherapy; in patients who have had a recent (in the preceding 2 weeks) myocardial infarction, those with serious arrhythmias, and those with unstable angina pectoris NRT should be used with caution.[169] However, regardless of this recommendation, NRT achieves lower nicotine plasma concentrations[178] and probably produces lower hemodynamic effects than smoking cigarettes, while also avoiding the toxic components of cigarette smoke that induce oxidative stress, inflammation and thrombosis. Although there have been occasional reports of hypertension with bupropion, non-NRT products (varenicline and bupropion) are safe and effective in patients with stable CVD and may be a better option for these patients.[181,182] Given the added risk posed by smoking on cardiac patients, every effort should be made toward cessation, including NRT and non-nicotine drugs.[183]

Nicotine Replacement Therapy

Nicotine replacement therapy is designed to achieve lower and slower-rising concentrations of nicotine in the blood and to provide a "weaning" mechanism[184] to reduce withdrawal symptoms and increase the likelihood of a successful quit attempt.[185] NRT approximately doubles the probabilities of a successful quit attempt, compared to placebo.[169] NRT products are absorbed through the oral or nasal mucosa, or skin. Signs and symptoms of nicotine intoxication may present with high doses of NRT, combined therapy or continued smoking while on NRT. These include gastrointestinal alteration, dizziness, profuse perspiration, flushing, hearing and vision disturbances, confusion, weakness, palpitations, altered respiration and hypotension.[186]

The nicotine gum is available as a 2 mg or a 4 mg piece, from which 1.4 mg and 3.4 mg, respectively, are extracted by the patient.[186] Peak plasma nicotine concentrations are reached in 30 minutes.[187] The gum should be chewed slowly until the flavor of the gum or a tingling sensation is felt, then "parked" between the lips and gums to allow for nicotine to be absorbed through the oral mucosa. Acidic beverages (e.g. coffee, fruit juice, wine) lower the nicotine absorption in the oral mucosa (a low pH reduces absorption) so should be avoided for 15 minutes before and while chewing the gum.[169] One piece should be used every 1–2 hours with a maximum of 24 pieces per day.[169]

The nicotine lozenge should be sucked rather than chewed or swallowed. As with the gum, when used as monotherapy, patients are more likely to succeed using a fixed schedule and should also avoid acidic beverages.[169] When used as a combination therapy (e.g. with the patch), it should be used as needed to control cravings. Its pharmacokinetic properties are similar to those of gum, although it releases 25% more nicotine.[188]

The nicotine nasal spray and oral inhaler are available only by prescription (gum, patch, and lozenge are available over-the-counter).[169] The nasal spray reaches peak plasma concentrations within 5–10 minutes, faster than any other NRT formulation (yet not faster than the concentrations reached when smoking).[186] Patients should use anywhere from 8 to 40 doses per day. Each dose consists of one spray of 0.5 mg in each nostril (total 1 mg).[169] The oral inhaler looks like a cigarette and its use mimics the hand-to-mouth motion that smokers are used to. It consists of a mouthpiece and an inserted cartridge. Eighty puffs deliver 4 mg of nicotine at room temperature, from which 2 mg is absorbed, but actual delivery increases with higher temperatures and deeper puffs.[169,184] Daily dose should be 6–16 cartridges.[169]

The nicotine patch delivers nicotine in a slow and continuous manner, reaching peak plasma concentrations in 5–10 hours. It is available in different dosages released over 24 hours. It has the advantage of being applied only once a day. It should be applied on dry, hairless skin and avoid repeating the area for at least 1 week to minimize skin irritation. Some users experience nightmares (vivid dreams) or insomnia with 24 hour use. Once the patch is removed before going to bed, nightmares usually resolve. Insomnia can also be a symptom of nicotine withdrawal (especially in those smokers who used to smoke before going to bed). The dose, duration of therapy and rate of tapering should be individualized in each user.[169]

Bupropion

Bupropion SR is an antidepressant which possibly blocks dopamine and norepinephrine postsynaptic reuptake and nicotinic receptors, possibly reducing the reinforcing effect of smoking.[189] It is used for 7–12 weeks beginning 1–2 weeks before quitting to allow for therapeutic plasma levels (half-life is 21 hours).[186] Bupropion is contraindicated in patients with a history of a seizure disorder, bulimia or anorexia, and in those using other bupropion medications or who have used a monoaminooxidase inhibitor in the previous 14 days.[169] Bupropion approximately doubles success rate compared with placebo and can be safely used with NRT.[169]

Varenicline

Of the nicotinic acetylcholine receptors, the $\alpha_4\beta_2$ has the highest sensitivity to nicotine and has been found to be important in nicotine dependence, reinforcement, tolerance and sensitization. Varenicline is an $\alpha_4\beta_2$-nicotinic acetylcholine receptor partial agonist and therefore induces the release of lower amounts of dopamine than those induced by nicotine, but helps prevent or alleviate nicotine withdrawal. It also competitively blocks these receptors, so smoking while on treatment is unlikely to produce the usual pleasure. Like bupropion, it should be started 1 week before quitting (half-life is 24 hours).[174] The dose is titrated to help reduce nausea and should be taken with food and a full glass of water. Physicians should ask for any psychiatric history in patients prior to initiating treatment and monitor for any change in mood or behavior while on this medication. In addition, since it is excreted unchanged in the urine, it is contraindicated in patients with severe renal dysfunction (creatinine clearance < 30 ml per minute).[169] Refer to Table 2 for dosage. Varenicline approximately triples the long-term abstinence rates compared to placebo at the FDA recommended dose (2 mg total daily dose). The 1 mg total daily dose approximately doubles success rate. Varenicline should not be used in combination with NRT.[169]

Patients prescribed bupropion or varenicline should be carefully monitored for any behavior changes, agitation, hostility, depressed mood, suicidal thoughts and behavior, or any other symptom not typical of nicotine withdrawal.[190]

TABLE 2

Pharmacotherapy options: products, dosing, recommended duration of treatment and adverse effects

Product	*Dosing*	*Duration*	*Adverse effects*
Nicotine gum			
Nicorette[1] Generic gum 2 mg, 4 mg; regular, mint, orange, cinnamon, fruit	≥ 25 cigarettes/day: 4 mg < 25 cigarettes/day: 2 mg Week 1–6: 1 piece q 1–2 hours Week 7–9: 1 piece q 2–4 hours Week 10–12: 1 piece q 4–8 hours	Up to 12 weeks	Mouth/jaw soreness, hiccups, dyspepsia, hypersalivation Effects associated with incorrect chewing technique: lightheadedness, nausea and vomiting, throat and mouth irritation
Nicotine lozenge			
Commit,[1] Generic Lozenge, Nicorette[1] (mini lozenge) 2 mg, 4 mg cherry, original (light-mint), mint	1st cigarette ≤ 30 minutes after waking: 4 mg 1st cigarette > 30 minutes after waking: 2 mg Week 1–6: 1 lozenge q 1–2 hours Week 7–9: 1 lozenge q 2–4 hours Week 10–12: 1 lozenge q 4–8 hours	Up to 12 weeks	Nausea, hiccups, cough, heartburn, headache, flatulence, insomnia
Nicotine transdermal patch			
Nicoderm CQ[1] 7 mg, 14 mg, 21 mg 24-hour release	> 10 cigarettes/day: 21 mg/day x 6 weeks 14 mg/day x 2 weeks 7 mg/day x 2 weeks ≤ 10 cigarettes/day: 14 mg/day x 6 weeks 7 mg/day x 2 weeks	8–10 weeks	Local skin reactions (erythema, pruritus, burning), headache, sleep disturbances (insomnia or abnormal/vivid dreams); associated with nocturnal nicotine absorption. May wear patch for 16 hours (remove at bedtime) if patient experiences sleep disturbances.
Generic Patch[2] (formerly Habitrol) 7 mg, 14 mg, 21 mg 24-hour release	> 10 cigarettes/day 21 mg/day x 4 weeks 14 mg/day x 2 weeks 7 mg/day x 2 weeks ≤ 10 cigarettes/day 14 mg/day x 6 weeks 7 mg/day x 2 weeks	8–10 weeks	
Nicotine nasal spray			
Nicotrol NS[3] Metered spray 0.5 mg nicotine in 50 µL aqueous nicotine solution	1–2 doses/hour (8–40 doses/day) One dose = 2 sprays (one in each nostril); each spray delivers 0.5 mg of nicotine to the nasal mucosa. For best results, initially use at least 8 doses/day. Do not exceed 5 doses/hour or 40 doses/day	3–6 months Gradually decrease usage over 3–6 months	Nasal and/or throat irritation (hot, peppery or burning sensation), rhinitis, tearing, sneezing, cough, headache
Nicotine oral inhaler			
Nicotrol Inhaler[3] 10 mg cartridge delivers 4 mg inhaled nicotine vapor (2 mg is absorbed)	6–16 cartridges/day; individualize dosing Initially, use 1 cartridge q 1–2 hours. Nicotine is depleted after 20 minutes of active puffing. Open cartridge retains potency for 24 hours.	3–6 months	Mouth and/or throat irritation, cough, rhinitis, dyspepsia, hiccups, headache
Bupropion SR			
Zyban[1], Generic 150 mg sustained-release tablet	150 mg po q AM x 3 days, then increase to 150 mg po bid Set quit date 1–2 weeks after initiation of therapy. Do not exceed 300 mg/day. Allow at least 8 hours between doses. Avoid bedtime dosing to minimize insomnia.	7–12 weeks Maintenance up to 6 months	Insomnia, dry mouth, nervousness, difficulty concentrating, rash, constipation, seizures (risk is 0.1%)
Varenicline			
Chantix[3] 0.5 mg, 1 mg tablet	Days 1–3: 0.5 mg po q AM Days 4–7: 0.5 mg po bid Weeks 2–12: 1 mg po bid Set quit date 1 week after initiation of therapy.	12 weeks An additional 12 weeks course may be used in selected patients	Nausea, sleep disturbances (insomnia, abnormal/vivid dreams), constipation, flatulence, vomiting, neuropsychiatric symptoms (including changes in behavior, hostility, agitation, depressed mood, suicidal thoughts and behavior, and attempted suicide)

[1]Marketed by GlaxoSmithKline
[2]Transdermal patch formulation previously marketed as Habitrol
[3]Marketed by Pfizer
For complete prescribing information, please refer to the manufacturers' package inserts.
(*Source:* Reference 178. Copyright © 1999–2010. The Regents of the University of California. All rights reserved. Updated April 12, 2010)

Second-line Treatments

Second-line treatments (clonidine and nortriptyline) have been used but have not been approved by the FDA for tobacco cessation treatment. They are not widely used and have more serious side effects.[169]

SMOKE-FREE ENVIRONMENTS AND THEIR EFFECT ON HEART ATTACK ADMISSIONS

In the United States, as of July 2010, 405 municipalities and 22 States had 100% comprehensive smoke-free laws covering all workplaces including restaurants and bars and protecting 47% of the population.[36] The World Health Organization Framework Convention on Tobacco Control (FCTC), the world's first public health treaty, aims to halt the global tobacco epidemic. Among its provisions, it encourages countries to "protect citizens from exposure to tobacco smoke in the workplaces, public transport and indoor public places".[191] Globally, as of February 2012, 172 nations and other parties had ratified the FCTC and, partially stimulated by it, as of April 2010, 44 countries had some sort of smoke-free law, 29 of which include both bars and restaurants.[36] Worldwide, in 2008, 154 million people became protected by new smoke-free laws; however, 95% of the world's population remains unprotected.[32]

Comprehensive smoke-free environment laws reduce SHS exposure, smoking prevalence and tobacco consumption.[192] Decreases in salivary cotinine after the implementation of a comprehensive smoke-free law range from 39% to 89%.[192] Among workplaces, bars and restaurants have been found to have the highest levels of SHS exposure[193,194] and so often see the greatest reductions in exposure when these laws are implemented. Smoke-free laws produce an immediate and substantial drop in hospital admissions for AMI and the effect grows with time. One-year after the implementation of a comprehensive smoke-free law AMI incidence drops by approximately 15% to 17%, an effect that increases to about 30% after 3 years (Fig. 3).[195,196] Since the first report in Helena, Montana,[197] reductions in AMI or CHD admission rates have also been observed in Italy (three studies analyzing data from four regions,[198] Rome[199] and the Piedmont region[200]), the United States (the cities of Pueblo, Colorado,[201,202] Bowling Green, Ohio[203] and Monroe County, Indiana,[204] and New York State[205]), the city of Saskatoon in Canada,[206] Scotland[207] and England.[208] Therefore, smoke-free environments should be a cornerstone of every comprehensive CVD control program.

While it has not been formally studied, these results combined with the rapid biological effects of SHS exposure on the cardiovascular system, strongly suggest that patients and people at risk of CVD would see immediate benefits from making their homes smoke free. All patients should be asked not only about their own smoking but also exposure to SHS and, if they are exposed at home, urged to make their home smoke free.

Smoke-free laws also protect smokers by encouraging them to quit or reduce their consumption. In Ireland, 46% of smokers report the law made them more likely to quit and most quitters said the law helped them to quit and to stay quit.[209] As recognized by the tobacco industry, workplaces are important

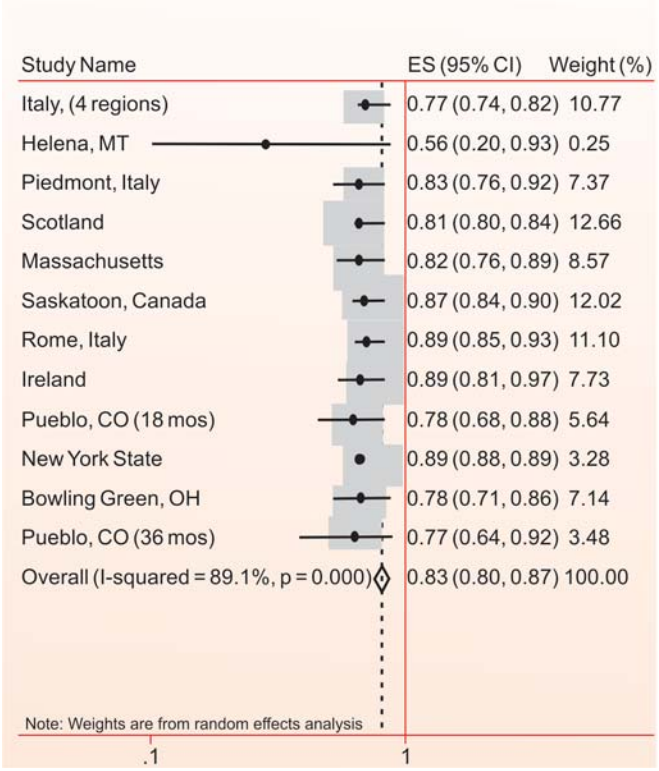


FIGURE 3: Meta-analysis of reduced acute myocardial infarction community risks. Effect size (ES) for all studies were adjusted to 12 months after implementation of 100% smoke-free workplace laws. (*Source:* Reference 195, with permission)

because that is where smokers spend most of their time.[210] Workers in smoke-free workplaces are almost twice as likely to quit as those whose workplace has no restriction.[211] In a systematic review, smoking prevalence decreased 3.6% after 100% smoke-free workplace policies were implemented. Continuing smokers reduced their consumption by 3.1 daily cigarettes.[212] Implementing a smoke-free workplace law has been found to be more cost-effective than a free NRT program at promoting smoking cessation ($799 and $7,020 per quitter respectively).[210]

SIMILAR EFFECTS AND MECHANISMS OF PARTICULATE AIR POLLUTION

Like cigarette smoke, air pollution is a combination of fine particles, gases and liquids. Indeed, SHS can be thought of as a form of indoor air pollution, and, as discussed earlier, research on fine particle air pollution has helped elucidate the biological mechanisms through which tobacco smoke compromises the cardiovascular system. Important pollutants include carbon monoxide, nitrogen oxides, sulfur dioxide, ozone, PM, and volatile and semivolatile organic compounds.[85,213] Carbon monoxide, PM, nitrogen dioxide and ultrafine particles have all been related to CVD, with most of the research done on PM.[214] The particles contained in SHS range in size from 0.01 to 1.0 μm and are therefore included whenever $PM_{2.5}$ is measured.[8] However, SHS cannot be viewed entirely as air pollution since their constituents are not identical. In addition, due to the higher concentration of certain components in SHS,

it is probably more toxic and responsible for more cardiovascular injury than ambient air pollution.[8,215]

The mechanisms by which CVD is caused by SHS and ambient air pollution are similar and include: increasing atherosclerotic plaque rate progression and vulnerability, endothelial dysfunction, prothrombotic state, oxidative stress, inflammation and altered autonomic function.[113,214,216] Due to the strong association with IHD, the inflammation/atherosclerosis pathway is probably the most representative of CVD induced by air pollution, although autonomic dysfunction could also play an important role.[217-219]

Similar to SHS, air pollution also has an acute effect on heart disease mortality.[216] A 2010 American Heart Association statement concluded that the evidence is strong enough to claim a causal relationship between ambient air pollution, specifically $PM_{2.5}$ and CVD.[85] While the RR of cardiovascular events from pollution is small compared to smoking, the large number of individuals exposed through a lifetime produces a significant public health issue.[218] It is estimated that 800,000 premature deaths a year worldwide are caused by $PM_{2.5}$, 69% from CVD.[85] A higher risk of AMI has been related to chronic and acute (even of a few hours) exposure to ambient air pollution. Fatal and nonfatal stroke incidence and hospitalizations from heart failure also increase in response to an increase in PM.[85] Analyzing PM_{10} (coarse particles < 10 µm, such as road and agricultural dust, tire wear emissions, and wood combustion), it has been estimated that an increase by 10 mg/m^3 is associated with up to a 1% increase in total daily mortality.[216] The amount of PM inhaled from air pollution is small compared to that from cigarette smoke, but the effect on CVD is larger than would be expected based on a simple linear dose-response curve. Indeed, as noted earlier, there is a highly nonlinear dose-response curve of PM and heart disease, with large effect at small doses (as in SHS or air pollution) reaching a plateau at higher doses (as in active smoking) (Fig. 1).

CARDIOLOGISTS AS TOBACCO CONTROL ADVOCATES

Despite the overwhelming evidence that smoking and SHS exposure are leading causes of preventable CVD death and disability, tobacco control and tobacco awareness among cardiologists have progressed at a slow pace. This is not surprising given the tobacco industry's multimillion dollars investment to hire lobbyists and consultants and sponsor research and symposia to mislead public opinion into questioning the adverse health effects of smoking and SHS exposure.[220-222]

Even though tobacco use is highly prevalent and lethal and there is effective therapy for quitting available, smoking cessation is not addressed properly by clinicians.[170] Among cardiologists, smoking cessation counseling does not figure among the most important interventions provided, despite the fact that it is an important preventive strategy for CVD, and it should be considered a fundamental responsibility of all cardiovascular specialists.[15] This, in part, reflects poor medical school and residency training on smoking cessation (only 5–37% of third-year students in health-related professions report having received formal training in smoking cessation counseling[223]). Smoking cessation training needs to be routinely integrated into medical education, cardiology fellowship training programs, clinical practice and cardiovascular hospitals, particularly given the relative simplicity and low cost of intervening and the rapid benefits to patients who successfully become smoke free.

In addition, cardiologists should also become actively involved in supporting, through their professional and community organizations, population based strategies that have been shown to decrease CVD mortality, in particular smoke-free environments, but also reductions in outdoor air pollution levels.

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Chapter 109

Exercise and Rehabilitation

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Chapter Outline

- Exercise: Definitions
- Exercise: Recommendations
- Responses to Exercise
- Benefits of Exercise
- Exercise Capacity
- Inflammation and Endothelial Function
- Safety Considerations
- Cardiac Rehabilitation Definition and Goals
- Cardiac Rehabilitation Phases
  - Inpatient (Phase I)
  - Early Outpatient (Phase II)
  - Long-term Outpatient (Phase III)
- Cardiac Rehabilitation Core Components
  - Medical Assessment
  - Psychosocial Assessment and Management
  - Nutrition
  - Risk Factor Management
  - Exercise Training
  - Medication Assessment and Management
- Clinical Population Considerations
  - Postsurgical
  - Angioplasty (with or without Stent)
  - Claudication/Peripheral Artery Disease
  - Atrial Fibrillation
  - Hypertension
  - Diabetes
  - Elderly
- Referral
- Reimbursement Issues

INTRODUCTION

While the prevalence and incidence of coronary artery disease (CAD) has declined over the past decade, it remains the number one killer of Americans.[1] Research evidence demonstrates that exercise and cardiac rehabilitation, two crucial secondary prevention strategies, promote recovery from acute cardiac events, reduce morbidity and mortality and increase health related quality of life. Unfortunately, in spite of mounting evidence related to the benefits of exercise and cardiac rehabilitation, referral to these programs is problematic. Provider recommendation and enthusiasm is vital to patient participation. This chapter has been designed to introduce the reader to exercise and rehabilitation concepts, review some of the latest research findings related to exercise and cardiac rehabilitation, and provide resources and guidelines for practice.

EXERCISE: DEFINITIONS

Physical activity is defined as any bodily movement produced by skeletal muscles resulting in energy expenditure. *Physical inactivity* and *Insufficient physical activity* are defined as doing less than 10 minutes total per week of moderate or vigorous-intensity lifestyle activities and doing more than 10 minutes total per week, but less than the recommended level of vigorous-intensity lifestyle activities.

Exercise is a subset of physical activity that is purposeful and carried out as part of a routine. More simply stated exercise is a planned, structured and repetitive physical activity that is performed to improve or maintain one or more components of physical fitness (i.e. cardiorespiratory fitness, muscle strength, body composition and flexibility). Exercise includes movement that is both aerobic (oxygen transport system) and resistance (musculoskeletal system).[2]

Aerobic exercise imposes a volume overload state on the cardiovascular system. In responses to the volume overload, the body increases oxygen uptake (VO_2), heart rate, cardiac output and stroke volume. Peripheral vascular resistance is simultaneously reduced and systolic blood pressure increases while diastolic blood pressure decreases; this allows active muscles to receive more blood flow (including the cardiomyocytes).[3] *Resistance training*, in contrast to aerobic training, produces a pressure overload state on the cardiovascular system. There is very little increase in oxygen uptake or cardiac output. However, heart rate, systolic and diastolic blood pressures rise proportionately to the resistance load. The cardiomyocytes respond to resistance training in a manner that is similar to skeletal muscle cells. The increased pressure load causes the cardiomyocytes to adapt by proportional growth in both their length and width (i.e. symmetric hypertrophy).[3] Further responses to resistance training include enhanced intrinsic contraction of the cardiomyocytes.[4]

Exercise capacity is the maximum amount of exercise an individual with CAD can sustain. Exercise capacity is generally defined in terms of maximal oxygen consumption (VO_2max)

or metabolic equivalents. *Maximal oxygen uptake* assesses the maximal rate at which oxygen can be transported from surrounding air to the peripheral skeletal muscles where it will then fuel oxidative metabolism. Because of its key role in cardiac and respiratory metabolism, it offers clinicians an accurate physiological measure of aerobic fitness.[4]

Metabolic equivalent (MET) is the unit used to estimate oxygen consumption during physical activity. At rest, an individual requires an average of 3.5 ml of oxygen per kilogram per minute or 1 MET. Varying levels of physical activity intensities are defined in terms of METs. Light-intensity activity, such as slow walking, would correspond to 1 to 3 METs. Moderate-intensity activity, such as brisk walking (3 miles per hour or faster, but not race pace) or water aerobics equates to between 3 and 6 METs of energy expenditure. During moderate intensity activity an individual can talk, but not sing during the activity. Finally, vigorous-intensity activity, such as race walking, jogging or swimming laps, equates to energy expenditure that is greater than 6 METs. At this level of intensity, an individual can still talk, but the conversation will be 'broken', as the individual needs to pause for a breath frequently.

EXERCISE: RECOMMENDATIONS

Current recommendations from the Centers for Disease Control (CDC) and the American College of Sports Medicine (ACSM) call for every American to accumulate at least 30 minutes of moderate-intensity physical activity on most days of the week. The American Heart Association (AHA) has established that physical inactivity is a major risk factor for CAD and its progression. Therefore, the AHA, American College of Cardiology (ACC) and the European Society of Cardiology (ESC) recommend that health care providers prescribe exercise programs to their patients with CAD that are congruent with the CDC and ACSM guideline recommendations. Unfortunately, according to the 2008 National Health Interview Statistics, approximately 59% of adults reported that they participated in no vigorous activity and approximately 25% of adults reported no participation in leisure-time physical activity.[5] Reasons surrounding these findings have not been fully elucidated, but several factors have been reported in the literature including: low referral rate, multiple comorbidities, lower socioeconomic status, greater distance to a cardiac rehabilitation facility and inadequate insurance reimbursement.[6]

RESPONSES TO EXERCISE

Exercise stimulates the cardiac system. Initially the sympathetic nervous system increases heart rate, contractile force and peripheral vasoconstriction. Cardiac output and blood flow to exercising muscles significantly increase in response to the increased oxygen demands. Active muscles (both skeletal and cardiac) increase extraction of O_2, thus increasing the A-VO_2 difference. Oxygen consumption can increase by almost 60 times the basal rate during moderate-intensity activities, with only a 15-fold increase in blood flow.[7] In the past, exercise therapy was not prescribed to individuals with CAD; it was believed that the damaged cardiovascular system could not withstand the increased oxygen demands required by moderate to vigorous activity. Currently, research provides strong support for the prescription of aerobic and resistance training exercise in individuals with CAD. Each mode of exercise provides various physiological and psychological benefits for the individual with CAD.

BENEFITS OF EXERCISE

This chapter examines several important benefits of exercise for the CAD population. However, because it is not possible to provide an exhaustive review of the benefits of exercise within the confines of this chapter, the reader is encouraged to explore the referenced meta-analyses and research studies for more detailed information about the benefits of exercise in individuals with CAD.

EXERCISE CAPACITY

In a meta-analysis, Valkeinen, Aaltonen and Kujala (2010)—the authors—examined the effects of exercise training on oxygen uptake in individuals with CAD. The majority of studies utilized aerobic interventions that exercised participants at about 70–80% of maximum heart rate or about 25–70% of VO_2max. The length of training for the programs varied between 2 weeks and 1 year, with an average of 14.2 weeks. Frequency of the programs averaged 3 times per week. Exercise interventions increased the VO_2max by about 3 ml/kg/min (a little < 1 MET; 1 MET is about 3.5 ml/kg/min). Because resistance training is a relatively new mode of exercise in the CAD population, only three resistance training studies were included in the meta-analysis; however, the results among the three resistance interventions did not vary significantly from the aerobic training intervention results. Length of training and whether or not the program was started within 3 months of a cardiac event had significant positive impacts the VO_2max.[8] The meta-analysis did not examine the relationship of improved exercise capacity on outcomes such as mortality. However, three large clinical trials found that for every 1-ml/kg/min increase in VO_2max, there was an approximate 10% decrease in cardiovascular mortality for women and men with CAD.[9,10] Furthermore, several large observational studies have provided evidence that increased aerobic capacity of 1-MET is associated with a 12–17% increase in survival in women and men with CAD.[11-13] These findings stress the importance of early referral to exercise programs for individuals with newly diagnosed CAD in order to increase exercise capacity and decrease mortality in this population.

INFLAMMATION AND ENDOTHELIAL FUNCTION

One of the most exciting benefits of exercise comes from its action against inflammation and improvement of endothelial function. Atherosclerosis occurs from the interaction of inflammation and the endothelium. Normally, the endothelial cells that line healthy endothelium resist leukocyte adhesion (an event that marks the atherosclerotic plaque formation). However, in the presence of cardiovascular risk factors, leukocytes adhere to the endothelium, causing plaque formation. In the active plaque, macrophages and T-lymphocytes produce proinflammatory cytokines such as interlukin 6 and 8 and tumor necrosis

factor. These elements propel the plaque toward the point of rupture and thrombotic complications. Increased production of proinflammatory cytokines increases systemic markers of inflammation such as C-reactive protein.[14,15] A common biomarker of inflammation in the cardiac population is C-reactive protein. Increased levels of high-sensitivity C-reactive protein have been identified as a risk factor for CAD, as well as an independent predictor of CAD events.[16-18] Milani et al. (2004) found that a 12-week aerobic exercise training program lowered high-sensitivity C-reactive protein levels by an average of 36%. Measures of endothelial function were not included in the analysis, but the authors did report that VO_2max increased by 9% in the exercise training group. Both the change in C-reactive protein levels and VO_2max were significantly different than the control group. These changes were maintained even after the authors controlled for confounding factors such as statin therapy and weight loss.[19]

Healthy endothelium produces many substances that are vital to overall vascular wall health, tone and the delicate balance between prothrombosis and anticoagulation.[20] Nitrous oxide (NO) is synthesized in the endothelium via endothelial nitrous oxide (eNOS) and is responsible for maintenance of vascular tone through its ability to produce vasodilatation in response to shear stress. Once plaques have formed, the eNOS system is disrupted and NO bioavailability is decreased leading to further deleterious effects on the endothelium and vasomotor function. As bioavailability of NO is diminished, the vessel is wracked with abnormal vasoconstriction. Exercise upregulates eNOS protein expression and phosphorylation in patients with CAD.[21,22] The effects of the increased levels of eNOS are apparent in the vessel's ability to relax and dilate, even in the presence of strong chemical vasoconstrictors.[23] Exercise was shown to be as efficacious as and more cost effective than percutaneous coronary intervention (PCI) in individuals with stable CAD.[24] Fifty participants randomized to 12-months of aerobic exercise training had a higher event-free survival rate and increased VO_2max compared to 50 participants randomized to PCI (e.g. angioplasty, stent). Because of its effects on inflammation and endothelial function, exercise can slow progression of CAD.[25] The important physiologic effects of exercise cannot be overemphasized to individuals with known CAD.

SAFETY CONSIDERATIONS

Despite the strong evidence supporting the benefits of exercise, some still question the safety of prescribing exercise in the CAD population. However, multiple studies have documented the safety of supervised exercise in the CAD population. Data collected from the AHA across the 1980s and 1990s indicated that the likelihood of a serious event such as cardiac arrest, acute myocardial infarction, or cardiac death was 8.6, 4.5 and 1.3 per 1,000,000 patient-hours of exercise therapy. The 2007 Scientific Statement from the AHA estimated the risk of any major cardiovascular complication to be 1 per 60,000 to 80,000 hours of supervised exercise therapy.[26] Certainly, clinicians should be mindful of the possibility of serious adverse events during exercise; however, this should not dissuade clinicians from prescribing exercise as it is the cornerstone for cardiac rehabilitation and provides benefits to many of cardiac rehabilitations core components. With a background in the benefits of exercise to CAD patients, the remaining sections will provide the reader with an introduction to modern cardiac rehabilitation programs.

CARDIAC REHABILITATION DEFINITION AND GOALS

Over two decades ago, the U.S. Department of Health and Human Services, Agency for Healthcare Policy and Research (AHCPR) published clinical practice guidelines for cardiac rehabilitation that used the following definition: "Cardiac rehabilitation services are comprehensive, long-term programs involving medical evaluation, prescribed exercise, cardiac risk factor modification, education, and counseling."[27] The key approaches used in cardiac rehabilitation services are education, counseling and behavioral modification.[27] This definition of cardiac rehabilitation holds true even today even as programs have expanded to cover more cardiac conditions. The goals of cardiac rehabilitation are to insure the best physical, psychological and social outcomes for the patient while slowing disease progression, reducing the risk of sudden cardiac death or reinfarction, and diminishing adverse psychological and social events. According to a 2007 AACVPR/ACC/AHA statement, cardiac rehabilitation eligible patients include: those patients with a primary diagnosis of myocardial infarction/acute coronary syndrome, coronary artery bypass graft, PCI, stable angina, heart valve surgical repair or replacement, heart or heart/lung transplantation surgery within the previous year. Most cardiac rehabilitation programs offer three phases.

CARDIAC REHABILITATION PHASES

INPATIENT (PHASE I)

Inpatient cardiac rehabilitation (phase I) occurs immediately following hospitalization for a cardiac event such as a myocardial infarction. The primary goal of phase I cardiac rehabilitation is to enhance the recovery time and reduce the risks of immobility, including orthostatic intolerance, muscle stiffness and wasting, and thrombus formation. In order to achieve the phase I goals, the cardiac rehabilitation team uses structured physical activity/exercise regimens, patient education, psychosocial support and active discharge planning. Activity is progressed within the first 24 hours of hospitalization to chair sitting, followed by self-care activities and even stair climbing prior to discharge. During activity progression the medical team monitors the patient's response to activity via heart rate response, systolic blood pressure response, electrocardiogram (ECG) rhythm stability and cardiac symptom stability. If the patient tolerates increase in activity without negative physical responses, patients are encouraged to exercise as they wish 2–4 times per day while hospitalized.

Because of the apprehension encountered during hospitalization following a cardiac event, patient education during phase I should be individualized to meet the patient's immediate concerns and questions. In general, topics will include the development of CAD and myocardial infarction, including symptom management; risk factor modification strategies,

especially related to smoking cessation, lipid management and nutritional counseling; and discharge instructions for home activities, including resumption of sexual activity, return to work and outpatient cardiac rehabilitation referral. The education received during phase I only serves as a starting point and is not meant to stand alone during the patient's recovery. All educational objectives should be reinforced during subsequent phases of cardiac rehabilitation.

Psychosocial support during phase I cardiac rehabilitation should focus on the family structure as the time period immediately surrounding a cardiac event is marked with stress and anxiety for both patients and family members. It is argued that the immediate hospitalization period is less than optimal for patient learning; family involvement allows family members to review and reinforce educational sessions presented by the rehabilitation team. Therefore, in addition to the education topics listed above, the rehabilitation team should provide information about available outpatient cardiac rehabilitation programs and other local support groups. Information on smoking cessation, lipid management and nutritional counseling are also best offered to family units, as adequate social support is crucial to recovery and risk factor modification.

EARLY OUTPATIENT (PHASE II)

Early outpatient cardiac rehabilitation should begin as soon as possible following hospital discharge in order to continue the clinical assessment and reinforce the risk factor modification and lifestyle change education, and psychosocial support that was initiated during the inpatient phase. Early outpatient rehabilitation requires a referral from the patient's cardiologist or primary care physician. The referral must contain the specific patient diagnosis, relevant history and indicate the need for phase II support. The physician referral is required for insurance reimbursement and preauthorization is usually required, so it is important to initiate the phase II referral quickly following a cardiac event. Reimbursement from insurance providers varies, but in general, phase II services are covered for the following cardiac events: acute myocardial infarction within the previous 12 months; coronary artery bypass grafting; or stable angina.

During phase II rehabilitation, improved exercise tolerance is a key objective. The cardiac rehabilitation team designs a program that emphasizes cardioendurance as well as flexibility. During early outpatient exercise training, it is crucial that the team provide continuous ECG monitoring and be readily available in the event of a cardiac emergency, although, as stated earlier, the cardiac event rate for rehabilitation programs is very low. The typical exercise prescription used in the phase II programs is outlined previously. Patients will begin with endurance training and add in weight training as appropriate for their given diagnosis (e.g. about 12 weeks for postsurgical patients and 4–8 weeks for acute myocardial infarction patients). Continued clinical assessments and risk factor modification education are other key components to phase II cardiac rehabilitation. Patients will continue education and support related to the core components of the cardiac rehabilitation program: nutritional counseling, weight management, blood pressure management, lipid management, diabetes management, tobacco cessation, use of preventive medications and psychosocial management.[26,28] Since other chapters cover the content of the core components, the authors refer you to those chapters for specific patient management issues.

LONG-TERM OUTPATIENT (PHASE III)

The final phase of cardiac rehabilitation involves transition to the maintenance of a healthy lifestyle, incorporating all of the education and fitness training previously achieved during the earlier phases of cardiac rehabilitation. Phase III cardiac rehabilitation is rarely reimbursed by insurance carriers. In general, phase III provides much less interaction with cardiac rehabilitation team members and the emphasis is on the patient's self management skills, although there is tremendous variation in the scope of services in individual cardiac rehabilitation programs. Due to this, it is essential that physician providers are aware of specific community resources.

CARDIAC REHABILITATION CORE COMPONENTS

During the past two decades cardiac rehabilitation programs have become more comprehensive in regards to secondary prevention strategies. The American Heart Association/American Association of Cardiovascular and Pulmonary Rehabilitation (AHA/AACVPR) Scientific Statement advocate several core components of a cardiac rehabilitation program.[26] Given the space constraints within this textbook, the core components can only be summarized; therefore, the authors strongly encourage the reader to review this statement which provides the full scope of practice expected of a cardiac rehabilitation program as well as the scientific evidence supporting the group's recommendation. Knowledge of these core components is essential as one considers patient referral to local cardiac rehabilitation programs, or if one is designing a new cardiac rehabilitation program.

MEDICAL ASSESSMENT

Initial assessment in the cardiac rehabilitation program consists of a complete medical history with emphasis on current and prior cardiovascular and surgical diagnoses and procedures (including left ventricle function), pertinent comorbidities (e.g. peripheral arterial disease, cerebral vascular disease, pulmonary disease, kidney disease, diabetes mellitus, depression), patient specific cardiac symptoms (e.g. angina, dyspnea, fatigue), current medications (including dosing schedule and adherence), immunization history (including most recent influenza and pneumonia vaccinations), cardiovascular risk profile, and educational history (including learning style preferences). The physical exam consists of a complete cardiopulmonary assessment, including a 12-lead resting ECG, resting pulse and blood pressure measurements, inspection of the lower-extremities for edema and peripheral pulses, postsurgical wound site inspection and cognitive testing. Follow-up assessment focus should be based on individual patient needs and as outlined below.

PSYCHOSOCIAL ASSESSMENT AND MANAGEMENT

Similar to medical assessment, psychosocial status should be initially evaluated, in particular noting presence of depressive

symptoms, anxiety, sexual dysfunction, substance abuse, diminished health related quality of life, and cognitive impairment. Periodic re-evaluation of psychosocial variables should be completed per specific clinic protocol, or as dictated by patient status. Psychosocial assessment is frequently not emphasized despite the fact that many psychosocial factors (e.g. depression, diminished quality of life and cognitive impairment) have a significant impact on morbidity and mortality following a cardiac event. Multiple instruments are available for clinic use that have brief administration times and have documented reliability and validity within the cardiac population. Appropriate medications and therapies should be identified and patients should be managed in conjunction with their primary care physicians for any psychosocial concerns.

NUTRITION

Nutritional counseling is critical for achievement of many goals within the cardiac rehabilitation program. Nutrition counseling plays a key role in the management of weight, blood pressure, diabetes and other comorbid illnesses. Initial and periodic assessments should be done in order to document caloric intake, saturated, trans-fat, cholesterol and sodium intake. Assessment of eating habits is necessary in order to appropriately prescribe diet modifications and educate patients about pertinent dietary goals based on individual patient needs.

RISK FACTOR MANAGEMENT

Risk factor management is a broad core component that covers several cardiovascular risk factors. *Lipid management* and *smoking cessation* are discussed at great length in other chapters of this textbook, so the authors refer the reader to those chapters. *Blood pressure* should be evaluated at every cardiac rehabilitation and clinic visit, as well as assessment of diet, medication and exercise adherence. Orthostatic hypotension should be ruled out prior to the start of the exercise component of the cardiac rehabilitation program. Blood pressure goals should be based on current Joint National Committee (JNC) report guidelines. According to the latest guidelines, for patients with CAD, an appropriate goal blood pressure is 130/80 mm Hg. *Weight management* and body mass index (BMI) calculations should be measured at every clinic and cardiac rehabilitation visit. Reasonable weight loss goals and maintenance plans should be established early in the cardiac rehabilitation program. In general, the goal BMI should be 18.5–24.9 kg/m^2, with a waist circumference less than 40 inches for men and less than 35 inches for women. Successful management of blood pressure and weight will primarily depend upon patient adherence to nutritional and exercise interventions, so the importance of patient education and adherence interventions cannot be emphasized enough in this section. Finally, the *management of other chronic illnesses,* such as diabetes and chronic obstructive lung disease, is essential in the management of cardiovascular risk factors, as well as the reduction of morbidity and mortality following a cardiac event. Comorbid chronic illnesses should be assessed during the initial visit to the cardiac rehabilitation program and managed in conjunction with the patient's primary care provider or designated specialist.

EXERCISE TRAINING

In general, cardiopulmonary stress testing is performed prior to admission into a cardiac rehabilitation program. The stress test is performed to determine maximal heart rate and to prevent ischemia, arrhythmia and other important symptoms from occurring during the cardiac rehabilitation sessions. The cardiopulmonary stress test should be performed using all of the patient's current medications. Based on cardiopulmonary stress testing results, an exercise prescription is written. The appropriate dose of exercise is determined from four factors: (1) the mode of activity, (2) frequency, (3) duration and (4) intensity of the activity.

The mode of activity will consist of aerobic (treadmills, stationary cycles and elliptical trainers are most commonly used in cardiac rehabilitation programs) or resistance (free weights, weight machines and bands are most commonly used in cardiac rehabilitation programs). In regards to frequency and duration, patients are advised to exercise for at least 30 minutes (preferably 45–60 minutes) most days of the week (at least 5, but preferably 6 or 7). Aerobic training should take place 4–5 times per week and resistance training 2–3 times per week (on nonconsecutive days). The intensity of the prescription is usually 70–85% of the peak heart rate (a measure that corresponds to about 60–70% of peak oxygen consumption achieved during the stress test.[29] If stress tests results are not available prior to initiation of cardiac rehabilitation, clinicians are advised to exercise patients at a moderate intensity (i.e. patients can still speak during the exercise session, or a rating of 12–14 on the Borg Scale).

Warm-Up

Exercise should be preceded by a warm-up period of between 5 minutes and 10 minutes in order to bring the resting heart rate gradually up to a rate that is approximately 20 beats per minute lower than the lower end of the target heart rate range. A common method of warm-up is performing the prescribed mode of exercise at a lower intensity (e.g. walking at a slower rate on the treadmill, or pedaling at a slower rate on the stationary cycle).

Cool-Down

Following the exercise session, a cool-down period is recommended in order to prevent postexercise complications such as hypotension and arrhythmias. Similar to the warm-up, patients can be advised to perform the cool-down using the same mode of exercise at lower intensities for about 5–10 minutes.

MEDICATION ASSESSMENT AND MANAGEMENT

Adherence to medications prescribed by all clinicians should be assessed at the initial visit and all subsequent visits. Education and counseling are crucial to adherence and therefore ongoing education and counseling is strongly recommended at all cardiac rehabilitation visits. Educational materials should be designed to take into account individual learning styles, allowing for easy tailoring of educational interventions based on individual need.

CLINICAL POPULATION CONSIDERATIONS

POSTSURGICAL

Cardiac rehabilitation should be initiated within 48 hours of surgery, beginning with range-of-motion exercises. Referral to a phase II cardiac rehabilitation program should be initiated during the hospitalization in order to attain insurance clearance prior to discharge. Patients can begin outpatient cardiac rehabilitation 1–2 weeks following surgery, providing there are no surgical complications. Vigorous aerobic activity involving the upper body should be avoided until they have received surgical clearance (the length of time will vary based on the type of surgery). In general, postsurgical patients can begin light-hand weights/bands following surgical clearance; however, in the case of traditional bypass surgery, traditional weight training may need to be deferred for up to 12 weeks in order to allow for sternal healing.

ANGIOPLASTY (WITH OR WITHOUT STENT)

Cardiac rehabilitation should be initiated 7–10 days following this procedure. In general, the exercise prescription listed above is appropriate for angioplasty patients with or without stent placement. If complications occurred during the postprocedure period, adjustments to the exercise prescription should be made according to individual need.

CLAUDICATION/PERIPHERAL ARTERY DISEASE

Patients who suffer from claudication are much more likely to drop out of cardiac rehabilitation programs secondary to issues with discomfort during exercises. Patients with claudication should walk to the point of maximum tolerable pain, followed by a period of rest and then resume walking. Patients should be encouraged to walk 3 or more times per week, but aerobic exercises, such as cycling that are often much better tolerated within this population, should be included in the exercise prescription in order to prevent patient attrition.

ATRIAL FIBRILLATION

Patients with atrial fibrillation are prescribed heart rate controlling medications; therefore, should not use heart rate as an indicator of intensity and should instead rely on other signs of intensity. Alternative methods to measure intensity, such as the ability to talk or sing during exercise or a Borg scale rating of 12–14 should be emphasized by the cardiac rehabilitation team. Furthermore, patients with chronic atrial fibrillation are often on anticoagulants such as warfarin. These individuals should be monitored to prevent falls and counseled to avoid contact sports.

HYPERTENSION

Patients with hypertension should be monitored closely during cardiac rehabilitation. First and foremost, hypertension should be controlled prior to the initiation of cardiac rehabilitation. According to the American Association of Cardiopulmonary Rehabilitation, individuals with a resting systolic blood pressure of greater than 200 mm Hg or a resting diastolic blood pressure of greater than 115 mm Hg should not be allowed to exercise.[30] Exercise intensity that ranges from 40% to 70% peak oxygen consumption is advised until the blood pressure is optimally controlled. Resistance training should be delayed until optimal blood pressure control is achieved and, when initiated, single-limb exercises are preferred because of the lower rise in blood pressure.[31]

DIABETES

Diabetic patients greatly benefit from cardiac rehabilitation because of the comprehensive nature of these programs. Cardiac rehabilitation programs can effectively decrease the complications of diabetes. However, when enrolling a diabetic patient, there are several important points to remember: first and foremost, diabetic patients, in general, suffer from silent ischemia and are at elevated risk for cardiac arrhythmias. Finally, monitoring pre-exercise and post-exercise glucose levels is a very important safety consideration during a diabetic patient's cardiac rehabilitation program.

ELDERLY

Cardiac rehabilitation in elderly patients can increase muscle strength, flexibility, balance, functional status and mood. In general, the exercise prescription given in this chapter can be followed with elderly patients. However, exercise goals may need to be modified to better fit the elderly patient's initial level of endurance, strength and flexibility. For example, initial resistance training may need to be lighter than recommended and progressed via increased repetitions instead of increased resistance.

REFERRAL

Low patient referral rate continues to be a major barrier for cardiac rehabilitation programs. In particular, women, elderly, non-white ethnicity and low medical insurance coverage populations are at particular risk of non-referral to appropriate cardiac rehabilitation programs.[28] Most frequently, referral to cardiac rehabilitation depends on the cardiologist and primary care physician. Physician education regarding the benefits of cardiac rehabilitation and location of local programs is crucial to improving referral rates. Also key to referral is physician accountability and adequate physician support in order to attain insurance reimbursement for the cardiac rehabilitation services. As the outcomes of cardiac rehabilitation are better disseminated it is hoped that insurance reimbursement for these services will improve, but in order to disseminate positive outcomes, cardiac rehabilitation must have patients enrolled and achieving these supportive results.

REIMBURSEMENT ISSUES

In spite of a documented 25% reduction in all-cause and cardiac mortality following cardiac rehabilitation participation,[29,32,33] reimbursement for cardiac rehabilitation continues to be a struggle. In order to combat some of the reimbursement issues, the ACC, AHA and AACVPR have issued guidelines for performance measures on cardiac rehabilitation programs.[34]

Initial findings are favorable regarding the cost effectiveness of cardiac rehabilitation, but more data are needed in order to change insurance reimbursement in the future.

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Section 14

PREVENTIVE STRATEGIES FOR OTHER CARDIOVASCULAR DISEASES

Chapter 110

Prevention of Heart Failure

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Chapter Outline

- Staging of Heart Failure
  - Stage A Heart Failure
  - Stage B Heart Failure
- Future Perspectives

INTRODUCTION

Heart failure is a clinical syndrome due to heterogeneous systemic and cardiac insults resulting in hemodynamic disturbances, neurohormonal dysregulation, leading to subsequent decreased cardiac function and multi-organ dysfunction. Data from the Framingham Heart Study demonstrated that heart failure is primarily a disease of the elderly, with an incidence of 10 per 1,000 population over the age of 65 years.[1] Nevertheless, the estimated lifetime risk for developing heart failure is 20% for both males and females. Even in the absence of antecedent myocardial infarctions, the lifetime risk is 1 in 9 for men and 1 in 6 for women.[1] Meanwhile, the number of heart failure related ambulatory visits and hospitalizations have steadily increased likely as a consequence of better survival due to advancements in treatment. In the United States, heart failure accounted for over 3.4 million ambulatory care visits, 1.1 million hospital discharges in 2007 and mortality approaching 300,000 in 2006 with 1 in 8 deaths having heart failure mentioned on the death certificates.[2] Over the past several decades, progress has been made to reduce morbidity and mortality of disease progression in patients with overt heart failure with neurohormonal blockade, internal cardioverter defibrillator prophylaxis, cardiac resynchronization therapy, mechanical circulatory assist devices and heart transplantations. Nevertheless, such benefit has been modest for patients and costly for health care systems.

Like detecting cancers only at their metastatic stages, the majority of "heart failure" cases present at the late stages of cardiac disease as a result of longstanding hypertension, coronary heart disease, valve disease, diabetes mellitus or primary cardiomyopathies. The prevention of heart failure encompasses primary prevention of cardiovascular disease with risk factor reduction, early recognition of at-risk patients with better understanding of how to protect them from developing heart failure, as well as the detection and management of asymptomatic structural heart diseases.

STAGING OF HEART FAILURE

Over the past decade, the American College of Cardiology (ACC) and the American Heart Association (AHA) have promoted a staging concept of heart failure by identifying four stages with the main objective to emphasize the disease as a continuum in both the development and progression of the disease (Table 1).[3] The " at-risk" stages describe patients who

TABLE 1

Stages of heart failure

Classification of heart failure by stages[3]		
Stage	*Description*	*NYHA Class*
A	Patients at high risk for developing heart failure • Hypertension, atherosclerotic disease, diabetes, obesity, metabolic syndrome, smoking • Exposure to cardiotoxins • Family history of cardiomyopathy	Not applicable
B	Development of structural heart disease without symptoms • Previous myocardial infarction • Left ventricular remodeling — Left ventricular hypertrophy — Impaired left ventricular function • Asymptomatic valvular disease	I
C	Symptomatic heart failure • Known structural heart disease with symptoms of heart failure	II–III
D	Refractory end-stage heart failure • Severe symptoms despite maximal medical therapy	IV

have a structural normal heart and are at high risk due to co-morbidities and cardiotoxic exposures that predispose the development of heart failure (Stage A), or who have structural abnormalities such as left ventricular hypertrophy or impaired left ventricular function (Stage B).[4] The later two stages describe patients with current or past symptoms of heart failure (Stage C) or patients with refractory heart failure symptoms requiring advanced "salvage" therapies or end-of-life care.[4]

Although the staging scheme implies the development and progression of heart failure as a continuum, our understanding of the pace and mechanisms of disease progression is still rudimentary. A classic example is of two men of the same age, both with hypertension, dyslipidemia, and are actively smoking (Stage A). Both suffer from a large myocardial infarction resulting in severe left ventricular dysfunction where one remains largely asymptomatic (Stage B) and the other develops symptoms of heart failure (Stage C). Prior to the index event the patients can be prognostically equivalent, yet their subsequent morbidity and mortality is likely disparate. Clinical focus on well-described cardiovascular risk factors (Stage A) and asymptomatic structural heart disease (Stage B) are therefore ideal targets for the prevention of heart failure.

STAGE A HEART FAILURE

Screening for and early detection of any disease is quite problematic in that one must define the population most at risk. Large-scale epidemiologic studies have provided population-attributable risks for the development of heart failure.[5-7] Established and hypothesized risk factors of heart failure are included in Table 2 (adapted from Reference 8).

TABLE 2

Established and hypothesized risk factors of heart failure

Major nonmodifiable risk factors	*Minor clinical risk factors*
• Age, Race, Sex	• Smoking
• Family history	• Dyslipidema
	• Sleep-disorders
Major clinical risk factors	• Chronic kidney disease
• Hypertension, left ventricular hypertrophy	• Albuminuria
• Coronary artery disease, myocardial infarction	• Homocysteine
	• Immune activation
	• Natriuretic peptides
• Diabetes mellitus	• Anemia
	• Dietary risk factors
	• Increased heart rate
	• Sedentary lifestyle
	• Low socioeconomic status
	• Psychological stress
Toxin risk precipitants	*Genetic/Molecular risk predictors*
• Chemotherapy	• SNP (a2cDel322-325, b1Arg389)
• Cocaine	• Cytoskeleton proteins
• NSAIDS	• Sarcomeric proteins
• Thiazolidinediones	• Intermediate filaments
• Doxazosin	
• Alcohol	*Morphological risk predictors*
	• Increased left ventricular internal dimension, mass
	• Asymptomatic left ventricular dysfunction
	• Left ventricular diastolic dysfunction

Age, Race and Gender

Advancing age is a natural risk factor that is becoming more clinical apparent as our aging population grows where elderly patients are more likely to have advanced heart failure on initial presentation and less likely to receive effective or respond appropriately standard medical therapies. However, it is important to emphasize that even though the incidence and prevalence of heart failure increases with age, the lifetime risk of developing heart for all patients after the age of 40 years remains 20%.

The impact of race and gender on risk of developing heart failure deserves some discussion, as it is likely that these nonmodifiable risk factors are linked to confounding factors of heightened risks rather than the influence of race and gender per se. This is an important point to make, as major focus have been made to develop unique management strategies for these patient populations without supportive evidence. For example, non-Hispanic blacks have higher rates of hypertension and hypertensive heart disease.[2] Men have increased incidence of heart failure most likely due to the increased prevalence of coronary heart disease.[8] Women are at increased risk of developing hypertension, obesity, and can be socioeconomically disadvantaged.[9,10] They may also have longer life-expectancies, which may further provide clues as to why women are at increased risk of developing heart failure with preserved left systolic function.[11] To date, there is limited data to suggest that age, race and gender should influence treatment or preventive strategies in heart failure.

Family History

Close to 90% of patients with hypertrophic cardiomyopathy and 30–50% of patients with dilated cardiomyopathy are familial.[12,13] Epidemiologic studies suggest that the prevalence of hypertrophic and dilated cardiomyopathies may be higher than clinically recognized.[14] Prospective data have suggested that treatable asymptomatic dilated cardiomyopathy was identified in 4.6% of relatives of patients with known dilated cardiomyopathy.[15] Genetic defects have been associated both forms of cardiomyopathy, although they are far from comprehensive or definitive. Nevertheless, while routine comprehensive genetic screening is still controversial, a detailed family history is recommended as part of clinical evaluation for those at risk of developing heart failure.[8]

Hypertension

Elevated systolic (> 140 mm Hg), diastolic (> 80 mm Hg) and pulse pressure (> 60 mm Hg) have been associated with increased risk of heart failure[16] The relationship for systolic and pulse pressure was stronger where 1-standard deviation increment (20 mm Hg) in systolic pressure and 1-standard deviation (16 mm Hg) in pulse pressure conferred a 56% and 55% increase risk in heart failure respectively. These associations were unrelated to age, duration of follow-up or initiation of treatment during follow-up.[16] Long-term hypertension increases the risk of heart failure primarily due to the development of left ventricular hypertrophy and atherosclerotic heart disease. Hemodynamically, hypertension increases

afterload, which over time can lead to cardiomyocyte hypertrophy and the development of left ventricular hypertrophy (a strong independent risk factor for developing heart failure). In addition, hypertension may further lead to myocardial fibrosis and loss of contractile tissue via increased incidence of myocardial infarction. Clinical studies have consistently demonstrated that optimizing blood pressure control with medical therapy can reduce the incidence of heart failure by 50%.[17-20]

There is also abundant data to suggest that therapeutic lifestyle changes can prevent the development of hypertension, including aerobic exercise and diet modification. Low-dose diuretics are likely the most effective first-line treatment in preventing heart failure, although by default they are also reducing the opportunity of congestion due to their mechanisms of action.[18] However, the paradigm still remains that agents should be chosen based on the patients concomitant co-morbidities such as the use of angiotensin converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) for patients with diabetes, coronary artery disease or left ventricular dysfunction.

Obesity, Diabetes Mellitus, Dyslipidemia and the Metabolic Syndrome

There has been a rapid increase in the percentage of overweight and obese American over the past 25 years. The prevalence of overweight adolescents and obese males as significantly increased from 1999 to 2004.[21] Framingham data has demonstrated that the increased body mass index (BMI) was an independent risk factor for developing heart failure where males had a 5% and females had a 7% increased risk with each 1 kg/m^2 increment of BMI.[22] Weight loss, proper diet and increased physical activity have been associated with cardiovascular risk factors such as hypertension, hyperlipidemia and diabetes type II. Interestingly, there has been a growing body of evidence that excessive body fat in patients with established may confer a lower all-cause and cardiovascular mortality, known as the obesity paradox. It is estimated that in patients with established heart failure, overweight and obese patients with heart failure may be 19% and 40% less likely to succumb to cardiovascular mortality respectively, when compared to that in patients with heart failure patients normal BMI.[23] These data are misleading and confounded by selection bias where obese/overweight patients may present with heart failure earlier than patients with normal BMI and patients with normal BMI and heart failure may have a relatively lower BMI due to cachexia of chronic disease. Nevertheless, weight reduction with physical activity is associated with decrease cardiovascular risk factors, insulin resistance diabetes and better lipid profiles.

The presence of underlying diabetes mellitus is associated with increased risk of developing heart failure itself as well as in concomitant with coronary heart disease and hypertension.[24] Observational data has demonstrated that diabetic men and women are 2.4 and 5.0 times more likely to develop heart failure independent of preexisting hypertension or coronary heart disease respectively.[25] Patients with diabetes mellitus have been shown to have incremental increased risk of developing heart failure with worse glycemic control where each 1% increase in hemoglobin A1c was associated with 8%.[26] The United Kingdom Prospective Diabetes Study demonstrated that blood pressure control with ACE inhibitors or beta-blockers in patients with diabetes mellitus is cardioprotective: hypertensive diabetics who demonstrated a 10 mm Hg systolic drop in blood pressure had a 56% reduced risk of developing heart failure.[27] However, when looking at tight glycemic control, there was little difference in the tight (blood glucose < 108 mg/dL) versus conventional (blood glucose < 270 mg/dL).[28] Despite these data, it is still generally agreed that strict glycemic control is preferable in the prevention of cardiovascular events and heart failure. Thus, the preventative heart failure strategy in patients with diabetes is optimal blood pressure with ace inhibition or beta-blockade as well as optimal management of blood glucose levels.

It has been well established that hypercholesterolemia is associated with increased risk of coronary artery disease. Elevated total cholesterol has not been shown to be a strong predictor of developing heart failure; however, dyslipidemia (ratio of total cholesterol to high density lipoprotein cholesterol) has been highly associated with the development of heart failure.[29,30] Statin therapy has been shown to reduce cardiovascular morbidity and mortality in primary[31,32] and secondary prevention trials.[33,34] It is believed that statins may exert there beneficial effect independent of simple cholesterol lowering capacity.[35] However, to date there is no data demonstrating that statins prevent heart failure or in patients with asymptomatic left ventricular dysfunction there role is even less clear. However, aggressive treatment with lipid-lowering medications for hyperlipidemia or dyslipidemia is a reasonable strategy in the prevention of heart failure.

Over the past several years, focus has been made on the increased risk of developing cardiovascular disease and the metabolic syndrome. The metabolic syndrome is characterized by dyslipidemia, impaired glucose tolerance, insulin resistance, obesity and hypertension. Recent meta-analysis suggested that the increased risk and accelerated disease progression found in patients with the metabolic syndrome is primarily due to the individual components rather than the syndrome itself.[36]

Coronary Artery Disease

Accounting for up to 70% of systolic heart failure, coronary artery disease is a major risk factor for the development of heart failure and a key target for hear failure prevention. In patients with coronary artery disease, many treatments, such as ACE inhibitors, beta-blockers, antiplatelet agents and statins, have been proven to be cardioprotective and prevent the progression to symptomatic heart failure. In select patients aggressive therapy is mandated. Over 15 million people in the United States have a history of myocardial infarction, symptomatic coronary artery disease or both.[1] The 5-year risk of developing heart failure after an acute myocardial infarction is 7% and 12% for men and women respectively, between the ages of 40 and 69.[1] For patients at the age of 70 years, the risk is 22% and 25% respectively.[1] The combination of cardioprotective medications as well as therapeutic lifestyle changes should be pursued aggressively in patients with coronary artery disease to reduce the risk of heart failure.

Tobacco abuse is the single most preventable of morbidity and mortality in the United States. Tobacco abusers have a 47% higher risk of incident heart failure compared to prior and nonsmokers. Interestingly, this same study demonstrated that patients who quit smoking 1-year prior had a 50% reduction in cardiovascular death compared to patients who continued to smoke.[37] Patients who are current tobacco abusers should be referred for cessation programs and offered pharmacological therapies to best their chances of cessation.

An unfortunate and frequent complication of many chemotherapeutic agents is cardiotoxicity. Anthracyclines, alkylating agents, antimetabolites, antimicrotubule agents, tyrosine kinase inhibitors and proteasome inhibitors have been associated with left ventricular dysfunction, ischemia, hypertension and heart failure (Table 3).[38] Risk factors for chemotherapy induced cardiotoxicity are poorly understood but may include advanced age, male gender, overweight, combination therapy, mediastinal radiotherapy, prior cardiac disease, hypertension, history of liver disease as well as dosage and schedule of chemotherapeutic administration. Currently, there are no guidelines for long-term monitoring. Cardiac imaging is the gold standard for detection of chemotherapy-induced cardiotoxicity. There are several industry chemicals that are well recognized to cause specific cardiomyopathies, but screening modalities are often poor and based on recall of known environmental exposures and lack of more specific clinical testing or histopathologic demonstration for validation.

There are other prescription drugs or over-the-counter drugs that are recognized to be associated with the development of cardiomyopathies such as ephedra-containing drugs or health foods (e.g. for body-building, weight loss).[39] In contrast, there is an extended list of medications that are thought to cause "heart failure", although there is a distinction between direct cardiotoxic effects of specific drugs versus the propensity to develop fluid retention that is exacerbated by underlying cardiac insufficiency. Some common examples include calcium channel blockers, thiazolidinediones, steroids, hormone replacement therapy (estrogen, progesterone and testosterone), nonsteroidal anti-inflammatory drugs, and newer drugs like pregabalin and dronedarone.[40] The reason why they may not possess direct cardiotoxic effects can be explained by the fact that withdrawal of these medications following episodes of fluid retention (particularly peripheral edema) may not result in long-term cardiotoxic sequelae.

TABLE 3

Chemotherapeutic agents associated with cardiotoxicity

Agent	*Cardiotoxicity*	*Incidence*
Anthracyclines		
Doxorubicin	LVD	3–26%
Epirubicin	LVD	0.9–3.3%
Alkylating agents		
Cyclophosphamide	LVD	7–28%
Ifosfamide	LVD	17%
Antimetabolite		
Capecitabine	Ischemia	3–9%
Fluorouracil	Ischemia	1–68%
Antimicrotubule agents		
Docetaxel	LVD	2.3–8%
	Ischemia	1.7%
Paclitaxel	Ischemia	< 1–5%
Tyrosine kinase inhibitors		
Bevacizumab	LVD	1.7–3%
	Ischemia	0.6–1.5%
	HTN	4–35%
Trastuzumab	LVD	2.28%
Dasatinib	LVD	2–4%
Sunitinib	LVD	2.7–11%
	HTN	17–43%
Erlotinib	Ischemia	2.3%
Sorafenib	Ischemia	2.7–3%
	HTN	5–47%
Proteasome inhibitor		
Bortezomib	LVD	2–5%

Abbreviations: LVD: Left ventricular dysfunction; HTN: Hypertension

Treatment for Stage A Heart Failure

Current emphasis on the treatment of Stage A heart failure remains to be aggressive risk factor modification for those at risk, and avoidance of cardiotoxic exposures. Much work is needed to better identify those at risk of disease progression to more advanced stages of heart failure, which may including genetic and proteomic evaluation as well as electrocardiography and advanced imaging techniques for at risk individuals so that appropriate patient identification for treatment is feasible.

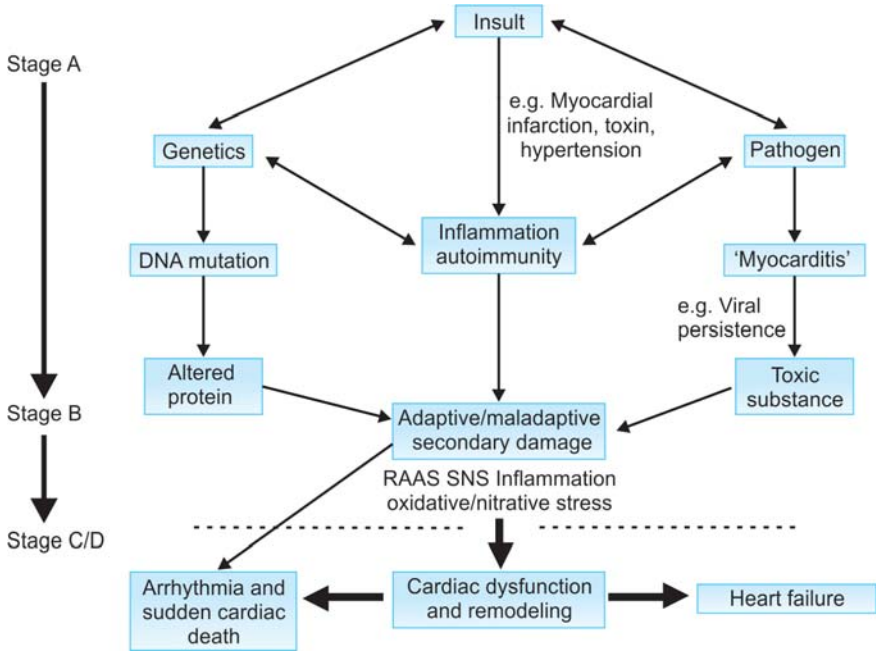
STAGE B HEART FAILURE

It is conceivable that patients with symptomatic heart failure were preceded by asymptomatic phase. "Stage B heart failure" is defined as the presence of structural heart disease without overt clinical presentation of signs and symptoms. Patients may have significant scar territory following a prior or silent myocardial infarction, progressive but preclinical valvular dysfunction, or asymptomatic left ventricular systolic dysfunction. An ill-defined combination of genetic, inflammation and autoimmune responses, and/or pathogen exposure can trigger progressive adaptive and subsequent maladaptive responses leading to development of symptoms (Flow chart 1). There are estimated 4-fold more patients with stage B heart failure than overt heart failure.[39] However, the true prevalence of stage B heart failure is unclear, even though this patient population represents a target that would greatly benefit from early intervention and prevention.

Asymptomatic Left Ventricular Systolic Dysfunction

In asymptomatic patients, the left ventricle enlarges to compensate for impaired contractility in maintaining an adequate stroke volume. Hence, significant cardiac pathology ensues, and a negative impact of left ventricular systolic dysfunction even in the absence of overt symptoms has been demonstrated in several large-scale studies. The SOLVD investigators found that almost 16% patients with asymptomatic left ventricular dysfunction died within 37 months—90% were cardiovascular

FIGURE 1: Pathophysiology of disease progression of at-risk patients (Stage A) from asymptomatic (Stage B) to symptomatic (Stages C and D) heart failure



deaths.[40] Kaplan-Meier analyses from the Framingham studies have shown 60% increased risk in patients with asymptomatic left ventricular systolic dysfunction.[41] Interestingly, almost half of the patients with asymptomatic left ventricular systolic dysfunction did not develop symptoms of clinical heart failure prior to their death, in part because symptomatic presentation depends on subjective perception as well as clinical recognition of disease progression and also in part because of the potential of sudden cardiac death due to arrhythmias (Table 4).

Current guidelines recommended the use of ACE inhibition and to a lower level of evidence antiadrenergic therapy to impede maladaptive left ventricular remodeling and, in hopes, to improve mortality and morbidity.[4] At 3-year follow-up, patients treated with ACE inhibition demonstrated reduced combined end-point of hospitalization or death in patients with asymptomatic left ventricular systolic dysfunction.[40] However, it is often a challenge for such patients to consistently take ACE inhibitors as drug therapy due to their lack of clinical symptoms.[42] Several obstacles, such as diagnostic uncertainty and unreliable physical exam signs, have been discussed in the literature as for possible reasons for the under-prescription of these life-saving medications.[43,44]

Many screening modalities for asymptomatic left ventricular systolic dysfunction have been evaluated in the literature: clinical scores, electrocardiograms, biochemical markers and imaging markers. However, several problems have been encountered: the poor specificity in an asymptomatic population, selecting the correct population and developing cost-effective screening strategies. Ideally, a screening test would possess a high specificity and positive predictive value to minimize false positives leading to unwarranted, more invasive testing.

TABLE 4

Heart Failure Society of America, Guideline recommendations for management of Stage B heart failure with left ventricular systolic dysfunction

	Recommendation	*Strength of evidence*
5.1	Regular exercise, optimize weight, blood pressure, diabetes control	C
5.2	Smoking cessation	B
5.3	Alcohol abstinence	C
5.4	Optimal blood pressure control	B
5.5	ACE inhibitors for LV systolic dysfunction (LVEF ≤ 40%)	A
5.6	Angiotensin receptor blockers for ACE inhibitor-intolerant patients (not combined)	C
5.7	Beta-blockers in post-MI Beta-blockers in non-post-MI	B C

Electrocardiogram and Biomarker Evaluation

Plasma B-type natriuretic peptide (BNP) and amino-terminal pro-B-type natriuretic peptide (NT-proBNP) have demonstrated diagnostic usefulness in only certain clinical settings. For example in patients presenting with an acute myocardial infarction, NT-proBNP measured 2–4 days after the index event was found to be independently associated with left ventricular function and 2-year mortality.[45] However, its clinical utility in a large, asymptomatic population is uncertain.

Electrocardiogram and natriuretic peptide testing have a high sensitivity but a relatively poor specificity for detecting left ventricular systolic dysfunction. When compared with each other, regardless of the natriuretic peptide cut-off point, BNP had a higher specificity than electrocardiograms with similar sensitivities.[46,47] When used in combination with each other, there was no difference in sensitivity and only limited improvement in specificity.[43] Some data suggest that both NT-

proBNP and BNP have value in diagnosing left ventricular systolic dysfunction in high-risk subgroups such as patients on diuretics, history of a previous myocardial infarction, angina, hypertension, or diabetes.[48] However, elevations in natriuretic peptide levels have been associated with pathologies other than left ventricular systolic dysfunction, such as diastolic dysfunction, atrial fibrillation, coronary artery disease, valvular heart disease and primary cardiomyopathies.[49] Overall, natriuretic peptide testing can be useful in excluding a cardiac source of symptoms, but lacks the specificity and positive predictive value in asymptomatic patients.

Cardiac Imaging for Screening

Echocardiography is highly specific in detecting and characterizing structural abnormalities such as left ventricular systolic dysfunction. Screening high-risk patients with limited echocardiography has been demonstrated to be feasible and have substantial yield. In a general medicine in-patient ward with an older population with hypertension, diabetes, coronary artery disease, or previous myocardial infarction and no history of heart failure, almost 8% of patients were found to have an estimated ejection fraction less than 45%.[50] Fifteen percent had a prior history of myocardial infarction, and 6.7% did not. However, the logistics and cost of this approach is prohibitive.

Hand-carried cardiac ultrasound offers a promising alternative to the traditional echocardiogram as it is portable and, perhaps, more cost effective if utilized in a similar manner as a stethoscope. Portable echocardiography has been demonstrated to increase diagnostic accuracy with coupled with a physical examination and has recently gained attention as a possible screening tool in the community.[51-53] The sensitivity and specificity from these studies approach 90% with experienced operators. A study evaluating the cost-effectiveness of screening different at-risk groups compared electrocardiogram, natriuretic peptide and handheld echocardiogram with traditional echocardiography. Sensitivity, specificity and negative predictive value for left ventricular systolic dysfunction were 96%, 98% and 99.6%. Furthermore, handheld echocardiography may provide cost saving compared with tradition echocardiography with additive benefits when used with electrocardiogram or natriuretic peptide testing.[54] With improving technology and lower cost, such devices may be widely available, and broader training may ensure competence and provide feasibility of such an approach.

Cost-effect Screening for Stage B Heart Failure

Despite the fact that many major and minor risk factors for the development of heart failure have been identified, the major barrier for screening for stage B heart failure is cost. Post hoc analysis from the North Glasgow MONICA Risk Factor Survey demonstrated that BNP was associated with left ventricular systolic dysfunction only in patients with ischemic heart disease and high risk clinical profiles; however, using BNP did reduce screening echocardiograms by 26%.[55] Clinical decision models have also been reviewed retrospectively which showed that over a 1% prevalence of left ventricular dysfunction is needed for a cost-effective use of BNP-based screening followed by a confirmatory echocardiogram.[56] However, the majority of individuals with abnormal BNP will have normal left ventricular systolic function. Utilization of composite variables, like clinical data, electrocardiograms, urinary natriuretic peptide and inflammatory markers has demonstrated limited improvement in specificity.[57] The latest guidelines have so far frowned upon routine testing to screen for asymptomatic left ventricular systolic dysfunction as the evidence has yet to support one, but future directions including multiple biomarkers and clinical variables may provide the most cost-effective combined approach for screening.

Treatment for Stage B Heart Failure

In the only large, prospective, randomized control trial specifically focused on patients with asymptomatic left ventricular systolic dysfunction, the SOLVD-Prevention study,[58] the use of enalapril was associated with significantly reduced the incidence of heart failure and the rate of heart failure related hospitalizations by 20% when compared to placebo (Fig. 1). There was also a trend toward decreased mortality due to cardiovascular related deaths in the enalapril arm compared to placebo.[40] Long-term follow-up data at 12 years in the X-SOLVD study clearly demonstrated mortality benefits with enalapril.[59] Data with beta-blockers are less convincing, although in CAPRICORN with a subset of patients with impaired left ventricular systolic dysfunction reported to be asymptomatic postinfarction, carvedilol therapy was associated with a 31% relative risk reduction in adverse long-term outcomes (Fig. 2).[60]

Preventative strategies with the use of statins to retard the progression of coronary artery disease in postinfarction patients have shown significant reduction in incident heart failure cases, most likely due to the prevention of subsequent myocardial infarctions.[60] These beneficial effects of statin therapy primarily appear to prevent or delay progression toward heart failure in patients with coronary artery disease.[61] In addition, Framingham data suggests that dyslipidemia influences the risk of heart failure independent to that of myocardial damage from coronary artery disease.[62] Interestingly, data from the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) which primarily excluded patients with coronary artery disease demonstrated that there was a reduction in coronary end-points without a reduction in heart incidence between the atorvastatin and placebo arms.[63] As there is conflicting data with respect to primary prevention of heart failure and lipid lowering agents, it does appear that ischemic heart failure can be prevented or, at least, postponed with statin therapy[64] (Fig. 3).

Adequate blood pressure control remains an important treatment goal to prevent disease progression, since hypertension remains one of the most common causes of heart failure and coronary artery disease. Lowering blood pressure over a 3–5 years period was effective in preventing left ventricular hypertrophy and heart failure regardless of the type of antihypertensive agent.[17] Independent of lower blood pressure, left ventricular hypertrophy regression is associated with decreased cardiovascular risk and thus reversal has been considered to be a therapeutic goal. Interestingly in the absence of underlying left ventricular systolic dysfunction, meta-analysis of double-blind trials that measured the effects of antihypertensive therapy on left ventricular mass have suggested that ACE inhibitors,

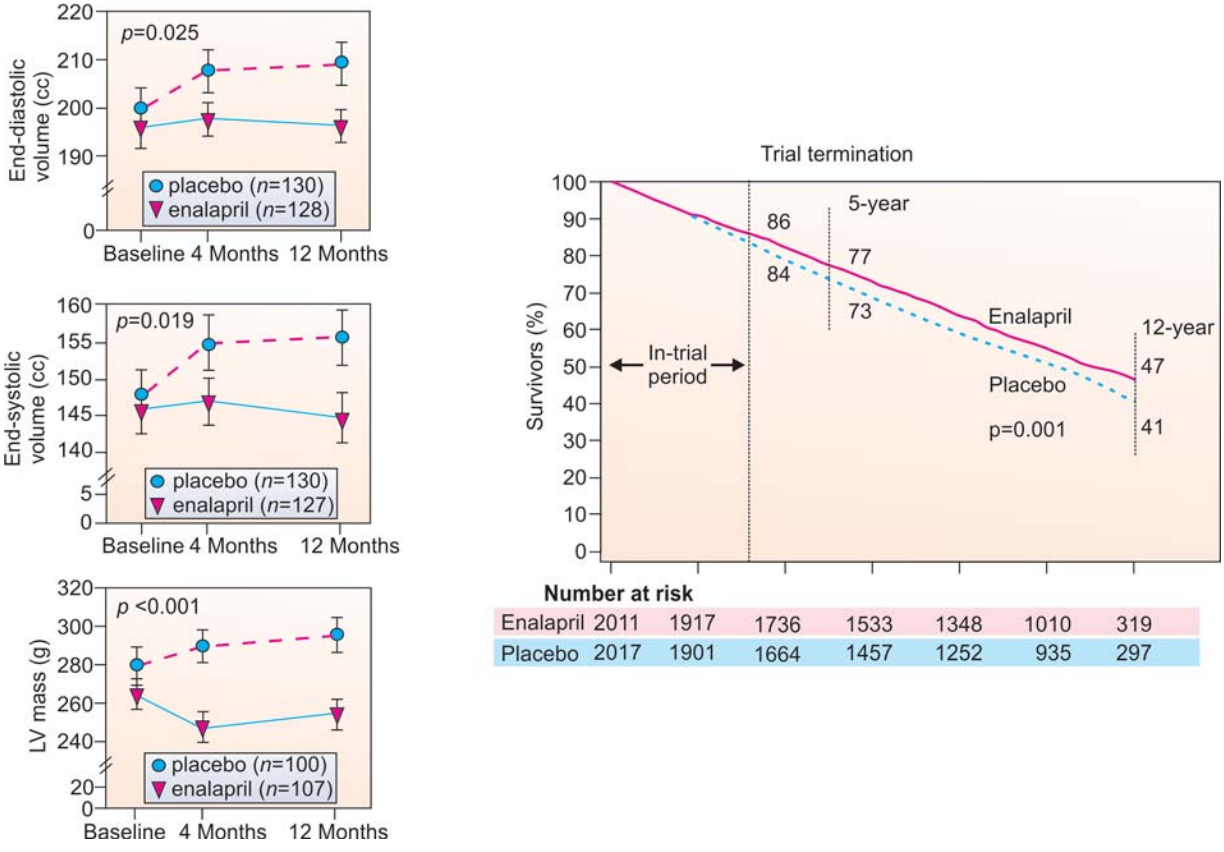


FIGURE 2: SOLVD-prevention: enalapril was associated with regression of left ventricular hypertrophy[58] (left panel) and improved long-term survival[59] (right panel). (*Source*: Reference no. 66)

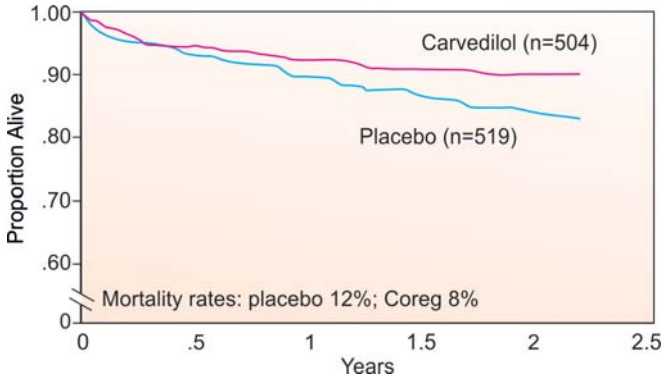


FIGURE 2: Carvedilol in postinfarction asymptomatic left ventricular systolic dysfunction in CAPRICORN. (*Source*: Reference no. 67)

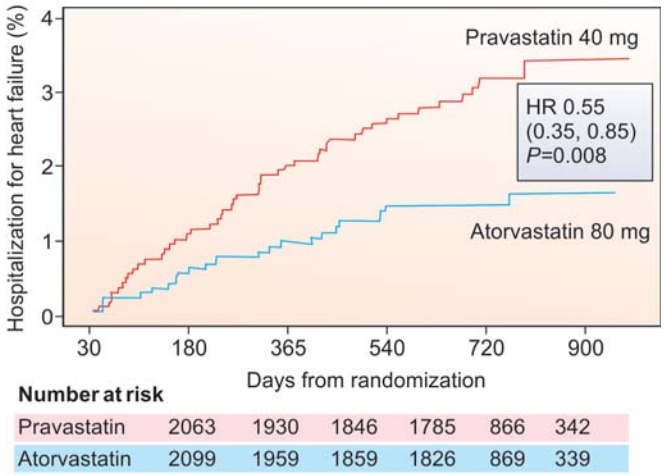


FIGURE 3: High-dose Statin therapy in preventing incident heart failure following acute coronary syndrome: results from the TIMI-22 trial

ARBs, and calcium antagonists were more effective than beta-blockade in reducing left ventricular mass.[65] Compelling evidence from several trials confirm that inhibition of the renin-angiotensin-aldosterone is the important for left ventricular hypertrophy regression. Thus, ACE inhibitors and ARBs are the preferred antihypertensive agents for patients with increased left ventricular mass.

FUTURE PERSPECTIVES

Early detection, aggressive treatment and risk factor modification remain the key to advances in the prevention of heart failure. The science in understanding what triggers early development and progression of heart failure and cardiomyopathy in humans continued to evolve. With advances in technologies, handheld imaging modalities, multiple biomarker and genetic profiles, and refined clinical predictors may some day provide the necessary screening and intervention strategies.

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Chapter 111

Stroke: Prevention and Treatment

Harold P Adams

Chapter Outline

- Definitions
- Stroke as a Symptom
  - Epidemiology and Highest Risk Groups
  - Clinical Presentations
  - Differential Diagnosis
  - Diagnostic Evaluation
- Prevention
- General Acute Treatment
- Treatment of Acute Ischemic Stroke
- Treatment of Acute Hemorrhagic Stroke
- General In-hospital Care
- Rehabilitation

INTRODUCTION

Stroke is the fourth most common cause of death in the United States and it is second to heart disease as a worldwide cause of death. Stroke also is a leading cause of long-term disability and institutionalized care; in many ways stroke is more feared for its potential to lead to dependency than it is for its likelihood to lead to premature mortality. Besides being a leading cause of human suffering, it also has huge economic consequences. The health care costs for prevention, acute care and rehabilitation are considerable but even more so are the direct or indirect costs of lost productivity. While the frequency of stroke declined during the last third of the 20th century largely due to improved management of risk factors for stroke, that course likely will be reversed largely because of the aging of populations around the world. In addition, improved treatment of patients with heart disease that was fatal in the past now allows high-risk individuals to live long enough to have stroke. Thus, the issues related to the prevention and treatment of stroke likely will increase in importance during the 21st century.



FIGURE 1: Lateral view of a magnetic resonance venogram demonstrates thrombosis of the anterior portion of the superior sagittal sinus (top of the image) in a patient with venous thrombosis

DEFINITIONS

The term stroke encompasses a broad spectrum of vascular diseases that affect the central nervous system. Approximately 80% of strokes involve ischemia and the remainder represent bleeding within or adjacent to the brain or spinal cord. Traumatic hemorrhages are not included in the category of hemorrhagic stroke. Vascular events of the spinal cord, while not rare, constitute a small minority of strokes. While most vascular events are due to arterial diseases, approximately 2–5% of strokes may be secondary to venous thrombosis; the presentation of cerebral venous/sinus thrombosis differs considerably from arterial occlusive events (Fig. 1). Ischemic stroke usually is due to thromboembolism including de novo thrombosis of an artery perfusing the brain (cerebral thrombosis) or a clot that has arisen elsewhere and that has migrated to the brain (embolism). The most common sources for such emboli are the proximal arteries of the chest or neck and the heart. Rarely, tumor, air, amniotic fluid, fat or atherosclerotic debris may embolize to the brain. Hemorrhages usually are due to arterial rupture with the primary anatomic site of the bleeding used to describe the pattern of the event: subarachnoid hemorrhage (SAH)—bleeding primarily in the subarachnoid space, intraventricular hemorrhage (IVH)—bleeding in the ventricles, and intracerebral hemorrhage (ICH)—bleeding within the parenchyma of the brain.

The time course is also used to describe the type of vascular event. A transient ischemic attack (TIA) in effect is not a risk

TABLE 1

$ABCD_2$ score: prediction of TIA and risk of stroke

Factors	
Age:	
≥ 60	1 point
Blood pressure:	
Systolic > 140 mm Hg or diastolic > 90 mm Hg	1 point
Clinical features:	
Unilateral weakness	2 points
Speech disturbance without weakness	1 point
Duration of symptoms:	
< 10 minutes	0 point
10–59 minutes	1 point
≥ 60 minutes	2 points
Diabetes mellitus:	
Present	1 point

(*Source:* Reference 3)
(Risk of stroke strongly increased if the score is greater than 3 points)

TABLE 2

Subtypes and causes of stroke

- Hemorrhagic stroke
  - — Hypertension
    - Acute hypertension
    - Sustained hypertension
  - — Aneurysms
    - Saccular (berry) aneurysms
    - Other aneurysms
  - — Vascular malformations
    - Arteriovenous malformations
    - Other vascular malformations
  - — Amyloid angiopathy
  - — Hemorrhagic transformation of infarction
  - — Bleeding diathesis
    - Congenital/inherited
    - Acquired including medications
  - — Drug abuse
  - — Tumors
  - — Primary brain tumor
    - Metastatic brain tumor
  - — Vasculitis
- Ischemic stroke
  - — Large artery atherosclerosis
    - Extracranial
    - Intracranial
  - — Small artery occlusive disease (lacunes)
  - — Cardioembolism
    - Higher risk
      - Atrial fibrillation with structural heart disease
      - Rheumatic mitral stenosis
      - Prosthetic heart valves
      - Acute myocardial infarction (anterior wall)
      - Dilated cardiomyopathy
      - Infective endocarditis
      - Nonbacterial thrombotic endocarditis
      - Libman-Sacks endocarditis
    - Undetermined or lower risk
      - Patent foramen ovale
      - Atrial septal aneurysm
      - Mitral valve prolapse
  - — Nonatherosclerotic vasculopathies
  - — Infectious vasculitis
  - — Noninfectious inflammatory vasculitis
  - — Noninflammatory arteriopathies
- Arterial dissection
  - — Fibromuscular dysplasia
  - — Moyamoya
  - — Hypercoagulable disorders
    - Genetic
    - Acquired
  - — Undetermined cause
- Venous thrombosis
- Pituitary apoplexy

factor for stroke but rather a relatively mild form of the disease; the patient has had a stroke that spontaneously and completely resolved. While the past definition of TIA included the clearance of symptoms within 24 hours, that time period is excessively long. In general, these events last under 10–20 minutes. Often, brain imaging, in particular magnetic resonance imaging (MRI), will demonstrate an ischemic lesion in the brain in a patient with a TIA, especially if the symptoms have persisted longer than 1 hour. Now a TIA is defined as an event that does not cause changes on brain imaging.[1] Although a patient's symptoms have cleared, a TIA should be considered to be a medical emergency because its occurrence implies instability of the underlying vascular disease. The $ABCD_2$ (age, blood pressure, clinical features, symptom duration and diabetes mellitus) score is used to predict the risk of stroke among persons with TIA (Table 1).[2] Asymptomatic cerebrovascular disease may also be diagnosed; for example, by the auscultation of a bruit over the carotid artery or the detection of an aneurysm or vascular malformation by brain imaging performed in a patient with chronic headaches. Not surprisingly, the risk of a major cerebrovascular event is lower among persons with asymptomatic disease than among those patients who have had warning symptoms.

Because much of the acute treatment of stroke is time-linked, the term acute ischemic stroke (brain attack) often is used to describe those events that are treated within the first few hours of onset; while the time limit for this term may evolve, it probably will remain with the maximal time period of 8–12 hours.[4] The term stroke-in-evolution is used to describe the situation in which a patient's signs are rapidly worsening.[5] A cerebral infarction (completed stroke) describes an event associated with persistent neurological impairments. Multiple strokes may lead to cognitive impairments that directly lead to dementia (vascular dementia) or exacerbate the effects of degenerative brain diseases.

STROKE AS A SYMPTOM

While stroke is a life-threatening or life-changing disease, it also is due to an underlying vascular disease. The cause of stroke greatly affects decisions about prevention, acute treatment, and long-term care. Thus, stroke should be considered to be a symptom and evaluation for the most likely etiology of the vascular event is a crucial component of management.

The most obvious division in stroke is between hemorrhages and infarctions (Table 2). Among patients with intracranial hemorrhages, the primary site of bleeding often reflects the most likely diagnosis (Fig. 2). A ruptured saccular aneurysm is the leading cause of nontraumatic SAH. The most common sites are the origin of the posterior communicating artery from the internal carotid artery, the anterior communicating artery or the bifurcation of the middle cerebral artery. Approximately 10%

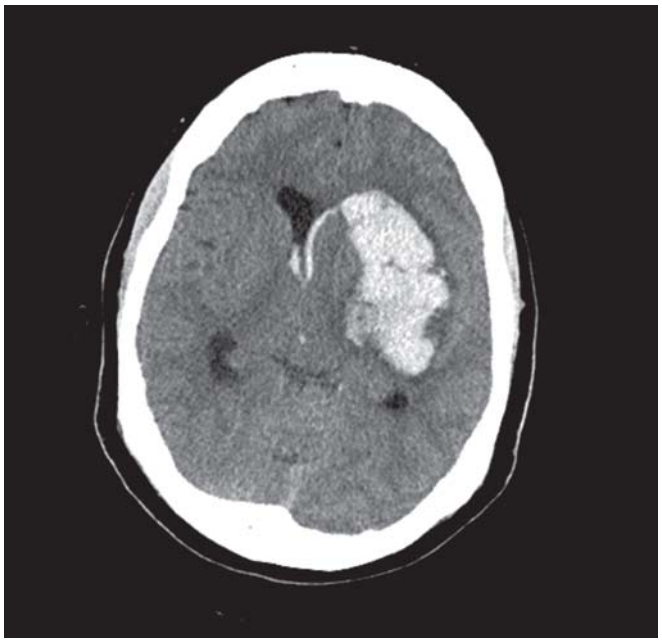


FIGURE 2: Axial CT of the brain demonstrates a hyperdensity in the left hemisphere. The abnormality is consistent with the diagnosis of hypertensive hemorrhage in the basal ganglia (putaminal hemorrhage)



FIGURE 3: Axial CT of the brain demonstrates a wedge-shaped hypodensity in the left hemisphere. The findings are compatible with a subacute infarction in a branch of the left middle cerebral artery

of aneurysms may arise from the posterior circulation. A perimesencephalic pattern of SAH seen on brain imaging has been associated with a more benign course than aneurysmal SAH; it appears to be secondary to rupture of a small vascular malformation.[6] While IVH is most commonly detected among patients with ICH and SAH, a primary IVH may also happen; the most common identified cause is a small vascular malformation. Hemorrhages located primarily in the deep structures of the cerebral hemisphere (thalamus, basal ganglia, internal capsule), the brainstem and cerebellum are most commonly ascribed to hypertension. Hypertensive hemorrhages may result from sustained elevations of blood pressure, in which the presumed cause of bleeding is rupture of a small penetrating arteriole (Charcot-Bouchard aneurysm), or from acute hypertensive events. The latter would include eclampsia, hypertensive crises or elevations of blood pressure secondary to vasopressor medications. Reperfusion injury leading to hemorrhage may also complicate carotid endarterectomy (CEA) or endovascular procedures. Lobar hemorrhages in younger persons may be due to a ruptured vascular malformation while hemorrhages located at the gray matter-white matter junction of the cerebral hemispheres usually are secondary to amyloid angiopathy. While congential bleeding disorders, such as hemophilia, or acquired disorders, such as thrombocytopenia may be the cause of a brain hemorrhage, intracranial bleeding is more often ascribed to the use of antithrombotic medications or thrombolytic agents. An ICH may be the initial manifestation of a primary brain tumor, such as a glioblastoma, or it may complicate metastatic disease. While carcinomas of the lung and breast often metastasize to the intracranial compartment, the relative risk of bleeding seems to be greater among patients with renal cell carcinoma, choriocarcinoma, carcinoma of the thyroid and malignant melanoma. Vasculitis is a rare cause of brain hemorrhage; it has been most commonly associated with the necrotizing vasculitides, in particular, periarteritis nodosa.

The differential diagnosis for the cause of ischemic stroke is extensive and it is partially influenced by the age of the patient. While atherosclerotic disease and acquired cardiac diseases are important etiologies for stroke in middle-aged adults and the elderly, these conditions are much less common in children and young adults. On the other hand, the relative frequency of inherited hematological disorders and nonatherosclerotic vasculopathies is considerably higher in younger populations (Fig. 3).

Atherosclerotic disease affecting large intracranial or extracranial arteries, which leads to severe narrowing or occlusion of the vessels, is a leading cause of cerebral infarction. Both the carotid and the vertebrobasilar circulations may be affected. As with coronary artery disease, instability of an atherosclerotic plaque with fracture and secondary thromboembolism may also result. The most common sites for severe atherosclerotic disease among whites are extracranial while blacks and Asians have more intracranial disease. With the advent of transesophageal echocardiograms (TEE), discovery of advanced or complex atherosclerotic disease of the proximal aorta has increased; aortic disease now is recognized as a potential source of embolization particularly in the elderly, which may mimic the symptoms of cardioembolism.[7] The frequency of atherosclerotic cerebrovascular disease increases with advancing age, and advanced disease is more commonly detected among men, persons with symptomatic peripheral artery or coronary artery disease, those with a family history of atherosclerosis, and among persons with diabetes mellitus, hypertension, hyperlipidemia or a history of smoking. Persons with evidence of or risk factors for accelerated atherosclerosis may also have evidence of disease of the small penetrating arteries that perfuse the deep structures of the

TABLE 3

$CHADS_2$ score: risk of stroke among persons with atrial fibrillation

Factors	
Congestive heart failure	1 point
Hypertension	1 point
Age > 75 years	1 point
Diabetes mellitus	1 point
Stroke (previous stroke or TIA)	2 points

(*Source:* Reference 11)

cerebral hemispheres, brainstem and cerebellum. These vessels are also the same that are associated with hypertensive hemorrhage. Microatheroma or lipohyalinosis may lead to occlusion of these small vessels that result in deep hemisphere infarctions (lacunar strokes).[8,9]

Atrial fibrillation complicating structural heart disease is a leading cause of embolism to the brain.[10] It is the most common etiology of ischemic stroke among women older than 75. While lone atrial fibrillation is not associated with a high risk of embolic infarction, there are factors that are included in the $CHADS_2$ (congestive heart failure, hypertension, age, diabetes mellitus, prior stroke or TIA) score that can predict risk (Table 3).[11] The occurrence of neurological symptoms is the single most important predictor of embolization among persons with atrial fibrillation. Among the persons with heart disease, the risk of cerebral embolization is the highest among persons with mechanical prosthetic valves, particularly those in the mitral position. Other high-risk heart diseases are listed in Table 2. The presence of an intra-atrial or intraventricular thrombus found on diagnostic testing is also associated with a high risk of stroke. The associated risk of stroke with a number of other cardiac conditions, including the presence of a patent foramen ovale, has not been determined. However, there is a growing perception that some of these cardiac lesions may not be especially dangerous.

A large number of nonatherosclerotic vasculopathies that affect intracranial or extracranial arteries may lead to stroke. While each of these conditions is relatively uncommon, they remain important diagnostic considerations particularly among children and young adults.[12] The most common is an arterial dissection, which may occur spontaneously or may complicate trauma (Fig. 4). The usual sites of arterial dissection are the extracranial segment of the internal carotid artery and the distal portion of the vertebral artery. Less commonly, intracranial arteries may be affected. Other noninflammatory vasculopathies include fibromuscular dysplasia, which most commonly affects the extracranial segment of the internal carotid artery, an unruptured saccular aneurysm and cystic medial necrosis. Cerebral autosomal dominant arteriopathy with subcortical leukoencephalopathy (CADASIL) is an inherited disorder that leads to stroke and vascular dementia.[13,14] A number of mitochondrial disorders, such as mitochondrial encephalopathy with lactic acidosis and stroke like episodes (MELAS), may cause symptoms similar to stroke. Moyamoya is a progressive occlusive disease of intracranial arteries that leads to ischemic stroke, vascular dementia, and SAH in children and young adults.[15] Moyamoya disease appears to be an autosomal

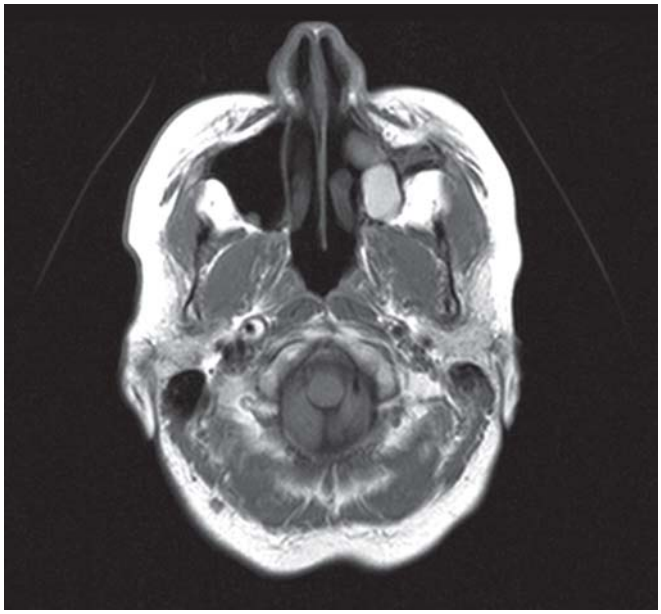


FIGURE 4: An axial view of a T1-weighted magnetic resonance imaging study of the base of the skull and brain shows a "crescent sign" in the right internal carotid artery. The finding is highly suggestive of a dissection of the artery

dominant illness that is most common in persons of East Asian background. Moyamoya sydrome involves an arteriopathy that produces vascular imaging findings similar to moyamoya disease but may be secondary to a number of causes including heavy smoking and use of oral contraceptives. Infections including syphilis, acquired immune deficiency syndrome, herpes zoster and opportunist infections may involve the cerebral vasculature and lead to stroke. Isolated vasculitis of the central nervous system and most of the multisystem vasculitides may cause an ischemic or hemorrhagic stroke.

Genetic or acquired prothrombotic disorders may also lead to ischemic stroke. While these diseases account for a small minority of ischemic strokes, they should be considered if a patient has a personal or family history of venous or arterial thromboembolic events. Children with sickle cell disease are at risk for stroke.[16] Other genetic illnesses that may be implicated include Factor V Leiden, and inherited disorders of protein C or S or antithrombin. The most common acquired hypercoagulable disorder that has been associated with ischemic stroke is the antiphospholipid antibody syndrome. Stroke among patients with pregnancy, cancer or dehydration, or those with recent surgery or in a postpartum state usually is ascribed to a prothrombotic disorder although the exact mechanism leading to the hypercoagulable state has not been described. Thrombosis of cerebral veins or sinuses may also occur with the hypercoagulable disorders or follow surgical procedures or infections of the head and neck.

EPIDEMIOLOGY AND HIGHEST RISK GROUPS

Stroke affects men and women of all ages. It is a leading cause of death and disability around the world.[17] Annually, approximately 800,000 Americans have a stroke.[18] Approximately, 3,00,000 Americans die directly from the stroke or indirectly from complications or comorbid conditions. There are

approximately 5.5 million stroke survivors in the United States. The per-capita rates of stroke are higher among men than among women in all age groups except those who are aged 20–40, where the rates are higher in women. This difference is attributed to the risk of stroke associated with pregnancy. While the frequency of stroke is higher in men, the longer life expectancy of women means that approximately 60% of affected persons are female. There is a striking increase in the risk of stroke with advancing age; it is the premier "risk factor" for stroke. Thus, the majority of persons affected by stroke are older than 65. While stroke is considered a disease of older persons, it is also a leading cause of acute neurological disease in young adults and approximately 3–5% of persons with ischemic stroke are aged 15–45.[19] Stroke also is among the leading causes of death in children.[20] The risk of stroke in the neonatal period is second only to the rate seen among the very elderly; many cases of cerebral palsy reflect cerebrovascular events that occurred in utero or at the time of delivery.

In the United States, the rates of both hemorrhagic and ischemic stroke are highest among African-Americans.[21,22] Cerebrovascular disease is especially prominent in younger persons and it is a leading medical reason for the shorter life expectancy of African-Americans than other ethnic groups. While differences are not as marked as that seen among African-Americans, the rates of stroke among Native Americans, Hispanics and Asian-Americans are also higher than among whites. Similar ethnic differences are seen in other parts of the world. Within the United States, a geographic variation in the rates of stroke is found. The highest rates are in the southeastern states (the Stroke Belt). The explanation for the high rates in this region is not yet obvious. Persons whose parents or siblings who have had a stroke also are at increased risk. Some of the familial relationship to stroke may be due to shared environmental factors such as diet or smoking. Other cases of familial stroke may be due to genetic disorders in lipid metabolism or other factors that predispose to arterial disease. Besides CADASIL and MELAS, other genetic diseases associated with stroke include hyperhomocysteinemia, Fabry disease, Marfan syndrome and polycystic kidney disease. The latter is associated with the presence of intracranial saccular aneurysms. In addition, the number of genetic mutations associated with an increased likelihood of a cerebrovascular event continues to grow.

Those factors that predispose to accelerated atherosclerosis and coronary artery disease also identify the persons as having a heightened risk for stroke; the most important are arterial hypertension, diabetes mellitus, hyperlipidemia and smoking.[23,24] Arterial hypertension, either diastolic or isolated systolic, is the most important modifiable risk factor for hemorrhagic or ischemic stroke. While the associated risks of hyperlipidemia and smoking with stroke may not be as pronounced as for coronary artery disease, the relationships are apparent, particularly among younger persons. Second-hand smoke is also associated with an increased risk of stroke. While moderate alcohol consumption may be associated with a modest reduction in the rate of ischemic stroke, heavy alcohol use, including binge drinking, is a risk factor for both ischemic and hemorrhagic stroke. The presence of obesity and a lack of exercise are associated with an increased risk of stroke; this association may be indirect through associations with diabetes mellitus, hypertension and hyperlipidemia.

Drug abuse, particularly with those agents that have sympathomimetic effects, has been correlated with both ischemic and hemorrhagic stroke. In some cases, a hypertensive crisis associated with the drug use may cause rupture of an aneurysm or vascular malformation. While the relationship between drug abuse and stroke is most commonly described among young adults; the widespread use of such drugs means that most patients with stroke should be screened for use of drugs of abuse. Ischemic and hemorrhagic strokes as well as cerebral venous thrombosis are well-recognized potential complications of pregnancy and the puerperium.[25] While stroke may be the result of conditions, such as aneurysms, heart disease or primary arteriopathies, specific pregnancy-related conditions also occur. Among these diseases are eclampsia, peripartum vasculopathy and peripartum cardiomyopathy. After the introduction of oral contraceptives, an association with an increased risk of either hemorrhagic or ischemic stroke was reported. While the dosages of hormones in the oral contraceptives have declined and the risk of stroke has also dropped, a potential relationship remains.[26,27] However, most strokes in young women taking oral contraceptives are due to a cause not related to use of the medication. Postmenopausal use of estrogens also appears to increase the risk of stroke. Migraine headaches occur in approximately 10% of men and 20% of women. With such a high prevalence, it is not surprising that stroke is diagnosed among persons with migraine. In most instances, migraine is not the cause of stroke. The usual scenario of a migrainous stroke would be the persistence of focal neurological symptoms that usually occur with a headache.

CLINICAL PRESENTATIONS

As the term stroke implies, vascular events of the brain are of sudden onset. While some patients may have waxing and waning of the symptoms or a slow evolution of the impairments, the deficits usually are of maximal severity shortly after the time of onset. The sudden onset of an unusually severe headache (thunderclap headache) often is the cardinal symptom of aneurysmal SAH. A headache is also a prominent symptom among patients with other intracranial hemorrhages. Headache is also reported in approximately 20% of patients with ischemic stroke, particularly with events that affect the brainstem and cerebellum. Most patients with intracranial hemorrhage will have nausea and vomiting. Patients with infarctions affecting the brainstem and cerebellum may also have nausea and vomiting; the presence of these symptoms in a patient who has other findings suggesting an event affecting the cerebral hemisphere usually points to a hemorrhage. Seizures occur at the time of event in approximately 5% patients; this complication is most likely among persons with intracranial hemorrhage and embolic ischemic events affecting the cerebral cortex. Impaired consciousness most commonly occurs among patients with larger intracranial hemorrhages. Patients with basilar artery occlusion leading to brainstem infarction may also be comatose.

Abnormalities in vital signs are common. An elevated blood pressure may be secondary to pre-existing hypertension or may be the result of the stress of the event, increased intracranial pressure, pain, nausea, vomiting or agitation. The elevated blood pressure may also be a physiological response in an effort to maintain perfusion pressure to the brain in the presence of

TABLE 4

Clinical features of ischemic stroke

- Sudden onset of focal neurological findings
- Often of maximal severity at onset
- May have stepwise worsening or waxing/waning
- Types of neurological findings
  - — Cortical hemisphere involvement—cognitive impairments (aphasia, neglect, etc.), contralateral homonymous hemianopia, contralateral hemiparesis, contralateral hemianesthesia, dysarthria
  - — Deep hemisphere involvement—contralateral hemiparesis, dysarthria or contralateral hemianesthesia
  - — Brainstem and/or cerebellar involvement—dysarthria, dysphagia, diplopia/abnormal ocular movements, vertigo/nystagmus, hearing loss, unilateral or bilateral weakness, contralateral hemianesthesia, truncal and gait ataxia, ipsilateral limb ataxia
- Headache in approximately 20% of cases
- Nausea and vomiting—brainstem and/or cerebellar involvement
- Loss of consciousness in uncommon
- Coma with large brainstem lesion
- Seizures are uncommon

TABLE 5

Clinical features of transient ischemic attack

- Usually of sudden onset with gradual resolution
- Usual duration is 5–20 minutes
- Loss of function
- Carotid circulation:
  - — Ipsilateral monocular visual loss (amaurosis fugax)
  - — Contralateral weakness, numbness, clumsiness arm, hand, side of face, half of body
  - — Dysarthria or aphasia
  - — Contralateral visual field loss
- Vertebrobasilar circulation:
  - — Binocular visual loss
  - — Vertigo
  - — Diplopia
  - — Imbalance or ataxia
  - — Dysarthria
  - — Unilateral or bilateral weakness, numbness, clumsiness
  - — Rarely loss of consciousness
  - — Rarely a drop attack

increased intracranial pressure or an arterial occlusion. Often the blood pressure will decline spontaneously in the first hours after stroke. Cardiac arrhythmias, including potentially life-threatening disturbances such as torsades-de-pointes or ventricular tachycardia may complicate stroke, particularly intracranial hemorrhage. The presence of an extracranial or intracranial bruit or a cardiac murmur may provide a hint for the cause of the stroke. Detection of lesions in the skin or other signs of peripheral embolization may also be found in patients with cardiac or aortic causes of stroke. Evidence of meningeal irritation (Brudzinski or Kernig sign) may be found; it is most commonly seen among patients with aneurysmal SAH.

While global symptoms, such as lightheadedness or nonspecific dizziness, occasionally occur with a stroke, patients generally have focal neurological symptoms and signs that reflect injury to one part of the brain. The usual scenario would be the sudden onset of findings such as hemiparesis, dysarthria, aphasia, visual loss, vertigo or cranial nerve palsies. Most patients will have a combination of neurological impairments such as hemiparesis and dysarthria. The patterns of impairments generally are stereotyped and reflect injury to the dominant or nondominant cerebral hemisphere, deep or more superficial locations of the cerebral hemispheres, the cerebellum or brainstem (Table 4). The patterns of ischemic stroke also fit the vascular territories of the internal carotid artery or vertebrobasilar circulation. The clinical features of a TIA are similar to those of an ischemic stroke but are transient (Table 5). Most patients with TIA will have a normal examination. Because the ophthalmic artery is the first major branch of the internal carotid artery, ocular symptoms, most commonly transient monocular blindness (amaurosis fugax), also portend an ischemic stroke. Vertigo, which is common with transient events in the vertebrobasilar circulation, may be the result of brainstem, cerebellar, or labyrinthine ischemia. While the presentation of an ICH may mimic an infarction, affected patients generally are sicker and more commonly have altered consciousness, severe headache, nausea and vomiting (Table 6).

TABLE 6

Clinical features of intracranial hemorrhage

- Headache
- Nausea and vomiting
- Photophobia and phonophobia
- Alteration in alertness
- Marked arterial hypertension
- Unstable vital signs
- Signs of meningeal irritation
- Focal neurological signs
  - — Hemiparesis
  - — Hemisensory loss
  - — Homonymous hemianopia
  - — Dysarthria
  - — Aphasia
  - — Ataxia

DIFFERENTIAL DIAGNOSIS

While the clinical presentations of stroke and TIA are relatively straightforward, errors in diagnosis occur; both over- and under-diagnosis happen. In particular the diagnosis of SAH may be missed if the patient has only a severe headache (Table 7). The occurrence of transient neurological symptoms may or may not

TABLE 7

Differential diagnosis of subarachnoid hemorrhage

- Migraine
- Thunderclap headache
- Viral meningitis
- Sinusitis
- Herniated cervical disk
- Drug or alcohol overdose
- Cerebral infarction
- Cerebral hemorrhage
- Myocardial infarction

TABLE 8

Differential diagnosis of transient ischemic attack

- Migraine
- Syncope
- Seizure
- Metabolic disturbance
  Hypoglycemia
- Intracranial mass lesion
  Tumor
  Subdural hematoma

TABLE 9

Differential diagnosis of hemorrhagic or ischemic stroke

- Hemorrhagic (ischemic) stroke
- Occult trauma
- Central nervous system infection
  Encephalitis
- Migraine with residual findings
- Seizures with postictal signs
- Metabolic disorder
  Hypoglycemia
- Intracranial mass
  Brain tumor
  Subdural hematoma

be secondary to a TIA. Alternative diagnoses include seizures, migraine, syncope, and metabolic disturbances such as hypoglycemia (Table 8).[28] In general, the neurological findings, which represent a loss of function, are of sudden onset with TIA; an evolution of symptoms or positive findings (such as involuntary movement or positive visual phenomena) is atypical for a vascular event. The differential diagnosis of ischemic stroke is relatively limited. The most important alternative diagnosis is hemorrhagic stroke (and vice versa) (Table 9).

DIAGNOSTIC EVALUATION

The goals of the diagnostic evaluation are: (1) to determine if a hemorrhagic or ischemic stroke is the most likely explanation for the patient's neurological symptoms; (2) to establish the most likely cause for the patient's stroke; (3) to screen for risk factors that would predispose to accelerated atherosclerosis and stroke and (4) to seek medical or neurological complications of the stroke or severe comorbid diseases.[29] The results of the evaluation affect prognosis and decisions about both acute and longer term treatment. The components include: (1) brain imaging; (2) neurological tests such as examination of the cerebrospinal fluid (CSF); (3) vascular and cardiac imaging; (4) electrophysiological studies including electroencephalography (EEG) and electrocardiography (ECG); (5) blood tests for the presence of risk factors, comorbid medical diseases or coagulation abnormalities; (6) immunological studies and (7) genetic testing. The selection of the diagnostic studies is made on a case-by-case basis; the evaluation may be done in a cost-effective manner through careful selection of studies to order. The groups of tests are clustered into those that are required in an emergency situation and those that are performed on a more elective basis to establish the most likely cause of stroke.[28,30,31]

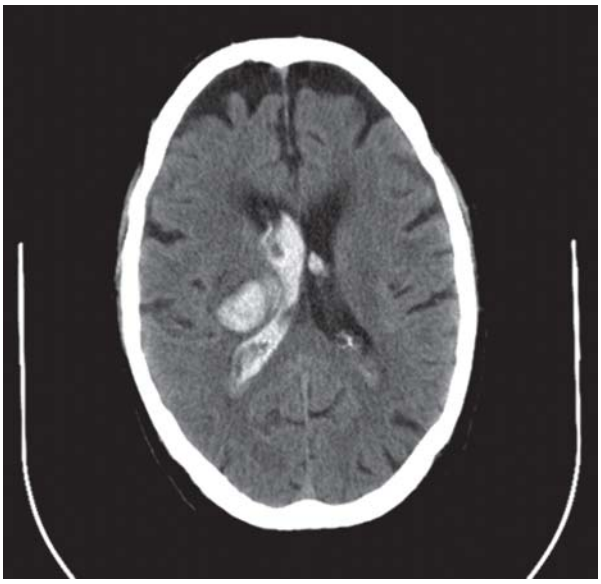


FIGURE 5: Axial CT of the brain shows a hyperdensity in the right thalamus with extension into the right lateral ventricle. The results are consistent with the diagnosis of thalamic hemorrhage with intraventricular extension of bleeding



FIGURE 6: Axial CT of the brain reveals hyperdensity in multiple locations at the base of the brain and a focal area of increased signal in the interhemispheric fissure. The findings are those of aneurysmal subarachnoid hemorrhage with the most likely location of the aneurysm being on the anterior communicating artery

Brain imaging remains the cornerstone in the evaluation of patients with suspected stroke.[28,30,33] Computed tomography (CT) of the brain revolutionized the diagnosis of stroke (Figs 5 and 6). It has a very high yield in detecting intracranial hemorrhage and within a few hours of onset, CT usually will detect the changes of cerebral infarction. In addition, the imaging study may demonstrate a large thrombus in the middle cerebral artery or other major intracranial artery (dense artery sign).

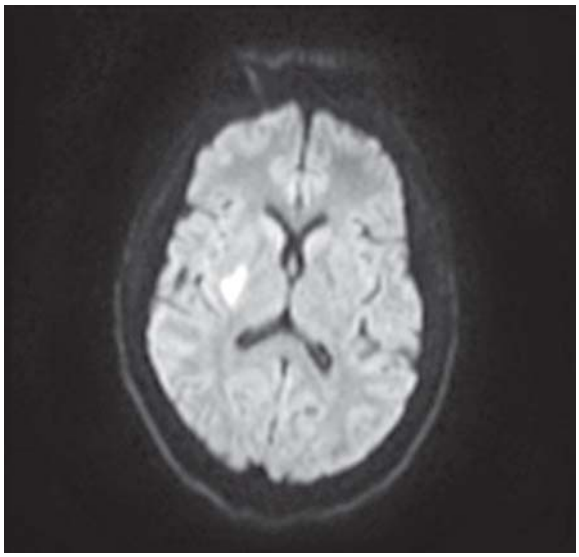


FIGURE 7: Diffusion-weighted sequence magnetic resonance imaging study of the brain reveals an area of increased intensity deep in the right hemisphere. The findings are those seen with an acute infarction in the territory of the right anterior choroidal artery

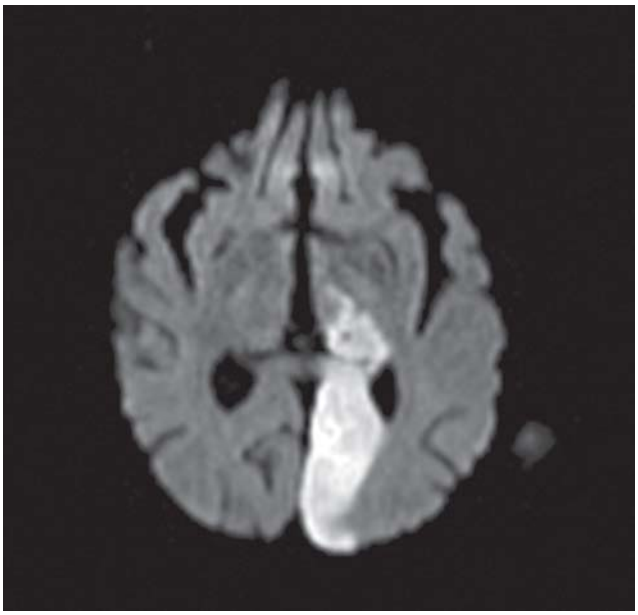


FIGURE 8: Diffusion-weighted sequence magnetic resonance imaging study of the brain shows an area of increased intensity involving the thalamus and the occipital cortex of the left hemisphere. The findings are consistent with an acute infarction in the distribution of the left posterior cerebral artery

CT also is useful in identifying neurological complications of stroke including hydrocephalus, brain edema and hemorrhagic transformation of an infarction. Contrast enhancement may be used to detect early changes of hypoperfusion. Several sequences of MRI are used to assess patients with suspected stroke.[33] Gradient echo studies are particularly useful in defining hemorrhages and diffusion-weighted imaging (DWI) usually detects the changes of cerebral infarction within minutes of the onset of the vascular event (Figs 7 and 8). Differences in the sizes of the areas of involvement on enhanced-perfusion imaging and DWI may be used to define mismatch, which may reflect the ischemic penumbra. MRI is less readily available than CT and it is more expensive. Patients with pacemakers cannot have an MRI study and issues such as renal disease or claustrophobia may limit the use of the test.

Patients with decreased consciousness or suspected seizures may be evaluated with an EEG. An EEG may also be used to monitor neurological responses among patients having CEA. Examination of the CSF has a limited role in patients with stroke. It may be performed in those patients whose history is highly suggestive of SAH and in whom a CT does not demonstrate bleeding. Key findings in this situation will be bloody CSF and xanthochromia of the fluid after centrifugation. Other potential indications would be to exclude alternative diagnoses such as infections or to screen for potential causes of stroke such as an infectious or inflammatory vasculitis.

Both computed tomographic angiography (CTA) and magnetic resonance angiography (MRA) are used to assess the extracranial and intracranial vasculature (Figs 9 to 11). The yields of these tests are relatively high. These noninvasive studies generally are used as screening tools to look for arterial causes of either hemorrhagic or ischemic stroke. Magnetic resonance venography (MRV) has become a valuable method

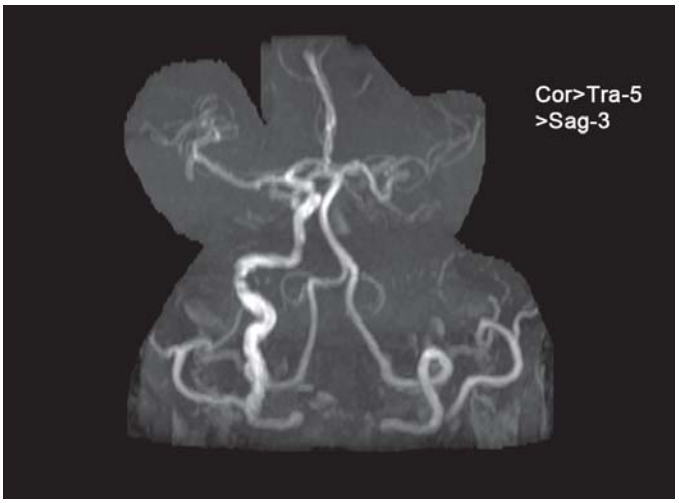


FIGURE 9: An anterior view of a magnetic resonance angiogram shows nonvisualization of the left internal carotid artery. The findings are those seen with occlusion of the vessel

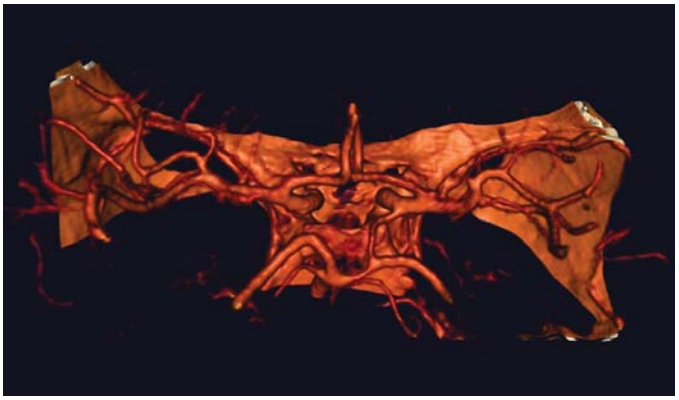


FIGURE 10: A basal view of an intracranial CT angiogram shows the circle of Willis and the proximal segments of the major intracranial arteries

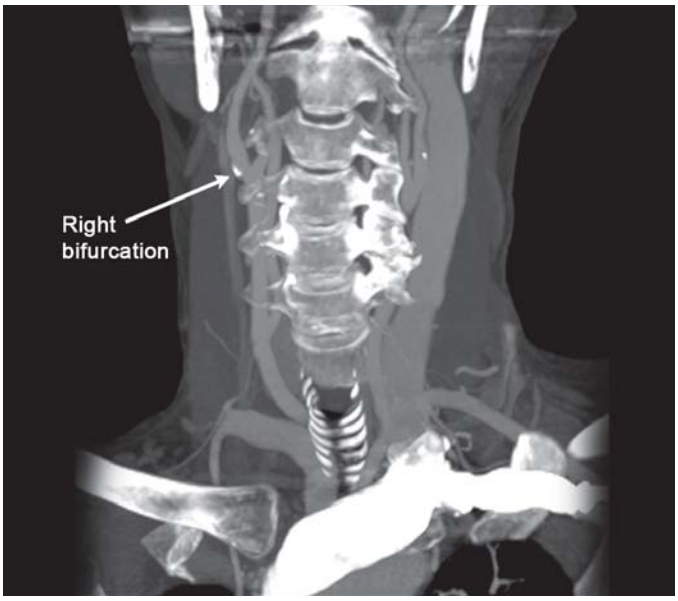


FIGURE 11: An anterior view of a CT study of the neck shows an area of calcification in the right internal carotid artery at the bifurcation (arrow)



FIGURE 12: A lateral subtraction view of a left carotid arteriogram shows a high-grade stenosis with ulceration of the proximal segment of the internal carotid artery

to screen for thrombosis of intracranial venous structures. Other noninvasive vascular imaging studies include carotid duplex examination and transcranial Doppler ultrasonography. The former is used to assess the severity of arterial narrowing and the appearance of an atherosclerotic plaque at the origin of the internal carotid artery. The latter is used to evaluate the severity of intracranial arterial diseases. Arteriography remains the most definitive method to examine the intracranial and extracranial vasculature (Fig. 12). It is invasive and associated with a risk of embolic cerebral infarction. As a result, it often now is reserved for evaluation of patients who also likely will have an endovascular intervention. Arteriography also remains important in the assessment of patients with suspected central nervous system vasculitis, intracranial aneurysms and vascular malformations.

Because of the strong association between stroke and heart disease, a cardiac evaluation is indicated in most patients with cerebrovascular disease. The usual studies include an ECG and echocardiography. The former is performed to screen for evidence of cardiac ischemia, hypertensive heart disease and cardiac arrhythmias. The latter may be a complication or a cause of the stroke. The use of prolonged cardiac monitoring is increasing in an effort to detect intermittent arrhythmias that may be implicated in the pathogenesis of stroke, in particular, atrial fibrillation. Both transthoracic echocardiography (TTE) and TEE are components of the evaluation of patients with stroke, especially those with cerebral infarction.[34] In general, the yield is higher with TEE. TTE is most commonly performed to look for a left ventricular lesion that may predispose to cardioembolism while the TEE provides more information about possible causes of embolization arising from the mitral valve, the left atrium, left atrial appendage and aorta. While TEE is an invasive study, the risk of major complications among patients with stroke appears to be relatively low. Rarely gated CT or MRI of the heart may be performed.

Blood tests include measures of hemoglobin, hematocrit, platelet count and white blood cell count (complete blood count/CBC). The CBC may provide evidence of severe anemia, polycythemia, infection or a coagulopathy that could cause or complicate either ischemic or hemorrhagic stroke. Some patients, particularly African-American children, should be screened for sickle cell disease. Screening for severe comorbid diseases or risk factors for accelerated atherosclerosis include blood glucose level, hemoglobin A1C level, lipid profile, renal and liver function tests and cardiac enzymes. Screening for an inflammatory process would include erythrocyte sedimentation rate and C-reactive protein; elevations may point to an illness such as a multisystem vasculitis. Elevations of the high-sensitivity C-reactive protein (hs-CRP) also denote patients at high risk for ischemic events. Less commonly, other immunological tests such as antineutrophil antibodies (ANA) or anticytoplasmic nuclear antibodies (ACNA) are performed. Additional hematological studies to look for acquired or genetic causes of a hypercoagulable disorder or bleeding disorders may be ordered in exceptional cases. The role of genetic testing for specific inherited disorders leading to stroke, such as autosomal dominant polycystic kidney disease or cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), may also be done. Pharmacogenetic testing may be needed to help guide treatment decisions, such as the use of clopidogrel in prophylaxis.

PREVENTION

The most cost-effective strategy for the management of patients with cerebrovascular disease is to prevent strokes from happening. While no intervention will eliminate the risk of stroke, interventions of proven efficacy are available to lower the risk of an event. Preventive measures are prescribed to asymptomatic individuals (primary prevention) or to persons

who have had prior neurological symptoms (secondary prevention).[23,24,35,36] The asymptomatic group includes persons with evidence of risk factors for atherosclerosis and stroke and those with symptomatic disease in other vascular territories (coronary artery disease or peripheral artery disease). Persons with atrial fibrillation also are included in the group that could receive primary prevention measures. Symptomatic patients would include those who have had a prior stroke, warning symptoms of ischemic stroke (TIA or amaurosis fugax) or warning symptoms of SAH (warning leak). Since the risk of a serious cerebrovascular event is considerably higher among the symptomatic patients, some interventions that may have inherent risk prescribed when the same therapies may not be recommended for asymptomatic persons. The higher risk therapies largely are surgical or endovascular interventions. However, the administration of antithrombotic medications is also influenced by the risk-benefit ratio (Table 10).

The components of management to prevent stroke can be aggregated into three groups: (1) interventions to control or treat those risk factors that promote the course of atherosclerosis and increase the risk of brain ischemia; (2) antithrombotic medications and (3) surgical or endovascular interventions.[23,24,35-38] The selections for treatment are made on a case-by-case basis. Several factors influence decisions about treatment including: (1) the presumed etiology of the patient's ischemic symptoms; (2) the most likely vascular territory; (3) responses to prior treatment; (4) specific contraindications to treatment (for example, allergy to aspirin) and (5) the preferences of the patient.

TABLE 10

Prevention of ischemic stroke

- Management of risk factors
- Hypertension (goal systolic blood pressure 120–130 mm Hg and diastolic blood pressure < 80 mm Hg)
  - — Lifestyle changes (weight loss, diet, increase exercise)
  - — Antihypertensive medications
- Diabetes mellitus (goal of Hgb A1C < 7%):
  - — Lifestyle changes
  - — Insulin or oral medications
- Hyperlipidemia:
  - — Lifestyle changes
  - — Statins or other lipid-lowering medications
- Smoking:
  - — Abstinence
  - — Nicotine replacement or other medications
- Antithrombotic agents:
  - — Oral anticoagulants
    - Warfarin
  - — Thrombin inhibitors
    - Dabigatran
  - — Antiplatelet agents
    - Aspirin
    - Aspirin/extended release dipyridamole
    - Clopidogrel
    - Aspirin and clopidogrel
    - Ticlopidine
- Surgical interventions:
  - — Carotid endarterectomy
  - — Extracranial-intracranial arterial bypass
  - — Other operations
  - — Angioplasty and stenting

(*Source:* References 23, 24, 32)

Important risk factors for an increased risk of stroke, such as advancing age, ethnicity, a family history of stroke or geographic location, are not modifiable. Other factors that are associated with an increased likelihood of stroke, such as a low-potassium diet, obesity or decreased exercise, probably convey an indirect risk through their effects on blood pressure, lipids and glucose levels. While heavy alcohol consumption including binge drinking is associated with an increased risk of both hemorrhagic and ischemic stroke, limited alcohol use may convey a reduction in the likelihood of ischemic events. The premier modifiable risk factors for stroke are arterial hypertension, hyperlipidemia, diabetes mellitus and tobacco use; of these, the most important is hypertension. While lifestyle changes, such as weight loss, dietary modifications and increased exercise, are recommended; most patients likely will need pharmacological therapies to help control these risk factors.

A reduction in blood pressure by as little as 5 mm Hg may result in a major decline in the risk of stroke. Evidence from clinical trials demonstrates that the several different antihypertensive agents are effective. In general, benefits are best with the use of the angiotensin converting enzyme inhibitors (ACE-I), angiotensin receptor blockers (ARB) and calcium channel blockers. The effects of these medications often are potentiated the use of diuretics. The efficacy of the beta-blockers seems to be less than the other classes of antihypertensive agents. In general, the goal of treatment should be a systolic blood pressure of less than 120–130 mm Hg and a diastolic blood pressure less than 80 mm Hg.[23]

While the evidence of efficacy of the statins in preventing ischemic stroke is not as robust as the data showing the usefulness of these medications in preventing cardiac ischemia, clinical trials demonstrate the efficacy of these medications. As a result, lipid-lowering medications now are part of a regimen to lower the risk of ischemic stroke. Currently, the desired levels of LDL cholesterol is less than 100 mg/dL (diabetic patients < 70 mg/dL) but this goal may be modified to treat the common concomitant of coronary artery disease. Current data do not provide strong information to guide recommendations about treatment of hypertriglyceridemia or elevations of alpha-lipoproteins. Some patients may develop myopathic or hepatic side effects that limit the use of statins. In these cases, other medications, such as ezetimibe, nicotinic acid or sequestrants, may be prescribed. Diabetic patients should have the goal of lowering the hemoglobin A1C level to less than 7%. More importantly, these patients need aggressive treatment of hyperlipidemia and hypertension.[23] One of the advantages of the ACE-I is that this class of medications may also lower the risk of renal complications of diabetes. Tobacco abuse, in particular cigarette smoking, is recognized as an important risk for ischemic stroke, especially in younger persons. Stopping smoking is a very cost-effective intervention; besides reducing health care costs, the expense of the tobacco also is avoided. Stopping smoking has dramatic effects in lowering the risk of stroke; overall, the risk may be reduced to that of persons who have never smoked within 5 years of stopping. Several options, including nicotine replacement therapies and medications, can be used to help the patient stop.

The choices for antithrombotic agents for prevention of stroke are listed in Table 10.[23,24,38,39] They are not as extensive as those for prevention of myocardial infarction; some of the recently evaluated medications, such as prasugrel or ticagrelor, have not been tested in stroke prevention. Oral anticoagulants are recommended for the prevention of ischemic stroke that is attributed to cardioembolism; the benefit is found with both primary and secondary prevention.[23] For most cardiac lesions, including atrial fibrillation complicating structural heart disease, the desired international normalized ratio (INR) is 2–3. For patients with mechanical prosthetic valves, in particular in the mitral position, the desired INR is 2.5–3.5. There is strong evidence of the efficacy of oral anticoagulants in preventing stroke among persons with atrial fibrillation; the overall relative risk reduction is approximately 70%. Rate or rhythm control has not been as effective as warfarin in prevention of stroke. The occurrence of neurological symptoms is a strong indication for oral anticoagulants. However, long-term administration of oral anticoagulants is associated with a risk of bleeding complications; the most serious are ICH and subdural hematoma. The risk of bleeding complications increases among elderly persons, those with dementia or a high risk for falls, those who abuse alcohol or drugs or those who are not compliant with the treatment regimen. Interactions with other medications and foods also complicate administration of warfarin. More recently, issues related to impairments in vitamin K epoxide reductase or the cytochrome P450 CYP2CP genetic mutation that alter metabolism of the medication have added to the complexity of treatment. A new vitamin K antagonist is being tested in comparison to warfarin.

The direct thrombin inhibitor, dabigatran, may replace warfarin for stroke prevention. The agent does not have the interactions with medications or food that plague warfarin treatment; thus it could be easier to use for both patients and physicians. A recent trial demonstrated that dabigatran 150 mg/day was as more effective than warfarin and was accompanied by a lower risk of bleeding.[40] Several other new antithrombotic drugs are being tested for their utility in prevention of stroke among persons with atrial fibrillation.

The use of oral anticoagulants for prevention of recurrent stroke among patients with intracranial or extracranial arterial disease has been tested in three clinical trials; these studies did not demonstrate its superiority to use of antiplatelet agents.[41-43] As a result, currently there is no established indication for the use of oral anticoagulants in patients with arterial diseases leading to stroke. Although no clinical trials have tested the role of anticoagulants in prevention of stroke among persons with prothrombotic disorders, these agents often are prescribed to patients with a hypercoagulable state. In particular, oral anticoagulants are given if the patient also has evidence of venous disease.

Antiplatelet agents remain the mainstay of management to lower the likelihood of stroke.[23,24,38,39,44] Current choices include aspirin and extended release dipyridamole, ticlopidine, clopidogrel, and the combination of aspirin and clopidogrel. Other medications, which may be used in the future, include prasugrel, ticagrelor and cilostazol. The antiplatelet agents have been tested in patients with a wide range of symptomatic and asymptomatic vascular diseases including those with peripheral artery disease, angina pectoris, coronary artery disease, TIA and ischemic stroke. These medications also have been tested in asymptomatic high-risk persons including those persons with risk factors for accelerated atherosclerosis. Overall, the antiplatelet agents reduce the risk of ischemic events by approximately 25%. They are effective in men and women of all ages. The presence or absence of hypertension or diabetes mellitus does influence treatment responses. These agents do increase the likelihood of bleeding complications but the risk appears to be less than with the oral anticoagulants.

Aspirin is the most widely tested and commonly used antiplatelet agent. Aspirin often is the standard against which other interventions are compared. It is effective in a wide range of doses; there is no evidence that doses larger than 75–325 mg/day are superior. While there appear to be cases of aspirin resistance or failure, overall the medication appears to be quite effective. Aspirin has several advantages. It is easy to administer, inexpensive, does not require monitoring and may be used as a monotherapy or in combination with oral anticoagulants or other antiplatelet agents. It has a well-established safety profile. Aspirin does increase the risk of bleeding but these effects are not dose related. Gastritis, peptic ulcer disease, and upper gastrointestinal hemorrhage are potential complications of treatment with aspirin and these side effects do have a dosage relationship. Lower doses of aspirin appear to be the least likely to cause gastric irritation. In addition, the use of enteric coated preparations lessens the risk of gastric complications. The combination of aspirin and oral anticoagulants often is used to treat patients with heart diseases that are associated with an extremely high risk of embolization. Aspirin monotherapy (325 mg/day) is prescribed to patients with cardiac lesions that are judged to be at low risk or as an alternative to oral anticoagulants in patients thought to have a potentially high risk for major bleeding complications.

The combination of aspirin and extended release dipyridamole is prescribed to patients with recent TIA or stroke. Dipyridamole is a potent vasodilator that also inhibits platelet aggregation through its inhibition of phosphodiesterase. When compared to aspirin monotherapy, the combination has been shown to be more effective in reducing the risk of stroke among persons with recent TIA or stroke. The combination medication (marketed in the United States as Aggrenox®) is more expensive than aspirin and is not superior to aspirin monotherapy in reducing the risk of vascular disease-related death. In addition, the vasodilatory effects of dipyridamole are associated with the development of severe headaches; this side effect limits the utility of the agent.

Ticlopidine was found to be superior to aspirin in preventing recurrent stroke among persons with TIA or minor stroke. Overall, the relative risk reduction was approximately 14%. Unfortunately, ticlopidine is associated with serious side effects including neutropenia and thrombotic thrombocytopenia purpura, which have greatly limited its use in prevention of stroke. Clopidogrel, another thienopyridine prodrug whose metabolites have potent antiplatelet effects, is widely used in prevention of stroke. It has been tested, alone or in combination with aspirin, in a several clinical trials enrolling patients with a wide range of ischemic diseases. Overall, the agent appears to be marginally superior to aspirin. One trial tested the

combination of clopidogrel and aspirin to monotherapy with clopidogrel among persons with TIA or stroke and found that the combination was not superior in reducing the risk of ischemic events but it was associated with an increase in the risk of bleeding complications. Another trial found that the combination of aspirin and clopidogrel was not superior to aspirin monotherapy in preventing events in a broad range of patients at risk for ischemia; however, the same study found a trend in favor of treatment among symptomatic patients. A short course of the combination of aspirin and clopidogrel for prevention of ischemic events in high-risk patients with recent TIA shows promise.[45] The combination of aspirin and clopidogrel is widely used as adjunctive therapy for patients having cerebrovascular endovascular procedures. Since clopidogrel is a prodrug that is metabolized through the cytochrome P450 system, there is the potential for interactions with other medications; in particular, a problem with the proton-pump inhibitors has been noted. In addition, a sizable percentage of persons may have a homozygous or heterozygous genetic polymorphism that alters responses to clopidogrel; the impact of this issue on the use of clopidogrel in management of high-risk patients has yet to be determined.

Carotid endarterectomy is of proven utility in lowering the risk of ipsilateral infarction among patients with severe (> 70% stenosis) of the extracranial segment of the internal carotid artery.[23,46-48] Evidence of efficacy is strongest for treatment of symptomatic patients although some patients with severe asymptomatic disease also can benefit from surgery. The potential benefit of surgery in preventing stroke must be weighed against the risks of the procedure. Overall the perioperative morbidity and mortality for CEA should be under 1% and 4% respectively. Factors associated with increased operative morbidity including neurological instability, severe comorbid diseases including severe heart disease, and extensive arterial disease. The skill of the surgeon also is an important variable. The operation may be done under general or local anesthesia with the morbidity appearing to be less with the latter approach. The most common complications of CEA are stroke and myocardial ischemia. Surgical correction of a very severe stenosis may be complicated by a hyperperfusion syndrome that presents with headache, seizures, focal neurological impairments and intracranial bleeding. This complication appears to reflect a sudden surge of blood flow to an area of brain with disturbed autoregulation and previous poor perfusion. There are little data to support the approach of simultaneous CEA and coronary artery bypass surgery. Extracranial-intracranial artery bypass operations were tested in a large clinical trial and no benefit from surgery was found. However, the potential utility of the operation is being re-examined in a clinical trial enrolling subjects with occlusion of the internal carotid artery and poor collateral circulation. Occasionally, other reconstructive operations are performed in patients with extensive extracranial arterial disease.

Endovascular procedures are being performed to treat stenotic intracranial and extracranial lesions. The most common site is the extracranial segment of the internal carotid artery. To date, the combination of angioplasty and stenting has not been shown to be equal to CEA and the conventional operation remains the first choice for surgical therapy to lower the risk of stroke.[49-51] At present, the potential indications for angioplasty and stenting for treatment of carotid stenosis include: (1) prior CEA; (2) previous radiation therapy to the neck and (3) a high risk for complications of surgery based on medical comorbidities. Information about the utility of endovascular interventions for treating the vertebrobasilar circulation or intracranial stenotic lesions is limited.

Cardiac procedures are being evaluated for their utility in preventing embolic stroke. These include endovascular or direct surgical obliteration of a PFO or ablation procedures or occlusion of the left atrial appendage among persons with atrial fibrillation. The usefulness of these operations has not been established.

Medical measures to lower the risk of hemorrhagic stroke primarily focus on control of arterial hypertension. Aggressive lowering of cholesterol values may be associated with an increased risk of intracranial bleeding. The level of LDL cholesterol that denotes an increase in the risk of hemorrhage has not been determined. Intracranial hemorrhage is a potential complication of long-term treatment with oral anticoagulants and antiplatelet agents, with the risk being lower with the latter. Optimal management to avoid excessive levels of anticoagulation is the primary preventive strategy. Treatment of a previously ruptured arteriovenous malformation is aimed at preventing recurrent hemorrhage but the utility of prophylactic treatment of an unruptured vascular malformation is not established. Patients with an unruptured intracranial saccular aneurysm may be treated with surgery or endovascular interventions with the latter appearing to be associated with better safety. Still, the risk of rupture of an aneurysm is relatively low. The highest risk lesions are those that are larger than 6–10 mm in diameter or located in the posterior circulation. In addition, persons with a prior SAH from another aneurysm or those with a family history of SAH may be candidates for prophylactic treatment. Overall, it appears that most patients with incidentally found saccular aneurysms do not need a surgical intervention.

GENERAL ACUTE TREATMENT

Acute stroke is a medical emergency. Acute treatment includes institution of interventions to limit the neurological injury and use of therapies to prevent or control general medical or neurological complications.[28,30,31,38] Besides a clinical evaluation and ordering diagnostic studies, urgent attention is paid to acute potentially life-threatening complications (Fig. 13) (Table 11). While most patients with stroke do not need cardiopulmonary resuscitation, the ABCs of life support are important. Persons with decreased consciousness and those with prominent dysfunction of the bulbar musculature usually need protection of the airway and ventilatory support; not surprisingly, the requirement of airway support is associated with a poor prognosis. Monitoring for and treatment of cardiac arrhythmias are also performed. Due to the high rate of stroke among patients with heart disease and vice versa, cardiac complications should be anticipated in particular among persons with intracranial bleeding. While sinus bradycardia is the most common arrhythmia, potentially life-threatening rhythm disorders including torsades de pointes or ventricular tachycardia may

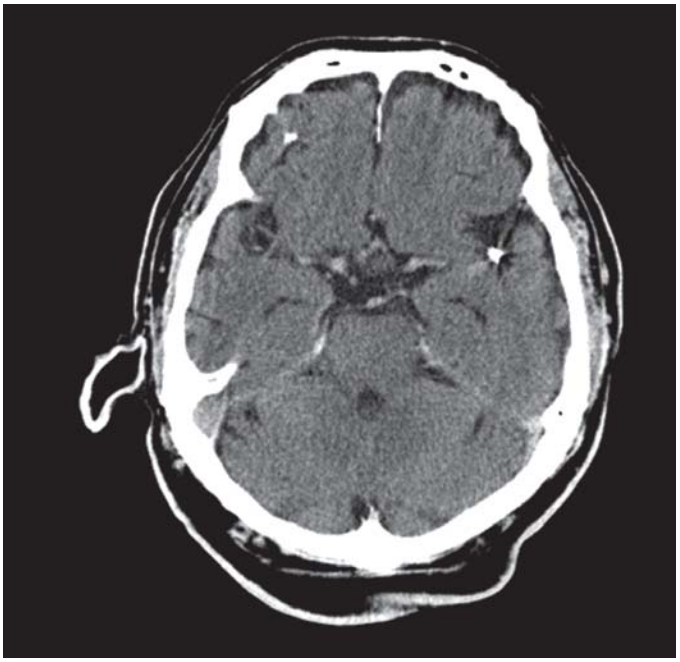


FIGURE 13: An axial CT study of the brain demonstrates a hyperdensity in the left middle cerebral artery. The finding is consistent with an embolus

TABLE 11

General emergency management: acute stroke

- ABCs of life support
  - Protect the airway (intubation)
  - Ventilatory assistance
  - Cardiac monitoring
  - Treat serious cardiac arrhythmias
- Management hypertension
  - Treatment with rt-PA (systolic < 185 mm Hg/diastolic < 10 mm Hg)
  - Parenteral administration of short acting medications
- Treat fever
- Treat seizures
- Treat hyperglycemia

(*Source:* References 28, 30, 31)

occur. Placement of an intravenous access, usually with administration of maintenance normal saline, is recommended. Dextrose and water is avoided because the hypo-osmolar solution may worsen development of brain edema.

Elevated arterial blood pressure is common after stroke. The finding may reflect pre-existing hypertension or may be a consequence of the stroke. Arterial hypertension may also be physiological response to maintain perfusion of the brain in the presence of an arterial occlusion or increased intracranial pressure. On the other hand, marked elevations of blood pressure may promote bleeding or hemorrhagic transformation of an infarction, aggravate development of brain edema, or preclude treatment with thrombolytic agents. A systolic blood pressure greater than 185 mm Hg or diastolic blood pressure greater than 100 mm Hg precludes early intravenous administration of rt-PA.[28] Unfortunately, data to guide management of arterial hypertension in patients with stroke are not available; for example, the level of blood pressure to treat, the desired rate of reduction and best medications to administer are not known. There is a concern that rapidly lowering blood pressure could exacerbate ischemia and lead to neurologic worsening. Current guidelines provide recommendations for administration of short-acting parenterally given agents including labetalol, hydralazine, nicardipine, nitropaste or sodium nitroprusside.[28,30,31,38] The goal is to reduce blood pressure by approximately 15%. In addition, many patients will have spontaneous declines in blood pressure during the first hours after stroke.

Most patients are not febrile at the time of stroke; the presence of a fever should lead to consideration of an infectious cause of stroke such as infectious endocarditis. Still, the presence of fever may potentiate the cellular damage of acute ischemia and as a result, measures to lower body temperature should be given to patients who are febrile. Choices include antipyretic medications or cooling devices. While there is evidence that hypothermia may limit the neurological injury resulting from cardiac arrest, the utility of induced hypothermia in treating stroke is not established. Anticonvulsants should be administered to those patients who are having seizures but prophylactic use of the medications is not recommended for most patients. Hyperglycemia often is found following stroke; it may reflect pre-existing diabetes mellitus or be a stress response to the brain illness. The presence of hyperglycemia is associated with an increased likelihood of a poor outcome. Data about the blood glucose level that should prompt emergency treatment and the desired reduction of the level in the setting of stroke are not available. Current guidelines recommend treatment of hyperglycemia when the blood glucose concentration is greater than 180 mg/dL with the goal of reducing the value to approximately 100–120 mg/dL but avoiding hypoglycemia.[28] Disturbances in electrolytes, in particular hyponatremia, are a potential acute complication of intracranial hemorrhage. The hyponatremia usually is the result of cerebral salt wasting secondary to increased release of atrial/ brain natruretic factor. Rather than fluid restriction, patients with hyponatremia are treated with 3% saline solutions.

TREATMENT OF ACUTE ISCHEMIC STROKE

Interventions to restore perfusion to an area of ischemic brain are the engine that drives treatment of acute ischemic stroke. Intravenous thrombolysis has revolutionized emergency management; rt-PA (dosage 0.9 mg/kg—maximum of 90 mg) has been approved for the treatment of carefully selected patients with acute ischemic stroke; 10% of the dose is given as a bolus and the remainder is infused over 1 hour. The original maximum time window was 3 hours, but the results of an European trial permitted expansion of the time period for treatment to 4.5 hours.[52-54] While intravenous thrombolysis increases the risk of symptomatic hemorrhagic transformation of an infarction or other serious bleeding, it does not increase mortality after stroke. The risk of bleeding is greatest among those persons with multilobar infarction; these are the same individuals that have the highest risk of dying from malignant brain edema and herniation. Guidelines provide recommendations for the administration of rt-PA; the criteria for eligibility for treatment differ for the time periods of less than 3 hours and 3–4.5 hours (Table 12).[28,55] The baseline assessment is relatively limited, which permits the use of the agent in community hospitals.

TABLE 12

Treatment of acute ischemic stroke

- Intravenous thrombolysis
- Interval from onset of stroke:
  - — < 3 hours for persons aged 81 or greater
  - — < 4.5 hours for younger persons
- Absence of medical contraindications (increased risk of bleeding):
  - — History of recent prior stroke
  - — History of recent myocardial infarction
  - — History of recent major trauma
  - — History of recent major operation
  - — History of recent serious bleeding
- Absence of other comorbid diseases that may mimic stroke:
  - — Blood glucose values are not hypoglycemic
  - — Seizures that occur with stroke do not contraindicate treatment
  - — A history of diabetes and prior stroke contraindicates treatment in 3–4.5 hours time period
- Survey of medications that the patient is taking:
  - — Warfarin may be treated < 3 hours if INR is < 1.8
  - — Any warfarin use precludes treatment in 3–4.5 hours time period
  - — Antiplatelet agents are not a contraindication
  - — Treatment of stroke with heparin is a contraindication
  - — Angiotensin converting enzyme inhibitors appear to increase the risk of angioedema after treatment—not a contraindication
- Findings on general medical examination:
  - — Blood pressure: < 185 mm Hg systolic and < 110 mm Hg diastolic
  - — If there is time, blood pressure may be lowered to allow treatment
  - — No evidence of acute bleeding
- Findings on neurological examination:
  - — Demonstrable focal neurological impairments
  - — May be treated even some improvement
  - — Patients with severe stroke have higher risk of bleeding
  - — Patients with NIH stroke scale score > 25 cannot be treated in 3–4.5 hours time period
- Coagulation studies are normal:
  - — Platelet count, prothrombin time, aPTT
- Brain imaging findings:
  - — Absence of brain hemorrhage
  - — Absence of other brain pathology
  - — A “normal” CT in a patient with acute symptoms is assumed to be compatible with acute ischemic stroke
  - — Detection of ischemic stroke (more likely with DWI sequence on MRI)
- Patient and/or family aware of the risks and potential benefits
  - — Overall risk of symptomatic intracranial bleeding is approximately 6% but is higher in severely affected patients
- Administration of rt-PA:
  - — Cannot substitute another thrombolytic agent
  - — Dosage is 0.9 mg/kg—maximum of 90 mg
  - — 10% of dose as intravenous bolus
  - — Remainder infused over 1 hour
- Ancillary treatment:
  - — Close observation for changes in status
  - — Aggressive lowering of increased blood pressure
  - — Delay placement of devices (indwelling bladder catheter, etc.) in order to avoid bleeding
  - — Do follow-up CT scan of brain to look for hemorrhagic transformation at approximately 24 hours after treatment
  - — Delay starting antiplatelet agents or anticoagulants until 24 hours after treatment and CT does not show bleeding

(*Source:* Reference 28)

Ancillary treatment includes close monitoring and aggressive management of arterial hypertension, delaying placement of catheters and other devices, and forestalling administration of anticoagulants and antiplatelet agents until 24 hours after the infusion. Current research is looking at strategies that change selection of patients that could be treated with rt-PA. Other thrombolytic agents are being tested but none has been shown to be superior to rt-PA. The combination of intravenous thrombolysis followed by an intra-arterial therapy for those patients who do not improve is also being evaluated.

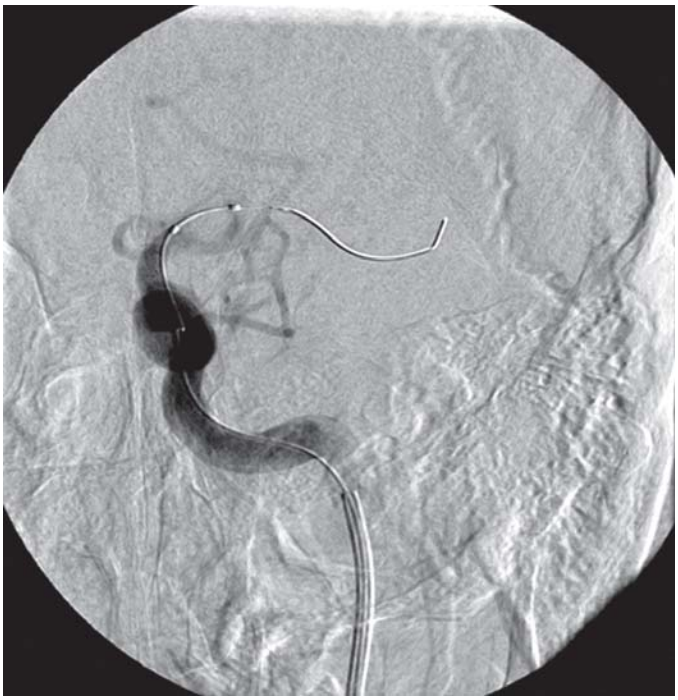


FIGURE 14: An oblique view of a left carotid arteriogram in a patient with a thromboembolic occlusion at the origin of the left middle cerebral artery demonstrates the placement of an intra-arterial microcatheter in the middle cerebral artery

Other interventions for improving perfusion to the brain include intra-arterial administration of a thrombolytic agent. While rt-PA often is given, the only data from a trial are with administration of prourokinase, an agent that is not available in the United States. It demonstrated efficacy for lysis of an intra-arterial thrombus. A variety of mechanical devices that foster lysis or removal of the intra-arterial thrombus are available, some of these have received government approval (Fig. 14).[56,57] While the potential time window for intra-arterial therapy may be longer than that for intravenous thrombolysis, mobilizing the resources to perform these emergency treatments takes time. Although there are programs increasing the number of neurointerventional physicians who can perform these procedures, most hospitals do not have the resources to support this type of therapy. There is uncertainty whether intra-arterial therapies will greatly increase the number of patients who can be treated.

Emergency administration of anticoagulants to persons with acute ischemic stroke was used for several years. The goals were to halt neurological worsening, forestall propagation of the thrombosis and reduce the risk of early recurrent stroke, such as recurrent cardioembolism. Several clinical trials have tested unfractionated heparin or a variety of low molecular weight heparins; no evidence of acute benefit in improving neurological outcomes has been found although these agents do increase the

risk of bleeding complications, including intracranial hemorrhage.[58] At present, there is no strong indication for early administration of anticoagulants to patients with stroke.[59,60] Clinical trials testing aspirin demonstrated a modest improvement of outcomes among persons with ischemic stroke; a small increase in bleeding complications is also found. The other oral antiplatelet agents have not been tested in the setting of acute stroke. Current guidelines recommend initiation of aspirin within 48 hours after stroke.[28] A large number of medications that have presumed neuroprotective effects have been shown to be effective in experimental stroke models. Unfortunately, that success has not been replicated in clinical trials. To date, no neuroprotective agent has been established as safe and effective in treatment of patients with acute ischemic stroke.[28]

TREATMENT OF ACUTE HEMORRHAGIC STROKE

At present, there is not an equivalent to the intravenous administration of rt-PA for treatment of patients with acute intracranial hemorrhage. While initial data suggested that emergency intravenous administration of recombinant Factor VIIa was effective in limiting intracranial hemorrhage and in improving outcomes, subsequent research was unable to confirm this finding. Current guidelines emphasize general emergency supportive care and treatment of arterial hypertension.[30,31] The latter component of management is aimed at limiting the extension of the hematoma. While neurosurgical evacuation of the hematoma is a consideration for treatment of patients with life-threatening bleeding, a clinical trial was unable to demonstrate that surgical treatment was associated with an increased likelihood of a favorable outcome. In particular, surgical treatment of hematomas located in the brainstem, thalamus and basal ganglia was not effective. Surgery may be useful for treating superficial lobar hematomas. Stereotactic surgery may be safer and more effective than open operative treatment. Neurosurgical evacuation of the hematoma is recommended for the treatment of mass-producing cerebellar hemorrhages. In addition, neurosurgical management may include placement of intraventricular catheters to remove CSF and to treat increased intracranial pressure.

Other acute treatment depends upon the presumed cause of the hemorrhage.[30] Patients with bleeding secondary to oral anticoagulants are treated with fresh frozen plasma, clotting factors or vitamin K. Protamine sulfate is administered to patients who have bleeding secondary to heparin. Persons with an inherited bleeding disorder, such as hemophilia, are also treated with clotting factors. Transfusions of platelets are given to those patients with intracranial bleeding secondary to thrombocytopenia. Intracranial hemorrhage following administration of thrombolytic agents, including that given for persons with acute myocardial infarction, usually is treated with a combination of platelets and clotting factor replacement. However, there is little evidence about the utility of this therapy.

Patients with aneurysmal SAH are at high risk for early recurrent aneurysmal rupture. Due to the markedly increased risk of morbidity and mortality with rebleeding, a focus of early management is aimed at treatment of the aneurysm (Figs 15 and 16).[31] While medical management including lowering blood pressure and administration of antifibrinolytic agents (aminocaproic acid or tranexamic acid) were used to lower the risk of bleeding, these agents have not improved outcomes and as a result a surgical intervention is preferred. The options for surgical management include direct surgical clipping of the aneurysmal neck or obliteration of the aneurysm through the endovascular placement of coils. Occasionally, the coiling is accompanied by the placement of a stent to maintain patency of the parent artery. With advances in endovascular technology and expertise, which have improved safety of the procedure, the percentage of patients treated with coiling has increased. A potential disadvantage of endovascular treatment is a subsequent compaction of the coils that will mandate another procedure. Besides rebleeding, patients with aneurysmal SAH have a high risk for cerebral vasospasm and ischemic stroke. This complication, which is correlated with the amount of blood

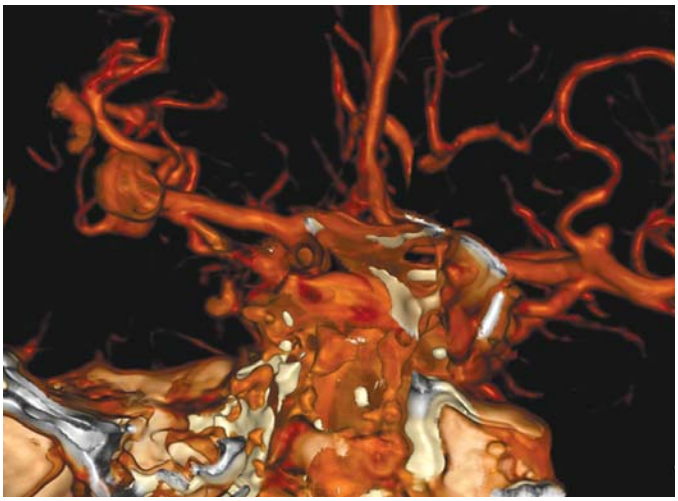


FIGURE 15: An intracranial CT angiogram shows a large aneurysm at the bifurcation of the left middle cerebral artery



FIGURE 16: An anterior-posterior view of a right internal carotid angiogram using subtraction techniques reveals a large intracranial aneurysm at the bifurcation of the middle cerebral artery. The irregular appearance of the aneurysm represents turbulent blood flow within the aneurysm



FIGURE 17: An oblique view of a right internal carotid angiogram shows a large arteriovenous malformation with early draining veins

in the basal cisterns, usually peaks at approximately 7–10 days after the initial hemorrhage. Nimodipine is approved for lessening the risks of ischemic stroke and poor outcomes after SAH and it is prescribed to most patients. Hypotension is a potential side effect. Other options for treatment include drug-induced hypertension and hemodilution that has the aim of improving perfusion through the narrowed intracranial arteries. This vigorous therapy may be accompanied by myocardial ischemia, congestive heart failure or pulmonary edema. Other therapies to treat vasospasm or prevent stroke include intra-arterial administration of nicardipine and angioplasty of the narrowed vessels. Prophylactic angioplasty among patients with asymptomatic vasospasm has not been successful. The utility of these interventions has not been established.

The early risk of recurrent hemorrhage is relatively low among patients with bleeding secondary to a ruptured vascular malformation (Fig. 17). In general, these patients are allowed to recover from their acute event. Subsequent treatment options include direct surgical resection, endovascular obliteration of feeding vessels, and focused high-intensity radiation to lead to scarring and occlusion of the vascular components of the malformation. The selection of treatment is based on the size of the malformation, its location, and the presence and number of feeding and draining vessels. In some cases, staged procedures or combinations of interventions may be prescribed.

GENERAL IN-HOSPITAL CARE

Patients with recent stroke are seriously ill and are at high risk for major neurological and medical complications that may lead to morbidity and mortality. The complications are similar whether the patient has had a hemorrhagic or ischemic stroke.[28,30,31,61] In addition, patients often have other serious comorbid diseases that need to be treated. As a result, patients with acute stroke are admitted to the hospital for monitoring, evaluation and treatment. The patient is observed for the development of neurological worsening or other events. Treatment involves both prophylactic measures and interventions aimed at the lessening the consequences of the stroke (Table 13).

TABLE 13

General management of patients hospitalized with stroke

- Monitoring of neurological status, blood pressure and vital signs:
  - — Frequently during first 24 hours and then intervals are expanded
  - — Cardiac monitoring for arrhythmias
- Intravenous access to be maintained to ease administration of medications
- Levels of activities:
  - — Initially bed rest (usually first 24 hours)
  - — Frequent turning in order to avoid pressure sores
  - — Then increase level of activity as tolerated
  - — Mobilization done with care because of risk for falls
- Diet:
  - — Intravenous fluids to maintain hydration
  - — No food, liquids or medications by mouth until swallowing is assessed and risk of aspiration is deemed to be low
  - — Consistency of oral intake adjusted to ease swallowing
  - — Diet modified to meet comorbid diseases and risk factors
  - — Nasogastric feedings to maintain nutrition and hydration for patients who cannot swallow
  - — If prolonged need for tube feedings, PEG may be needed
  - — Laxatives or suppositories as needed to treat constipation
- Bladder treatment:
  - — Avoid indwelling bladder catheters if possible
  - — Acidification of the urine to help reduce risk of infection
- Prevention of deep vein thrombosis:
  - — Subcutaneous administration of heparin or low molecular weight heparin
  - — Alternating pressure devices and support hoses for those patients who cannot receive anticoagulants
- Passive range of motion of joints
- Prevention of recurrent stroke depends upon type of stroke and etiology:
  - — Antiplatelet agents
  - — Anticoagulants
- Consultation to rehabilitation services for assessment and treatment:
  - — Physical therapy
  - — Occupational therapy
  - — Speech pathology
  - — Social services and discharge planning
- Symptomatic treatment on a case-by-case basis:
  - — Analgesics
  - — Stomach protective medication
  - — Sedatives
  - — Anti-depressants
- Treatment of comorbid diseases and risk factors:
  - — Diabetes mellitus
  - — Hypertension
  - — Heart disease
  - — Lung disease
  - — Renal disease

In general, the major neurological complications of stroke develop within the first week and they include brain edema, hemorrhagic transformation of an infarction, hydrocephalus, increased intracranial pressure and seizures (Figs 18 and 19).[61] Medical and surgical measures are available to address these problems on a case-by-case basis. Subsequently, general medical problems predominate. The leading causes of death after the first week following stroke include infections (especially pneumonia and urinary tract infection), pulmonary embolism and cardiac events. Other medical complications include pressure sores, contractures, fall with a fracture, electrolyte



FIGURE 18: An axial CT scan of the brain shows a large area of hypodensity in the right hemisphere. The findings are compatible with a multilobar cerebral infarction with shift of midline structures

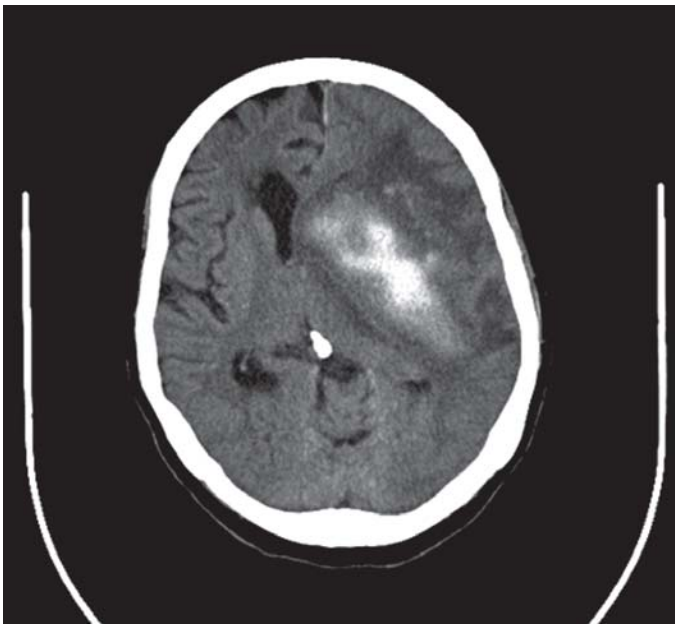


FIGURE 19: An axial CT scan of the brain demonstrates a large area of hyperdensity within a larger area of hypodensity in the left hemisphere. The changes are consistent with hemorrhagic transformation of a large cerebral infarction

disturbances, gastrointestinal bleeding, urinary and/or fecal incontinence, diarrhea and constipation. All these problems need to be prevented or treated. For example, there is strong evidence that the subcutaneous administration of heparin or a low molecular weight heparin may reduce the frequency of deep vein thrombosis among bedridden patients.[62]

REHABILITATION

While early and effective treatment of stroke may prevent residual impairments and eliminate the need for rehabilitation, many survivors of stroke require rehabilitation to maximize recovery after stroke.[63] Assessment of the individual patient's needs is done as soon as the patient is medically stable. Physical therapy, occupational therapy and speech therapy form the core efforts in rehabilitation. Physical therapy is focused on improving general mobility and major motor function. Occupational therapy aims at improving fine motor function (especially the hand) and often uses assistive devices. Speech therapy is aimed at improving swallowing, articulation and recovery of language function. Other potential interventions include cognitive rehabilitation, vocational counseling, recreational therapy, music therapy, etc. The setting of the rehabilitation depends upon the severity and types of impairments and the ability of the patient to collaborate in the rehabilitation program. Possible venues include inpatient rehabilitation (in an independent or hospital-based unit); outpatient therapy in which the patient comes to the facility, in-home treatment with professionals, or at-home therapy provided by the patient and family. The locations of the rehabilitation likely will change as the patient passes through the program.

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Chapter 112

Rheumatic Fever

V Jacob Jose, DM Card

Chapter Outline

- Pathogenesis
  - Group A Beta Hemolytic Streptococci (GABHS) Infection
  - Host Factors—Susceptibility to Acute Rheumatic Fever
  - Immune Response
  - Aschoff's Body
- Epidemiology
- Diagnosis of Rheumatic Fever
  - Recurrent Rheumatic Fever
- Clinical Features
  - Age and Gender
  - Arthritis
  - Carditis
  - Chorea
  - Erythema Marginatum
  - Subcutaneous Nodules
  - Preceding Group A Strep Infection
  - Tests for Active Inflammation (ESR/CRP)
- Treatment
  - Eradication of Streptococci: AHA Statement (Circulation March 2009)
  - Anti-inflammatory Drugs: Salicylates or Steroids
  - Recommended Bed Rest of Varying Duration
  - Secondary Prevention of Rheumatic Fever
  - Duration of Secondary Prophylaxis
  - Rheumatic Fever Recurrence Rates Using Drugs
  - Treatment Algorithm for Rheumatic Fever
  - Prevention in RF/RHD
- Residual Heart Disease
- Management of Chorea

INTRODUCTION

Rheumatic fever (RF) is generally classified as a connective tissue disease or collagen vascular disease. Its anatomical hallmark is damage to collagen fibrils and to the ground substance of connective tissue. The clinical manifestations of RF follow a group A streptococcal infection of the throat after a latent period of approximately 3 weeks.

PATHOGENESIS

For the development of RF, three things are required: (1) Strep infection by the Group A beta hemolytic group; (2) Susceptible host and (3) Immune response (Fig. 1).

GROUP A BETA HEMOLYTIC STREPTOCOCCI (GABHS) INFECTION

The streptococcal etiology of RF is universally accepted. The facts regarding the same are given below:

- Some strains of strep are more likely to result in RF and they are called as Rheumatogenic strains. They are namely, M types of 1, 3, 5, 6, 14, 18, 19, 27 and 29.
- Only when these strains affect the throat they are likely to result in RF. The same strains when they cause pyoderma do not result in RF.
- Streptococci contain certain antigenic determinations that cross react with various tissues in the body.
- Cross reactivity or antigenic mimicry is supposed to result in RF.
- The attack rate of Rheumatic fever**:** Not all patients affected with strep sore throat develop RF. It has been found that only 3% of persons with strep sore throat develop RF in an epidemic and about 0.3% in sporadic cases**.**

HOST FACTORS—SUSCEPTIBILITY TO ACUTE RHEUMATIC FEVER

Several lines of evidence indicate that there could be a genetic susceptibility to the development of acute rheumatic fever. The risk was estimated to be around 2.93 from a study done in Israel.[1] Although significant associations have been found between genetic factors as given below, no definite pattern of inheritance has been identified.

HLA Association

Two theories have been put forward: one is the antibody theory and the other is antigen theory. According to the antibody theory, it is assumed that the streptococcal antigen may mimic the HLA molecule, which results in cytokine production, poor antigenic clearance, prolonged B cell stimulation and increased antibody production.

According to the antigen theory, streptococcal antigens may stimulate the T cells in the context of specific HLA molecules,

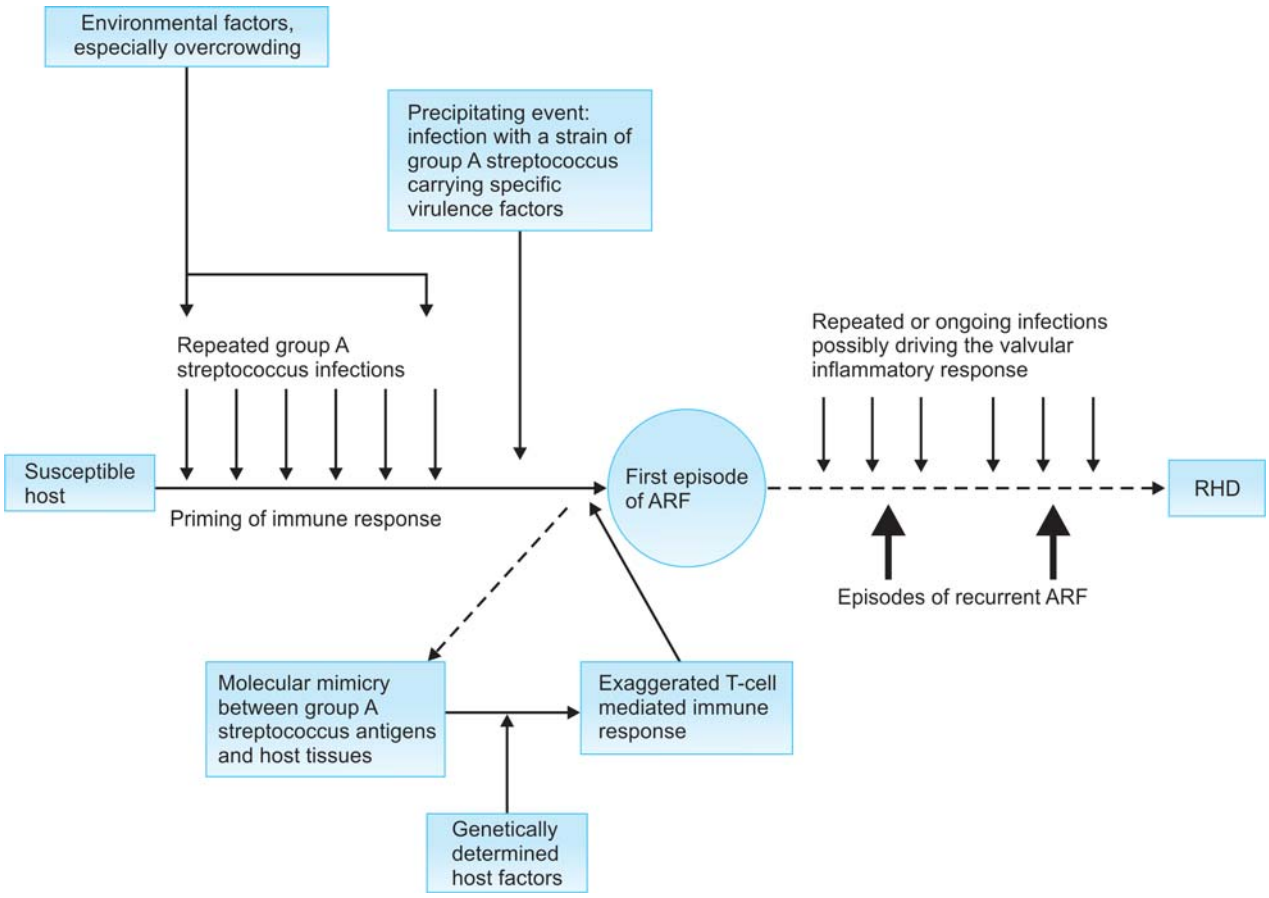


FIGURE 1: Pathogenesis of acute rheumatic fever and rheumatic heart disease.
(*Source:* Modified from Lancet. 2005;366:155-68)

which are cross reactive to tissues affected by the acute rheumatic fever.

B Cell Alloantigens

A strong relationship has been found with a B-cell antigen designated 883; this was expressed on the B cells of 71–74% of rheumatic fever patients compared with only 17% of control subjects. Subsequently another B-cell surface antigen that identified more accurately ARF patients was D8/17. When population specific antibodies were used, it was found that more than 90% of patients in Indian population were positive when compared to controls.[2]

IMMUNE RESPONSE

When a susceptible host develops a GABHS infection, an immune response occurs. There is a molecular mimicry between the epitopes of the strep and many components of the cardiac cell, which leads on to the tissue damage. For example, antibodies formed against the N-acetylglucosamine of the strep carbohydrate cross reacts with the cardiac valve tissue.

ASCHOFF'S BODY

This pathological finding is pathognomonic of RF. This was described in the year 1904. It is made up of perivascular infiltrate of large cells with polymorphous nuclei and basophilic cytoplasm arranged in a rosette around anavascular center of fibrinoid. Some of the cells may be multinucleated or may have an owl eyed nucleus with an eccentric dot and fibrillae radiating to the nuclear membrane or caterpillar nucleus. These cells are called as *Antischkow myocyte*.

Aschoff's bodies are present in the myocardium; these are most marked in the interventricular septum and left atrial appendage. It is not present in areas such as brain or joints. They are found more frequently in younger subjects with mitral stenosis than in those with pure mitral regurgitation.

EPIDEMIOLOGY

The overall incidence of RF/RHD is coming down in most parts of the world except in some parts of Africa—Sub-Saharan Africa. The prevalence of RHD is around 5 per 1,000 whereas in most developed countries it is around 0.5 per 1,000. The Table 1 gives the prevalence of RHD in many parts of the world based on school surveys.

DIAGNOSIS OF RHEUMATIC FEVER

For the diagnosis of acute rheumatic fever, we have been following the Jone's criteria since 1944. However, there are many patients who do not fulfill the criteria of the Jone's criteria and, presently, a new dimension has been added with the advent of echocardiography. The sensitivity of Jone's criteria is 77% and the specificity is 97%.

TABLE 1

Prevalence of RHD across the world[3]

Country	*Prevalence per 1,000*
USA	0.02
Cuba	2.9
Brazil	3.6
Egypt	5.1
Ethiopia	6.4
Saudi Arabia	2.4
India	0.6[4]
Nepal	1.2
Bangladesh	1.2
Aboriginal Australia	6.8

TABLE 2

For the diagnosis of initial attacks of rheumatic fever[5] (1992 updated)

Major	Arthritis Carditis Chorea Erythema marginatum Subcutaneous nodules
Minor	Fever Arthralgia Elevated ESR or CRP Prolonged PR interval in ECG
Supporting evidence of preceding strep infection within the last 45 days	Elevated or rising ASO or other strep antibody test or positive throat culture or rapid antigen test

The current guideline was put forward in the year 1992 as an update. These criteria are to be used only for the initial attacks of rheumatic fever. This does not apply for patients with past history of RF or rheumatic heart disease. For the diagnosis of RF, the criteria have been divided into Major, Minor and Supporting evidence. To diagnose RF, patient should have one major plus two minor or two major with evidence of preceding strep infection (Table 2).

Exceptions to Jone's criteria:

- Chorea
- Indolent carditis
- Recurrent rheumatic fever
- Post streptococcal arthritis

With the above four conditions, Jone's criteria do not apply.

RECURRENT RHEUMATIC FEVER

The 1992 criteria of Jone is only for the initial attacks of RF. Since recurrences are the main reason for worsening of the cardiac damage and due to the fact that recurrences cause only subtle manifestations, WHO has put forward criteria that are given in Table 3. The WHO criteria for the diagnosis of recurrent RF allow us to make a diagnosis of recurrence based on two minor manifestations itself provided there is evidence of preceding strep infection.

TABLE 3

WHO criteria (2002–2003) for the diagnosis of rheumatic fever (RHD)

First episode	Two major or one major and Two minor (similar to Jone's criteria)
Recurrent without RHD	Two major or one major + Two minor
Recurrent with RHD	Two minor with preceding strep infection
Rheumatic chorea	Preceding strep infection criteria not required

CLINICAL FEATURES

AGE AND GENDER

The commonest age at which RF occurs is between 5 and 15 years. Recurrences can occur at any age but the rate falls steadily beyond adolescence. Both genders are affected equally for the acute RF, but chorea is more common in women.

ARTHRITIS

- Occurs in 70% of cases.
- Asymmetrical and migratory in nature.
- Large joint arthritis (knees, ankles, elbows and wrist are involved).
- Pain, swelling, heat and redness are noted.
- Lasts for 2–3 weeks.
- Rapid response to salicylates within 48 hours.
- No residual deformity.

Jaccoud's Arthritis

This is a permanent deformity of small joints, secondary to rheumatic fever, which is very rare.

Post Strep Reactive Arthritis (PSRA)

This form of joint involvement is seen early after an episode of strep infection (10 days vs 14–21 days for RF). It also involves small joints, lasts longer and does not respond to salicylates as easily as RF. Experts believe that these patients be treated with secondary prophylaxis for up to one year at least after the onset of symptoms. But in endemic areas of RF, it may be wise to give prophylaxis for 5 years.

CARDITIS

The cardiac involvement in RF is pancarditis. It involves all the layers of the heart. Carditis occurs in 50% of patients with acute rheumatic fever. In South Asian countries, the incidence of carditis is higher than the western data (range 70–86%). Since carditis includes some or one of the following, the features are given in increasing order of severity.

- Tachycardia (out of proportion to the degree of fever) is common; its absence makes the diagnosis of myocarditis unlikely.
- A heart murmur of valvulitis [caused by mitral regurgitation (MR) and/or aortic regurgitation (AR)] is almost always present; without the murmurs of MR and/or AR, carditis should not be diagnosed.

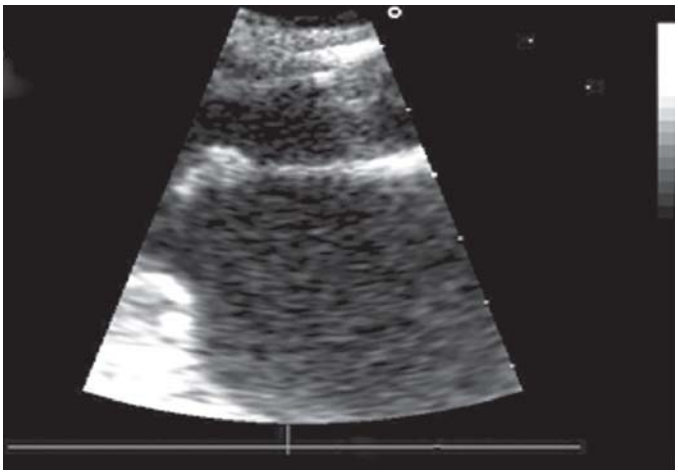


FIGURE 2: Echo showing rheumatic vegetations on the anterior mitral leaflet

- Pericarditis (friction rub, pericardial effusion, chest pain and ECG changes) may be present.
- Cardiomegaly on chest X-ray is indicative of pericarditis or congestive heart failure (CHF).
- Signs of CHF (gallop rhythm, distant heart sounds, cardiomegaly) are indications of severe carditis.

Valve involvement in acute rheumatic fever:
Mitral: 70–75%.
Mitral and Aortic: 20–25%.
Aortic: Isolated 5%.

Carditis—Role of Echo

It is difficult to clinically diagnose mild carditis. Echo is a valuable tool for the diagnosis of a valvular lesion. Echo is capable of evaluating the presence and degree of mitral and aortic regurgitation. The first report regarding the role of echo was by Steinfield in the year 1986. He found that Doppler showed mitral regurgitation even when there was clinically no murmur.[6] Echo Doppler is extremely useful in the diagnosis of carditis by identifying valvular disease even in patients without clinical evidence of carditis. Echo can also identify the presence of pericardial effusion and in some cases identify the fine rheumatic valvular vegetations. However, echo should not be used as sole criteria for the diagnosis of carditis (Fig. 2).

The WHO report recognizing the usefulness of Echo has suggested that Echo be used in the presence of equivocal pathological murmur or in patients with poly arthritis and equivocal minor manifestations.

CHOREA

Also called as *Sydenham's chorea*, or *St. Vitus dance* is the third most common major manifestation. It occurs in 15% of patients in recent outbreaks; however, the overall figure may be around 5% or less. The period of latency between the GABHS infection and the onset of chorea is around three months.

Chorea can occur in two circumstances:

1. As an isolated manifestation of RF and frequently recurs following a new bout of streptococcal pharyngitis. This is called as *Pure chorea.*
2. It may occur as a part of otherwise active RF with manifestations, such as joint pains etc.

After puberty, chorea is almost entirely seen only in women. It may last for a few weeks to few months. It seems to be due to immune mediated reaction to auto antibodies of the basal ganglia. Severe chorea responds to treatment with intravenous IgG.

Chorea is closely related to Post infectious Auto Immune Neurological Diseases (PANDA). These manifestations include Tic, Tourettes syndrome and obsessive-compulsive behavior, all of which are also observed in some patients with chorea. The clinical findings include involuntary and purposeless movements with muscle in co-ordination of the extremities and labile mood.

Signs

- Hyperextension of the fingers, *spooning* when the arms are extended.
- *Pronation* of hands when arms are raised vertically.
- *Milkmaid's grip*—irregular contraction of the hand muscles when the patient presses the hand of the examiner.
- *Wormian tongue*—gross fasciculations of the tongue when extended.
- Clumsiness in fine movements such as buttoning of the shirt.

Duration

Usually self limited and lasts for 2–4 weeks; can last for a few months to 2 years.

Sequlae

- Studies suggest that many patients with chorea may eventually have obsessive-compulsive behavior. No residual neurological deficit is seen in most patients.
- When chorea is associated with other signs of RF, the incidence of valve damage is comparable to that caused by other patients without chorea.
- When chorea is an isolated event—pure chorea, the valve damage is less frequent and mitral stenosis is the late manifestation.

ERYTHEMA MARGINATUM

This is the least frequent manifestation of RF. This is seen as pink macules with a clear center with serpiginous edge. The usual location is in the trunk and sometimes in the limbs but never seen in the face.

SUBCUTANEOUS NODULES

Nowadays the incidence of the same is only around 5%. They are discrete, nontender, measuring 5–20 mm and are located over the extensor surfaces of elbows, knees, ankles, spinous process of vertebra. They occur in crops, appear late in the course of the disease, often 3 weeks or so. They disappear in 2 weeks time. Since it appears late into the disease, it is not useful in the early diagnosis (Fig. 3).

PRECEDING GROUP A STREP INFECTION

Throat culture is the gold standard for identification of a preceding infection. However, children can be carriers of the



FIGURE 3: This picture of patient's elbow showing the subcutaneous nodule

organism rather than have actual infection. At the time of diagnosis of acute RF, only about 11% of patients have positive throat culture. Hence, throat culture is less reliable than streptococcal antibody tests.

RADT: Rapid antigen tests: These tests have become popular to diagnose quickly a strep infection. The specificity is very good but sensitivity is very low.

Anti-streptolysin O (ASO) titer is the one that is used routinely. It is elevated in 80% of patients with acute RF and in 20% of normal individuals. Only 67% of patients with isolated chorea have an elevated ASO titer. ASO titer of at least 333 Todd units in children and 250 Todd units in adults are considered as elevated.

If the clinical suspicion is high but the ASO titer is low, this does not exclude the diagnosis of acute rheumatic fever. Then you must do one more test such as anti-deoxyribonuclease B test (ADNB) or repeat the ASO titer after a week. A rising titer of ASO can be taken as evidence for acute rheumatic fever. Both ASO and ADNB levels rise at 1 week, peak at 3–6 weeks and persist for several months.

Streptozyme test is relatively simple agglutination test but it is less standardized and less reproducible than the other antibody test. It should not be used as a definitive test for evidence of preceding group A streptococcal infection.

TESTS FOR ACTIVE INFLAMMATION (ESR/CRP)

Erythrocyte sedimentation rate: ESR is almost always elevated in patients with acute RF. A normal ESR is uncommon. However, ESR is likely to be normal in patients with chorea or isolated erythema marginatum or severe cardiac failure.

CRP is so named because of its reactivity with the C polysaccharide of pneumococcus, appears in blood during the course of any inflammatory condition. According to some authors, it reflects rheumatic activity more closely than the ESR since it is not affected by factors such as anemia, changes in serum proteins. It is useful in identifying rebounds during withdrawal of suppressive anti-inflammatory drugs.

TREATMENT

- Eradication of streptococci
- Anti-inflammatory salicylates or steroids
- Bed rest
- Secondary prophylaxis

ERADICATION OF STREPTOCOCCI: AHA STATEMENT (CIRCULATION MARCH 2009)[7]

Of the several regimens given below, intramuscular benzathine penicillin and oral penicillin V are the recommended antimicrobial drugs for the treatment of GABHS except in individuals with penicillin allergy (Table 4).

In the 2009 recommendations of AHA, the treatment of choice is oral or intramuscular penicillin. The main changes are following :

- *Once-a-day Amoxicillin* is a suitable alternative for young children who cannot take pills and who can instead take amoxicillin suspension, which also has the advantage of being more palatable than penicillin.
- With *allergic to penicillin*, not type-1, can be given cephalosporin or clindamycin. The macrolides, such as azithromycin are de-emphasized because there is increasing resistance of GAS to this group of antibiotics and they are not as well tolerated, often provoking gastrointestinal symptoms.
- For those with *severe type-1 allergies to penicillin, clindamycin should be the first choice,* because there is a

TABLE 4

Treatment of strep tonsillopharyngitis

Drug	*Dose*	*Mode*	*Duration*
Benzathine penicillin	600,000 if weight ≤ 27 kg 120,000 if weight > 27 kg	Intramuscular	Once
Penicillin V	250 mg 3 times daily < 27 kg 500 mg 3 times daily > 27 kg	Oral	10 days
Amoxicillin	50 mg/kg once daily	Oral	10 days
Cephalexin/Cefadroxil	Variable dose	Oral	10 days
Clindamycin	20 mg/kg divided in 3 doses Maximum 1.8 g/day	Oral	10 days
Azithromycin	12 mg/kg once daily, maximum 500 mg/day	Oral	5 days
Clarithromycin	15 mg/kg divided into 2 doses	Oral	10 days

TABLE 5

Duration of anti-inflammatory agents

Clinical manifestation	*Prednisolone*	*Aspirin*
Arthritis alone	-	1–2 weeks
Mild carditis	-	3–4 weeks
Moderate carditis	-	6–8 weeks
Severe carditis	2–6 weeks*	6 weeks–4 months

*For severe carditis, prednisolone should be tapered and aspirin be started during the final week and the total duration of anti-inflammatory therapy can be between 6 weeks and 4 months, depending on the need.

10% crossover (for allergy) with narrow-spectrum cephalosporins.

The following drugs are not acceptable**:**

1. Sulphanomides
2. Trimethoprim
3. Tetracyclines
4. Fluroquinolines

ANTI-INFLAMMATORY DRUGS: SALICYLATES OR STEROIDS

They must not be started until a definitive diagnosis is made. Early therapy with these drugs may interfere with definitive diagnosis of acute rheumatic fever (see the treatment algorithm given below) (Table 5):

a. Prednisolone is used in a dose of 2 mg/kg/day in 4 divided doses for a period of 2–6 weeks in cases with severe carditis.
b. For mild moderate carditis, aspirin can be used in a dose of 90–100 mg/kg/day in 4–6 divided doses. This dose is continued for a period of 4–8 weeks depending on the clinical response. After improvement, the therapy is withdrawn gradually over 4–6 weeks.
c. For arthritis alone, aspirin is continued for 2 weeks and gradually withdrawn for a period of 3 weeks. In acute RF there is rapid resolution of joint symptoms within 24–36 hours.

RECOMMENDED BED REST OF VARYING DURATION

The duration depends on the severity of the clinical manifestation. ESR is a helpful guide to the rheumatic activity and, therefore, the duration of restriction of activities. Table 6 will give you a general guideline for bed rest/restricted ambulation period.

TABLE 6

General guidelines of restricted activities in acute rheumatic fever

Clinical feature	*Duration of bed rest/ limited ambulation*
Arthritis alone	Only 2 weeks
Mild carditis	3–4 weeks
Moderate carditis (definite but mild cardiomegaly)	4–6 weeks
Severe carditis (marked cardiomegaly, cardiac failure, pericardial effusion)	Bed rest as long as patient has heart failure and indoor ambulation for a period of 2–3 months

TABLE 7

Drugs used in secondary prophylaxis

	Drug	*Dose*	*Route*
1.	Benzathine penicillin G	1.2 million units every 3–4 weeks	IM
2.	Penicillin V	250 mg twice daily	Oral
3.	Sulfadiazine	0.5 gm once daily for patients ≤ 27 kg or 1.0 gm once daily for patients > 27 kg	Oral
4.	Allergic to penicillin and sulfadiazine: Erythromycin	Erythromycin 250 mg twice daily	Oral

SECONDARY PREVENTION OF RHEUMATIC FEVER

The following table (Table 7) gives the dose and the duration for secondary prophylaxis. Tri-weekly regimen of benzathine penicillin is justified and recommended for countries, like India, where the incidence of RF is high. It has been shown that in warm countries, the drug level may fall well below the protective level in the 3rd week itself. The drugs used for secondary prophylaxis is given in Table 6.

DURATION OF SECONDARY PROPHYLAXIS

The table below gives the duration of prophylaxis as per two guidelines. In Table 7, the AHA one is given. In Table 8, WHO one is given. These two guidelines differ in the duration and age cut-off as given below. According to the ACC/AHA, the cut-off age is 21 years whereas in the WHO, the cut-off age given is different (Table 9).

TABLE 8

Duration of secondary prophylaxis—AHA 2009

	Category	*Duration*
1.	RF with carditis and residual valvular disease	At least 10 years after last episode and at least until age 40 years. Sometimes lifelong prophylaxis
2.	RF with carditis but no residual valvular disease	10 years or up to 21 years of age whichever is longer
3.	RF without carditis	5 years or up to 21 years of age, whichever is longer

TABLE 9

Duration of secondary prophylaxis as per WHO (WHO Tech report 923). The WHO's secondary prophylaxis duration gives a different cut-off age limits in comparison to the ACC/AHA one. The AHA uses a uniform cut-off age of 21 years

Category	*Duration*
RF with Carditis with severe valvular disease or After Valvular Surgery	Lifelong
RF with carditis (healed or mild mitral regurgitation)	10 years after the last attack or 25 years of age whichever is longer
RF without carditis	5 years or age of 18 years whichever is longer

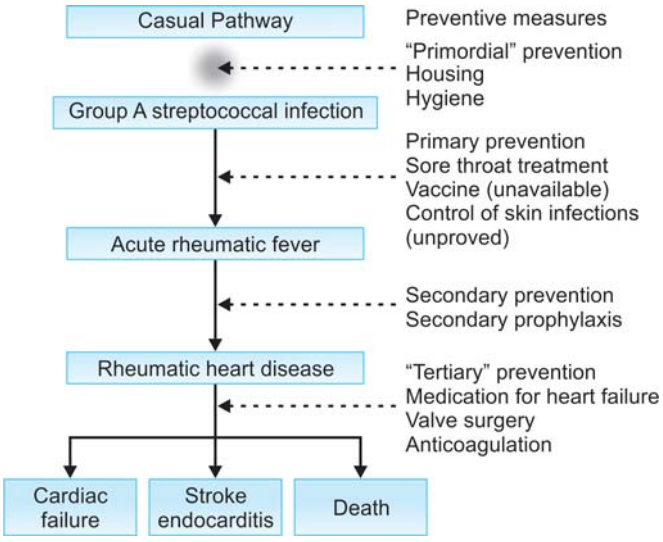
RHEUMATIC FEVER RECURRENCE RATES USING DRUGS

- 3 weekly Benzathine penicillin — 0.25/100 person years
- 4 weekly Benzathine penicillin — 1.29/100 person years
- Sulfadiazine — 2.8/100 person years
- Oral penicillin — 5.5/100 person years

Since risk of recurrence is higher with oral penicillin, it is usually given for individuals who have reached young adulthood and remained free of rheumatic attacks for at least 5 years.

TREATMENT ALGORITHM FOR RHEUMATIC FEVER (FLOW CHART 1)

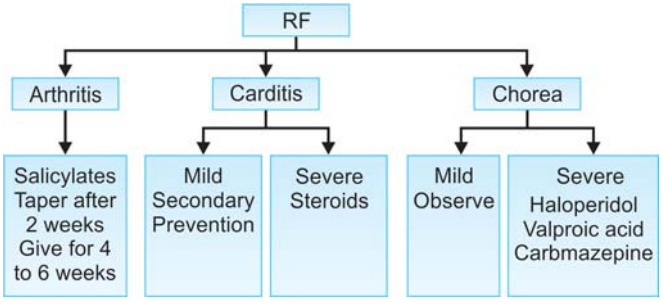
FLOW CHART 1: Algorithm for rheumatic fever



PREVENTION IN RF/RHD

The overall prevention of RF/RHD can be listed as Primordial, Primary, Secondary and Tertiary as shown in Flow chart 2 below.

FLOW CHART 2: Types of prevention with RF/RHD



(*Source:* Modified from NEJM. 2007;357(2):439-41)

RESIDUAL HEART DISEASE

With the advent of primary and secondary prophylaxis, there is a decrease in the incidence of RF and recurrences as well. The net result is that death due to RF and RHD also has come down. In a 10-year follow-up of 115 patients with regular prophylaxis, it was found that 70% of patients with mitral regurgitation murmur and 27% of patients with aortic regurgitation had disappeared.[8] It is also interesting to note that none in this group developed aortic or mitral stenosis. This data suggest that regular prophylaxis can be helpful in the prevention of residual heart disease developing in a large proportion of cases.

MANAGEMENT OF CHOREA

Anti-inflammatory drugs, such as salicylates or steroids, do not alter the course of chorea and are not indicated unless there is clear indication for concomitant carditis. One of the following drugs may be used:

1. Phenobarbital—15–30 mg every 6th hourly.
2. Haloperidol—2 mg every 8th hourly or as needed.
3. Valproate—20 mg/kg/day.

CONCLUSION

Acute RF and rheumatic heart disease still forms a major health problem in developing countries. Early diagnosis and proper treatment of the disorder will prevent the marked disability left behind by this disease.

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Section 15

EVOLVING CONCEPTS

Chapter 113

The Genomics of Cardiovascular Disease

Samir B Damani, Eric J Topol

Chapter Outline

- A Genomic Primer
- Intermediate Phenotypes
  - Lipid Traits
  - Hypertension
- Coronary Artery Disease
  - Lipoprotein (a)
  - 9p21
- Arrhythmias
  - Atrial Fibrillation
  - QT Interval and Sudden Cardiac Death
- Cardiovascular Pharmacogenomics
  - Antiplatelet Agents
  - Warfarin
  - Statins
  - Beta-blockers in Heart Failure
- SNP Profiling Studies
- Future Directions

INTRODUCTION

Over the last four years, an unprecedented number of discoveries illuminating the genetic underpinnings of scores of common 'polygenic' traits have materialized.[1] These findings are the primary byproduct of hundreds of large-scale Genome-Wide Association Studies (GWAS) that have been spawned by a combination of rapidly advancing DNA genotyping technologies and striking reductions in financial cost.[2] Through GWAS, dozens of novel pathobiologic pathways in numerous cardiovascular disorders have been identified.[2] Moreover, several pharmacogenetic variants with a significant impact on drug efficacy and toxicity have emerged.[3-7] Now, targeted and whole genome sequencing is enabling the discovery of rare susceptibility variants at a pace equal to that seen with common variants in GWAS.[8,9] Together, these findings have the potential to radically change the practice of medicine. Herein, the authors outline some fundamental concepts that will allow the reader to comprehend the current developments in the field, highlight the most transformative genomic and pharmacogenomic findings to date as they relate common cardiovascular conditions, and underscore the areas needed for future progress.

A GENOMIC PRIMER

Prior to embarking on a detailed review of the genomic findings that have taken place over the last decade, it is first important to understand a few fundamental concepts regarding the heritability of traits. Simple 'monogenic' disorders or traits typically follow classic Mendelian patterns of inheritance. To date, over 5,000 monogenic phenotypes have been identified with an autosomal dominant, recessive, X-linked or a mitochondrial mode of inheritance.[10] However, despite this formidable number, monogenic disorders are exceedingly rare with the most common of these disorders affecting no more than one in several hundred people.[11] Examples of such simple traits in cardiovascular disease include familial hypertrophic cardiomyopathy, familial hypercholesterolemia and the long-QT syndromes (LQTS). In contrast, the vast majority of illnesses that affect public health follow complex inheritance patterns and involve multiple gene-gene and gene-environmental interactions.[12] These complex polygenic traits include coronary artery disease (CAD), MI, diabetes, dyslipidemia and atrial fibrillation (AF) to name a few.

Earlier approaches to defining the genetic basis of complex traits involved selectively investigating DNA polymorphisms in single or multiple candidate genes based on the known biologic significance of these genes. This hypothesis driven approach precludes the discovery of genes with yet unknown, but potentially substantial impact on disease susceptibility. It is this vital omission that has resulted in the failure of most of these single gene studies to replicate their findings in independent cohorts. On the other hand, GWAS can simultaneously assay for hundreds of thousands of common DNA variants in a hypothesis-free manner for disease and drug response associations.[13,14] It is this latter unbiased approach to gene discovery that has allowed for the identification of nearly 800 gene variants that are strongly tied to over 150 common polygenic traits.[1] Most importantly, these susceptibility variants have now been independently validated as legitimate predictive biomarkers in hundred of large cohorts involving millions of cases and controls. Notably, the genomic underpinnings illuminated through these studies have spanned the spectrum of human diseases from common traits, such as CAD and diabetes, to more uncommon disorders such as exfoliative glaucoma and various cancers[13,14] (Table 1).

TABLE 1

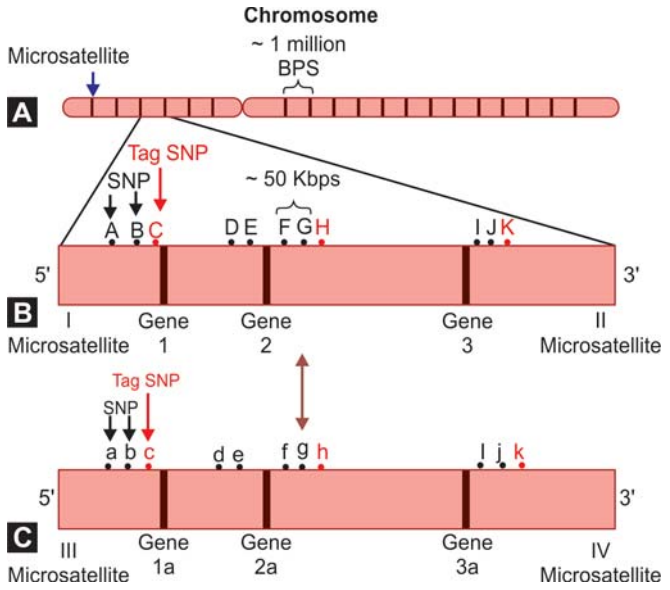
Recent common and rare gene variants strongly linked to cardiovascular phenotypes*

Gene or Locus	*Phenotype*	*Experimental method*	*Effect size (OR)† (single allele)*	*Effect size (OR) (multiple alleles)*	*References*
9p21.3 (CDKN2A, CDKN2B)	MI AAA IA PAD	GWAS	1.2–1.4 1.31 1.29 1.14	1.6–2.0 1.74 1.72 —	*49–52, 55*
DAB2IP	Early Onset MI AAA PE PAD	GWAS	1.18 1.21 1.20 1.14	— — — —	*54*
LPA	CAD	GWAS, candidate gene, resequencing	1.7–1.9	2.5–4.0	*38, 41*
APOE	CAD LDL	GWAS, candidate gene, resequencing	1.1–1.4	1.2–1.6	*27, 103*
PCSK9	CAD LDL	GWAS, resequencing	0.11–0.5; 1.13° —	— —	*19, 20, 27*
LDLR	CAD LDL	GWAS	1.3 —	— —	*27*
SORT1	CAD LDL	GWAS	1.3 —	— —	*27*
ANGPTL4	HDL	GWAS	—	—	*27*
CETP	HDL	GWAS, candidate gene	—	—	*27*
ABCA1	HDL	GWAS	—	—	*27*
ANGPTL3	TG	GWAS	—	—	*27*
APOA5	HTG	GWAS, resequencing	3.28	—	*8*
GCKR	HTG	GWAS, resequencing	1.75	—	*8, 27*
LPL	HTG	GWAS, resequencing	0.32	—	*8, 27*
APOB	HTG	GWAS, resequencing	1.67	—	*8, 27*
4q25(PITX2)	AF	GWAS	1.4–1.7	3.7	*64, 65*
ZFHX3	AF	GWAS	1.2	—	*66*
KCNN3	AF	GWAS	1.5	—	*64*
NOS1AP	QT interval SCD	GWAS, candidate gene	— 1.31, 0.57^	—	*73–76*
21q21 (CXADR)	VF	GWAS	1.5–1.8	—	*77*

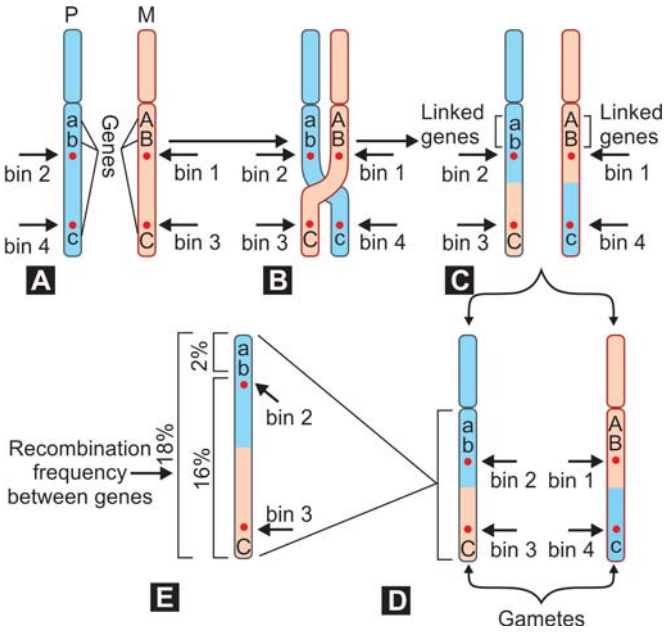
*Newly discovered non-Mendelian common and rare susceptibility variants. All variants in genes listed have reached stringent statistical association criteria.
†Effect size for continuous variables not listed.
°Rare loss-of-function variants in *PCSK9* result in a significant protective effect, while common variants identified through GWAS confer heightened risk for CAD.
^Independent susceptibility and protective allele in NOS1AP reported.
(Abbreviations: MI: Myocardial infarction; AAA: Abdominal aortic aneurysm; IA: Intracranial aneurysm; PAD: Peripheral arterial disease; PE: Pulmonary embolism; CAD: Coronary artery disease; LDL: Low density lipoprotein; HDL: High density lipoprotein; HTG: Hypertriglyceridemia; AF: Atrial fibrillation; VF: Ventricular fibrillation; GWAS: Genome-wide association study)

The main enabling component of GWAS has been the identification of the 10 million or so single nucleotide polymorphisms (SNPs) that commonly vary between individuals and carry at least a 5% minor allele frequency (MAF).[13-16] Interestingly, these SNPs are not inherited independently but as groups of SNPs in 'blocks' or 'bins' otherwise known as haplotypes. Further, the genotype of one SNP can infer the genotypes of all other SNPs within a haplotype block, thereby tagging an entire genomic region of interest (Figs 1A to C). Therefore, by assaying just 1 million of these common 'tag' SNPs, a GWAS is essentially assessing hundreds of thousands of genomic blocks for disease associations.

Another recent key advance is the striking reduction in costs associated with DNA sequencing.[2,17,18] In the decade, since the publication of the initial draft of the human genome, the cost for sequencing 1 million DNA bases has dropped by over 15,000 fold. This has led to large scale resequencing programs, which are rapidly identifying rare genetic polymorphisms (MAF < 5%) involved in a number of common cardiovascular traits. As an example, Cohen et al. recently identified rare loss-of-function variants in *PCSK9* [MAF 2% in African Americans (AAs)] by resequencing nine exons and intron sequences of *PCSK9* in 32 individuals with very low LDL levels from an initial cohort of over 2,000 AA and European individuals.[19] The rare variants



FIGURES 1A TO C: Single nucleotide polymorphisms (SNPs), Tag SNPs and microsatellites as genomic markers. (A) Autologous chromosome with evenly spaced microsatellites. (B) Segment of DNA between microsatellite markers. Single nucleotide polymorphisms are noted (A, B, C…) within the DNA segment. Tag SNPs (C, H, K) travel with other noted SNPs as blocks (haplotypes) and can serve as a surrogate for these haplotypes and more importantly disease causing genes in close proximity. (C) DNA segment with alternative alleles and genomic markers of the same genes designated in part B of the figure. Note that the microsatellite markers are not as close in proximity to the genes as the noted SNPs. (*Source:* Damani SB, Topol EJ. Future use of genomics in coronary artery disease. J Am Coll of Cardiol. 2007;50:1933-40, with permission)



FIGURES 2A TO E: Schematic of genetic linkage and recombination. (A) Two homologous chromosomes: blue (paternal) and orange (maternal). Three genes with separate alleles and linkage disequilibrium 'bins' noted. (A,a; B,b; C,c; bins 1–4). (B) Crossing over during meiosis. (C) Two alleles and their linked bins (C,c; bins 3 and 4) have switched locations via recombination. Four additional alleles and their associated bins (A,a; B,b; Bins 1 and 2) have not switched and are considered linked. (D) Recombined haploid chromosomes segregate separately during meiosis as gametes prior to fertilization. (E) Sample recombination frequencies between genes demonstrating higher rates of recombination for genes further apart. (*Source:* Damani SB, Topol EJ. Future use of genomics in coronary artery disease. J Am Coll of Cardiol. 2007;50: 1933-40, with permission)

identified resulted in a 40% reduction in LDL plasma levels, and in a subsequent study, conferred an impressive 50% reduction in risk for CAD, thereby underscoring the importance of life-long reduction of LDL cholesterol.[20]

Novel approaches to genetic association studies using "Mendelian randomization" principles are also producing key findings on genetic contributors to important intermediate phenotypes such as inflammation, plasma lipoproteins and homocysteine.[21,22] This approach leverages the fact that genes undergo recombination prior to gamete formation and then are randomly transferred from parent to offspring during conception.[23,24] Thus, a Mendelian randomization study that assesses the impact of a gene product on disease phenotype is in essence tantamount to a randomized clinical trial and in some aspects superior. However, confounders of these trials do exist and include potential causative variants that are nearby or in linkage disequilibrium (LD) (Figs 2A to E) with the gene variants being studied, as well as population admixture from ancestral populations that carry different risks for disease and different genotypes.[24] Notably, both of these confounders can be easily accounted for by proper methodology and study design.

Zacho et al. recently leveraged Mendelian randomization principles in their study of genetically elevated C-reactive protein (CRP) and ischemic vascular disease.[22] For several decades, CRP has been an established inflammatory biomarker strongly tied to ischemic vascular disease. However, it was unclear whether CRP was simply a biomarker or actually contributed to disease causation. Therefore, the investigators assessed two independent populations of over 50,000 cases and controls for the effect of CRP polymorphisms on plasma CRP levels and subsequently on ischemic vascular disease. Interestingly, four CRP polymorphisms resulted in a difference of plasma CRP levels of up to 64%. However, individuals with genetically elevated CRP did not possess an increased risk for vascular disease. Conversely, the link between elevated CRP and vascular disease remained strong with CRP levels greater than 3 mg/dL conferring a 60% and 30% increase in risk for coronary and cerebrovascular disease respectively. Thus, for the first time, these results clearly demonstrated that CRP is likely a marker of disease, rather than causative.

When reconciling the genetic data on CRP with the recent high profile JUPITER (Justification for the Use of Statin in Prevention: an Intervention Trial Evaluating Rosuvastatin) trial, the value of Mendelian randomization becomes more apparent.[25] In JUPITER, 17,802 otherwise healthy men with normal LDL (< 130 mg/dL) and CRP levels greater than 2 mg/dL were randomized to rosuvastatin or placebo. Patients on rosuvastatin experienced an average 50% reduction in LDL cholesterol and a 37% reduction in CRP. After two years, the trial was stopped early secondary to an impressive 50% reduction of MI and stroke risk in patients on rosuvastatin. Unfortunately, an additional control group with normal CRP and LDL levels was not included. Nevertheless, upon integration of CRP genetic data with JUPITER, it is clear that CRP was not mediating the

observed benefit. Rather, diminished systemic inflammation secondary to rosuvastatin therapy was the more likely culprit. Interestingly, this latter observation would be consistent with the purported pleiotropic effects of statin therapy on decreasing inflammation.

INTERMEDIATE PHENOTYPES

LIPID TRAITS

Recently, three seminal studies on lipid traits have contributed substantially to our understanding of the complex genetic architecture of this important and highly heritable phenotype.[8,26,27] First, a GWAS meta-analysis that assessed 2.6 million SNPs in over 100,000 individuals from diverse ancestries found an impressive 95 loci strongly linked to LDL, HDL and plasma triglyceride levels ($p < 5 \times 10^{-8}$).[27] Of these, 59 were novel, 39 were, in previously, established lipid genes and 18 were in genes involved in classic Mendelian lipid disorders. Notably, a risk score based on these 95 loci showed that individuals in the top quartile were 13 times as likely to have high LDL, 4 times as likely to have high HDL, and a striking 44 times as likely to be hypertriglyceridemic as compared to individuals in the lowest quartile of genetic risk.

In an accompanying report, the investigators further defined the genomic region on chromosome 1p13, which was the most significantly associated LDL locus from the original GWAS meta-analysis ($p = 1 \times 10^{-170}$).[26] Remarkably, wild-type (wt) homozygotes had significantly elevated small dense and total LDL cholesterol levels (16 mg/dL), as well as a corresponding 40% increase in risk for ischemic heart disease when compared to minor allele homozygotes. The protective SNP (rs12740374) resides in a noncoding region between the two genes *CELSR2*, *PSRC1* and nearby another gene *SORT1*, which functions as a cell-surface receptor sorting protein. Importantly, prior to this study, none of these genes had clearly defined roles in lipid metabolism. Hence, the investigators designed multiple rigorous experiments to conclusively determine how the 1p13 variants impact lipid metabolism. First, using expression quantitative trait locus (eQTL) analysis, they found that minor allele carriers of rs12740374 displayed a 12-fold increase in liver *SORT1* and *PSRC1* expression, but not of *CELSR2*. Second, they demonstrated that rs12740374 enhanced binding of the liver specific transcription factor *CEBPA* and resulted in large changes of *SORT1* expression in the liver, but not in adipose tissue. Third, adenovirus mediated *SORT1* transfection in mice resulted in significantly reduced levels of small dense and total LDL cholesterol, which completely replicated the human phenotype. Then, in a final confirmatory step, *SORT1* knockdown through small-interfering RNA (siRNA) was shown to reverse the observed effect on LDL cholesterol incontrovertibly demonstrating that the protective LDL phenotype conferred by the 1p13 variant is mediated through *SORT1* gene expression and not *PSRC1* or *CELSR2*.

In the third and final lipid related study, Johansen et al.[8] followed up a GWAS of over 2,000 hypertriglyceridemia (HTG) cases and controls with extensive resequencing of coding regions of the top four gene hits from their GWAS (*APOA5, GCKR, LPL* and *APOB*). The *APOA5* variant, rs964184 (MAF 0.33, 0.14; cases vs controls), was the most significantly associated gene variant and conferred a striking 328% increase in risk for HTG in heterozygous carriers. The other top variants also exhibited remarkably strong effects and underscore the substantial contribution of common gene variants to HTG relative to other lipid traits. Resequencing of these regions revealed 47 rare functional variants in HTG cases versus only 9 in the healthy controls ($p = 4.4 \times 10^{-5}$). However, the number of accumulated rare variants surprisingly did not predict the strength of the association. Subsequently, logistic regression showed that common and rare DNA sequence variants explained a greater portion of the risk for HTG than clinical variables (22% vs 19%). Hence, for the first time, they show that genetic contributors to common lipid phenotypes have substantive clinical values.

Several additional groundbreaking aspects of these studies require emphasis. First, by using a meta-analytic approach in variant detection, the investigators were able to dramatically increase their sample size and hence, their ability to detect additional loci that would otherwise be missed by smaller less powerful GWAS. Second, substantial heritability of lipid traits across diverse ancestries (Europeans, AAs, South and East Asians) has now been confirmed in a large population study for the first time and, most importantly, the *SORT1* story serves as the reference standard on how genomic studies can illuminate novel biologic pathways of disease that can serve as key targets for future therapies, independent of the magnitude of effect on the studied phenotype.

HYPERTENSION

The growing success stories of GWAS unraveling the genetic underpinnings of complex traits have not fully translated to hypertension. In fact, the first six GWAS conducted on this phenotype failed to produce any findings that reached genome-wide significance ($p < 5 \times 10^{-8}$).[28-33] This is despite the strong heritability of this trait, which is estimated to be 50–60% in some studies.

A multitude of variables accounts for this discrepancy. Foremost, accurate baseline phenotyping in the thousands of cases and controls required by most GWAS is extremely difficult secondary to daily BP fluctuations, concomitant medication use and variability in measurement techniques. Additionally, accurate recording of vitally important lifestyle factors, such as salt intake and daily exercise, is equally as challenging. Further, many GWAS conducted to date have incorporated thousands of population based 'healthy' controls with minimal phenotyping, a process that would miss cases of occult hypertension. Lastly, despite the fact that the majority of complex trait susceptibility variants identified through GWAS are highly significant from a statistical standpoint, their effect sizes have been modest in most cases. Thus, even minor inaccuracies or failure to account for the confounders above could result in false negative findings.

Despite these challenges, three recent GWAS have produced findings of interest by utilizing larger sample sizes and the extending their studies to include ancestral populations originating outside of Europe.[34-36] These critical differences provide two key advantages. First, larger samples sizes enhance

statistical power and the potential for detecting disease-causing variants as exemplified by the recent success in lipid traits. Second, the study of 'older' ancestral populations (AAs) with denser haplotype maps allow for DNA variant identification that may otherwise be missed if studying 'younger' European populations, which on average possess fewer common variants.

Notably, two of the three recent GWAS were meta-analyses and assessed approximately 2.5 million SNPs in over 70,000 cases and controls.[35,36] Remarkably, 18 SNPs were found to be tied to either hypertension or blood pressure at a genome-wide significance level. The effects of the variants were quite modest with each variant contributing an average 0.5–1 mm Hg to systolic or diastolic BP. On the other hand, the variants detected are in regions of plausible biologic significance and include pathways of mineralocorticoid excess, cardiac malformations, atrial natriuretic peptide formation and voltage-gated calcium channels. The 3rd GWAS conducted in AAs revealed an additional 6 BP associated SNPs. However, of the 24 newly discovered susceptibility loci, only 3 were replicated between the studies, thus highlighting the substantial genetic complexity behind common forms of hypertension that has yet to be explained.

A primary source of the missing heritability in hypertension may be rare DNA sequence variants (MAF < 5%) and gene copy number changes that are in genomic regions not accessible to common SNP-centric GWAS. As proof of principle, Ji et al.[37] resequenced all coding exons and flanking intron sequences of SLC12A3, SLC12A1 and KCNJI in over 2,000 participants from the Framingham Heart Study (FHS) offspring cohort. Recessive loss-of-function mutations in these genes have been linked to Bartter's and Gitelman's disease, which are rare Mendelian syndromes associated with renal salt wasting and hypotension. Strikingly, 1 in 64 FHS participants were noted to carry a functional mutation in the genes, which is far greater than the estimated prevalence of 1 in 1 million and 1 in 40,000 of Bartter's and Gitelman's syndromes respectively. Most importantly, these rare mutations were highly protective with heterozygous carriers showing an average 9.0 mm Hg lower systolic BP and an impressive 60% reduction in risk for hypertension by age of 60.

CORONARY ARTERY DISEASE

LIPOPROTEIN (a)

Of the 95 common lipid altering DNA sequence variants identified in the GWAS meta-analysis noted above (Lipid Traits), 14 of them conferred statistically significant risk for CAD.[27] The vast majority of these loci involve pathways implicated in LDL metabolism (71%), thereby underscoring the significant role and appropriate attention that LDL cholesterol receives in routine clinical practice. However, in the last year, common and rare susceptibility variants in the lipoprotein (a) gene (*LPA*) have emerged as one of the strongest genetic predictors for CAD and MI seen to date.[38] The lipoprotein (a) molecule is an LDL particle covalently linked to the plasminogen-like glycoprotein, apolipoprotein (a) [apo (a)] (Fig. 3). For over four decades, Lp (a) has been a putative risk factor for IHD.[39] However, the extent of its contribution has been arguable.[40]

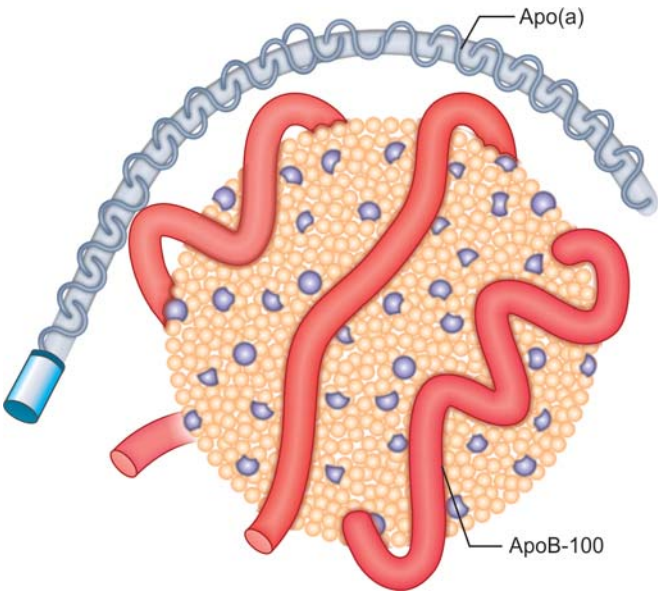


FIGURE 3: Lipoprotein(a) Molecule. Lipoprotein(a) consists of an LDL particle and a glycoprotein molecule, Apo(a), attached to the ApoB-100 moiety of the LDL particle through a disulfide bond. Apo(a) size is determined by the number of kringle repeats. (*Source:* Modified from Danesh J, Erqou S. Lipoprotein(a) and coronary disease—moving closer to causality. Nat Rev Cardiol. 2009;6:565-7)

Now, three independently conducted studies have confirmed the *LPA* link to CAD and MI.[21,38-41] The initial confirmatory study was a three-stage GWAS.[41] In the first stage, over 500,000 SNPs were assessed in over 2,000 CAD cases and controls. The most significantly associated SNPs (p < 10-5) were then validated in the second stage. Subsequently, four SNPs in two haplotype blocks on chromosome 6q26-27, which encompasses the *LPA* gene, were tested in a third stage. On final population-adjusted analysis of all stages, both haplotypes were significantly associated ($p = 1.0 \times 10^{-13}$, $p = 1.0 \times 10^{-15}$) with CAD with odds ratios (OR) of 1.2 and 1.8 respectively.

In a second study, Kamstup et al.[21] demonstrated that common kringle IV type II (KIV-2) copy number polymorphisms (CNPs) in *LPA* conferred a 50% increase in risk for CAD independent of plasma Lp (a) levels in a prospective cohort of 9,000 subjects followed for 16 years. Importantly, *LPA* KIV-2 CNPs have been linked to both quantitative and qualitative features of Lp (a), with increasing CNPs directly correlating to apo (a) size, but inversely correlating to Lp (a) levels and CAD risk. Notably, larger apo (a) isoforms hamper hepatocyte secretion of the molecule and result in lower plasma Lp (a) levels.

In a final related study, a novel cardiac gene chip incorporating over 48,000 SNPs was used to assess CAD risk in over 7,000 cases and controls.[38] The *LPA* locus on 6q26-27, initially identified in the GWAS above, was the strongest susceptibility locus in this study as well. The at-risk variants include a common (rs10455872; MAF 7%) and rare variant (rs3798220; MAF 2%) with ORs of 1.7 and 1.92 respectively. However, when both SNPs were present together, an impressive 250% increase in risk for CAD was observed. These variants were found to tag *LPA* alleles with a lower number of CNPs, thereby confirming data by Kamstrup et al. that showed qualitative features of apo (a) are important for a predisposition to CAD.

Recently, the European Atherosclerosis Society (EAS) issued a statement advocating for routine Lp (a) screening and subsequent treatment with niacin for those with plasma Lp (a) levels greater than 50 mg/dL.[42] However, the findings covered herein would suggest genetic screening for *LPA* variants would be incrementally more useful. The reasoning behind this is several-fold. First, current Lp (a) tests do not adequately account for important qualitative features such as apo (a) size and KIV-2 CNPs.[43] Second, no consensus on the optimal Lp (a) assay is currently available. Third, existing assays have demonstrated highly variable sensitivities and specificities for detecting specific isoforms of Lp (a) and, most importantly, *LPA* susceptibility variants have shown a consistent and reproducible effect on CAD risk, which has been lacking for several decades with respect to plasma Lp (a) levels.[39,44-46] Finally, the *LPA* variants effects appear to be independent of age and gender.

9p21

One of the most provocative findings of the genome-wide association era has been the identification of a novel MI susceptibility locus on chromosome 9p21.[47,48] The at-risk variants lie in a 'desert' region of the genome with the closest annotated genes (*CDKN2A* and *CDKN2B*), being greater than 100,000 base pairs away. Initial reports of the link between MI and 9p21 appeared in 2007, when four separate GWAS involving over 50,000 cases and controls demonstrated a striking twofold increase in risk for MI in the approximate 25% of Europeans that are homozygote carriers of the risk alleles.[28,47-49] Further, a clear gene dosage effect has been observed with the number of 9p21 alleles directly correlating with the risk for CAD.[50] Recently, a meta-analysis of 16 studies involving over 100,000 cases and controls has confirmed this association.[51] In addition, 9p21 has now been linked to more progressive CAD, abdominal aortic aneurysm (AAA) and surprisingly intracranial aneurysm.[52,53] This latter finding suggests that the common thread between these vascular disorders may relate to vascular remodeling rather than atherosclerosis.

As confirmation of these initial findings, a recent GWAS replicated the association between 9p21 susceptibility variants and AAA ($p < 1.7 \times 10^{-7}$).[54] In addition, a new locus in an intron of the gene *DAB2IP*—a cell cycle regulator whose expression is frequently downregulated in human cancers—was also associated with AAA (OR = 1.24, $p = 1.8 \times 10^{-9}$), myocardial infarction (OR = 1.18, 3.1×10^{-5}), peripheral arterial disease (OR = 1.14, 3.9×10^{-5}) and surprisingly, pulmonary embolism (OR = 1.2, 3.0×10^{-4}). Thus, tying together several previously discrete, seemingly unrelated phenotypes and potentially providing new therapeutic targets.

To date, the mechanism by which 9p21 variants impart their MI risk remains unclear. However, preliminary evidence suggests that these variants may mediate their effects through nearby tumor suppressor genes (*CDKN2A* and *CDKN2B*).[55,56] By deleting a region orthologous to 9p21 in mice, Visel et al. showed a dramatic reduction in expression of *CDKN2A* and *CDKN2B*. Moreover, a doubling in smooth muscle cell proliferation, enhanced weight gain, tumor development and an increased death rate was also observed in the mutant versus wt mice. Although informative, these findings raise several additional questions. For example, why there was no increased burden of atherosclerosis in the knockout mice, when this has clearly been the case in humans? Moreover, is the effect of deleting an entire chromosomal region in a mouse, similar to having a few SNPs as humans do? Overall, it appears that extrapolating results from 9p21 knockout mice to human disease will be challenging. Going forward, different animal or perhaps stem cell models should be developed to further study the biologic effects of 9p21 variants on MI risk.

ARRHYTHMIAS

ATRIAL FIBRILLATION

Atrial fibrillation (AF) represents one of the most common heritable cardiovascular conditions in the world.[57,58] If diagnosed before the age of 60 in an individual without risk factors (lone AF), the risk for a first degree relative developing the disorder is greater than fivefold.[59,60] Deleterious mutations resulting in rare Mendelian forms of the disorder have been documented.[61-63] However, those variants provide little, if any, explanation for the common AF phenotype.

Now, several studies shed light on the common genetic contributors to common forms of AF.[64-66] The most surprising discovery relates to three SNPs in an LD block on chromosome 4q25 that correlates strongly with AF ($p = 2.1 \times 10^{-9}$, 1.6×10^{-10} and 1.9×10^{-9}).[65] Importantly, no individual has been found to carry all three variants. Hence indicating an embryonic lethal combination. Nevertheless, individually, these SNPs are highly prevalent with 20% of Europeans and over 50% of Asian individuals carrying the at-risk variants. In addition, the ORs for European and Chinese homozygotes are a striking 3.7 and 1.7, thereby making this susceptibility loci one of the most predictive complex trait markers to surface from the genome-wide association era.

Notably, the closest annotated gene to the 4q25 SNPs is over 200,000 DNA base pairs away in a neighboring LD block. This gene, *PITX2* (paired-like homeodomain transcription factor 2), is an interesting candidate given its role in cardiac development and left-right asymmetry of the heart.[65,67] Importantly, *PITX2* knockout mice have been observed to have severe cardiac malformations and embryonic lethality. *PITX2* has also been demonstrated to be important in the development of the sleeve of cardiomyocytes that comprise the pulmonary vein attachment to the left atrium—an area of the heart with documented importance in generation of ectopic atrial activity and subsequent AF.[68] Emerging data now also links 4q25 variants to *PITX2* isoform levels in resected left atrial appendage tissue and most recently has demonstrated that atrial expression of *PITX2* is dramatically reduced in AF hearts versus normal hearts (unpublished data),[69] thereby, significantly bolstering evidence on *PITX2* as a new candidate gene for AF.

Several additional propitious findings on 4q25 have immediate clinical implications. First, a recent GWAS demonstrated that 4q25 SNPs segregate with cardioembolic and cryptogenic stroke subtypes.[70] Along the same lines, another study involving mobile telemetry units showed over 25% of patients diagnosed with cryptogenic stroke had brief runs of AF.[10] Accordingly, cryptogenic stroke patients harboring 4q25 variants might

benefit from closer monitoring with rapidly evolving wireless technologies.[58] Second, 4q25 variant carriers have now been shown to have a twofold and fourfold increase in risk for early and late recurrence of AF after catheter ablation.[71] In contrast, no clinical or echocardiographic features were predictive of AF recurrence in the same study. Therefore, alternative surveillance and ablation strategies in those harboring 4q25 susceptibility variants should be considered.

Overall, the 4q25 story has been the most transformative with respect to genomics of AF. However, several additional variants in genes influencing both the PR interval and the AF have surfaced, albeit at much more modest levels of significance. Many of these variants are in genomic regions of plausible biologic significance and involve genes functioning cardiac ion channels (*SCN5A*), cardiac development (*TBX5*) and signal transduction (*CAV1* and *CAV2*) to name a few. In addition, a recent GWAS meta-analysis on AF involving close to 15,000 cases and controls identified an atrial potassium channel protein, *KCNN3*, that conferred a 50% increase in risk for lone AF ($p = 1.83 \times 10^{-21}$).[64]

QT INTERVAL AND SUDDEN CARDIAC DEATH

In a seminal GWAS on the QT interval, Arking et al.[72] assessed 88,000 SNPs in 200 women that were at the extremes of a population-based QT interval distribution. The most significant SNPs were then replicated in two separate stages involving over 6,000 cases and controls. Subsequently, on joint analysis, common variants in the *NOS1AP* gene most strongly correlated with QT interval duration. Interestingly, *NOS1AP* is known to regulate neuronal nitric oxide synthase and calcium influx via the NMDA receptor, but had no previously known role in cardiac repolarization.

Further bolstering the *NOS1AP* story, a recent study evaluating over 500 European and AA SCD victims from two separate prospective cohorts demonstrated that even small increments in the QT interval predisposes individuals to a heightened risk for SCD.[73] Additionally, one *NOS1AP* variant (rs16847548) was predictive for both QT interval and SCD in Europeans (OR = 1.31 95% CI 1.1–1.56), while another *NOS1AP* variant (rs12567209) correlated with SCD alone (OR 0.57 95% CI 0.39–0.83). These contrasting results underscore the need for further defining the functional genomics of *NOS1AP* variants through basic research in model organisms and cardiac stem cells.

Two recent GWAS meta-analyses conducted on Europeans have replicated the *NOS1AP* findings in striking fashion ($p = 2 \times 10^{-78}$, 1.0×10^{-35}).[42,74] Moreover, many additional ion channel genes were found to be of genome-wide significance. Four of these are in ion channel proteins previously implicated in Mendelian LQTS (*KCNQ1, KCNH2, SCN5A* and *KCNJ2*). Combined, these variants contribute an approximate 7% to QT variation, which, although substantial, leaves much of the heritability of the QT interval (~30%) unexplained. Going forward, rare DNA sequence variants identified through large-scale resequencing programs should help fill some of the gap in this knowledge.

Consequently, genomic markers of ventricular fibrillation (vfib) are also emerging. In a GWAS comparing 515 cases with MI and vfib to 457 controls with MI alone, a variant in the gene *CXADR* (rs2824292) conferred an impressive 180% increase in risk for vfib.[75] Perhaps even more compelling is that *CXADR* encodes the transmembrane tight junction coxsackievirus and adenovirus receptor protein, which has been implicated in viral cardiomyopathies and sudden cardiac death in previous candidate gene studies. Future functional genomic and prospective cohort studies validating *CXADR* variants as predictive biomarkers will be necessary before moving forward in the context of risk altering therapies.

CARDIOVASCULAR PHARMACOGENOMICS

Many of the discoveries on the genomic basis of common cardiovascular conditions will take several years before the data can be fully translated to new therapies and validated predictive algorithms developed. In contrast, dozens of recently identified pharmacogenomic variants with significant influence on drug safety and efficacy have immediate clinical ramifications.[5,6,76-79] Most importantly, these pharmacogenetic variants are highly significant with risk ratios for adverse events approaching 50-fold in particular cases.[3] This section will provide a brief overview of the most compelling pharmacogenomic findings in cardiovascular medicine known to date (Table 2).

ANTIPLATELET AGENTS

The adjunctive use of clopidogrel and aspirin has significantly reduced the risk of recurrent ischemia, stent thrombosis and death in individuals undergoing coronary stenting.[80-82] However, in 2006, Hulot et al. demonstrated a blunted antiplatelet response to clopidogrel in healthy carriers of gene variants in the hepatic cytochrome 2C19 (*CYP2C19*) system.[83] Now, several large studies have extended these initial findings to individuals with acute coronary syndromes (ACS).[84-86] Notably, the at-risk variants confer close to a twofold increase in risk for MI and death, and a striking threefold increase in risk for stent thrombosis.[84-87] This heightened risk relates to a diminished capacity of individuals harboring *CYP2C19* polymorphisms to convert clopidogrel—a prodrug—to its active metabolite. Remarkably, these common *CYP2C19* reduced function variants are present in over 30% of Europeans and close to 50% of AA and Asians.

These initial *CYP2C19* susceptibility data were generated from hypothesis driven single gene studies.[88] Therefore, Shulidner et al. sought to conclusively determine the genetic contributors to clopidogrel responsiveness by conducting a GWAS. First, they assessed baseline platelet reactivity using platelet function testing (PFT) in all participants. Subsequently, PFT was repeated after 7 days of clopidogrel therapy. Not surprisingly, the SNPs most significantly associated with platelet reactivity after clopidogrel administration clustered around the *CYP2C19* locus—an association not observed at baseline. More importantly, the carriers exhibited a striking 345% increase in the composite outcome of stent thrombosis and death at 1 year, which closely mirrors the results seen in earlier candidate gene studies.

Recently, the results of two genetic substudies from trials that compared newer antiplatelet agents (prasugrel, ticagrelor) to clopidogrel in patients presenting with ACS have further

TABLE 2

Recent pharmacogenomic breakthroughs

Gene or Locus	*Condition/Therapeutic use*	*Effect*	*Effect size (CI)*	*References*
GRK5	Heart failure	Enhanced uncoupling of βAR leading to an intrinsic β-blockade and protection from progressive heart failure and death	0.31 (0.13–0.73)	114
LPA	CAD	Enhanced response to aspirin	2.2 (1.39–3.52)°	94
SCLOB1	Lipid therapy	Myopathy	4.5 (2.6–7.7); 16.9 (4.7–61.1)^	6
		Musculoskeletal side effects	2.2 (1.4–3.6)	100
APOE	MI	Enhanced Statin response in APOE4 variant carriers	1.8 (1.1–3.1)†	101
VKOR	Anticoagulation	VKOR "A" haplotype carriers require a 60% reduction in daily warfarin maintenance dosing compared to individuals with the more common "B" haplotype	—	79, 97
CYP2C9	Anticoagulation	Individuals with *2 and *3 reduced-function alleles have diminished metabolism of warfarin, reduced warfarin requirements and increased risk for bleeding when compared to *1 allele carriers	2.57 (1.16–5.73)	97, 98
CYP2C19	Stent thrombosis (*2–*8)	Reduced conversion of clopidogrel to its active metabolite secondary to CYP2C19 LOF variants (*2–*8) results in excess risk for stent thrombosis, while GOF mutations result in increased bleeding events	3.5 (2.14–5.57); 4.68 (1.55–14.11)^	86
	Bleeding (*17)		1.8 (1.03–3.14)	78, 88
ABCB1	MI, death, stroke	Homozygote variant carriers of ABCB1 (3435 C→T) have reduced bioavailability of clopidogrel and an increased risk for adverse outcomes	1.72 (1.22–2.44)	86, 89

°OR represents the increased risk for CAD in rs3798220 carriers. This enhanced risk was completely abrogated by aspirin therapy.
^Homozygous odds ratio.
†OR represents heightened risk of future MI in APOE4 carriers, which was abolished with Statin therapy.
*Common and rare DNA variants present in each respective gene.
(Abbreviations: CI: 95% Confidence interval; LOF: Loss-of-function; GOF: Gain-of-function)

underscored the need for genotyping prior to selecting antiplatelet therapy. In the Platelet Inhibition and Patient Outcomes (PLATO) trial, an overall analysis revealed that ticagrelor was superior to clopidogrel at 30 days and 1 year (8.6% vs 11.2%, p = 0.0380).[89] However, when restricting the analysis to individuals with wt *CYP2C19* alleles, this benefit was significantly attenuated (8.6% vs 10.0%, p = 0.06). Along the same lines, in TRITON TIMI-38, a benefit seen with prasugrel was completely abolished when removing individuals with clopidogrel resistance alleles from the analysis.[90] Thus it suggests that the incremental benefit from newer more potent antiplatelet agents is most likely to be conveyed to individuals who are genetically prone to resistance. These data are particularly important given that generic equivalents to clopidogrel will soon be available.

Interestingly, another recent genetic substudy from the CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events) and ACTIVE A trials (Atrial Fibrillation Clopidogrel with Irbesartan for Prevention of Vascular Events) demonstrated no link between *CYP2C19* variants and adverse CV outcomes.[91] On closer examination, however, several logical explanations for this discrepancy are evident. First, in previous studies, stent thrombosis has been a major contributor (greater than threefold increase in risk) to *CYP2C19* related CV risk. Thus, given that the majority of patients in CURE were managed conservatively, the null findings should not be surprising. In fact, in TRITON TIMI 38, where the highest *CYP2C19* related CV risk was observed (11.5% vs 6.3%; HR 1.97 95% CI 1.38–2.82), greater than 95% of individuals received coronary stents. This is in direct contrast to PLATO trial where 60% of patients underwent coronary stenting and CURE where a mere 14% received stents.[91,92] Second, less than one-quarter of CURE patients had documented evidence of myocardial injury, while the vast majority of patients enrolled in PLATO trial (> 80%) and TRITON TIMI-38 had MIs, thereby indicating a higher risk patient population that might be at greater risk for adverse outcomes from reduced function *CYP2C19* alleles.[82,92,93] Third, the need for long-term antithrombotic therapy in patients receiving drug-eluting stents (DES) has been well established. Accordingly, the fact that over 50% of TRITON TIMI-38 patients received DES versus less than 30% in PLATO trial and 0% in CURE cannot be overlooked. Certainly, a meta-analysis of all MI patients from these studies that received DES may definitively address this issue.

Additionally, in TRITON TIMI-38, homozygotes variant carriers of ABCB1 (3435 C→T) who were on clopidogrel had a 70% increase in risk for adverse cardiovascular events. This effect was also observed in a prior French study of over 2,000 patients with acute myocardial infarction.[86] Interestingly, ABCB1 has relevant biologic significance given that it encodes the efflux pump P-glycoprotein, which transports various molecules including clopidogrel across cell membranes. Moreover, recent data has demonstrated altered clopidogrel levels in healthy carriers with 3435 C→T variant, thus bolstering the current clinical trial data.[90]

In summary, the clopidogrel story represents the ideal scenario for individualizing cardiovascular medicine based on pharmacogenomic information.[4] It is the second most highly prescribed drug in the nation and is used for a procedure performed in over 1 million people in the United States annually.[94] Further, over 50% of individuals are carriers of at-risk clopidogrel resistance alleles with clinical alternatives for these patients including the administration of more potent *P2Y12* receptor blocking agents such as prasugrel and ticagrelor or higher clopidogrel dosing readily available.[4] Furthermore, genotyping of individuals prior to coronary stenting would enable the prospective identification of individuals at high-risk for resistance and allow for appropriate tailoring of therapy with adjunctive PFT or administration of prasugrel or ticagrelor. Such an approach would significantly reduce the risk for catastrophic arterial events seen in many of the studies covered here.

Another antiplatelet pharmacogenomic story with important implications involves a rare variant (MAF ~4%) in *LPA* that predicts an enhanced response to aspirin.[95] Remarkably, this *LPA* SNP (rs3798220), which results in an isoleucine for methionine substitution, conferred a twofold increase in MI risk and an eightfold increase in plasma Lp (a) levels in the large Women's Health Initiative (WHI) study.[95] Moreover, rs3798220 was recently identified as the strongest CAD risk factor in a GWAS involving over 7,000 cases and controls.[38] Most importantly, the heightened risk was completely abolished by aspirin in WHI. Consequently, given that recent meta-analysis data demonstrated a diminished benefit of aspirin in patients taking the drug for primary prevention of CAD, a selective strategy of aspirin administration solely in *LPA* variant carriers would likely maximize the protective benefit and minimize the bleeding risk associated with aspirin therapy.[96]

WARFARIN

DNA polymorphisms (*2, *3) in hepatic cytochrome 2C9 (*CYP2C9*) and vitamin K epoxide reductase (VKOR) have been found to confer up to a threefold increase in risk for bleeding.[97-99] However, several challenges exist to successfully utilizing this data in clinical settings. First, non-genetic factors, such as diet, body mass index, alcohol use, medications and coexisting illnesses, play a substantial role in warfarin response.[98] Thus, it is not surprising that recent data shows algorithms based on clinical risk factors fare equally as well in achieving stable doses for the vast majority of patients.[100] Second, the financial cost of such pharmacogenetic dosing has been estimated to be $170,000 per quality adjusted life year saved, which is a number far beyond the acceptable norm of $50,000.[97] Third, many newer oral anticoagulants soon to be available will preclude the need for warfarin in a large portion of patients. Fourth, although advocates quote the recent Medco-Mayo Clinic comparative effectiveness study as proof-of-principle for pharmacogenetic warfarin dosing, this study suffered from many limitations including the use of a historical control group and the extremely long delay in turnaround time of genotyping results (~30).[101] Thus, unless these issues are sufficiently addressed, traditional warfarin dosing will likely remain standard of care.

STATINS

A recent GWAS that assessed 3,16,000 SNPs in just 160 cases and controls found that a highly significant ($p = 4 \times 10^{-9}$) nonsynonymous SNP in *SLCOB1*—encoding the organic anion transporting polypeptide (*OATP1B1*)—conferred a fourfold increase in risk for statin related myopathy in heterozygous carriers (MAF ~13%) and a striking 16-fold increase in homozygotes.[6] In a follow-up study, Ginsburg et al. examined the association between *SLCOB1* and the more common musculoskeletal side effects. Importantly, the SCLO1B1*5 variant carriers were not only 170% more likely to experience side effects, but were also significantly more likely to discontinue therapy.[102] Curiously, these observations were confined to individuals on simvastatin, not atorvastatin or pravastatin. However, on further analysis, greater simvastatin accumulation and higher blood levels in variant carriers compared to wt allele carriers provide a relevant biologic explanation. Notably, no such accumulation of pravastatin was noted. Thus, an individual intolerant to simvastatin secondary to musculoskeletal related side effects may benefit from switching to another agent such as atorvastatin or pravastatin.

In addition to SNPs serving as predictive biomarkers for adverse events, an enhanced statin response in carriers of apolipoprotein E (*APOE*) gene variants has also been observed.[103] Importantly, E4 allele carriers (MAF ~20%) have higher cholesterol levels than their E2 and E3 counterparts and are at significantly higher risk for CAD.[104,105] This heightened risk is well established and has been validated in several recent GWAS.[27,106] Further, in a five-year study evaluating 966 MI survivors, *APOE4* carriers had a twofold increase in risk for dying, which was notably abrogated by simvastatin therapy.[103] Interestingly, the benefits were independent of lipid reduction. Thus, the protective mechanism remains unclear, but is consistent with the highly touted pleiotropic effects of statin therapy. Based on these data, a prospective trial evaluating statin response in *APOE4* carriers with moderate CAD risk factors and normal LDL levels may be warranted. Alternatively, examining existing data from a randomized, placebo-controlled statin trial with multi-year follow-up would also be reasonable. Critics of this strategy will cite the ethical issues surrounding disclosure of *APOE4* status given its link to Alzheimer's. However, recent data demonstrating that conveying genotype status to adult children of an affected Alzheimer's parent did not result in substantial psychological distress or anxiety indicate that current concerns regarding this issue may be presumptous.[107]

In contrast to the *APOE4* pharmacogenetic story, which has clear biologic relevance, claims that a *KIF6* gene variant predicts statin response have been misleading. Recently, three observational studies demonstrated a modest increase in CAD risk (OR 1.1–1.5) in European carriers of a common *KIF6* 719Arg variant allele.[108-110] Moreover, in an observational cohort of the PROVE IT-TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy in Myocardial Infarction) trial, statin therapy was found to eliminate this risk.[111] Consequently, over 150,000 *KIF6* gene tests have been ordered with the pretext that this variant predicts enhanced statin response. However, several troublesome aspects of the data exist making

these claims dubious. First, unlike *APOE*, *KIF6* is not expressed in the vasculature and has no known biologic role in dyslipidemia or CAD.[112] Second, none of the over 10 GWAS on lipids or CAD have identified *KIF6* as a significant contributor to genetic risk.[27,28,41,47-49,101,106,113,114] Third, a recent well-conducted meta-analysis in over 17,000 individuals found no link between CAD and *KIF6*, thereby completely invalidating the *KIF* 'Statincheck' test. Notably, this scenario serves as an explicit reminder that all future pharmacogenetic variants must undergo stringent vetting in appropriately designed studies before implementing their use in clinical practice.

BETA-BLOCKERS IN HEART FAILURE

Beta(β)-blocker use has resulted in significant reductions in heart failure morbidity and mortality. However, a substantial heterogeneity in response exists that is not explained by clinical variables. To further investigate this phenomenon, Liggett et al.[115] performed extensive resequencing of the β1 adrenergic receptor (AR) gene in several independent cohorts. A common nonsynonymous SNP resulting in an arginine (Arg) for glycine (Gly) substitution in the β1AR was detected. This variant, which is highly conserved across species, is present in 60% and 70% of AA and Europeans respectively. Importantly, the Arg variant enhances β1AR coupling to Gs and hence, stimulation of adenylyl cyclase. In addition, enhanced contractility upon isoproterenol stimulation of explanted right ventricular trabeculae and an augmented negative ionotropic response to the non-selective β-blocker bucindolol was demonstrated.

These findings led to the retrospective β-blocker evaluation of survival trial (BEST), which examined the effect of bucindolol in class III/IV HF patients. In BEST, genotype was not associated with outcome in placebo patients, thereby indicating no genotype specific effect on HF natural history. However, bucindolol did result in a selective 38% survival benefit in Arg versus Gly variant carriers. Although interesting, these results have not gained traction in the clinical community for several reasons. Foremost, the pharmacologic effect of carvedilol, which is widely accepted as the β-blocker of choice in HF, is independent of β1AR genotype. Second, to our knowledge, no data showing that bucindolol is superior to carvedilol or other commonly used agents exist. Third, a GWAS assessing β-blocker response in HF has not yet been performed. Thus, it is difficult to know whether other more substantial and unexpected genetic mediators of β-blocker response exist.

A pharmacogenetic finding with a more immediate impact in the treatment of HF involves a nonsynonymous SNP in the G-protein coupled receptor kinase (*GRK*) gene.[116] Notably, *GRK2* and *GRK5* participate in downregulation of the β1AR through phosphorylation and recruitment of the uncoupling protein β-arrestin (Fig. 4). Recently, Liggett et al. found a nonsynonymous SNP in *GRK5* that resulted in a leucine (Leu) for glycine (Gly) substitution and provided more effective βAR uncoupling upon isoproterenol administration in transgenic mice. Furthermore, an impressive 70% (OR 0.31 95% CI 0.13–0.73) reduction in mortality in a cohort of 375 AA HF patients was observed. This benefit mirrored that conferred by β-blocker therapy in the wt allele carriers (0.19 95% CI 0.10–0.37). Importantly, carriers of the *GRK*-Leu variant received no incremental benefit from β-blocker therapy, thereby confirming an 'intrinsic' genetic β-blockade effect from the variant. *GRK*-Leu is present in over a third of AA, while only 1.3% of Europeans. Accordingly, it appears that many AA HF patients may be receiving limited benefit and be at excess risk for adverse events from β-blocker use.

SNP PROFILING STUDIES

The outpouring of hundreds of disease associated SNPs from GWAS have potentiated a number of studies evaluating "genetic risk scores" in the context of their predictive ability for various diseases.[117,118] Most recently, Paynter et al. reported on the prognostic capabilities of 101 SNPs identified from GWAS on CAD.[117] Although the genetic risk score based on these SNPs were predictive for CAD, they did not add incremental value to traditional clinical models. Critics of GWAS have cited this

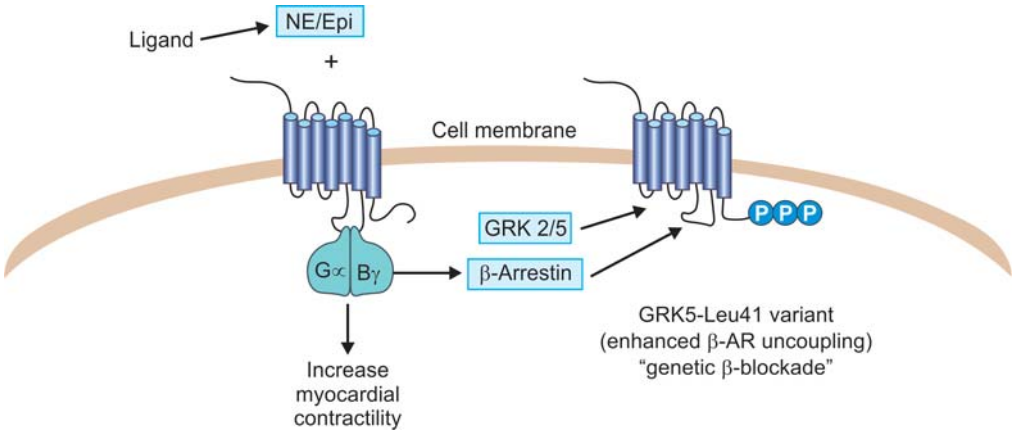


FIGURE 4: Genetic β-Blockade. Norepinephrine (NE) and Epinephrine (Epi) binding to the β-adrenergic receptor (β-AR) results in recruitment of heterotrimeric G proteins, Gα and Gγ. This stimulates adenylyl cyclase activity, which results in downstream increases in myocardial contractility. G-protein coupled receptor kinases (GRK) uncouple the heterotrimeric proteins and limit persistent myocardial stimulation present in hyperadrenergic states such as heart failure. A gene variant in GRK 5 results in enhanced β-AR uncoupling and diminished response to adrenergic stimulation, thereby conferring a 'genetic' β-Blockade. (*Source:* Damani SB, Topol EJ. Emerging clinical applications in cardiovascular pharmacogenomics. WIREs Syst Biol Med. 2011;3206-15, with permission)

study as illustrative of the failure of genomics to change the practice of medicine. However, such claims are premature, highly inaccurate and require addressing.

Foremost, most SNP profiling studies published to date suffer from a number of limitations that skew results in favor of negative results. For example, all 101 susceptibility SNPs included in the Paynter et al. study received equal weighting in their statistical model, despite clear evidence that SNPs such as those on chromosome 9p21 confer much greater risk for disease and should have been weighted appropriately. Second, many GWAS on CAD have used variable definitions for what constitutes a case and control and has thus made incorporation of these results into a 'score' troublesome. Third, some of the most important CAD susceptibility SNPs, such as those in *LPA*, have been omitted. Fourth, in most studies, a family history of CAD continues to be predictive of risk beyond traditional modeling, thereby indicating genetic underpinnings of CAD that have yet to be uncovered. Certainly, recent resequencing studies that have illuminated many rare susceptibility SNPs with large effects are consistent with this hypothesis. Additionally, recent data indicate that simultaneously assessing all disease-related SNPs proportionally increase an individual's predisposition to disease. Consequently, any genetic risk model should include all common and rare susceptibility SNPs (including those yet to be discovered) with appropriate weighting in statistical models. To date, no such model exists.

FUTURE DIRECTIONS

The year 2010 marks the completion of the first decade since the publication of the initial draft sequence of the human genome. During these ten years, the genomic bases of most common diseases, including many cardiovascular conditions, have begun to be unraveled. However, as noted, a substantial amount of the heritability remains unexplained. This missing heritability or "dark matter" of the genome will incrementally be revealed over the next decade via a multifaceted approach that utilizes large-scale whole-genome sequencing for the detection of rare susceptibility variants, de novo genome assembly and single molecule sequencing for the identification of disease causing structural variants including insertions, deletions and gene copy number changes, and detailed cataloguing of important tissue specific epigenetic factors such as DNA methylation, histone modification and chromatin state. This latter approach will be particular challenging in cardiovascular conditions given the need for accessing relevant myocardial and coronary tissue. Thus, novel strategies that leverage stem cell and rare cell biology technology in order to provide relevant models for genomic and epigenomic investigations will be critical. Most importantly, the continued integration of high-throughput proteomic and metabolomic technologies with genomic data will enable a deeper understanding of the subtle biological alterations present in various disease states, while also providing novel therapeutic targets.

In summary, the genomic and pharmacogenomic findings discussed in this chapter represent a preview of the transformative discoveries that will continue to surface in the years ahead. Going forward, the challenge will be in determining when and how to translate these findings to real-world clinical applications. For this to happen, clinicians and scientists must work together in order to optimally design the experimental methods, precisely phenotype the cases and controls, integrate and disseminate all relevant data in the appropriate clinical and academic settings. Only then may the full potential of individualized medicine be realized.

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Chapter 114

Cardiovascular Pharmacogenetics

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Chapter Outline

- Principles of Pharmacogenetics
- HMG-CoA Reductase Inhibitors
  - Low-density Cholesterol Lowering
  - Reduction in Cardiovascular Events
  - Statin Induced Musculoskeletal Side Effects
  - Compliance with Statin Therapy
  - Clinical Implications
- Thienopyridines
  - Laboratory Response to Clopidogrel
  - Clinical Response to Clopidogrel
  - Clinical Implications
- Aspirin
- Warfarin
  - Warfarin Dose Requirements
  - Clinical Response to Warfarin
  - Tailored Warfarin Therapy
- Diuretics
  - Blood Pressure Lowering Response
  - Clinical Outcomes
- Beta-blockers
  - Heart Rate and Blood Pressure Reduction
  - Improvement in Ventricular Function in Patients with Systolic Heart Failure
  - Clinical Benefit in Patients with Cardiovascular Disease
  - Adverse Events
  - Clinical Implications
- Antiarrhythmic Drugs
  - Digoxin and Calcium Channel Blockers
  - Procainamide
  - Propafenone
  - Antiarrhythmic Efficacy
  - Toxicity
  - Clinical Implications
- Future Directions

INTRODUCTION

"The right dose of the right drug to the right person" is one of the often-stated goals of pharmacogenomics and personalized medicine. *Pharmacogenetics* primarily uses genetic variation to identify subgroups of patients that may respond differently to a certain medication. The broader term of *pharmacogenomics* implies utilizing genome-wide technologies such as gene expression, proteomics or metabolomics to achieve the same goal. The two terms are often used interchangeably. In this chapter, authors have focused on pharmacogenetics of cardiovascular medicine. First conceptualized in 1957 by Motulsky, the concept that genetically determined differences in our ability to handle or to respond to medications is not new.[1] The application of pharmacogenetics to cardiovascular medicine began in 1964 when O'Reilly identified a family whose members required unusually high (i.e. 145 mg/day) warfarin doses to achieve therapeutic anticoagulation—a trait that was transmitted in an autosomal dominant manner.[2] Since its first description, the field of pharmacogenetics has expanded to study a broad range of cardiovascular drugs and has become a mainstream research discipline. The need for pharmacogenomic research is underscored by the following example: the novel platelet P2Y12 receptor inhibitors, prasugrel and ticagrelor, both result in relatively small (~2%) absolute risk reductions in composite endpoints over the current standard of care with clopidogrel. At the same time, both are associated with a higher risk of adverse events due to hemorrhage and come at a significant cost disadvantage compared to clopidogrel.[3,4] Therefore, there is a critical need to target cardiovascular therapeutics to individual patients who stand to benefit from the drug; and at the same time identify those who might suffer from adverse events in terms of cost, side effects and quality of life.

PRINCIPLES OF PHARMACOGENETICS

A particular drug is a candidate for pharmacogenetic investigation or intervention if there is a clinically relevant heterogeneity in drug response. If a drug has a uniform effect across individuals, it is unlikely that genetic variation plays a major role in determining response. Furthermore, if there is variability that is not large enough to be clinically significant then it is unlikely that interventions tailored around genetic variants will have clinical utility. The definitions of a response to a drug include laboratory measurements, quality of life and clinical endpoints. For example, the response to warfarin is often measured as either international normalized ratio (INR, a laboratory endpoint) or thrombosis/hemorrhage/death (clinical endpoints).

Evidence that variation in drug response may be under genetic control often comes from studying drug responses within families—that is, by assessing the heritability of drug response. If a large proportion of the variability in drug response is explained by the relatedness within family members (i.e. a high heritability estimate) then it is likely that the drug response is under genetic control. For example, the laboratory responses to aspirin and clopidogrel have both been shown to be highly heritable traits.[5,6] These observations form the foundation for the in-depth studies aimed at identifying genetic factors that determine the drug response. Another method of assessing if a drug response is under genetic control is to study different ethnic populations under the same environmental conditions.[7] The assumption here is that variation in drug response between individuals of varying ethnic backgrounds, if studied in the same environmental conditions, can be attributed to differences in the genetic make-up of these individuals. For example, rosuvastatin drug levels are nearly twofold higher from individuals of Chinese, Malay and Asian-Indian decent compared to whites living in the same environment[8] suggesting that genetic variation might underlie the observed variability in drug response.

Once there is evidence of a genetic component to a particular drug response the initial approach stems from principles of pharmacology, namely pharmacokinetics and pharmacodynamics (Table 1). In the former, variation in drug response correlates with variation in the concentration of drug at the site of the drug's target. For example, cigarette smoking induces hepatic enzymes that are responsible for the clearance and bioactivation of cardiovascular drugs, such as warfarin[9] and clopidogrel[10] respectively, that influence the drug response. Genetic variation in the enzymes and transporters responsible for clearing drugs from the circulation have been known for decades and variants that either eliminate or enhance the function of these enzymes exert important effects on the subsequent drug response, as is outlined below.

Complementing pharmocokinetics is a drug's pharmacodynamic profile, which is dictated by a drug's ability to exert an effect on the drug target (e.g. receptor) to achieve the drug response (Table 1). As with pharmacokinetic variation, pharmacodynamic variation is also subject to genetic and nongenetic influences. For example, nonsteroidal anti-inflammatory agents (NSAIDs) bind to and reversibly inhibit cyclooxygenase 1 (COX1 or PTGS1) in a manner that interferes with the irreversible inhibition by aspirin when the two drugs are taken together.[11] Genetic variation in drug target loci exists and influences drug response through a variety of mechanisms. For example, single nucleotide polymorphisms (SNPs) in the promoter for the target of warfarin, vitamin K reductase (*VKORC1*) lead to higher gene expression and ultimately a higher concentration of *VKORC1* to be inhibited by warfarin.[12] Pharmacodynamic variation is independent of pharmacokinetic variation, and therefore forms an additive level of variation in drug response.

The final source of potential variation that may influence drug response is outside the realm of pharmacology, but instead relates to the underlying disease process (Table 1). It is well known that individuals with the most aggressive or advanced forms of disease receive the greatest absolute benefits (or toxicity) of a particular therapeutic. For example, women who carry prothrombotic SNPs in platelet receptor genes GP1BA and/or GP6 are at heightened risk for coronary heart disease when exposed to hormone therapy, whereas those who do not are *protected* by hormone therapy.[13] Applying this concept to pharmacogenetics research has seen few successes due to the complex, multifactorial and polygenic process of cardiovascular disease. Although there are few examples of this type in the literature, this area of cardiovascular pharmacogenetics research is likely to be realized as a large and important source of genetic variation in drug response. For example, despite the large heritability (0.73) for the laboratory response to clopidogrel, the only SNP to emerge from a recent genome wide association study (GWAS), *CYP2C19*2*, explains 12% of the total variation in drug response.[6] Therefore, the vast majority of the genetic contribution to the drug response to clopidogrel remains uncharacterized and likely relates to preclopidogrel platelet function (i.e. the underlying disease), given the high correlation between pre-clopidogrel and post-clopidogrel platelet function.[14]

The remainder of this chapter has discussed specific drugs and the current state of knowledge on how genetic variation in pharmacokinetic, pharmacodynamic and disease-related loci influence both laboratory and clinical drug responses. In each case, the authors have organized their discussion by applying these pharmacogenetic principles to each drug. An additional source of well-curated, pharmacogenetic information can

TABLE 1

Sources of pharmacogenetic variation

Category	*Description*	*Types of genes*	*Examples*
Pharmacokinetic	Variability in the concentration of drug at the site of drug effect	• Drug metabolizing enzymes • Drug transporters	• Warfarin: *CYP2C9* • Clopidogrel: *CYP2C19* • Simvastatin: *SLCO1B1* • Metoprolol: *CYP2D6*
Pharmacodynamic	Variability in the drug ability to influence its target	• Transmembrane receptors • Intracellular enzymes	• Clopidogrel: *P2RY12* • Simvastatin: *HMGCR* • Metoprolol: *ADBR1*
Underlying disease	Variability in the disease being treated	• Often downstream or independent of drug target	• HCTZ: *ADD1* • Simvastatin: *APOE*

(Abbreviations: HCTZ: Hydrochlorothiazide; APOE: Apolipoprotein E; ADBR1: Beta-1 adrenergic receptor; HMGCR: Hydroxy-methylglutaryl-CoA reductase)

be found at the Pharmacogenetics Knowledge Base (www.pharmgkb.org).

HMG-CoA REDUCTASE INHIBITORS

Statins (3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors) are widely prescribed for the primary and secondary prevention of coronary heart disease and stroke primarily through the reduction in low-density lipoprotein cholesterol (LDLc). There is considerable heterogeneity with respect to both efficacy and toxicity and considerable investigation into the genetic determinants of both. In this context, there are four types of statin "responses": (1) LDLc lowering; (2) protection from cardiovascular events; (3) musculoskeletal side effects and (4) adherence with statin therapy.

LOW-DENSITY CHOLESTEROL LOWERING

While most patients derive a moderate (30–50%) reduction in LDLc cholesterol with statin therapy there is wide inter-individual variation in the LDLc lowering response to statin therapy.[15] Therefore, factors that influence the magnitude of LDLc reduction are relevant for reaching target LDLc goals. Nongenetic factors, such as race, age and smoking status, have only mild influences on statin response.[16,17] Therefore, the genetic influences of LDLc lowering have received considerable attention. A variety of approaches (i.e. candidate gene, resequencing and genome wide association studies) have been used in a variety of statin and dose combinations to assess the genetic influences of statin-induced LDLc lowering. The totality of the evidence thus far supports four loci that have the strongest levels of evidence that each have modest effects on LDLc lowering: ABCB1 (pharmacokinetic), HMGCR (pharmacodynamic), APOE (underlying disease) and PCSK9 (underlying disease) (Table 2). Finally, because of the strong association between baseline LDLc and *absolute* LDLc lowering and to focus on pharmacogenetic effects—as opposed to those that influence baseline LDLc—the authors highlight those variants that influence *relative* LDLc lowering.

ABCB1

The ATP-binding cassette, sub-family B (MDR/TAP), member 1 (*ABCB1*) gene encodes a protein that resides in the apical membrane of the enterocyte and hepatocyte and is primarily responsible for the efflux of molecules out of the cell and into the intestinal lumen and biliary tree respectively. Therefore, the action of this transporter serves to reduce the oral bioavailability of a drug. All statins appear to be handled by this transporter and a common haplotype defined by three SNPs—C1236T (rs1128503), G2677T (rs2032582) and C3435T (rs1045642)—captures the genetic variation at this locus. Individuals who carry a T-allele at each of the three SNPs (i.e. the T-T-T haplotype) have higher systemic exposure to simvastatin and atorvastatin.[18] This higher systemic exposure likely reflects a lower hepatic exposure (because the transporter is responsible for hepatic efflux) since the T-T-T haplotype is associated with an attenuated LDLc reduction. In one study (n = 3,916; half on 10 mg atorvastatin, half on a variety of other statins), homozygote carriers of the T-allele for G2677T experienced a mildly attenuated LDLc reduction compared to those who carry the major allele: 35% versus 38% (p = 0.002).[19] Further, in another study (n = 1,507), carriers of this haplotype had a 10.5% lesser reduction in LDLc on pravastatin.[20] Therefore, the influence of the G2677T polymorphism in *ABCB1* has a mild, but reproducible, effect on LDLc lowering.

HMGCR

Statins achieve their LDLc lowering effect through competitive inhibition of 3-hydroxy-3-methylglutaryl-CoA reductase (*HMGCR*) in the liver, which controls the rate-limiting step in endogenous cholesterol synthesis. In one study (n = 1,536), carriers of the minor allele for an SNP in *HMGCR* (rs17244841) were associated with a diminished LDLc response: 28 versus 34 mg/dL reduction (p = 0.005) with pravastatin. This finding was expanded upon in another study (n = 335 blacks and 609 whites) that focused exclusively on genetic variation in *HMGCR*,[21] where the H7 haplotype (defined by the minor alleles of rs17244841, rs17238540 and rs3846662) was associated with an attenuated reduction in LDLc, although only in blacks treated with 40 mg simvastatin: 33% versus 39% (p = 0.02). The mechanism by which the H7 haplotype confers an attenuated LDLc response appeared to be due to higher levels of an alternatively expressed *HMGCR* transcript (*HMGCRv_1*) that skips the substrate binding exon 13, producing a version of *HMGCR* that is less sensitive to in vitro inhibition by simvastatin.[22] Therefore, it appears that alternative splicing of *HMGCR* is a novel mechanism for genetically mediated statin resistance. Despite these encouraging associations, none of the SNPs that make-up the H7 haplotype were associated with LDLc lowering induced by atorvastatin in recent candidate gene or genome wide association studies.[19,23] Whether this represents a failure to replicate these SNPs or a statin-specific effect (i.e. simvastatin vs atorvastatin) is unknown. Therefore the bulk of the evidence supports an association with SNPs in the H7 haplotype in *HMGCR* with a mildly attenuated LDLc reduction with simvastatin; whether this association holds for other statins is unclear.

APOE

The apolipoprotein E (*APOE*) locus encodes a lipoprotein that is a constituent of many lipid particles. This locus has been studied extensively with respect to lipid, cognitive and thrombotic traits and two nonsynonymous polymorphisms have received the greatest attention: rs7412 and rs429358. The alleles at these two loci are then used to define the three most common haplotypes: ε2, ε3 and ε4. In one trial, from 43 SNPs selected from 16 candidate genes that were chosen based on a literature based search for genes thought to be implicated in the LDLc lowering response the authors identified carriers of the major allele of rs7412 in *APOE* (ε3 haplotype) as having a mild, reduced LDLc response compared to those with the minor ε2 haplotype in those treated with atorvastatin: 36% versus 40% (p = 0.002) reduction in LDLc.[19] In another study, investigators tested 148 SNPs guided by common genetic variants and linkage disequilibrium (LD) patterns in 10 candidate genes related to lipoprotein metabolism in 1,536 patients treated with 40 mg pravastatin.[24] A trend (corrected p = 0.047) toward reduced

LDLc lowering was reported in carriers of an SNP that was in LD with the rs7412 SNP in *APOE*. In a study of 509 patients randomly assigned to three statins (10 mg atorvastatin, 20 mg simvastatin, 10 mg pravastatin) there was an attenuated LDLc lowering with the major ε3 haplotype versus the ε2 haplotype: 30% versus 36% (p = 0.005) after adjustment for statin type.[25] In a genetic substudy (n = 1,507) of a randomized clinical trial, the strongest association was seen with the rs7412 SNP in *APOE* where, carriers of the ε3 haplotype had an 8% lower LDLc lowering and carriers of the ε4 haplotype had an 13–24% reduced lowering with either atorvastatin or pravastain.[20] Finally, in a GWAS of 3,761 patients treated with 10 mg atorvastatin, the rs7412 allele was the most significant SNP ($p = 6 \times 10^{-30}$) and carriers of the ε3 haplotype experienced a 6 mg/dL smaller drop in LDLc compared to carriers of ε2.[23] Therefore, the totality of the evidence for *APOE* suggests that there is a consistent, mild attenuation of LDLc lowering across a variety of statins and doses in carriers of the ε3 haplotype in *APOE*. To test if the influence of the ε3 haplotype on LDLc lowering could be modulated by dose escalation, as part of one study all patients were treated with low-dose and high-dose statin therapies. After 8 weeks on low-dose therapy, they were treated with 80 mg atorvastatin, 80 mg simvastatin or 40 mg pravastatin. With maximally prescribed doses, carriers of ε3 haplotype improved their LDLc but continued to have diminished LDLc lowering compare to carriers of ε2: 39% versus 45% (p = 0.009 after adjusting for statin type).[25] Therefore, although the influence of ε3 on LDLc lowering is mild, its effect cannot simply be overcome by dose escalation.

PCSK9

The proprotein convertase subtilisin/kexin type 9 serine protease gene (*PCSK9*) has recently been identified as a novel locus that controls LDLc concentrations.[26] Specifically one variant (rs11591147) has been associated with lower LDLc concentrations and lower incident cardiovascular disease,[27] although there has been limited evaluation with its influence on statin-induced LDLc lowering. In the recent genome-wide screen[23] for variants that influenced LDLc lowering by atorvastatin, carriers of the minor allele of rs11591147 experienced an increased LDLc lowering (43% vs 40%, p = 0.0003) compared to noncarriers. This association did not meet their genome-wide level of significance, although, and will need to be replicated in further studies.

REDUCTION IN CARDIOVASCULAR EVENTS

It is well established that statins induce their salutary effects primarily through the reduction of LDLc. However, it has also been described that statins have pleiotropic effects, and there are benefits of statin therapy that are independent of LDLc lowering that may explain part of the reduced risk of cardiovascular events.[28] The genetic predictors for those who receive these pleiotropic benefits have not been well described, but the rs20455 polymorphism in kinesin-like protein 6 (KIF6, an underlying disease locus) has received recent attention (Table 2). In the absence of statin exposure carriers of the minor allele are at a 50% higher risk for cardiovascular events. Furthermore, carriers of the minor allele received a greater benefit with pravastatin compared to placebo [odds ratio for carriers vs noncarriers (0.50 vs 0.94), interaction p-value = 0.01].[29] Lastly, carriers of the minor allele who experience an acute coronary syndrome have greater reduction in subsequent events from intensive statin therapy versus moderate statin therapy compared to noncarriers [hazard ratios for carriers vs noncarriers (0.59 vs 0.94), interaction p-value = 0.018] despite equal on-treatment LDLc, triglycerides, or C-reactive protein

TABLE 2

Genetic associations with the response to statins

Gene	*Variant(s)*	*Statin response/ Type of study*	*Effect of variant(s)*	*Statin-type*	*References*
APOE	ε2, ε3 and ε4 haplotypes defined by alleles at rs7412 rs429358	LDLc lowering/GWAS, CG	• ↓ LDL reduction with ε3 vs ε2 • ↓ LDL reduction with ε4 vs ε2	Class effect	19, 20, 23, 25
HMGCR	H7 haplotype defined by alleles at rs17244841, rs17238540 and rs3846662	LDLc lowering/CG	↓ LDL reduction within H7 carriers	Simvastatin	21, 24
PCSK9	rs11591147	LDLc lowering/CG	↑ LDLc reduction with minor allele	Simvastatin	23
KIF6	rs20455	Reduction in CV events/CG	↑ Reduction in events with minor allele	Pravastatin, atorvastatin	29, 30
SLCO1B1	rs4149056	Musculoskeletal side effects/GWAS, CG	• ↑ In CK positive symptoms • ↑ In CK negative symptoms with minor allele	Simvastatin, atorvastatin	35, 36
SLCO1B1	rs4149056	Nonadherence/CG	↑ Risk of nonadherence with minor allele	Simvastatin, atorvastatin	36

(Abbreviations: LDLc: Low-density lipoprotein cholesterol; CV: Cardiovascular; CK: Creatine kinase; GWAS: Genome wide association study; CG: Candidate gene association study)

levels.[30] Therefore statins may have a greater and intensity-dependent benefit in the reduction of cardiovascular events in carriers of the minor allele of rs20455 than noncarriers.

STATIN INDUCED MUSCULOSKELETAL SIDE EFFECTS

In numerous placebo-controlled clinical trials, statins have a well-defined safety profile with a small but real risk of predominantly musculoskeletal side effects: myalgia [with or without creatine kinase (CK) elevation], asymptomatic CK elevations and rhabdomyolysis.[31] In clinical practice the incidence of mild statin-induced side effects appears to be higher than that seen in controlled trials and is estimated at 5–10%.[32] This discrepancy is unexplained. However, it is the consensus that these symptoms can be caused by statins and is supported by observations that statin-induced side effects appear to be a class effect,[33] improve with withdrawal of the drug and recur with rechallenge of drug.[34] Although the mechanisms for these side effects are unclear, certain patient characteristics have been identified that contribute to the risk: lower body mass, female sex,[35,36] and hepatic or renal dysfunction.[37] Although statin-induced LDLc lowering can, in large part, be predicted from the baseline LDLc,[23] statin-induced side effects are less predictable. Several observations have identified that these side effects are related to statin pharmacokinetics: dose-dependent relationship,[38] increased risk with concomitant drugs that impair statin disposition and metabolism[38] and association with elevated levels of statin metabolites.[34] Therefore, there has been considerable investigation into genetic variation in *SLCO1B1* (pharmacokinetic) and cytochrome P450 (pharmacokinetic) drug metabolizing enzymes as a cause of statin-induced side effects (Table 2).

SLCO1B1

Genetic variation in the solute carrier organic anion transporter family, member *1B1* gene (*SLCO1B1*, also referred to as *SLC21A6*, *OATP-C* or *OATP1B1*) is unique compared to other genetic variants. The *5 variant is defined by the C allele of the SNP rs4149056, which encodes an alanine for valine substitution at amino acid position 174, thus, interfering with the localization of this hepatic drug transporter to the plasma membrane[39] and leads to higher systemic statin concentrations.[40-42] The importance of the *5 allele was highlighted by its identification through a GWAS and validation in patients with severe simvastatin-induced myopathy (defined as CK > 10x the upper limit of normal in those with symptoms and > 3x in those without symptoms) in patients taking 40 mg or 80 mg of simvastatin.[35] The *5 allele was associated with a 4.5-fold increase in the odds for myopathy per allele and was found to explain a large proportion of the risk for this severe form of myopathy and no other significant SNPs in *SLCO1B1* or its flanking sequences were identified. Although an important finding, the endpoint, was rare (122 cases/16,300 exposed) in the combined discovery and validation arms, which is in contrast to the observed prevalence of milder, statin-induced side effects in clinical practice of 5–10%. Whether the *5 allele also contributes to these milder side effects was assessed in a trial focused on predominantly CK negative statin-induced side effects (90% were myalgia and drug discontinuation for any adverse event). The *5 allele was associated with a 2.2-fold increase (p = 0.03) per allele in the odds of this mild side effect, which was seen in 20% of this trial's participants.[36]

Whether statin-induced side effects are class effects has been debated. Cerivastatin, according to some, has the highest risk of musculoskeletal side effects—especially rhabdomyolysis—when compared with other statins.[43] In contrast, pravastatin in blinded clinical trials is no more associated with laboratory and clinical evidence of myopathy than placebo.[44] In a trial of randomly assigned statins, there was a suggestion that there may be differential risks of the *5 allele depending on the statin type; the highest risk with simvastatin, followed by atorvastatin, and the least with pravastatin. Therefore, the *5 allele is associated with a range of statin induced side effects; however, the statin-specific effects need to be evaluated in other larger populations.

CYP450 Drug Metabolizing Enzymes

In addition to *SLCO1B1**5, several cytochrome P450 (CYP) drug metabolizing enzyme SNPs have shown associations with statin-induced side effects, although these are inconsistent. Genetic variation in CYP enzymes follows a unique nomenclature. Each gene harbors genetic variants that have been described; each variant is numerically and sequentially labeled beginning with the wild type copy of the gene. For example, the *1 (referred to as "star 1") allele refers to the unmutated copy of the gene, with each of the many variants labeled *2, *3, *4, etc. A catalog of all known variants and their function, if known, is available at http://www.cypalleles.ki.se/

In a large series of nearly 120 cases of atorvastatin-induced and simvastatin-induced adverse events 388 SNPs in drug metabolizing enzymes were tested, and only the loss of function allele (*4, rs3892097) of *CYP2D6* was associated (p = 0.004) and validated (p = 0.04) with an increased risk of events.[45] However, in a case-control study of 50 patients with statin-induced muscle complaints, no SNPs in *CYP3A4*, *CYP2D6* and *CYP2C9* were associated with adverse events.[46] Furthermore, the results of another study (n = 100 cases) and a GWAS of simvastatin-induced side effects (n = 96 cases) failed to identify any significant associations in CYP enzyme SNPs.[35,36] Therefore it does not appear that SNPs in CYPs influence statin induced side effects.

COMPLIANCE WITH STATIN THERAPY

The ultimate goal of statin therapy is to reduce the burden of cardiovascular disease. Often this goal is hampered by nonadherence to statin therapy, which is a multifactorial problem with a prevalence of 20–40% in patients with coronary artery disease (CAD).[47] Although the genetics of adherence to statins has not been studied in any great depth, one study included discontinuation as part of the composite primary outcome, which was associated with the *SLCO1B1*5* allele.[36] Whether the *5 allele underlies drug discontinuation in a larger, more general population at risk is unknown.

CLINICAL IMPLICATIONS

Despite the high levels of evidence surrounding statin pharmacogenetic associations, it remains premature to recommend their

use in the clinical care of patients for a variety of reasons. For example, statins are often titrated to a desired LDLc goal, thus a *priori* knowledge of an individual's LDLc trajectory while on statin therapy might be advantageous to reduce the number of titrations and dose adjustments and physicians encounters. However the locus with the most consistent association, *APOE*, confers small (i.e. < 10% per allele) differences in LDLc lowering in carriers and on the order of readily available clinical data such as age, race and smoking. Furthermore, since the magnitude of LDLc reduction is closely correlated with pretreatment LDLc,[23] physicians can reasonably forecast the LDLc lowering response without the need for genetics. Therefore, it seems unlikely that prospective genotyping of this valid and clinically relevant gene-drug marker will result in improved patient outcomes.

In contrast, statin-induced side effects and nonadherence are less predictable on the basis of clinical data alone and are not predicted by statin potency.[48] The current level of evidence surrounding *SLCO1B1**5 does not support prospective genotyping at this time. A potential strategy would be to use *5 testing to reassure noncarriers that they are at very low risk for developing rhabdomyolysis and should they develop mild myalgias in order to improve drug adherence. However, additional evidence that strengthens the initial associations as well as identifies alternate statin strategies that mitigate the increased risk of the *5 allele are currently needed.

THIENOPYRIDINES

Clopidogrel has become a mainstay, along with aspirin, in the management of patients with CAD, with acute coronary syndromes (ACS) and/or after percutaneous coronary interventions (PCI).[49,50] Despite its proven efficacy, there remain a significant proportion of patients who remain at risk for subsequent death, myocardial infarction (MI), stent thrombosis and stroke. Variation in the laboratory response to clopidogrel can be assessed by platelet function testing using ADP, and studies have shown that reduced inhibition is associated with an increased risk of future cardiovascular events.[51] Lastly, ADP induced platelet aggregation is a highly heritable trait,[6] thus clopidogrel is a prime candidate for pharmacogenetic study. The vast majority of the evidence surrounding clopidogrel pharmacogenetics has centered around two loci, *CYP2C19* (pharmacokinetic) and *ABCB1* (pharmacokinetic), although *CYP2C9* (pharmacokinetic) and *P2RY12* (pharmacodynamic) may also influence drug response (Table 3).

LABORATORY RESPONSE TO CLOPIDOGREL

CYP2C19

Clopidogrel (a 2nd generation thienopyridine) is an inactive prodrug that requires hepatic bioactivation via several CYP enzymes to generate an active metabolite, which irreversibly inhibits the platelet ADP receptor, P2Y12.[52] *CYP2C19* is one of the CYPs required in this process and there are known genetic variants that eliminate the enzymatic activity of *CYP2C19*. The *1 ("star 1") allele is the normal copy that has full enzymatic activity. The *2 ("star 2", rs4244285) is the most common reduced-function variant and results in complete loss of enzymatic activity.[53] Additional loss of function variants exist [e.g. *3 (rs4986893), *4 (rs28399504), *5 (rs56337013)] are rare and produce similar enzymatic defects as the *2 allele.[54] Carriers of *2 have reduced formation of clopidogrel's active metabolite and clopidogrel-induced platelet inhibition.[55,56] The prevalence of the *2 and *3 alleles vary by ethnicity. In Caucasians, Blacks and Asians the proportion who carry at least one copy of *2 is 25%, 30% and 40–50% respectively, and for *3 is less than 1%, less than 1% and 7% respectively. The rare additional variants (e.g. *4 and *5) have not been well tested with respect to laboratory outcomes. Finally, one variant *17 (rs3758581) is present in nearly 40% of Caucasians, Blacks and Asians, and results in increased *CYP2C19* activity, higher production of active metabolite and improved clopidogrel-induced platelet inhibition.[56,57]

TABLE 3

Main genetic associations with the response to clopidogrel

Gene	*Variant(s)*	*Drug response/Type of study*	*Effect of variant(s) with minor allele*	*References*
CYP2C19	*2 (rs4244285)	Drug concentration, platelet function, recurrent MI, stent thrombosis/GWAS, DMET, CG	• ↓ Active metabolite concentration • ↓ Inhibition of platelet function • ↑ Risk of recurrent MI, stroke, stent thrombosis • Graded risk with 0, 1 or 2-alleles	55, 56, 70, 71–73, 77
CYP2C19	*17 (rs3758581)	Drug concentration, platelet function, bleeding/CG	• ↑ Active metabolite concentration • ↑ Inhibition of platelet function • ↑ Risk bleeding	56, 57, 75
ABCB1	T-T-T haplotype defined by T-allele at C1236T (rs1128503), G2677T (rs2032582) and C3435T (rs1045642)	Drug concentration, platelet function, recurrent MI, stroke, death/CG	• ↓ Active metabolite concentration • ↓ No change in inhibition of platelet function • ↑ Risk of recurrent MI, stroke, death (in carriers of two T-T-T haplotypes)	54, 65, 66, 67, 70, 74, 77
P2RY12	F haplotype defined by following alleles: rs6798347, rs6787801, rs9859552, rs6801273, rs9848789 and rs2046934	Inhibition of platelet function	• ↑ Inhibition of platelet function	68

(Abbreviations: MI: Myocardial infarction; DMET: Drug metabolizing enzyme and transporter panel; HCTZ: Hydrochlorothiazide; APOE: Apolipoprotein E; ADBR1: Beta-1 adrenergic receptor; HMGCR: Hydroxy-methylglutaryl-CoA reductase)

Two potential alternative treatment strategies for carriers of *2 are either higher doses of clopidogrel or alternate P2Y12 inhibitors. Higher loading and maintenance doses (e.g. 1,200 mg loading and 150 mg maintenance) appear, in part, to overcome the genetic deficiency of the *2 allele[54,58,59] although not completely,[60] and can require maintenance doses of up to 300 mg/day to achieve adequate platelet inhibition in some individuals.[61] Ticlopidine (1st generation thienopyridine) is also a prodrug, but it is unclear to what extent *CYP2C19* is required for its bioactivation. Prasugrel (3rd generation thienopyridine) is also a prodrug, but is unique in that its bioactivation appears to be less dependent on *CYP2C19*, such that carriers of the *2 allele produce equivalent concentrations of active metabolite and achieve similar degrees of platelet inhibition compared to noncarriers.[62-64]

ABCB1

An additional locus, *ABCB1*, has also received considerable attention with respect to the response to clopidogrel due to its known role as a hepatocyte/enterocyte efflux pump. Genetic variation at this locus (detailed above) results in two main haplotypes that influence clopidogrel handling and those who carry the minor T-T-T haplotype have higher hepatic/enterocyte efflux of drugs. Initial reports suggested that carriers of the T-T-T haplotype had reduced production of clopidogrel's active metabolite (likely due to lower hepatocyte exposure).[65] Despite this initial observation, the link to reduced platelet inhibition in carriers has been difficult to establish,[6,54] although may be present for individuals who carry two copies of the T-T-T haplotype.[66,67] As with the *CYP2C19* variants, the use of prasugrel does not appear to influence carriers of the T-T-T haplotype.[67]

Additional Loci

Although the majority of evidence for clopidogrel pharmacogenetics is focused on *CYP2C19*, there has been considerable effort to search for additional variants because SNPs at this locus do not account for all of the heritability in the laboratory response to clopidogrel. Using GWAS and candidate-gene approaches of platelet specific genes, investigators have been unable to identify variants beyond the *CYP2C19* locus associated with response to clopidogrel.[6] Despite the power of GWAS, haplotype analyses may better characterize the genetic variation at a particular locus. For example, using such an approach investigators identified a *P2YR12* haplotype that is carried by 22% of Caucasians and is comprised of the following SNPs: rs6798347; rs6787801; rs9859552; rs6801273; rs9848789 and rs2046934. Carriers of this haplotype experienced improved platelet inhibition whether assessed by either ADP aggregometry (absolute difference of 4–6%) or the VerifyNow assay (11 unit difference).[68] The mechanism by which this haplotype confers its effect is unknown.

Finally, *CYP2C9* has also been implicated in the bioactivation of clopidogrel. As with *CYP2C19*, known loss of function alleles exist that follow a similar nomenclature (e.g. *2, *3, etc.). Despite initial reports of an association with decreased active metabolite production and reduced platelet inhibition in carriers of *3,[63] this initial observation has been difficult to validate by other groups.[6,56] One explanation may be that due to its minor contribution to clopidogrel bioactivation, the effect of the *CYP2C9*3* allele may only be apparent with the 300 mg loading dose of clopidogrel and not the 75 mg daily dose.[69]

CLINICAL RESPONSE TO CLOPIDOGREL

CYP2C19

Because of the profound influences of genetic variation in *CYP2C19* with clopidogrel-induced laboratory outcomes discussed above, there has been considerable investigation in extending these observations to clinical outcomes. In patients who received PCI after ACS and were treated with clopidogrel, carriers of at least one *2 allele experienced a 1.5-fold increase in the risk of cardiovascular death, MI and stroke in the subsequent year of follow-up compared to noncarriers.[56] In patients treated for ST-segment elevation MI, carriers of any two alleles (*2, *3, *4 or *5) who were treated with clopidogrel had a twofold increase in the risk of the same composite outcome during follow-up.[70] The highest risk appears to be in young (age < 45) patients with ST-segment elevation MI with a threefold increased risk conferred by carrying at least one *2 allele. In addition to an increased risk of this composite endpoint, these and additional studies demonstrated that in patients treated with PCI, the incidence of stent thrombosis is increased threefold in carriers of at least one *2 allele with highest risk (up to sixfold) in those who carry two *2 alleles.[56,71-73] These risks appear to be consistent across indications for PCI (elective vs ACS) and stent type (bare metal vs drug-eluting) and there is a graded, increased risk in those who carry none, one or two variant alleles.[74] Finally, although the bulk of clinical outcomes research centers on *loss* of function variants, one *gain* of function variant, *CYP2C19*17*, has been associated with an increased risk of bleeding (OR = 1.85, 95% CI: 1.19–2.86, p = 0.006) as would be expected for this variant.[75] Therefore the associations with *CYP2C19* genetic variants and the laboratory response to clopidogrel are mirrored in the clinical response to clopidogrel and are constrained to those patients with ACS receiving PCI, and not to those receiving clopidogrel for atrial fibrillation or ACS without PCI.[76]

As was the case with the laboratory response, the 3rd generation thienopyridine, prasugrel is not associated with an increased risk of cardiovascular death, MI, stroke or stent thrombosis in carriers of the *2 allele,[62] thus providing the scientific rationale for prescribing prasugrel in carriers of *2 instead of clopidogrel to mitigate this increased risk. Finally, ticagrelor, a novel, nonthienopyridine P2Y12 receptor antagonist, which is not a prodrug does not seem to be influenced by genetic variation at either *CYP2C19* or *ABCB1*, thus providing an additional option for carriers.[77]

Additional Loci

Unlike the variants at *CYP2C19*, those in *P2RY12* have not been consistently linked to clinical outcomes. Investigators have found either no association[70,78] or an inverse association from what would be predicted by the laboratory outcomes.[79] Therefore, further investigation is needed to clarify the role of genetic variation at the *P2RY12* locus in relation to clinical outcomes in clopidogrel treated patients.

Genetic variation at *ABCB1* has been linked to adverse clinical events in several reports. ACS carriers of two copies of the T-T-T haplotype are at an increased risk for subsequent death, MI or stroke compared to those who carried none, thus mirroring the platelet function data.[67,70,77] As with carriers of the *CYP2C19* variants, neither prasugrel nor ticagrelor appears to be sensitive to genetic variation at the *ABCB1* locus, thus providing an alternative to carriers of this variant.[67,77]

CLINICAL IMPLICATIONS

The current state of evidence reflects a strong and consistent association with the *CYP2C19**2 allele and an increased risk for cardiovascular outcomes in patients treated with clopidogrel. These associations are based on altered bioactivation of clopidogrel's active metabolite resulting reduced platelet inhibition and inadequate protection from ischemic events. The association with *CYP2C19*2* is not due to confounding as preclopidogrel platelet function is no different in carriers versus noncarriers.[6] Finally, alternative drugs (i.e. prasugrel and ticagrelor) are drugs for the same indications as clopidogrel, which mitigate the adverse laboratory and clinical effects of the *CYP2C19*2* allele and the *ABCB1* T-T-T haplotype. Whether genotype guided thienopyridine therapy will improve patient outcomes or reduce costs has yet to be determined. However, the current evidence justifies *CYP2C19*2* genotyping to guide thienopyridine use.

ASPIRIN

Aspirin is the antiplatelet of choice used by millions for the primary and secondary prevention of MI, stroke and death. It produces its pharmacological effect by irreversibly inhibiting (through acetylation) prostaglandin G/H synthase 1 (PTGS1 or COX-1), thus inhibiting the conversion of arachidonic acid to thromboxane. Thromboxane is a potent platelet activator and facilitates the action of a variety of other platelet agonists (e.g. ADP, collagen, epinephrine). The laboratory response to aspirin is primarily measured through light transmittance aggregometry, although additional platforms exist (e.g. Verify Now, serum thromboxane B2). However, unlike clopidogrel, a variety of agonists are available to monitor the platelet inhibitory effect of aspirin. An agonist, such as arachidonic acid, is completely dependent on COX-1 to produce platelet activation and is an excellent surrogate for the biochemical effects of aspirin. When compliance is ensured, aspirin is capable of completely inhibiting COX-1 (as assessed by arachidonic acid aggregation) in greater than 99% of individuals.[80] Therefore aspirin's ability to inhibit COX-1 is uniform and complete; consequently, it is unlikely that there is a strong pharmacogenetic component underlying this laboratory response to aspirin.

However, alternate agonists, such as ADP and collagen (i.e. non-COX-1 dependent), are capable of producing robust aggregation in the face of complete COX-1 inhibition.[81] This ability to aggregate despite COX-1 inhibition demonstrates wide interindividual variability and is a highly heritable trait.[5] Therefore, considerable investigation has centered on identifying the genetic determinants of non-COX-1 dependent platelet function on aspirin. Aspirin is not metabolized, has a high bioavailability and uniformly inhibits COX-1, thus there are no pharmacokinetic or pharmacodynamic genetic considerations. Instead, investigators have focused on a variety of platelet function (underlying disease) loci and *LPA* (underlying disease).

Candidate gene approaches in platelet specific genes: *PEAR1*, *ITGB3*, *VAV3*, *GPVI*, *F2R* and *GP1BA* have identified some associations with the laboratory response to aspirin.[82-86] The most robust association has been in carriers of the minor allele of the rs5918 in *ITGB3* gene who have higher residual non-COX-1 dependent platelet function on aspirin.[87-89] Recent GWAS of the laboratory response to aspirin have identified additional genetic loci that have yet to be replicated.[90]

The link to an increased risk of clinical events (MI and stroke) in aspirin users has not been convincingly established with the largest study to date failing to find a significant association with any variant.[91] Interestingly, a genetic variant at *LPA* seems to modify the protective effects of aspirin. *LPA* codes for apolipoprotein(a). When linked with low-density lipoprotein particles, apolipoprotein(a) forms Lp(a)—a well-studied molecule known to be associated with the development of CAD, although not known to affect platelet function. An uncommon (found in < 5% of Caucasians) variant, rs3798220, is associated with markedly higher concentrations of Lp(a), and a twofold increased risk of cardiovascular disease.[92] In a genetic substudy of the Women's Health Study where over 25,000 women were randomly assigned either placebo or low-dose aspirin, carriers of this variant had a more than twofold reduction in the risk for cardiovascular disease with aspirin, whereas noncarriers (> 95% of Caucasians) had none.[93] Therefore, this marker could be used to select patients for whom low-dose aspirin may be beneficial in the primary prevention of cardiovascular disease, although this hypothesis has not been tested.

WARFARIN

Warfarin is the most commonly used anticoagulant for the primary and secondary prevention of stroke and venous thromboembolism. Warfarin is manufactured as a racemic mixture of its R- and S-enantiomers. S-warfarin is the more biologically potent form in terms of inhibiting the key enzyme *VKORC1* and producing its anticoagulant effect. S-warfarin is metabolized primarily through oxidation in the liver by *CYP2C9*. Clinically, it is well recognized that warfarin therapy is characterized by a wide interindividual variation in dose requirements and by a narrow therapeutic index. Therefore, accurate dosing is critical for safely managing patients on this drug. Because nongenetic influences, such as body size and age, are poor predictors of an individual's dose requirement, there has been considerable investigation into the genetic influences on warfarin dose requirements, despite the lack of formal heritability studies. These investigations have identified the following loci as influencing the response to warfarin: *CYP2C9* (pharmacokinetic) and *VKORC1*, *CYP4F2* and *CALU* (all pharmacodynamic) (Table 4). Because the standard of care for warfarin therapy is to titrate the dose to achieve an INR value of 2.0-3.0, the "laboratory response" to warfarin is reflected in the dose required to achieve this goal INR. The clinical response can be measured in terms of efficacy (e.g. protection from thrombosis) or an adverse event such as a supratherapeutic INR (i.e. > 4–5) or hemorrhage.

TABLE 4

Main genetic associations with the response to warfarin

Gene	*Variant(s)*	*Drug response/Type of study*	*Effect of variant(s) in carriers of minor allele*	*References*
CYP2C9	• *2 (rs1799853) • *3 (rs1057910)	Drug concentration, warfarin dose requirements, out-of-range INR values, hemorrhage/GWAS, CG	• ↓ Clearance of S-warfarin • ↓ Dose requirements • ↑ Risk of out-of-range INR values • ↑ Time to stable, therapeutic INR • ↑ Risk of hemorrhage	94, 95, 102, 103, 110-112
VKORC1	• –1639 (rs9923231)	Warfarin dose requirements, out-of-range INR values/linkage (human/animal), GWAS, CG	• ↓ Dose requirements • ↑ Risk of out-of-range INR values • ↑ Time to stable, therapeutic INR	97, 98, 99, 102, 103
CYP4F2	rs2108622	Warfarin dose requirements/ GWAS, DMET	• ↑ Dose requirements	101-103
CALU	rs2290228	Warfarin dose requirements/CG	• ↑ Dose requirements	106

(Abbreviations: INR: International normalized ratio; DMET: Drug metabolizing enzyme and transporter panel; HCTZ: Hydrochlorothiazide; APOE: Apolipoprotein E; ADBR1: Beta-1 adrenergic receptor; HMGCR: Hydroxy-methylglutaryl-CoA reductase)

WARFARIN DOSE REQUIREMENTS

CYP2C9

The initial genetic associations with warfarin dose requirements came from candidate gene associations in *CYP2C9*. The results of these investigations have identified two SNPs in *CYP2C9*. The nomenclature for the *CYP2C9* SNPs follows other CYPs: a normal copy is referred to as *1 ("star 1") and the two polymorphic versions of *CYP2C9* are *2 ("star 2", rs1799853) and *3 ("star 3", rs1057910). While the *1 copy metabolizes warfarin normally, the *2 copy reduces warfarin metabolism by 30% and the *3 copy by 90%.[94] Reduced metabolism results in need for lower warfarin doses to achieve anticoagulation, thus carriers of the *2 and *3 alleles in *CYP2C9* require, on average, a 19% and 33% reduction per allele in warfarin dose compared to those who carry the *1 allele.[95] The prevalence of each variant also varies by race with Caucasians carrying the *2 and *3 copies in 10% and 6% respectively, while both are rare (< 2%) in those of African or Asian descent.[96]

VKORC1

The vitamin K epoxide reductase complex, subunit 1 (*VKORC1)* gene was co-discovered as the target of warfarin by detailed genetic studies of (1) families with congenitally deficient *VKORC1* activity[97] and (2) warfarin resistant rats.[98] Identification of the haplotypes in *VKORC1* associated with warfarin dose requirements followed from in-depth resequencing of the gene and haplotype analysis.[99] It is now understood that a single SNP in the promoter region of *VKORC1* referred to as—1639 (also referred to as the 3673 SNP and rs9923231) where the common G-allele is replaced by the A-allele is the causal SNP that influences warfarin dose requirements. This SNP is important because it controls the amount of *VKORC1* produced in the liver that will need to be inhibited by warfarin to produce its anticoagulant effect.[12] Individuals with an A-allele (or the "A haplotype") produce less *VKORC1* than those with the G-allele (or the "non-A haplotype"). A higher amount of *VKORC1* translates to a need for higher warfarin dose requirements to achieve anticoagulation, thus, carriers of the A-allele in *VKORC1* require, on average, a 28% reduction per allele in their warfarin dose compared to those who carry none. The prevalence of these variants also varies by race with 37% of Caucasians and 14% of Africans carrying the A-allele,[99] although their influence is consistent across races.[100]

CYP4F2

To search for additional genetic variants that may influence warfarin dose requirements, investigators have used more comprehensive approaches with larger sample sizes. Following the hypothesis that variation in warfarin pharmacology is a critical driver of the wide variation in dose response, investigators used a custom "chip" that specifically assays for all known variants that affect drug metabolizing enzymes. In addition, GWAS has been used to identify novel SNPs, haplotypes, as well as structural variants (i.e. insertions, deletions and copy number variations). These broader approaches not only confirm prior observations but also identified a novel association between SNP rs2108622, in *CYP4F2* identified in 20–30% of Caucasians and associated with higher warfarin doses.[101-103] The mechanism by which the minor allele exerts its effect appears to be due to reduction in the hepatic concentration of *CYP4F2*, an enzyme that metabolizes vitamin K, which leads to higher hepatic levels of vitamin K, and thus higher warfarin dose requirements.[104]

Additional Loci

Most studies of warfarin pharmacogenetics were performed in Caucasians; however, because of the lower allele frequencies of variants in *CYP2C9, VKORC1* and *CYP4F2* in individuals of African descent, these variants are not as predictive of African patients' warfarin dose requirements.[105] By resequencing a human gene, *CALU*, which was originally identified in warfarin resistant rats, SNP rs2290228 (prevalent in 11–14% of African-Americans) is associated with higher 15–20% higher warfarin dose requirements and *CALU* gene expression.[106] *In vitro*, the addition of recombinant CALU was observed to protect *VKORC1* from warfarin inhibition, thus suggesting a potential mechanism for the effects of rs2290228. Similarly, *GGCX* which

encodes the enzyme responsible for gamma carboxylation of vitamin K dependent coagulation factors has been surveyed through resequencing and carriers of one SNP, rs11676382, required a lower warfarin dose in one study,[107] although this has not been replicated in others.[108]

Attempts to combine each of the known variants implicated in warfarin dose requirements along with nongenetic factors, such as age and body size, have led to multivariable algorithms that allow clinicians to estimate, *a priori*, a patient's warfarin dose requirements. Using genetic and clinical factors to predict the maintenance warfarin dose is the more accurate than using clinical factors alone.[109] Because incorporating the various factors that influence warfarin dose is difficult to implement clinically online warfarin dosing calculators are available to help with make the appropriate dose adjustments (for example, www.warfarindosing.org).[105]

CLINICAL RESPONSE TO WARFARIN

As suggested above, the clinical implications of these SNPs relate to (1) the risk of bleeding or of supratherapeutic (> 4) INR values and (2) the time required to achieve a stable therapeutic dose.

Initiating warfarin in carriers of the *CYP2C9* and *VKORC1* variants with standard dosing algorithms (i.e. a 5 mg or 10 mg loading dose followed by titration based on the INR) often leads to adverse clinical outcomes because of their genetically mediated sensitivity to the drug. In particular, standard dosing algorithms lead, on average, to a twofold to threefold increased risk of serious or life threatening bleeding or an out-of-range INR (> 4.0) in carriers of the *2 or *3 alleles of *CYP2C9*.[110,111] Carriers of the A-allele of the *VKORC1* SNP, when dosed with standard dosing algorithms, are also at a twofold to threefold higher risk of an INR greater than 4 during initiation of warfarin therapy;[112] however, this association has not been linked to an increased risk of bleeding complications.[100] Finally, because of the sensitivity of these individuals to warfarin and the additional dose adjustments, the time required to achieve a "stable" INR between 2.0 and 3.0 is significantly delayed in carriers of all three SNPs.[110,112]

TAILORED WARFARIN THERAPY

The observation that carriers of *CYP2C9* and *VKORC1* variants are at higher risk for adverse events and algorithms that can be used to predict the warfarin dose requirements have motivated prospective studies to mitigate their risk. Three attempts have been made to improve laboratory outcomes by initiating warfarin therapy using a pharmacogenetics guided approach. Two randomized studies were small (< 200 patients) and prospectively tailored the warfarin dose based on the *CYP2C9* and/or *VKORC1* SNPs. One only used the *CYP2C9* SNPs and showed that those patients who were randomized to pharmacogenetics-based therapy achieved a stable INR significantly sooner than those given standard warfarin therapy.[113] The other tailored the dose to all three SNPs, but failed to show any significant advantage of a pharmacogenetic-guided approach with respect to their primary endpoint of percent out-of-range INRs, although they showed it more accurately approximated stable doses with smaller and fewer dosing changes and INRs.[114] Finally, a single arm study of 896 patients prescribed genotype-guided warfarin therapy showed a reduction in subsequent hospitalizations for bleeding and hemorrhage when compared to historical controls.[115] Because small sizes and study designs of the existing trials, two ongoing prospective clinical trials—the Clarification of Optimal Anticoagulation through Genetics (COAG) and the Genetics Informatics Trial of Warfarin to Prevent Deep Venous Thrombosis (GIFT) trials—will each enroll over 1,200–1,600 patients and will prospectively test the hypothesis that genetically guided warfarin therapy will improve laboratory (COAG study) and thrombotic/hemorrhagic (GIFT study) outcomes.

DIURETICS

BLOOD PRESSURE LOWERING RESPONSE

The locus of greatest interest in diuretic pharmacogenetic research is the adducin 1 (alpha) gene (*ADD1*, underlying disease) which was hypothesized to be pathogenic in animal forms of hypertension with enhanced renal sodium reabsorbtion.[116] Extension of this observation to genetic variation in human *ADD1* in siblings with essential hypertension identified carriers of the W-allele of the G460W variant as being more salt sensitive.[117] This association, in humans, appears to be due to enhanced renal sodium reabsorbtion, thus mirroring the animal model on which its initial discovery was based.[118] A series of studies then demonstrated that carriers of the W-allele experience an enhanced reduction in blood pressure with thiazide diuretic treatment.[117]

CLINICAL OUTCOMES

The goal of antihypertensive therapy is to reduce the blood pressure to prevent renal failure, heart failure, MI and stroke, for example. Because antihypertensive therapy is constantly titrated in clinical practice, one would not expect the *ADD1* variants to be associated with long-term outcomes since carriers of the G-allele would simply be treated with additional agents to control the blood pressure. However, the salt-sensitivity exhibited by carriers of the W-allele appears to be associated with cardiovascular events, independent of blood pressure control.[119] In an observational study, carriers of the W-allele, when treated with thiazide diuretics, experienced a significantly greater protection from MI and stroke than carriers of the G-allele.[120] However, this diuretic by gene interaction could not be replicated in several, larger genetic studies of patient with hypertension treated with diuretics.[121-123] Therefore, the potential use of this genetic variant in guiding treatment options in hypertension is limited.

BETA-BLOCKERS

Beta-adrenergic receptor antagonists (or beta-blockers) are a diverse class of pharmacologic agents that primarily antagonize the beta-1 adrenergic receptor. This class of medications are recommended as a first-line agent for various diseases, including heart failure, hypertension, and angina, as well as after MI. With over 17 agents in this class, each possesses a variety of ancillary properties such as beta-1 versus beta-2 selectivity, intrinsic

TABLE 5

Main genetic associations with the response to beta adrenergic receptor antagonists

Gene	*Variant(s)*	*Drug response/ Type of study*	*Effect of variant(s) in carriers of minor allele*	*Beta-blocker type*	*References*
CYP2D6	**4* (rs3892097)	Drug concentration, heart rate and blood pressure reduction/CG	• ↓ Clearance • ↑ Reduction in blood pressure and heart rate • ↑ Risk of bradycardia	Metoprolol	128, 129, 151, 152
ADRB1	Ser49Gly (rs1801252)	Heart rate, blood pressure reduction/CG	• ↓ Reduction in blood pressure and HR	Metoprolol	134
ADRB1	Arg389Gly (rs1801253)	Heart rate, improvement in LVEF, blood pressure reduction, hospitalization or death in CHF/CG	• ↓ Reduction in blood pressure and HR • ↓ Improvement in LVEF	• Metoprolol (blood pressure/HR/LVEF • Carvedilol (LVEF) • Bucindolol (hospitalization/death)	135, 140-142, 143

*In high linkage disequilibrium (Abbreviations: HR: Heart rate; LVEF: Left ventricular ejection fraction; HCTZ: Hydrochlorothiazide; APOE: Apolipoprotein E; ADBR1: Beta-1 adrenergic receptor; HMGCR: Hydroxy-methylglutaryl-CoA reductase)

sympathomemetic activity, hydrophilic versus hydrophobic properties, routes of elimination and alpha-adrenergic receptor antagonism. Despite this diversity in pharmacologic properties, it is well accepted that the primary benefit of beta-blocker therapy derives from its beta-1 antagonist properties. Accordingly, reductions in heart rate and blood pressure are considered the "laboratory" responses to this therapy and they are often used as surrogates for clinical responses such as protection from MI, stroke, death or heart failure. Variation in the blood pressure lowering response to beta-blocker therapy has long been recognized. Evidence that genetics may underlie this response came from observed ethnic differences in the heart rate and blood pressure lowering response to propranolol[124,125] and heart rate reduction during exercise with atenolol.[126] There has since been considerable investigation into the genetic determinants of the response to beta-blocker therapy that has focused on the following genes: *CYP2D6* (pharmacokinetic) and *ADRB1*, *ADRB2*, and *GRK5* (pharmacodynamic) (Table 5).

HEART RATE AND BLOOD PRESSURE REDUCTION

CYP2D6

Ethnic differences in hepatic clearance[127] of propranolol have stimulated investigation into the pharmacokinetics of beta blockers. Many drugs in this class are substrates for CYP enzymes including metoprolol, carvedilol, propranolol, labetalol and timolol. Of these, metoprolol is extensively metabolized into inactive metabolites by hepatic *CYP2D6*. *CYP2D6* is polymorphic, and several variations of the gene (i.e. SNPs, insertions, deletions) have been identified, are common in the population and result in loss of enzymatic function. The most studied is the *CYP2D6*4* allele (rs3892097) which is present in 10–15% of Caucasians and 20–25% of Africans. Carriers of the *4 allele have reduced *CYP2D6* activity and thus have a higher systemic exposure[128] to metoprolol, which translates into a greater reduction in heart rate, diastolic blood pressure and mean arterial pressure,[129] and a blunted heart rate increase with the coadministration of isoproterenol (a beta-receptor *agonist*).[130]

ADRB1

Just as ethnic differences have led to pharmacogenetic discoveries for other drugs,[7] initial investigations identified ethnic differences in the dose response curve for propranolol where a larger dose was required in blacks to achieve the same response in whites.[131] The beta-1 adrenergic receptor (*ADBR1)* is the target of all beta blockers. Two variants, the Ser49Gly (rs1801252) and Arg389Gly (rs1801253), have been most extensively studied. Receptors with the Ser49 variant appear to have impaired agonist-induced downregulation versus the Gly49 variant.[132] Similarly, receptors with the Arg389 variant have higher agonist induced downstream signal transduction versus those with Gly389.[133] Carriers of either Ser49 or Arg389 variants would be expected to have enhanced, endogenous beta-1-receptor activity and, as such, would be *more* sensitive to beta-blocker therapy. Healthy volunteers who carry two Arg389 variants have a greater exercise induced heart rate reduction due to metoprolol versus noncarriers.[134] Similarly, when treated with metoprolol, hypertensive patients who carried two Arg389 alleles had a greater reduction in diastolic blood pressure and those with both the Ser49 and Arg389 alleles had the greatest reductions in diastolic blood pressure.[135] Extrapolating these findings to the heart rate and blood pressure lowering properties of other beta blockers has been more difficult with many conflicting reports.[136]

ADRB2

Genetic variation in the beta-2 adrenergic receptor has centered around two common genetic variants: (1) Arg16Gly (rs1042713) and (2) Glu27Gln (rs1042714) that are in high LD with each other. Receptors that carry an Gly16 versus Arg16 have enhanced down-regulation upon stimulation with agonist, whereas the influence of the Glu27 variant is less clear although it appears to be resistant to receptor down-regulation.[137] Unlike the scenario with *ADRB1*, the influence of genetic variation at *ADRB2* and the blood pressure or heart rate lowering response to beta-blocker therapy has not been demonstrated.[136]

Downstream of the beta-1-adrenergic receptor in the signal transduction cascade are G-protein coupled receptor kinases responsible for desensitization of the beta-1-adrenergic receptor. Genetic studies in one, G-protein-coupled receptor kinase 5 (*GRK5*), have identified a Glu41Leu variant that is more prevalent in African-Americans. GRK5-L41 more effectively uncoupled isoproterenol-stimulated responses than GRK5-Q41 in transfected cells and transgenic mice, thus producing a pharmacological—like "beta-blockade".[138] Despite the expected enhanced effect with beta-blocker therapy, carriers of this variant do not exhibit altered atenolol induced heart rate reductions during exercise in humans.[139]

IMPROVEMENT IN VENTRICULAR FUNCTION IN PATIENTS WITH SYSTOLIC HEART FAILURE

Beta blockers are now the standard of care for patients with a reduced left ventricular function. One beneficial effect of chronic beta-blocker therapy is protection from deteriorating ventricular function (or reverse remodeling) and in some patients, improvement in ventricular function. As an extension to the heart rate and blood pressure associations, changes in ventricular function during beta-blocker therapy also seem to be under genetic control. Specifically, in patients with systolic heart failure treated with either metoprolol or carvedilol, carriers of two copies of the Arg389 variant had significantly greater improvements in ventricular function compared to the Gly389 carriers (~6–10% vs 0–1% improvement in ejection fraction).[140-142] In heart failure patients treated with bucindolol; however, there was no association with the Arg389 allele.[143]

CLINICAL BENEFIT IN PATIENTS WITH CARDIOVASCULAR DISEASE

ADRB1

Beta-blocker therapy is the standard of care in patients with a reduced ejection fraction due to its benefits in preventing death or hospitalization for congestive heart failure exacerbations. Extending the pharmacogenetic associations with blood pressure and heart rate lowering to important clinical outcomes in patients with reduced ejection fraction would represent a critical, translational step. As anticipated, there are some reports where the beneficial effects of beta-blocker therapy are greater in carriers of certain genetic variants. For example, when compared to placebo, Arg389 homozygotes had a 34% reduction in the time to first hospitalization or death when treated with bucindolol versus a 13% reduction seen in the Gly-389 carriers.[143] This initial observation with bucindolol has been difficult to extend to clinical outcomes in patients treated with alternative beta blockers such as carvedilol or metoprolol whether studied as part of a randomized controlled clinical trial[144] or registries of patients with heart failure treated with beta blockers.[145-149] Whether differences in the ability to detect variation in the treatment benefit in carriers of the Arg389 variant are due to drug specific effects (i.e. bucindolol vs metoprolol) or the play of chance has not been adequately tested.

Outside of patients with reduced ejection fraction, patients with CAD are also commonly treated with beta-blocker therapy for the treatment of angina, after MI for the prevention of death, or concomittant hypertension. In a genetic substudy of patients with CAD randomized to either verapamil or atenolol, carriers of at least one copy of the Ser 49/Arg389 haplotype had a ninefold versus twofold worsened prognosis when assigned to verapamil versus atenolol.[150] Interestingly, this association was, despite equivalent blood pressure and heart rate control in both groups, suggesting that these two parameters may not be adequate surrogates for the cardioprotective effects of beta-blocker therapy.

ADRB2

One study has examined the influence of genetic variation at *ADRB2* and its influence on clinical outcomes in patients who recovered from an acute coronary syndrome and were treated with beta-blocker therapy and found those homozygous for both the Arg16 and Glu27 alleles had a 20% rate of subsequent death versus 6% of those homozygous for both Gly16 and Gln27.[149] This initial observation has been observed in some studies of patients with heart failure,[148] although not all.[146,147,150]

GRK5

Extending the laboratory associations of the Glu41Leu variant to clinical outcomes of patients treated with beta-blocker therapy has mixed associations. Specifically, in African-American heart failure patients receiving beta blockers, Leu41 carriers exhibited improvement in survival compared to Glu41 carriers in one,[138] although not in another, larger study.[145]

ADVERSE EVENTS

Anticipated by the pharmacokinetic influence of *CYP2D6* variants on metoprolol metabolism were observations that metoprolol-induced adverse events (e.g. bradycardia) were associated with loss of function *CYP2D6* alleles in two studies, each numbering over 1,000 treated patients.[151,152] Smaller studies have been unable to replicate these associations, although this may be due to their limited statistical power.[153,154]

CLINICAL IMPLICATIONS

The majority of the attention and evidence surrounding beta-blocker pharmacogenetics revolves around *ADRB1* locus and in particular the Arg389Gly variant. In general, carriers of the Arg389 variant have an improved reduction in heart rate, blood pressure, ejection fraction and survival when treated with chronic beta-blocker therapy compared to those with the Gly389 variant. Although it is unlikely that beta-blocker therapy will ever be withheld for carriers of the Arg389 variant, one potential application of these findings would be to consider advanced heart failure therapies (e.g. left ventricular assist devices, biventricular pacing or transplantation) at an earlier stage in patients with the Gly389 variant.

ANTIARRHYTHMIC DRUGS

DIGOXIN AND CALCIUM CHANNEL BLOCKERS

As described above, *ABCB1* encodes a transmembrane drug transporter that resides on the apical membrane of enterocytes

and hepatocytes. Its primary function is protective and serves to limit systemic exposure to a drug or accumulation of a drug within a body compartment protected by a blood-tissue barrier (e.g. blood:brain, blood:placenta and blood:testis barriers). Genetic variation has been identified and a common haplotype defined by three SNPs—C1236T (rs1128503), G2677T (rs2032582), C3435T (rs1045642)—captures the genetic variation at this locus. Individuals who carry a T-allele at each of the three SNPs (i.e. the T-T-T haplotype) have higher gene expression and as a consequence higher *ABCB1* transporter activity leading to lower systemic exposure. Many cardiovascular drugs are known substrates and some have been highlighted above. In addition verapamil, diltiazem and digoxin are *ABCB1* substrates and this genetic variation results in a pharmacokinetic mechanism for altered drug exposure in some studies although not consistently.[155-157] None have been linked to outcomes in patients treated with these agents.

PROCAINAMIDE

Procainamide, a class 1 antiarrhythmic agent, is commonly used to control ventricular arrhythmias and is rapidly metabolized via acetylation into N-acetylprocainamide by hepatic acetyltransferases (NAT2, primarily). Variability in hepatic acetylation capacity has long been observed to follow a bimodal distribution.[158] Individuals with reduced acetylation capacity (i.e. "slow acetylators") have a reduced formation of NAPA. Major genetic determinants of the aceytlation capacity are genetic variants in the *NAT2* gene (*5/rs1801280, *6/rs1799930, *7/rs1799931 and *14/rs1801279), which have substantially decreased acetylation activity, are common across populations, and can be used to predict acetylation capacity[159] and the NAPA/procainamide ratio during procainamide challenge.[160] Although procainamide efficacy does not appear to be related to variation in its pharmacokinetics, the induction of drug induced lupus associated autoantibodies has been linked to the slow acetylator status.[161,162] However, the link between these genetic variants and a clinically manifest drug induced lupus syndrome has been less consistent.[161,162]

PROPAFENONE

Propafenone, a Class 1 antiarrhythmic agent, used for the control of atrial and ventricular arrhythmias undergoes hepatic hydroxylation by *CYP2D6* into 5-hydroxypropafenone and demonstrates wide interindividual variability.[163] The beta-blocking properties of propafenone are best correlated with the concentrations of the parent drug which has the higher affinity for the beta-2 adrenergic receptor.[164] As discussed above, *CYP2D6* is highly polymorphic with multiple loss-of-function (e.g. **3, *4, *5, *6, *7* and **8*) and reduced function [e.g. alleles (**9, *10* and **41*] as well as gene duplications identified in the general population that can be used to predict *CYP2D6* activity into "poor metabolizer (PM), extensive metabolizer (EM), intermediate metabolizer (IM) and ultra metabolizer (UM)".[165] PMs and IMs are characterized by low-oral clearance of propafenone, resulting in accumulation of propafenone and often levels of undetectable 5-hydroxypropafenone.[163,166,167] In contrast, EMs are characterized by high clearance of propafenone into its 5-hydroxy metabolite.[163]

ANTIARRHYTHMIC EFFICACY

The observed propafenone pharmacokinetic differences between PMs and EMs can be extrapolated to its antiarrhythmic properties. At low-dose propafenone, PMs have greater reduction in exercise- or isoproterenol-induced heart rate compared to EMs.[164] However, when studied at higher doses or without the "stress" of exercise/isoproterenol, changes in propafenone-induced heart rate, PR-prolongation, QRS durations are equivalent in EMs and PMs.[163,164,167] In studies of patients with atrial fibrillation or premature ventricular contractions, PMs and IMs had enhanced suppression of atrial and ventricular arrhythmias compared to EMs and UMs; consistent with the pharmacokinetic data.[166,168] However, on the other hand, there is an equal number of reports failing to find differences in efficacy between EMs and PMs treated with propafenone.[163,167] Therefore, there is insufficient data to make any conclusions regarding *CYP2D6* status and antiarrhythmic efficacy of propafenone.

TOXICITY

Central nervous system (CNS) side effects can be induced by propafenone and includes visual blurring, dizziness and paresthesias, as well as excessive beta-blockade manifesting as bradycardia. The incidence of these symptoms is correlated with a higher concentration of systemic propafenone and, accordingly, the *CYP2D6* PM phenotype.[163]

CLINICAL IMPLICATIONS

Antiarrhythmic drug pharmacogenetics represents a mixed collection of associations that do not convincingly translate to consistent association of meaningful clinical outcomes. As such, there is currently no role for pharmacogenetic testing in the clinical use of these medications.

FUTURE DIRECTIONS

Beyond genetic variants, it is anticipated that other genomics platforms will soon be able to guide the use of cardiovascular pharmaceuticals. In general, the data to date have identified largely common, genetic variants that alter the pharmacological properties of a drug (i.e. pharmacokinetic or pharmacodynamic). Despite these advances the next steps will be to understand more about the genetic underpinnings of the underlying biology that is being modified by drug therapy. The required tools for these next steps will need to go beyond genotyping candidate genes and GWAS. For example, an unbiased approach of lipid and intermediary metabolism metabolites has identified a panel of molecules, or a "signature" that is associated with not only simvastatin-induced LDLc reduction but also C-reactive protein lowering.[169] Alternative platforms, such as gene expression profiling and proteomics based analyses, may be better suited to identify novel subgroups with differential treatment responses. Such platforms have several advantages over traditional genetics based research: (1) being responsive to the environment (i.e. diet, smoking, drug therapy) and age, and (2) are amenable to a systems-based approach to understand how the activity of entire pathways, instead of individual genes, influences drug response. Finally, whole genome sequencing is now a reality and for rare drug responses, such as drug toxicity, may quickly be able to identify novel genes and variants.

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Chapter 115

Preventing Errors in Cardiovascular Medicine

Robert M Wachter

Chapter Outline

- Modern Approach to Patient Safety
- How to Improve Patient Safety?
  - — Redundancies, Standardization and Forcing Functions
  - — Role of Computerization
- Communication and Culture
- Learning from Mistakes
- Creating a Safe Workforce
- Preventing Diagnostic Errors
- What Can Patients Do to Keep Themselves Safe?
- Changing Policy Context for Patient Safety

INTRODUCTION

Although medical mistakes have long bedeviled physicians and patients, the patient safety movement is a relatively recent phenomenon. Prior to the turn of this century, few hospitals or health care organizations made substantial investments in patient safety or possessed substantial safety programs. What little effort did go into preventing mistakes was often organized by the risk management department, and therefore had a legalistic character—including a general reluctance to share lessons from errors throughout the organization, not to mention outside the organization. Trainees received no instruction in key principles of safety, and there was next-to-no research in the area.

All of that changed in 2000, when the Institute of Medicine published *To Err is Human: Building a Safer Health System*.[1] This seminal report, which estimated that 44,000 to 98,000 people in the United States die each year from medical errors (the equivalent of a jumbo jet crashing each day), created a revolution in our approach to patient safety.

Let's begin with some definitions.[2] Because patients can be harmed even when receiving pristine care, it is important to separate errors from adverse events. An error is usually defined as "an act or omission that leads to an unanticipated, undesirable outcome or to substantial potential for such an outcome". Adverse events, on the other hand, are injuries due to medical management rather than the patient's underlying illness. Although patients experiencing errors and adverse events may be injured equally, the distinction makes a large difference because the approaches to the two types of problems may be quite different. For example, a patient appropriately treated with a blood thinner like warfarin (coumadin) for atrial fibrillation who develops gastrointestinal bleeding despite being on the correct dose of the blood thinner has suffered an adverse event, but not a medical error. Preventing problems like the one suffered by this patient will take an improved scientific understanding of the situation, for example, developing safer anticoagulants or new ways of protecting the stomach from bleeding complications.

On the other hand, the treating physician would have committed a medical error if the patient became overanticoagulated because the patient prescribed a new medication without checking for possible drug interactions. Potentially useful solutions, in this case might be a computerized system to remind the doctor of potential interactions or having new medications double-checked by a pharmacist.

MODERN APPROACH TO PATIENT SAFETY

Our traditional approach to medical mistakes has been to point fingers at the provider who was at the "sharp end" of care; the cardiologist performing the angioplasty and placing the stent or the nurse administering an intravenous medication. This approach comes naturally to us. We all tend to seek individual accountability for our actions, particularly in a country like the US, where we emphasize individual responsibility. A generation ago, the notion of individuals being at fault for most medical errors might well have made some sense.

Today, however, the process of delivering care is so complex—with so many different providers, technologies and medications having to come together seamlessly, all at a breathtaking pace—that the idea that a physician can keep patients safe by being well trained and careful is hopelessly naïve. The underlying problem is something completely different.

Indeed, in the past decade we have learned that most medical mistakes are committed by hard working, well-trained caregivers. Given this, trying to get people to be more careful, or shaming or suing them is unlikely to be very helpful. Rather, the modern approach to medical errors, drawn largely from safer industries such as commercial aviation and nuclear power, emphasizes "systems thinking", which holds that human error is inevitable, and that the only way to productively deal with the problem is to try to build reliable systems that anticipate

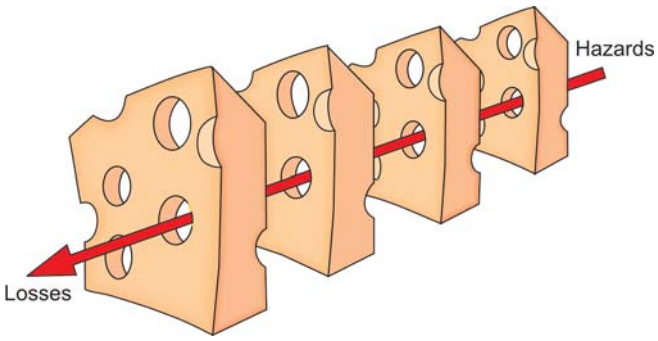


FIGURE 1: The Swiss cheese model for medical mistakes (*Source:* Modified from Reference 4)

errors and either prevent or block them before they cause harm to patients.[2] This model, well known in other industries and among safety scientists, was first introduced to medicine in the mid-1990s[3] and did not become widely accepted until the past decade.

The best accepted mental model for systems thinking is the "Swiss cheese model" of "organizational accidents", articulated by English psychologist James Reason[4] (Fig. 1). Reason developed his model after studying terrible accidents from a variety of non-health care fields, including aviation and rail transport. He always found the same pattern: the organization had several protections that had each failed at the time of the error. The model thus emphasizes that in complex organizations, "sharp end" errors are usually not sufficient by themselves to cause a significant error. Instead, everyday human errors (forgetting to double check an allergy list, for example) penetrate multiple incomplete layers of protection (holes in the Swiss cheese) to cause a serious accident. The Swiss cheese model highlights that it is important for us to not immediately focus on the smoking gun—the individual at the "sharp end" whose error began the cascade of events that led to harm—but rather to try to shrink the holes in the cheese and create multiple overlapping layers of protection to decrease the probability that the holes will ever align and let an error slip through to harm a patient.

Even when a physician understands the Swiss cheese model and instinctively tries to shore up the holes in the Swiss cheese rather than assigning blame, improving complex systems is a difficult thing to do. As one example, envision a system with so many robust double and triple checks that no patient with an ST-segment elevation myocardial infarction ever receives the wrong medication in the Emergency Department. That's great, but if the fix was too time-consuming and cumbersome, one of two problematic things would happen: either some patients would have unacceptably long door-to-needle times while their caregivers were performing their triple checks (and some would be harmed by this delay), or the providers would begin bypassing steps in order to give the patient the care he needed (workarounds).[5] These two scenarios do not mean that creating new layers of defense (e.g. a checklist or a new double check) is wrong (it is often the right thing to do), but rather that systems need to be modified thoughtfully, with a lot of attention paid to how providers actually do their work. Some solutions that seem perfectly sensible when they are thought up in a committee meeting turn out to be unfeasible, and even unsafe, when they are implemented in a real practice settting.

HOW TO IMPROVE PATIENT SAFETY?

REDUNDANCIES, STANDARDIZATION AND FORCING FUNCTIONS

In keeping with the Swiss cheese model, the modern approach to patient safety focuses on the need to create robust, resilient systems that catch errors before they happen or prevent them from leading to patient harm. For example, errors in routine behaviors (slips) can best be prevented by building in redundancies and cross checks, in the form of checklists, read-backs (Let me read your order back to you) and other standardized safety procedures (e.g. counting the sponges and needles in the operating room to be sure that none have been left inside the patient, signing a surgical site prior to an operation to be sure to operate on the correct limb, asking patients their name before giving them a medication or drawing their blood).[2] Checklists, in particular, have gathered tremendous momentum in recent years following two prominent studies that demonstrated that their use was associated with significant decreases in central line-associated bloodstream infections[6] and in surgical complications.[7] Their value was summarized in a bestselling book by surgeon-author Atul Gawande.[8]

Another important concept in safety is known as the "forcing function". The concept here is that increasing numbers of errors in health care occur as a result of people interacting with complex machinery and technologies. A forcing function is an engineering solution that decreases the probability of human error.[9] In other words, in an error-prone interaction between people and machines, it is best to try to change the machine to prevent the error. This is virtually always easier and more reliable than trying to change the person. The classic example was when, after a spate of horrible accidents in which parents inadvertently shifted their car into reverse with their foot off the brake and ran over their children (who were walking behind the car), automotive engineers changed the system. In any car manufactured in the past 20 years, it is now impossible to put the car into reverse without a foot on the brake. This forcing function is far more effective than trying to educate every driver to avoid this mistake, or putting up prominent reminders on the windshield of every car, or admonishing drivers to be more careful, or shaming or criminalizing the perpetrators.

In health care, an example of a forcing function was changing the gas nozzles and connectors so that it is now physically impossible for anesthesiologists to mistakenly connect the wrong gas (such as nitrogen instead of oxygen) to a patient. Given the ever-increasing complexity of modern medicine, building in these forcing functions (in intravenous pumps, defibrillators, mechanical ventilators and computerized order entry systems) will be crucial to safety.

ROLE OF COMPUTERIZATION

Health care is among humankind's most information intensive endeavors. Here's one vivid example: a large integrated health care system will process many times more computerized

transactions each day than the NASDAQ stock exchange. But the challenge goes well beyond simply the number of transactions. Consider the challenge of trying to keep current and accurate information about one patient's current medical problems, past medical history, medications, allergies and test results. Now add in some complexity typical of the American health care system, unless the patient is followed within an integrated system (like the Veteran's Administration medical system), he or she will be seen by many different doctors, often working for different health care organizations. Let's assume the patient has a myocardial infarction while visiting a relative in another state. In the ideal world, the providers seeing the patient would be able to quickly see the entire patient's information, including an old electrocardiogram, risk factors, medications and allergies.

Of course, virtually none of this happens in today's health care system, at least in the United States (most other countries are far more "wired"). Most information today is stored on paper, frequently illegibly and not entered or stored as structured data, making it next to impossible to aggregate it and analyze it for patterns. As patients move from office to office, hospital to hospital, even a clinical laboratory in a town back to their doctor's office down the street, information rarely flows seamlessly. The result is an extraordinarily error-prone process in which crucial data rarely accompanies patients as they move around. For example, studies have shown that two-thirds of post-discharge hospital visits take place without a hospital discharge summary available to the primary care doctor,[10] and in more than two-thirds of outpatient subspecialty referrals, the specialist received no information from the primary care physician to guide the consultation.[11] The Joint Commission has promoted the value of "medication reconciliation" (checking the medication list for consistency and accuracy at every visit and transition, such as when the patient leaves the ICU and goes to the floor) as a way to try to improve safety.[12]

But medication reconciliation and managing most of our information flow problem, is clearly going to be dependent on wiring our health care system. Because of the absence of incentives for doctor's offices and hospitals to computerize, the pace of IT adoption has been extraordinarily slow. Luckily, health care is finally on the path to computerization, partly driven by the pressures to improve quality and safety (accompanied by increasingly aggressive requirements to report on clinical care and act on the results). In addition, in 2009, the US federal government committed approximately $20 billion to support the adoption of health care information technology.[13] The result is that many hospitals and doctors' offices are implementing computer systems including computerized provider order entry (CPOE), electronic health records and a several other information technology solutions (bar-coding for medication administration, "smart" intravenous pumps).

The wiring of health care is crucial to our efforts to promote patient safety. Many studies have shown that well constructed CPOE systems can decrease medication error rates by more than 50% by eliminating illegible prescriptions, alerting doctors or pharmacists to potential drug interactions and ensuring that doses and frequencies are in acceptable ranges.[14] More recent data have demonstrated the value of bar coding systems, which can help decrease medication administration errors.[15]

Health care information technology systems will become even more useful when they build "decision support", prompting a doctor to use a preferred antibiotic for a given infection, for example, or reminding her to check the creatinine after beginning an angiotensin-converting enzyme inhibitor.[16] And newer decision support engines are emerging that will provide even more sophisticated decision-support, prompting the physician to consider a variety of diagnoses after he enters the patient's history, physical examination and laboratory results.

Ultimately, CPOE systems, when combined with electronic health records that are interoperable (meaning that even different computer systems can "talk to each other", in the same way that you can withdraw money from an ATM of a bank you do not generally use), are likely to provide new levels of safety. Modern systems are improving, becoming more user-friendly and intuitive and building in critical functions sought by caregivers. And patients are becoming key participants, as some modern systems allow them to schedule visits, review their laboratory data and read the literature about their medical problems. While this level of patient engagement will present new challenges (particularly since patients may be misinformed by some of the things they read on the internet), the potential to improve quality and safety is great.

While computers will undoubtedly improve the safety of health care, we have also learned that computers can create their own safety hazards, particularly if they are designed poorly.[17] New types of medical errors have been reported that stem from clunky interfaces, incorrect data in the computer system and non-intuitive functionality. For health care to gain the maximum benefit from information technology, it will be crucial for systems to evolve that learn from past mistakes and take provider workflow into account.

COMMUNICATION AND CULTURE

In addition to the system-oriented fixes, described above, we have also come to appreciate the importance of communication and teamwork in health care. In the Joint Commission's (the main accreditor of US hospitals) database, communication failures underlie the majority of serious errors (Fig. 2). Analysis of these errors has taught us that many are caused by dysfunctional relationships between doctors and nurses, between trainees and supervisors or between patients and providers. We have learned that medicine tends to have "steep hierarchies" in which individuals lower on the totem pole are reluctant to question the opinion of a superior. This problem, also known as an "authority gradient", manifests itself many ways: a nurse sees a physician beginning a procedure without having cleaned his hands but is unwilling to question him; or a surgical intern is unsure that she is competent to perform a procedure but decides not to call in her supervising physicians because it might be seen as a sign of weakness. Unlike in health care, "safe industries" (such as aviation and nuclear power) have learned the importance of creating environments and cultures in which it is not only acceptable for a junior or less powerful person to raise a concern, it is seen as absolutely mandatory.

As we have recognized the importance of culture, health care has begun to import some of the training models from other industries. After several tragic airline crashes in the 1970s and

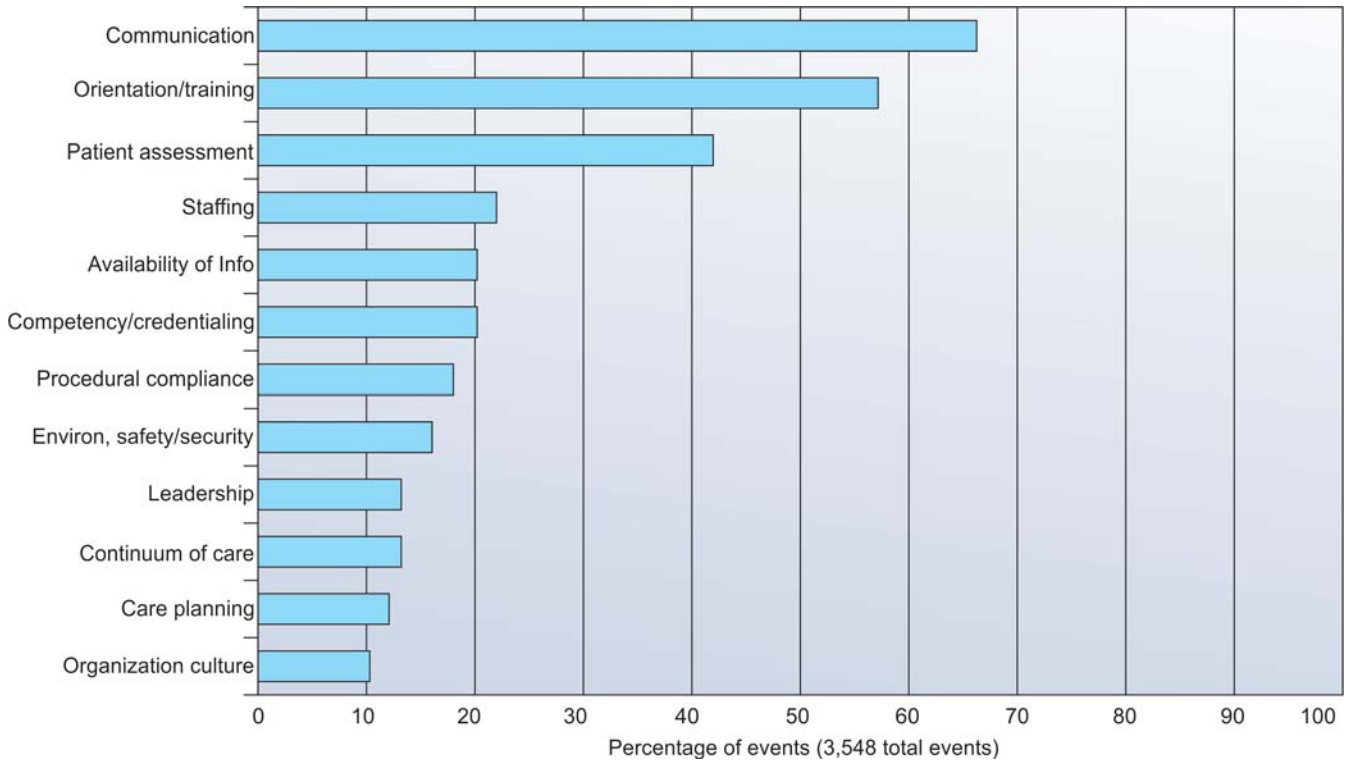


FIGURE 2: Root causes of sentinel events reported to the Joint Commission (previously the Joint Commission on the Accreditation of Health Care Organizations, JCAHO) 1995-2005

1980s demonstrated the hazards of a poor communication environment (including the worst crash of all time, the collision of two 747s in the Canary Islands, which killed nearly 600 people), all commercial flight crews are now required to participate in Crew Resource Management (CRM) training, in which participants practice for emergencies, and learn to flatten hierarchies that might get in the way of open communication, communicate clearly using standard language, and utilize checklists, pre-flight briefings, and other systemic approaches.[2] The early evidence that health care CRM will improve patient safety is encouraging but somewhat mixed, partly because changing the culture of a busy med-surg floor or cardiac intensive care unit is substantially more difficult than doing so in a sealed cockpit.[18] Many CRM programs are now coupled with the use of realistic simulation; the latter can help enhance both procedural competence as well as provide a more authentic environment for caregivers to practice communication and teamwork.

The term "culture of safety" is used as shorthand for an environment in which teamwork, clear communication and openness about errors (both to other health care professionals and to patients) is at work.[19] While this term has, in the past, implied a completely blameless culture, a more mature model has emerged in recent years, often described as a "Just Culture".[20] The Just Culture model recognizes that most errors are, in fact, blameless—committed by good people trying to get it right—and that blaming and finger pointing are counter-productive in these circumstances. On the other hand, willful disregard of safety rules, disruptive behavior or non-remediable incompetence are not blameless, they are blameworthy. The patient safety field is presently grappling with how to get this balance between "no blame" and accountability right.[21]

LEARNING FROM MISTAKES

Another key safety principle is to learn from one's mistakes. Safe systems have a culture in which errors are openly discussed, often in morbidity and mortality (M&M) conferences.[22] Over the past several years, there has been an increasing emphasis on this area, since it is difficult for caregivers and systems to improve if they do not learn from their prior errors. While traditional M&M conferences often involved only physicians, there is a modern emphasis on interdisciplinary communication (involving the appropriate disciplines, including doctors, nurses and hospital administrators), identifying errors and emphasizing systems thinking and solutions.[23] In addition to open discussions at conferences, health care organizations seeking to improve safety create opportunities to hear about unsafe conditions and errors from front-line staff, often via "incident reporting systems"[24] or through Patient Safety Walk Rounds by senior leaders.[25] Moreover, many organizations have embraced a technique drawn from engineering called Root Cause Analysis—a blame-free forum that brings together experts and leaders as well as the involved providers. The goal of these sessions is to analyze major errors in detail, to discover all of the system weaknesses that need to be improved and to create action plans with strong follow-up.[26]

CREATING A SAFE WORKFORCE

While systems are critical to patient safety, there is no substitute for a well-trained, well-staffed and well-rested workforce in delivering safe care. There is now strong evidence linking low nurse-to-patient ratios, long resident work hours and lack of physician board certification to poor patient outcomes.[27-29] A variety of interventions have been implemented in response to this evidence. For example, the State of California now mandates ratios of nurses to patients no higher than 1:2 in intensive care units, and 1:5 on general medical floors. And the Accreditation Council for Graduate Medical Education (ACGME), the organization that accredits US postgraduate training programs, now mandates that residents get at least one day off per week, and work no more than 80 hours per week.[30] Although the impact of these regulations on patient safety is still debated, the new focus on the workforce is overdue and welcome. It seems only a matter of time before some similar work hour restrictions are placed on the work of practicing physicians, mirroring limits on commercial airline pilots and truck drivers.

PREVENTING DIAGNOSTIC ERRORS

The modern patient safety movement has emphasized medication errors, handoff errors, infections and surgical errors over diagnostic errors, both because the former categories are easier to measure and fix. Yet many studies have demonstrated that diagnostic errors are common and that they can be lethal.[31] For example, nearly 1 in 25 patients with heart attacks who come to emergency rooms are mistakenly sent home with a different (incorrect) diagnosis.[32] And autopsy studies have shown high rates of missed diagnoses, rates that have not gone down appreciably over recent years despite new imaging technologies, such as CAT and MRI scanners, and laboratory studies such as troponins and BNPs.[33]

Part of the reason for the relative inattention to diagnostic errors is that they seem, at first glance, to represent simple human failings and bad thinking. But recent research has demonstrated that some, perhaps many, diagnostic errors can be prevented. As described earlier, some of the improvements will come from modern computerized decision-support systems,[34] which are beginning to develop the capacity to automatically suggest possible diagnoses and point users to helpful resources and articles.

But better information technology is only part of the solution. Improving diagnostic accuracy also requires that we truly understand how doctors think and how these thought patterns can lead them down incorrect diagnostic paths. For example, many errors occur when doctors are too quick to come to a decision (this is definitely a case of heart failure) and then defend that judgment too vigorously even in the face of contradictory evidence. This process of getting "stuck" on a diagnosis, known as "anchoring bias", is one of many pitfalls that clinicians fall into, particularly when they are applying cognitive shortcuts (heuristics) to improve their mental efficiency. Other shortcuts that can lead to errors include the availability heuristic (relying too strongly on memorable past cases), blind obedience (deferring too strongly to an authority figure's opinion or the results of a high-tech test) and the framing bias (getting too strongly wed to a certain way of thinking about a case without considering alternative ways of "framing" the situation).

How can these errors caused by faulty thinking be prevented? As always, the answer will come through a systems approach, but here this means the creation of better systems to train physicians to avoid common diagnostic mistakes. The most hopeful approach is known as "metacognition", in which physicians are trained to think about their own thinking, and be aware of risk factors for diagnostic errors. This is often best done by asking hypothetical questions like, "what is the worst thing this could be?" or "if this patient dies tonight and I had missed the diagnosis, what would that diagnosis have been?"[35,36]

WHAT CAN PATIENTS DO TO KEEP THEMSELVES SAFE?

Given the frequency and the impact of medical errors, many patients are understandably interested in what they, or their loved ones, can do to protect themselves. Without doubt, some errors can be prevented by engaged patients or family members who remain vigilant and are willing to ask questions when they notice something amiss, whether it is a medication that seems wrong or a doctor who has failed to wash his hands before touching them.[37]

There are several additional reasons why patient engagement has only limited value as a safety strategy. First, many patients receiving health care are sufficiently confused or anxious that they simply cannot be active participants in their own care. Significant numbers do not speak English (or whatever the dominant language of health care is) or have low health literacy.[38,39] Even when patients are capable of understanding health information and advocating for themselves, there is so much activity that takes place behind the curtains that there will be many circumstances in which patients are unable to shield themselves from errors. Finally, there is evidence that many patients feel guilty when they or a loved one are a victim of a medical error.[40] There is a risk that placing more of the responsibility to prevent errors on the backs of patients or families will only serve to increase this feeling of guilt. Ultimately, patients need to be able to trust that their physician and health care system have done everything possible to keep them safe.

CHANGING POLICY CONTEXT FOR PATIENT SAFETY

Reviewing this list of potential approaches to improving patient safety illustrates one of the great challenges of the emerging field in the absence of comparative evidence, and in light of the high cost of some of the interventions (improved staffing, information technology, teamwork training and simulation), even institutions committed to safety will be understandably confused about which approach to emphasize.[41-43] Increasingly, their focus is being determined by the policy context. For example, most American hospitals are accredited by the Joint Commission, which has issued dozens of safety standards in the past several years, and now engages in unannounced surveys at regular intervals. Similarly, a prominent group called the

National Quality Forum has created a list of "Never Events"—serious adverse events that "should never happen in health care". The majority of US states now require reporting of any of these events, reports that can trigger state inspections and fines. Finally, Medicare, the dominant payer for US health care, will now no longer reimburse hospitals for the cost of caring for some of these "never events".[44]

Obviously, these policy initiatives, combined with other quality-oriented initiatives that emphasize public reporting of key outcome and process data, create an environment in which hospitals and physicians now *must* focus on certain quality and safety hazards. This is generally a good thing, but it will be crucial to reserve some "bandwidth" to focus on the kinds of problems that are emerging within an individual practice or hospital, rather than using all safety-oriented resources to meet these accreditation and regulatory mandates.

The overall impact of these policy changes, many of which began to take hold after the publication of *To Err is Human*,[1] is that a business case to promote safe care has begun to emerge in American medicine.[41] Up until recently, most health care in the U.S. was paid based on volume. Under this payment system, an unsafe hospital was paid the same as a safe one and an unsafe physician the same. Patients, sadly, had few ways to distinguish between those providers and organizations that were focusing relentlessly on improving safety and those paying it lip service. Many of these policy initiatives can be seen as attempts by policymakers to put "skin in the game" when it comes to safety. Since many safety fixes are extraordinarily expensive (fully computerizing a 500-bed hospital may run upward of $100 million and computerizing a doctor's office may cost more than $50,000 per doctor), creating a business case for safety is crucial to getting the work done.

In the end, thinking about patient safety is hard, particularly since health care offers so many miraculous benefits for our patients, and because health care providers and administrators work very hard to do the right thing. But, as quality guru Paul Batalden famously said, "Every system is perfectly designed to achieve the results it achieves". For too long, ours has emphasized progress, technology and volume over safety and reliability. There is no reason that our future health care system cannot continue to provide its extraordinary benefits to patients, while achieving a level of safety that permits patients to trust that they will not be harmed in the process of being helped.

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Chapter 116

Economics in Cardiovascular Medicine

Paul A Heidenreich

Chapter Outline

- Cost of Cardiovascular Care
- Trends in Health Expenditures (US vs Non-US)
- CV Contribution to the Rising Cost of Care
- Variation in Resource Use
- Resource Scarcity and Value
- Basic Concepts of Health Economics
  - — Determining Economic and Health Outcomes: Trials versus Modeling
  - — Measuring Cost
  - — Measuring Outcome
  - — Incorporating Quality of Life
- Benchmarks for Cost-effectiveness
- Evaluating Uncertainty
- Perspective
- Efficiency
- Government's Use of Cost-effectiveness
  - — United States
  - — Non-US: Britain's NICE
- Cost-effectiveness of Individual Treatments and Strategies
  - — Heart Failure
  - — Coronary Artery Disease
  - — Atrial Fibrillation
- Cost-effectiveness of Quality Improvement Interventions
- Future Estimates of the Cost of Heart Disease

COST OF CARDIOVASCULAR CARE

Cardiovascular disease accounts for over 16% of total cost of care in the United States.[1] In 2010, this represents 503 billion dollars according to the estimates of the National Heart Lung and Blood Institute and includes both direct (cost of care) and indirect costs (lost productivity).[1] The costs (Fig. 1) can be separated into direct cost of care (hospital, nursing home, drugs, home care, physician and other providers) and indirect costs (costs due to inability to work from disability or death). The direct cost of care in 2009 for cardiovascular disease was $324 billion, with indirect costs of $41.7 billion for morbidity and $137.4 billion due to premature death.[1]

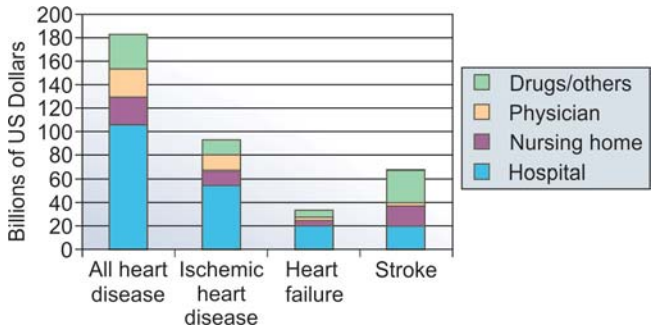


FIGURE 1: Cost of care estimates for different types of cardiovascular disease, split by type of resource use (hospital costs are the greatest component of total cost for ischemic heart disease and heart failure)

Cardiovascular disease has a significant and direct impact on employers. Among 88 US companies, those with heart disease cost their companies an average of $6052 in sick leave, $4,845 per year in short-term disability and $981 in worker's compensation costs.[2] The mean annual payment for employees with heart disease at large in US companies was $4000 per patient, double the average payment for all other conditions.[3]

TRENDS IN HEALTH EXPENDITURES (US VERSUS NON-US)

The US has by far the highest per capita health expenditures [$7538 vs $3033 (in US dollars) for all Organisation for Economic Cooperation and Development (OECD) countries].[4] The second highest is Norway at $5,003 per capita. In 2008, the US health expenditures were 16% of GDP, almost double that of the OECD average (8.9%). However, other countries are catching up as the growth in health care expenditures in the United States (3.4% per capita per year) is now below the OECD average (4.1% per capita per year).

Trends in cardiac revascularization highlight differences between the United States and Canada (Fig. 2). Use of percutaneous coronary interventions (PCIs) has increased over the last 10 years while coronary artery bypass graft (CABG) rates have dropped for both countries.[5] Of note, the US-Canadian differences have narrowed and now CABG rates are equal. For PCI, while the absolute rate remains higher in the United States, the rate of growth has been higher in Canada over the last 10 years.

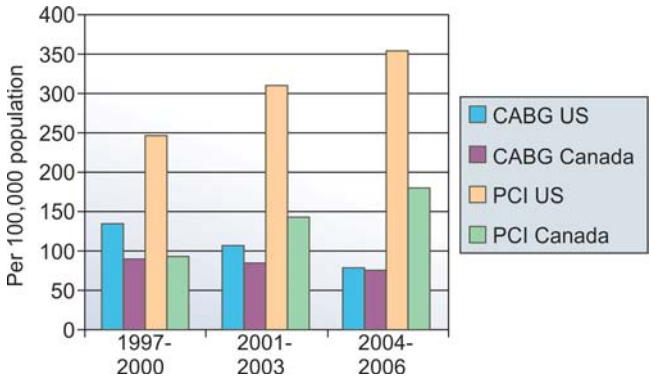


FIGURE 2: Trends in cost of care for PCI and CABG for the US and Canada.[5] CABG (coronary artery bypass grafting) has decreased in both countries and now rates of use are similar. PCI use remains higher in the US than Canada although the rate of increase has been higher in Canada

CV CONTRIBUTION TO THE RISING COST OF CARE

The management of heart disease has been an important contributor to the rising cost of health care. Cost of care has increased for ischemic heart disease, heart failure and stroke (Fig. 3). Over the prior decade, five conditions (heart disease, pulmonary disease, mental disorders, cancer and hypertension) accounted for more than 30% of the rise in health care costs.[6] The explanation for the increase can be separated into one of three categories: (1) an increasing population size; (2) an increasing prevalence for a given population or (3) an increase in cost per treated case. The increase in cost due to heart disease was explained by an increase in cost per case (70%) and an increase in the population (30%). This finding suggests that greater use of more expensive technologies has been the major impetus for increasing costs of heart disease.[7]

Has this increase in expenditure on cardiovascular disease made a difference in health in the United States? To estimate this, we can examine life-expectancy of older adults as many of the interventions developed for cardiovascular disease have had a greater impact on the elderly given their higher prevalence of heart disease. In 1970, US life-expectancy at age 65 for females ranked 3rd of 30 OECD countries and 12th for males.[9] At the time, the United States was spending 48% more on heath care as a percent of GDP than other OECD countries (7% vs 4.8%). By 2007, the United States was spending 87% more (16% vs 8.6%), yet the United States had dropped to 17th in female longevity at age 65 and 16th for males.[9] This suggests the additional health expenditures in the United States were not an efficient use of resources when compared with other countries.

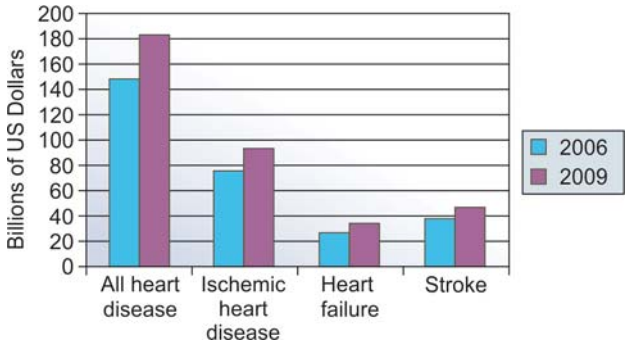


FIGURE 3: Trends in cost of care for different types of cardiovascular disease. Data are estimated by the American Heart Association[8] and indicate that costs have increased similarly for different types of cardiovascular disease during the last five years

However, health is influenced by many factors despite the quality of medical care. It is possible that prenatal care and health behaviors are better outside the United States. Compared to nine countries similar in development, the United States ranked last at birth in life-expectancy and tied for last at age 40.[7] However, for life-expectancy at age 80, the United States was third out of nine suggesting better medical care for the elderly with treatment of heart disease a likely factor.

VARIATION IN RESOURCE USE

The United States has substantial regional variation in the cost care for patients with heart disease. The Dartmouth Atlas has documented unwarranted variation in both quality of care and amount of care provided to Medicare patients during their last two years of life.[10] Cost of care varied more than twofold across regional health markets for a tertiary medical center (hospital referral regions). The average annual spending per enrollee in 2000–2001 was $4,346 in Appleton, Wisconsin compared to $11,544 per enrollee in the Bronx, New York.[10] Severity of illness also varies across areas; however, only 4% of the variation in Medicare spending was explained by variation in severe chronic illnesses. The Dartmouth investigators found that half of the variation in utilization is due to supply-sensitive care and that it is differences in volume and not price that drives the overall cost differences. An example of supply-sensitive care is the number of cardiologists per Medicare enrollee which varies from less than 2 to13 per 100,000, and has a strong relationship with visits to cardiologists per enrollee. The variation in supply sensitive care appears to be due to cultural views of local providers (and possibly patients) regarding what constitutes optimal care. Such supply sensitive care accounts for well over half of Medicare spending.

RESOURCE SCARCITY AND VALUE

The growing interest in cost of heart disease and any unwarranted variation is due in part to the generally accepted premise that our society does not have enough resources to provide all effective treatments to every patient. Health providers already weigh cost and health benefit on a daily basis as part of prudent care. For example, few cardiologists order an echocardiogram to evaluate every murmur they hear even though the accuracy of echocardiography is superior. Appropriate use criteria, developed by the American College of Cardiology explicitly considers cost of care when determining the appropriateness of cardiac interventions or testing for specific indications.[11] However, this is the exception as most professional society's guidelines (e.g. American College of Cardiology/American Heart Association) and government benefit decisions (e.g. Medicare) do not allow cost to be considered in treatment recommendations or coverage.

Those paying for health care resources want value whether they are individual patients or large health plans.

Although improved survival and quality of life are the ultimate goals for any society, cost of care must be considered in order to optimize health when resources are limited. Thus, value in health care can be considered the primary outcome for all of us wishing to improve our health care systems. Cost-effectiveness is the explicit measurement of value.

BASIC CONCEPTS OF HEALTH ECONOMICS

Care that improves quality at lower cost will lead to an increase in value while the reverse will decrease it. However, the value of care that is both more expensive and of greater quality is difficult to quantify. The most common method of quantifying value is cost-effectiveness based on economic principles.[12,13] The term cost-utility is sometimes used when the benefit is expressed in quality adjusted life-years (QALYs). Alternatively, a cost-benefit analysis converts benefit and cost to the same units and requires placing a dollar value on a year of life (e.g. willingness of a patient to pay for a treatment with certain benefits).

By definition, cost-effectiveness is a comparison of two or more strategies:

$$\frac{\text{Cost (Strategy A)} - \text{Cost (Strategy B)}}{\text{Outcome (Strategy A)} - \text{Outcome (Strategy B)}}$$

The relationship between cost and outcome can be displayed graphically (Fig. 4) by placing outcome on one axis and cost on another. Most new technologies will fall in the upper right quadrant where both cost and effectiveness are increased and cost-effectiveness analysis is useful for determining outcome. If the intervention decreases cost while improving outcome (lower right quadrant), it is considered "dominant" and a calculation of cost-effectiveness ratio is not needed. Rarely, a new diagnostic strategy is less costly and less accurate compared to the current standard of care (lower left quadrant).

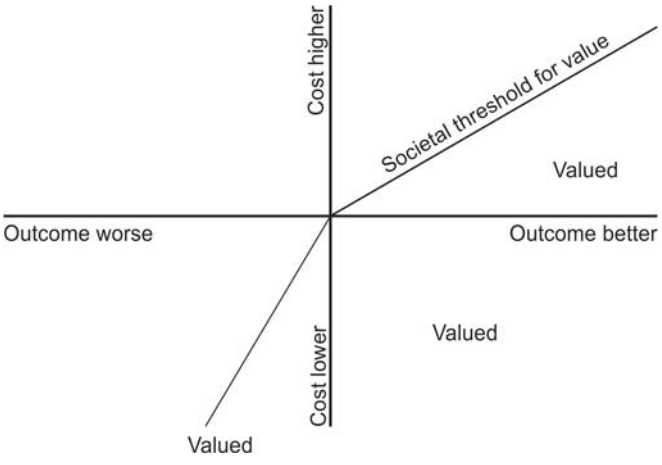


FIGURE 4: Cost and effectiveness are displayed with cost on the Y-axis and effectiveness on the X-axis. Value is defined as a combination of cost and outcome that lies to the right of a hypothetical cost-effectiveness threshold, represented by a two line from the origin, one heading up and to the right, and the other down and to the left. Strategies that lead to a result in the lower right quadrant (better outcome, lower cost) are considered dominant

DETERMINING ECONOMIC AND HEALTH OUTCOMES: TRIALS VERSUS MODELING

There are two options for measuring cost and outcomes: (1) direct measurement often as part of a clinical trial and (2) estimation (modeling). Trial data have the advantage of allowing patient level analyses, with clear applicability to the trial population. However, it is less clear how results of trial based cost-effectiveness studies can be applied to patients not enrolled in the trial. In addition, trial data are often limited by the duration of the trial. If survival, quality of life or cost of care is affected by one of the interventions beyond the trial duration, then results limited to the trial data will be biased. For these reasons, many trial based cost-effectiveness studies add a component of modeling to estimate economic and health outcomes over the patient's remaining lifetime.

Modeling has the advantages of applicability to any population; however, it is limited by the assumptions that are necessary to model patient outcome. Health providers make assumptions during every patient visit when deciding on treatments (what is the risk, what is the benefit, what is the cost to the patient and to the health system). Cost-effectiveness analysis makes all of these assumptions explicit and highlights the important factors that need to be considered when making a decision.[14] However, accurate models are usually complex and it is difficult if not impossible to convey to readers the entire workings of a model within a typical journal article's length. Intended or unintended biases in assumptions cannot be reliable avoided by peer review. For this reason, many journals will not consider cost-effectiveness models funded by industry.[15]

MEASURING COST

The relevant costs are those likely to differ between strategies. They often includes costs of medical and procedural treatment, diagnostic tests and hospitalizations, but should be customized to the intervention of interest.[16] Downstream costs related to any intervention, particularly for diagnostic strategies must be included. Frequently, other direct costs such as caregiver's costs and costs due to time accessing care must be considered. Caution must be exercised if certain costs are excluded, since unexpected effects of different strategies may lead to increased cost of care unrelated to the primary diagnosis. An additional challenge with economic analyses of medical care is that the variation in medical costs is often quite high compared to the mean cost. Thus, large numbers of patients are often needed to be confident that any observed cost difference is not due to sampling error. Costs are usually obtained from the perspective of a universal health care system or from society where indirect costs, such as lost employment, are included.[16]

The process of determining cost can use micro-costing, where individual resources are identified, counted and valued or macro/gross costing, where costs are applied to events (e.g. Diagnostic Related Groups or DRGs for hospitalization costs). The choice of micro or gross costing will depend on which costs are expected to differ. If important differences in catheterization laboratory costs are expected, then micro-costing of laboratory resources is needed. However, if the main differences are hospitalization rates, then a single hospitalization cost can be used.

An alternative is to obtain hospital charges from hospital bills and convert these to costs using cost-charge ratios that each hospital reports to Center for Medicare and Medicaid Services (CMS).[12]

MEASURING OUTCOME

Outcome can be measured in multiple ways including survival, quality adjusted survival or an intermediate marker such as strokes prevented. The benefit of measuring outcome in life-years (LYs) gained or QALYs gained is that the cost-effectiveness ratio can be compared with other unrelated medical interventions (e.g. hypertension treatment vs colon cancer screening). By definition, a dollar spent on treatment of heart disease is a dollar not available for treatment of other conditions. Thus, units of value must be comparable across conditions in order to prioritize health care spending.

If trial data are used, direct measurement of within-trial outcomes is possible, but modeling will usually be necessary to estimate long-term outcomes. For example, analyses from trials of implantable cardioverter defibrillator (ICD) therapy that used only in-trial/short-term results have very high costs per LY gained.[17] However, when a benefit beyond the trial duration was assumed, the cost-effectiveness ratio dropped markedly.

An alternative to extrapolating the in-trial treatment benefit is to estimate the long-term effect of nonfatal events (e.g. myocardial infarction and stroke).[18] This is attractive if significant differences are noted for these nonfatal events but not for mortality or quality of life. This approach has face validity, since the nonfatal events are significantly related to treatment. However, such an approach may be biased toward or against treatment if the trial was underpowered to detect other important effects. For example, in trials of antiplatelet therapy, bleeding events may be increased while myocardial infarctions are reduced. As with ischemic events, those with bleeding episodes have higher long-term mortality than those without bleeding. Knowing how to balance these effects is difficult.

INCORPORATING QUALITY OF LIFE

Quality of life can be measured in multiple ways, but the cost-effectiveness ratio has meaning across different disease states only if a measure is used that translates length of life to quality of life. Such a utility measure (1.0 for perfect health, 0 for death) is multiplied by length of life in that health state to determine the quality adjusted survival.[12] If the subject transitions between several states of health, separate utilities can be collected for each health state or at different time points.

The classic utility measures include the standard gamble (which incorporates risk) or time-trade off measure.[19] The time-tradeoff asks patients to consider living a certain life-expectancy at their current health status. They are then asked how much life-expectancy they would be willing to give up (trade), if they could be returned to normal health status. To determine a standard gamble utility, the subject is presented with a chance for normal health but with a certain risk of immediate death. This risk is varied until the subject is ambivalent regarding the gamble. A major limitation is that these utility measures can be difficult to explain to patients and they are expensive to collect in clinical trials.

Both general (e.g. Short Form-36)[20] and disease specific surveys (e.g. Kansas city Cardiomyopathy Questionnaire)[21] provide quality of life estimates but it is unclear how to translate the patient responses into a utility.

BENCHMARKS FOR COST-EFFECTIVENESS

Value will have different meanings depending on the wealth of society. For this reason, some have argued that a society's threshold for value should be based on Gross Domestic Product (GDP) per capita.[22] As a country becomes wealthier, it is reasonable to increase the amount spent to save one year of life. In 2008, the GDP per capita in the United States ($46,800) was higher than most other countries (Canada $39,400, Britain $36,100, Japan $34,200) but not all (Norway $56,800, all in US dollars).[23]

The traditional benchmark for cost-effectiveness has been dialysis.[14] American society has agreed to provide dialysis and without dialysis, the patient will die. Thus, the cost of dialysis over one year can be considered to be a cost per LY gained society is willing to pay. This value has varied but appears to be between $50,000 and $100,000 per LY gained. This range is similar to the upper limit of cost-effectiveness approved by Britain's National Institute for Health and Clinical Excellence for coverage decisions.[24]

However, just because the US society is willing to pay for dialysis does not mean it will not pay more. Indeed, data from patients suggest that American society is willing to pay much more to gain one year of life.[25] They cite data from studies of our willingness to pay for safety and estimate it to be equivalent to $265,000 in 1997 ($345,000 per LY gained in today's dollars).

When one is given the opportunity to prevent someone from dying, the intervention can take on unusually high value.[26] Although we may be willing to spend a small amount of money to prevent children from falling into a well, we are willing to spend extreme amounts of money to save someone if they do fall in. This rule of rescue, defined as the sense of immediate duty to save those endangered, shows that we are willing to pay much greater amounts to increase the LYs of an identified individual when the number needed to treat is one than for a population of anonymous individuals where many need to be treated to impact one life. The lack of accounting for the rule-of-rescue is likely to have contributed to the failure of implementation of cost-effectiveness as a way of prioritizing health care in Oregon.[27]

EVALUATING UNCERTAINTY

As with studies of effectiveness, uncertainty in cost-effectiveness studies can impact the decision to adopt a treatment or diagnostic strategy. Uncertainty can be evaluated in several ways that will vary depending on the nature of the analysis. For trials or other cost-effectiveness studies using data from observations, a technique known as the bootstrap provides an estimate of the variation in the cost-effectiveness ratio.[28,29] With this technique, multiple datasets (each the same size as the original) are created by sampling with replacement from the original dataset. The cost-effectiveness is then determined for this replicated dataset. The process is repeated numerous times and distribution of the cost-effectiveness ratios is determined.

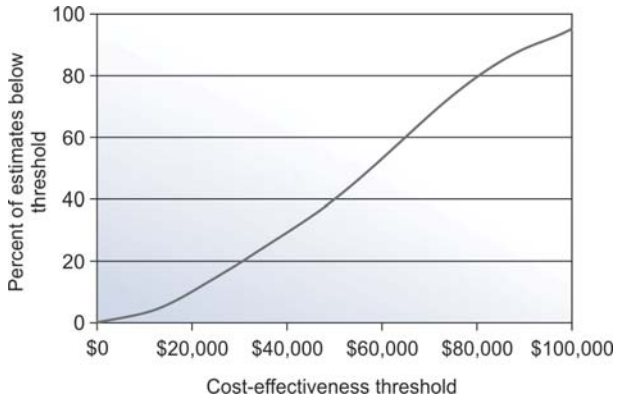


FIGURE 5: A hypothetical cost-effectiveness acceptability curve is shown. The curve is generated from trial (or modeling) data by creating multiple samples (sampling with replacement) and recalculating the cost-effectiveness ratio. The percent of samples that are below the X-axis threshold are displayed on the Y-axis. Such curves are used to demonstrate the uncertainty in the cost-effectiveness ratio

If a model is used, a probabilistic sensitivity analysis can be performed where the best estimate for each assumption is replaced with a distribution of plausible values.[30] Random sampling from these distributions is performed and the model is recalculated. This is repeated numerous times until a clear picture of the distribution of the cost-effectiveness ratios is obtained.

The results from these analyses of uncertainty can be displayed using a cost-effectiveness acceptability curve (Fig. 5). This curve displays the fraction of samples that are below any particular cost-effectiveness threshold. The effectiveness analogy to the cost-effectiveness threshold is the harm/benefit threshold. In typical "effectiveness" analyses if 95% of bootstrap estimates indicate benefit ($p < 0.05$), then the benefit is considered statistically significant. No such standard has been accepted for cost-effectiveness ratios.

PERSPECTIVE

While all can agree that value is important, different perspectives may lead to different calculations and estimate of value. A rehospitalization for heart failure may have no financial impact for the patient if they have adequate insurance, it may be financially beneficial to a hospital if they receive usual payment and at the same time be a significant cost to the payer (e.g. health plan or Medicare). In general, a societal perspective (includes all relevant costs) should be included in any published cost-effectiveness analyses.[31]

Even if the cost-effectiveness of a treatment is economically attractive from a societal perspective, a more formal business case such as a budget impact analysis is often needed to convince policy makers.[32] Such analyses consider the perspective of the health care decision-maker that controls the relevant budget. Unlike standard cost-effectiveness analyses, it must also consider the size of the population that is eligible for the intervention.

EFFICIENCY

Interest in assessing the value of providers continues to grow. While process of care and outcome performance measures have been increasingly used to assess quality, there remains an interest in determining which providers can deliver high quality care at a reasonable cost.[33] The term efficiency has been used to describe this attribute and efficiency measures are gaining interest among payers as a metric for determining contracts.[34] Ideally, the cost and quality of care can be attributed to a single provider, adjusted for case mix and a cost per level of quality provided can be determined.

There are several readily apparent problems in determining the efficiency of providers. Resource use is easy to document, thus, many efficiency measures have focused only on the cost aspect of efficiency assuming that quality is similar across providers. For example, health plans may rank providers based on the cost of evaluating chest pain or performing a PCI assuming that outcome will not differ. In fact, outcome is likely to differ but providers will usually not see enough patients during a reasonable time frame with a given condition to prove that their quality of care is significantly different from others.

Recently, an AHA consensus statement listed attributes that should be incorporated in any published efficiency measures.[34] These recommendations emphasize the importance of including both quality and cost, using valid cost measurement and analysis, minimizing incentives that result in adverse effects and proper attribution.

GOVERNMENT'S USE OF COST-EFFECTIVENESS

UNITED STATES

Despite its appeal as measure of value, the use of cost-effectiveness to evaluate medical care has rarely been adopted by governments within the United States. A notable exception was the failed attempt in Oregon in the early 1990s.[35,36] This is in contrast to other countries such as Canada, Australia and many European nations where authorities currently use cost-effectiveness to decide on coverage for medical treatment. In the United States, the Center for Medicare and Medicaid Services does not formally acknowledge the cost of care when determining coverage. In 1998, Medicare created the Medical Coverage Advisory Commission (MCAC), but with a charge to determine care that was reasonable and necessary.[37] There was no mandate to consider value.

NON-US: BRITAIN'S NICE

One country that has had success in using value to decide on treatment is Britain. In 1999, the National Institute for Health and Clinical Excellence (NICE) was established as a part of the British National Health Service to set standards for the adoption of new health care technologies using cost-effectiveness.[24] NICE has three mandates that explicitly incorporate cost-effectiveness: developing guidelines for care, evaluating classes of technology (e.g. statins) and evaluating single interventions (public health, health services related). The cost-effectiveness evaluation uses QALYs when quality of life data are available and LYs when such data are lacking. No specific cost-effectiveness threshold is used; however, several interventions with values over $100,000/QALY gained have not been approved (US dollars). In general, interventions with cost-effectiveness ratios in the range of $30,000 to $50,000 LY gained have had a reasonable chance of approval. The impact

on the budget of the National Health Service is not considered and all recommendations are not mandatory. However, all NICE approved technologies must be offered.

COST-EFFECTIVENESS OF INDIVIDUAL TREATMENTS AND STRATEGIES

HEART FAILURE

Several trials have examined the cost-effectiveness of heart failure treatments known to prolong survival. Beta-blockers, angiotensin converting enzyme inhibitors and aldosterone antagonists have all been shown to be highly cost-effective (less than $30,000 per QALY gained). In a model based on the Metoprolol CR/XL Randomized Intervention Trial in Chronic Heart Failure (MERIT-HF) trial, metoprolol succinate reduced costs between $395 and $1,112 per patient during the first two years of use, depending on whether the cost of hospitalizations for other causes was included.[38] Savings were maintained in 90% of bootstrap simulations. Using published data from the first hydralazine or nitrate and ACE inhibitor trials in heart failure, a decision model estimated that hydralazine-isosorbide dinitrate combination therapy cost $5,600 per year of life gained compared to no therapy and enalapril cost an addition $9,700 per LY gained compared to hydralazine-isosorbide dinitrate therapy.[39] More recent studies (Table 1) have shown that the addition of aldosterone antagonists is also cost-effective (compared to treatment with ACE-inhibitors and beta-blockers) for patients with reduced left venticular function postmyocardial infarction with cost per LY gained estimated at $21,000.

The cost-effectiveness of ICDs is not as attractive as the above medications; however, most estimates indicate that costs will be less than $100,000 per LY gained (Table 1). A model based on the published trials estimated that treating a 65-year-old heart failure patient with cardiac resychronization therapy (without ICD) would cost $10,000 per QALY gained and $9,400 per LY gained.[43] The incremental cost-effectiveness of CRT-ICD compared with CRT-Pacing was $64,100 per quality adjusted LY gained and $48,100 per LY gained.

In contrast, left ventricular assist devices (LVADs) as destination therapy have not been shown to be cost-effective. Using a model based on a systematic review of existing trials, LVADs were estimated to cost over $250,000 if used as destination therapy.[42]

CORONARY ARTERY DISEASE

Many studies have examined primary prevention of coronary artery disease in patients less than 70 years of age.[44] Smoking cessation counseling with or without nicotine replacement has been highly cost-effective in the majority of studies. Treating hypertension is highly cost-effective, although there is uncertainty regarding the optimal first drug.[45] Primary prevention with statin therapy increases costs with a cost-effectiveness threshold that is highly sensitive to the risk in the underlying population (lower for men and those with diabetes).[44]

For acute coronary syndromes, past studies have demonstrated that PCI is economically attractive compared to reperfusion with t-PA,[46] and use of clopidogrel is cost-effective compared to aspirin alone, if given for nine months post event.[47] In the Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy (TACTICS) trial, an early invasive strategy was slightly more expensive at a cost per LY below $20,000 compared to a conservative strategy.

For chronic coronary disease, the cost-effectiveness of treatments is often less attractive due to the lower risk compared to acute coronary syndromes. An example is high dose statin therapy as shown in Table 2.[48,49] The cost-effectiveness ratio was almost three times higher for high dose statins in patients with stable angina compared to those with acute coronary syndromes.

Percutaneous coronary intervention has been shown to be cost-effective for moderately to highly symptomatic patients

TABLE 1

Selected cost-effectiveness analyses in heart failure

Design (Trial name)	*Population*	*Intervention*	*Comparator*	*Increase in outcome with the intervention*	*Increase in cost with the intervention*	*Cost/Life-year gained comment*
Models based on eight primary prevention ICD trials[40]	Depressed LVEF	ICD	No ICD	1.0–2.9 QALY	$68,300–101,500	$34,000–70,200/ QALYICD dominated in two trials
Trial (SCD-HFT)[41]	Symptomatic heart failure and low LVEF	ICD	Amiodarone	2.46 years	$79,842	$38,389/LY < $100,000/LY gained in 100% of bootstrap samples
Trial (EPHESUS)[18]	Systolic heart failure post MI	Eplerenone	Placebo	0.1 years	$2,136	$21,072/LY Based on Framingham survival
Model[42]	End-stage heart failure	LVAD	Medical therapy	0.6 years	$156,000	$265,000/LY for destination therapy based on model

(Abbreviations: ICD: Implantable cardioverter defibrillator; LVAD: Left ventricular assist device; LVEF: Left ventricular ejection fraction; EPHESUS: Eplerenone post-acute myocardial infarction heart failure efficacy and survival study; SCD-HFT: Sudden cardiac death in heart failure Trial; MI: Myocardial infarction; QALY: Quality adjusted life years; LY: Life-year)

when compared to medical therapy.[53] When compared with bypass surgery, PCI is usually less costly (by 30% or more), although this difference narrows over time as more patients need repeat revascularization when compared to patients undergoing CABG initially. CABG has often led to more symptom relief than PCI and thus slightly greater QALY gained, though there has been uncertainty in the cost-effectiveness of CABG versus PCI.[54] In a recent trial of patients with medically refractory angina, PCI was less costly and slightly more effective compared to CABG.[52] Drug eluting stents appear to be cost-effective compared to bare-metal stents with a cost of $27,500 per quality adjusted LY gained.[51] In this case, the benefit is due to improved quality of life due to less angina.

ATRIAL FIBRILLATION

Early studies have demonstrated that warfarin is cost-effective compared to aspirin or no therapy for patients with atrial fibrillation who are at least at moderate risk of stroke and, that warfarin may be cost-savings in those at high risk.[55] Genotyping to determine initial warfarin dosing is not clearly cost-effective (Table 1). However, the cost-effectiveness of genotyping is highly sensitive to its ability to improve time in therapeutic range.[56] The incremental cost-effectiveness ratio falls below $50,000 per quality-adjusted LY if genotyping increases the time spent in range by 9 percentage points. Recently, The Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) found that dabigatran is at least as effective as warfarin in reducing strokes without the need for frequent monitoring.[57,58] An economic model based on the trial found that the cost-effectiveness of dabigatran relative to warfarin appears reasonable [< $50,000 per QALY, (Table 3)].[59]

The value of transesophageal echocardiography (TEE) compared to several weeks of anticoagulation prior to cardioversion was evaluated in an analysis of the Assessment of Cardioversion Using Transesophageal Echocardiography (ACUTE).[62] There were no significant differences in outcomes or cost, although the TEE guided strategy was slightly more costly. An economic analysis of rate versus rhythm control was based on the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial. Rate control was less expensive with a trend toward improvement in outcome (Table 2),[61] and thus a dominant strategy.

COST-EFFECTIVENESS OF QUALITY IMPROVEMENT INTERVENTIONS

An analysis of cost-effectiveness of treatment is just the initial point in determining if a health care system should make efforts to implement a new treatment. Usually, additional resources are required to speed up adoption and these are often labeled quality improvement (QI) interventions. Typically, the per-person cost of the QI intervention is added to per-person cost of treatment and their sum is divided by the per-person benefit. For example, beta-blockers have been shown to improve outcome for patients with heart failure while being cost neutral or cost-saving. In a cost-effectiveness analysis of Metoprolol CR/XL Randomized Intervention Trial in Chronic Heart Failure (MERIT-HF), beta-blockers were found to decrease costs by at least $400 per person over 2 years.[38] In a health services research randomized trial, a clinical reminder attached to an echocardiography report increased beta-blocker use by 8% (number needed to remind of 12.5).[65] If the reminder costs $2.50 per person, then an additional $23 dollars are needed to increase the number of

TABLE 2

Selected cost-effectiveness analyses in coronary artery disease

Trial or Model	*Population*	*Intervention*	*Comparator*	*Increase in Outcome with the Intervention*	*Increase in cost with the intervention*	*Cost/LY comment*
TACTICS[50]	Unstable angina/ NSTEMI	Invasive strategy	Conservative Strategy	0.053 years	$670	$12,700/LY
SIRIUS[51]	Complex coronary stenosis	Drug eluting stent	Bare metal stent	0.011 years	$309	$27,500/QALY
Chan Model[48]	60 years old with ACS	High dose statin	Conventional dose statin	0.35 years	$4,500	< $30,000/QALY
Chan Model[48]	60 years with stable angina	High dose statin	Conventional dose statin	0.09 years	$3,200	$100,000/QALY
Pignone Model[49]	Men without cardio-vascular disease 10 years risk 7.5%	Aspirin, statins or both	No therapy	3 days for statins	$79 for statins	Statin cost $56,200/QALY Aspirin was dominant
AWESOME[52]	Medically refractory ischemia	PCI	CABG	0.03 years	$20,500	PCI dominated CABG PCI more effective and less costly in 92.6% of bootstrap replications

(Abbreviations: ACS: Acute coronary syndrome; NSTEMI: Non ST-elevation MI; AWESOME: Angina with extremely serious operative mortality evaluation; TACTICS: Treat angina with aggrastat and determine cost of therapy with an invasive or conservative strategy; SIRIUS: Sirolimus-eluting balloon expandable stent in the treatment of patients with *de novo* native coronary artery lesions; MI: Myocardial infarction; QALY: Quality adjusted life years; LY: Life-years)

TABLE 3

Atrial fibrillation studies of cost and cost-effectiveness

Trial or Model (reference)	*Population*	*Intervention*	*Comparator*	*Increase in outcome with the intervention*	*Increase in cost with the intervention*	*Cost-effectiveness/ Comment*
Eckman Model[60]	Those starting warfarin	Genotype guided warfarin dosing	Usual care	0.77 days of life	$361	> $170,000/QALY
AFFIRM[61]	Older adults	Rate control	Rhythm control	0.08 years (p = 0.10)	$5,077 less	Rate control dominant in 95% of estimates
ACUTE[62]	Cardioversion candidates	TEE guided cardioversion	Usual care	No difference	$269	$80 cost difference favoring usual car in analytic model
McKenna Model[63]	Symptomatic	Ablation	Usual care	1.35 QALY	$16,300	$12,200/QALY
RASCABG[64]	Immediate post-CABG	Amiodarone	Usual care	Less atrial fibrillation	-$234	Amiodarone dominant
Model based on RE-LY[59]	Afib CHADS2 ≥ 1	Dabigatran	Warfarin	0.56 QALY	$25,205	$45,372/QALY

(Abbreviations: ACUTE: Assessment of cardioversion using transesophageal echocardiography; AFFIRM: Atrial fibrillation follow-up investigation of rhythm management; RASCABG: Reduction of atrial fibrillation study in patients undergoing coronary artery bypass grafting; RE-LY: Randomized evaluation of long-term anticoagulation therapy; QALY: Quality adjusted life years; LY: Life-years)

patients on beta-blockers by one. When this $23 is subtracted from the overall cost savings (e.g. $400–$23), the reminder to use beta-blockers is still a dominant QI strategy. Other QI interventions may not be as attractive if the treatment itself is borderline cost-effective and the QI intervention is expensive.

FUTURE ESTIMATES OF THE COST OF HEART DISEASE

As the population ages, the cost of heart disease is expected to increase markedly given the high prevalence of disease and associated resource use among the elderly. In order to estimate the future cost of heart disease, the American Heart Association developed a methodology to project future costs of care for hypertension, coronary heart disease, heart failure, stroke and all other CVD from 2010 to 2030.[66] This method avoids double counting of costs for patients with multiple cardiovascular conditions which had been an issue with previous estimates.

This study estimated that by year 2030, 41% of the US population is projected to have some form of cardiovascular disease. This would result in an increase in the prevalence of ischemic heart disease by 17% (8.0–9.3%) and heart failure by 25% (2.8–3.5%). The associated costs of ischemic heart disease are expected to increase from $36 to $106 billion (US dollars). The cost of heart failure is estimated to increase from $25 to $78 billion.

All direct medical costs of cardiovascular disease combined are expected to triple between 2010 and 2030 from $273 billion to $818 billion (in 2008 US dollars). Costs due to lost productivity (indirect costs) for all cardiovascular disease are estimated to increase by 61% from $172 billion in 2010 to $276 billion in 2030.

These estimates did not consider several factors that may influence cost substantially such as improved prevention (lower cost), loss of patent protection for existing treatments (cost) or development of new therapies (increased costs). The authors concluded that a greater focus on prevention strategies is needed in order to limit the projected increase in cost of care.[66]

SUMMARY

The evaluation of cost and value is becoming increasingly important as society recognizes the limited resources available and the growing need associated with an aging population. The United States in particular has spent much more on health care than other countries without a clear survival benefit with substantial regional variation in care. Treatment of heart disease is responsible for a large proportion of the increase in cost of care and new estimates indicate it will grow even further as the population ages. Fortunately, many interventions shown to improve survival for patients with heart disease are relatively inexpensive. Cost-effectiveness is the primary tool for the assessment of value, although the science of cost-effectiveness has limitations including the lack of an accepted threshold to define value. Understanding the cost and value of cardiac care will remain an important endeavor for researchers and policy makers in order to optimize the health of the population.

GLOSSARY

Budget-impact analysis: A cost-effectiveness analysis from the perspective of the payer/decision-maker that accounts for the size of the affected population covered by the health care budget.

Cost-benefit analysis: An economic analysis that assigns a cost (dollar) value to benefit. Willingness to pay for a given intervention is an example of a patient derived measure of cost-benefit.

Cost-effectiveness analysis: An economic analysis that assigns different units for costs in the numerator (dollars) and benefit in the denominator (usually life-years or QALYs gained).

Cost-minimization analysis: An economic analysis that determines the least expensive intervention. This type of analysis is used for interventions that are assumed to have a similar benefit.

Cost-utility analysis: A cost-effectiveness analysis that uses quality-adjusted years of life gained in the denominator.

Costs-direct: Costs of medical care and time-costs (such as transportation to the medical encounter) related to providing medical care. Direct costs included fixed (e.g. lab overhead costs) and variable costs (e.g. cost of devices).

Costs-indirect: Non-medical costs that due to disease or its treatment such as lost productivity (e.g. lost wages). Patients may incorporate their own estimate of indirect costs in giving a value to their quality of life. Thus, there is the potential for double counting indirect costs in cost-utility analyses.

Discount rate: The rate used to calculate the net present value of any future costs and health outcomes. A value of 3% is usually used for the United States (range 0–5%).

Efficiency: A measure of care defined as (quality of care)/cost.

Perspective: The focus of the analysis which determines which costs and outcomes measured.

Quality adjusted life-year (QALY): A year of life multiplied by a utility (0-death to 1.0-best health) that adjusts for quality of life.

Sensitivity analysis: The process of recalculating the cost-effectiveness ratio having varied one or more assumptions.

Time horizon: The time over which costs and benefits are measured. Ideally, this should cover the lifetime of the individuals in question.

Utility: A value between 0 and 1.0 that reflects the patient's preference for a particular health state. A value of 0 is given to death, a value of 1.0 is given to perfect health.

Value: The combination of outcome and cost, usually defined using cost-effectiveness, although also influenced by equity.

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Chapter 117

Stem Cell Therapy in Cardiology

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Chapter Outline

- Stem Cell
  - Embryonic Stem Cells
  - Adult Stem Cells
  - Bone Marrow Derived Stem Cells
- Skeletal Myoblast
- Adipose Tissue Derived Stem Cells
- Cardiac Stem Cells
- Fetal and Umbilical Cord Blood Cells
- Induced Pluripotent Stem Cells
- Stem Cell Clinical Trials
  - Acute Myocardial Infarction
  - Chronic Coronary Artery Disease and Chronic Heart Failure
  - Refractory Angina
  - Pulmonary Hypertension
  - Routes and Methods of Cell Delivery

ABSTRACT

Over the past decade, stem cell therapies have been the focus of intense research in the field of cardiology. Clinical trials have produced mixed results. Many questions regarding the therapeutic potential and the mechanisms involved remain unanswered. In this chapter, an overview of the different stem cells lines, delivery techniques and results of some of the most relevant preclinical and clinical studies for the treatment of cardiac disease are discussed.

INTRODUCTION

Cardiovascular disease is the leading cause of death worldwide. Despite major advances in therapy in the last few decades, the global burden remains substantial.[1] A major limitation of the current therapeutic strategies post-myocardial infarction (MI) is the inability to replace dead myocardium with functional new cardiomyocytes and vessel.[2-4] With the discovery of various stem cell populations possessing cardiogenic and differentiation potential, and the subsequent ability to isolate and expand these cells, stem cell therapy has emerged as a new treatment approach in the battle against cardiovascular disease. Although much knowledge has been gained in the last two decades in regards to stem cell therapy, numerous barriers to true cardiac regeneration remain and there are many unanswered questions. The ideal cell or cell product, timing for administration, delivery system, and patient selection are unknown at the present time. This chapter reviews stem cell therapies for the treatment of cardiac disease.

STEM CELL

Stem cells are distinguished from other cell types by two important characteristics. First, they are capable of self-renewal through cell division, sometimes after long periods of inactivity. Second, under certain physiologic or experimental conditions, they can be induced to become tissue-specific or organ-specific cells with special functions. Until recently, stem cells were categorized into either embryonic stem cells (ESCs) or non-embryonic "somatic" or "adult" stem cells. More recently, however, it has been shown that adult cells can be "reprogrammed" genetically to assume a more ESC-like state.[5,6] This new type of stem cell, called induced pluripotent stem cells (iPSCs), seems to share many characteristics with ESCs. Each stem cell population has its own advantages and disadvantages for therapeutic use. In this section, we have briefly outlined the various stem cell lines and discussed their benefits, disadvantages and preclinical evidence supporting their use in cardiac research. Subsequently, we have reviewed the clinical trial evidence for stem cell therapy in cardiovascular diseases.

EMBRYONIC STEM CELLS

Embryonic stem cells are undifferentiated cells derived from a 5-day preimplantation embryo capable of self renewal for a prolonged period in culture (Fig. 1). ESCs can give rise and differentiate into the cells of the three primary germ layers (i.e. ectoderm, endoderm and mesoderm).[7] Under certain culture conditions, ESCs can be directed to differentiate into cardiomyocytes [also called ESC-derived cardiomyocytes (ESC-CM)].[8-10] This process of CM derivation from ESCs is not very efficient yet, but significant strides are being made in research to better understand the molecular signals that will allow for this process to occur more efficiently in the future.[11-16]

Given the pluripotent nature of these cells, concerns regarding the safety of ESCs as a treatment modality have been raised in terms of the risk for tumor formation. [17] This risk may potentially be overcome if the embryoid bodies fully

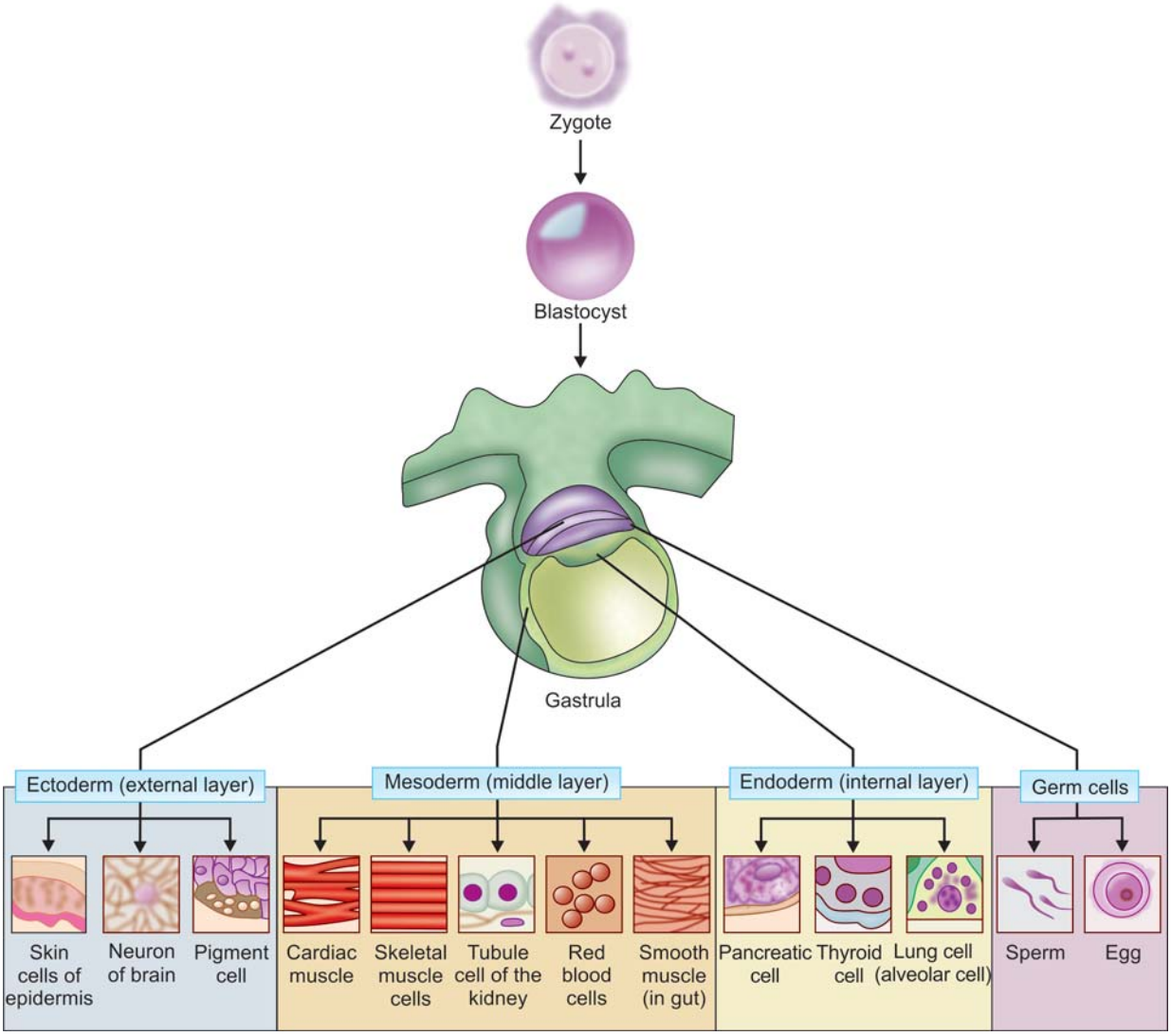


FIGURE 1: Differentiation of human tissues by pluripotent stem cells. Embryonic stem cells originate as inner mass cells within a blastocyst. A pluripotent stem cell refers to a single stem cell that has the capability of developing into cells of all three germ layers (endoderm, mesoderm and ectoderm). These three germ layers are the embryonic source of all cells of the body (© 2001 Terese Winslow, Caitlin Duckwall, with permission)

differentiate into the specific cell types prior to clinical use.[10,18,19] However, long-term studies will be required to assess the risk of tumor formation even with ESC-CMs.

A second important concern associated with the use of ESCs is the issue of immune reaction. There is increasing evidence that ESCs express specific human leukocyte antigen (HLA) subclasses[17] and this raises the concern for graft rejection and the possible need of concomitant immunosuppression. These issues remain to be investigated in the future.

Finally, the use of ESCs is ethically controversial given the origin of these cells. The recent discovery of iPS cells may resolve the ethical and immunogenic issues associated with the use of ESCs.[20-22] To date, no human trials have been carried out using ESCs, iPS cells or ESC-CM for cardiac repair.

ADULT STEM CELLS

Adult or somatic stem cells are cells that have not yet developed into a specialized cell type. They are found throughout the body and can renew themselves and differentiate to yield some or all of the major specialized cell types of the tissue or organ. The primary role of adult stem cells seems to be to maintain and repair the tissue in which they are found. The use of adult stem cells potentially avoids the complications associated with ESCs, including tumor formation, immunogenicity and ethical concerns. Given the safety profile of the adult stem cells, numerous clinical trials have been undertaken with the use of these cells (see below for details). There are a number of different types of adult stem cells that have been utilized in the cardiovascular field. These include the bone marrow (BM) derived stem cells; skeletal myoblast cells; adipose tissue derived stem cells and native cardiac progenitor cells. A brief description of each of these cell lines are summarized below.

BONE MARROW DERIVED STEM CELLS

The adult BM is a reservoir of cells that have enormous plasticity.[23-30] It harbors numerous types of cells, including the

hematopoietic stem cells (HSCs),[31] circulating angiogenic cells (CACs),[32] mesenchymal stem cells (MSCs)[33] and the very small embryonic-like stem cells (VSELs),[34] among others.

Bone marrow HSCs, as well as the circulating peripheral blood cells, are a well-characterized source of progenitor cells.[29,35,36] A number of preclinical studies using BM-derived cells have shown significant improvement in cardiac function.[25-27,29,36-40] Whether these cells lead to true cardiac regeneration is more controversial.[29,38,41] Numerous recent reports point to paracrine mechanisms rather than cell differentiation or fusion as the main mechanism of beneficial effects in improving cardiac function post-MI using BM-derived HSCs.[37,39,42-45] Which paracrine factors and through which mechanisms these benefits are achieved are currently under investigation. Notably, BM-derived cells are a heterogenic population and the functionality of HSCs may be impacted by host factors in determining the quality and ability of the cells to achieve the desired effects.[46]

Another well studied BM-derived cell type is the CACs [previously called early endothelial progenitor cells (EPCs)]. These cells have also been considered as a potential candidate for therapeutic purposes.[47,48] EPCs were first described by Asahara et al.[32] as a population of circulating BM-derived circulating cells able to contribute to postnatal neovasculogenesis. These cells can be mobilized from the BM in response to tissue ischemia[49] or endothelial injury by the release of chemokines such as vascular endothelial growth factor (VEGF), stromal derived factor-1 and tumor necrosis factor-alpha.[50] Although there is controversy regarding their true definition, these cells can be identified by their ability to acquire endothelial cell characteristics in culture and in vivo.[51-54] They express cell-surface makers such as cluster of differentiation molecule 133 (CD133), the VEGF receptor 2 kinase (also known as KDR), CD34 and vascular endothelial cadherin (VE-cadherin).[53] Peripheral blood EPC counts can be increased by systemic administration of VEGF, G-CSF, GM-CSF or other agents that mobilize mononuclear cells from the BM. After isolation, the number of cells can be increased though an ex vivo expansion protocol.[55] Endothelial-lineage cells can also be cultured from umbilical cord blood[56] and from human ESCs.[57] Notably, CACs are a heterogenic population, their stem cell pool is quite limited and ex vivo expansion can also be difficult. In addition, the therapeutic potential of progenitor cells, regardless of the selection method, is profoundly reduced in the presence of cardiovascular risk factors or established disease.[55,58-60] Several groups have shown benefit with CACs modified to overexpress genes of interest (e.g. eNOS,[61,62] adrenomedullin,[63] IGF-1[64,65]) and as such, CACs have shown some promise as a gene delivery tool.

Myocardial infarction results in mobilization of CACs from the BM,[66] and it is thought that these cells contribute to neovessel formation.[67,68] The initial preclinical studies with implanted CACs were performed in hind-limb ischemia experiments in rodents, which demonstrated the significant improvement in blood flow recovery and limb salvage.[53,69] Injection of CACs into infarcted myocardium has also been shown to improve left ventricular function and to inhibit fibrosis in animal studies.[53,70] CACs have been studied in animal models of pulmonary hypertension (PH) as well. These studies have reported varying success in reducing mortality, decreasing right ventricular hypertrophy, right ventricular systolic pressure, pulmonary vascular resistance, pulmonary arterial wall thickness and other cardiovascular parameters.[61-71] CACs derived from a variety of sources, including autologous CACs,[71] BM-derived CACs,[72] peripheral blood CACs[73,74] and umbilical cord[63] have been used for these studies. The discrepancy in the reported findings could relate to the differences in the source of CACs, derivation and methods used to define and isolate CACs, and the animal models utilized.[75]

Another stem cell for therapeutic use derived from the BM is the MSCs. MSCs are undifferentiated, pluripotent cells that differentiate into various mesoderm-derived cells such as osteoblasts, chondroblasts, adipocytes, skeletal muscle cells,[76-78] and have the capacity to secrete several cytokines.[79,80] MSCs can be isolated from BM, cultured ex vivo, and expanded many fold.[77,78] In addition, MSCs have the ability to migrate from the BM toward regions of damaged tissue, including to infarcted regions within the heart.[81-83] Finally, in vitro and in vivo experiments have showed that MSCs may have immune-privileges.[84,85] MSCs constitutively express HLA class I molecules at low levels but do not express HLA class II molecules on the cell surface,[86] which makes allogenic transplant an acceptable approach. Preclinical studies using transplantation of MSCs in infarct models demonstrated improved left ventricular function, reduction in infarct size, and a decrease in mortality,[87-89] despite the fact that only a small number of cells underwent differentiation.[88,90-92] Although promising, because of the significant heterogeneity among MSC populations, they are also less predictable when implanted. For example, some reports have noted that implanted MSCs had differentiated into osteoblasts inside ventricular tissue,[93-95] which is a clear concern.

More recently, the VSELs have been described. These cells have been characterized as a population of small $CXCR4^+$ cells that are nonhematopoietic and express markers of lineage commitment for several different tissues, thereby exhibiting the potential to differentiate into various lineages.[34,96,97] VSELs are Sca-1+/Lin-/CD45-; express (among other lineage markers) cardiac markers, including Nkx2.5/Csx, GATA-4 and MEF2C; and seem to acquire a cardiomyocytic phenotype in vitro under specific culture conditions.[97] In a rodent model, transplantation of a relatively small number of CD45- VSELs was sufficient to improve LV function and alleviate myocyte hypertrophy after MI, supporting the potential therapeutic utility of these cells for cardiac repair.[98] Because they are endogenous, autologous, unmodified and pluripotent, this cell type seems to share characteristics of both adult and ESCs. Although very promising, many questions need to be addressed as clinical application of VSELs is considered. Whether these cells are functional in steady-state conditions or represent a population of dormant cells residing in the BM as leftover remnants from developmental embryogenesis is unknown. If these cells have true embryonic cell behavior and potential, limitations associated with ESC therapy such as teratoma and tumor formation may also apply. Moreover, VSELs are rare. Either refinement of methods to isolate larger numbers of VSELs or ways to expand them ex vivo may be required for clinical application. Finally, the number of these cells diminishes with age and with other risk factors of

heart disease, which may limit their usefulness in the older patients with MI.[99]

Overall, proof-of-concept preclinical experiments have been performed with the different BM-derived cells as outlined above and results of animal experiments have generated mixed results in support of the use of BM-derived cells to repair cardiac tissue.[25-27,29,36,38-40] Numerous mechanisms, some controversial, have been postulated to explain the beneficial effect of BM-derived cells on cardiac function. Preclinical animal studies have demonstrated possible BM-derived cell transdifferentiation into new cardiomyocytes,[29,38] cell fusion,[100] enhanced neovascularization,[101] inhibition of apoptosis,[70] and/or paracrine mechanisms.[37,102] Even though the underlying mechanism remains controversial, results from these preclinical models have led investigators to perform clinical trials of BM cell infusions in patients with heart disease. Several randomized clinical trials have been conducted using BM-derived cells therapy. The clinical evidence for stem cell therapy is summarized in Table 1 and has been discussed in more detail later in this chapter.

SKELETAL MYOBLAST

In addition to the BM-derived stem cells, another adult stem cell that has received considerable attention in the cardiovascular field is the skeletal myoblast, also called satellite cells. These cells are found beneath the basal membrane of muscle tissue where they lie dormant until stimulated to proliferate by muscle injury or disease.[103] Skeletal myoblasts were among the earliest cell types considered for cardiac repair due to their resistance to ischemia,[103] their capacity to differentiate in vitro into contracting myotubules and their relative ease of isolation.[104] Preclinical studies with the use of skeletal myoblasts in ischemic heart disease have shown the improved left ventricular function and decreased remodeling possibly due contracting myotubules regeneration.[103,105,106] Moreover, therapy was associated with a decrease in matrix breakdown in the peri-infarct area and in the remote myocardium.[107]

Skeletal myoblasts however do not fully differentiate into cardiomyocytes after transplantation and do not operate in synchrony with the surrounding myocardium,[108] possibly increasing the risk of cardiac arrhythmias.[109,110] Additional limitations to the clinical utility of these cells include the relative paucity of engraftment of the injected cell; poor survival early after implantation,[111] and lack of true regenerative capacity as the engrafted cells do not differentiate into cardiomyocytes. Finally, the process of culturing these cells is labor intensive and takes considerable time, which may preclude autologous use in acute ischemic events such as MI.

ADIPOSE TISSUE DERIVED STEM CELLS

Adipose tissue contains multipotent cells called adipose-derived stem cells (ASCs). ASCs are similar to BM-derived MSCs for being multipotent and they can grow rapidly in culture media and secrete various growth factors such as VEGF and hepatocyte growth factor (HGF).[112,113] ASCs transplantation has been reported to improve cardiac repair by inducing angiogenesis and forming cardiomyocyte-like structures in rodent models of myocardial ischemia.[114-116] However, similar to the other transplanted adult stem cells, the overall retention and survival of implanted cells are low, and these cells appear to have limited capacity to differentiate into cardiomyocytes and to functionally integrate with the host myocardium.[117] Further, research is necessary to establish the ideal subpopulation of these cells for cardiovascular repair. Finally, the possibility of other adverse events must be ruled out for these cells to be useful clinically post-MI. One main concern is the risk of bleeding when harvesting adipose tissue from post-MI patients who are on antiplatelet and anticoagulant treatments.

CARDIAC STEM CELLS

Contrary to the traditional belief that the mammalian heart is an organ without regenerative capacity, it has recently been discovered that, in fact, this organ has intrinsic regenerative potential.[118,119] Numerous reports have confirmed the existence of cardiac stem cells (CSCs) that can be expanded in vitro from either normal or infarcted hearts.[120-129] Various methods have been used to isolate CSCs, including immune selection of cells using various cell surface markers or, alternatively, growth of cardiospheres (CSs) in culture. CSs have the following characteristics: (1) express stem cell markers, such as receptor for stem cell factor (c-kit) and stem cell antigen 1 (Sca-1); (2) are clonogenic; (3) are capable of long term self-renewal and (4) are multipotent (i.e. they can differentiate into cardiomyocytes, smooth muscle and endothelial cells[127,129-131]). In addition, cardiosphere-derived cells are capable of producing secreted factors.[132] A recent report however has suggested that CSs are composed of fibroblasts and are not true stem cells.[133] Despite this report, numerous groups are reporting that CSs do indeed contain stem cells that are capable of clonal expansion and tri-lineage differentiation.

An equivalent human cardiac stem cell population can be obtained via endomyocardial biopsy and subsequently grown in suspension as CSs that exhibit proliferation and differentiation capacity.[126,127] Once isolated, this cell population can be induced to differentiate into spontaneously beating aggregates of cardiomyocytes, which can then be implanted into injured myocardium at a later time. Preclinical studies have demonstrated that CSCs support myocardial regeneration in the infarcted hearts,[127,130,131] confirming the therapeutic potential of these cells. However, the regeneration and engraftment rate seem to be low for these cells as well. Furthermore, it appears that the cardiac stem cell pool may diminish with aging, possibly contributing to the decreased efficacy of regeneration in elderly patients of post-MI.[134,135]

FETAL AND UMBILICAL CORD BLOOD CELLS

Fetal and umbilical cord blood cells relative cellular immaturity compared to adult sources suggests a potentially unrivaled degree of plasticity.[136,137] However, to date, evidence of pluripotency after in vitro expansion is lacking. Human umbilical cord blood contains a number of progenitor cell populations, including HSCs and MSCs, in addition to a population of unrestricted somatic stem cells, which have been shown to have proliferative potential.[138-140] Results from animal studies have been conflicting in regard to improvements in left ventricular

TABLE 1

Representative randomized clinical trials of cell therapy for refractory angina: study design and efficacy

Trial	*Cell type/ Sample size*	*Clinical scenario*	*Method(s)*	*Route of delivery*	*Cell dose*	*Primary endpoint*	*Follow-up*	*Baseline LVEF*	*Follow-up LVEF*	*Δ LVEF*	*P value (Δ LVEF)*
Losordo et al.[141] 2006	$CD34^+$:18 Control:6	Refractory angina	SPECT	TE/EMM during GABG	$5x10^4$, $1x10^5$, and $5x10^5$ $CD34^+$ (cells/kg)	Safety/ feasibility	12 months	$CD34^+$:NA Control:NA	$CD34^+$:NA Control:NA	$CD34^+$:NA Control:NA	NA
Tse et al.[142] (PROTECT-CAD) 2007	MNC HD:9 MNC LD:10 Control:9	Refractory angina	MRI SPECT	TE/EMM	HD:$2x10^7$ LD:$1x10^7$	LVEF	6 months	MNC: 51.9±8.5% Control: 45.7±8.3%	MNC: 55.6±9.5% Control: 45.3±8.2%	MNC:3.7±5.1 Control: –0.4±7.5	0.044
Van Ramshort et al.[143] 2009	MNC:25 Control:25	Refractory angina	SPECT MRI	TE/EMM	Average $40x10^6$	Summed stress score (SPECT)	3 months	MNC: 56±12% Control: 54±10%	MNC: 59±11% Control: 53±10%	MNC:3±5 Control: -1±3	0.03

(Abbreviations: MNC: Mononuclear cells; HD: High dose; LD: Low dose; MRI: Magnetic resonance imaging; SPECT: Single photon emission computed tomography; TE/EMM: Transmyocardial/ electromechanical mapping; LVEF: Left ventricle ejection fraction)

function[144] and as such, these cells have not yet been investigated in the clinical setting.

INDUCED PLURIPOTENT STEM CELLS

Induced pluripotent stem cells are somatic (adult) cells reprogrammed to enter an ESC-like state by expressing factors important for maintaining the "stemness" of ESCs. Mouse iPSCs were first reported in 2006,[5] and human iPSCs were first reported in 2007.[6,20,21] iPSCs demonstrate the important characteristics of pluripotent stem cells, including the expression of stem cell markers, the formation of tumors containing cells from all three germ layers, and the ability to contribute to many different tissues when injected into mouse embryos at a very early stage in development.[6,20,21] Although very promising, at the present time, iPS cells are generated with the use of viruses, which can be mutagenic and have the potential to activate oncogenes. This limits their therapeutic potential; however, ongoing research is investigating nonviral methods of obtaining iPS from adult cells.[145] Future research will also clarify whether the iPS cells have the same properties and potentials as ESCs. These cells have not yet been investigated in the clinical setting.

STEM CELL CLINICAL TRIALS

ACUTE MYOCARDIAL INFARCTION

Bone Marrow Mononuclear Cells

Table 2 lists some of the most relevant randomized clinical trials using stem cell therapy post-MI. Most of the randomized studies have utilized bone marrow mononuclear cells (BMMNCs) and have delivered the cells via the intracoronary administration into the infarct-related artery as first described by Strauer et al.[146] A direct comparison between these studies is difficult as they vary in a number of significant ways, including patient selection, methods of BMMNC isolation, timing and number of cells delivered, imaging studies utilized, and duration of follow-up. Three recent meta-analyses evaluated the results of several clinical studies of percutaneous intracoronary infusion of BM-derived progenitor cells for the treatment of MI. Abdel-Latif and colleagues analyzed 18 controlled studies including 12 randomized trials.[147] Cell transplantation was associated with a 3.66% increase in left ventricular ejection fraction (LVEF) [95% confidence interval (CI), 5.40% vs 1.93%; $p < 0.01$], a 5.49% reduction in infarct size (95% CI, 9.10% to 1.88%; $p < 0.003$), and a decreased left ventricular end-systolic volume (LVESV) (4.80 ml; 95% CI, 8.20% to 1.41%; $p < 0.006$). Overall no adverse events were reported. The meta-analysis by Lipinski and colleagues[148] included 10 studies, 7 of which were randomized. Cell transplantation was associated with a 2.97% increase in LVEF (95% CI, 4.04% to 1.88%; $p < 0.001$), a decreased LVESV (7.43 ml; 95% CI, 12.21 ml vs 2.66 ml; $p < 0.002$), and a 5.28% reduction in perfusion defect size. In addition, therapy was associated with a decrease in recurrent MI. Finally, Martin-Rendon and colleagues[149] performed a Cochrane systematic review of 13 randomized controlled trials, including 880 patients investigating the use of autologous BM stem and progenitor cells for the treatment of acute MI. The authors concluded that cell therapy for acute MI may be safe and moderately beneficial. There was a consistent pattern indicating that BMSC treatment generally improved short-term LVEF, with similar trends for LVESV and LVEDV, infarct size and cardiac wall motion.[150]

A notable trial from the ones listed in Table 2 is the study conducted by Schachinger et al. (REPAIR-MI). This is the largest randomized clinical trial using BMC post-MI to date,[151-153] and included 204 patients randomized to receive an intracoronary infusion of BMMNC or placebo medium in the infarct artery. After 4 months follow-up, mean LVEF increased from 47% to 50% in the placebo group, and from 48% to 54% in the group treated with BMMNC. The mean absolute change in favor of BMMNC treatment was 2.5% ($p = 0.01$; Table 2). There was also a significant reduction in clinical events (prespecified cumulative endpoint of death, MI or necessity for revascularization) after 12 months in the treatment group compared with placebo [respectively, 24% ($n = 24$) vs 41% ($n = 42$); $p = 0.009$]. Likewise, the combined endpoints of death, recurrence of MI and re-hospitalization for heart failure were significantly reduced in the patients receiving intra-coronary BMMNC administration [2% ($n = 2$) vs 12% ($n = 12$); $p = 0.006$]. The benefits of functional improvement were reported to be achieved in those patients with larger infarcts (EF < 49%) (change in LVEF 7.5% vs 2.5%, $p = 0.002$) and those who received the cell therapy after 5 days post-MI (change in LVEF 7% vs 1.9%, $p = 0.004$) and interestingly, there was no benefit if the infarct was small (baseline EF > 49%) or if the therapy was delivered within 5 days post-MI. Of note, the LVEF reported in this study was measured by LV angiography. Recently, the same group has published an MRI sub-study of 54 patients (27 BMMNC, 27 placebo) and the authors demonstrate that only in patients with a baseline EF less than or equal to 48.9%, BMMNC administration was associated with a significantly improved EF (+6.6%, $p = 0.01$), reduced LVEDV increase ($p = 0.02$), and stabilization of LVESV ($p = 0.01$) at 12 months.[154]

Four recently published studies which are not included in the above mentioned meta-analyses include FINCELL,[155] BONAMI-data presented at the November 2008 American Heart Association Scientific Sessions meeting, HEBE,[156] SCAMI[157] (Table 2). Of these trials, only the FINCELL study demonstrated that cell infusion was associated with improvement in LVEF.[155]

Despite numerous clinical trials using BMMNCs post-MI, many questions remain unanswered and the absolute benefits of cell-based therapy remain controversial. Overall, BMMNC seems to have at best a modest effect on the short-term LVEF post-therapy, with similar favorable trends on end-systolic, end-diastolic volumes and myocardial scar size.[35,36] The BOOST Trial, as far as randomized trial are concerned, has the longest follow-up of 18 months after cell therapy post-MI to date.[158] At 6 months, the increase in global LVEF measured by MRI was significantly greater in the BMMNC group than in the control group ($p = 0.0026$); however, global LVEF change at 18 months was not significantly enhanced in the BMMNC group compared with the control group (Table 2, $p = 0.27$). Interestingly, the speed to LVEF recovery over the entire course of 18 months was significantly higher in the BMMNC treatment group ($p = 0.001$). In addition, the 5-year follow-up of the first report by Strauer et al. using BMMNC via the intracoronary

TABLE 2

Representative randomized clinical trials of cell therapy for acute myocardial infarction: study design and efficacy

Trial	*Cell type/ Sample size*	*Method(s)*	*Route of delivery*	*Timing from MI*	*Cell dose*	*Primary endpoint*	*Follow-up*	*Baseline LVEF*	*Follow-up LVEF*	*Δ LVEF*	*P value (Δ LVEF)*
Janssens et al.[159,160] 2006	MNC:33 Control:34	MRI	Intra-coronary	24–48 hours	$3±1.28x10^8$	Changes on LVEF	4 months	MNC:48.5±7.2% Control: 46.9±8.2%	MNC:51.8±8.8% Control: 49.1±10.7%	MNC:3.4±6.9% Control: 2.2±7.3%	NS
Meyer et al. (BOOST),[158] 2006	MNC:30 Control:30	MRI	Intra-coronary	Mean 6 days	$2.46±0.94x10^9$	Changes on LVEF	6 and 18 months	MNC:50±10% Control: 51.3±9.3%	MNC: 38.9±10.3% Control:41.3±9%	MNC:NA Control:NA	NS
Huang et al.[161] 2006.	MNC:20 Control:20	Angiography	Intra-coronary	24–48 hours	$1.8±4.2x10^8$	Not stated	6 months	MNC:44.5±7.1% Control:43.4±6.7%	MNC:51.5±5.2% Control:47.9±6.7%	MNC:6.95±3.33% Control:4.5±1.68%	0.047
Lunde et al. (ASTAMI),[162,163] 2006	MNC:50 Control:51	SPECT, Echocardio-graphy, MRI	Intra-coronary	Median of 6 days	$0.54–1.3x10^8$	Changes on LVEF	6 and 12 months	MNC:45.7±9.4% Control:46.9±9.6%	MNC:48.8±10.7% Control:49±9.5%	MNC:3.1±7.9% Control:2.1±9.2%	NS
Schachinger et al. (REPAIR-AMI),[151,152] 2006	MNC:101 Control:103	Angiography	Intra-coronary	3–6 days	$2.36±41.74x10^8$	Changes in LVEF	4 and 12 months	MNC: 48.3±9.2% Control: 46.9±10.4%	MNC: 53.8±10.2% Control: 49.9±13%	MNC: 5±7.3% Control: 3±6.5%	0.01
Meluzin et al.[164,165] 2006	MNC HD:20 MNC LD:20 Control:20	SPECT	Intra-coronary	Mean 7 days	$0.9–2x10^8$ and $0.9–2x10^7$	Change in regional systolic function of the infarcted wall	6 and 12 months	HD:40±2% LD:41±2% Control:40±2%	Not reported	HD:7±2% LD:4±1% Control:0±2%	0.027*
Huikuri et al. (FINCELL),[155] 2008	MNC:39 Control:38	Angiography; Echocardio-graphy	Intra-coronary	3–5 days	$4.02±1.96x10^8$	Changes on LVEF	6 months	MNC:56±10% Control: 57±10%	MNC:60±8% Control: 56±10%	MNC:4±11.3% Control: -1.4 ±10.1%	0.03
Moquet et al. (BONAMI), 2008#	MNC:52 Control:49	SPECT, RNA, Echocardio-graphy	Intra-coronary	9.3±1.7 days	$1x10^6$	Myocardial viability; LVEF	3 months	MNC:NA Control:NA	MNC: 53.8±10.2% Control:49.9±13%	MNC: 5.5±7.3% Control:3±6.5%	NS
Van der Laan et al. (HEBE), 2008[156]	MNC:67 PB:62 Control:60	MRI	Intra-coronary	3–8 days	NA	Changes in regional myo-cardial function	4 months	NA	NA	MNC:3.8% PB:4.2% Control:4%	NS
Wöhrle et al. (SCAMI), 2010[157]	MNC:29 Control:12	MRI	Intra-coronary	6.8±2.5 days	$381±130x10^6$	Changes in LVEF	6 months	MNC:NA Control:NA	MNC:NA Control:NA	MNC:5.7±8.4% Control:1.8±5.3%	NS
Tendera et al. (REGENT), 2009[166]	MNC:80 $CD34^+$ $CXCR4^+$:80 Control:40	MRI	Intra-coronary	1–25 hours	$1.78x10^8$ and $1.9x10^6$	Change in LVEF	6 months	MNC:37(19-44)% $CD34^+CXCR4^+$: 40(24–57)% Control:39(23–44)%	MNC:35(12–45)% $CD34^+CXCR4^+$: 38(17–77)% Control:39(32–58)%	MNC:3% $CD34^+CXCR4^+$:3% Control:0%	NS
Chen et al. 2004[167]	MSC:34 Control:35	SPECT, EMM, Angiography, Echocardiography	Intra-coronary	18.4±0.55 days	$48–60x10^9$	LVEF	6 months	MSC:49±9 Control:48±10	MSC: 67±3 Control:54±5	MSC:NA Control:NA	0.01
Hare et al. 2009[168]	MSC:39 Control:21	Echocardio-graphy, MRI (subset)	Intra-coronary	1–10 days	0.5, 1.6 or $5x10^6$/Kg	Safety	6 months	MSC:50.4±10.6 Control: 48.7±9.6	MSC:56.9 (53.3–60.5) Control:56.1 (53.3–58.9)	MSC:NA Control:NA	NS

(Abbreviations: MNC: Mononuclear cells; HD: High dose; LD: Low dose; PB: Peripheral blood mononuclear cells; MRI: Magnetic resonance imaging; SPECT: Single photon emission computed tomography; RNA: Radionuclide angiography; EMM: Electricomechanical mapping; LVEF: Left ventricle ejection fraction; LVED: Left ventricle end-diastolic; MSC: Mesenchymal stem cells)

*HD vs Control

#Data presented at the November 2008 American Heart Association Scientific Sessions meeting.

route in the infarct-related artery 5–9 days post-MI was recently pulished.[146,169] Although, nonrandomized, this is the longest follow-up trial reported thus far. In this small study, an early significant improvement in LVEF and infarct size at 3 months and 1 year was followed at 5 years by greater exercise capacity and lower mortality (1 death vs 7 deaths) in the treated patients.[146,169]

Many of the reported studies have significant limitations in terms of their small sample size and design, and there are many differences amongst trials that make comparison of the results very challenging. In many of these trials, LVEF has been the primary endpoint and the methods used to evaluate this have been variable (echocardiography, SPECT, left ventricular angiography or MRI). The trials also diverge in many other ways including the clinical characteristics of the patients enrolled, the size and type of the infarct size on admission, methods of cell isolation, the number and timing of cells delivered, and the time points for follow-up assessments of outcome. It is possible that the apparently conflicting results among different trials are secondary to these differences. Importantly, there is clearly a need for further large-scale randomized, placebo-controlled trials to assess the safety and efficacy of infused BM cells post-MI.

To address some of these limitations and unresolved issues, several clinical studies for acute MI aiming to determine the optimal timing, dosage, and route of cell delivery are currently being conducted. Among these trials, there are two on-going phase III trials. REGEN-AMI (NCT00765453, 102 patients) is a randomized, double-blinded, placebo-controlled clinical trial aiming to determine whether intracoronary infusion of autologous BM-derived progenitor cells to patients undergoing primary angioplasty for acute anterior MI will lead to an improvement in cardiac function greater than that seen by placebo alone. The second and larger (300 patients) ongoing clinical trial is a multicenter prospective randomized double blind trial sponsored by the Brazilian Ministry of Health (NCT00350766) also aiming to determine the benefits of autologous BM-derived progenitor cells in post-MI patients.

Circulating Angiogenic Cells

Circulating angiogenic cells have also been used in a number of clinical trials. As stated previously, the therapeutic potential of progenitor cells, regardless of the selection method, is reduced in the presence of cardiovascular risk factors or established disease.[55,58-60,170,171] Thus, all autologous cell therapies post-MI seem to have had the limitation of potentially using dysfunctional cells as they were derived from patients with known coronary artery disease (CAD) and cardiovascular risk factors. In a nonrandomized study by Bartunek et al.[172] the use of selected "progenitor" cells based on surface markers (i.e. CD133)[172] in post-MI patients was associated with improved left ventricular performance paralleled with increased myocardial perfusion and viability. However, it also demonstrated that intracoronary infusion of enriched CD133+ BMC post-MI was associated with a higher incidence of in-stent restenosis and de novo coronary lesions in the infarct-related arteries. The SELECT-MI randomized trial (ClinicalTrials.gov NCT00529932) is on-going to better define the risk and mechanisms of potential side effects on the epicardial coronary circulation with the infusion of CD133+ BMC or BM-MSC.[173]

A recent study (REGENT trial) additionally isolated cells that coexpress CD34 and the chemokine receptor CXCR4 and compared the intracoronary infusion of BMMNCs or selected $CD34^{+}CXCR4^{+}$ cells in patients with acute MI and reduced LVEF of less than 40%.[166] Treatment with these cells did not lead to a significant improvement of LVEF or volumes but a trend in favor of cell therapy in patients with most severely impaired LVEF was noted in both treated groups. In addition, the clinical improvement seen in these pilot studies with isolated hematopoietic cells appears similar to that obtained with treatment with total BMCs. Moreover, a current ongoing phase IIb, double-blind, parallel, randomized placebo-controlled trial (ENACT-AMI, ClinicalTrials.gov NCT00936819), with four participating centers in Ontario and Quebec, is looking into the benefits of autologous CACs, and autologous CACs transfected with eNOS in post-MI patients. A total of 99 patients will be randomized into one of three arms, receiving either Plasma-Lyte A (placebo), or either of the cell therapies by coronary injection to the infarct-related artery.[174]

Mesenchymal Stem Cells

As shown in Table 2, MSCs have also been clinically tested. Intracoronary injection of a large number of BM-derived MSCs resulted in improvement in global LVEF and regional wall motion, and reduction in infarct size, LVESV, as well as LVEDV in patients with acute MI.[167] More recently, a randomized clinical trial using MSCs in post-infarct patients demonstrated that intravenous allogeneic hMSCs is safe.[168] In this study, the global symptom score, defined from subject interviews at day 10 and 6 months after treatment compared with pretreatment, was better in MSCs versus placebo ($p = 0.027$), while the LVEF was significantly better only in the subset of anterior MI patients compared to control. The efficacy and safety of MSC therapy in patients with acute MI are currently being evaluated in larger randomized clinical trials. An ongoing phase II, multi-center, randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of ex vivo cultured adult human MSCs intravenous infusion following acute MI is expecting to recruit around 300 patients (ClinicalTrials.gov NCT00877903).

Adipose-derived Stem Cell

The safety, feasibility and efficacy of freshly isolated adipose-derived stem cells in acute MI are also being clinically investigated. APOLLO (ClinicalTrials.gov NCT00442806) was a prospective, double-blind, randomized, placebo-controlled, sequential dose-escalation trial in which ASCs were delivered through intracoronary infusion after appropriate infarct-related artery therapy with stent implantation.[175] This study aimed to investigate the benefits of freshly isolated ASCs in patients with acute MI and LVEF impairment. Preliminary results confirm safety.[175a] Now, a phase II/III ADVANCE trial has been initiated to evaluate their efficacy (ClinicalTrial.gov NCT01216995).

Cardiosphere-derived Stem Cells

CADUCEUS (ClinicalTrials.gov NCT00893360) was a phase I randomized, dose escalation study of the safety and efficacy of intracoronary delivery of cardiosphere-derived stem

cells in patients with ischemic left ventricular dysfunction and a recent MI (up to 12 months). At 6 months, therapy with CSCs demonstrated to be safe and associated with increased areas of viable myocardium. Further assessments of clinical outcomes are needed to address efficacy of this therapy.[175b]

CHRONIC CORONARY ARTERY DISEASE AND CHRONIC HEART FAILURE

Table 3 summarizes a few of the key clinical trials that have been performed in the setting of chronic CAD and chronic heart failure (CHF). Compared to the acute post-MI trials, there are fewer studies that have been performed in this setting using stem cells.

Bone Marrow Cells

Surgical trials using BM-derived cell therapy have focused on chronic stable myocardial ischemia. These trials have generally included patients with a remote history of MI, who have evidence of akinetic or dyskinetic infarct scars, and an indication for elective coronary artery bypass grafting (CABG). Overall, the results of these studies have been disappointing. The nonrandomized study by Mocini et al.[176] (36 patients) reported a 3-month significant improvement in regional and global LV function compared with baseline, but these outcome measures did not significantly differ from those obtained in control patients. Hendrikx et al.[177] (20 patients) showed that after 4 months, there was a significantly greater wall thickening in cell-transplanted patients (as assessed by MRI) but no improvement in LVEF or perfusion defects beyond values in control patients (Table 3). Finally, the trial by Ang et al.[178] in which cells were injected both in the myocardium and in the bypass grafts, also failed to meet its primary endpoint. Altogether, these results suggest that surgical transplantation of unfractionated BM in chronically infarcted myocardium may not provide a functional benefit.

On the other hand the intracoronary approach of BMMNCs was also tested in patients with chronic CAD[179] and CHF,[180] and the results are to some extent similar to those in patients with acute MI, showing mixed effectiveness in terms of improvement in regional and global left ventricular function (Table 3). Assmus et al.[180] investigated the benefits of intracoronary infusions of either circulating progenitor cells (CPCs) or BMMNCs. BMMNCs were associated with moderate but significant improvement in LVEF after 3 months when compared to CPCs or the control. On the other hand, Yao and colleagues investigated whether intracoronary infusion of BMMNCs into the infarct-related artery in 47 patients with stable ischemic heart disease could lead to improvement in LVEF.[179] They concluded that BMMNCs did not lead to significant improvement of cardiac systolic function, infarct size or myocardial perfusion, but did lead to improvement in diastolic function. These data need validation by large-scale randomized controlled trials.

Mesenchymal Stem Cells

In parallel, two small randomized studies investigated the use of MSC in patients with chronic CAD. Chen et al.[181] demonstrated that intracoronary injection of culture-expanded MSCs in patients after percutaneous coronary intervention (PCI) of the chronically occluded left anterior descending artery improved myocardial perfusion, improved exercise tolerance and NYHA class and LVEF in treated patients. In contrast, in the cohort study by Katritsis et al.[182] which included patients with acute as well as old MI, treatment with a relatively small number (2–4 million) of MSCs showed no significant improvement in global LVEF, LVESV or LVEDV following intracoronary MSC transplantation despite improved myocardial perfusion and viability. Additional studies are clearly needed to better understand the effect of MSCs in chronic CAD. Notably, to our knowledge, two studies are currently registered for the assessment of MSC intramyocardial injections in conjunction with CABG in patients with ischemic heart failure (Prometheus NCT00587990 and NCT00418418). The endpoints are efficacy and safety and will evaluate whether treatment with MSCs into postinfarction scars will drive these cells toward an osteogenic phenotype and result in intramyocardial calcification.[94]

Skeletal Myoblast Cells

More than a period of 10 years has passed since clinical trials of myoblast transplantation were first started. Four non-randomized, noncontrolled adjunct-to-CABG transplantation studies were initially performed.[183-186] These studies demonstrated the feasibility of the procedure as well as the safety of multiple needle punctures in the postinfarction scar and along its borders. The notable safety concern has been an increased risk of arrhythmias after some of these early-phase trials reported postoperative episodes of sustained ventricular tachycardia.[184,186] On the other hand, outcomes were found to range from stabilization of LVEF and volumes[184] to improvements in regional and global LV function[184] and in metabolic viability of transplanted areas.[183,186,187] However, since these trials were not design to address efficacy along with their open-label design and the lack of controls, the data was inconclusive.

Following the above studies, a multicenter, randomized, double blind, placebo-controlled trial (MAGIC—Myoblast Autologous Grafting in Ischemic Cardiomyopathy), including patients with severe LV dysfunction, postinfarction nonviable scar, and indication for CABG,[188] was performed (Table 3). An internal cardioverter-defibrillator was implanted in all patients before hospital discharge. At 6 months, there were no overall differences in the incidence of arrhythmias between groups. However, the arrhythmias tended to be clustered in the early postoperative period in the myoblast-treated groups, and more evenly distributed in the placebo group. Although neither regional nor global LV function were significantly improved by myoblast injections, the highest dose of cells (800 million vs 400 million) resulted in a decrease in LVEDV and LVESV compared with the placebo group, possibly suggesting some beneficial effects in terms of remodeling.[187]

In parallel to these surgical trials, a catheter based study randomized 23 patients with LVEF less than 40% and old (> 10 years) MI to endoventricular myoblast injections or optimal medical management alone (CAuSMIC trial).[189] The 12-month interim results point toward improvement in ventricular viability, and evidence of reverse ventricular remodeling. There results are in contradiction with those of the randomized SEISMIC trial reported by Serruys at the 2008 American College

TABLE 3

Representative randomized clinical trials of cell therapy for chronic coronary artery disease (CAD) and chronic heart failure (CHF): study design and efficacy

Trial	*Cell type/ Sample size*	*Clinical scenario*	*Method(s)*	*Route of delivery*	*Cell dose*	*Primary endpoint*	*Follow-up*	*Baseline LVEF*	*Follow-up LVEF*	*Δ LVEF*	*P value (Δ LVEF)*
Hendrikx et al.[177] 2006	MNC:10 Control:10	Chronic CAD	MRI SPECT	Intramyocardial during CABG	$60\pm31x10^6$	LVEF	4 months	MNC: 42.9±10.3% Control: 39.5±5.5%	MNC: 48.9±9.5% Control: 43.1±10.9%	MNC:NA Control:NA	NS
Assmus et al.[46] (TOPCARE-CHD), 2007	MNC:28 CPC:24 Control:23	Chronic CAD	Angiography MRI (subset) Echocardio-graphy	Intracoronary	MNC: $20.5\pm11x10^7$ CPC: $22\pm11x10^6$	Changes on LVEF	3 months	MNC:41±11% CPC:39±10% Control: 43±13%	MNC:43±10% CPC:39±10 Control: 42±13%	MNC: 2.9±3.6 CPC: –0.4±2.2 Control: –1.2±3	0.02
Yao et al.[179] 2008	MNC:24 Control:23	Chronic CAD	Echocardio-graphy MRI SPECT	Intracoronary	$3.6x10^7$	LVEF	6 months	MNC: 46.3±7.2% Control: 45.4±7.2%	MNC: 48.9±9.5% Control: 47.6±7.4%	MNC: 3.5±3.3 Control: 2.3±2.7	NS
Chen et al.[181] 2006	MSC:23 Control:22	Chronic CAD	Echocardio-grapy, SPECT	Intracoronary	$5x10^6$	LVEF	12 months	MSC:26±6% Control:23±8%	MSC: 30±4% Control:30±5%	MSC:NA Control:NA	NS
Menasche et al.[188] (MAGIC), 2008	SkM^1:33 SkM^2:34 Control:30	Chronic CAD	Echo stress MRI (subset)	Intramyocardial during CABG	$400x10^6$ $800x10^6$	LVEF	6 months	SkM^1:25.2.6% SkM^2:28.7% Control:29.6%	SkM^1:32.6% SkM^2:32.3% Control:35.1%	SkM^1:3.4% SkM^2:3.4% Control:4.4%	NS

(Abbreviations: MNC: Mononuclear cells; CPC: Circulating progenitor cells; MSC: Mesenchymal stem cells; SkM: Skeletal myoblast; CAD: Coronary artery disease; MRI: Magnetic resonance imaging; SPECT: Single photon emission computed tomography; RNA: Radionuclide angiography; CABG: Coronary artery bypass grafting; LVEF: Left ventricle ejection fraction; LVED: Left ventricle end-diastolic)

of Cardiology meeting which randomized 31 patients to myoblast injections while 16 patients received "optimal medical therapy", and they showed no added benefit of cell therapy on LVEF at 6 months after the procedure.[187]

REFRACTORY ANGINA

Stem cells have also been investigated in a few small studies as therapy for refractory angina in patients who are already on maximal conventional treatments (i.e. judged to have no further revascularization options and are on aggressive medical therapy). Fuchs et al.[190] have shown symptomatic improvement in some of these "no option" patients following transendocardial delivery of autologous MNC. However, the subjective nature of the primary endpoint, i.e. angina relief, the open-label design of this study, and the lack of controls, make these findings difficult to interpret. Three small-sized randomized controlled trials have been performed in patients with chronic ischemia refractory to medical therapy[141,142] (Table 1). Losordo et al.[141] reported the feasibility and safety of intramyocardial injection of granulocyte-colony stimulating factor-mobilized $CD34^+$ stem cells. There was no significant difference in angina frequency, exercise time or angina class, but this may have been due to underpowering for these outcomes. In the PROTECT-CAD[142] trial, the effect of intramyocardial BM cell injection on clinical outcome, myocardial perfusion, and LV function was assessed in 19 BM cell-treated patients and 9 placebo-treated patients. BM cell injection was associated with a modest increase in exercise capacity and LVEF compared with placebo. However, no difference in myocardial perfusion between the groups was observed. Van Ramshort et al.[143] studied 50 patients with severe angina pectoris despite optimal medical therapy and myocardial ischemia. They demonstrated that intramyocardial BMMNCs resulted in a statistically significant but modest improvement in myocardial perfusion and increased LVEF compared with placebo.

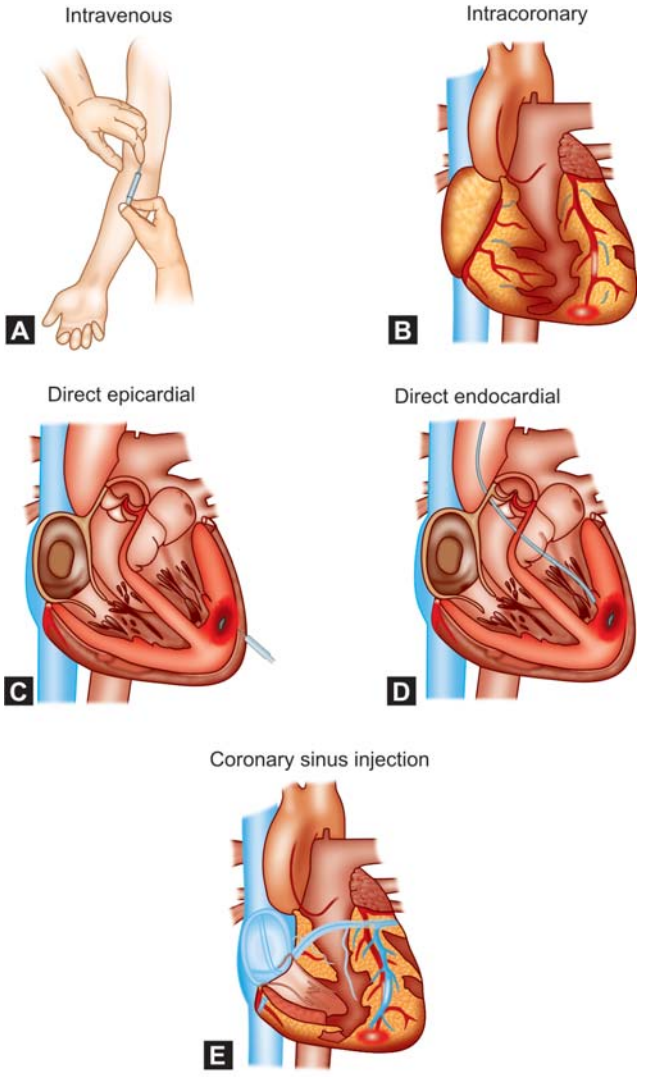
Freshly isolated ASCs have also been studied as therapy for chronic myocardial ischemia. PRECISE was a prospective, double-blind, randomized, placebo-controlled, sequential dose-escalation trial randomizing patients with end-stage CAD not amenable to revascularization and with moderate-severe left ventricular dysfunction to receive freshly isolated ASCs or placebo in a 3:1 ratio. The cells were delivered via transendocardial injections after left ventricle electromechanical mapping.[175] Preliminary results suggest that ASCs therapy is safe and results in a stabilization of infarct size and improvement in maximal oxygen consumption. Larger studies are still necessary to confirm these findings.[190a]

PULMONARY HYPERTENSION

In the last few years, there has been increasing interest in the role of endothelial progenitor cells, either as a potential therapeutic target, predictive biomarker for outcome or cell-based therapy in patients with PH.[191-194] Two small pilot studies in adults[195] and in children with idiopathic PH[196] have evaluated the efficacy of therapy with a single intravenous infusion of autologous mononuclear cells. In the adult patients (n = 15), at twelve weeks, this therapy resulted in improvement in the six-minute walk test distance (42.5 mean; 28.7 to 56.3; 95% CI; p = 0.001), reduced mean pulmonary artery pressure (–4.0 mm Hg, –6.2 to –1.9; 95% CI; p = 0.001) and pulmonary vascular resistance (–157.6 dyn/s/cm^5; –250 to –65; 95% CI; p = 0.002), and increased cardiac output (0.32 L/min; 0.05 to 0.59; 95% CI; p = 0.021), compared with patients receiving conventional therapy (n = 16). Similar responses were also found in children. Importantly, no undesirable effects of cell-based therapies were described. Currently, a phase I trial to establish safety of autologous progenitor cell-based gene therapy delivery of human eNOS in patients with severe PH refractory to conventional treatment is being conducted in Canada (PHACeT trial, NCT00469027).

ROUTES AND METHODS OF CELL DELIVERY

There are currently a number of different routes of cell administration available to introduce stem cells to the heart. These approaches include (Figs 2A to E):[168] intravenous,[168]



FIGURES 2A TO E: Methods of cell delivery for cardiac implantation: (A) intravenous administration; (B) intracoronary infusion using a balloon catheter after restoration of arterial patency; (C) transepicardial injection via thoracotomy into the border zone of the infarct; (D) transendocardial approach using electromechanical voltage mapping to define tissue viability and (E) intravenous injection into the coronary veins via the coronary sinus, enabling cell delivery into myocardial areas subserved by occluded coronary vessels. (*Source:* Modified from Gersh BJ, et al. Cardiac cell repair therapy: a clinical perspective. Mayo Clin Proc. 2009;84:876-92, with permission)

intracoronary,[159] transmyocardial (by direct epicardial injection),[177,188] catheter-based transendocardial injection using electromechanical voltage mapping,[142] and transvenous injection into coronary veins.[198] The success of cell therapy relies on delivery of an adequate cell number to an area of injury, which requires an appropriate microenvironment for cell survival, retention and/or homing. However, cell delivery and cell retention in the myocardium appears to be inefficiently low with all of the above techniques.[197,199-201] In addition, the ideal timing in relationship to the onset of disease, and place for delivery (scar or border zone) remain to be elucidated.[197] In general, many questions in regards to stem cell delivery methods and cell retention (+/- scaffolds) remain unanswered and ongoing research will undoubtedly address these issues.

CONCLUSION AND FUTURE DIRECTIONS

In the last two decades there has been a wealth of research into the potential of regenerating injured tissue using stem cell therapies. The current evidence suggests that stem cell therapy may have promise for attenuating remodeling and transforming inert scar into biochemically functional myocardium. However, the past decade has also shown that translating the potential of stem cell therapy into actual practice is not easy, and many barriers would need to be overcome before this therapy attains its full potential.

The publication of multiple clinical trials suggests that cell therapy, with the cells that have thus far been tested, appears to be generally safe (may be with the cautionary exception of myoblast cells) and may lead to a modest improvement in left ventricular function over conventional therapies. However, many challenges remain to be overcome, including the inclusion criteria for which patients would get the most benefit, the optimal cell type(s), methods of cell processing, timing and dose of product delivery and issues surrounding retention and engraftment in the heart after delivery. Moreover, the potential mechanism(s) of benefit of stem cell therapy on cardiac function needs to be further investigated in the preclinical small and large animal settings.

Despite these obstacles, the observed functional improvement has spurred continued animal and clinical studies along several different directions. First, there is ongoing research into ways to better enhance the recruitment, survival and long-term engraftment of implanted stem cells. If true regeneration is to take place, then a sizeable percentage of the stem cells need to remain viable, differentiate into fully functional cardiomyocytes and incorporate into the resident tissue. Potential alternatives using biomaterials and cell engineering techniques that will increase cell retention and engraftment are being studied. Second, further analyses of stem cells that exhibit the robust cardiac potential (i.e. human ESCs and autologous iPS cells) are also needed to generate pure cell populations of cardiomyocytes with appropriate functional characteristics. The discovery of various cardiac stem cell populations has renewed interest in the innate regenerative capacity of the human heart to enhance endogenous repair or mimic it with exogenous stem cell therapy. Third, the interesting notion that stem cells exert their influence largely through paracrine activity has sparked research into a new and promising direction. Could it be that most of the benefits are paracrine derived and live cells themselves will not be as crucial and one could use the extract from stem cells for therapeutic purposes in the future?[37] Of course, a lot more research is required with the numerous different types of stem cells and it is likely that different stem cells will work through different mechanisms.

In summary, we are still in the early days of stem cell therapy to treat heart disease. Much more work remains to be performed to better understand the potential of this potentially powerful therapy.

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Chapter 118

Gene Therapy and Angiogenesis

Matthew L Springer

Chapter Outline

- Gene Therapy Overview
  - — Gene Replacement, Gene Correction and Gene Overexpression
  - — Plasmid DNA Delivery versus Viral Transduction
  - — Ex Vivo Gene Therapy with Retrovirus
  - — Gene Transfer to Myocardium
- Basic Concepts of Angiogenesis
  - — Blood Vessel Growth: Vasculogenesis, Angiogenesis and Arteriogenesis
  - — Cellular Involvement in Blood Vessel Growth
  - — Angiogenic Growth Factors and Response to Hypoxia
- Angiogenic Protein Therapy
- Angiogenic Gene Therapy
  - — Angiogenic Gene Therapy in Animal Models
  - — Angiogenic Gene Therapy Clinical Trials in Heart
- Gene Therapy for Chronic Heart Failure

INTRODUCTION

In perhaps one of the main ironies of cardiovascular medicine, the heart, which pumps blood to every tissue in the body, is itself one of the most susceptible tissues to the consequences of insufficient blood supply. Myocardial ischemia manifests as mild-to-debilitating angina pain, and progressive or acute blockage of a major supply artery to the heart leads to myocardial infarction. Most of the other tissues in the body, if temporarily deprived of blood, can undergo local tissue death and then regenerate through efficient healing processes; but myocardium is subject to remodeling and scar formation. Therefore, much effort has gone into developing potential therapies that increase blood supply by growing new blood vessels, primarily through gene therapy.

This chapter centers on therapeutic angiogenesis with an emphasis on gene therapy approaches and explains gene therapy with an emphasis on cardiac applications. Notably, the vast majority of cardiac gene therapy trials have been aimed at angiogenesis, and the vast majority of therapeutic angiogenesis attempts in the heart have involved gene therapy, so it is difficult to separate the two topics. They are intertwined both technically and historically. Thus, we will begin with an overview of gene therapy approaches and technologies, consider several approaches for gene transfer to myocardium, explore blood vessel structure and growth mechanisms, and discuss gene therapy applications for both angiogenesis and heart failure.

GENE THERAPY OVERVIEW

GENE REPLACEMENT, GENE CORRECTION AND GENE OVEREXPRESSION

Gene therapy is a general term that describes the replacement of a defective gene, the molecular repair of a defective gene, and the addition of a gene that was already present but is added under conditions that lead to its expression at higher levels (Fig. 1). *Gene replacement* is uncommon in cardiovascular

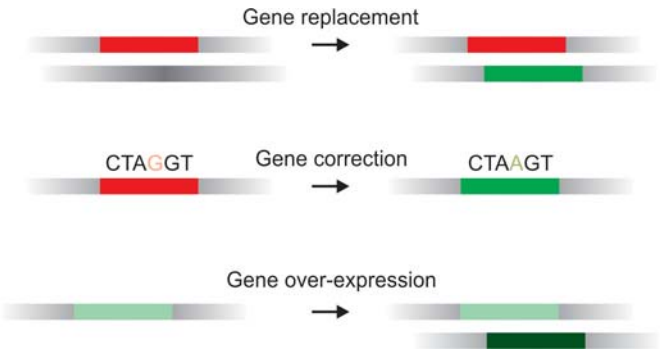


FIGURE 1: Different gene therapy strategies. In gene replacement, a non-functional mutant gene (red) is replaced or supplemented with a functional wild-type allele (green). In gene correction, the actual mutation in the non-functional gene (red nucleotide) is changed into the wild-type sequence (green nucleotide) in the chromosome itself or upon transcription of the gene; or a compensating second mutation can restore a frame-shift mutation (not pictured). In gene overexpression, normal wild-type cells are engineered to express another copy of a pre-existing gene (light green), but with control elements that cause it to be expressed at higher levels and/or constant expression (dark green)

therapeutic strategies but has been clinically successful in the treatment of Leber congenital amaurosis, a hereditary blindness, for which a defective gene that encodes a protein responsible for retinoid cycling in photoreceptor cells is supplemented by viral delivery of the functional gene.[1-3] (The defective copy of the gene typically remains, but is inconsequential.) Replacement strategies have also shown clinical benefit in two different severe combined immunodeficiency diseases, in which wild-type alleles are supplied to replace mutated genes encoding adenosine deaminase and the cytokine receptor γ_c chain.[4,5] An example of a *gene repair* strategy is the potential treatment of Duchenne muscular dystrophy (DMD), in which a deletion in the dystrophin gene can result in a frame-shift mutation that leads to a truncated RNA transcript and protein in skeletal and cardiac muscle. In addition to various gene replacement approaches, gene therapy strategies for DMD have included the targeting and repair of the mutated sequence,[6-8] and the addition of another mutation that restores the correct reading frame and results in a still-functional protein.[9,10] The last case, *gene overexpression*, which involves delivery of an upregulated gene to supplement an endogenous gene that is not in itself defective, is the most common approach in cardiac applications and is exemplified by delivery to the tissue of a gene encoding an angiogenic growth factor,[11-13] as discussed in detail below. This can be considered a form of drug therapy, but the genetically altered tissue itself is the production source of the drug.[14]

The aim of most cardiac gene therapy strategies is to deliver therapeutic levels of a protein that will improve cardiac function or vascular perfusion. This typically is accomplished through the local overexpression of the therapeutic genes in the heart. Effective gene therapy requires that the therapeutic DNA reaches the desired target tissue, accesses the cell nucleus, and is expressed at the necessary levels with the appropriate timing. A number of gene delivery strategies exist, which can essentially be divided into the non-viral and viral vectors.

PLASMID DNA DELIVERY VERSUS VIRAL TRANSDUCTION

The non-viral systems use plasmid DNA containing the therapeutic gene, either by itself as "naked plasmid" or complexed with various chemicals to enhance uptake. Treatment with naked plasmid has the advantages of being cheap, simple and safe because these constructs do not initiate inflammation if purified appropriately, are not immunogenic and incur insignificant risk of insertional mutagenesis.[15-17] However, plasmid gene therapy has been hampered by low transfection and expression levels.[18] To increase transfection efficacy, plasmids have been complexed with cationic lipids,[17] and mechanical approaches, such as electroporation and destruction of targeted ultrasound bubbles that contain the plasmid, have also been applied.[19] In fact, it was initially assumed that these enhancement techniques were essential, and naked plasmid DNA delivery began as a negative control for liposome-enhanced delivery that showed unexpected positive results.[20] Regardless, low plasmid transfection efficiency limits its use as a viable strategy for the treatment of cardiovascular disease, although there have been some notable exceptions to be discussed later in the chapter.[18,21,22]

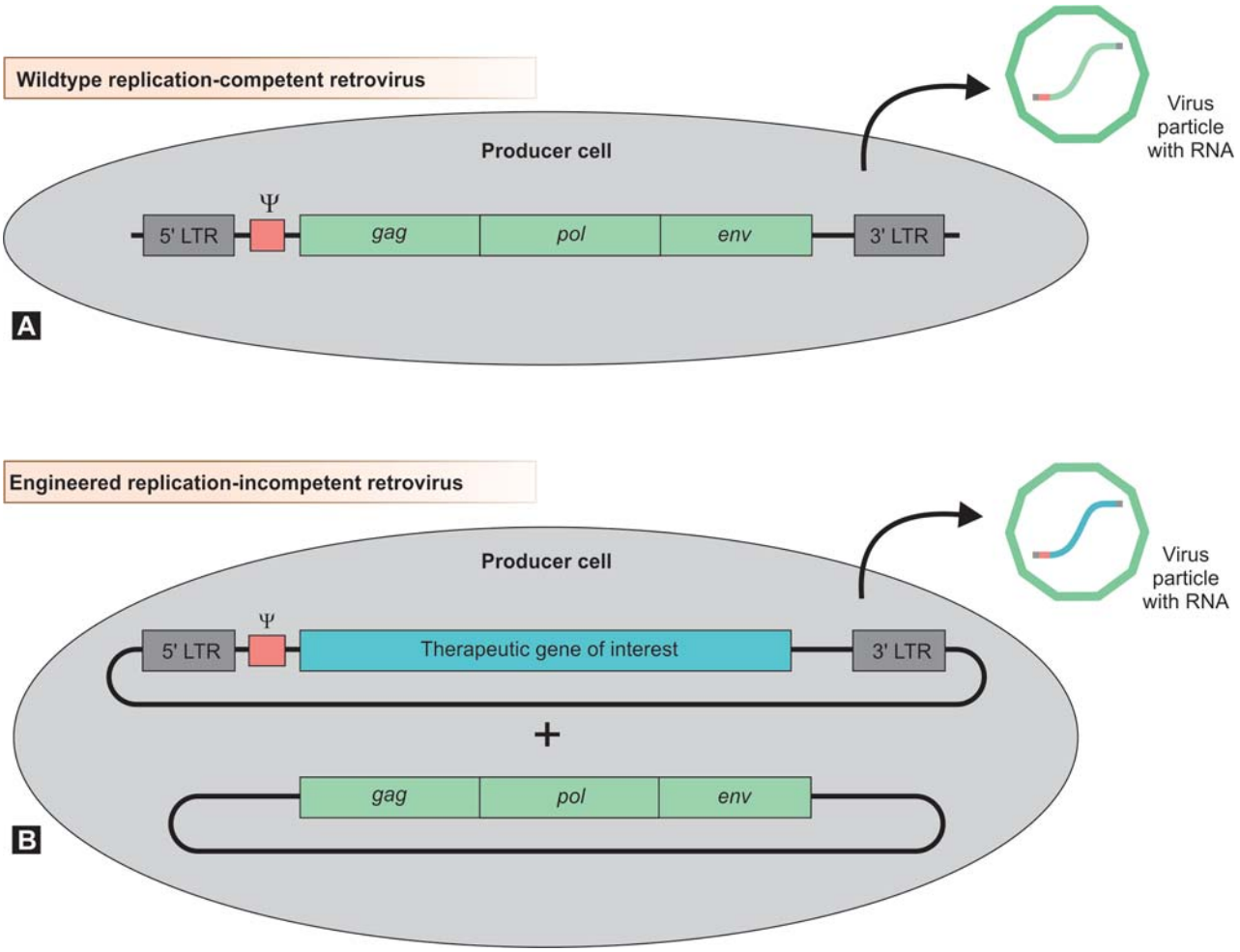
On the other hand, the major advantage of viral constructs over plasmid DNA is their high infection efficiency, strong expression and the capability of large-scale infection of organs in large animals.[18,23] Viruses hold these advantages because, unlike plasmid DNA, viruses have evolved extremely efficient mechanisms to infect cells and to ensure that their genes are transcribed by the host cells' genetic machinery. The basic strategy of viral infection for the purpose of genetic alteration, referred to as *transduction*, is to use a variety of molecular biology maneuvers to generate a viral genome that retains only the nucleotide sequence necessary to ensure gene expression by the host cell, with most or all of the other viral genes replaced by the therapeutic gene of interest (Figs 2A and B). The main viruses used for direct cardiac gene transfer have been adenovirus, adeno-associated virus (AAV) and lentivirus.[24,25] They differ in the size of the DNA insert that they can accommodate, duration of expression, cardiac tropism, immunogenicity, and whether they integrate into the host genome (resulting in greater stability but increased risk of insertional mutagenesis and cancer).

Adenovirus

Much of the earliest cardiac gene transfer experiments used adenoviral vectors, derived from one of the DNA viruses that cause the common cold. Adenovirus transduction results in very strong gene expression for several days after infection, which then falls substantially over the following 2 weeks.[18] However, adenoviruses are highly immunogenic, and the infected cells typically are rejected after that time,[26] which is not surprising if one considers the self-contained time course of a cold virus infection. This results in only short-lived expression of the transgene in immunocompetent hosts. Transgene expression can last for as long as a year if the host is immunodeficient (such as a SCID mouse, which lacks T and B cells). The immune response also prevents repeated administration, a problem that can be partially obviated by using different serotypes of adenovirus for the subsequent administrations, but this would complicate the approval and performance of the therapy. Therefore, to limit the immune response, the viral genes have been increasingly removed from the vectors. In fact, in so-called "gutted" adenoviral vectors, the entire viral genome is missing, leaving only the sequences required for DNA packaging and for replication.[27] In some cases, this results in the long-term expression of the transgene comparable to that in immunodeficient animals. However, the viral genome does not integrate into the chromosome, instead remaining extrachromosomal in the nucleus, which means that while insertional mutagenesis is not a problem, the transgene can get lost from the host cell population if the cells undergo many rounds of division. Despite the existence of the gutted vectors, the potential for inflammation and immune rejection has substantially reduced enthusiasm for the adenoviral approach in general, and many developing gene therapy strategies at this time rely instead on AAV and lentivirus.

Adeno-Associated Virus

Adeno-associated virus is a DNA virus that infects many kinds of human cells, but is not known to cause any disease. At least nine naturally occurring human serotypes are known with



FIGURES 2A AND B: Non-replicating viral vectors. A prototypical viral gene transfer approach is shown, based on the original *Maloney murine leukemia* virus (retrovirus) that was used for many of the earliest gene transfer experiments. Various viral systems have different viral genes and genome organization, but the general concept is the same. The wild-type virus contains the genes that are necessary for production in the host cell of new infectious virus particles, containing the viral RNA genome and capable of infecting other cells. For gene therapy, the viral RNA sequence, in which some or all of the viral genes have been replaced with the therapeutic gene, is cloned into a plasmid (circular DNA); and the viral genes necessary to produce new virus particles are put on a separate plasmid (or sometimes more than one plasmid to reduce chances of recombination). The two plasmids are transfected into a cultured producer cell, which can thus make viral particles, but packages the viral RNA that contains only the therapeutic gene. Hence, the virus produced can infect a cell, but cannot replicate because it does not carry the viral genes required for viral propagation, and instead delivers a therapeutic gene to the target cell. In this example, the LTRs are specialized retroviral genomic end sequences, ψ is the packaging signal that ensures the viral RNA molecule will be inserted into the virus particles, and the viral genes *gag*, *pol* and *env* encode a structural protein, reverse transcriptase and a viral envelope protein respectively

different tropisms and tissue specificities, and additional hybrid serotypes have been generated in the attempt to tailor these qualities. The viral genome integrates into the chromosome, and while the strong tendency of wild-type AAV to integrate at a specific location in the genome led to initial assumptions that random insertional mutagenesis would thus be avoided, the engineered AAV vectors have lost this specificity and have also sometimes been reported to exist primarily in episomal form.[28,29] AAV suffers from a relative difficulty in generating enough viral particles, and also from the small capacity for therapeutic genes owing to the small size of the viral capsid, which limits its use to genes of small-to-medium length. Nonetheless, the lack of known human pathology, and the relatively non-immunogenic nature makes AAV a useful vector for gene therapy. AAV efficiently transduces cardiac and skeletal muscle cells, and gene expression can be detected for up to a year.[30] AAV vectors have been designed to target expression to specific cells, both by driving expression from tissue-specific conditional promoters and enhancers,[31,32] and by engineering the capsid to include specific cell-surface targeting sequences.[33,34] This is exemplified by the delivery of therapeutic genes to be expressed specifically in the heart and under specific hypoxic conditions by using transcriptional control elements taken from cardiomyocyte-specific genes and hypoxia-inducible genes.[31]

Lentivirus

Lentiviruses are a specific class of retroviruses that rely on conversion of their RNA sequences to DNA that subsequently integrates in the host chromosome after infection of the cell. Other retroviruses, particularly the Maloney murine leukemia virus, were the original retroviruses used for the first gene therapy trials, but they could not fully infect cells in the presence

of an intact nuclear envelope, and thus required cells to be proliferating in order for infection to be possible.[35] In contrast, lentiviruses are able to transport their genomes through the intact nuclear membrane and can therefore multiply in nondividing cells, offering a substantial advantage over the other retroviruses.[36] The lentiviruses do not appear to induce inflammatory and immune responses and are efficient at transducing myocardium with a stable gene expression profile owing to integration into the chromosome.[37] Because lentiviruses integrate into the chromosome, the concern about mutagenesis remains. Furthermore, lentiviral vectors are derived from the human immunodeficiency type 1 virus (HIV-1) and similar viruses, a fact that was initially cause for concern about the vectors' potential to recombine in the host cell with dormant viral sequences in the genome, generating a competent immunodeficiency virus infection; but this concern has not been borne out in practice.

EX VIVO GENE THERAPY WITH RETROVIRUS

Most gene therapy approaches involve direct genetic alteration of the cells in the tissue; that is, in vivo gene therapy. However, some current strategies, and all of the initial gene therapy strategies, involved removal of cells of interest from the body, transduction of these cells in culture, and reintroduction of the genetically altered cells to the body; or ex vivo gene therapy.[38] The ex vivo approach was used initially not only because of the disease targets, but because the retroviral vectors used at the time could not infect nondividing cells and were the most efficacious if the target cells were proliferating in culture. In addition, this skirted issues of viral tropism and cellular specificity because only the target cells were infected in culture. Ex vivo gene therapy of T-cells with retroviral vectors was used for the initial gene therapy clinical trials in the early 1990s for severe combined immunodeficiency caused by adenosine deaminase deficiency (ADA-SCID).[39] While those trials resulted in only limited benefit related to the gene therapy, retroviral ex vivo trials that were published in the early 2000s led to lasting cures for a number of patients of both ADA-SCID and a related X-linked SCID;[4,5] a triumph that was tempered by leukemias that appeared in a small number of the patients caused by insertion of the strong viral promoter next to progrowth genes in the genome. Most of these leukemias were successfully treated,[40] but this confirmed the long standing concern described above about integrating viruses and the risk of insertional mutagenesis.

Ex vivo gene therapy using transduced skeletal muscle myoblasts has been explored as a gene therapy approach for skeletal muscle, because the myoblasts fuse with the preexisting muscle fibers, which subsequently express the transgene.[41-43] While this has relevant applications to peripheral vascular disease,[44-48] this approach is of lesser direct utility for cardiac gene therapy because the myoblasts remain as a distinct tissue from the surrounding host myocardium.[49] Nonetheless, an *ex vivo* gene therapy approach using genetically modified myoblasts is in the early stages of a Phase I trial described under heading "Gene Therapy for Chronic Heart Failure".

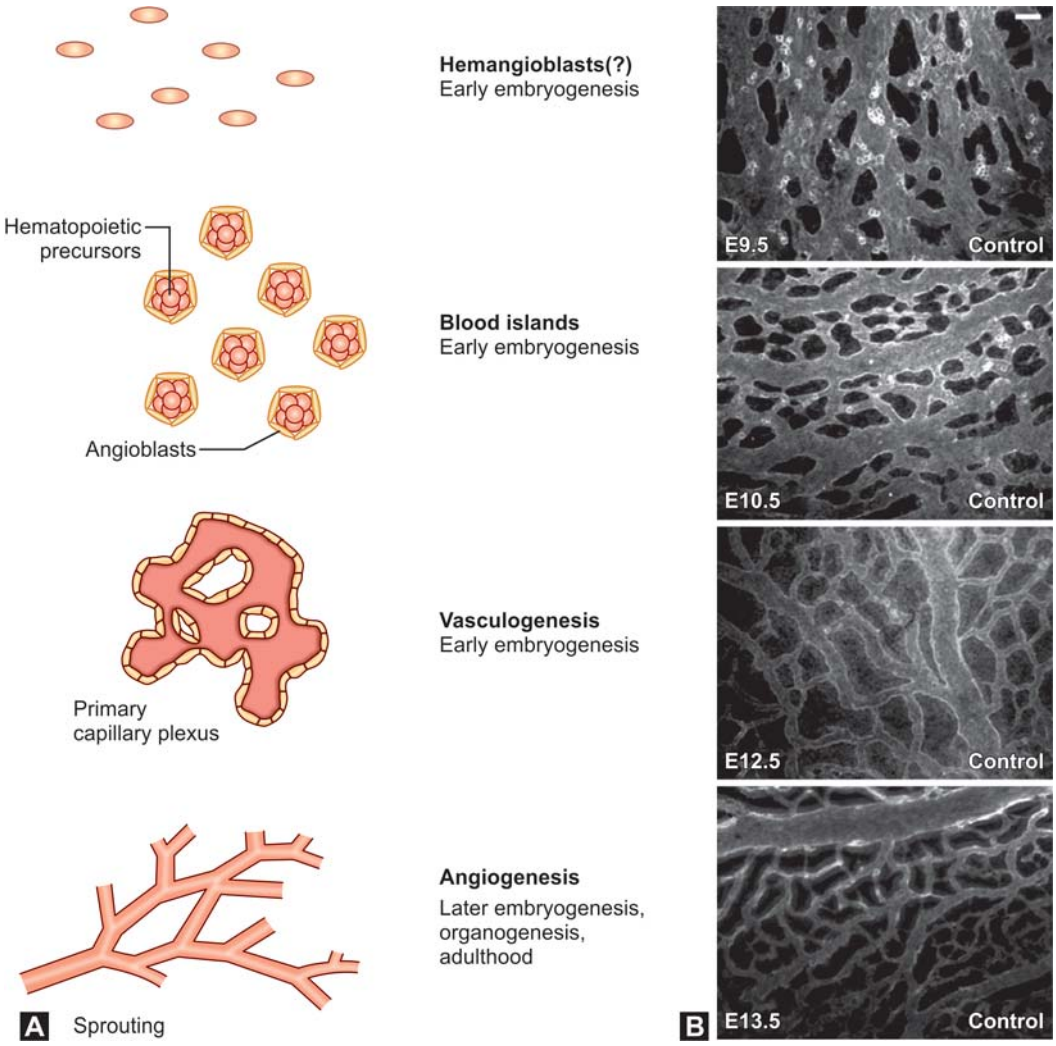
GENE TRANSFER TO MYOCARDIUM

As discussed earlier, most cardiac gene therapy trials to date have involved the delivery of angiogenic genes to ischemic myocardium. More recently, gene therapy for chronic heart failure has become a promising approach and is currently in clinical trials.

The three most important considerations for successful gene transfer to the heart are DNA/vector delivery to the desired cardiac location, appropriate choice of vector for gene transfer to the nucleus and ability of the expressed transgene to affect the cardiac physiology. The modes of delivery to the heart are quite similar to those used for cell therapy applications, and are discussed in detail in the cell therapy chapter elsewhere in this textbook. Intracoronary infusion of vectors appears to be safe and effective for adenoviral delivery but not for plasmid even when complexed with liposomes.[50] The intravascular route also holds the disadvantages of the inefficient distribution to ischemic tissues, which by definition are poorly vascularized, and the endothelial barrier between the vector and the target myocytes. Endothelial permeability can be enhanced by using high perfusion pressure during intracoronary administration[51,52] or by simultaneous treatment with permeability-enhancing drugs like histamine.[53] Pressure-regulated retrograde infusion through the coronary veins appears to be a particularly effective alternative.[54] In contrast, direct intramyocardial injection is more localized and is also better suited for plasmid delivery. This has been performed via mini-thoracotomy,[55,56] but is now typically accomplished by percutaneous endomyocardial injection due to its less invasive nature and the increased likelihood of approval for placebo controls. Of the several such systems in use, the most successful so far has been a catheter-based transendocardial injection using electromechanical voltage mapping (NOGA),[22] although its complexity and low availability over the years has limited its use for widespread clinical application. Other approaches toward targeting the delivery include the ultrasound-mediated administration of plasmid DNA complexed with ultrasonic-destructible microbubbles, which has been successfully implemented in rodent hind limb muscle.[57]

Regarding appropriate choice of vector, many of the clinical experiments involving cardiac gene transfer have relied on adenovirus,[50,55,56,58-61] and AAV-based trials are beginning to appear at this time.[62] In both cases, the choice of serotype is critical, as different serotypes vary widely in their ability to transduce cardiomyocytes and other cell types.[63] Despite its relative inefficiency, naked plasmid injection works in the myocardium, as it does in skeletal muscle,[15,16] and plasmid-based gene therapy with both naked and liposome-complexed DNA has been the subject of several clinical trials because it avoids the potential complications of viral gene delivery.[21,22,50,64]

The ability of the expressed transgene to affect cardiac physiology is a function of the choice of gene, the expression strategy (e.g. strength and specificity of the promoter) and the disease target. Most cardiac gene therapy strategies so far have involved delivery of angiogenic growth factor genes, constitutively expressed in chronically ischemic heart. The author has discussed this more thoroughly later in the chapter,



FIGURES 3A AND B: Vasculogenesis. (A) Diagrams of the stages of vasculogenesis in the embryo. Putative hemangioblasts give rise to blood islands consisting of endothelial progenitors surrounding hematopoietic progenitors, which fuse into a vascular plexus that subsequently gets remodeled into a capillary bed. (B) Vasculogenesis. Photomicrographs of several steps of remodeling from plexus to capillary bed in mouse yolk sac vessels from embryonic day 9.5–13.5. Endothelial cells are immunofluorescently stained for PECAM-1. Scale bar = 100 μm. (*Source:* Oas RG, Xiao K, Summers S, et al. p-120-Catenin is required for mouse vascular development. Circ Res. 2010;106:941-51, with permission)

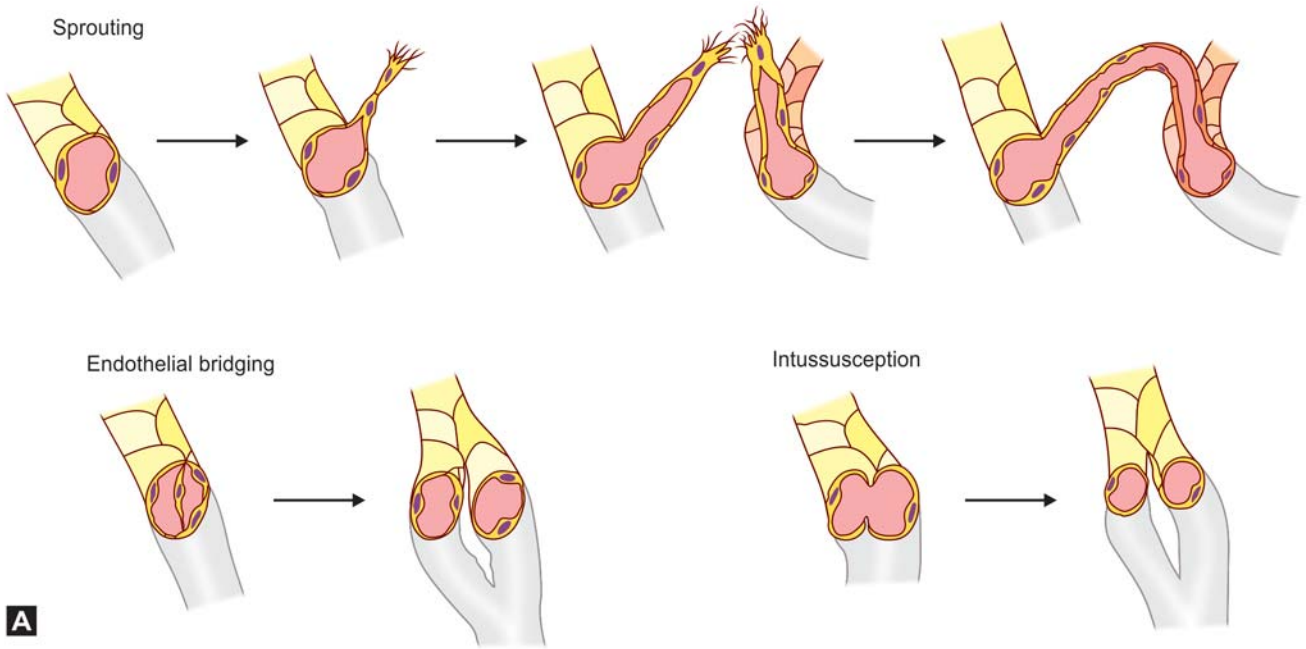
but first, it is important to understand the process of angiogenesis that is the goal of most of these attempted therapies.

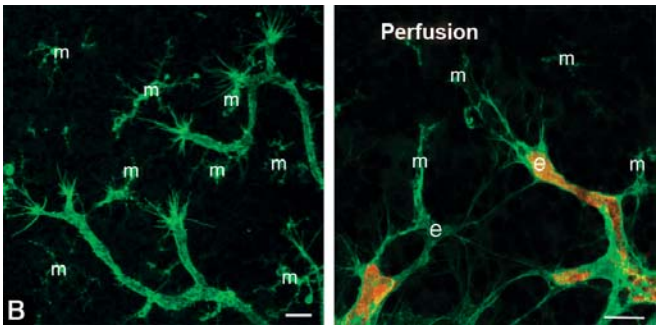
BASIC CONCEPTS OF ANGIOGENESIS

BLOOD VESSEL GROWTH: VASCULOGENESIS, ANGIOGENESIS AND ARTERIOGENESIS

The earliest vasculature in the vertebrate embryo is formed de novo from precursor cells through the process of *vasculogenesis* (Figs 3A and B). The initial structure formed is a vascular plexus, a redundantly interconnected series of channels lined by endothelial cells, incapable of active circulation.[65] As development proceeds, these channels mature and are pruned into a hierarchical vascular tree in which large vessels branch into smaller ones in what becomes the capillary bed. Arterial and venous specification occur at this point; even the capillary endothelial cells on the arterial side of the capillary bed show arterial markers, such as ephrin B2, and those on the venous side express venous markers, like EphB4, during an arterio-venous specification process that is directed in part by Notch signalling.[66-68]

From this point on, *angiogenesis* takes over as the primary mode of capillary growth (Figs 4A and B). Angiogenesis is the growth by sprouting or splitting of capillaries from pre-existing capillaries, with or without involvement of auxiliary cells. This can occur by sprouting of an endothelial cord that later develops an interior lumen and merges with another sprout to make a contiguous loop.[69] The growth of the sprout is reminiscent of both neuronal growth, in which a growth cone sends out filopodia to guide the growth of its unicellular sprout (the axon); and plant shoot growth, in which a specialized apical cell sends signals to the dividing cells behind it to inhibit them from giving rise to more apical cells. In the case of endothelial sprouting, a specialized tip cell that is guided by its filopodia produces the ligand for Notch, Dll4, which induces Notch signaling in the



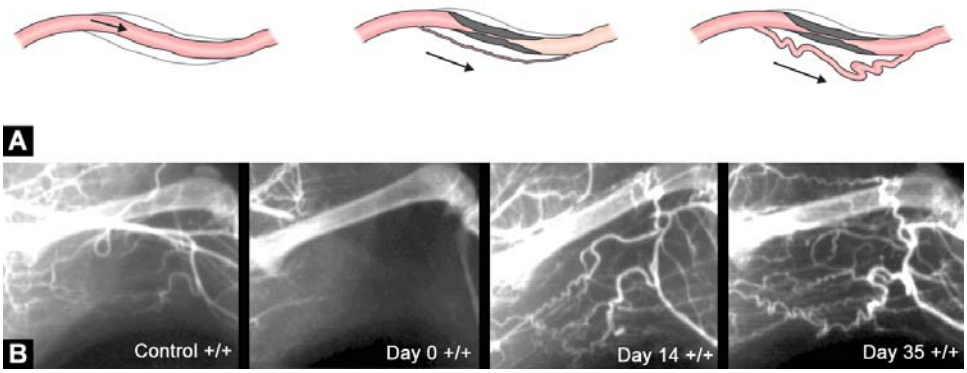


FIGURES 4A AND B: Angiogenesis. (A) Angiogenesis frequently consists of sprouting of a tip cell followed by stalk cells into a cord that lumenizes and joins lumens with another sprout from a different region of capillary to form a new loop. Alternate mechanisms that have been reported under some circumstances, such as vascular plexus remodeling and response to high levels of growth factors, include endothelial bridging and separation of a capillary into two vessels, and intussusception to split a capillary into two vessels. (B) Photomicrographs of endothelial sprouts (green isolectin B4 staining) with tip cells in the developing mouse retina. One panel shows sprouts from a capillary network that has been perfused with fluorescent red dextran to show the lumens. Some endothelial cells are labeled as "e" and others are unlabeled; "m" denotes microglia that have also stained green. Scale bar = 20 μm. (*Source:* Figure 4B Courtesy of Christer Betsholtz, reprinted with permission from Gerhardt et al. ©Rockefeller University Press. Originally published in J Cell Biol. 2003;161:1163-77. DOI 10.1083/jcb.200302047, with permission)

stalk cells further back in the sprout and inhibits them from being sprout cells.[70] Two other mechanisms have been reported at specific stages of development or after treatment with high levels of angiogenic factors, which occur by radial enlargement and splitting of one capillary into two parallel capillaries (intussusception and endothelial bridging).[71,72] The sprouting mechanism has been shown to be important during embryonic vascularization of initially avascular tissues, notably the retina,[69] but it is less clear which mechanism is more important during adult angiogenic processes such as wound healing, response to ischemia, placental growth and tumor growth. In the postnatal heart, angiogenesis occurs in parallel with myocardial hypertrophy and in response to exercise,[73,74] and it is an important goal of therapies for ischemic diseases, as the author has discussed later in the chapter.

The growth of the larger vessels occurs through completely different means, by *arteriogenesis* (Figs 5A and B). While the initial large conduit vessels are formed de novo as developmental structures in the embryo, other smaller vessels are recruited as needed to ensure adequate blood flow to capillary beds. This can occur on several levels. Large crucial vascular beds such as the cardiac and leg muscles possess collateral small arterioles that accompany the conduit arteries, offering alternate pathways for blood flow that are typically not used because of their much smaller diameter, and thus much higher resistance than the main conduit vessel. If a coronary artery, for example, is unable to pass enough blood to the downstream myocardium due to partial blockage or atherosclerotic narrowing, the blood is forced into the smaller collaterals and the shear stress causes molecular changes in the arterial wall, leading to radial enlargement of the vessel and thickening of the smooth muscle layer, and ultimately to the appearance of a new conduit artery that becomes visible by standard angiography.[75-77] There is evidence that arterioles can form from pre-existing capillaries in a similar fashion: if more blood supply is needed in the downstream tissue, capillaries under stress to deliver blood can obtain a smooth muscle layer and enlarge.[45]

In addition to the blood vessels of the circulatory system, characterized by capillaries leading from arterial to venous conduits, a parallel system of lymphatic vessels coexists that leads from closed-ended lymphatic capillaries in the interstitial space through lymph nodes for filtration and then to lymph ducts for drainage into veins. These lymphatic capillaries are endothelial tubes that share many physiological features and growth mechanisms with blood capillaries, although the endothelial cells are phenotypically distinct from those of the



FIGURES 5A AND B: Arteriogenesis. (A) The left-most diagram shows a hypothetical artery accompanied by two collateral vessels that are too small to show up on an angiogram and carry little, if any, blood. In the middle diagram, a stenosis of the artery has blocked most of the blood flow, and some blood is being forced through a collateral that is still too small to serve as a sufficient conduit. In the right-most diagram, that collateral has responded to chronic shear stress by remodeling into a large muscular conduit collateral artery. (B) Angiograms are shown at the following stages of the response to femoral artery ligation in the mouse: control (without ligation), immediately after ligation (day 0), 14 days postligation and 35 days postligation. The femoral artery is clear in the control, and the ligation point is apparent at day 0 where the femoral artery image abruptly ends. Increasing collateral vessels appear at days 14 and 35, presumably from vessels that were already present in the control but too small to be visible by angiogram. (*Source:* Sullivan CJ, Doetschman T, Hoying JB. Targeted disruption of the Fgf2 gene does not affect vascular growth in the mouse ischemic hindlimb. J Appl Physiol. 2002;93:2009-17, with permission)

blood circulation system, expressing different receptors and surface markers.[78]

It is debatable whether angiogenesis or arteriogenesis should be the primary goal of therapies for ischemic disease. Angiogenesis leads to an increase in capillaries and a greater potential blood volume in the target tissue, but if the conduits leading into that larger volume are limiting, then the increased capillary bed may not provide any benefit. Interestingly, if a pro-angiogenic therapy leads to a sufficiently large increase in the number of capillaries, the influence of pro-arteriogenic signals relayed toward the upstream conduits may obviate this potential problem. In fact, it is notable that delivery of the vascular endothelial growth factor (VEGF) gene to ischemic rabbit and human legs has been reported to lead not only to a local increase in capillaries but also to an upstream increase in angiographically detectable collateral arteries.[76,79-82]

CELLULAR INVOLVEMENT IN BLOOD VESSEL GROWTH

In the late 1990s, evidence began to accumulate that both angiogenesis and re-endothelialization of denuded arterial intima involved not only the pre-existing local endothelium but circulating cells as well.[83,84] The cells that played this role appeared to be bone marrow-derived, expressed both endothelial and hematopoietic markers, and were sometimes but not always reported to take on an endothelial phenotype.[85] Of the many names used for these cells, the name "endothelial progenitor cells" (EPCs) stuck. An unfortunate consequence of that name, however, was that it suggested a single cell population; whereas many different preparation methods yielded different populations of cells and most of them were heterogenous.[86]

It quickly became apparent that there are at least two major components of the so-called EPCs found in peripheral blood. The first (called various names including early EPCs, colony forming unit-Hill cells, proangiogenic cells and circulating angiogenic cells or CACs) is a relatively rare population that expresses various permutations of CD34, CD133 (ACC133; a stem cell marker) and VEGF receptor 2 (VEGFR2, or KDR, an endothelial marker also known as Flk-1 in the mouse).[87] These cells can be isolated from human blood by marker expression or by selective growth conditions of adherent cells in culture.[83,88] This population expresses CD45 and has a number of hematopoietic characteristics, including the expression of the monocytic marker CD14, and the ability to engulf bacteria in a macrophage-like manner.[86] It also has endothelial characteristics after several days in culture, like expression of endothelial NO synthase (eNOS), and the cells migrate toward a variety of angiogenic factors (discussed under heading "Angiogenic Growth Factors and Response to Hypoxia") including VEGF, SDF-1 and pleiotrophin.[88-92] This population does not appear to differentiate into endothelial cells, and is thought to be a variation of monocytes, although this is controversial.[93,94] Despite the lack of differentiation into true endothelial cells, this population of cells appears to have therapeutic properties when delivered to ischemic heart and limb in rodents and in humans, presumably through the paracrine delivery of angiogenic factors from the cells.[95-98] The number and in vitro functional properties of this early population have been repeatedly shown to provide a useful read-out of cardiovascular health, correlating positively with endothelium-dependent flow-mediated vasodilation and diet, and correlating negatively with a number of cardiovascular risk factors such as age, smoking, cholesterol, diabetes and hypertension.[88,99-104]

The second population (late EPCs, endothelial colony forming cells, late outgrowth endothelial cells) is even rarer and expands with several weeks in culture into colonies that appear endothelial for all intents and purposes.[105,106] These cells have been proposed to be true endothelial progenitors, or alternatively to have always been rare circulating endothelial cells derived from the intima.[86] While the controversy is not settled, a picture that continues to gain credence is that the early population consists of hematopoietic cells related to monocytes that respond to pro-angiogenic molecular signals from local angiogenic sites,

home to those sites and produce their own growth factors that help the underlying endothelium, or perhaps the late "EPC" population, to grow.

It should be noted that while the putative contribution of circulating cells to growing endothelium is frequently referred to as vasculogenesis, this is distinct from the classical definition of vasculogenesis in the embryo as described above, in which individual cells coalesce to form a functional vasculature de novo.

ANGIOGENIC GROWTH FACTORS AND RESPONSE TO HYPOXIA

Despite its high relevance to ischemic diseases and vascular insufficiency, the field of angiogenesis research actually had its origins in tumor biology.[107] Solid tumors cannot grow to more than 2 mm without the tumor core being too far away from the blood supply; thus tumor cores are typically hypoxic. The hypoxia induces the expression of genes that encode angiogenic growth factors, which stimulate the growth of capillaries into the tumor and allow it to grow further. The concept that these factors could be identified and inhibited to treat cancer took many years to take hold, but ultimately led to discovery of many angiogenic factors, most of which are expressed more strongly under hypoxic conditions. The main known sensor for this regulation is a transcription factor, hypoxia-inducible factor-1 (HIF-1),[108] which senses O_2 concentration through the level of hydroxylation of prolines in its regulatable subunit HIF-1α and targets itself for ubiquitin-mediated degradation as long as enough O_2 is present.[109-111] Under hypoxic conditions, HIF-1α is not degraded and participates in the HIF-1 complex to transcribe many hypoxia-inducible genes. Interestingly, von Hippel-Lindau (VHL) disease, characterized by highly angiogenic tumors, is caused by the absence of a functional VHL tumor suppressor gene product that normally participates in the targeting for ubiquitination and degradation of HIF-1α; its absence results in stable HIF-1 levels that keep the cells' angiogenic program turned on even under normoxic conditions.[112] The same mechanism that induces angiogenic factor genes in tumors also causes them to be upregulated in ischemic myocardium and other tissues. Sometimes, this upregulation is enough to maintain homeostasis, but frequently the expression of these angiogenic factors is insufficient to counter the ischemic state and a major goal of angiogenic therapies is to deliver even more of these growth factors to compensate.[12,113]

The most-characterized angiogenic factor is VEGF, a secreted potent regulator of endothelial cell survival, proliferation and migration.[114,115] VEGF is a crucial vasculogenic and angiogenic signal during embryonic development and plays an important role in post-natal processes including bone growth plate development, wound healing, tumor angiogenesis and pathological angiogenesis in the eye.[115-120] It is also required for the survival of newly formed capillaries, which are initially VEGF-dependent but later obtain coverage with pericytes (mural cells similar to smooth muscle cells) and are then capable of survival, even when VEGF is withdrawn.[121,122] Even though, VEGF is produced in response to hypoxia, it can be sequestered at the cell surface through various extracellular matrix-mediated mechanisms and the subsequent liberation of VEGF by matrix metalloproteases is thought to be the crucial step of the "angiogenic switch" in tumor metastasis.[123]

There are five known members of the VEGF family: (1) VEGF-A (also called simply VEGF); (2) VEGF-B; (3) VEGF-C (also called VEGF-2); (4) VEGF-D and (5) placenta growth factor (PlGF; sometimes referred to as placental growth factor). An additional member of the VEGF family, VEGF-E, has been identified in certain viral transcripts.[124] VEGF-A, the first member identified and the best characterized, was initially discovered under the guise of its other main property, enhancement of vascular permeability, and was therefore also called vascular permeability factor (VPF).[125,126] Alternative mRNA splicing results in several isoforms of VEGF-A (VEGF121, VEGF165, VEGF189, VEGF206 are the main isoforms in humans, although there are a few others) with different biological properties, mainly the extent to which they bind heparin in the extracellular matrix and remain localized versus diffusing through the tissue.[115,127,128] Tissue-specific physiological differences have been ascribed to the different splice variants,[129] and differential diffusion through tissue appears to influence embryonic angiogenesis sprouting patterns,[69,130] although all of the main isoforms possess angiogenic activity and even the non-heparin-binding shortest isoform is capable of localized effects on vascular patterning in adult muscle.[48,81] VEGF-B appears to have a more potent angiogenic effect in the heart than in many other tissues including skeletal muscle, although the biological impact of this is unclear.[131] VEGF-C and VEGF-D have angiogenic properties, but appear to be heavily involved in lymphangiogenesis as well.[78,132-134] PlGF is thought to modulate the angiogenic effects of the VEGFs.[135,136] Taken together, the VEGFs are widely considered to be a crucial family of angiogenic and vasculogenic signals. In fact, the importance of VEGF-A is illustrated by the embryonic-lethal phenotype of lack of even a single allele.[137,138]

VEGF has two angiogenesis-specific tyrosine kinase receptors, VEGFR1 (Flt-1 in mouse) and VEGFR2 (KDR in human, Flk-1 in mouse),[139-142] plus a pair of receptors that are also involved in neuronal path finding (neuropilin-1 and neuropilin-2; consider the similarities between axonal growth and capillary sprouting described above), and that appear to be specific for the VEGF-A165 splice variant.[143,144] Of these, VEGFR2 appears to play the most active and crucial role, in that its absence also leads to embryonic lethality and its kinase activity is necessary for it to function properly.[145,146] This activity sets in motion signaling cascades that include the PI3 kinase/Akt/eNOS, p38MAP kinase and Raf/MEK/Erk pathways.[146,147] In contrast, VEGFR1 is also essential, but its kinase domain can be deleted with no apparent effect;[148] in other words, its ability to bind VEGF seems to be the important trait. For this reason, it has been suggested that VEGFR1's role is to compete with VEGFR2 for VEGF or to possibly act as a co-receptor for some of the other members of the VEGF family. One other receptor, VEGFR3, is involved in the functions of VEGF-C and VEGF-D.[78,133] The complex interplay between the various VEGF receptors and the members of the VEGF family is summarized in Table 1.

The fibroblast growth factor (FGF) family is the other main angiogenic factor group that has been heavily studied for

TABLE 1

VEGF family and receptors

Receptor	*Ligand*
VEGFR1	VEGF-A VEGF-B PlGF
VEGFR2	VEGF-A VEGF-C VEGF-D VEGF-E
VEGFR3	VEGF-C VEGF-D
Neuropilin-1,2	VEGF-A165

therapeutic purposes. FGFs in the heart are involved in both angiogenesis and cardioprotection.[149] Moreover, the importance of the FGF family in angiogenesis is underscored by the involvement of FGF receptor homologues in branching and growth of the tracheal system in *Drosophila*, which has many features in common with the blood vasculature in vertebrates.[150,151] Even though, FGFs are involved in the growth of many different cell types, gene delivery of FGF-1 (acidic FGF), FGF-2 (basic FGF) and FGF-5 were shown early on to have profound effects on vessel growth.[152-154] Therapeutically, FGF-4 is the one that has received the most attention and made it into widespread clinical trials (discussed under heading "Angiogenic Gene Therapy").

An ever-growing list of angiogenic growth factors drives home how complicated the process is. Angiopoietin-2 is involved in destabilizing capillaries to allow new sprouting or branching, whereas angiopoietin-1 and platelet-derived growth factor (PDGF) play a role in the stabilization of the vessels.[155-159] Such stabilization factors are candidates for co-delivery with angiogenic growth factors with the aim of stable vessel growth.[160,161] Others, such as hepatocyte growth factor (HGF), stromal cell-derived factor-1 (SDF-1), pleiotrophin, thrombopoietin and so on all play roles and may be potentially exploited for the therapeutic induction of angiogenesis.[18] However, the implementation of therapeutic angiogenesis has been anything but straightforward, as we are about to discuss.

ANGIOGENIC PROTEIN THERAPY

The simplest view of how therapeutic angiogenesis might be induced is to use a purified angiogenic protein like VEGF as a drug, directly administering it to the region of tissue in which neovascularization is desired. Not surprisingly, this was the first approach to be attempted in animal models. VEGFs and FGFs in their various forms were delivered as protein therapies in animals and in clinical trials, in ischemic heart and leg. Animal experiments generally led to changes in the vasculature, such as increased capillary density in the tissue or increased collateral artery formation. However, functional improvement was difficult to demonstrate, especially on the clinical level.

One problem with the protein therapy approach to angiogenesis is that soluble protein is cleared very quickly from the muscle, especially from beating myocardium. Angiogenesis occurs over a time scale of several days, so a single injection of protein is not ideal to achieve a lasting effect if the tissue levels of the protein quickly drop below efficacious concentrations. Therefore, the bolus effect is a concern, where in order to inject lasting amounts of the growth factor; the initial injection must be at very high levels that may have deleterious side effects. This concern was borne out in the case of VEGF, for which animal experiments revealed hypotension as a problem at high doses due to VEGF's vascular permeability enhancing abilities.[162,163] Therefore, in the first Phase II clinical trial of VEGF protein therapy for chronic myocardial ischemia (the VIVA trial[164]), sub-hypotensive doses of VEGF protein were infused into the coronary arteries. The results were disappointing, with a lack of clear difference in angina and exercise duration between the VEGF and placebo groups until 120 days, and an unclear level of clinical benefit. FGF1 and FGF2 have been infused down the coronary arteries in Phase I clinical trials, with evidence of increased vascularity and exercise capacity, although Phase II trials have not been successful with toleratable doses.[165-168] Multiple administrations of growth factor proteins still suffer from these potential problems, and in the case of the heart, multiple deliveries are impractical at any therapeutically relevant number of repetitions.

Timed-release of angiogenic proteins has been proposed as an alternate strategy. Whereas implantation of osmotic pumps and other delivery devices is not straightforward in cardiac and skeletal muscle, the injection of growth factors complexed to biocompatible polymers that slowly release the proteins may result in a long-term depot of the active growth factors without disrupting muscle architecture. FGF2 (basic FGF) delivered from implanted alginate microcapsules in ischemic hearts of patients undergoing coronary artery bypass grafting led to an increase in myocardial perfusion in Phase I trials.[169] Similarly, various researchers are exploring several approaches that involve gelling polymers after injection to retain macromolecules and cells, including alginate and fibrin gels, as well as self-assembling peptide nanofibers.[170,171] However, it is currently unclear whether this approach will result in larger clinical benefits.

ANGIOGENIC GENE THERAPY

ANGIOGENIC GENE THERAPY IN ANIMAL MODELS

In contrast to angiogenic protein therapy, gene therapy with angiogenic factors holds several advantages. First, the bolus effect of protein injections is avoided, because a gene is expressed at constant levels (if that is the intent); thus, a successful constitutive gene therapy strategy can theoretically avoid both excessive and insufficient levels of gene product. Second, if the angiogenic protein is needed only under certain tissue conditions and not others (e.g. myocardial ischemia), a single gene therapy administration can provide this control if the appropriate promoters and enhancers are used. Third, gene therapy can actually be easier to accomplish than protein therapy if the angiogenic factor of interest is difficult to purify even from recombinant sources, because the gene therapy only requires that the DNA or virus is expanded and purified, a fairly simple process resulting in stable material.

Gene transfer-induced angiogenesis has been quite successful in a number of animal models. It is far easier to demonstrate an increase in capillary vascularity in animals than

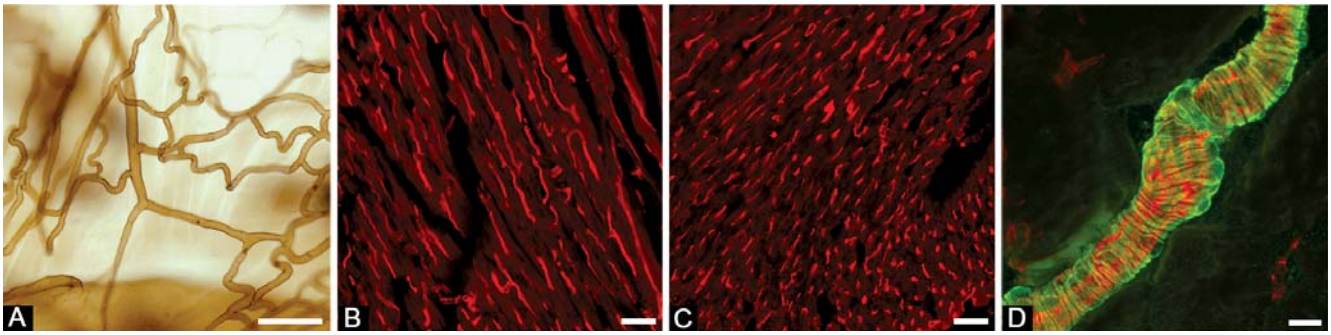
in humans, because of the ease with which target tissue can be isolated and sectioned for histological analysis.[172] The typical histological analysis will include specific staining for the transgene, a marker gene like that which encodes β-galactosidase or both; and stains that visualize capillary endothelial cells and the smooth muscle cells of arterioles and venules. Endothelial cell detection typically involves staining with antibody or avidin detection for CD31/PECAM and biotinylated BS-1 isolectin B4 from *Griffonia simplicifolia*, and smooth muscle cells are most commonly visualized by antibody staining for α-smooth muscle actin (Figs 6A to D). Angiography (both standard and CT scan) and vascular casting can determine how numerous the larger arteries and veins are in the living animal and after tissue harvest, respectively. A number of technologies are available to measure vascular perfusion, including adenosine single-photon-emission computed tomography (SPECT) and positron emission tomography (PET), ultrasound, laser Doppler to a limited depth in the leg, and fluorescent microspheres injected into the circulation that get lodged in the capillary bed.

Using techniques like these, it has been demonstrated that transfection of VEGF-A and VEGF-C plasmid DNA into the arterial wall, or direct injection of VEGF-A plasmid, adenovirus, or AAV into the skeletal muscle or myocardium can lead to an increase in capillary density and upstream collateral artery formation.[80,173-177] Laser Doppler is frequently used to document successful increase in blood flow in rodent limbs, although such studies need to be interpreted with the understanding that most laser Doppler systems have a penetration depth of ~0.5 mm and thus measure skin perfusion, rather than perfusion in the target muscle. Systems with greater depth exist but are very much in the minority. That said, VEGF gene therapy in ischemic mouse hind limbs has repeatedly been shown to improve (skin) perfusion in the treated leg. Similar histological evidence of therapeutic benefit exists for FGF gene delivery to ischemic myocardium.[152] Frequently, the gene transfer is carried out with constitutively expressed gene constructs, but alternate strategies have been reported that use promoter/enhancer combinations that are tissue-specific and hypoxia-inducible, to keep the transgene off in tissues other than the myocardium and only expressed under ischemic conditions.[31]

Retroviral transduction of skeletal muscle myoblasts with the VEGF-A gene under a strong constitutive promoter, and subsequent implantation of the myoblasts into mouse skeletal muscle such that the implanted cells fused with pre-existing muscle fibers, have shown that the resulting transgenic muscle can form large hemangiomas if the gene is expressed too highly, even in a small region of muscle.[44,45,48] This effect has also been observed after myoblast implantation into mouse myocardium (in which case they do not fuse with the cardiomyocytes) and myocardial VEGF plasmid injection in the rat.[49,178] This underscores a limitation of such angiogenic gene therapy approaches, that it is possible to express too much of the gene and trigger undesirable consequences. However, controlling the amount and tissue distribution of VEGF that is produced can avoid the deleterious consequences and still induce growth of new capillaries that are persistent and functional.[31,46,47,121]

ANGIOGENIC GENE THERAPY CLINICAL TRIALS IN HEART

The promising results of angiogenesis gene therapy experiments in animals have been difficult to translate into successful clinical treatments. Because of obvious differences between working with animals and patients, the outcome measures of angiogenesis gene therapy clinical trials have been less focused on histological evidence of an increase in vessel number, and more on vascular perfusion, blood pressure, angina, exercise tolerance and other functional parameters. Many of these are subject to a substantial placebo effect that has confounded a fair share of clinical trials. There is also naturally a preference for lower expression levels that are insufficient versus higher effective levels that could lead to hypotension or hemangioma formation. While there have been several clinical trials that have suggested that efficacy is possible, none have been officially successful for reasons to be discussed below and it is currently unknown whether such



FIGURES 6A TO D: Stained blood vessels for microscopic analysis. (A) Blood vessels in the mouse ear have been stained on the luminal surface by injection of biotinylated *Griffonia simplicifolia* lectin into the tail vein, followed by harvesting of ear tissue (in whole mount) and staining with horseradish peroxidase-conjugated avidin (brown). (B and C) Staining of mouse heart 10 μm cryosections with biotinylated isolectin B4 followed by a fluorescent avidin conjugate (or immunostaining for PECAM-1; not shown) visualizes capillaries as line segments if oblique to the plane of the section, and dots if perpendicular to the plane of the section. (D) Three-dimensional reconstruction by confocal microscopy of an arteriole in mouse skeletal muscle stained fluorescently for PECAM-1 to detect endothelial cells (red) and for α-smooth muscle actin to detect smooth muscle cells (green). (*Source:* A to C are presented by the author, unpublished; D is from Springer et al. Mol Ther. 2003;7:441-9. Scale bars: (A to C) 50 μm, (D) 10 μm, with permission)

approaches will ultimately succeed. It should be understood that it is difficult to describe clinical work in progress in a textbook because the description will be out of date almost immediately after publication, if not before.

Interestingly, the first angiogenesis clinical trial involved gene therapy, rather than protein therapy. This was a Phase I single patient trial of VEGF plasmid transfection of the arterial wall in the leg, at a time before clinical-grade VEGF protein was available at high enough levels, but plasmid could be mass-produced and purified relatively easily. Angiomas were reported but they resolved and not much more could be interpreted about efficacy because it was Phase I.[82]

Since then, a number of controlled clinical trials of myocardial gene therapy using genes from the VEGF and FGF families have been completed.[13] Parallel efforts have occurred in skeletal muscle, but the author has focused on the heart for this chapter. The reader will recognize a recurrent pattern in these trials in that early results from Phases I and II trials can be quite promising, and lead to larger Phase III trials that are unsuccessful for one reason or another. The two largest factors that have confounded the translation from small to large clinical trials have been the difficulty in expanding specialized catheter technology for widespread testing and a substantial placebo effect coupled with the potential for spontaneous improvement in these patients.

Initial Phase I studies using VEGF165 (the most prevalent splice variant of VEGF-A) showed evidence of therapeutic effect in patients with intractable angina.[64] However, larger randomized trials that followed yielded mixed results.[13] One of these, the Kuopio Angiogenesis Trial (KAT),[50] was a Phase II trial that compared intracoronary VEGF165 gene therapy with plasmid/liposomes and adenoviral vectors to placebo. Interestingly, the plasmid group showed no improvement over placebo, but the adenovirus group showed an improvement in myocardial perfusion as detected by SPECT imaging. The difference between the plasmid/liposome and adenoviral results are presumably due to the efficient infection capabilities of the virus; whereas plasmid tends to be more effective when injected into solid tissue. Consistent with this interpretation, the Euroinject One trial,[179] in which naked plasmid encoding VEGF165 was directly injected into the myocardium by NOGA-guided catheter (discussed under section "Gene Therapy Overview"), LVEF and regional wall motion were improved in the VEGF-treated group; but no improvement was observed in myocardial stress perfusion defects or Canadian Cardiovascular Society (CCS) angina class between groups. In contrast, the NOGA Angiogenesis Revascularization Therapy: Assessment by RadioNuclide imaging (NORTHERN) trial, a multi-center Canadian trial of NOGA-guided VEGF plasmid injection,[61] failed to show a difference between the VEGF and placebo groups in any of the endpoints studied at 3 or 6 months, including myocardial perfusion, exercise treadmill testing (ETT), and angina symptoms.The reason for the contradictory results of similar trials is unclear. However, the observation of significant improvements for all endpoints in both the DNA and placebo groups (even in the reduction in ischemic area) underscores the difficulty in detecting a positive result against the background of a large placebo effect, and spontaneous improvement in perfusion that may occur in patients with severe chronic ischemia.

VEGF121 is a shorter VEGF-A splice variant that does not bind heparin, and thus has been used by several research groups in the hope that it will diffuse freely through the tissue[55,56]and reduce the possibility of hemangiomas and other deleterious effects of high local expression of the longer isoforms.[44,46,47,82,178] It is unknown whether the choice of splice variant truly affects efficacy or adverse effects because the two have not been directly compared in a clinical setting, and the mouse equivalent of VEGF121 is still capable of causing highly localized effects on capillaries.[48] Nonetheless, the angiogenic effects of VEGF121are similar to those of VEGF165, and the short isoform has been tested clinically by injection of adenovirus via mini-thoracotomy. The first attempt was a Phase I trial that showed a trend toward improvement of angina symptoms and exercise tolerance, but improvement could not be concluded in the Phase I setting.[55] In a subsequent larger test from different investigators (the REVASC trial[56]), which was a randomized, open-label Phase II study, the exercise time to 1 mm ST depression was significantly greater at 26 weeks. This study was somewhat hindered by its open-label design, which was unavoidable due to the invasiveness of the surgical delivery route and the ethical concerns surrounding such invasive procedure in the placebo group.

Another member of the VEGF family, VEGF-C (called VEGF-2 in some of the earlier papers), plays an important role in lymphangiogenesis but has also been one of the more promising candidates for therapeutic angiogenesis. VEGF-C plasmid delivery by NOGA-guided catheter was initially tested in a controlled Phase I pilot trial[21] and a subsequent Phase I/IIa trial in patients with chronic myocardial ischemia who were not candidates for revascularization.[22] The Phase I trial was promising and, while such trials are not designed to demonstrate efficacy, it is interesting that this single-blind trial showed an initial placebo effect that reduced angina symptoms equally in the VEGF-C and placebo groups, which subsequently diverged and the experimental group continued to show reduced angina symptoms while the placebo group's angina worsened again.[21] The Phase I/II trial also resulted in an improvement in CCS angina class after 12 weeks that was significantly better in the VEGF-C group than the placebo group.[22] This led to a larger multicenter Phase IIb trial that planned to enroll ~400 subjects with placebo and three different dosages of VEGF-C plasmid. However, the earlier trials had been conducted with the NOGA system, which was not widely distributed and it was difficult to supply the systems and necessary expertise to the large number of medical centers that would be involved in this larger trial. The Phase IIb study was therefore initiated using the Stiletto catheter system. This trial was ultimately suspended due to what have been described as catheter-related complications, and the data remain unpublished at this time.[13] Unfortunately, the inertia and hurdles that must be overcome for the organization and sponsorship of such a trial can be significant in the face of ambiguous prior results, and this potentially promising therapeutic avenue may remain a question mark for the foreseeable future.

The use of FGF for myocardial gene therapy has also shown potentially promising results for which confirmation has remained elusive. After several promising animal experiments using FGF gene delivery (described above), FGF4 gene therapy was evaluated in the AGENT (Angiogenic Gene Therapy) trials; which evaluated intracoronary adenoviral delivery of the human FGF4 gene (Ad5FGF4) in patients with symptomatic CAD. The AGENT Phase I/IIa and AGENT-2 Phase IIb trials were randomized, double-blind, placebo-controlled trials that demonstrated that Ad5FGF4 was safe and showed positive effects on ETT and myocardial perfusion defect size.[58,59] Subsequently, the AGENT-3 and AGENT-4 Phase IIb/III studies were larger trials with similar designs; AGENT-3 was in the US and AGENT-4 was in Europe.[60] Both trials were ended prematurely because an interim analysis of AGENT-3 indicated that a significant difference in ETT was unlikely to be achieved. Because of the similar design, the data from these two trials were pooled for analysis. As in the case with the VEGF trials, the placebo effect was substantial and prevented a significant difference in ETT and CCS angina class from being detected. However, subgroup analysis indicated that the placebo effect was disproportionally large in the males and extremely low in the females, and the female subgroup showed a significant difference in total ETT time, time to 1 mm ST-segment depression, time to onset of angina and CCS angina class. Despite these promising findings, the stated goal was to evaluate the effects on the total population. Moreover, the subgroups were naturally smaller than the total, and presumably under-powered for statistical significance. Therefore, as the authors of the pooled analysis pointed out,[60] the results of this subgroup analysis could only be hypothesis-generating, and a well-designed study evaluating Ad5FGF4 in women was required. At this time, follow-up studies in the US and Russia are planned to address these observations.

GENE THERAPY FOR CHRONIC HEART FAILURE

Up to this point, all cardiac gene therapy trials have been aimed at therapeutic angiogenesis. However, other targets have been considered for the treatment of chronic heart failure, including β-adrenergic signal transduction[180-183] and Ca^{2+} reuptake into the sarcoplasmic reticulum.[184-190] In particular, the first gene therapy clinical trial for heart failure is currently underway, a Phase I/II trial evaluating the AAV-mediated delivery of the gene encoding the sarcoplasmic/endoplasmic reticulum Ca^{2+}-ATPase 2a isoform (SERCA2a).[62] SERCA2a is involved in the return of calcium ions to the sarcoplasmic reticulum in cardiomyocytes after a contraction/relaxation cycle, a process that appears to be impaired in heart failure patients.[191,192] Referred to as the calcium upregulation by percutaneous administration of gene therapy in cardiac disease (CUPID) trial, this approach delivers an AAV1 vector carrying the SERCA2a gene through a coronary artery infusion. While it is too early in the trial to know the results as this chapter is being written, the trial represents two milestones for the field by its very nature: the use of AAV rather than adenovirus or plasmid, and the targeting of a mechanism of contractility in the cardiomyocytes rather than inducing growth of blood vessels or influencing their physiology. Similarly, a variety of hybrid cell/gene therapy approaches are at various stages of testing, such as the REGEN trial, in which myoblasts isolated from skeletal muscle of congestive heart failure patients are engineered to express SDF-1 and implanted into the heart in an attempt to recruit therapeutic endogenous cells to the deficient regions.

CONCLUSION

Gene therapy for cardiac disease is still in its infancy. The approaches tried up to this point (2010) are all based on constitutive promoters that are not influenced by physiology or the need for the therapeutic gene product. Viewed in the terms of the development of heart transplantation for comparison, it is as if a rudimentary device is being spliced into the circulation at a random and variable location that pumps blood at a constant volume and rate regardless of the surrounding conditions, a primitive phase. The evolution of cardiac gene therapy will presumably move toward much more flexible and sophisticated manipulation of gene expression before it becomes a mature part of the clinical repertoire.

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Chapter 119

Sleep and the Heart

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Chapter Outline

- Physiologic Sleep
- Effects of Non-rapid Eye Movement Sleep on Cardiovascular Physiology
- Effects of Rapid Eye Movement Sleep on Cardiovascular Physiology
- Arousal
- Arrhythmias and Sleep
  - Heart Rate Variability
  - Bradyarrhythmias
  - Nocturnal QT Interval Changes
  - Sudden Infant Death Syndrome
  - Ventricular Arrhythmias
  - Brugada Syndrome and Sudden Unexplained Nocturnal Death Syndrome
  - Atrial Fibrillation
- Sleep Disordered Breathing
  - Obstructive Sleep Apnea
  - Effects of Obstructive Sleep Apnea on Cardiovascular Physiology
- Diagnosis of Sleep Apnea
  - Screening Questionnaires
  - Overnight Oximetry
  - Polysomnography
- Treatment of Obstructive Sleep Apnea
  - Obesity and Sleeping Position
  - Continuous Positive Airway Pressure
  - Oral Appliances and Surgery
- Central Sleep Apnea
  - Heart Failure
  - Treatment of Central Sleep Apnea

PHYSIOLOGIC SLEEP

Interest in the mysteries of sleep spans the ages. Some of the world's greatest philosophers and scientists have sought to explain its functions and implications. The invention of electroencephalography (EEG) by German psychiatrist Hans Berger in 1928 allowed scientific categorization of sleep and its various phases. Normal human sleep can be divided into rapid eye movement (REM) sleep characterized by desynchronized EEG signals, muscle atony and dreaming, and non-rapid eye movement (NREM) sleep characterized by synchronous EEG patterns. Humans begin sleep with NREM and after progressing through deeper NREM stages (Stages II, III and IV), the first episode of REM sleep is reached (approximately 80–100 minutes after initiation of sleep).[1] Subsequently, the cycles of NREM and REM occur, each lasting approximately 90 minutes. NREM constitutes the majority of sleep time (approximately 75%) while REM comprises the remaining quarter.

EFFECTS OF NON-RAPID EYE MOVEMENT SLEEP ON CARDIOVASCULAR PHYSIOLOGY

Non-rapid eye movement sleep—sometimes also called "the quiet sleep"—consists of four distinct stages during which the frequency of EEG activity decreases and its amplitude increases.[2] Deeper sleep has been correlated with a substantial drop in heart rate, blood pressure and sympathetic nerve activity (Fig. 1).[3] Arterial blood pressure nadir usually occurs during Stages III and IV, and the timing is likely related to the reduction in sympathetic tone during these deep NREM stages.[4] Studies focusing on RR intervals during NREM have identified an increase in high frequency power of RR variability with concomitant decrease in low frequency power.[5] The extent of these changes progressively increases from Stage I to Stage IV and suggests an increase in vagal output, as well as decrease in sympathetic output during deeper NREM sleep.[6]

EFFECTS OF RAPID EYE MOVEMENT SLEEP ON CARDIOVASCULAR PHYSIOLOGY

Even though the tone of the voluntary muscles is suppressed during REM sleep, the brain is very active. The majority of people woken up from REM sleep report dreaming (compared to only 10–15% in NREM),[7] and the emotions expressed in these dreams are mostly filled with anger or fear.[2] The brain's increased excitability during REM leads to episodes of sympathetic and vagal instability which may produce erratic cardiac function (Fig. 1).[8] When the underlying vagal influence predominates, the cardiovascular system is more prone to bradyarrhythmias such as sinus pauses, and first degree as well as second degree atrio-ventricular (AV) block.[9] When the parasympathetic state becomes interrupted by spikes and bursts of sympathetic activity, increased heart rate and blood pressure may occur. Sympathetic nerve activity during REM sleep rises to twice the levels seen in wakefulness, leading to consequent

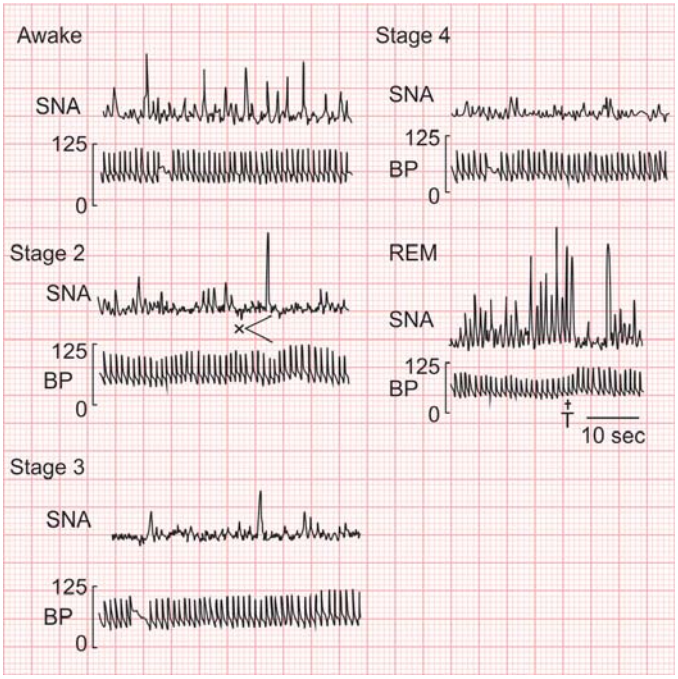


FIGURE 1: Blood pressure (BP) and sympathetic nerve activity (SNA) in one subject during wakefulness, stages 2, 3 and 4 of non-rapid eye movement (NREM) sleep, and during rapid eye movement (REM) sleep.[3] As the subject progresses from wakefulness through the NREM stages, recordings show reduced heart rate, BP, BP variability and SNA. This trend is reversed in REM, during which heart rate, BP and BP variability increase. SNA during REM increases both in frequency and amplitude (*Source:* Modified from Somers VK, Dyken ME, Mark AL, et al. Sympathetic-nerve activity during sleep in normal subjects. N Engl J Med. 1993;328:303-7)

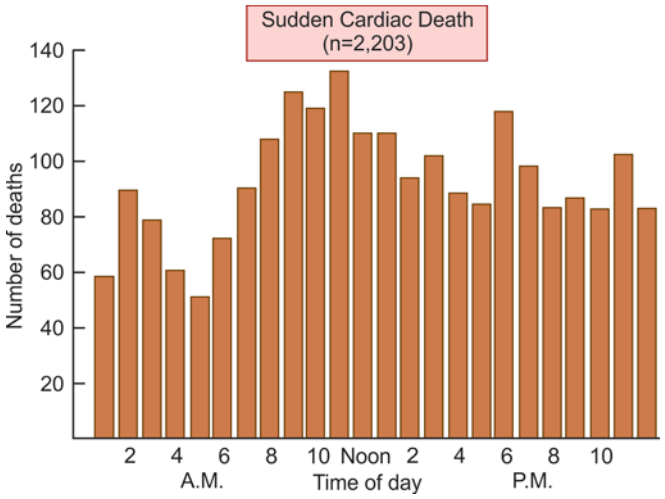


FIGURE 2: Incidence of sudden cardiac death plotted against the time of the day. Diurnal variation of out-of-hospital arrests has been reported in these 2,203 individuals who died in Massachusetts in 1983. (*Source:* Modified from Muller JE, Ludmer PL, Willich SN, et al. Circadian variation in the frequency of sudden cardiac death. Circulation. 1987;75:131-8)

increase in average blood pressure related to the higher sympathetic drive.[3,10] This autonomic and hemodynamic stress has been proposed as a potential trigger for adverse cardiovascular events.[3] It is important to realize that any studies focusing on REM sleep should pay close attention to the profound diversity of autonomic processes during this dynamic sleep period, that is, tonic and phasic epochs during REM should be studied separately especially when assessing their hemodynamic effects.

AROUSAL

Arousal from sleep is an important protective mechanism that allows an animal (or human) to escape or confront intruding danger (or an alarm clock). Naturally, this "fight or flight" response leads to an increase in heart rate and blood pressure. Arousals related to acoustic signals show especially significant changes in these variables, as well as alterations of pulse transit time and skin blood flow.[11,12] In canines, these arousal-related hemodynamic effects seem to be mainly influenced by a sudden withdrawal of parasympathetic tone but whether this finding applies completely to humans is not clear.[13] The arousal-related increases in blood pressure and heart rate coincide with increases in sympathetic traffic, suggesting a very rapid reset of the baroreflexes.[14]

All the above arousal-related mechanisms could be seen as part of a multifaceted preparation for a rapid assumption of standing posture; however, the question arises as to whether in some patients these same processes could contribute to the development of pathological stress, manifested by an increased incidence of adverse cardiovascular events in the early hours of the morning after waking from sleep (Fig. 2).[2]

ARRHYTHMIAS AND SLEEP

HEART RATE VARIABILITY

Heart rate and respiratory activity are physiologically coupled during sleep, and together they produce a near sinusoidal modulation.[15] In healthy individuals the heart rate increases temporarily during inspiration (sinus arrhythmia), and this in consequence leads to briefly increased cardiac output. The lack of such heart rate variability has been associated with cardiovascular disease.[16]

BRADYARRHYTHMIAS

Sympathetic outflow during Stage IV of NREM sleep decreases to less than half of the wakefulness values.[3,17] Temporally related increases in vagus nerve activity help to set the stage for the occurrence of bradycardias, which may be particularly profound during transitions between NREM and REM sleep.[15] Benign asystoles can be found in the nocturnal electrocardiographic tracings of normal individuals as well as trained athletes, and common related rhythms include sinus pauses, prolonged AV conduction and Mobitz type I second degree AV block (Wenckebach).[15] Highly increased vagal tone has been implicated in prolonged sinus pauses (up to 9 seconds) in young adults.[9] It is thought that the surges of acetylcholine occurring during increased vagal activity could initiate vasoconstriction in patients with coronary artery disease via impairment of endothelium-derived relaxing factor release, but the clinical impact of this finding has yet to be clarified.[18]

NOCTURNAL QT INTERVAL CHANGES

The above bradycardias and autonomic fluctuations may conceivably lead to lethal arrhythmias in a subset of patients with the long QT syndrome, particularly LQT2 and LQT3. Of

importance is the fact that lethal arrhythmias in these patients tend to occur predominantly during sleep or rest.[15] Nocturnal bradycardias could also contribute to the occurrence of early after-depolarizations which would progress to torsades de pointes in those individuals carrying the appropriate predisposition (see below). More studies are needed to clarify the possible effect of nocturnal bradycardias on patients using medications with QT-prolonging effects.

SUDDEN INFANT DEATH SYNDROME

Unexpected death of an infant that remains unexplained even after thorough investigation which includes biopsy has been termed sudden infant death syndrome (SIDS). Other terms for a similar tragic event used around the world include "crib death", or "cot death". SIDS, which most commonly occurs during sleep, causes approximately 2,500 infant deaths annually in the United States, and ranks as the number one cause of death among infants between 1 week and 1 year of age.[15] Altered autonomic control during sleep (potentially as a consequence of a binding deficit in the arcuate nucleus) has been postulated as a significant factor in the development of SIDS.[19,20] Those who survive a SIDS equivalent have been shown to have autonomic instability during NREM sleep.[21] Prolongation of the QT interval may play a role in SIDS, as was suggested by an observational study of over 34,000 infants.[22]

VENTRICULAR ARRHYTHMIAS

In general, the incidence of ventricular arrhythmias reaches a trough during sleep hours, which is consistent with observations of decreased nocturnal occurrence of myocardial ischemia or sudden cardiac death (SCD).[23,24] Nevertheless, approximately 15% of all SCDs occur during the night, which translates to an annual rate of nearly 50,000 night-time SCDs in the United States. The hourly distribution of these nocturnal deaths is uneven throughout the night suggesting physiological triggering (Fig. 2).[15,25] Surges of sympathetic neural activity during REM sleep could contribute to these nocturnal events, especially in patients with pre-existing cardiovascular pathology.[24] It has also been reported that the decrease in nocturnal sympathetic activity is altered in those with cardiovascular pathologies, such as coronary artery disease or myocardial infarction.[24,26] Sympathetic drive could theoretically increase any predisposition to ventricular tachyarrhythmias. Whether such adverse arrhythmic events could be triggered by intense anger or fear often experienced in dreams during REM sleep is not known. However, such emotions have been linked to the onset of myocardial infarction and sudden death during wakefulness.[27]

BRUGADA SYNDROME AND SUDDEN UNEXPLAINED NOCTURNAL DEATH SYNDROME

Brugada syndrome was first described in 1992[28] in patients with recurrent aborted sudden death, structurally normal hearts and classic electrocardiographic changes (ST elevation in anterior leads), and was later found to cause adverse outcomes via triggering of ventricular tachyarrhythmias during sleep.[29,30] The Brugada syndrome is thought to cause 20% of SCDs in patients who suffer such fatal episodes despite having structurally normal hearts.[31] Even though mutation of the sodium channel on the SCN5A gene has already been linked to the Brugada syndrome, identification of other mutations will likely continue to emerge.[15] Recent pilot studies suggest that the presence of sleep disordered breathing (SDB) may be common in Brugada patients, and that the worrisome ST segment changes may occur more likely during REM sleep or within 1 minute of an arousal.[32]

Sudden unexplained nocturnal death syndrome (SUNDS) likely represents a disorder very closely related or perhaps identical to the Brugada syndrome. It was described in Southeast Asian men under various names including lai-tai ("sleep death", Laos), pokkuri ("sudden and unexpected death", Japan) and bangungut ("to rise and moan in sleep", Philippines).[15] SUNDS victims were found to have developmentally altered pathways of the cardiac conduction system, and the vagal tone of those who survived SUNDS was lower compared to healthy controls.[33,34]

ATRIAL FIBRILLATION

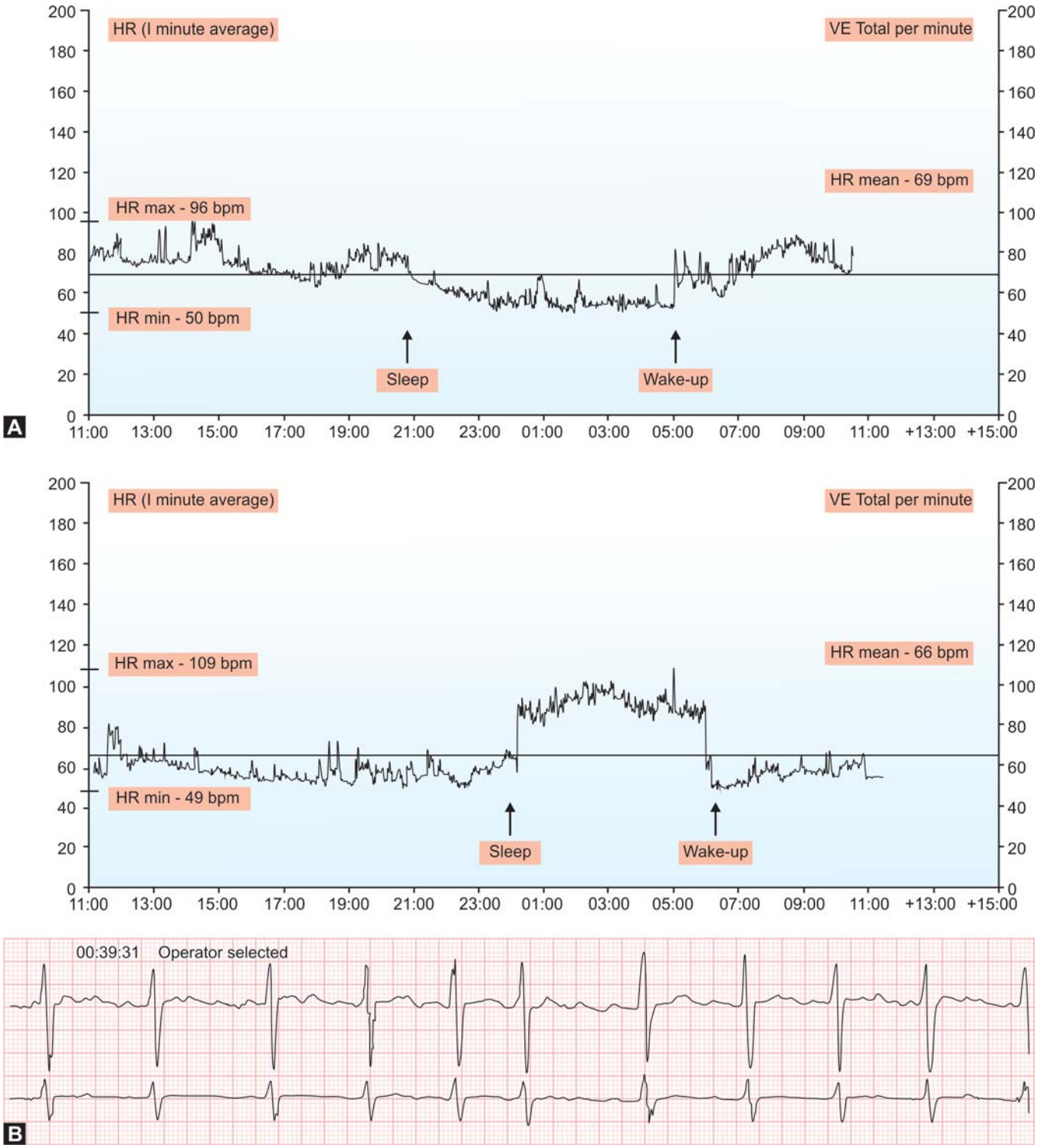
Nocturnal onset of atrial fibrillation may manifest as an increase or irregularity of heart rate (Figs 3A and B).[35] Increased peak vagal activity during sleep in some individuals was proposed as a likely culprit, and studies of heart rate variability are in support of this theory, coining the term "vagally mediated atrial fibrillation".[35-37] Complex interactions between the parasympathetic and the sympathetic autonomic nervous system likely contribute to altered intra-atrial conduction via changes in atrial refractoriness and repolarization dispersion.[15] The atrial fibrillation has also been closely linked with obstructive sleep apnea (OSA) (see below).

SLEEP DISORDERED BREATHING

Sleep disordered breathing constitutes an important connection between sleep and cardiovascular pathology. Its prevalence in the general population is strikingly high, affecting 24% and 9% of middle-aged men and women respectively.[38] Characteristic of SDB is the cessation or decrease in respiratory airflow during sleep, leading to a fall in peripheral oxygen saturation of at least 4%. The number of these repetitive interruptions of ventilation divided by the length of sleep (in hours) defines the apnea-hypopnea index (AHI). A diagnosis of SDB is given to patients who are found to have AHI greater than or equal to 5. Based on the mechanism of airflow cessation, SDB can be divided into two categories: (a) OSA and (b) central sleep apnea (CSA).

OBSTRUCTIVE SLEEP APNEA

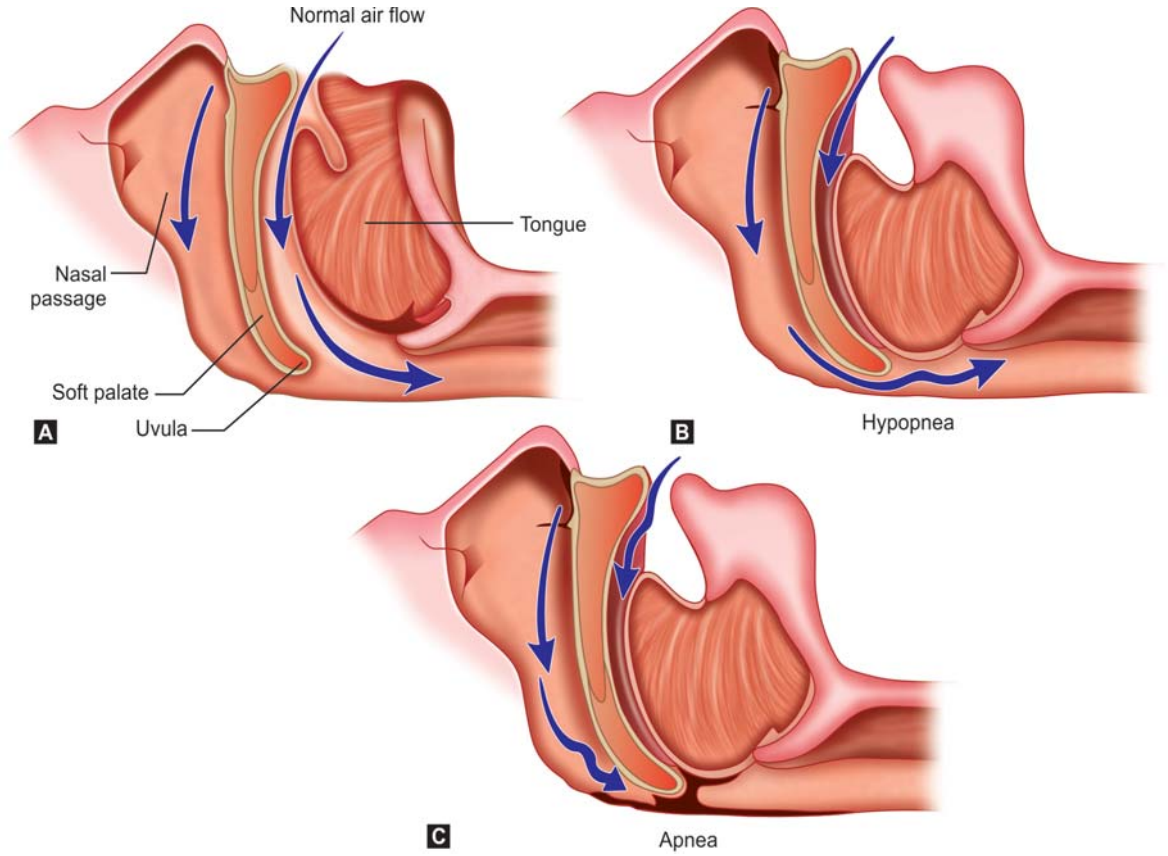
Obstructive sleep apnea occurs when tissue around the upper airway collapses as a result of inspiration in the setting of decreased muscle tone (Figs 4A to C). This results in partial or complete obstruction despite an increased ventilatory effort.[39] A complete cessation of airflow lasting greater than or equal to 10 seconds defines an apnea, while incomplete cessation of ventilation accompanied by an associated fall in peripheral oxygen saturation or arousal defines a hypopnea.[40] Such obstructions most commonly occur in the hypopharynx, nasopharynx and oropharynx as the airway in these segments lacks the support of bony structures and is mainly dependent



FIGURES 3A AND B: Sleep related paroxysmal atrial fibrillation.(A) Depicts normal circadian rhythm with sleep-related decrease in heart rate. (B) Shows a Holter recording from a patient with paroxysmal atrial fibrillation with a nocturnal onset which is then documented on the rhythm strip below. (*Source:* Modified from Singh J, Mela T, Ruskin J. Images in cardiovascular medicine. Sleep (vagal)-induced atrial fibrillation. Circulation. 2004;110:e32-3)

on muscle tone to remain patent. Obstructions often occur during REM sleep secondary to atony of the voluntary musculature positioned between the posterior nasal septum and the epiglottis. Certain anatomical variations increase the likelihood of obstruction: elongated soft palate, enlarged uvula, receding jaw and redundant peripharyngeal tissue.[39]

The prevalence of OSA is thought to be striking: mild OSA is present in approximately one in five adults, and moderate to severe OSA (with AHI $\geq$ 15) is found in one in fifteen.[40] The vast majority of these patients remain undiagnosed (see "Screening Questionnaires" under section "Diagnosis of Sleep Apnea"). Clinical presentation of patients with OSA may include



FIGURES 4A TO C: Partial and complete airway obstruction resulting in hypopnea and apnea respectively. (*Source:* Modified from Hahn PY, Somers VK. Sleep apnea and hypertension. In: Lip GYH, Hall JE (Eds). Comprehensive Hypertension. St Louis, MO: Mosby; 2007. pp. 201-7. Copyright Elsevier 2007)[40]

snoring, gasping for air, enlarged neck size and daytime somnolence, but a variety of additional signs and symptoms have been identified (Table 1).[40]

EFFECTS OF OBSTRUCTIVE SLEEP APNEA ON CARDIOVASCULAR PHYSIOLOGY

The pathological mechanisms that lead to increased cardiovascular morbidity in patients with OSA likely involve a combination of the following factors: OSA produces hypoxemia (peripheral oxygen saturation drops, to levels as low as 60% or less where oximeter readings are unreliable), retention of CO_2, chemoreflex mediated increases in peripheral vasoconstriction and changes in heart rate that may persist even during wakefulness.[3,41] Systemic blood pressure rises during the release of OSA episodes to values as high as 240/130 mm Hg.[42] Left ventricular and left atrial size and function have been shown to be acutely affected by simulated episodes of OSA in healthy subjects, likely secondary to marked changes in intrathoracic and transmural pressure.[43,44] Other measurements that have been correlated with the presence of OSA include increased cardiovascular variability, endothelin release, levels of proinflammatory molecules (interleukin-6, C-reactive protein), oxidative stress, endothelial dysfunction, insulin resistance and platelet activation with a prothrombotic milieu.[40]

TABLE 1

Signs, symptoms and risk factors for obstructive sleep apnea

- Disruptive snoring
- Witnessed apnea or gasping
- Obesity and/or enlarged neck size
- Hypersomnolence (not common in children or in heart failure)
- Other signs and symptoms include male gender, crowded-appearing pharyngeal airway, increased blood pressure, morning headahce, sexual dysfunction, behavioral changes (especially in children)

(*Source:* Reproduced with permission from Somers VK, White DP, Amin R, et al. Sleep apnea and cardiovascular disease: an American Heart Association/American College of Cardiology Foundation Scientific Statement from the American Heart Association Council for High Blood Pressure Research Professional Education Committee, Council on Clinical Cardiology, Stroke Council and Council on Cardiovascular Nursing. J Am Coll Cardiol. 2008;52:686-717)

Hypertension

Obstructive sleep apnea and hypertension commonly coexist; half of OSA patients suffer from hypertension, while approximately 30% of hypertensive patients have OSA.[45] Severity of OSA maintains a linear relationship with 24-hour blood pressure recordings even after adjusting for confounding factors.[46] In the Wisconsin Sleep Cohort, OSA was shown as an independent risk factor for the development of essential hypertension, independent of age, gender, body mass index and anti-hypertensive medications.[47] Several studies attempted to answer the question of whether treatment of OSA can improve

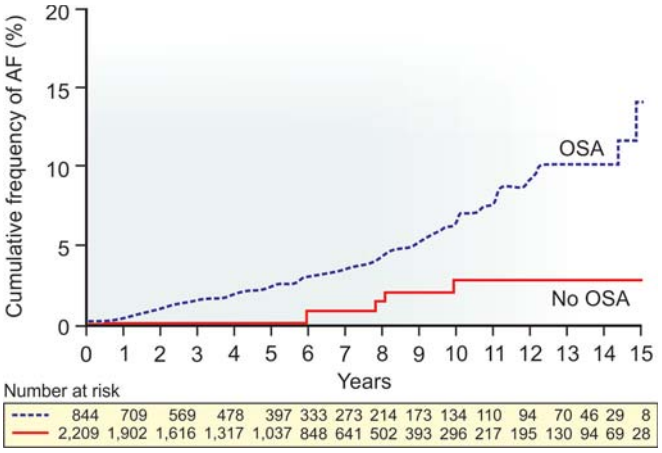


FIGURE 5: Plot of the cumulative frequency of new onset atrial fibrillation versus time after diagnostic polysomnography in years. This study included 3,542 adults younger than 65 years of age, and the follow-up averaged 4.6 years. (*Source:* Modified from Gami AS, Hodge DO, Herges RM, et al. Obstructive sleep apnea, obesity, and the risk of incident atrial fibrillation. J Am Coll Cardiol. 2007;49:565-71)

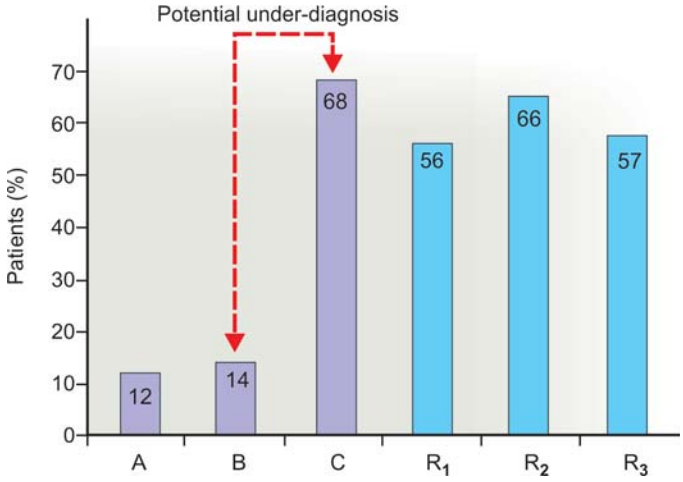


FIGURE 6: Differences between the likely prevalence of obstructive sleep apnea (OSA) in patients with acute myocardial ischemia and the documentation, diagnosis or investigation of sleep apnea during their hospital stay. (A) Documented or suspected OSA in patients with myocardial infarction (MI). (B) Documented or suspected OSA in MI patients recruited for polysomnography. (C) Prevalence of OSA in MI patients recruited for polysomnography. (R1–R3) Prevalence of OSA in studies of patients with acute coronary syndromes shown for comparison.[58-60] (*Source:* Modified from Konecny T, Kuniyoshi FH, Orban M, et al. Under-diagnosis of sleep apnea in patients after acute myocardial infarction. J Am Coll Cardiol. 2010;56:742-3)

blood pressure control. In a meta-analysis of these studies, the net reduction in blood pressure was statistically significant but modest (approximately 2 mm Hg).[48,49] The patient groups which benefited most from continuous positive airway pressure (CPAP) treatment included those with more severe OSA, difficult to control hypertension and higher CPAP compliance.

Atrial Fibrillation

Substantial evidence has recently emerged implicating OSA as a potential contributing factor to the development and recurrence of atrial fibrillation. Even though the Framingham Study did not specifically examine OSA as a risk factor for the incidence of atrial fibrillation, the results showed that obesity can serve as an important marker of progression to atrial fibrillation. Interestingly, after adjustment for left atrial enlargement that was also measured in this study, the significance of obesity on atrial fibrillation was lost. OSA has been linked to atrial enlargement, and the role of OSA in linking obesity to atrial fibrillation in this population remains to be determined.[50,51]
In over 3,500 adults who had no history of atrial fibrillation and who also underwent PSG, the severity of nocturnal hypoxemia was found to be an independent predictor of atrial fibrillation occurrence, but only in those less than or equal to 65 years old (Fig. 5).[52] The presence of postoperative atrial fibrillation may also be more common in patients with OSA.[53] In an observational study of patients who underwent the successful cardioversion for atrial fibrillation, the presence of untreated OSA was associated with an 82% risk of recurrence within 1 year, which is approximately twice the risk of those who were on CPAP treatment.[54] Even though the argument for screening and treating OSA in patients with atrial fibrillation is strong, no randomized study has been done to address whether treatment with CPAP provides mortality or morbidity benefit.

Coronary Artery Disease and Sudden Cardiac Death

Several aspects of OSA could theoretically predispose patients to an increased cardiovascular stress which could trigger myocardial ischemia: intermittent hypoxemia, acidosis, increased blood pressure, and sympathetic vasoconstriction.[40] Robust observational data suggest that the prevalence of SDB among patients with coronary artery disease is twice that of those without coronary disease.[55] Unfortunately, even among high risk cohorts, such as patients with myocardial infarction, the rate of diagnosis and treatment of SDB is suboptimal (Fig. 6) (for details see section "Diagnosis of Sleep Apnea").[56] SDB was associated with an increase in the composite endpoint of death, myocardial infarction and stroke at 5 years of follow-up; however, this association was not significant after adjustment for many confounding comorbidities.[57]

The timing of SCD may provide another argument supporting the role of OSA as a potentially lethal nocturnal stressor of patients with SCD. More than half of those with diagnosed OSA suffer the fatal cardiac event between the hours of 10 p.m. and 6 a.m., which is dramatically different from those without OSA who experienced the greatest likelihood of SCD between 6 a.m. and 11 a.m.[61]

Several large longitudinal studies concluded that patients with untreated OSA can expect an increased risk of death from cardiovascular disease, but data from a randomized trial examining the effect of CPAP on cardiovascular mortality and morbidity is lacking.[62]

Hypertrophic Cardiomyopathy

Sleep disordered breathing may be relatively common among patients with hypertrophic cardiomyopathy (HCM) as one study found that up to two-thirds of HCM patients have abnormal oximetry findings.[63] HCM patients with SDB are more likely to suffer from atrial fibrillation, which is a major determinant

of their morbidity and mortality.[64,65] The potential mechanisms likely lie in the associated increase in left atrial size which is a key contributor to propensity to atrial fibrillation, and which has been correlated with the presence and severity of SDB in patients with or without HCM.[64,66] Even though screening for OSA in this patient population presents a promising opportunity, data from randomized trials are needed to prove a potential beneficial effect of CPAP treatment on morbidity and mortality in this unique patient population.[67]

Stroke

The inherent selection biases of studies focusing on patients with stroke make an objective interpretation of these data challenging. Only stroke survivors can be studied, and the altered post-stroke performance could potentially affect the sleep study results, raising the question whether "stroke causes SDB or SDB causes the stroke". Many stroke patients have limitations in assuming certain body positions during sleep studies. Nevertheless, several plausible mechanisms could theoretically implicate OSA as a risk factor for stroke: blood pressure swings, hypoxemia, reduction in cerebral blood flow, altered cerebral autoregulation, impaired endothelial function, accelerated atherogenesis, and heightened prothrombotic and proinflammatory states.[40]

In one study the presence of severe SDB was associated with the occurrence of first time stroke, but a multivariate analysis adjusting for age, gender and body mass index did not reveal a statistically significant odds ratio.[68] A study of stroke patients followed over 10 years showed that patients with OSA incurred increased rates of death, and in this case the finding remained significant even after adjusting for potential confounders.[69] Other studies of stroke patients that focused on the success of rehabilitation noted that those with OSA had markedly reduced post-stroke survival and lower rehabilitation success, but whether treatment with CPAP can reverse this trend has not yet been established.[70,71] Additionally, the treatment of stroke patients with OSA presents challenging obstacles, and the compliance with and tolerability of CPAP is likely to be low.[72]

DIAGNOSIS OF SLEEP APNEA

Patients with diagnosed and treated sleep apnea likely represent only the "tip of the iceberg" as perhaps up to 85% of those with clinically significant and treatable OSA have not yet been diagnosed.[73,74] A striking under-diagnosis may exist even among certain high risk populations; several studies estimated the prevalence of OSA among patients with acute coronary syndrome to exceed 50%. However, only about 14% of such patients have documented diagnosis or investigation of OSA during their hospital stay (Fig. 6).[56] Methods available to screen and diagnose SDB range from highly affordable questionnaires, to the gold standard in SDB diagnosis–attended polysomnography (PSG). In order to select the method best suited for a given clinical scenario, it is crucial for the clinician to know the advantages and limitations of each of these tests.

SCREENING QUESTIONNAIRES

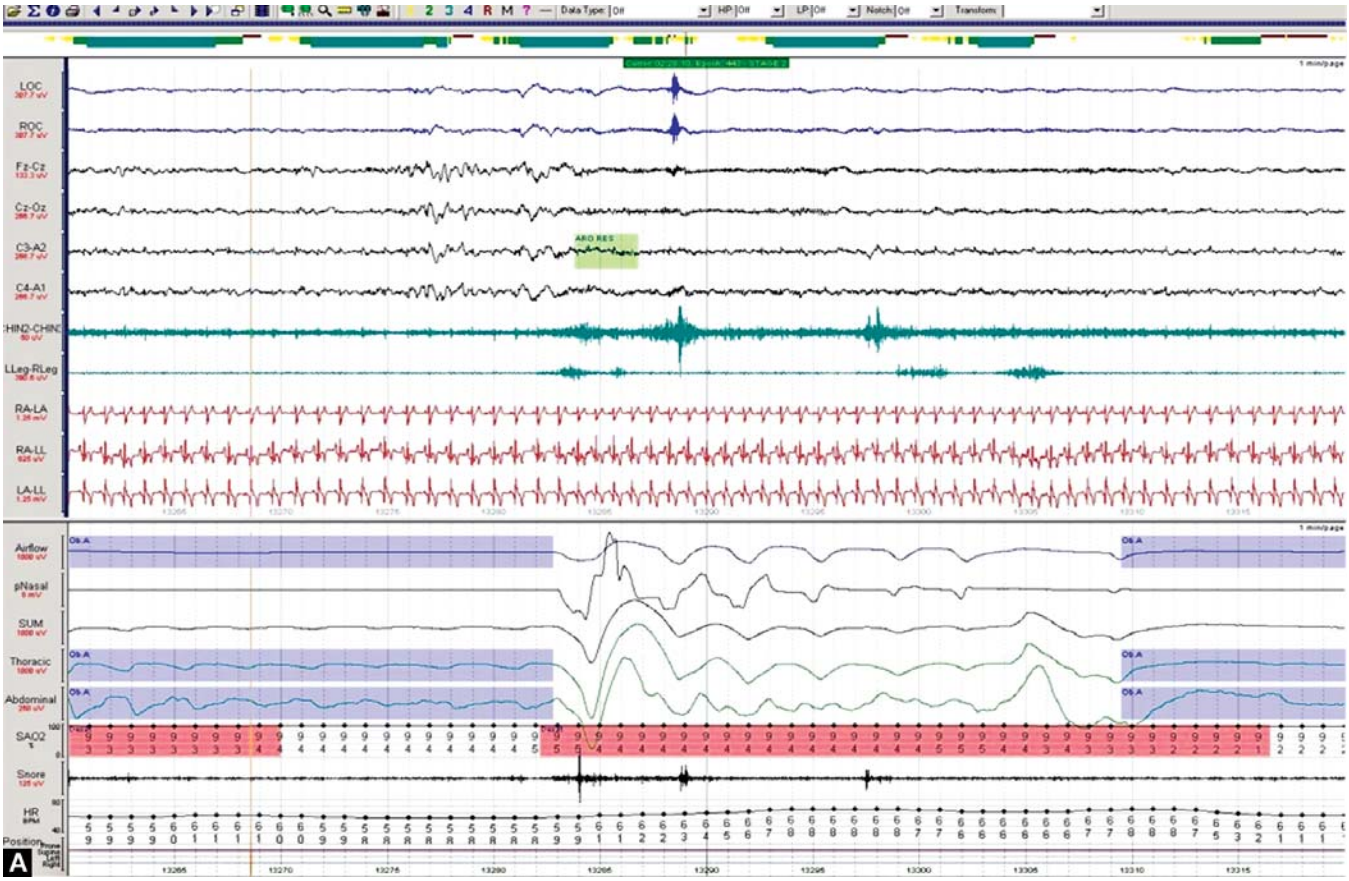
Patient characteristics which increase the likelihood of OSA being present include increased age, body mass index, neck circumference, presence of hypertension, loud snoring, and witnessed apneas.[75] Several dedicated questionnaires help gauge the various clinical manifestations of sleep apnea. The Epworth Sleepiness Scale determines patient's sense of sleepiness, using a standardized 24-point score which has been correlated with the severity of OSA. The Berlin Questionnaire incorporates additional characteristics such as body mass index, snoring severity and frequency, daytime somnolence (including falling asleep while driving), and the presence of hypertension. While economical and easy to perform, these methods do not have optimal sensitivity and specificity.

OVERNIGHT OXIMETRY

This relatively affordable, convenient and widely available tool in the diagnosis of SDB measures and records arterial oxygen saturation on a continuous basis during the night, and this tracing is later analyzed for the presence of oxygen desaturations of greater than or equal to 4% from a "floating baseline." Modern portable pulse oximeters can be taken home by the patient, and therefore allow for recording in the actual sleeping environment of each individual. High quality probes on the finger or ear should be used as these can deliver accurate values that differ from arterial blood gas probes by less than 0.5%.[76] The key measure from overnight oximetry is called the oxygen desaturation index (ODI), and is calculated by dividing the number of desaturations by the length of the recording in hours. Various cut-off values for ODI have been previously used to signify the presence of SDB, most commonly greater than or equal to 5 desaturations/hour, which is analogous to similar AHI cut-off values.[76] The main disadvantages of overnight oximetry include its inability to reliably distinguish between OSA and CSA, as well as its lower sensitivity and specificity in the diagnosis of SDB when compared to complete PSG.

POLYSOMNOGRAPHY

Attended overnight PSG constitutes the gold standard in the diagnosis of SDB, and it traditionally includes monitoring of brain waves by electroencephalogram, sound recording by microphone, respiratory movement of the chest and abdomen, naso-oral airflow, oxygen saturation by oximetry, heart rhythm by electrocardiogram, eye movement by oculogram, and muscle tone by submental and tibial electromyogram (Figs 7A and B).[39] In some sleep centers, "split-night" PSGs can be divided into the first half of the night during which the patient is being assessed for the presence and severity of SDB, and the second half during which CPAP treatment is applied with the purpose of finding an effective CPAP pressure (titration). Even though PSG offers the most complete data gathering modality it also carries some limitations including its cost (approximately $2,000), geographical and temporal availability, and also the potential artifact created by the difference in the sleeping environment in the sleep lab as compared to patient's home. In recent years, the development of portable systems that allow analysis of nocturnal respiration as well as cardiovascular function has brought to the market various other options which can help in situations where PSG is unobtainable or impractical.[77]





FIGURES 7A AND B: Polysomnography (PSG). (A) Recording of a sleep apnea episode in a standard PSG: tracings from top to bottom include electroencephalogram, electromyogram, electrocardiogram, airflow tracing, oxygen saturation, sound recording, heart rate and sleeping position type. (B) Sleep laboratory set-up. (*Source:* Mayo Foundation)

TREATMENT OF OBSTRUCTIVE SLEEP APNEA

OBESITY AND SLEEPING POSITION

The single most important modifiable factor in the treatment of OSA is obesity. Weight reduction via bariatric surgery has been shown to reduce or abolish OSA.[78] Obesity control via behavioral changes can help in prevention of OSA: a gain of 10% of body weight was reported to increase AHI by 32%, while 10% weight loss was estimated to reduce AHI by 26%.[79]

Some patients with OSA respond to a change in sleeping position and are labeled as having "positional apnea". Because OSA may lead to greater obstruction during sleep in a supine posture (on the back), a behavioral change that leads to the patient sleeping mostly in a lateral posture (on the side) can be effective. Such sleep position changes can be enforced with the use of an object (i.e. a tennis ball) sewn into the back of a nightshirt, or with the use of a positional alarm.[40]

CONTINUOUS POSITIVE AIRWAY PRESSURE

Positive airway pressure applied to a nasal mask effectively splints the nasopharynx and allows free passage of air even with relaxation of the surrounding muscles, hence preventing apneas. Even though CPAP has been shown to improve consequences of OSA such as daytime sleepiness, adherence to this therapy

remains an issue, especially in patients who do not perceive OSA symptoms as serious. Extra attention should be given to the selection of an appropriate mask, as well as to the correct choice of CPAP device (possible features include humidification, pressure ramp or autotitration). Some patients benefit from bilevel positive airway pressure. Adjustment of CPAP machines and masks are best performed in the sleep laboratory.

ORAL APPLIANCES AND SURGERY

Appliances that act via anterior mandibular repositioning can be offered to those patients who cannot tolerate CPAP. These adjustable devices can—when used regularly—anteriorly displace the lower jaw and hence increase the diameter of the pharyngeal airway.[80] Even though oral appliances may be preferred over CPAP by many patients, as reported by a recent analysis by the American Academy of Sleep Medicine, only approximately 52% of these devices appropriately relieve OSA.[81]

The potential surgical procedures serving as treatment for OSA include uvulopalatopharyngoplasty, modified uvulopalatopharyngoplasty with the use of CO_2 laser, and tracheostomy; however, their use and efficacy is rather limited.[40]

CENTRAL SLEEP APNEA

Central sleep apnea consists of a ventilatory cessation during sleep that lasts greater than or equal to 10 seconds and is secondary to a loss in respiratory effort.[40] The exact etiology of CSA has not been fully elucidated, and potential contributing factors include circulatory delay, CO_2 hypersensitivity, pulmonary congestion with related J-receptor stimulation, and adrenergic modulation of the chemoreflexes. CSA seems to be more common with increasing age: the prevalence of CSA with a severity of CSA index greater than or equal to 2.5 in general population was reported as 0%, 1.7% and 12% for men below 45, below 65 and above 65 years of age respectively; CSA with severity index greater than or equal to 20 was rarely seen in women, and in men it was reported only in those older than 65 years of age.[82,83]

Clinical presentation of patients with CSA may include paroxysmal nocturnal dyspnea, nocturnal episodes of witnessed breathing cessation, hypersomnolence, atrial fibrillation and, especially, concomitant congestive heart failure (Table 2).[40]

HEART FAILURE

The association of CSA with heart failure and left ventricular dysfunction has been reproducibly shown, but whether CSA constitutes a contributing factor or consequence of heart failure is not clear.[40] A common occurrence in heart failure patients is Cheyne-Stokes respiration (CSR) which manifests by a crescendo-decrescendo pattern of breathing. CSR likely results from a high-gain ventilatory control system with increased hypercapnic responsiveness, and from prolonged circulatory time.[40] Resting sympathetic activity, which is already elevated in heart failure patients, was found to be further increased in those with both heart failure and CSA.[84] OSA and CSA often coexist, and recent evidence suggests that nocturnal rostral fluid shift could constitute a contributing factor to both of these SDB types in heart failure patients.[85]

TABLE 2

Signs, symptoms and risk factors for central sleep apnea

- Congestive heart failure
- Paroxysmal nocturnal dyspnea
- Witnessed apnea
- Fatigue/hypersomnolence
- Other signs and symptoms include male gender, older age, mitral regurgitation, atrial fibrillation, CSR while awake, periodic breathing during exercise, hyperventilation with hypocapnia

(*Source:* Somers VK, White DP, Amin R, et al. Sleep apnea and cardiovascular disease: an American Heart Association/American College of Cardiology Foundation Scientific Statement from the American Heart Association Council for High Blood Pressure Research Professional Education Committee, Council on Clinical Cardiology, Stroke Council, and Council on Cardiovascular Nursing. J Am Coll Cardiol. 2008;52(8):686-717)

Whether CSA could pose an increased risk for the progression of heart failure has not been well established. When CSA was assessed along with various traditional markers of heart failure severity (including New York Heart Association class), the two most significant predictors of mortality were left atrial size and CSA severity.[86] Increased mortality and higher rates of cardiac transplantation have been reported in patients with CSA, but the question remains as to whether CSA plays a contributing role, or whether it is simply a marker of heart failure severity.[40]

TREATMENT OF CENTRAL SLEEP APNEA

Several studies attempted to answer the question of whether treatment of CSA improves outcomes of patients with heart failure. Smaller trials of CPAP reported improvements in left ventricular ejection fraction, mitral regurgitation, norepinephrine levels, quality of life, and combined 5-year mortality plus cardiac transplantation (although for this endpoint intention to treat analysis did not show a significant difference).[87-89] A large randomized multicenter trial of CPAP [Canadian positive airway pressure trial for patients with congestive heart failure (CANPAP)] suggested mild improvements of ejection fraction and nocturnal desaturation, but similar mortality and cardiac transplantation rates. This trial, however, identified an early difference in transplant-free survival favoring the control group.[90]

Adaptive servoventilation technology was designed to treat CSA by positive pressure on expiration while servo-controlling the inspiratory pressure. It has been suggested that servoventilation could be more effective than CPAP in the treatment of CSA, possibly due to better adherence.[91] Non-randomized studies with "as treated" analysis showed improvements in left ventricular function and quality of life in those CSA patients using servoventilation.[92]

Whether CPAP or adaptive servoventilation should be used for the treatment of CSA in heart failure patients, at what levels and for which exact indications continues to be under investigation.[40]

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Chapter 120

Integrative Cardiology: The Use of Complementary Therapies and Beyond

Kevin Barrows

Chapter Outline

- Non-conventional Therapies and Cardiology
- What is Integrative Medicine?
- What is Integrative Cardiology?
- Lifestyle Heart Trial
- What Other Integrative Medicine Therapies are Effective for Cardiovascular Conditions?
- Dyslipidemia
  - Diet
  - Exercise
  - Weight Loss
  - Botanical Medicines and Supplements
- Hypertension
  - Diet
  - Exercise
  - Weight Loss
  - Sleep
  - Mental Health
  - Mind-body Medicine
  - Botanical Medicines and Supplements
  - Whole Medical Systems
- Coronary Artery Disease
  - Diet
  - Exercise
  - Weight Loss
  - Sleep
  - Mental Health
  - Mind-body Medicine Therapies
  - Enhanced External Counterpulsation
  - Botanical Medicines and Supplements
  - Chelation
- Heart Failure
  - Diet
  - Exercise
  - Sleep
  - Mental Health
  - Mind-body Therapies
  - Thermal Vasodilation
  - Enhanced External Counterpulsation
  - Botanical Medicines and Supplements
- Botanical Medicines with Adverse Cardiovascular Effects

NON-CONVENTIONAL THERAPIES AND CARDIOLOGY

The use of non-conventional medical therapies is tremendously popular and growing in the United States with 38% of adults using some form of complementary and alternative medicine (CAM) according to the 2007 National Health Interview Survey.[1] Cardiovascular patients are no exception. Select surveys suggest half or more of cardiovascular patients are using CAM.[2,3] And yet one report reveals that cardiologists have little knowledge about CAM and harbor negative attitudes toward it.[4]

This situation begs the question: is it possible to use CAM in cardiology in a way that is evidence-based and integrates CAM therapies with the many effective and powerful conventional cardiovascular therapies? The answer is addressed by the field of integrative cardiology.

WHAT IS INTEGRATIVE MEDICINE?

Integrative Medicine is the integration of CAM and conventional medicine, but also much more. The majority of its foundational tenets are shared by conventional medicine. Integrative Medicine is evidence-based and patient-centered. It recognizes the importance of the relationship with the patient, seeing it as the central therapeutic element. It is holistic in its approach, assessing the mind, body, spirit, social, community and environmental dimensions of health. It strongly emphasizes foundational health practices such as nutrition, exercise, sleep and stress management. It aims foremost to prevent disease. It recognizes that the human being has a powerful, innate, spontaneous capacity for healing, and it identifies and removes obstacles to this natural healing capacity. It chooses the safest therapies first. It incorporates CAM modalities when clinically indicated, in a way that is safe and synergistic with conventional therapies.

According to the useful system of categorization proposed by the National Institutes of Health (NIH) [through the National Center for Complementary and Alternative Medicine (NCCAM)], CAM can be divided into the following five categories:

1. Biologically based therapies (e.g. use of natural products such as fish oil, probiotics, botanical medicines, etc.)

2. Mind-body medicine (e.g. biofeedback, meditation, hypnosis, guided imagery)
3. Manual medicine (e.g. osteopathy, chiropractic, massage therapy)
4. Energy medicine (e.g. reiki, therapeutic touch)
5. Whole systems (e.g. traditional Chinese medicine, ayurveda, homeopathy).

Some of the CAM therapies, especially some of the Whole Systems, are thousands of years old and as complete systems they include elements from all other categories. For example, traditional Chinese medicine uses acupuncture (which might be considered to be an energy medicine therapy), botanical medicines (biologically based therapies), an acupressure-based massage technique known as Tui Na (manual medicine) and Qigong (mind-body medicine).

WHAT IS INTEGRATIVE CARDIOLOGY?

Integrative cardiology is the application of Integrative Medicine principles to the field of cardiology. The Lifestyle Heart Trial is an instructional example.

LIFESTYLE HEART TRIAL

The Lifestyle Heart Trial led by Dr Dean Ornish is a powerful example of integrative cardiology. This is a rigorous randomized controlled trial with 5-year follow-up. The original trial, published in Lancet in 1990, demonstrated that reversal of coronary atherosclerosis can be achieved with comprehensive lifestyle changes and usual cardiologic care (excluding, importantly, lipid-lowering medications).[5] Forty-eight patients with 195 coronary lesions were randomized to either the 1-year intervention or usual care only. The intervention had multiple elements: low-fat vegetarian diet, smoking cessation, stress management training (yoga-based stretching, meditation, guided imagery and breathing) and moderate exercise. By the end of the trial the vast majority of patients in the experimental group showed angiographically proven regression of coronary atherosclerosis while the usual care group showed progression of coronary atherosclerosis. The effect was largest in those with lesions of 50% stenosis or greater.

Five-year follow-up of these patients showed extension of these findings, i.e. the experimental group showed further regression of disease and the control group showed further progression.[6] Furthermore the experimental group experienced half as many cardiac events compared to the control group in the 5-year period.

These trials demonstrate the tremendous potency of an approach where CAM and conventional medicine are integrated together. In fact the Centers for Medicare and Medicaid Services (CMS) have determined that the Ornish Program for Reversing Heart Disease meets the criteria for an intensive cardiac rehabilitation (ICR) program and thus effective from January 1, 2010; Medicare Part B covers this program for qualified patients.

WHAT OTHER INTEGRATIVE MEDICINE THERAPIES ARE EFFECTIVE FOR CARDIOVASCULAR CONDITIONS?

There are many other integrative therapies that have evidence of efficacy for cardiovascular conditions. Below are presented some of the integrative therapies for the most common cardiovascular conditions: Dyslipidemia; Hypertension; Coronary artery disease (CAD) and heart failure (HF). Data are first discussed for foundational health practices (diet, exercise, sleep, stress, mental health, spirituality, etc.) because they are the most fundamental part of the Integrative Medicine approach. Specific integrative therapies, classified according to the NCCAM system (see above), are then reviewed. When botanical medicines or supplements are introduced for the first time in this chapter, the following aspects of each product are briefly summarized: history of the substance, mechanism of action, clinical research, important interactions or side effects and dosage.

DYSLIPIDEMIA

DIET

The following is a brief summary of the effect of whole diets and specific foods on dyslipidemia. With respect to whole diets controversy continues over which are the most successful whole dietary changes for dyslipidemia. Favorable data have been published for a vegetarian diet, low-fat diet, a diet which substitutes polyunsaturated or monounsaturated fat for saturated fat, diets which replace or eliminate trans fats, low-carbohydrate diet and others. Noteworthy also is the Mediterranean Diet which has demonstrated strongly favorable clinical endpoints (see "Coronary Heart Disease–Diet"). The diet that may be most consistent with Integrative Medicine is the Portfolio Diet. This approach begins with a baseline healthy diet for dyslipidemia (e.g. primarily plant-based ATP step III diet) and integrates additional specific foods that have been shown to improve dyslipidemia (soluble fiber, soy, almonds and plant sterols). Outcomes from the Portfolio approach have been excellent and comparable to low-dose statin therapy.[7,8]

In addition to whole diets there are several specific foods that have been shown to effectively treat dyslipidemia:

- Plant sterols[9]
- Soy[10] (Fig. 1)
- Nuts[11] (Fig. 2)
- Barley[12]
- Oats[13]
- Alcohol[14] [increases high density lipoprotein (HDL)]
- Fish (reduces triglycerides)[15]
- Berries (increases HDL)[16] (Fig. 3)



FIGURE 1: Soy



FIGURE 2: Nuts



FIGURE 3: Berries

- Kale juice (increases HDL)[17]
- Olive oil[18]
- Cocoa[19]

EXERCISE

Studies consistently show that aerobic exercise reduces serum triglycerides and increases HDL cholesterol.[20] This effect is independent of weight loss, although with weight loss the effect is potentiated. There is also a dose-response relationship between exercise and improvement in triglycerides and HDL cholesterol, with greater amount of exercise or more intense exercise resulting in greater lipid benefits. Aerobic exercise can also benefit total and low-density lipoprotein (LDL) cholesterol levels in some patients although results of these studies are not as universally positive.

WEIGHT LOSS

For people who are overweight, weight loss can potentially improve all of the lipid parameters.[21] The degree of improvement in total and LDL cholesterol and triglycerides is proportional to the amount of weight lost.

BOTANICAL MEDICINES AND SUPPLEMENTS

Fish Oil

Health benefits from fish oil come from its content of the essential omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). DHA and EPA can be acquired by consuming cold water fatty fish such as herring, sardine, anchovy, kipper, menhaden, salmon and trout. The most potent lipid-related effect that fish oil has is to lower triglycerides. There are multiple mechanisms by which fish oils are thought to lower triglycerides, most notably by decreasing synthesis and secretion of very low-density lipoproteins (VLDLs) and by increasing VLDL apolipoprotein B secretion.

There are dozens of clinical trials that have proven the effectiveness of fish oil for reducing serum triglycerides.[22] The magnitude of benefit can be comparable to pharmaceutical treatment. Additional clinical trials examining the combination of a statin with fish oil have shown added benefit on lipid profiles.

Supplemental omega-3 fatty acids are safe with gastrointestinal (GI) disturbances (e.g. nausea, halitosis, oily stool) being the most commonly reported side effect. Occasionally patients experience a slight increase (up to 5%) in LDL cholesterol levels, but this appears to be due to increased size and buoyancy of LDL particles. An even smaller rise in HDL can occur with fish oil. There is a theoretical risk of increased bleeding for patients on anticoagulant or antiplatelet drugs due to fish oil's antiplatelet effects; however, this only appears relevant at doses of 3 gm/day or higher of fish oil. Research examining fish oil's effect on INR and bleeding in patients taking warfarin does not show a clear effect. It is likely that the absorption of fish oil is reduced in patients taking orlistat.

There is a linear dose-response relationship for triglyceride lowering with benefit observed from doses as low as 2 gm of omega-3 fatty acids per day. A dose of 4 gm/day can lower triglyceride levels by 25–40%. The American Heart Association recommends that people with hypertriglyceridemia consume 2–4 gm of omega-3 fatty acids per day and there is a proprietary formulation of fish oil that is FDA-approved for use in patients with hypertriglyceridemia. Fish oil supplements should be dosed based on their content of EPA and DHA.

Red Rice Yeast

Red rice yeast (often called "red yeast rice") is the product of rice fermented with *Monascus purpureus* yeast and has been used in China since at least 800 AD as part of Chinese medicine to enhance circulation and for other indications. Red rice yeast contains a family of naturally occurring substances called monacolins that have 3-hydroxy-3-methyl-glutaryl (HMG)-CoA reductase inhibitor activity. One of these compounds is lovastatin. These compounds constitute about 0.4% of red rice yeast. A typical dose delivers the equivalent of approximately 4 mg of lovastatin daily. The fact that so little lovastatin is present, and that red rice yeast also contains beta-sitosterol, isoflavones and monounsaturated fatty acids, suggests this medicine works to lower cholesterol through multiple mechanisms.

There are several randomized control trials (RCTs) from the US examining this product's capacity to improve dyslipidemia and over one-hundred from China. The majority of trials show total and LDL cholesterol-lowering benefit.[23] A review and meta-analysis of Chinese RCTs, including almost 10,000 patients, similarly concluded that red rice yeast lowers total and LDL cholesterol.[24] Interestingly one trial examined patients who

had discontinued statin therapy because of myalgias and found that the majority tolerated treatment with red rice yeast while achieving significant reductions in LDL-C.[25] One large Chinese RCT of 591 diabetics also looked at clinical outcomes and found reduced CAD events in the red rice yeast group.[26] There are two things that hamper clinical use of this product in the United States. First, the Food and Drug Administration (FDA) considers these products to be unapproved drugs when they contain statins. This has limited their availability in the United States. Second, due to lack of standardization, the content of lovastatin and other monacolins can vary widely between products. Nevertheless, although beyond the scope of this chapter, it is possible to use a reliable red rice yeast product for clinical management of hyperlipidemia in the United States.

In controlled trials reported side effects are headache and GI discomfort. Because red rice yeast contains statins and statin-like compounds; it must be assumed that it is capable of having similar interactions and similar side effects as low-dose pharmaceutical statins. For example, there have been case reports of myopathy and rhabdomyolysis. Some products contain citrinin, a mycotoxin sometimes produced by *Monascus purpureus* during fermentation that may have nephrotoxicity. It is recommended to use an independently tested red rice yeast product that is proven to be free of citrinin.

Dosages used in studies range 1,200–2,400 mg/day (daily or twice daily dosing).

In summary, red rice yeast appears to be an effective agent for lowering total and LDL-cholesterol and may have a role in pharmaceutical-statin-intolerant patients; however, a high-quality independently tested product must be used.

Plant Stanols and Sterols

Plant stanols and sterols occur naturally in various plants and as such they are available through diet. They can be ingested as supplements in the form of enhanced margarine, or other enhanced food products, and as tablets. They inhibit cholesterol absorption from the GI tract by displacing cholesterol from mixed micelles. Beta-sitosterol may also lower cholesterol by increasing bile acid secretion.

There are many high-quality studies, including thousands of patients, show plant stanols lower total and LDL cholesterol.[27,28] There are also good studies showing this is an effective adjunctive therapy to statins.[29] There are no studies, however, that adequately assess clinical endpoints such as reduced incidence of CAD.

Plant stanols and sterols naturally occur in foods and are generally recognized as safe. They are very well tolerated. There has been concern raised that they might impair absorption of fat-soluble vitamins and beta-carotene; however, research on this question has been inconclusive. For this reason, some clinicians recommend increased intake of beta-carotene rich foods or supplementation with a multivitamin for patients taking therapeutic doses of plant sterols and stanols. The rare condition sitosterolemia, an inherited lipid storage disease, is a contra-indication to plant stanol/sterol use. Primary biliary cirrhosis is a relative contraindication.

Plant sterols in the form of margarine spreads have been shown effective in a dose range of 1.6–9 gm of phytosterols per day. Beta-sitosterol doses range from a few hundred milligrams to several grams per day.

Psyllium

Psyllium is the common name of plants in the genus *Plantago*. Husks of the seeds of *Plantago ovata* are widely used medicinally for constipation, hyperlipidemia and other indications. Psyllium decreases serum cholesterol levels by binding dietary fats in the GI tract and decreasing systemic absorption. Bile acid excretion of cholesterol in the feces is also increased and enterohepatic recirculation is decreased. Furthermore in response the liver uses more cholesterol to make bile acid.

Dozens of RCTs and at least three meta-analyses prove the efficacy of psyllium to reduce total and LDL cholesterol levels, both in the 5–10% range.[30,31] Benefit is additive with statin medications.[32]

Minor GI side effects from psyllium are common, e.g. flatulence, diarrhea, constipation. Beginning with a low dose and very slowly titrating up is essential, as is adequate fluid intake daily. Rarely, patients can have allergic reactions to psyllium. Psyllium can reduce absorption of iron from iron supplements if taken concurrently. A similar effect should be assumed with lithium and calcium.

For hyperlipidemia a total daily dose of approximately 10 gm/day has been shown efficacious. Higher doses have also been studied and proven beneficial.

Beta-Glucan

Beta-glucan is a soluble fiber from the cell walls of plants and microscopic organisms. It is found especially in whole grains such as oats and barley. Most supplements are yeast-derived (*Saccharomyces cerevisiae*). Beta-glucan lowers cholesterol by blocking cholesterol absorption at the luminal surface of the intestinal mucosa, forming a physical barrier. Like psyllium, beta-glucan may also work by binding bile acids in the intestinal lumen.

Although not as extensively studied in clinical trials as psyllium, and although the results are not as universally positive as is the case for psyllium, beta-glucan supplementation does appear to modestly reduce total and LDL cholesterol levels, usually in the 2–8% range.[33,34]

No adverse effects have been reported with oral beta-glucan supplementation.

Benefit has been found for total and LDL cholesterol with beta-glucan at total daily doses ranging 3–15 gm.

Artichoke Leaf Extract

Artichoke is one of the oldest medicinal plants. It was used by the ancient Egyptians, Greeks and Romans. In traditional European medicine, it was used as a choleretic. In the middle of the 20th century, cynarin was isolated from the leaf of the artichoke plant. Synthetic cynarin preparations were then used as a drug to stimulate the liver and gallbladder and to treat elevated cholesterol from the 1950s to the 1980s.[35,36] Artichoke leaf extract does indeed stimulate bile flow.[37] Additional mechanisms of action which may account for lipid-lowering effect are inhibition of cholesterol synthesis and inhibition of HMG-CoA reductase by luteolin (Fig. 4).



FIGURE 4: Artichoke

Six randomized trials of artichoke leaf extract for the treatment of hypercholesterolemia have been published. The largest and most methodologically rigorous study of 143 people with hypercholesterolemia showed reduced total and LDL cholesterol.[38] Total cholesterol was reduced by 18.5% compared to 8.6% in the placebo group and LDL cholesterol was reduced by 23% compared to 6% in the placebo group. Another RCT of 75 people with hyperlipidemia showed artichoke leaf extract significantly reduced total cholesterol compared to placebo, but it did not lower LDL.[39] A 2009 Cochrane review concluded that the lipid-lowering effects of artichoke extract are supported by in vitro and animal studies, but more trials with larger sample sizes are needed to recommend its use for lipid-lowering in humans.[40]

People with allergies to the *Asteraceae* family (daisy) should avoid artichoke plant products. Because of its choloretic effect artichoke leaf extract should be used with caution in people with gallstones and not at all in people with bile duct obstruction.

The dose of a specific artichoke extract product used in research studies is 1,800–1,920 mg/day divided into 2 or 3 doses. Alternatively a dose of 6 gm of the dried herb (or its equivalent) per day can be used, divided into 3 doses.

Garlic

Garlic is one of the most popular medicinal herbs in Europe and the United States. It has been used since antiquity for the treatment of cardiovascular and infectious diseases. The German Federal Health Agency Commission E and the European Scientific Cooperative on Phytotherapy have approved its use for the treatment of hyperlipidemia and atherosclerosis. The primary mechanism of action of garlic is theorized to be HMG-CoA reductase inhibition. Another proposed mechanism is increased excretion of bile salts.

Despite the publication of many dozens of trials over many years, evidence of the effect of garlic on serum lipids is inconclusive. Many early studies seemed to prove that garlic could reduce cholesterol in hyperlipidemic patients.[41] However, the many studies in the last several years, including several well-designed trials, have failed to find the benefits with garlic (whether as raw garlic, garlic powder or aged garlic).[42] A meta-analysis of 29 trials published in 2009 concluded that garlic significantly lowered total cholesterol and triglycerides but had no effect on LDL or HDL cholesterol and yet another meta-analysis, published the same year, of 13 trials concluded that garlic had no effect on any lipid measures.[43,44] One possible explanation for these inconsistent results is the lack of standardization of garlic preparations. Among powdered preparations the allicin content of brands used in trials has been shown to vary as much as 230-fold.

Garlic is well tolerated and apparently safe for long-term use. Common side effects include GI upset, nausea, flatulence and halitosis. There is inconsistent information about the effects of garlic on cytochrome P450 3A4 (CYP3A4) isoenzymes. In spite of the theoretical risk of increased bleeding due to its possible antiplatelet effect, two studies of patients taking warfarin show no increased bleeding with medicinal garlic use.

The dose of garlic extract used in clinical trials is 600–1,200 mg divided and given three times daily. Many clinical studies have used a standardized garlic powder extract containing 1.3% allicin.

In summary, although garlic is safe and may have benefit for other cardiovascular conditions (see below) the evidence for a beneficial effect in hyperlipidemia is unclear.

Cocoa

Cocoa is made from the beans of the cacao tree (*Theobroma cacao*) and has been cultivated for human consumption beginning at least 3,500 years ago in Mesoamerica.

The blood-pressure lowering effect of cocoa (see below) is better understood and better proven than its lipid-lowering effect, but proposed mechanisms for lipid-lowering are: (1) delayed LDL oxidation thereby reducing LDL concentration and (2) reduced intestinal absorption of cholesterol and bile acids by decreasing solubility of micellar cholesterol (Fig. 5).

Although there is good evidence of benefit for reduction of blood pressure and vascular endothelium reactivity, there is only early clinical evidence of cocoa's effect on lipids.

One RCT of 57 people with hyperlipidemia showed reduced total and LDL cholesterol levels from ingestion of a snack bar enriched with cocoa flavanols after 6 weeks.[45] Two other



FIGURE 5: Cocoa pods and cocoa beans

preliminary studies show that consumption of cocoa can raise HDL.[46]

Orally, cocoa can cause allergic skin reactions, shakiness, increased urination, increased heart rate, constipation and might trigger migraine headaches. All drug interactions that can occur with caffeine can be expected to occur with chocolate as well, e.g. monoamine oxidase inhibitors (MAOIs) stimulants, certain medications for dysrhythmias, insomnia and anxiety.

Dosages in studies examining cocoa's effect on lipids have been 13–26 gm of cocoa per day or enough cocoa to deliver 200 mg of cocoa flavanols per day (divided bid).

Niacin

Niacin is a water-soluble B vitamin found in many foods. The effects of niacin are dose-dependent and very high doses of niacin are required for treating dyslipidemia (primarily treating low HDL). Prescription niacin products are typically 500 mg or higher, whereas dietary supplement forms of niacin usually come in strengths of 250 mg or less.

Whereas there are abundant convincing studies of the efficacy of pharmaceutical doses of niacin for improving lipid profiles, there is only a single study suggesting that a low dose, such as what may be found in a dietary supplement, is beneficial. In that study a very low dose of niacin, 50 mg daily, increased HDL cholesterol by 2.1 mg/dL, when added to statin therapy.[47] This raises the possibility of using doses lower than traditionally prescribed as an adjunctive therapy and possibly avoiding the vexing side effect of flushing.

Side effects from niacin are much less likely at non-prescription doses; however, it is theoretically possible that the side effects familiar from pharmaceutical doses may still occur: flushing, nausea, pyrosis, exacerbation of gout, etc.

Green Tea Extract *(Camellia sinensis)*

Green tea is made from the dried leaves of *Camellia sinensis*. While green tea has multiple health-related effects for which mechanisms have been elucidated the mechanism of action for a possible lipid-lowering effect is unknown. Green tea has a high concentration of polyphenols to which many of its effects are attributed. Green tea also inhibits LDL oxidation.

While epidemiologic studies suggest that drinking multiple cups of tea per day lowers LDL cholesterol, there are only four prospective clinical trials. Three of these show beneficial effect, but two have significant methodological limitations. The best of these studies, an RCT of 240 hypercholesterolemic people using a theaflavin-enriched green tea extract, found significantly lowered total and LDL cholesterol levels.[48]

Green tea as a food is generally recognized as safe in low to moderate consumption. It is commonly drunk in Asia in small amounts throughout the day. With green tea extract however there are case reports of hepatotoxicity, although no cases have occurred in clinical trials.

Dosage in the above-mentioned study was 375 mg of theaflavin-enriched green tea extract taken daily.

In summary, green tea extract should be used cautiously, if at all, until its definitive safety profile has been established.

Guggul *(Commiphora mukul)*

Commiphora mukul is a plant native to India and Africa that produces a sticky sap resin known as gum guggul. Gum guggul is the medicinal extract of guggulipid which has been used for thousands of years in the Ayurvedic medical system. Guggulipid contains guggulsterones which can inhibit the synthesis of cholesterol in the liver. Guggulsterones also reduce the production of bile acids. Other proposed mechanisms include HMG-CoA reductase inhibition and increase uptake of cholesterol by the liver.

The efficacy of guggul for lowering cholesterol is unknown. Multiple studies from India have shown benefit. The best quality US study showed no benefit.[49] Vigorous debate has raised questions of methodological weaknesses in positive studies, the possibility of population differences leading to discrepant results and whether it is appropriate to use an Ayurvedic medicine outside of the treatment paradigm in which it was developed.

Gastrointestinal side effects (nausea, vomiting, bloating and diarrhea) are common. Headache and allergic reactions in the form of rash and pruritus have also been reported.

The appropriate clinical dose delivers 75–150 mg of guggulsterones daily by ingesting 1,000–2,000 mg of guggulipid, standardized to 2.5% guggulsterones, 2–3 times per day.

Policosanol

Policosanol is a mixture of waxy alcohols extracted from sugar cane wax.

The proposed mechanism is inhibition of hepatic synthesis of cholesterol and possible increased LDL catabolism.

Early studies on the clinical efficacy of policosanol were all conducted by a single group in Cuba.[50] These studies showed benefit comparable to low-dose statin therapy, but subsequent higher quality studies from other countries have not shown any cholesterol-lowering effect.[51]

Policosanol is very well tolerated but can inhibit platelet aggregation therefore a theoretical risk exists in combining it with other antiplatelet or anticoagulant drugs.

A typical dose of policosanol is 5–10 mg twice daily, but higher doses have been used.

Coenzyme Q10

Although coenzyme Q10 (CoQ10) appears to be effective for some cardiovascular conditions (reducing blood pressure and treating HF–see below) it does not have a lipid-lowering effect. Nevertheless it merits consideration in the treatment of dyslipidemia because of its possible utility in patients taking statin drugs. Statins block the synthesis of CoQ10, dramatically reduce CoQ10 levels in plasma and, according to some studies, skeletal muscle. It has been widely theorized therefore that some of the statin-related side effects, such as myalgia, myositis and rhabdomyolysis, may be mediated through CoQ10 depletion. There have only been two small RCTs to examine whether CoQ10 supplementation can prevent statin-induced myalgias. One reported the positive effect of CoQ10 and the other reported no effect.[52,53] Further study is needed. Many authors have pointed out that because of its safety (see below) it is reasonable to have a low threshold for attempting a therapeutic trial of

CoQ10 for patients with myalgia or at risk of myalgia or myopathic complications.[54] Indeed some clinicians recommend CoQ10 supplementation for all patients on statins.

The dose of CoQ10 for this use is 100–200 mg daily. (Doses above 100 mg should be divided bid.) See below for further details regarding the use of CoQ10.

HYPERTENSION

DIET

A variety of dietary modifications are beneficial in the prevention and treatment of hypertension, including the DASH diet, increased fruit and vegetable consumption, reduction of sodium intake, moderation of alcohol, vegetarian diet and possibly increasing potassium and calcium intake. There are also specific foods that help to lower blood pressure such as cocoa, soy, fish and fiber.

The DASH diet (from the Dietary Approaches to Stop Hypertension trial) has been well-proven to reduce blood pressure in hypertensive patients. The original DASH trial studied a combination diet rich in fruits and vegetables and low-fat dairy products and low in saturated and total fat. Results showed significantly lower systolic and diastolic blood pressure levels in the DASH diet group than in the control diet group.[55]

Increased fruit and vegetable intake has also been independently shown to reduce blood pressure in hypertensives, as have salt reduction and alcohol reduction.[56-58] Vegetarian diet also appears to reduce blood pressure, as does a diet with increased fiber.[59,60]

As an individual food, cocoa has also been shown in multiple well-designed studies to be effective at lowering blood pressure. Cocoa is a remarkably bioactive plant that has a very high content of flavanols which increases nitric oxide levels and improves endothelium-dependent vasodilation.[61] Doses of dark chocolate that have been studied are mostly in the 45–105 gm/day range (which would deliver 200–500 mg of cocoa polyphenols), but one high-quality study showed the benefit with a dose as low as 6.3 gm/day (the equivalent of one small square in a typical 100 gm bar).[62]

Adding soy to the diet likely also lowers blood pressure.[63] And the same may be true for fish.[64]

EXERCISE

It is well-established that in patients with essential hypertension regular aerobic exercise can lower blood pressure. Resistance training also lowers blood pressure although typically to a lesser degree.[65] Tai Chi, a Chinese martial art that today is practiced more commonly for its health benefits, also appears to lower blood pressure. There are dozens of studies on Tai Chi and hypertension, although only a few are of high methodological quality.[66] Yoga similarly can lower blood pressure according to three RCTs and a few other studies; however, it has been recommended that patients with cardiovascular risk factors or known cerebrovascular disease should avoid inverted postures (e.g. shoulderstand, headstand) due to risk of acute elevation of intracerebral pressure (Fig. 6).[67]

WEIGHT LOSS

Obese people have a higher incidence of hypertension. Data from the Framingham heart study and elsewhere show that weight loss can reduce blood pressure.[68,69]



FIGURE 6: Tai-chi

SLEEP

Sleep is fundamental to good health. Night time blood pressure in particular importantly affects cardiovascular health. The common sleep disorder obstructive sleep apnea has a strong correlation with hypertension and cardiovascular mortality. Perhaps more importantly in terms of overall number of people affected, studies have also shown a link between both insomnia and sleep deprivation and the incidence of hypertension.[70,71] A holistic and integrative approach to the patient with hypertension therefore includes optimizing sleep, an area in which Integrative Medicine has much to offer, although it is beyond the scope of this chapter.

MENTAL HEALTH

Although the relationship between depression and cardiovascular morbidity and mortality has been known for some time (see below), the more recent research on positive emotions raises the corollary possibility: that cultivating positive emotions may lower blood pressure and improve cardiovascular health.[72] Again, an integrative evaluation and treatment of hypertension would include addressing mental health.

MIND-BODY MEDICINE

Biofeedback and meditation are two mind-body medicine modalities which have been researched for their effects on hypertension.

Biofeedback

Biofeedback is a behavioral therapy method that teaches a patient to gain greater awareness and control of autonomic nervous function that is not normally under conscious control. This is achieved by using technology that presents to the patient in visual or auditory form the level of activity of a physiologic parameter, such as muscle tension, skin temperature, sweat gland activity, respiratory muscle activity, PCO_2, heart rate variability (HRV) or brain wave pattern.

Studies on the blood pressure lowering effect of biofeedback have been published for over 40 years. Meta-analyses consistently show that compared with wait-list or other inactive control groups, biofeedback can significantly lower patients' systolic and diastolic blood pressures (approximately 5–8 mm Hg systolic and 3–5 mm Hg diastolic pressure).[73] However,

when biofeedback is compared with active control group (e.g. sham biofeedback or nonspecific behavioral control), it is often not statistically superior in its effect on blood pressure except when coupled with relaxation training or cognitive therapy.

According to the many studies on this topic thermal (i.e. skin temperature) and electrodermal (i.e. galvanic skin response) biofeedback methods most consistently help patients lower their blood pressure more than other types of biofeedback. These are both surrogate measures for autonomic activity, so these varieties of biofeedback may work by training the patient to decrease sympathetic tone and increase parasympathetic tone. More recently several studies have shown that a type of respiratory biofeedback is effective for lowering blood pressure. In this type of biofeedback, a particular pattern of respiration is practiced for 15 minutes daily with the help of a simple device. In 2002, the FDA approved this device (RESPeRATE®) for home use.

Meditation

The two forms of meditation that have been most thoroughly examined for medical indications are mindfulness meditation and transcendental meditation (TM). With respect to cardiology TM has been more studied. Transcendental meditation is a mantra-based meditation method derived from the ancient Vedic practices of India. TM was developed by Maharishi Mahesh Yogi and introduced in the United States in 1959. It is a trademarked method and has centers worldwide. According to the TM organization, several million people have learned this technique (Fig. 7).

The fundamental practice is to repeat silently a mantra (a sound usually in the form of a Sanskrit word or group of words) in one's mind. Whenever the mind is distracted, the objective is to return attention to the mantra. Transcendental meditation is typically practiced for 20 minutes twice a day.

Research on the basic science and physiology of TM began in the early 1970s and, although the precise mechanism of action is unknown, extensive studies have been conducted showing reduced respiratory rate, decreased total peripheral resistance, decreased beta-receptor sensitivity, reduced epinephrine and norepinephrine levels, increased alpha wave activity on EEG and reduced skin conductance (a surrogate marker for decreased sympathetic tone).



FIGURE 7: Art of meditation

There are also many clinical studies on TM; however, almost all come from authors with affiliation to the TM organization.[74] A meta-analysis of nine RCTs concluded that the regular practice of TM may have the potential to reduce systolic and diastolic blood pressure by approximately 4.7 mm Hg and 3.2 mm Hg respectively.[75]

BOTANICAL MEDICINES AND SUPPLEMENTS

Garlic

The proposed mechanism for the effect of garlic on blood pressure is increased nitric oxide production and endothelium-dependent dilation.

According to two 2008 meta-analyses of ten and eleven studies respectively, garlic has significant blood-pressure lowering capacity in hypertensive patients, on the order of 8–16 mm Hg systolic and 7–9 mm Hg diastolic.[76,77]

The dose of garlic powder extract for hypertension is 600–1,200 mg divided and given three times daily, standardized to contain at least 1.3% allicin.

Fish Oil

The mechanism by which fish oil lowers blood pressure is increased production of prostacyclin, a prostaglandin that causes vasodilation and reduces platelet aggregation. Fish oil also appears to improve arterial compliance.

Three different meta-analyses, the largest of which included 36 randomized trials, conclude that fish oil supplementation at higher doses significantly lowers blood pressure (systolic by 3–6 mm Hg and diastolic by 2–4 mm Hg).[78] An additional randomized trial showed fish oil augmented the blood pressure benefit achieved through weight loss.

The dose of fish oil for treating hypertension is higher than what is used in patients with coronary heart disease (see below), but comparable to the doses used to lower triglyceride levels (see above). Recommended dose is enough fish oil to deliver 3 gm of the omega-3 fatty acids DHA and EPA per day.

Coenzyme Q10

Coenzyme Q10 (also known as ubiquinone) is a fat-soluble compound with many functions, most notably its role as a cofactor in electron transport during oxidative phosphorylation. It is produced by most cells in the human body and serves as an important antioxidant also. CoQ10 appears to lower blood pressure by increasing endothelial production of prostacyclin and thereby enhancing endothelium-independent arterial relaxation and endothelium-dependent vasodilation.

Reviews and meta-analyses of the approximately one dozen trials of CoQ10 conclude that it is effective and potent for blood pressure lowering (16–17 mm Hg systolic, 10 mm Hg diastolic).[79,80]

Side effects from CoQ10 are rare. GI side effects, such as nausea, vomiting, pyrosis and diarrhea, have been reported. There are no significant herb-drug interactions. CoQ10 is relatively expensive as an over-the-counter supplement.



FIGURE 8: Hibiscus

Absorption of CoQ10 is greatly enhanced by choosing a product that contains an oil base (e.g. soy oil) and by ingesting it with a meal that contains fat.

Dosage of CoQ10 supplementation for hypertension is 120–200 mg daily, divided in two doses.

Hibiscus *(Hibiscus sabdariffa)*

This red-flowered plant is well-known around the world as an ornamental and as a type of herbal tea. Extracts of hibiscus contain significant amounts of vitamin C, anthocyanins, and polyphenols but the mechanism by which it lowers blood pressure is unknown (Fig. 8).

In vitro and animal studies suggest the possible mechanisms of action which include calcium channel antagonism, diuresis and inhibition of angiotensin-converting enzyme.

Prior to 2010, three human studies had been conducted on hibiscus examining its blood pressure effect. All three studies showed benefit, but had significant methodological weaknesses. Finally, a double-blind, placebo-controlled RCT was published of 65 hypertensive and prehypertensive people consuming three 240 ml doses of hibiscus tea per day for 6 weeks.[81] Results showed significant systolic blood pressure lowering effect (mean reduction 7.2 mm Hg) and a greater response to hibiscus treatment in those with higher systolic blood pressures at baseline.

Because hibiscus tea is widely consumed as a beverage it has "generally recognized as safe" (GRAS) status from the FDA. Except for transient GI side effects, no significant adverse reaction has been reported.

The recommended dose, based on the aforementioned study, is one commercially available tea bag (containing 1.25 gm of dried calyces) steeped for 6 minutes in 240 ml of water taken three times a day.

Pycnogenol

Pycnogenol® is the brand name for an extract of the bark of the French Maritime Pine tree (*Pinus pinaster).* Like most botanical products it contains a large number of bioactive compounds. The high concentration of flavonoids, particularly oligomeric proanthocyanidins (OPCs), is particularly noteworthy because of their strong antioxidant activity. Mechanisms by which pycnogenol may reduce blood pressure are increased nitric oxide production, decreased thromboxane B2 levels (a vasoconstrictor) and angiotension-converting enzyme inhibition.

Clinical trial evidence for the efficacy of pycnogenol to reduce blood pressure has been evaluated in three RCTs, totalling 117 patients. All three studies show signficant blood pressure-lowering with pycnogenol. One of these studies examined hypertensives on nifedipine and found pycnogenol supplementation allowed reduction of nifedipine dosage.[82] The second study examined diabetics taking ACE inhibitors and found pycnogenol supplementation allowed the reduction of ACE inhibitor dose in 50% of patients, compared to 20% in the placebo group.[83] A third study, the smallest of these, examined people with mild hypertension not on medications and showed a 5% reduction of systolic blood pressure, but no significant lowering of diastolic pressure.[84]

Pycnogenol is well tolerated. Mild GI upset, headache and vertigo have been reported. Pycnogenol may have a glucose-lowering effect (and therefore therapeutic application in diabetes). There are reports that pycnogenol inhibits platelet aggregation so there is a theoretical risk of bleeding when using it with anticoagulants or antiplatelet agents. Finally, there are three animal and in vitro studies suggesting pycnogenol has immune-modulating activity, so it should be used with caution in patients on immunosuppressants.

The dose of pycnogenol for hypertension is 100–200 mg daily.

Pomegranate *(Punica granatum)*

Pomegranate fruit has been enjoyed as a food and used as a medicine since ancient times.

Pomegranate juice increases nitric oxide synthetase activity in blood vessel endothelium, thereby increasing nitric oxide levels leading to vasodilation. The juice also reduces angiotensin converting enzyme (ACE) activity. The polyphenol content of pomegranate juice is very high.

Conclusions about the clinical efficacy of pomegranate juice for hypertension cannot be drawn yet. There are just three clinical trials of pomegranate juice for hypertension, totaling 60 patients. Two show the beneficial effect and one shows no effect.[85]

Doses studied range from 50 ml per day to 240 ml per day. Orally, pomegranate is well tolerated and safe. Allergic reactions have been reported.

Potassium

Dozens of trials show that potassium supplementation modestly lowers the blood pressure in hypertensive patients.[86] The effect is small (2–4 mm Hg systolic, 0–3 mm Hg diastolic) but significant. Nevertheless, a 2006 Cochrane review concluded that additional high quality trials are needed before a conclusion can be made.[87]

The usual cautions with potassium apply (i.e. caution with renal disease, potassium-sparing diuretics, ACE inhibitors, etc.)

The typical dose for hypertension is 10–20 mEq taken 3–4 times daily.

Arginine is an amino acid found in many foods, including dairy products, meat, poultry and fish. Arginine increases nitric oxide levels which causes vasodilation and reduction of blood pressure. Although there are several studies on the use of L-arginine for other cardiovascular conditions (e.g. coronary heart disease, chronic HF, peripheral vascular disease, see below) there are only three trials totaling 66 patients looking at its effect on hypertension. They all show benefit. Interestingly, there is some evidence in humans that arginine supplementation may potentiate the effect of ACE inhibitors.[88]

Side effects from oral supplementation with arginine include including nausea, diarrhea and abdominal cramping. L-arginine supplementation may also cause asthma exacerbations.

The typical dose for hypertension is 2–4 gm three times a day.

Stevia *(Stevia rebaudiana)*

The stevia plant has a long history of native use in South America as a medicine and as a sweetener. It contains stevioside which is hundreds of times sweeter than sugar and is now used worldwide as a sweetener. Animal studies suggest stevia may reduce blood pressure by acting as a calcium-channel blocker and possibly also as a diuretic.

Clinical research on stevia so far is scant and equivocal. Two RCTs from China show stevia to be effective at lowering blood pressure, but two studies from Latin America show no blood pressure effect.[89,90]

Stevia is well-tolerated and no serious drug-herb interactions have been reported.

Dosage is determined by stevioside content. A standardized extract delivering 250–500 mg of stevioside three times daily has been used in studies.

WHOLE MEDICAL SYSTEMS

The effect of traditional Chinese medicine treatment (acupuncture and herbs) on hypertension has been studied, but no firm conclusion can be drawn in spite of the approximately one dozen RCTs that have been completed.[91]

CORONARY ARTERY DISEASE

DIET

With respect to diet there are whole diets and specific foods that are associated with prevention of CAD. The whole diets are: (1) the Mediterranean diet; (2) a fruit and vegetable-rich diet; (3) the Ornish diet; (4) a low glycemic index diet; (5) a diet that replaces saturated fat and trans fat with monounsaturated or polyunsaturated fat and (6) a high-fiber diet. Specific foods that prevent or improve coronary heart disease are fish, alcohol, red wine and nuts.

The Mediterranean diet has been defined as a diet high in fruits and vegetables, whole grains and legumes, with low-to-moderate amounts of fish, poultry and dairy products (mostly as cheese and yogurt), 0–4 eggs per week, and olive oil as the principal fat. The diet is very low in meat and a low-to-moderate amount of wine is consumed.[92] Total fat in this diet, mostly monounsaturated from olive oil, is 25–35% of calories, with saturated fat at 8% of calories or less. Research evidence of its efficacy in reducing cardiac events in patients with heart disease is impressive.[93,94]

Independent of the Mediterranean diet, according to many large observational studies, a diet high in fruits and vegetables is strongly associated with prevention of coronary heart disease.[95,96]

The Ornish diet is a very low-fat vegetarian diet comprised mostly of beans, fruits, vegetables and whole grains. Its best-proven effect has occurred as part of a multifaceted program created by Dr Ornish for reversing atherosclerotic heart disease (see above).[5,6] The exact extent to which the Ornish diet contributed to the positive effect of the intervention in the Lifestyle Heart Trial studies is unknown.

Epidemiologic data strongly suggest the glycemic index/load also influences risk of CAD. High glycemic load has been prospectively associated with increased risk of CAD and conversely low glycemic load has been associated with reduced risk.[97,98]

Replacing saturated fat in the diet with polyunsaturated or monounsaturated fat also reduces CAD risk.[99,100]

Finally there is a very strong inverse association between fiber intake and CAD.[101,102]

In contrast to the positive effects of diets noted above, diets high in trans fats and diets high in meat have a detrimental effect on cardiovascular disease.[103,104]

Regarding specific foods that impact cardiovascular disease outcomes, fish, especially rich in omega-3 fatty acids, has impressive evidence for both primary and secondary prevention.[105-107]

The effect of alcohol intake on cardiovascular disease has similarly been extensively studied with the conclusion that light to moderate alcohol consumption reduces risk of CAD (both primary and secondary prevention).[108,109]

As a form of alcohol, the additive effect of red wine is controversial. Some, but not all, studies suggest that it is the most heart-healthy form of alcohol. There are compounds in red wine that have antiplatelet and antioxidant effects, making this theory mechanistically plausible. Consensus at this time is that low-to-moderate intake of alcohol, of any kind, is clearly beneficial and low-to-moderate intake of red wine may or may not have additional benefit beyond what is already conferred by its alcohol content.[110,111]

In addition to their clear beneficial effect on lipid profiles, nuts have a strongly positive effect on CAD outcomes according to several large epidemiologic studies.[112,113] Pooled analysis showed that subjects in the highest intake group for nut consumption had an approximately 35% reduced risk of CAD incidence.[114]

EXERCISE

Sedentary lifestyle is a confirmed risk factor for the development of CAD and exercise is proven to beneficially impact CAD risk factors. There is also abundant observational data correlating increased exercise with decreased CAD.[115] However, it should be noted that there are surprisingly few prospective clinical trials proving primary prevention. In the case of secondary prevention however, thanks to the existence of cardiac rehabilitation

programs, there is both observational and trial evidence of efficacy.[116]

WEIGHT LOSS

Obesity exacerbates many CAD risk factors and is probably itself an independent risk factor. As in the case of the exercise literature, research on the CAD effect of voluntary weight loss in obese people is comprised of consistent and strong observational data, but no trial data.[117]

SLEEP

As noted above (see "Hypertension–Sleep") there is an association between sleep and cardiovascular health. In prospective observational studies, an inverse relationship is found between all markers of poor sleep quality (i.e. reduced sleep duration, difficulty falling asleep, frequent awakenings and unrefreshing sleep) and risk of CAD.[118] Another prospective study found that difficulty falling asleep correlated with CAD mortality.[119] Thus, again, an integrative approach to the management of CAD would include attention to sleep health.

MENTAL HEALTH

The effect that the mind has on cardiovascular health manifests in many ways. Stress, aspects of personality, mood, social factors and spirituality have all these been investigated for their effect on CAD.

Stress

The relationship of stress to cardiovascular disease has been a challenging topic for research, but some conclusions can be drawn. At the physiological level stress causes endothelial dysfunction and increases cardiovascular work demand. Animal studies show that stress can lead to the development and progression of CAD. In humans there is an association between chronic stress and increased CAD. Stress can cause angina and stressful life events are associated with an increase in cardiovascular events.[120] Importantly, there is clinical trial evidence that managing stress reduces CAD events and mortality.[121,122]

Personality

Personality factors that appear to predispose to CAD are hostility and social competitiveness. In 1959, the cardiologist Dr. Meyer Friedman published the first of several articles proposing a link between Type A personality type (impatience or time urgency, free-floating and easily triggered hostility, competitiveness) and CAD. Subsequent prospective and retrospective observational research by psychologists elucidated that hostility alone was the personality trait that was associated with additional risk.[123,124] It should be noted also that there is a correlation between acute anger and myocardial infarction.[125,126] Competitiveness as a personality trait has also been shown to be correlated with CAD in prospective observational data.[127]

Mood

Aspects of mood that have been studied are depression as well as positive emotions. Depression has been very strongly correlated with incidence of CHD as well as worsening of CHD outcomes.[128,129] The effect of depression on mortality in those with pre-existing cardiovascular disease is profound: a 3.5 times greater risk of death compared to patients who have cardiovascular disease but are not depressed. Although it has been shown that both behavioral and pharmaceutical methods can successfully treat depression in patients with CHD, the research on whether treatment of depression can improve CHD outcomes is less clear.[130] One of the highest quality trials showed no effect on recurrent MI or CAD mortality.[131]

Positive emotions and their effect on health have been of great interest in recent years. A large prospective 10-year observational study has shown positive effect may reduce the risk of heart disease by 22%.[132]

Social Factors

Decades ago the Roseto studies concluded that social factors contributed directly to CAD mortality.

In those studies, a strikingly large difference in mortality from myocardial infarction was found between inhabitants of the town of Roseto, Pennsylvania and neighboring towns despite the Rosetans similar (or possibly worse) health habits such as diet, exercise and smoking. Roseto was an ethnically homogeneous, recently-immigrated, Italian community with very high social cohesion. This difference (the so-called "Roseto Effect") disappeared over time as the communities in Roseto developed social patterns typical of their neighbors and the rest of the United States (i.e. increased mobility of younger generations, fewer three-generation households, less overall participation in civic groups, less family-centered social life, increased economic stratification, etc.).[133,134]

In additional studies of other populations since then a lack of social support has been repeatedly observed to negatively impact cardiac mortality.[116,135]

Spirituality

Most observational studies of religious affiliation and participation consistently have shown an inverse correlation with cardiovascular mortality.[136,137] A recent large multiethnic cross-sectional study however found no effect.[138]

MIND-BODY MEDICINE THERAPIES

The mind-body medicine modalities of biofeedback, guided imagery, meditation and hypnosis have been studied in relation to CAD.

Biofeedback is a modality that has proven capacity to favorably affect HRV, including in patients with heart disease.[139] Poor HRV in post-MI patients is strongly predictive of short-term and long-term mortality.[140] A single RCT does conclude the biofeedback can reduce post-MI mortality, although further research is clearly needed.[141]

Guided imagery appears to be effective in reducing pain and anxiety perioperatively in cardiac surgical patients.[142]

Transcendental meditation studies have shown benefit from this modality for several CAD risk factors as well as HRV, but there are no randomized, controlled trials with hard clinical CAD outcomes.

The modality of hypnosis similarly has not been studied for any effect on clinical CAD outcomes, but one study interestingly shows an effect on repolarization that likely has therapeutic implications for arrhythmogenesis.[143]

ENHANCED EXTERNAL COUNTERPULSATION

Enhanced external counterpulsation (EECP) is a nonpharmacologic, noninvasive therapy that uses three sets of pneumatic stockings on each lower extremity (calves, lower thighs and upper thighs/buttocks) whose inflation and deflation are timed to the patient's electrocardiogram. The hemodynamic effect of EECP is similar to the intra-aortic balloon pump in that it increases diastolic coronary blood flow (diastolic augmentation), decreases afterload and increases venous return and preload. EECP may also favorably affect endothelial function and the development of collateral coronary circulation.

There are more than a dozen studies of EECP in patients with chronic angina, including two RCTs and many prospective observational studies. The most important trial, a multicenter trial conducted over 10 years ago, showed EECP significantly improved time to 1 mm ST-segment depression and reduced anginal episodes, but did not change exercise duration.[144] Results from other studies also suggest that EECP is safe and effective although more RCTs are needed. EECP appears to have benefit in patients with refractory angina on maximal conventional therapy, HF patients with angina (see below), diabetics with angina, elderly with angina and women with angina. Benefits have included less angina, improved exercise capacity, improved quality of life, fewer emergency department visits and hospitalizations. Comparable rates of survival/Coronary artery bypass grafting/Percutaneous coronary intervention have been found in patients with CAD who received EECP compared to patients who underwent PCI even though EECP patients had more severe disease at baseline. Follow-up studies show benefits are maintained for one, two and 3 years post-EECP.

In summary, EECP appears to be a safe, noninvasive therapy for chronic stable angina although additional experimental trial data are needed.

BOTANICAL MEDICINES AND SUPPLEMENTS

Fish Oil

Interest in the effect of fish oil on CAD began 30 years ago when it was learned that the Inuit population of Greenland had low rates of CAD despite consuming a high fat diet. It was subsequently discovered that protection was conferred by the omega-3 fatty acids EPA and DHA in the fish that the Inuit consumed.

It is likely that multiple mechanisms explain the beneficial effects of omega-3 fatty acids for both primary and secondary prevention of cardiac disease. These include reductions in dysrhythmias, inflammation, blood pressure, blood clotting, atherosclerotic plaque formation, triglyceride levels and improvements in arterial and endothelial function.

The clinical trial evidence for the efficacy of omega-3 fatty acids in secondary and primary prevention of CAD is based on dozens of studies including hundreds of thousands of patients. One of the most impressive secondary prevention studies was the 1999 GISSI-Prevenzione study which showed a large reduction in sudden cardiac death, total cardiovascular mortality and overall mortality.[145] More recent systematic reviews and meta-analyses similarly conclude there is benefit in CAD prevention and CAD mortality.[146] The largest primary prevention study was a prospective observational study in Japan that included over 41,000 patients.[147] Subjects in the highest quintile of omega-3 fatty acid intake had a 67% lower incidence of nonfatal coronary compared with those in the lowest quintile. Two of three randomized clinical trials that examined the effect of fish oil directly on progression of atherosclerosis also showed benefit. A recent RCT of 30 people with CAD and aspirin resistance found that fish oil supplementation was equivalent to aspirin dose escalation in restoring aspirin sensitivity.[148] The American Heart Association recommends 1 gm/day of omega-3 fatty acids for those with CAD and 500 mg/day for those without CAD.

Garlic

The antiatherosclerotic mechanisms of garlic are thought to be reduction of oxidative stress to endothelial cells, possibly by preventing glutathione depletion in these cells, and inhibition of LDL oxidation.

Garlic preparations have been found to slow atherosclerosis in animal studies. In humans, there are a few small and medium-sized studies showing reduced progression of atherosclerotic plaque and attenuation of age-related loss of vascular elasticity (aortic and femoral) with garlic use although methodological limitations of these studies make any conclusion tentative. There is a controlled trial of 432 post-MI patients who took 2–3 cloves of garlic daily for 3 years.[148] After the first year, there was no difference in the rate of infarction between the groups; however, in the second year, fatal and nonfatal MIs and incidence of angina decreased in the garlic eaters by 30% or more and this difference continued in the third year.

Arginine

Prior to 2006, there were a few studies strongly suggesting a role for arginine in the management of chronic stable angina. Study results showed decreased symptoms, improved exercise tolerance and improved quality of life.[149,150] It also appeared to be effective for supporting nitrate therapy by extending nitrate efficacy and reducing nitrate tolerance.[151,152] However, in 2006, the VINTAGE MI Trial examined the use of arginine supplementation within 3–21 days of acute MI. This RCT of 153 patients showed increased mortality with L-arginine supplementation.[153] Thus, until further study arginine cannot be recommended in the treatment of CAD patients.

Carnitine

Carnitine is a quaternary ammonium compound obtained in the diet, primarily from red meats and dairy products, and also synthesized by the body from lysine and methionine. It serves a key metabolic role in the carnitine shuttle where it transports fatty acids from the cytosol into the mitochondria where they are oxidized for the generation of cellular energy.

The precise mechanism by which carnitine may work in CAD is not known. Tissue carnitine levels have been shown to decrease in people with angina and myocardial ischemia, so the known essential role of carnitine in the generation of cellular energy may explain its effect in angina. Carnitine may also have a vasodilatory effect that is prostaglandin-dependent and not nitric oxide-dependent.

Several small RCTs of carnitine (either intravenously or orally) for patients with angina have been published and the majority have reported either reduced symptoms, greater exercise tolerance or both.[154,155] One trial specifically showed a significant benefit when carnitine was added to maximal conventional antianginal therapy.[156] Several trials have also looked at carnitine use post-MI. Many benefits were reported including improved myocardial viability, less left ventricular (LV) dilation, better LV function and less ventricular tachycardia.[157] Unfortunately, there are significant methodological limitations in many of these studies.

No serious adverse events have been reported with carnitine use. GI side effects, such as pyrosis, nausea, vomiting and abdominal cramps, have occurred. It is not known whether carnitine interacts with warfarin, but there have been reported interactions (increased INR) with acenocoumarol, a coumarin-derivative.

The dose of oral L-carnitine for chronic stable angina is 1 gm twice daily.

The dose used following myocardial infarction is 2–6 gm daily.

Ribose

Ribose is a five-carbon sugar needed for the synthesis of nucleotides such as ATP. There is animal evidence that in hypoxic myocardial tissue ribose supplementation helps to restore ATP levels. And there is a single human RCT of 20 patients with CAD concluding that ribose significantly prolongs the time to ST-segment depression and angina during exercise treadmill testing.[158]

Oral ribose supplementation appears to be safe, with only mild GI side effects and headache being reported. Intravenous infusion of ribose may increase insulin levels and cause hypoglycemia. There are no significant drug interactions reported. One study concludes that ribose facilitates thallium redistribution in patients with CAD and may enhance identification of ischemic myocardium.

The dose for CAD is 15 gm four times a day, although lower doses may be effective.

Folate and B Vitamins

Although not as important as the traditional CAD risk factors, hyperhomocysteinemia is an independent risk factor for atherosclerotic vascular disease. Increased blood levels of homocysteine can occur due to deficiency of folate or other B vitamins and supplementation with B vitamins can lower homocysteine levels. Furthermore, an inverse association between dietary folate and atherosclerosis has been seen in prospective observational studies. Nevertheless multiple well-designed RCTs have all concluded that folate and B vitamin supplementation aimed at lowering homocysteine levels in patients with CAD do not yield improvement in clinical outcomes.[159] Thus, folate and B vitamin supplementation is not recommended for CAD.

Vitamin E

Similar to folate and the B vitamins, there was much reason to believe that vitamin E supplementation might reduce CAD, but clinical trials have not born this out. Oxidation is a key step in the atherogenic process, and vitamin E has antioxidant activity. Furthermore vitamin E has been shown to attenuate some endothelial dysfunction, inhibit platelet aggregation and intra-arterial thrombus formation. And large observational studies showed a strong correlation between vitamin E intake, either through diet or supplementation, and reduced CAD. Nevertheless, surprisingly, multiple RCTs have found no benefit for vitamin E in either primary or secondary prevention of CAD.[160,161] The American Heart Association has stated that the evidence does not justify use of vitamin E supplementation for reducing the risk of cardiovascular disease. Importantly it has been noted however, as a point of debate, that most of the aforementioned studies used only synthetic α-tocopherol (including the non-naturally occurring l-isomer) as the vitamin E intervention rather than the natural form of the vitamin. And there are other aspects to vitamin E use that also may not have been appreciated in much of this research such as dose, use of tocopherol/tocotrienol mixtures and biomarkers.[162]

Beta-Carotene

Beta-carotene has failed to show benefit when taken as a supplement for primary or secondary prevention of CAD.[162a,163] In smokers with CAD beta-carotene may increase cardiac events.[164]

Calcium

Calcium is not used as a supplement for treating CAD, but many people, especially postmenopausal women, take daily calcium supplements and there was significant debate in 2010 on whether calcium supplementation affected cardiovascular disease. One meta-analysis of several large trials found calcium supplementation seemed to increase risk of myocardial infarction.[165] Two other meta-analyses examined women who had taken calcium supplementation along with vitamin D supplementation and found neither increased cardiovascular events nor calcified coronary plaque burden respectively.[166,167] Dietary calcium, in distinction to supplemental calcium, has never had an association with cardiovascular disease.

CHELATION

Chelation is a process whereby a chelating agent, typically an organic heterocyclic compound with multiple ligands available

to bind a central ion, is administered to remove a cation. Since calcium is an element of atherosclerotic plaques, it has been postulated that removal of this calcium may reduce atherosclerosis. Intravenous ethylenediaminetetraacetic acid (EDTA) is the chelating agent that has been used for this purpose. A definitive review in 2000 concluded that EDTA chelation therapy is no more effective than placebo in CAD prevention or treatment.[168] A well-designed RCT of 84 patients with CAD showed no significant difference in efficacy between control and chelation groups.[169] In 2008, enrollment for a larger NIH-funded RCT was halted presumably due to use of improper consent forms.[170] In 2010, the FDA warned several companies that promoting their chelation products as treatments for autism, cardiovascular disease and other serious health problems is dangerous and illegal.[171]

HEART FAILURE

DIET

High sodium intake has been associated with HF exacerbations. Low sodium intake and fluid restriction are recommended for people with HF, including by the American College of Cardiology. And although there are favorable clinical outcomes documented for patients with hypertension who restrict sodium intake, there is surprisingly little research on HF outcomes.

EXERCISE

A much better evidence base exists for the benefits of aerobic exercise in HF. Several RCTs have shown outcomes of enhanced exercise capacity, reduced hospitalization, increase survival and improved quality of life.[172] Resistance training, in contrast to aerobic exercise, has been less extensively studied in HF. Some, but not all, studies that have looked at adding resistance training to aerobic exercise have shown benefit.[173,174] A specific kind of strength training, inspiratory muscle training (IMT), has been shown in several studies to be effective for reducing symptoms, increasing exercise tolerance and improving quality of life.[175]

Neuromuscular Electrical Stimulation (NMES) has also been shown in multiple trials to increase exercise capacity, leg muscle strength and quality of life.[176] This therapy uses electricity to stimulate lower extremity muscles to simulate strength training. At least two studies have also shown that Tai Chi has benefits for patients with HF. An RCT of 30 people with HF on standard medical therapy was conducted using a 12-week Tai Chi program that consisted of a 1-hour class twice a week. Significant improvements in 6-minute walking distance, quality of life scores and B-type natriuretic peptide (BNP) levels were reported in the Tai Chi group. Catecholamine levels were unaffected.[177] A similar randomized study of 52 patients also showed improvement in self-reported symptoms and quality of life scores, but no change in objective exercise tolerance.[178] A few pilot studies have been conducted looking at yoga and yogic breathing in HF. All have shown benefits including improved exercise tolerance, dyspnea, endurance and strength.[178A,178b]

SLEEP

It is well-known that the severe sleep disorder, obstructive sleep apnea, portends higher mortality in HF patients.[179] But even the much more common complaint of insomnia is highly prevalent in people with HF and is strongly associated with increased fatigue, depression, reduced functional status and lower quality of life.[180,181] In addition to other measures for improving sleep in patients with HF, increased general physical activity and specifically Tai Chi may be useful.[182,183]

MENTAL HEALTH

Depression has an important bidirectional relationship with HF. HF is associated with much higher rates of depression than exists in the general population (or even the chronic disease population) and conversely depression is associated with higher mortality and hospital readmission rate in HF.[184] To date three RCTs have been published looking at the treatment of depression in HF. Two examined the effect of sertraline and citalopram respectively, and both showed that pharmacologic therapy was no more effective than placebo in ameliorating depression or improving cardiovascular status.[185,186] A third RCT, of a nonpharmacologic intervention, did show a positive effect. This trial of 74 patients with NYHA Class II–III HF compared a combination of exercise plus cognitive behavioral therapy (CBT) versus exercise alone versus CBT alone versus usual care and found that the combined treatment reduced depression and improved 6-minute walk distance at 24 weeks.[187]

MIND-BODY THERAPIES

Biofeedback and meditation have been examined for their effect in treating HF. In a controlled pilot study of elders with HF, a 10-week training in HRV-based biofeedback significantly improved psychological parameters and increased 6-minute walk distance. Surprisingly HRV did not change.[188] Similarly a small RCT of 29 patients with HF looked at the effectiveness of a 6-week program of HRV-based biofeedback plus breathing retraining and found significantly improved 6-minute walk distance in patients with ejection fraction greater than 31% but no effect on HRV itself.[189]

There are three studies of meditation and HF. One study examined a multimodal program that included mindfulness meditation, one study examined TM and one examined a composite meditation method. The mindfulness program was a prospective cohort study of 208 patients using an 8-week program that included training in mindfulness meditation, coping skills, and support group discussion. In addition to improvements in psychological parameters, HF patients in the intervention group had fewer self-reported symptoms and improved clinical scores compared to controls. However there was no difference in rates of death or hospitalization between groups.[190] The TM study was a small pilot RCT of 23 African American men with HF and found improved 6-minute walk distance, improved self-reported symptom score and fewer rehospitalizations at 6-month follow-up.[191] Potentially invalidating this result, however, is that the TM group had higher exercise capacity compared to the control group at baseline. Another pilot RCT of 19 patients used a meditation program that included elements of concentration meditation (mantra-based like TM), mindfulness meditation and guided imagery and examined multiple physiological parameters as well as quality of life.[192] The meditation group had reduced norepi-

nephrine levels, improved ventilatory efficiency and improved quality of life. LV ejection fraction and diastolic diameter index did not change.

THERMAL VASODILATION

Thermal vasodilation therapy (immersion in hot bath or sauna once or twice a day) is an interesting and good example of an Integrative Medicine therapy. Even though it had been proscribed in cases of HF by conventional medical dogma in the United States, it has a long history of use in medicine in many different cultures; it appears to be safe; it has a plausible mechanism of action (reduced peripheral vascular resistance and reduced sympathetic tone); it is "low-tech"; it is simple to use; it is likely to be well-accepted by patients and it can be integrated with conventional HF therapies. Preliminary studies show that it is well-tolerated, improves hemodynamics and possibly endothelial function.[193,194] A pilot RCT of this therapy used a home-based approach in 15 patients with HF and found reduction of symptoms, improvement in quality of life scores, improved heart rate response to graded bicycle exercise test and no adverse effects.[195] More clinical study is needed.

ENHANCED EXTERNAL COUNTERPULSATION

Another creative nonpharmacologic therapy that addresses the hemodynamics of HF is EECP. Enhanced external counterpulsation (EECP) increases diastolic filling, reduces afterload and appears to be effective for the treatment of angina (see above). Subsets of patients with HF in angina studies appear to have benefitted from EECP. Furthermore a prospective cohort study of 450 patients with HF and refractory angina showed reduction in emergency room visits and hospitalization at 6-months after EECP.[196] The only RCT of EECP in HF was a multicenter trial of 187 subjects where the experimental group received 35 one-hour EECP treatments over 8 weeks. Results of the two primary endpoints after 6 months showed significantly improved exercise tolerance, although no change in peak oxygen uptake. Two of the secondary endpoints, change in NYHA functional class and quality of life, showed significant improvement as well. There was no difference however in number of cardiovascular events between groups.[197]

BOTANICAL MEDICINES AND SUPPLEMENTS

Hawthorn *(Crataegus monogyna)*

Hawthorn has been used as a food and medicine in Europe and China since ancient times. Although the fruit of the plant is edible and has a history of medicinal use, most modern clinical studies have examined extracts of the leaf and flower portions of the plant.[198] The plant's content of flavonoids and oligomeric proanthocyanidins are thought to be responsible for most of its physiologic effects. Hawthorn has many mechanisms by which it may affect HF. It increases cardiomyocyte membrane permeability to calcium and inhibits phosphodiesterase (thus increasing intracellular cAMP). At the physiological level hawthorn has been shown to increase cardiac output, increase inotropy, increase coronary blood flow, decrease blood pressure and decrease total peripheral resistance, all of which may be favorable hemodynamic changes for congestive HF. Since



FIGURE 9: Hawthorn in berryx

hawthorn prolongs the refractory period of cardiomyocytes, it is less arrhythmogenic than other inotropic agents. Indeed animal research shows antidysrhythmic activity (Fig. 9).

Clinical research on hawthorn in HF is extensive. At least a dozen RCTs (including over a thousand patients) and two meta-analyses have shown hawthorn has benefit. A 2008 Cochrane review concluded: "there is a significant benefit in symptom control and physiologic outcomes from hawthorn extract as an adjunctive treatment for chronic heart failure".[199] Specific benefits were improved symptoms of shortness of breath and fatigue, improved exercise tolerance, increased maximal workload, reduced cardiac oxygen consumption and infrequent, mild adverse events. Later in 2008, an RCT of 2,681 patients found no difference in time to first cardiac event between placebo and hawthorn groups overall, but did find a significant reduction of sudden cardiac death in the hawthorn subgroup of patients with EF greater than 25%.[200] The least positive study of hawthorn looked at 120 patients and found improved EF in the hawthorn group, but no benefit in 6-minute walking distance, functional capacity nor quality of life.[201]

Hawthorn is generally safe. Most commonly reported side effects are nausea, dizziness and GI complaints.

The most extensively studied product is known as "standardized extract WS 1442" which is standardized to 18.75% oligomeric procyanidins. Its dose is 60 mg three times daily. An extract standardized to 2.2% flavonoids, known as "extract LI 132", has been studied at a dose of 100 mg three times daily and higher.

Coenzyme Q10 (Ubiquinone)

As noted above (see "Hypertension"), CoQ10 is critical in the production of cellular energy. Furthermore, myocardial biopsies from patients with HF have demonstrated depletion of CoQ10. Therefore the main proposed mechanism of action of CoQ10 in HF is the replenishment of CoQ10 levels leading to improved myocardial ATP production. Indeed it has been shown that

CoQ10 preserves myocardial sodium-potassium ATPase activity, increases in vitro myocardial tolerance to hypoxia-reoxygenation stress and improves diastolic function in patients taking statins. Other mechanisms may include lowering of blood pressure (see above) and prevention of oxidative damage.

There are at least eight RCTs of CoQ10 in HF. Six show benefit (total $n = 820$) and two do not (total $n = 85$). Two meta-analyses also conclude overall benefit of CoQ10.[202,203] Benefits have included decreased dyspnea and peripheral edema, improved NYHA classification, reduced hospitalization rates, improved quality of life and improved insomnia in HF patients.

Side effects, safety and drug interactions are described above in the Hypertension section.

The most commonly studied dose of CoQ10 for HF is 100 mg per day divided into 2 or 3 doses, but benefits have also been demonstrated with 60 mg/day.

Fish Oil

The strong and beneficial effects of fish oil on other cardiovascular conditions (hyperlipidemia, hypertension and CAD) are described above in those respective sections. But the omega-3 fatty acids found in fish oils also appear to be beneficial for HF. The main mechanism by which they provide clinical benefit in HF appears to be a reduction of dysrhythmias through a membrane stabilizing effect involving sodium, potassium and calcium channels. Other possible mechanisms include vasodilation, improved arterial compliance, reduction of heart rate, anti-inflammatory effect, reduction of BNP and maintenance of favorable renal hemodynamics.

Of the three RCTs examining the effect of fish oil supplementation on HF by far the largest is the GISSI-HF study which examined 6,975 patients and found fish oil was well tolerated and led to a significant reduction of all-cause mortality and hospitalization due to cardiovascular causes.[204] Two other very small randomized controlled clinical trials report that fish oil supplementation in HF patients reduces TNF-α, helps prevent cachexia and improves endothelium-dependent vasodilation.

Fish oil should not be used in patients with implantable cardiac defibrillators due to conflicting results from clinical trials and the possibility, shown in one study, that fish oil could be pro-dysrhythmic in these patients.[205,206]

The recommended dose for fish oil in HF is based on the GISSI-HF study: 1 gm of fish oil daily, delivering 850–882 mg of EPA plus DHA.

Ribose

As noted above ribose is a five-carbon sugar that may help ATP production in stressed myocardial tissue.

A single small RCT of 15 patients with HF examined the effect of ribose supplementation for 3 weeks, followed by a 1-week washout period and crossover. Echocardiography, functional capacity and quality of life were assessed. The ribose supplementation group had significantly improved echocardiographic parameters (e.g. left atrial size, atrial contribution to ventricular filling) and improved quality of life, but neither group showed a change in performance on cycle ergometer.[207]

The dose of oral ribose in HF is 5 gm three times daily, taken with meals.

Taurine

Taurine is an amino acid synthesized by the human body and also obtained in the diet through ingestion of animal protein. The mechanism by which it may affect HF is unknown, but there is evidence that it may reduce catecholamine levels and sympathetic tone as well as increase LV function by modulating intracellular calcium influx.

There are three old RCTs examining the effect of taurine supplementation on HF. All three studies are from the same research group and had methodological limitations. Benefits reported include reduced symptoms and improved NYHA classification.[208]

Taurine appears safe and well-tolerated. The dose for HF is 2 gm three times a day.

Carnitine

As noted above in the CAD section, carnitine supplementation may enhance myocardial energy production. This is the likely mechanism for any effect in HF as well. Several RCTs of variable quality have examined the effect of carnitine in HF. Some of the studies used propionyl-L-carnitine and some used L-carnitine. The highest quality of study showed no statistically significant effect of propionyl-L-carnitine for the primary endpoint: exercise capacity.[209] However, all the other studies showed benefits, including reduced mortality,[210] reduced symptoms, improved exercise capacity, oxygen consumption and echocardiographic parameters including ejection fraction. Side effects and interactions are as stated above.

The dose in HF is 1 gm twice daily of L-carnitine or 500 mg of propionyl-L-carnitine thrice daily.

Arginine

Arginine's mechanism of action in HF is likely the same as in hypertension: increased production of nitric oxide and consequent vasodilation. Arginine may also have ACE inhibiting activity. It also seems to potentiate pharmaceutical ACE-inhibitors (see above).

Results of clinical trials are mostly, but not universally, positive. Three RCTs with a total sample size of 70 showed improvements in exercise capacity, symptoms, glomerular filtration rate and vasodilation.[211] One study in particular showed the improvement in endothelium-dependent vasodilation was equivalent to and additive with that produced by regular exercise. Two small non-randomized studies failed to find improvement in exercise capacity and forearm endothelial function respectively. For side effects and drug interactions see above.

The oral arginine dose for HF ranges 2–6 gm thrice daily.

Creatine

Creatine is another naturally occurring substance that when used as a supplement may have beneficial effects on myocardial energy metabolism. Creatine as phosphocreatine forms a pool of energy-containing phosphate bonds from which muscle (both skeletal and myocardial) cells can draw when replenishing their ATP levels. The ratio of phosphocreatine to ATP in the myocardium of patients with HF is lower than the ratio found

in people without HF and the ratio correlates inversely with the severity of HF. Creatine's proposed mechanism of action in HF therefore is to maintain myocardial ATP levels.

One large and three small RCTs have examined the effect of creatine supplementation in HF. The largest, of over 1,000 patients, studied the effect of intravenous creatine. Results showed improved NYHA classification, significantly improved symptoms including a less angina, reduced nitroglycerin use and fewer ventricular premature beats.[212] The smaller studies, using oral supplementation, showed positive results including less fatigue, improved exercise capacity and improved skeletal muscle strength. One study examined the effect of a single week of oral creatine supplementation and found no effect on ejection fraction.

Mild GI side effects can occur with oral creatine supplementation. Muscle cramping has also been reported. A single case report of lone atrial fibrillation has been published. Weight gain of 0.5–1.5 kg, thought to be due to water retention in skeletal muscle, can occur with creatine supplementation and should not be mistakenly interpreted as a sign of worsening HF.

Since creatine is metabolized by the kidneys concern has been raised over potential nephrotoxicity. None of the hundreds of trials conducted with creatine for various indications have reported significant renal side effects. Furthermore, several safety trials and retrospective analyses, lasting as long as 5 years, have not found evidence of renal toxicity. There have been however at least three case reports of nephritis or impaired renal function in association with creatine supplementation, as well as two cases of rhabdomyolysis. At this time, it is advisable to avoid creatine supplementation in patients with impaired renal function. There are case reports of patients with bipolar affective disorder developing mania while on creatine supplementation so it is prudent to avoid use in this population. No significant drug interactions are known; however, due to the theoretical nephrotoxicity risk it is advisable to avoid concomitant use of nephrotoxic drugs. Creatine supplementation can cause an increase in measured serum creatinine. This usually does not reflect impaired renal function but in such cases further clinical investigation would of course be warranted.

The oral dose of creatine for HF is 5 gm four times per day. The intravenous dose is 1 gm of creatine phosphate twice daily.

Magnesium (Mg^{++})

Magnesium regulates key ion channels in myocardial cells and helps to maintain the critical transmembrane gradients of sodium and potassium. The purported mechanisms of action of magnesium supplementation in HF are antiarrhythmic effect, decreased coronary vascular resistance, increased coronary artery blood flow and decreased systemic vascular resistance.

Hypomagnesemia is one of the most common electrolyte abnormalities in HF patients. Diuretic therapy likely is a common cause as are poor dietary habits. Although hypomagnesemia is associated with increased ventricular ectopic activity in HF, the clinical significance of this is unknown.[213]

There are at least six RCTs of magnesium therapy in HF including 262 patients. Four trials used oral magnesium and two used intravenous magnesium. In the oral magnesium trials the following significant effects were reported: improved symptoms, improved survival, reduced systemic vascular resistance, reduced mean arterial pressure, reduced ventricular dysrhythmias (PVCs, couplets and non-sustained V-tach) and improved HRV.[214,215] One study showed improvement in small arterial endothelial function, but not large arterial endothelial function nor exercise capacity, quality of life and NYHA classification.[216] The two trials examining intravenous magnesium supplementation for HF clearly showed significant reductions in ventricular ectopy.[217,218]

The most common side effects of oral magnesium supplementation are diarrhea, nausea and vomiting. Intravenous magnesium can cause hypotension, bradycardia, flushing and reduced skeletal muscle tone. Impaired renal function and neuromuscular disease are relative contraindications to magnesium use. Magnesium may have additive effects when used concomitantly with calcium-channel blockers. Oral magnesium can reduce the absorption of quinolone and tetracycline antibiotics, bisphosphonates and mycophenolate. Intravenous magnesium if combined with intravenous aminoglycosides can cause severe neuromuscular weakness.

Oral doses studied range from 300 mg to 400 mg once daily of magnesium chloride or citrate to 800 mg once daily of magnesium oxide to 6,000 mg (3,000 mg twice daily) of magnesium orotate. Intravenous doses studied were 8 gm over 12 hours of magnesium sulfate and 0.3 mEq/kg bolus over 10 minutes followed by an infusion of 0.08 mEq/kg per hour for 24 hours of magnesium chloride.

Thiamine

Thiamine is a water-soluble B vitamin, important as a cofactor in carbohydrate metabolism and production of ATP. Thiamine deficiency can cause a syndrome that includes HF (wet beriberi). Loop diuretics increase urinary thiamin excretion and can cause thiamine deficiency. This may be a common phenomenon.

One pilot study suggested that thiamine supplementation could improve ejection fraction in HF patients on high doses of loop diuretics.[219] A larger RCT of 30 patients showed thiamine supplementation significantly improved ejection fraction, diuresis and sodium excretion.[220]

Thiamin is safe when administered orally. There are no known significant drug interactions.

The dose studied in HF patients on loop diuretics is 200 mg once daily, although much higher doses are commonly ingested without any known ill effect.

BOTANICAL MEDICINES WITH ADVERSE CARDIOVASCULAR EFFECTS

Fortunately, almost none of the botanical medicines used in integrative cardiology have significant cardiovascular toxicity. However there are botanical products used, and misused, for other indications that can have serious cardiovascular toxicity.

Most of the botanical products that cause serious adverse cardiovascular events fall into one of three groups which cause an increased adrenergic state: (1) ephedrine-containing plants; (2) caffeine-containing plants and (3) other stimulant plants. Most cases of toxicity have occurred when the plant is used inappropriately, either in excess or out of the medicinal context in which it was historically developed.

Ephedra, an extract of the plant *Ephedra sinica* (known in Chinese medicine as "ma huang"), has been banned in the United States due to severe case reports including hypertension, myocardial infarction, stroke and death. Ephedra contains ephedrine and pseudoephedrine which are alpha-receptor and beta-receptor agonists that can lead to profound sympathetic nervous system stimulation and consequent increased blood pressure, vasoconstriction, increased myocardial stress and dysrhythmia. Case reports of ephedra's toxicity occurred when the substance was taken out of the context of its traditional medical system (Chinese medicine) and used in very high doses, often in combination with caffeine for the purpose of selling over-the-counter weight loss supplements. Ephedra as used in the Chinese medicine system, in very low dose and in combination with multiple other herbs, is likely safe. In this system it is commonly used as part of an herbal combination to treat asthma and other conditions.

The botanical medicine Country Mallow (*Sida cordifolia*), also known as "Bala", is from the Ayurvedic medical system. Although no adverse events have been reported in the United States from the use of this plant, it too has been banned because it contains ephedra. Again, when used selectively and in appropriate doses in the context of the Ayurvedic medical system this herb is thought to be safe. Similar to ma huang or ephedra in its traditional context, it is used to treat asthma and related conditions.

Commonly available caffeine-containing plants are coffee, tea, guarana, cola nut and maté. In excess, caffeine can cause tachycardia, high blood pressure and dysrhythmia. As noted above the combination of ephedra and caffeine seems especially dangerous.

Other plants with stimulant properties are bitter orange (*Citrus aurantium*), yohimbine (concentrated extract from the bark of the *Pausinystalia yohimbe tree)*, khat *(Catha edulis) and coca (Erythroxylum coca*). Bitter orange has replaced ephedra in many of the over-the-counter stimulant weight loss products. It contains synephrine, a potent vasoconstrictor. Yohimbine is used for erectile dysfunction (for which there is significant supportive clinical research evidence). It has alpha-2-adrenergic antagonist activity in the central nervous system which stimulates the sympathetic nervous system. Khat contains cathinone, which has an amphetamine-like effect. Coca contains cocaine which is an alpha- and beta-receptor agonist.

CONCLUSION

Integrative cardiology is the field that brings Integrative Medicine principles to the practice of cardiology. It is holistic in that it addresses all factors that influence cardiovascular health, such as nutrition, exercise, sleep, mental health, social health, spirituality and environment, in addition to the conventionally recognized biomedical factors. It incorporates therapies from other medical systems when indicated and integrates them with conventional therapies. Most of the CAM therapies that are used in integrative cardiology are very safe and therefore it is reasonable to have a low threshold for using them if there exists potential for clinical benefit. These therapies are well-received by patients, enhance the therapeutic alliance between practitioner and patient, increase patient autonomy and encourage greater patient participation and responsibility. In the mission to best care for patients with cardiovascular disease, integrative cardiology has much to offer to the world of conventional cardiovascular medicine.

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GUIDELINES FOR HEART FAILURE

RECOMMENDATIONS FOR INITIAL CLINICAL ASSESSMENT OF PATIENTS PRESENTING WITH HEART FAILURE

Class I

1. A thorough history and physical examination should be obtained/performed in patients presenting with HF to identify cardiac and noncardiac disorders or behaviors that might cause or accelerate the development or progression of HF (Level of Evidence: C)
2. A careful history of current and past use of alcohol, illicit drugs, current or past standard or "alternative therapies", and chemotherapy drugs should be obtained from patients presenting with HF (Level of Evidence: C)
3. In patients presenting with HF, initial assessment should be made of the patient's ability to perform routine and desired activities of daily living (Level of Evidence: C)
4. Initial examination of patients presenting with HF should include assessment of the patient's volume status, orthostatic blood pressure changes, measurement of weight and height, and calculation of body mass index (Level of Evidence: C)
5. Initial laboratory evaluation of patients presenting with HF should include complete blood count, urinalysis, serum electrolytes (including calcium and magnesium), blood urea nitrogen, serum creatinine, fasting blood glucose (glycohemoglobin), lipid profile, liver function tests and thyroid-stimulating hormone (Level of Evidence: C)
6. Twelve-lead electrocardiogram and chest radiograph (posterior-anterior and lateral) should be performed initially in all patients presenting with HF (Level of Evidence: C)
7. Two-dimensional echocardiography with Doppler should be performed during initial evaluation of patients presenting with HF to assess LVEF, left ventricular size, wall thickness and valve function. Radionuclide ventriculography can be performed to assess LVEF and volumes (Level of Evidence: C)
8. Coronary arteriography should be performed in patients presenting with HF who have angina or significant ischemia unless the patient is not eligible for revascularization of any kind (Level of Evidence: B)

Class IIa

1. Coronary arteriography is reasonable for patients presenting with HF who have chest pain that may or may not be of cardiac origin who have not had evaluation of their coronary anatomy and who have no contraindications to coronary revascularization (Level of Evidence: C)
2. Coronary arteriography is reasonable for patients presenting with HF who have known or suspected coronary artery disease but who do not have angina unless the patient is not eligible for revascularization of any kind (Level of Evidence: C)
3. Noninvasive imaging to detect myocardial ischemia and viability is reasonable in patients presenting with HF who have known coronary artery disease and no angina unless the patient is not eligible for revascularization of any kind (Level of Evidence: B)
4. Maximal exercise testing with or without measurement of respiratory gas exchange and/or blood oxygen saturation is reasonable in patients presenting with HF to help determine whether HF is the cause of exercise limitation when the contribution of HF is uncertain (Level of Evidence: C)
5. Maximal exercise testing with measurement of respiratory gas exchange is reasonable to identify high-risk patients presenting with HF who are candidates for cardiac transplantation or other advanced treatments (Level of Evidence: B)
6. Screening for hemochromatosis, sleep-disturbed breathing, or human immunodeficiency virus is reasonable in selected patients who present with HF (Level of Evidence: C)
7. Diagnostic tests for rheumatologic diseases, amyloidosis or pheochromocytoma are reasonable in patients presenting with HF in whom there is a clinical suspicion of these diseases (Level of Evidence: C)
8. Endomyocardial biopsy can be useful in patients presenting with HF when a specific diagnosis is suspected that would influence therapy (Level of Evidence: C)
9. Measurement of natriuretic peptides (BNP and NT-proBNP) can be useful in the evaluation of patients presenting in the urgent care setting in whom the clinical diagnosis of HF is uncertain. Measurement of natriuretic peptides (BNP and NT-proBNP) can be helpful in risk stratification (Level of Evidence: A)

Class IIb

1. Noninvasive imaging may be considered to define the likelihood of coronary artery disease in patients with HF and LV dysfunction (Level of Evidence: C)
2. Holter monitoring might be considered in patients presenting with HF who have a history of MI and are being considered for electrophysiologic study to document VT inducibility (Level of Evidence: C)

Class III

1. Endomyocardial biopsy should not be performed in the routine evaluation of patients with HF (Level of Evidence: C)
2. Routine use of signal-averaged electrocardiography is not recommended for the evaluation of patients presenting with HF (Level of Evidence: C)
3. Routine measurement of circulating levels of neurohormones (e.g. norepinephrine or endothelin) is not recommended for patients presenting with HF (Level of Evidence: C)

RECOMMENDATIONS FOR SERIAL CLINICAL ASSESSMENT OF PATIENTS PRESENTING WITH HEART FAILURE

Class I

1. Assessment should be made at each visit of the ability of a patient with HF to perform routine and desired activities of daily living (Level of Evidence: C)
2. Assessment should be made at each visit of the volume status and weight of a patient with HF (Level of Evidence: C)
3. Careful history of current use of alcohol, tobacco, illicit drugs, "alternative therapies", and chemotherapy drugs, as well as diet and sodium intake, should be obtained at each visit of a patient with HF (Level of Evidence: C)

Class IIa

1. Repeat measurement of EF and the severity of structural remodeling can be useful to provide information in patients with HF who have had a change in clinical status or who have experienced or recovered from a clinical event or received treatment that might have had a significant effect on cardiac function (Level of Evidence: C)

Class IIb

1. The value of serial measurements of BNP to guide therapy for patients with HF is not well established (Level of Evidence: C)

PATIENTS AT HIGH RISK FOR DEVELOPING HEART FAILURE (STAGE A)

RECOMMENDATIONS

Class I

1. In patients at high risk for developing HF, systolic and diastolic hypertension should be controlled in accordance with contemporary guidelines (Level of Evidence: A)
2. In patients at high risk for developing HF, lipid disorders should be treated in accordance with contemporary guidelines (Level of Evidence: A)
3. For patients with diabetes mellitus (who are all at high risk for developing HF), blood sugar should be controlled in accordance with contemporary guidelines (Level of Evidence: C)
4. Patients at high risk for developing HF should be counseled to avoid behaviors that may increase the risk of HF (e.g. smoking, excessive alcohol consumption and illicit drug use) (Level of Evidence: C)
5. Ventricular rate should be controlled or sinus rhythm restored in patients with supraventricular tachyarrhythmias who are at high risk for developing HF (Level of Evidence: B)
6. Thyroid disorders should be treated in accordance with contemporary guidelines in patients at high risk for developing HF (Level of Evidence: C)
7. Healthcare providers should perform periodic evaluation for signs and symptoms of HF in patients at high risk for developing HF (Level of Evidence: C)
8. In patients at high risk for developing HF who have known atherosclerotic vascular disease, healthcare providers should follow current guidelines for secondary prevention (Level of Evidence: C)
9. Healthcare providers should perform a noninvasive evaluation of LV function (i.e. LVEF) in patients with a strong family history of cardiomyopathy or in those receiving cardiotoxic interventions (Level of Evidence: C)

Class IIa

1. Angiotensin converting enzyme inhibitors can be useful to prevent HF in patients at high risk for developing HF who have a history of atherosclerotic vascular disease, diabetes mellitus or hypertension with associated cardiovascular risk factors (Level of Evidence: A)
2. Angiotensin II receptor blockers can be useful to prevent HF in patients at high risk for developing HF who have a history of atherosclerotic vascular disease, diabetes mellitus, or hypertension with associated cardiovascular risk factors (Level of Evidence: C)

Class III

1. Routine use of nutritional supplements solely to prevent the development of structural heart disease should not be recommended for patients at high risk for developing HF (Level of Evidence: C)

PATIENTS WITH CARDIAC STRUCTURAL ABNORMALITIES OR REMODELING WHO HAVE NOT DEVELOPED HEART FAILURE SYMPTOMS (STAGE B)

RECOMMENDATIONS

Class I

1. All Class I recommendations for Stage A should apply to patients with cardiac structural abnormalities who have not developed HF (Levels of Evidence: A, B and C as appropriate)
2. Beta blockers and ACEIs should be used in all patients with a recent or remote history of MI regardless of EF or presence of HF (Level of Evidence: A)
3. Beta blockers are indicated in all patients without a history of MI who have a reduced LVEF with no HF symptoms (Level of Evidence: C)
4. Angiotensin converting enzyme inhibitors should be used in patients with a reduced EF and no symptoms of HF, even if they have not experienced MI (Level of Evidence: A)
5. An ARB should be administered to post-MI patients without HF who are intolerant of ACEIs and have a low LVEF (Level of Evidence: B)
6. Patients who have not developed HF symptoms should be treated according to contemporary guidelines after an acute MI (Level of Evidence: C)
7. Coronary revascularization should be recommended in appropriate patients without symptoms of HF in accordance with contemporary guidelines (see ACC/AHA/ACP-ASIM Guidelines for the Management of Patients with Chronic Stable Angin) (Level of Evidence: A)
8. Valve replacement or repair should be recommended for patients with hemodynamically significant valvular stenosis or regurgitation and no symptoms of HF in accordance with contemporary guidelines (Level of Evidence: B)

Class IIa

1. Angiotensin converting enzyme inhibitors or ARBs can be beneficial in patients with hypertension and LVH and no symptoms of HF (Level of Evidence: B)
2. Angiotensin II receptor blockers can be beneficial in patients with low EF and no symptoms of HF who are intolerant of ACEIs (Level of Evidence: C)
3. Placement of an ICD is reasonable in patients with ischemic cardiomyopathy who are at least 40 days post-MI, have an LVEF of 30% or less, are NYHA functional Class I on chronic optimal medical therapy, and have reasonable expectation of survival with a good functional status for more than 1 year (Level of Evidence: B)

Class IIb

1. Placement of an ICD might be considered in patients without HF who have nonischemic cardiomyopathy and an LVEF less than or equal to 30% who are in NYHA functional Class I with chronic optimal medical therapy and have a reasonable expectation of survival with good functional status for more than 1 year (Level of Evidence: C)

Class III

1. Digoxin should not be used in patients with low EF, sinus rhythm, and no history of HF symptoms, because in this population the risk of harm is not balanced by any known benefit (Level of Evidence: C)
2. Use of nutritional supplements to treat structural heart disease or to prevent the development of symptoms of HF is not recommended (Level of Evidence: C)
3. Calcium channel blockers with negative inotropic effects may be harmful in asymptomatic patients with low LVEF and no symptoms of HF after MI (Level of Evidence: C)

PATIENTS WITH CURRENT OR PRIOR SYMPTOMS OF HF (STAGE C)

RECOMMENDATIONS

Class I

1. Measures listed as Class I recommendations for patients in stages A and B are also appropriate for patients in Stage C (Levels of Evidence: A, B and C as appropriate)

2. Diuretics and salt restriction are indicated in patients with current or prior symptoms of HF and reduced LVEF who have evidence of fluid retention (Level of Evidence: C)
3. Angiotensin-converting enzyme inhibitors are recommended for all patients with current or prior symptoms of HF and reduced LVEF, unless contraindicated (Level of Evidence: A)
4. Use of 1 of the 3 beta blockers proven to reduce mortality (i.e. bisoprolol, carvedilol and sustained release metoprolol succinate) is recommended for all stable patients with current or prior symptoms of HF and reduced LVEF, unless contraindicated (Level of Evidence: A)
5. Angiotensin II receptor blockers are recommended in patients with current or prior symptoms of HF and reduced LVEF who are ACEI-intolerant (see text for information regarding patients with angioedema) (Level of Evidence: A)
6. Drugs known to adversely affect the clinical status of patients with current or prior symptoms of HF and reduced LVEF should be avoided or withdrawn whenever possible (e.g. nonsterodal anti-inflammatory drugs, most antiarrhythmic drugs, and most calcium channel blocking drugs; see text) (Level of Evidence: B)
7. Exercise training is beneficial as an adjunctive approach to improve clinical status in ambulatory patients with current or prior symptoms of HF and reduced LVEF (Level of Evidence: B)
8. An implantable cardioverter-defibrillator is recommended as secondary prevention to prolong survival in patients with current or prior symptoms of HF and reduced LVEF who have a history of cardiac arrest, ventricular fibrillation or hemodynamically destabilizing ventricular tachycardia (Level of Evidence: A)
9. Implantable cardioverter-defibrillator therapy is recommended for primary prevention of sudden cardiac death to reduce total mortality in patients with nonischemic dilated cardiomyopathy or ischemic heart disease at least 40 days post-MI, an LVEF less than or equal to 35%, and NYHA functional Class II or III symptoms while receiving chronic optimal medical therapy, and who have reasonable expectation of survival with a good functional status for more than 1 year (Level of Evidence: A)
10. Patients with LVEF of less than or equal to 35%, sinus rhythm, and NYHA functional Class III ambulatory Class IV symptoms despite recommended optimal medical therapy and who have cardiac dyssynchrony, which is currently defined as a QRS duration greater than or equal to 0.12 seconds, should receive cardiac resynchronization therapy, with or without an ICD, unless contraindicated (Level of Evidence: A)
11. Addition of an aldosterone antagonist is recommended in selected patients with moderately severe to severe symptoms of HF and reduced LVEF who can be carefully monitored for preserved renal function and normal potassium concentration. Creatinine should be 2.5 mg/dL or less in men or 2.0 mg/dL or less in women and potassium should be less than 5.0 mEq/l. Under circumstances where monitoring for hyperkalemia or renal dysfunction is not anticipated to be feasible, the risks may outweigh the benefits of aldosterone antagonists (Level of Evidence: B)
12. The combination of hydralazine and nitrates is recommended to improve outcomes for patients self-described as African-Americans, with moderate-severe symptoms on optimal therapy with ACEIs, beta blockers and diuretics (Level of Evidence: B)

Class IIa

1. It is reasonable to treat patients with atrial fibrillation and HF with a strategy to maintain sinus rhythm or with a strategy to control ventricular rate alone (Level of Evidence: A)
2. Maximal exercise testing with or without measurement of respiratory gas exchange is reasonable to facilitate prescription of an appropriate exercise program for patients presenting with HF (Level of Evidence: C)
3. Angiotensin II receptor blockers are reasonable to use as alternatives to ACEIs as first-line therapy for patients with mild to moderate HF and reduced LVEF, especially for patients already taking ARBs for other indications (Level of Evidence: A)
4. Digitalis can be beneficial in patients with current or prior symptoms of HF and reduced LVEF to decrease hospitalizations for HF (Level of Evidence: B)
5. The addition of a combination of hydralazine and a nitrate is reasonable for patients with reduced LVEF who are already taking an ACEI and beta blocker for symptomatic HF and who have persistent symptoms (Level of Evidence: B)
6. For patients who have LVEF less than or equal to 35%, a QRS duration of greater than or equal to 0.12 seconds, and atrial fibrillation (AF), CRT with or without an ICD is reasonable for the treatment of NYHA functional Class III or ambulatory Class IV heart failure symptoms on optimal recommended medical therapy (Level of Evidence: B)
7. For patients with LVEF of less than or equal to 35% with NYHA functional Class III or ambulatory Class IV symptoms who are receiving optimal recommended medical therapy and who have frequent dependence on ventricular pacing, CRT is reasonable (Level of Evidence: C)

Class IIb

1. A combination of hydralazine and a nitrate might be reasonable in patients with current or prior symptoms of HF and reduced LVEF who cannot be given an ACEI or ARB because of drug intolerance, hypotension or renal insufficiency (Level of Evidence: C)
2. The addition of an ARB may be considered in persistently symptomatic patients with reduced LVEF who are already being treated with conventional therapy (Level of Evidence: B)

Class III

1. Routine combined use of an ACEI, ARB and aldosterone antagonist is not recommended for patients with current or prior symptoms of HF and reduced LVEF (Level of Evidence: C)
2. Calcium channel blocking drugs are not indicated as routine treatment for HF in patients with current or prior symptoms of HF and reduced LVEF (Level of Evidence: A)
3. Long-term use of an infusion of a positive inotropic drug may be harmful and is not recommended for patients with current or prior symptoms of HF and reduced LVEF, except as palliation for patients with end-stage disease who cannot be stabilized with standard medical treatment (see recommendations for Stage D) (Level of Evidence: C)
4. Use of nutritional supplements as treatment for HF is not indicated in patients with current or prior symptoms of HF and reduced LVEF (Level of Evidence: C)
5. Hormonal therapies other than to replete deficiencies are not recommended and may be harmful to patients with current or prior symptoms of HF and reduced LVEF (Level of Evidence: C)

RECOMMENDATIONS

Class I

1. Physicians should control systolic and diastolic hypertension in patients with HF and normal LVEF, in accordance with published guidelines (Level of Evidence: A)
2. Physicians should control ventricular rate in patients with HF and normal LVEF and atrial fibrillation (Level of Evidence: C)
3. Physicians should use diuretics to control pulmonary congestion and peripheral edema in patients with HF and normal LVEF (Level of Evidence: C)

Class IIa

1. Coronary revascularization is reasonable in patients with HF and normal LVEF and coronary artery disease in whom symptomatic or demonstrable myocardial ischemia is judged to be having an adverse effect on cardiac function (Level of Evidence: C)

Class IIb

1. Restoration and maintenance of sinus rhythm in patients with atrial fibrillation and HF and normal LVEF might be useful to improve symptoms (Level of Evidence: C)
2. The use of beta-adrenergic blocking agents, ACEIs, ARBs, orcalcium antagonists in patients with HF and normal LVEF and controlled hypertension might be effective to minimize symptoms of HF (Level of Evidence: C)
3. The usefulness of digitalis to minimize symptoms of HF in patients with HF and normal LVEF is not well established (Level of Evidence: C)

RECOMMENDATIONS

Class I

1. Meticulous identification and control of fluid retention is recommended in patients with refractory end-stage HF (Level of Evidence: B)
2. Referral for cardiac transplantation in potentially eligible patients is recommended for patients with refractory end-stage HF (Level of Evidence: B)
3. Referral of patients with refractory end-stage HF to an HF program with expertise in the management of refractory HF is useful (Level of Evidence: A)
4. Options for end-of-life care should be discussed with the patient and family when severe symptoms in patients with refractory end-stage HF persist despite application of all recommended therapies (Level of Evidence: C)
5. Patients with refractory end-stage HF and implantable defibrillators should receive information about the option to inactivate the defibrillator (Level of Evidence: C)

Class IIa

1. Consideration of an LV assist device as permanent or “destination” therapy is reasonable in highly selected patients with refractory end-stage HF and an estimated 1-year mortality over 50% with medical therapy (Level of Evidence: B)

Class IIb

1. Pulmonary artery catheter placement may be reasonable to guide therapy in patients with refractory end-stage HF and persistently severe symptoms (Level of Evidence: C)

2. The effectiveness of mitral valve repair or replacement is not well established for severe secondary mitral regurgitation in refractory end-stage HF (Level of Evidence: C)
3. Continuous intravenous infusion of a positive inotropic agent may be considered for palliation of symptoms in patients with refractory end-stage HF (Level of Evidence: C)

Class III

1. Partial left ventriculectomy is not recommended in patients with nonischemic cardiomyopathy and refractory end-stage HF (Level of Evidence: C)
2. Routine intermittent infusions of vasoactive and positive inotropic agents are not recommended for patients with refractory end-stage HF (Level of Evidence: A)

HOSPITALIZED PATIENT

RECOMMENDATIONS

Class I

1. The diagnosis of HF is primarily based on signs and symptoms derived from a thorough history and physical examination. Clinicians should determine the following:
   - adequacy of systemic perfusion;
   - volume status;
   - the contribution of precipitating factors and/or comorbidities;
   - if the heart failure is new onset or an exacerbation of chronic disease and
   - whether it is associated with preserved ejection fraction.

   Chest radiographs, electrocardiogram and echocardiography are key tests in this assessment (Level of Evidence: C)
2. Concentrations of B-type natriuretic peptide (BNP) or N-terminal pro-B-type natriuretic peptide (NT-proBNP) should be measured in patients being evaluated for dyspnea in which the contribution of HF is not known. Final diagnosis requires interpreting these results in the context of all available clinical data and ought not to be considered a stand-alone test (Level of Evidence: A)
3. Acute coronary syndrome precipitating HF hospitalization should be promptly identified by electrocardiogram and cardiac troponin testing, and treated as appropriate to the overall condition and prognosis of the patient (Level of Evidence: C)
4. It is recommended that the following common potential precipitating factors for acute HF be identified as recognition of these comorbidities is critical to guide therapy:
   - acute coronary syndromes/coronary ischemia;
   - severe hypertension;
   - atrial and ventricular arrhythmias;
   - infections;
   - pulmonary emboli;
   - renal failure and
   - medical or dietary noncompliance (Level of Evidence: C)
5. Oxygen therapy should be administered to relieve symptoms related to hypoxemia (Level of Evidence: C)
6. Whether the diagnosis of HF is new or chronic, patients who present with rapid decompensation and hypoperfusion associated with decreasing urine output and other manifestations of shock are critically ill and rapid intervention should be used to improve systemic perfusion (Level of Evidence)
7. Patients admitted with HF and with evidence of significant fluid overload should be treated with intravenous loop diuretics. Therapy should begin in the emergency department or outpatient clinic without delay, as early intervention may be associated with better outcomes for patients hospitalized with decompensated HF (Level of Evidence: B). If patients are already receiving loop diuretic therapy, the initial intravenous dose should equal or exceed their chronic oral daily dose. Urine output and signs and symptoms of congestion should be serially assessed, and diuretic dose should be titrated accordingly to relieve symptoms and to reduce extracellular fluid volume excess (Level of Evidence: C)
8. Effect of HF treatment should be monitored with careful measurement of fluid intake and output; vital signs; body weight, determined at the same time each day; clinical signs (supine and standing) and symptoms of systemic perfusion and congestion. Daily serum electrolytes, urea nitrogen and creatinine concentrations should be measured during the use of IV diuretics or active titration of HF medications (Level of Evidence: C)
9. When diuresis is inadequate to relieve congestion, as evidenced by clinical evaluation, the diuretic regimen should be intensified using either: (a) higher doses of loop diuretics; (b) addition of a second diuretic (such as metolazone, spironolactone or intravenous chlorothiazide) or (c) continuous infusion of a loop diuretic (Level of Evidence: C)
10. In patients with clinical evidence of hypotension associated with hypoperfusion and obvious evidence of elevated cardiac filling pressures (e.g. elevated jugular venous pressure; elevated pulmonary artery wedge pressure), intravenous inotropic or vasopressor drugs should be administered to maintain systemic perfusion and preserve end-organ performance while more definitive therapy is considered (Level of Evidence: C)

11. Invasive hemodynamic monitoring should be performed to guide therapy in patients who are in respiratory distress or with clinical evidence of impaired perfusion in whom the adequacy or excess of intracardiac filling pressures cannot be determined from clinical assessment (Level of Evidence: C)
12. Medications should be reconciled in every patient and adjusted as appropriate on admission to and discharge from the hospital (Level of Evidence: C)
13. In patients with reduced ejection fraction experiencing a symptomatic exacerbation of HF requiring hospitalization during chronic maintenance treatment with oral therapies known to improve outcomes, particularly ACEIs or ARBs and beta-blocker therapy, it is recommended that these therapies be continued in most patients in the absence of hemodynamic instability or contraindications (Level of Evidence: C)
14. In patients hospitalized with HF with reduced ejection fraction not treated with oral therapies known to improve outcomes, particularly ACEIs or ARBs and beta-blocker therapy, initiation of these therapies is recommended in stable patients prior to hospital discharge·(Level of Evidence: B)
15. Initiation of beta-blocker therapy is recommended after optimization of volume status and successful discontinuation of intravenous diuretics, vasodilators and inotropic agents. Betablocker therapy should be initiated at a low dose and only in stable patients. Particular caution should be used when initiating beta blockers in patients who have required inotropes during their hospital course (Level of Evidence: B)
16. In all patients hospitalized with HF, both with preserved and low EF, transition should be made from intravenous to oral diuretic therapy with careful attention to oral diuretic dosing and monitoring of electrolytes. With all medication changes, the patient should be monitored for supine and upright hypotension, and worsening renal function and HF signs/symptoms (Level of Evidence: C)
17. Comprehensive written discharge instructions for all patients with a hospitalization for HF and their caregivers is strongly recommended, with special emphasis on the following six aspects of care: diet; discharge medications, with a special focus on adherence, persistence, and uptitration to recommended doses of ACEIIARB and beta-blocker medication; activity level; follow-up appointments; daily weight monitoring; and what to do if HF symptoms worsen (Level of Evidence: C)
18. Postdischarge systems of care, if available, should be used to facilitate the transition to effective outpatient care for patients hospitalized with HF (Level of Evidence: B)

Class IIa

1. When patients present with acute HF and known or suspected acute myocardial ischemia due to occlusive coronary disease, especially when there are signs and symptoms of inadequate systemic perfusion, urgent cardiac catheterization and revascularization is reasonable where it is likely to prolong meaningful survival (Level of Evidence: C)
2. In patients with evidence of severely symptomatic fluid overload in the absence of systemic hypotension, vasodilators, such as intravenous nitroglycerin, nitroprusside or nesiritide, can be beneficial when added to diuretics and/or in those who do not respond to diuretics alone (Level of Evidence: C)
3. Invasive hemodynamic monitoring can be useful for carefully selected patients with acute HF who have persistent symptoms despite empiric adjustment of standard therapies, and
   a. whose fluid status, perfusion, or systemic or pulmonary vascular resistances are uncertain;
   b. whose systolic pressure remains low, or is associated with symptoms, despite initial therapy;
   c. whose renal function is worsening with therapy;
   d. who require parenteral vasoactive agents; or
   e. who may need consideration for advanced device therapy or transplantation. (Level of Evidence: C)
4. Ultrafiltration is reasonable for patients with refractory congestion not responding to medical therapy (Level of Evidence: B)

Class IIb

1. Intravenous inotropic drugs, such as dopamine, dobutamine or milrinone, might be reasonable for those patients presenting with documented severe systolic dysfunction, low blood pressure and evidence of low cardiac output, with or without congestion, to maintain systemic perfusion and preserve end-organ performance (Level of Evidence: C)

Class III

1. Use of parenteral inotropes in normotensive patients with acute decompensated HF without evidence of decreased organ perfusion is not recommended (Level of Evidence: B)
2. Routine use of invasive hemodynamic monitoring in normotensive patients with acute decompensated HF and congestion with symptomatic response to diuretics and vasodilators is not recommended (Level of Evidence: B)

TREATMENT OF SPECIAL POPULATIONS

RECOMMENDATIONS

Class I

1. The combination of a fixed dose of isosorbide dinitrate and hydralazine to a standard medical regimen for HF, including ACEIs and beta blockers, is recommended in order to improve outcomes for patients self-described as African Americans,

with NYHA functional Class III or IV HF. Others may benefit similarly, but this has not yet been tested (Level of Evidence: A)
2. Groups of patients including (a) high-risk ethnic minority groups (e.g. blacks), (b) groups under-represented in clinical trials and (c) any groups believed to be underserved should, in the absence of specific evidence to direct otherwise, have clinical screening and therapy in a manner identical to that applied to the broader population (Level of Evidence: B)
3. It is recommended that evidence-based therapy for HF be used in the elderly patient, with individualized consideration of the elderly patient's altered ability to metabolize or tolerate standard medications (Level of Evidence: C)

PATIENTS WITH HEART FAILURE WHO HAVE CONCOMITANT DISORDERS

RECOMMENDATIONS

Class I

1. All other recommendations should apply to patients with concomitant disorders unless there are specific exceptions (Level of Evidence: C)
2. Physicians should control systolic and diastolic hypertension and diabetes mellitus in patients with HF in accordance with recommended guidelines (Level of Evidence: C)
3. Physicians should use nitrates and beta blockers for the treatment of angina in patients with HF (Level of Evidence: B)
4. Physicians should recommend coronary revascularization according to recommended guidelines in patients who have both HF and angina (Level of Evidence: A)
5. Physicians should prescribe anticoagulants in patients with HF who have paroxysmal or persistent atrial fibrillation or a previous thromboembolic event (Level of Evidence: A)
6. Physicians should control the ventricular response rate in patients with HF and atrial fibrillation with a beta blocker (or amiodarone, if the beta blocker is contraindicated or not tolerated) (Level of Evidence: A)
7. Patients with coronary artery disease and HF should be treated in accordance with recommended guidelines for chronic stable angina (Level of Evidence: C)
8. Physicians should prescribe antiplatelet agents for prevention of MI and death in patients with HF who have underlying coronary artery disease (Level of Evidence: B)

Class IIa

1. It is reasonable to prescribe digitalis to control the ventricular response rate in patients with HF and atrial fibrillation (Level of Evidence: A)
2. It is reasonable to prescribe amiodarone to decrease recurrence of atrial arrhythmias and to decrease recurrence of ICD discharge for ventricular arrhythmias (Level of Evidence: C)

Class IIb

1. The usefulness of current strategies to restore and maintain sinus rhythm in patients with HF and atrial fibrillation is not well established (Level of Evidence: C)
2. The usefulness of anticoagulation is not well established in patients with HF who do not have atrial fibrillation or a previous thromboembolic event (Level of Evidence: B)
3. The benefit of enhancing erythropoiesis in patients with HF and anemia is not established (Level of Evidence: C)

Class III

1. Class I or Ill antiarrhythmic drugs are not recommended in patients with HF for the prevention of ventricular arrhythmias (Level of Evidence: A)
2. The use of antiarrhythmic medication is not indicated as primary treatment for asymptomatic ventricular arrhythmias or to improve survival in patients with HF (Level of Evidence: A)

END-OF-LIFE CONSIDERATIONS

RECOMMENDATIONS

Class I

1. Ongoing patient and family education regarding prognosis for functional capacity and survival is recommended for patients with HF at the end of life (Level of Evidence: C)
2. Patient and family education about options for formulating and implementing advance directives and the role of palliative and hospice care services with reevaluation for changing clinical status is recommended for patients with HF at the end of life (Level of Evidence: C)

3. Discussion is recommended regarding the option of inactivating ICDs for patients with HF at the end of life (Level of Evidence: C)
4. It is important to ensure continuity of medical care between inpatient and outpatient settings for patients with HF at the end of life (Level of Evidence: C)
5. Components of hospice care that are appropriate to the relief of suffering, including opiates, are recommended and do not preclude the options for use of inotropes and intravenous diuretics for symptom palliation for patients with HF at the end of life (Level of Evidence: C)
6. All professionals working with HF patients should examine current end-of-life processes and work toward improvement in approaches to palliation and end-of-life care (Level of Evidence: C)

IMPLEMENTATION OF PRACTICE GUIDELINES

RECOMMENDATIONS

Class I

1. Academic detailing or educational outreach visits are useful to facilitate the implementation of practice guidelines (Level of Evidence: A)
2. Multidisciplinary disease-management programs for patients at high risk for hospital admission or clinical deterioration are recommended to facilitate the implementation of practice guidelines, to attack different barriers to behavioral change, and to reduce the risk of subsequent hospitalization for HF (Level of Evidence: A)

Class IIa

1. Chart audit and feedback of results can be effective to facilitate implementation of practice guidelines (Level of Evidence: A)
2. The use of reminder systems can be effective to facilitate implementation of practice guidelines (Level of Evidence: A)
3. The use of performance measures based on practice guidelines may be useful to improve quality of care (Level of Evidence: B)
4. Statements by and support of local opinion leaders can be helpful to facilitate implementation of practice guidelines (Level of Evidence: A)

Class IIb

1. Multidisciplinary disease-management programs for patients at low risk for hospital admission or clinical deterioration may be considered to facilitate implementation of practice guidelines (Level of Evidence: B)

Class III

1. Dissemination of guidelines without more intensive behavioral change efforts is not useful to facilitate implementation of practice guidelines (Level of Evidence: A)
2. Basic provider education alone is not useful to facilitate implementation of practice guidelines (Level of Evidence: A)

GUIDELINES FOR VALVULAR HEART DISEASES

CARDIAC MURMURS

CLASSIFICATION OF CARDIAC MURMURS

1. Systolic murmurs
   - Holosystolic (pansystolic) murmurs
   - Midsystolic (systolic ejection) murmurs
   - Early systolic murmurs
   - Mid-to-late systolic murmurs
2. Diastolic murmurs
   - Early high-pitched diastolic murmurs
   - Mid-diastolic murmurs
   - Presystolic murmurs
3. Continuous murmurs

INTERVENTIONS USED TO ALTER THE INTENSITY OF CARDIAC MURMURS

Respiration

Right-sided murmurs generally increase with inspiration. Left-sided murmurs usually are louder during expiration.

Valsalva Maneuver

Most murmurs decrease in length and intensity. Two exceptions are the systolic murmur of hypertrophic cardiomyopathy (HCM), which usually becomes much louder, and that of mitral valve prolapse (MVP), which becomes longer and often louder. After release of the Valsalva, right-sided murmurs tend to return to baseline intensity earlier than left-sided murmurs.

Exercise

Murmurs caused by blood flow across normal or obstructed valves [e.g. pulmonic stenosis (PS) and mitral stenosis (MS)] become louder with both isotonic and isometric (handgrip) exercise. Murmurs of mitral regurgitation (MR), ventricular septal defect (VSD) and aortic regurgitation (AR) also increase with handgrip exercise.

Positional Changes

With standing, most murmurs diminish, two exceptions being the murmur of HCM, which becomes louder, and that of MVP, which lengthens and often is intensified. With brisk squatting, most murmurs become louder, but those of HCM and MVP usually soften and may disappear. Passive leg raising usually produces the same results as brisk squatting.

Postventricular Premature Beat or Atrial Fibrillation

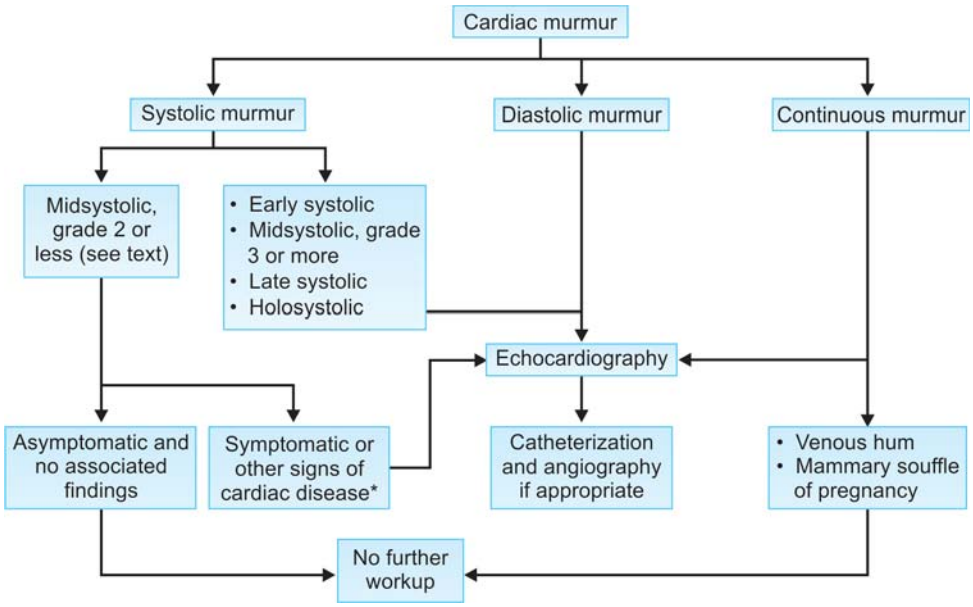
Murmurs originating at normal or stenotic semilunar valves increase in intensity during the cardiac cycle after a ventricular premature beat (VPB) or in the beat after a long cycle length in atrial fibrillation (AF).
By contrast, systolic murmurs due to atrioventricular valve regurgitation do not change, diminish (papillary muscle dysfunction), or become shorter (MVP).

Pharmacological Interventions

During the initial relative hypotension after amyl nitrite inhalation, murmurs of MR, VSD and AR decrease, whereas murmurs of aortic stenosis (AS) increase because of increased stroke volume. During the later tachycardia phase, murmurs of MS and right-sided lesions also increase. This intervention may thus distinguish the murmur of the Austin-Flint phenomenon from that of MS. The response in MVP often is biphasic (softer then louder than control).

Transient Arterial Occlusion

Transient external compression of both arms by bilateral cuff inflation to 20 mm Hg greater than peak systolic pressure augments the murmurs of MR, VSD and AR but not murmurs due to other causes.



*If an electrocardiogram or chest X-ray has been obtained and is abnormal, echocardiography is indicated.

FIGURE 1: Strategy for evaluating heart murmurs

ECHOCARDIOGRAPHY

Class I

1. Echocardiography is recommended for asymptomatic patients with diastolic murmurs, continuous murmurs, holosystolic murmurs, late systolic murmurs, murmurs associated with ejection clicks, or murmurs that radiate to the neck or back (Level of Evidence: C)
2. Echocardiography is recommended for patients with heart murmurs and symptoms or signs of heart failure, myocardial ischemia/infarction, syncope, thromboembolism, infective endocarditis or other clinical evidence of structural heart disease (Level of Evidence: C)
3. Echocardiography is recommended for asymptomatic patients who have grade 3 or louder midpeaking systolic murmurs (Level of Evidence: C)

Class IIa

1. Echocardiography can be useful for the evaluation of asymptomatic patients with murmurs associated with other abnormal cardiac physical findings or murmurs associated with an abnormal ECG or chest X-ray (Level of Evidence: C)
2. Echocardiography can be useful for patients whose symptoms and/or signs are likely noncardiac in origin but in whom a cardiac basis cannot be excluded by standard evaluation (Level of Evidence: C)

Class III

Echocardiography is not recommended for patients who have a grade 2 or softer midsystolic murmur identified as innocent or functional by an experienced observer (Level of Evidence: C)

ENDOCARDITIS PROPHYLAXIS

Class IIa

1. Prophylaxis against infective endocarditis is reasonable for the following patients at highest risk for adverse outcomes from infective endocarditis who undergo dental procedures that involve manipulatlon of either gingival tissue or the periapical region of teeth or perforation of the oral mucosa:
   - Patients with prosthetic cardiac valve or prosthetic material used for cardiac valve repair (Level of Evidence: B)
   - Patients with previous infective endocarditis (Level of Evidence: B)
   - Patients with CHD (Level of Evidence: B)
   - Unrepaired cyanotic CHD, including palliative shunts and conduits (Level of Evidence: B)
   - Completely repaired congenital heart defect repaired with prosthetic material or device, whether placed by surgery or by catheter intervention, during the first 6 months after the procedure (Level of Evidence: B)
   - Repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device (both of which inhibit endothelialization) (Level of Evidence: B)

Class III

1. Prophylaxis against infective endocarditis is not recommended for nondental procedures (such as transesophageal echocardiogram, esophagogastroduodenoscopy or colonoscopy) in the absence of active infection (Level of Evidence: B)

ENDOCARDITIS PROPHYLAXIS FOR DENTAL PROCEDURES

Reasonable

Endocarditis prophylaxis is reasonable for patients with the highest risk of adverse outcomes who undergo dental procedures that involve manipulation of either gingival tissue or the periapical region of teeth or perforation of the oral mucosa.

Not Recommended

Endocarditis prophylaxis is not recommended for:

- Routine anesthetic injections through noninfected tissue
- Dental radiographs
- Placement or removal of prosthodontic or orthodontic appliances
- Adjustment of orthodontic appliances
- Placement of orthodontic brackets
- Shedding of deciduous teeth
- Bleeding from trauma to the lips or oral mucosa

TABLE 1

Regimens for a dental procedure*

		Regimen: Single dose 30 to 60 min before procedure	
Situation	*Agent*	*Adults*	*Children*
Oral	Amoxicillin	2 g	50 mg/kg
Unable to take oral medication	Ampicillin	2 g IM or IV	50 mg/kg 1M or IV
	OR		
	Cefazolin or ceftriaxone	1 g IM or IV	50 mg/kg 1M or IV
Allergic to penicillins or ampicillin—oral	Cephalexin†‡	2 g	50 mg/kg
	OR		
	Clindamycin	600 mg	20 mg/kg
	OR		
	Azithromycin or clarithromycin	500 mg	1.5 mg/kg
Allergic to penicillins or ampicillin and unable to take oral medication	Cefazolin or ceftriaxone‡	1 g IM or IV	50 mg/kg 1M or IV
	OR		
	Clindamycin	600 mg IM or IV	20 mg/kg IM or IV

*This table corresponds to Table 4 in the ACC/AHA 2008 Guideline Update on Valvular Heart Disease: Focused Update on Infective Endocarditis (1069). †Or use other first-or second-generation oral cephalosporin in equivalent adult or pediatric dosage. ‡Cephalosporins should not be used in an individual with a history of anaphylaxis, angioedema or urticaria with penicillins or ampicillin. (Abbreviations: IM: Intramuscular; IV: Intravenous)

TABLE 2

Primary prevention of rheumatic fever

Agent	*Dose*	*Mode*	*Duration*
Benzathine/Penicillin G	Patients 27 kg (60 lb) or less; 600 000 U Patients greater than 27 kg (60 lb): 1200 000 U	Intramuscular	Once
or			
Penicillin V (phenoxymethyl penicillin)	Children: 250 mg 2–3 times dally Adolescents and adults: 500 mg 2–3 times daily	Oral	10 d
For individuals allergic to penicillin			
Erythromycin estolate	20–40 mg/kg/day 2–4 times daily (maximum 1 g/day)	Oral	10 d
or			
Ethylsuccinate	40 mg/kg/day 2–4 times daily (maximum 1 g/day)	Oral	10 d
or			
Azithromycin	500 mg on first day 250 mg/day for the next 4 days	Oral	5 d

(*Source:* Modified from Dajani A, Taubert K, Ferrieri P, et al. Treatment of acute streptococcal pharyngitis and prevention of rheumatic fever: a statement for health professionals. Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease of the Council on Cardiovascular Disease in the Young, the American Heart Association. Pediatrics. 1995;96:758-64)

TABLE 3

Secondary prevention of rheumatic fever

Agent	*Dose*	*Mode*
Penicillin G benzathine	1,200,000 U every 4 week (every 3 wk for hlgh-risk* pts such as those with residual carditis)	Intramuscular
or		
Penicillin V	250 mg twice daily	Oral
or		
Sulfadiazine	0.5 g once daily for pts 27 g (60 lb) or less; 1.0 g once daily for pts greater than 27 kg (60 lb)	Oral
For Individuals allergic to penicillin and sulfadiazine		
Erythromycin	250 mg twice daily	Oral

*High-risk patients include patients with residual rheumatic carditis and patients from economically disadvantaged populations. (Abbreviation: Pts: Patients). (*Source:* Dajani A, Taubert K, Ferrieri P, et al. Treatment of acute streptococcal pharyngitis and prevention of rheumatic fever: a statement for health professionals. Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease of the Council on Cardiovascular Disease in the Young. The American Heart Association. Pediatrics. 1995;96:758-64)

TABLE 4

Duration of secondary rheumatic fever prophylaxis

Category	Duration
Rheumatic fever with carditis and residual heart disease (persistent valvular disease)	10 yrs or greater since last episode and at least until age 40 yrs; sometimes lifelong prophylaxls*
Rheumatic fever with carditis but no residual heart disease (no valvular disease)	10 yrs or well into adulthood, whichever is longer
Rheumatic fever without carditis	5 yrs or until age 21 yrs, whichever Is longer

*The committee's interpretation of "lifelong" prophylaxis refers to patients who are at high risk and likely to come in contact with populations with a high prevalence of streptococcal infection, that is, teachers and daycare workers. (*Source:* Modified from Dajani A, Taubert K, Ferrieri P, et al. Treatment of acute streptococcal pharyngitis and prevention of rheumatic fever: a statement for health professionals. Committee on Rheumatic Fever, Endocarditis and Kawasaki Disease of the Council on Cardiovascular Disease in the Young, the American Heart Association. Pediatrics. 1995;96:758-64)

ECHOCARDIOGRAPHY (IMAGING, SPECTRAL AND COLOR DOPPLER) IN AORTIC STENOSIS

Class I

1. Echocardiography is recommended for the diagnosis and assessment of AS severity (Level of Evidence: B)
2. Echocardiography is recommended in patients with AS for the assessment of LV wall thickness, size and function (Level of Evidence: B)
3. Echocardiography is recommended for re-evaluation of patients with known AS and changing symptoms or signs (Level of Evidence: B)
4. Echocardiography is recommended for the assessment of changes in hemodynamic severity and LV function in patients with known AS during pregnancy (Level of Evidence: B)
5. Transthoracic echocardiography is recommended for re-evaluation of asymptomatic patients: every year for severe AS; every 1–2 years for moderate AS and every 3–5 years for mild AS (Level of Evidence: B)

Class IIIb

1. Exercise testing in asymptomatic patients with AS may be considered to elicit exercise-induced symptoms and abnormal blood pressure responses (Level of Evidence: B)

Class III

1. Exercise testing should not be performed in symptomatic patients with AS (Level of Evidence: B)

INDICATIONS FOR CARDIAC CATHETERIZATION

Class I

1. Coronary angiography is recommended before AVR in patients with AS at risk for CAD (Level of Evidence: B)

2. Cardiac catheterization for hemodynamic measurements is recommended for assessment of severity of AS in symptomatic patients when noninvasive tests are inconclusive or when there is a discrepancy between noninvasive tests and clinical findings regarding severity of AS (Level of Evidence: C)
3. Coronary angiography is recommended before AVR in patients with AS for whom a pulmonary autograft (Ross procedure) is contemplated and if the origin of the coronary arteries was not identified by noninvasive technique (Level of Evidence: C)

Class III

1. Cardiac catheterization for hemodynamic measurements is not recommended for the assessment of severity of AS before AVR when noninvasive tests are adequate and concordant with clinical findings (Level of Evidence: C)
2. Cardiac catheterization for hemodynamic measurements is not recommended for the assessment of LV function and severity of AS in asymptomatic patients (Level of Evidence: C)

LOW-FLOW/LOW-GRADIENT AORTIC STENOSIS

Class IIa

1. Dobutamine stress echocardiography is reasonable to evaluate patients with low-flow/low-gradient AS and LV dysfunction (Level of Evidence: B)
2. Cardiac catheterization for hemodynamic measurements with infusion of dobutamine can be useful for evaluation of patients with low-flow/low-gradient AS and LV dysfunction (Level of Evidence: C)

INDICATIONS FOR AORTIC VALVE REPLACEMENT

Class I

1. AVR is indicated for symptomatic patients with severe AS (Level of Evidence: B)
2. AVR is indicated for patients with severe AS undergoing coronary artery bypass graft surgery (CABG) (Level of Evidence: C)
3. AVR is indicated for patients with severe AS undergoing surgery on the aorta or other heart valves (Level of Evidence: C)
4. AVR is recommended for patients with severe AS and LV systolic dysfunction (ejection fraction < 0.50) (Level of Evidence: C)

Class IIa

1. AVR is reasonable for patients with moderate AS undergoing CABG or surgery on the aorta or other heart valves (Level of Evidence: B)

Class IIb

1. AVR may be considered for asymptomatic patients with severe AS and abnormal response to exercise (e.g. development of symptoms or asymptomatic hypotension) (Level of Evidence: C)
2. AVR may be considered for adults with severe asymptomatic AS if there is a high likelihood of rapid progression (age, calcification and CAD) or if surgery might be delayed at the time of symptom onset (Level of Evidence: C)
3. AVR may be considered in patients undergoing CABG who have mild AS when there is evidence, such as moderate-to-severe valve calcification, that progression may be rapid (Level of Evidence: C)
4. AVR may be considered for asymptomatic patients with extremely severe AS (aortic valve area < 0.6 cm^2, mean gradient > 60 mm Hg, and jet velocity > 5.0 m/sec) when the patient's expected operative mortality is 1.0% or less (Level of Evidence: C)

Class III

1. AVR is not useful for the prevention of sudden death in asymptomatic patients with AS who have none of the findings listed under the Class IIa/IIb recommendations (Level of Evidence: B)

AORTIC BALLOON VALVOTOMY

Class IIb

1. Aortic balloon valvotomy might be reasonable as a bridge to surgery in hemodynamically unstable adult patients with AS who are at high risk for AVR (Level of Evidence: C)
2. Aortic balloon valvotomy might be reasonable for palliation in adult patients with AS in whom AVR cannot be performed because of serious comorbid conditions (Level of Evidence: C)

Class III

1. Aortic balloon valvotomy is not recommended as an alternative to AVR in adult patients with AS; certain younger adults without valve calcification may be an exception (Level of Evidence: B)

DIAGNOSIS AND INITIAL EVALUATION

Class I

1. Echocardiography is indicated to confirm the presence and severity of acute or chronic AR (Level of Evidence: B)
2. Echocardiography is indicated for diagnosis and assessment of the cause of chronic AR (including valve morphology and aortic root size and morphology) and for assessment of LV hypertrophy, dimension (or volume) and systolic function (Level of Evidence: B)
3. Echocardiography is indicated in patients with an enlarged aortic root to assess regurgitation and the severity of aortic dilatation (Level of Evidence: B)
4. Echocardiography is indicated for the periodic re-evaluation of LV size and function in asymptomatic patients with severe AR (Level of Evidence: B)
5. Radionuclide angiography or magnetic resonance imaging is indicated for the initial and serial assessment of LV volume and function at rest in patients with AR and suboptimal echocardiograms (Level of Evidence: B)
6. Echocardiography is indicated to re-evaluate mild, moderate or severe AR in patients with new or changing symptoms (Level of Evidence: B)

Class IIa

1. Exercise stress testing for chronic AR is reasonable for assessment of functional capacity and symptomatic response in patients with a history of equivocal symptoms (Level of Evidence: B)
2. Exercise stress testing for patients with chronic AR is reasonable for the evaluation of symptoms and functional capacity before participation in athletic activities (Level of Evidence: C)
3. Magnetic resonance imaging is reasonable for the estimation of AR severity in patients with unsatisfactory echocardiograms (Level of Evidence: B)

Class IIb

1. Exercise stress testing in patients with radionuclide angiography may be considered for assessment of LV function in asymptomatic or symptomatic patients with chronic AR (Level of Evidence: B)

MEDICAL THERAPY

Class I

1. Vasodilator therapy is indicated for chronic therapy in patients with severe AR who have symptoms or LV dysfunction when surgery is not recommended because of additional cardiac or noncardiac factors (Level of Evidence: B)

Class IIa

1. Vasodilator therapy is reasonable for short-term therapy to improve the hemodynamic profile of patients with severe heart failure symptoms and severe LV dysfunction before proceeding with AVR (Level of Evidence: C)

Class IIb

1. Vasodilator therapy may be considered for long-term therapy in asymptomatic patients with severe AR who have LV dilatation but normal systolic function (Level of Evidence: B)

Class III

1. Vasodilator therapy is not indicated for long-term therapy in asymptomatic patients with mild-to-moderate AR and normal LV systolic function (Level of Evidence: B)
2. Vasodilator therapy is not indicated for long-term therapy in asymptomatic patients with LV systolic dysfunction who are otherwise candidates for AVR (Level of Evidence: C)
3. Vasodilator therapy is not indicated for long-term therapy in symptomatic patients with either normal LV function or mild-to-moderate LV systolic dysfunction who are otherwise candidates for AVR (Level of Evidence: C)

INDICATIONS FOR CARDIAC CATHETERIZATION

Class I

1. Cardiac catheterization with aortic root angiography and measurement of LV pressure is indicated for assessment of severity of regurgitation, LV function or aortic root size when noninvasive tests are inconclusive or discordant with clinical findings in patients with AR (Level of Evidence: B)
2. Coronary angiography is indicated before AVR in patients at risk for CAD (Level of Evidence: C)

Class III

1. Cardiac catheterization with aortic root angiography and measurement of LV pressure is not indicated for assessment of LV function, aortic root size or severity of regurgitation before AVR when noninvasive tests are adequate and concordant with clinical findings and coronary angiography is not needed (Level of Evidence: C)
2. Cardiac catheterization with aortic root angiography and measurement of LV pressure is not indicated for assessment of LV function and severity of regurgitation in asymptomatic patients when noninvasive tests are adequate (Level of Evidence: C)

INDICATIONS FOR AORTIC VALVE REPLACEMENT OR AORTIC VALVE REPAIR

Class I

1. AVR is indicated for symptomatic patients with severe AR irrespective of LV systolic function (Level of Evidence: B)
2. AVR is indicated for 91 asymptomatic patients with chronic severe AR and LV systolic dysfunction (ejection fraction 0.50 or less) at rest (Level of Evidence: B)
3. AVR is indicated for patients with chronic severe AR while undergoing CABG or surgery on the aorta or other heart valves (Level of Evidence: C)

Class IIa

1. AVR is reasonable for asymptomatic patients with severe AR with normal LV systolic function (ejection fraction > 0.50) but with severe LV dilatation (end-diastolic dimension > 75 mm or end-systolic dimension > 55 mm)* (Level of Evidence: B)

Class IIb

1. AVR may be considered in patients with moderate AR while undergoing surgery on the ascending aorta (Level of Evidence: C)
2. AVR may be considered in patients with moderate AR while undergoing CABG (Level of Evidence: C)
3. AVR may be considered for asymptomatic patients with severe AR and normal LV systolic function at rest (ejection fraction > 0.50) when the degree of LV dilatation exceeds an end-diastolic dimension of 70 mm or end-systolic dimension of 50 mm, when there is evidence of progressive LV dilatation, declining exercise tolerance or abnormal hemodynamic responses to exercise* (Level of Evidence: C)

Class III

1. AVR is not indicated for asymptomatic patients with mild, moderate or severe AR and normal LV systolic function at rest (ejection fraction > 0.50) when degree of dilatation is not moderate or severe (end-diastolic dimension < 70 mm, end-systolic dimension < 50 mm)* (Level of Evidence: B)

*Consider lower threshold values for patients of small stature of either gender.

BICUSPID AORTIC VALVE WITH DILATED ASCENDING AORTA

Class I

1. Patients with known bicuspid aortic valves should undergo an initial transthoracic echocardiogram to assess the diameters of the aortic root and ascending aorta (Level of Evidence: B)
2. Cardiac magnetic resonance imaging or cardiac computed tomography is indicated in patients with bicuspid aortic valves when morphology of the aortic root or ascending aorta cannot be assessed accurately by echocardiography (Level of Evidence: C)
3. Patients with bicuspid aortic valves and dilatation of the aortic root or ascending aorta (diameter > 4.0 cm* should undergo serial evaluation of aortic root/ascending aorta size and morphology by echocardiography, cardiac magnetic resonance or computed tomography on a yearly basis (Level of Evidence: C)
4. Surgery to repair the aortic root or replace the ascending aorta is indicated in patients with bicuspid aortic valves if the diameter of the aortic root or ascending aorta is greater than 5.0 cm* or if the rate of increase in diameter is 0.5 cm per year or more (Level of Evidence: C)

5. In patients with bicuspid valves undergoing AVR because of severe AS or AR, repair of the aortic root or replacement of the ascending aorta is indicated if the diameter of the aortic root or ascending aorta is greater than 4.5 cm* (Level of Evidence: C)

Class IIa

1. It is reasonable to give beta-adrenergic blocking agents to patients with bicuspid valves and dilated aortic roots (diameter > 4.0 cm*) who are not candidates for surgical correction and who do not have moderate-to-severe AR (Level of Evidence: C)
2. Cardiac magnetic resonance imaging or cardiac computed tomography is reasonable in patients with bicuspid aortic valves when aortic root dilatation is detected by echocardiography to further quantify severity of dilatation and involvement of the ascending aorta (Level of Evidence: B)

*Consider lower threshold values for patients of small stature of either gender.

INDICATIONS FOR ECHOCARDIOGRAPHY IN MITRAL STENOSIS

Class I

1. Echocardiography should be performed in patients for the diagnosis of MS, assessment of hemodynamic severity (mean gradient, MV area and pulmonary artery pressure), assessment of concomitant valvular lesions and assessment of valve morphology (to determine suitability for percutaneous mitral balloon valvotomy) (Level of Evidence: B)
2. Echocardiography should be performed for re-evaluation in patients with known MS and changing symptoms or signs (Level of Evidence: B)
3. Echocardiography should be performed for assessment of the hemodynamic response of the mean gradient and pulmonary artery pressure by exercise Doppler echocardiography in patients with MS when there is a discrepancy between resting Doppler echocardiographic findings, clinical findings, symptoms and signs (Level of Evidence: C)
4. Transesophageal echocardiography in MS should be performed to assess the presence or absence of left atrial thrombus and to further evaluate the severity of MR in patients considered for percutaneous mitral balloon valvotomy (Level of Evidence: C)
5. Transesophageal echocardiography in MS should be performed to evaluate MV morphology and hemodynamics in patients when transthoracic echocardiography provides suboptimal data (Level of Evidence: C)

Class IIa

1. Echocardiography is reasonable in the re-evaluation of asymptomatic patients with MS and stable clinical findings to assess pulmonary artery pressure (for those with severe MS, every year; moderate MS, every 1–2 years; and mild MS, every 3–5 years) (Level of Evidence: C)

Class III

1. Transesophageal echocardiography in the patient with MS is not indicated for routine evaluation of MV morphology and hemodynamics when complete transthoracic echocardiographic data are satisfactory (Level of Evidence: C)

MEDICAL THERAPY: PREVENTION OF SYSTEMIC EMBOLIZATION

Class I

1. Anticoagulation is indicated in patients with MS and atrial fibrillation (paroxysmal, persistent, or permanent) (Level of Evidence: B)
2. Anticoagulation is indicated in patients with MS and a prior embolic event, even in sinus rhythm (Level of Evidence: B)
3. Anticoagulation is indicated in patients with MS with left atrial thrombus (Level of Evidence: B)

Class IIb

1. Anticoagulation may be considered for asymptomatic patients with severe MS and left atrial dimension greater than or equal to 55 mm by echocardiography* (Level of Evidence: B)
2. Anticoagulation may be considered for patients with severe MS, an enlarged left atrium, and spontaneous contrast on echocardiography (Level of Evidence: C)

INDICATIONS FOR INVASIVE HEMODYNAMIC EVALUATION

Class I

1. Cardiac catheterization for hemodynamic evaluation should be performed for assessment of severity of MS when noninvasive tests are inconclusive or when there is discrepancy between noninvasive tests and clinical findings regarding severity of MS (Level of Evidence: C)
2. Catheterization for hemodynamic evaluation including left ventriculography (to evaluate severity of MR) for patients with MS is indicated when there is a discrepancy between the Doppler-derived mean gradient and valve area (Level of Evidence: C)

Class IIa

1. Cardiac catheterization is reasonable to assess the hemodynamic response of pulmonary artery and left atrial pressures to exercise when clinical symptoms and resting hemodynamics are discordant (Level of Evidence: C)
2. Cardiac catheterization is reasonable in patients with MS to assess the cause of severe pulmonary arterial hypertension when out of proportion to severity of MS as determined by noninvasive testing (Level of Evidence: C)

Class III

1. Diagnostic cardiac catheterization is not recommended to assess the MV hemodynamics when 2D and Doppler echocardiographic data are concordant with clinical findings (Level of Evidence: C)

INDICATIONS FOR SURGERY FOR MITRAL STENOSIS

Class I

1. MV surgery (repair if possible) is indicated in patients with symptomatic (NYHA functional class III–IV) moderate or severe MS when: (1) percutaneous mitral balloon valvotomy is unavailable; (2) percutaneous mitral balloon valvotomy is contraindicated because of left atrial thrombus despite anticoagulation or because concomitant moderate-to-severe MR is present or (3) the valve morphology is not favorable for percutaneous mitral balloon valvotomy in a patient with acceptable operative risk (Level of Evidence: B)
2. Symptomatic patients with moderate-to-severe MS who also have moderate-to-severe MR should receive MV replacement, unless valve repair is possible at the time of surgery (Level of Evidence: C)

Class IIa

1. MV replacement is reasonable for patients with severe MS and severe pulmonary hypertension (pulmonary artery systolic pressure > 60 mm Hg) with NYHA functional Class I-II symptoms who are not considered candidates for percutaneous mitral balloon valvotomy or surgical MV repair (Level of Evidence: C)

Class IIb

1. MV repair may be considered for asymptomatic patients with moderate or severe MS who have had recurrent embolic events while receiving adequate anticoagulation and who have valve morphology favorable for repair (Level of Evidence: C)

Class III

1. MV repair for MS is not indicated for patients with mild MS (Level of Evidence: C)
2. Closed commissurotomy should not be performed in patients undergoing MV repair; open commissurotomy is the preferred approach (Level of Evidence: C)

INDICATIONS FOR PERCUTANEOUS MITRAL BALLOON VALVOTOMY

Class I

1. Percutaneous mitral balloon valvotomy is effective for symptomatic patients (NYHA functional Class II, III or IV) with moderate or severe MS and valve morphology favorable for percutaneous mitral balloon valvotomy in the absence of left atrial thrombus or moderate-to-severe MR (Level of Evidence: A)
2. Percutaneous mitral balloon valvotomy is effective for asymptomatic patients with moderate or severe MS and valve morphology that is favorable for percutaneous mitral balloon valvotomy who have pulmonary hypertension (pulmonary artery systolic pressure > 50 mm Hg at rest or > 60 mm Hg with exercise) in the absence of left atrial thrombus or moderate-to-severe MR (Level of Evidence: C)

Class IIa

1. Percutaneous mitral balloon valvotomy is reasonable for patients, with moderate or severe MS who have a nonpliable calcified valve, are in NYHA functional Class III-IV, and are either not candidates for surgery or are at high risk for surgery (Level of Evidence: C)

Class IIb

1. Percutaneous mitral balloon valvotomy may be considered for asymptomatic patients with moderate or severe MS and valve morphology favorable for percutaneous mitral balloon valvotomy who have new onset of atrial fibrillation in the absence of left atrial thrombus or moderate-to-severe MR (Level of Evidence: C)
2. Percutaneous mitral balloon valvotomy may be considered for symptomatic patients (NYHA functional Class II, III or IV) with MV area greater than 1.5 cm^2 if there is evidence of hemodynamically significant MS based on pulmonary artery systolic pressure greater than 60 mm Hg, pulmonary artery wedge pressure of 25 mm Hg or more, or mean MV gradient greater than 15 mm Hg during exercise (Level of Evidence: C)
3. Percutaneous mitral balloon valvotomy may be considered as an alternative to surgery for patients with moderate or severe MS who have a nonpliable calcified valve and are in NYHA functional Class III-IV (Level of Evidence: C)

Class III

1. Percutaneous mitral balloon valvotomy is not indicated for patients with mild MS (Level of Evidence: C)
2. Percutaneous mitral balloon valvotomy should not be performed in patients with moderate-to-severe MR or left atrial thrombus (Level of Evidence: C)

EVALUATION AND MANAGEMENT OF THE ASYMPTOMATIC PATIENT

Class I

1. Echocardiography is indicated for the diagnosis of MVP and assessment of MR, leaflet morphology and ventricular compensation in asymptomatic patients with physical signs of MVP (Level of Evidence: B)

Class IIa

1. Echocardiography can effectively exclude MVP in asymptomatic patients who have been diagnosed without clinical evidence to support the diagnosis (Level of Evidence: C)
2. Echocardiography can be effective for risk stratification in asymptomatic patients with physical signs of MVP or known MVP (Level of Evidence: C)

Class III

1. Echocardiography is not indicated to exclude MVP in asymptomatic patients with ill-defined symptoms in the absence of a constellation of clinical symptoms or physical findings suggestive of MVP or a positive family history (Level of Evidence: B)
2. Routine repetition of echocardiography is not indicated for the asymptomatic patient who has MVP and no MR or MVP and mild MR with no changes in clinical signs or symptoms (Level of Evidence: C)

EVALUATION AND MANAGEMENT OF THE SYMPTOMATIC PATIENT

Class I

1. Aspirin therapy (75–325 mg/day) is recommended for symptomatic patients with MVP who experience cerebral transient ischemic attacks (Level of Evidence: C)
2. In patients, with MVP and atrial fibrillation, warfarin therapy is recommended for patients aged greater than 65 or those with hypertension, MR murmur, or a history of heart failure (Level of Evidence: C)
3. Aspirin therapy (75–325 mg/day) is recommended for patients with MVP and atrial fibrillation who are less than 65 years old and have no history of MR, hypertension or heart failure (Level of Evidence: C)
4. In patients with MVP and a history of stroke, warfarin therapy is recommended for patients with MR, atrial fibrillation or left atrial thrombus (Level of Evidence: C)

Class IIa

1. In patients with MVP and a history of stroke who do not have MR atrial fibrillation, or left atrial thrombus, warfarin therapy is reasonable for patients with echocardiographic evidence of thickening (5 mm or greater) and/or redundancy of the valve leaflets (Level of Evidence: C)

2. In patients with MVP and a history of stroke, aspirin therapy is reasonable for patients who do not have MR, atrial fibrillation, left atrial thrombus or echocardiographic evidence of thickening (5 mm or greater) or redundancy of the valve leaflets (Level of Evidence: C)
3. Warfarin therapy is reasonable for patients with MVP with transient ischemic attacks despite aspirin therapy (Level of Evidence: C)
4. Aspirin therapy (75–325 mg/day) can be beneficial for patients with MVP and a history of stroke who have contraindications to anticoagulants (Level of Evidence: B)

Class IIb

1. Aspirin therapy (75–325 mg/day) may be considered for patients in sinus rhythm with echocardiographic evidence of high-risk MVP (Lever of Evidence: C)

INDICATIONS FOR TRANSTHORACIC ECHOCARDIOGRAPHY

Class I

1. Transthoracic echocardiography is indicated for baseline evaluation of LV size and function, RV and left atrial size, pulmonary artery pressure and severity of MR in any patient suspected of having MR (Level of Evidence: C)
2. Transthoracic echocardiography is indicated for delineation of the mechanism of MR (Level of Evidence: B)
3. Transthoracic echocardiography is indicated for annual or semiannual surveillance of LV function (estimated by ejection fraction and end-systolic dimension) in asymptomatic patients with moderate-to-severe MR (Level of Evidence: C)
4. Transthoracic echocardiography is indicated in patients with MR to evaluate the MV apparatus and LV function after a change in signs or symptoms (Level of Evidence: C)
5. Transthoracic echocardiography is indicated to evaluate LV size and function and MV hemodynamics in the initial evaluation after MV replacement or MV repair (Level of Evidence: C)

Class IIa

1. Exercise Doppler echocardiography is reasonable in asymptomatic patients with severe MR to assess exercise tolerance and the effects of exercise on pulmonary artery pressure and MR severity (Level of Evidence: C)

Class III

1. Transthoracic echocardiography is not indicated for routine follow-up evaluation of asymptomatic patients with mild MR and normal LV size and systolic function (Level of Evidence: C)

INDICATIONS FOR TRANSESOPHAGEAL ECHOCARDIOGRAPHY

Class I

1. Preoperative or intraoperative transesophageal echocardiography is indicated to establish the anatomic basis for severe MR in patients in whom surgery is recommended to assess feasibility of repair and to guide repair (Level of Evidence: B)
2. Transesophageal echocardiography is indicated for evaluation of MR patients in whom transthoracic echocardiography provides nondiagnostic information regarding severity of MR, mechanism of MR and/or status of LV function (Level of Evidence: B)

Class IIa

1. Preoperative transesophageal echocardiography is reasonable in asymptomatic patients with severe MR who are considered for surgery to assess feasibility of repair (Level of Evidence: C)

Class III

1. Transesophageal echocardiography is not indicated for routine follow-up or surveillance of asymptomatic patients with native valve MR (Level of Evidence: C)

INDICATIONS FOR CARDIAC CATHETERIZATION

Class I

1. Left ventriculography and hemodynamic measurements are indicated when noninvasive tests are inconclusive regarding severity of MR, LV function or the need for surgery (Level of Evidence: C)
2. Hemodynamic measurements are indicated when pulmonary artery pressure is out of proportion to the severity of MR as assessed by noninvasive testing (Level of Evidence: C)

3. Left ventriculography and hemodynamic measurements are indicated when there is a discrepancy between clinical and noninvasive findings regarding severity of MR (Level of Evidence: C)
4. Coronary angiography is indicated before MV repair or MV replacement in patients at risk for CAD (Level of Evidence: C)

Class III

1. Left ventriculography and hemodynamic measurements are not indicated in patients with MR in whom valve surgery is not contemplated (Level of Evidence: C)

MANAGEMENT

Class I

1. Tricuspid valve repair is beneficial for severe TR in patients with MV disease requiring MV surgery (Level of Evidence: B)

Class IIa

1. Tricuspid valve replacement or annuloplasty is reasonable for severe primary TR when symptomatic (Level of Evidence: C)
2. Tricuspid valve replacement is reasonable for severe TR secondary to diseased/abnormal tricuspid valve leaflets not amenable to annuloplasty or repair (Level of Evidence: C)

Class IIb

1. Tricuspid annuloplasty may be considered for less than severe TR in patients undergoing MV surgery when there is pulmonary hypertension or tricuspid annular dilatation (Level of Evidence: C)

Class III

1. Tricuspid valve replacement or annuloplasty is not indicated in asymptomatic patients with TR whose pulmonary artery systolic pressure is less than 60 mm Hg in the presence of a normal MV (Level of Evidence: C)
2. Tricuspid valve replacement or annuloplasty is not indicated in patients with mild primary TH (Level of Evidence: C)

INDICATIONS FOR MITRAL VALVE OPERATION

Class I

1. MV surgery is recommended for the symptomatic patient with acute severe MR (Level of Evidence: B)
2. MV surgery is beneficial for patients with chronic severe MR and NYHA functional Class II, III or IV symptoms in the absence of severe LV dysfunction (severe LV dysfunction is defined as ejection fraction < 0.30) and/or end-systolic dimension greater than 55 mm (Level of Evidence: B)
3. MV surgery is beneficial for asymptomatic patients with chronic severe MR and mild-to-moderate LV dysfunction, ejection fraction 0.30–0.60 and/or end-systolic dimension greater than or equal to 40 mm (Level of Evidence: B)
4. MV repair is recommended over MV replacement in the majority of patients with severe chronic MR who require surgery, and patients should be referred to surgical centers experienced in MV repair (Level of Evidence: C)

Class IIa

1. MV repair is reasonable in experienced surgical centers for asymptomatic patients with chronic severe MR with preserved LV function (ejection fraction > 0.60 and end-systolic dimension < 40 mm) in whom the likelihood of successful repair without residual MR is greater than 90% (Level of Evidence: B)
2. MV surgery is reasonable for asymptomatic patients with chronic severe MR, preserved LV function, and new onset of atrial fibrillation (Level of Evidence: C)
3. MV surgery is reasonable for asymptomatic patients with chronic severe MR, preserved LV function and pulmonary hypertension (pulmonary artery systolic pressure > 50 mm Hg at rest or > 60 mm Hg with exercise) (Level of Evidence: C)
4. MV surgery is reasonable for patients with chronic severe MR due to a primary abnormality of the mitral apparatus and NYHA functional Class III-IV symptoms and severe LV dysfunction (ejection fraction < 0.30 and/or end-systolic dimension > 55 mm) in whom MV repair is highly likely (Level of Evidence: C)

Class IIb

1. MV repair may be considered for patients with chronic severe secondary MR due to severe LV dysfunction (ejection fraction < 0.30) who have persistent NYHA functional Class III-IV symptoms despite optimal therapy for heart failure, including biventricular pacing (Level of Evidence: C)

Class III

1. MV surgery is not indicated for asymptomatic patients with MR and preserved LV function (ejection fraction > 0.60 and end-systolic dimension < 40 mm) in whom significant doubt about the feasibility of repair exists (Level of Evidence: C)
2. Isolated MV surgery is not indicated for patients with mild or moderate MR (Level of Evidence: C)

EVALUATION AND MANAGEMENT OF INFECTIVE ENDOCARDITIS

Class I

1. Patients at risk for infective endocarditis who have unexplained fever for more than 48 hours should have at least two sets of blood cultures obtained from different sites (Level of Evidence: B)

Class III

1. Patients with known valve disease or a valve prosthesis should not receive antibiotics before blood cultures are obtained for unexplained fever (Level of Evidence: C)

TRANSTHORACIC ECHOCARDIOGRAPHY IN ENDOCARDITIS

Class I

1. Transthoracic echocardiography to detect valvular vegetations with or without positive blood cultures is recommended for the diagnosis of infective endocarditis (Level of Evidence: B)
2. Transthoracic echocardiography is recommended to characterize the hemodynamic severity of valvular lesions in known infective endocarditis (Level of Evidence: B)
3. Transthoracic echocardiography is recommended for assessment of complications of infective endocarditis (e.g. abscesses, perforation and shunts) (Level of Evidence: B)
4. Transthoracic echocardiography is recommended for reassessment of high-risk patients (e.g. those with a virulent organism, clinical deterioration, persistent or recurrent fever, new murmur or persistent bacteremia) (Level of Evidence: C)

Class IIa

1. Transthoracic echocardiography is reasonable to diagnose infective endocarditis of a prosthetic valve in the presence of persistent fever without bacteremia or a new murmur (Level of Evidence: C)

Class IIb

1. Transthoracic echocardiography may be considered for the re-evaluation of prosthetic valve endocarditis during antibiotic therapy in the absence of clinical deterioration (Level of Evidence: C)

Class III

1. Transthoracic echocardiography is not indicated to re-evaluate uncomplicated (including no regurgitation on baseline echocardiogram) native valve endocarditis during antibiotic treatment in the absence of clinical deterioration, new physical findings or persistent fever (Lever of Evidence: C)

TRANSESOPHAGEAL ECHOCARDIOGRAPHY IN ENDOCARDITIS

Class I

1. Transesophageal echocardiography is recommended to assess the severity of valvular lesions in symptomatic patients with infective endocarditis, if transthoracic echocardiography is nondiagnostic (Level of Evidence: C)
2. Transesophageal echocardiography is recommended to diagnose infective endocarditis in patients with valvular heart disease and positive blood cultures, if transthoracic echocardiography is nondiagnostic (Level of Evidence: C)
3. Transesophageal echocardiography is recommended to diagnose complications of infective endocarditis with potential impact on prognosis and management (e.g. abscesses, perforation and shunts) (Level of Evidence: C)
4. Transesophageal echocardiography is recommended as first-line diagnostic study to diagnose prosthetic valve endocarditis and assess for complications (Level of Evidence: C)
5. Transesophageal echocardiography is recommended for preoperative evaluation in patients with known infective endocarditis, unless the need for surgery is evident on transthoracic imaging and unless preoperative imaging will delay surgery in urgent cases (Level of Evidence: C)
6. Intraoperative transesophageal echocardiography is recommended for patients undergoing valve surgery for infective endocarditis (Level of Evidence: C)

Class IIa

1. Transesophageal echocardiography is reasonable to diagnose possible infective endocarditis in patients with persistent staphylococcal bacteremia without a known source (Level of Evidence: C)

Class IIb

1. Transesophageal echocardiography might be considered to detect infective endocarditis in patients with nosocomial staphylococcal bacteremia (Level of Evidence: C)

SURGERY FOR NATIVE VALVE ENDOCARDITIS

Class I

1. Surgery of the native valve is indicated in patients with acute infective endocarditis who present with valve stenosis or regurgitation resulting in heart failure (Level of Evidence: B)
2. Surgery of the native valve is indicated in patients with acute infective endocarditis who present with AR or MR with hemodynamic evidence of elevated LV end-diastolic or left atrial pressures (e.g. premature closure of MV with AR, rapid decelerating MR signal by continuous-wave Doppler (v-wave cutoff sign), or moderate or severe pulmonary hypertension) (Level of Evidence: B)
3. Surgery of the native valve is indicated in patients with infective endocarditis caused by fungal or other highly resistant organisms (Level of Evidence: B)
4. Surgery of the native valve is indicated in patients with infective endocarditis complicated by heart block, annular or aortic abscess, or destructive penetrating lesions (e.g. sinus of Valsalva to right atrium, right ventricle or left atrium fistula; mitral leaflet perforation with aortic valve endocarditis; or infection in annulus fIbrosa) (Level of Evidence: B)

Class IIa

1. Surgery of the native valve is reasonable in patients with infective endocarditis who present with recurrent emboli and persistent vegetations despite appropriate antibiotic therapy (Level of Evidence: C)

Class IIb

1. Surgery of the native valve may be considered in patients with infective endocarditis who present with mobile vegetations in excess of 1.0 mm with or without emboli (Level of Evidence: C)
   Patients with left-sided native valve endocarditis complicated by congestive heart failure, systemic embolization to vital organs, or presence of a large vegetation on echocardiography have poor outcomes on medical treatment alone. A large cohort study using a multivariate model reported that valve surgery was associated with improved 6-month survival. An additional benefit of early surgery is likely to include successful valve repair as an outcome, especially for the MV. When at all possible, MV repair should be performed instead of MV replacement in the setting of active infection because of the risk of infection of prosthetic materials. Aortic valves may often be repaired as well if there are leaflet perforations) and this is preferable to AVR for the same reasons.

SURGERY FOR PROSTHETIC VALVE ENDOCARDITIS

Class I

1. Consultation with a cardiac surgeon is indicated for patients with infective endocarditis of a prosthetic valve (Level of Evidence: C)
2. Surgery is indicated for patients with infective endocarditis of a prosthetic valve who present with heart failure (Level of Evidence: B)
3. Surgery is indicated for patients with infective endocarditis of a prosthetic valve who present with dehiscence evidenced by cine fluoroscopy or echocardiography (Level of Evidence: B)
4. Surgery is indicated for patients with infective endocarditis of a prosthetic valve who present with evidence of increasing obstruction or worsening regurgitation (Level of Evidence: C)
5. Surgery is indicated for patients with infective endocarditis of a prosthetic valve who present with complications (e.g. abscess formation) (Level of Evidence: C)

Class IIa

1. Surgery is reasonable for patients with infective endocarditis of a prosthetic valve who present with evidence of persistent bacteremia or recurrent emboli despite appropriate antibiotic treatment (Level of Evidence: C)
2. Surgery is reasonable for patients with infective endocarditis of a prosthetic valve who present with relapsing infection (Level of Evidence: C)

Class III

1. Routine surgery is not indicated for patients with uncomplicated infective endocarditis of a prosthetic valve caused by first infection with a sensitive organism (Level of Evidence: C)

SELECTION OF ANTICOAGULATION REGIMEN IN PREGNANT PATIENTS WITH MECHANICAL PROSTHETIC VALVES

Class I

1. All pregnant patients with mechanical prosthetic valves must receive continuous therapeutic anticoagulation with frequent monitoring (Level of Evidence: B)
2. For women requiring long-term warfarin therapy who are attempting pregnancy, pregnancy tests should be monitored with discussions about subsequent anticoagulation therapy so that anticoagulation can be continued uninterrupted when pregnancy is achieved (Level of Evidence: C)
3. Pregnant patients with mechanical prosthetic valves who elect to stop warfarin between weeks 6 and 12 of gestation should receive continuous intravenous UFH, dose-adjusted UFH or dose-adjusted subcutaneous LMWH (Level of Evidence: C)
4. For pregnant patients with mechanical prosthetic valves, up to 36 weeks of gestation, the therapeutic choice of continuous intravenous or dose-adjusted subcutaneous UFH, dose-adjusted LMWH or warfarin should be discussed fully. If continuous intravenous UFH is used, the fetal risk is lower, but the maternal risks of prosthetic valve thrombosis, systemic embolization, infection, osteoporosis and heparin-induced thrombocytopenia are relatively higher (Level of Evidence: C)
5. In pregnant patients with mechanical prosthetic valves who receive dose-adjusted LMWH, the LMWH should be administered twice daily subcutaneously to maintain the anti-Xa level between 0.7 and 1.2 U per ml 4 hourly after administration (Level of Evidence: C)
6. In pregnant patients with mechanical prosthetic valves who receive dose-adjusted UFH, the aPTT should be at least twice control (Level of Evidence: C)
7. In pregnant patients with mechanical prosthetic valves who receive warfarin, the INR goal should be 3.0 (range 2.5–3.5) (Level of Evidence: C)
8. In pregnant patients with mechanical prosthetic valves, warfarin should be discontinued and continuous intravenous UFH given starting 2–3 weeks before planned delivery (Level of Evidence: C)

Class IIa

1. In patients with mechanical prosthetic valves, it is reasonable to avoid warfarin between weeks 6 and 12 of gestation owing to the high risk of fetal defects (Level of Evidence: C)
2. In patients with mechanical prosthetic valves, it is reasonable to resume UFH 4–6 hours after delivery and begin oral warfarin in the absence of significant bleeding (Level of Evidence: C)
3. In patients with mechanical prosthetic valves, it is reasonable to give low-dose aspirin (75–100 mg/day) in the second and third trimesters of pregnancy in addition to anticoagulation with warfarin or heparin (Level of Evidence: C)

Class III

1. LMWH should not be administered to pregnant patients with mechanical prosthetic valves unless anti-Xa levels are monitored 4–6 hours after administration (Level of Evidence: C)
2. Dipyridamole should not be used instead of aspirin as an alternative antiplatelet agent in pregnant patients with mechanical prosthetic valves because of its harmful effects on the fetus (Level of Evidence: B)

EVALUATION OF ASYMPTOMATIC ADOLESCENTS OR YOUNG ADULTS WITH AORTIC STENOSIS

Class I

1. An ECG is recommended yearly in the asymptomatic adolescent or young adult with AS who has a Doppler mean gradient greater than 30 mm Hg or a peak velocity greater than 3.5 m/sec (peak gradient > 50 mm Hg) and every 2 years if the echocardiographic Doppler mean gradient is less than or equal to 30 mm Hg or the peak velocity is less than or equal to 3.5 m/sec (peak gradient $\leq$ 50 mm Hg) (Level of Evidence: C)
2. Doppler echocardiography is recommended yearly in the asymptomatic adolescent or young adult with AS who has a Doppler mean gradient greater than 30 mm Hg or a peak velocity greater than 3.5 m/sec (peak gradient > 50 mm Hg and every 2 years if the Doppler gradient is less than or equal to 30 mm Hg or the peak jet velocity is less than or equal to 3.5 m/sec (peak gradient $\leq$ 50 mm Hg) (Level of Evidence: C)
3. Cardiac catheterization for the evaluation of AS is an effective diagnostic tool in the asymptomatic adolescent or young adult when results of Doppler echocardiography are equivocal regarding severity of AS or when there is a discrepancy between clinical and noninvasive findings regarding severity of AS (Level of Evidence: C)

4. Cardiac catheterization is indicated in the adolescent or young adult with AS who has symptoms of angina, syncope, or dyspnea on exertion if the Doppler mean gradient is greater than 30 mm Hg or the peak velocity is greater than 3.5 m/sec (peak gradient > 50 mm Hg) (Level of Evidence: C)
5. Cardiac catheterization is indicated in the asymptomatic adolescent or young adult with AS who develops T-wave inversion at rest over the left precordium if the Doppler mean gradient is > 30 mm Hg or the peak velocity is > 3.5 m/sec (peak gradient > 50 mm Hg) (Level of Evidence: C)

Class IIa

1. Graded exercise testing is a reasonable diagnostic evaluation in the adolescent or young adult with AS who has a Doppler mean gradient greater than 30 mm Hg or a peak velocity greater than 3.5 m/sec (peak gradient > 50 mm Hg) if the patient is interested in athletic participation, or if the clinical findings and Doppler findings are disparate (Level of Evidence: C)

INDICATIONS FOR AORTIC BALLOON VALVOTOMY IN ADOLESCENTS AND YOUNG ADULTS

Class I

1. Aortic balloon valvotomy is indicated in the adolescent or young adult patient with AS who has symptoms of angina, syncope or dyspnea on exertion and a catheterization peak LV-to-peak aortic gradient greater than or equal to 50 mm Hg without a heavily calcified valve (Level of Evidence: C)*
2. Aortic balloon valvotomy is indicated for the asymptomatic adolescent or young adult patient with AS who has a catheterization peak LV-to-peak aortic gradient greater than 60 mm Hg (Level of Evidence: C)*
3. Aortic balloon valvotomy is indicated in the asymptomatic adolescent or young adult patient with AS who develops ST or T-wave changes over the left precordium on ECG at rest or with exercise and who has a catheterization peak LV-to-aortic gradient greater than 50 mm Hg (Level of Evidence: C)*

Class IIa

1. Aortic balloon valvotomy is reasonable in the asymptomatic adolescent or young adult patient with AS when catheterization peak LV-to-peak aortic gradient is greater than 50 mm Hg, and the patient wants to play competitive sports or desires to become pregnant (Level of Evidence: C)*
2. In the adolescent or young adult patient with AS, aortic balloon valvotomy is probably recommended over valve surgery when balloon valvotomy is possible. Patients should be referred to a center with expertise in balloon valvotomy (Level of Evidence: C)*

Class III

1. Aortic balloon valvotomy should not be performed when the asymptomatic adolescent or young adult patient with AS has a catheterization peak LV-to-peak aortic gradient less than 40 mm Hg without symptoms or ECG changes (Level of Evidence: C)*

*Gradients are usually obtained with patients sedated. If general anesthesia is used, the gradients may be somewhat lower.

AORTIC REGURGITATION

Class I

1. An adolescent or young adult with chronic severe AR with onset of symptoms of angina, syncope or dyspnea on exertion should receive aortic valve repair or replacement (Level of Evidence: C)
2. Asymptomatic adolescent or young adult patients with chronic severe AR with LV systolic dysfunction (ejection fraction < 0.50) on serial studies 1–3 months apart should receive aortic valve repair or replacement (Level of Evidence: C)
3. Asymptomatic adolescent or young adult patients with chronic severe AR with progressive LV enlargement (end-diastolic dimension greater than 4 standard deviations above normal) should receive aortic valve repair or replacement (Level of Evidence: C)
4. Coronary angiography is recommended before AVR in adolescent or young adult patients with AR in whom a pulmonary autograft (Ross operation) is contemplated when the origin of the coronary arteries has not been identified by noninvasive techniques (Level of Evidence: C)

Class IIb

1. An asymptomatic adolescent with chronic severe AR with moderate AS (peak LV-to-peak aortic gradient > 40 mm Hg at cardiac catheterization) may be considered for aortic valve repair or replacement (Level of Evidence: C)
2. An asymptomatic adolescent with chronic severe AR with onset of 5T depression or T-wave inversion over the left precordium on ECG at rest may be considered for aortic valve repair or replacement (Level of Evidence: C)

MITRAL REGURGITATION

Class I

1. MV surgery is indicated in the symptomatic adolescent or young adult with severe congenital MR with NYHA functional Class III or IV symptoms (Level of Evidence: C)
2. MV surgery is indicated in the asymptomatic adolescent or young adult with severe congenital MR and LV systolic dysfunction (ejection fraction ≤ 0.60) (Level of Evidence: C)

Class IIa

1. MV repair is reasonable in experienced surgical centers in the asymptomatic adolescent or young adult with severe congenital MR with preserved LV systolic function if the likelihood of successful repair without residual MR is greater than 90% (Level of Evidence: B)

Class IIb

1. The effectiveness of MY surgery is not well established in asymptomatic adolescent or young adult patients with severe congenital MR and preserved LV systolic function in whom valve replacement is highly likely (Level of Evidence: C)

MITRAL STENOSIS

Class I

1. MV surgery is indicated in adolescent or young adult patients with congenital MS who have symptoms (NYHA functional Class III or IV) and mean MV gradient greater than 10 mm Hg on Doppler echocardiography (Level of Evidence: C)

Class IIa

1. MV surgery is reasonable in adolescent or young adult patients with congenital MS who have mild symptoms (NYHA functional Class II) and mean MV gradient greater than 1.0 mm Hg on Doppler echocardiography (Level of Evidence: C)
2. MV surgery is reasonable in the asymptomatic adolescent or young adult with congenital MS with pulmonary artery systolic pressure 50 mm Hg or greater and a mean MV gradient greater than or equal to 10 mm Hg (Level of Evidence: C)

Class IIb

1. The effectiveness of MV surgery is not well established in the asymptomatic adolescent or young adult with congenital MS and new-onset atrial fibrillation or multiple systemic emboli while receiving adequate anticoagulation (Level of Evidence: C)

EVALUATION OF TRICUSPID VALVE DISEASE IN ADOLESCENTS AND YOUNG ADULTS

Class I

1. An ECG is indicated for the initial evaluation of adolescent and young adult patients with TR, and serially every 1–3 years, depending on severity (Level of Evidence: C)
2. Chest X-ray is indicated for the initial evaluation of adolescent and young adult patients with TR, and serially every 1–3 years, depending on severity (Level of Evidence: C)
3. Doppler echocardiography is indicated for the initial evaluation of adolescent and young adult patients with TR, and serially every 1–3 years, depending on severity (Level of Evidence: C)
4. Pulse oximetry at rest and/or during exercise is indicated for the initial evaluation of adolescent and young adult patients with TR if an atrial communication is present, and serially every 1–3 years, depending on severity (Level of Evidence: C)

Class IIa

1. If there is a symptomatic atrial arrhythmia, an electrophysiology study can be useful for the initial evaluation of adolescent and young adult patients with TA (Level of Evidence: C)
2. Exercise testing is reasonable for the initial evaluation of adolescent and young adult patients with TR, and serially every 1–3 years (Level of Evidence: C)

Class IIb

1. Holter monitoring may be considered for the initial evaluation of asymptomatic adolescent and young adult patients with TR, and serially every 1–3 years (Level of Evidence: C)

INDICATIONS FOR INTERVENTION IN TRICUSPID REGURGITATION

Class I

1. Surgery for severe TR is recommended for adolescent and young adult patients with deteriorating exercise capacity (NYHA functional Class III or IV) (Level of Evidence: C)
2. Surgery for severe TR is recommended for adolescent and young adult patients with progressive cyanosis and arterial saturation less than 80% at rest or with exercise (Level of Evidence: C)
3. Interventional catheterization closure of the atrial communication is recommended for the adolescent or young adult with TR who is hypoxemic at rest and with exercise intolerance due to increasing hypoxemia with exercise, when the tricuspid valve appears difficult to repair surgically (Level of Evidence: C)

Class IIa

1. Surgery for severe TR is reasonable in adolescent and young adult patients with NYHA functional Class II symptoms if the valve appears to be repairable (Level of Evidence: C)
2. Surgery for severe TR is reasonable in adolescent and young adult patients with atrial fibrillation (Level of Evidence: C)

Class IIb

1. Surgery for severe TR may be considered in asymptomatic adolescent and young adult patients with increasing heart size and a cardiothoracic ratio of more than 65% (Level of Evidence: C)
2. Surgery for severe TR may be considered in asymptomatic adolescent and young adult patients with stable heart size and an arterial saturation of less than 85% when the tricuspid valve appears repairable (Level of Evidence: C)
3. In adolescent and young adult patients with TR who are mildly cyanotic at rest but who become very hypoxemic with exercise, closure of the atrial communication by interventional catheterization may be considered when the valve does not appear amenable to repair (Level of Evidence: C)
4. If surgery for Ebstein's anomaly is planned in adolescents and young adult patients (tricuspid valve repair or replacement), a preoperative electrophysiological study may be considered to identify accessory pathways. If present these may be considered for mapping and ablation either preoperatively or at the time of surgery (Level of Evidence: C)

EVALUATION OF PULMONIC STENOSIS IN ADOLESCENTS AND YOUNG ADULTS

Class I

1. An ECG is recommended for the initial evaluation of pulmonic stenosis in adolescent and young adult patients, and serially every 5–10 years for follow-up examinations (Level of Evidence: C)
2. Transthoracic Doppler echocardiography is recommended for the initial evaluation of pulmonic stenosis in adolescent and young adult patients, and serially every 5–10 years for follow-up examinations (Level of Evidence: C)
3. Cardiac catheterization is recommended in the adolescent or young adult with pulmonic stenosis for evaluation of the valvular gradient if the Doppler peak jet velocity is greater than 3 m/sec (estimated peak gradient greater than 36 mm Hg) and balloon dilation can be performed if indicated (Level of Evidence: C)

Class III

1. Diagnostic cardiac catheterization is not recommended for the initial diagnostic evaluation of pulmonic stenosis in adolescent and young adult patients (Level of Evidence: C)
   The clinical diagnosis of pulmonary valve stenosis is straightforward, and the severity can usually be determined accurately by 2D and Doppler echocardiograpby. Diagnostic catheterization is rarely required.

INDICATIONS FOR BALLOON VALVOTOMY IN PULMONIC STENOSIS

Class I

1. Balloon valvotomy is recommended in adolescent and young adult patients with pulmonic stenosis who have exertional dyspnea, angina, syncope, or presyncope and an RV-to-pulmonary artery peak-to-peak gradient greater than 30 mm Hg at catheterization (Level of Evidence: C)
2. Balloon valvotomy is recommended in asymptomatic adolescent and young adult patients with pulmonic stenosis and RV-to-pulmonary artery-peak-to-peak gradient greater than 40 mm Hg at catheterization (Level of Evidence: C)

Class IIb

1. Balloon valvotomy may be reasonable in asymptomatic adolescent and young adult patients with pulmonic stenosis and an RV-to-pulmonary artery peak-to-peak gradient 30–39 mm Hg at catheterization (Level of Evidence: C)

Class III

1. Balloon valvotomy is not recommended in asymptomatic adolescent and young adult patients with pulmonic stenosis and RV-to-pulmonary artery peak-to-peak gradient less than 30 mm Hg at catheterization (Level of evidence: C)

MAJOR CRITERIA FOR AORTIC VALVE SELECTION

Class I

1. A mechanical prosthesis is recommended for AVR in patients with a mechanical valve in the mitral or tricuspid position (Level of Evidence: C)
2. A bioprosthesis is recommended for AVR in patients of any age who will not take warfarin or who have major medical contraindications to warfarin therapy (Level of Evidence: C)

Class IIa

1. Patient preference is a reasonable consideration in the selection of aortic valve operation and valve prosthesis. A mechanical prosthesis is reasonable for AVR in patients under 65 years of age who do not have a contraindication to anticoagulation. A bioprosthesis is reasonable for AVR in patients under 65 years of age who elect to receive this valve for lifestyle considerations after detailed discussions of the risks of anticoagulation versus the likelihood that a second AVR may be necessary in the future (Level of Evidence: C)
2. A bioprosthesis is reasonable for AVR in patients aged 65 years or older without risk factors for thromboembolism (Level of Evidence: C)
3. Aortic valve re-replacement with a homograft is reasonable for patients with active prosthetic valve endocarditis (Level of Evidence: C)

Class IIb

1. A bioprosthesis might be considered for AVR in a woman of childbearing age (Level of Evidence: C)

MYXOMATOUS MITRAL VALVE

Class I

1. MV repair is recommended when anatomically possible for patients with severe degenerative MR who fulfill clinical indications, and patients should be referred to surgeons who are expert in repair (Level of Evidence: B)
2. Patients who have undergone successful MV repair should continue to receive antibiotics as indicated for endocarditis prophylaxis (Level of Evidence: C)
3. Patients who have undergone successful MV repair and have chronic or paroxysmal atrial fibrillation should continue to receive long-term anticoagulation with warfarin (Level of Evidence: B)
4. Patients who have undergone successful MV repair should undergo 2D and Doppler echocardiography before discharge or at the first postoperative outpatient visit (Level of Evidence: C)
5. Tricuspid valve repair is beneficial for severe TR in patients with MV disease that requires MV surgery (Level of Evidence: B)

Class IIa

1. Oral anticoagulation is reasonable for the first 3 months after MV repair (Level of Evidence: C)
2. Long-term treatment with low-dose aspirin (75–100 mg/day) is reasonable in patients who have undergone successful MV repair and remain in sinus rhythm (Level of Evidence: C)
3. Tricuspid annuloplasty is reasonable for mild TR in patients undergoing MV repair when there is pulmonary hypertension or tricuspid annular dilatation (Level of Evidence: C)

Class IIb

1. In patients with MR and a history of atrial fibrillation, a Maze procedure may be considered at the time of MV repair (Level of Evidence: B)

SELECTION OF A MITRAL VALVE PROSTHESIS

Class I

1. A bioprosthesis is indicated for MV replacement in a patient who will not take warfarin, is incapable of taking warfarin, or has a clear contraindication to warfarin therapy (Level of Evidence: C)

Class IIa

1. A mechanical prosthesis is reasonable for MV replacement in patients under 65 years of age with long-standing atrial fibrillation (Level of Evidence: C)
2. A bioprosthesis is reasonable for MV replacement in patients 65 years of age or older (Lever of Evidence: C)
3. A bioprosthesis is reasonable for MV replacement in patients under 65 years of age in sinus rhythm who elect to receive this valve for lifestyle considerations after detailed discussions of the risks of anticoagulation versus the likelihood that a second MV replacement may be necessary in the future (Level of Evidence: C)

TRICUSPID VALVE SURGERY

Class I

1. Severe TR in the setting of surgery for multivalvular disease should be corrected (Level of Evidence: C)

Class IIb

1. Tricuspid annuloplasty is reasonable for mild TR in patients undergoing MV surgery when there is pulmonary hypertension or tricuspid annular dilatation (Level of Evidence: C)

INTRAOPERATIVE ASSESSMENT

Class I

1. Intraoperative transesophageal echocardiography is recommended for valve repair surgery (Level of Evidence: B)
2. Intraoperative transesophageal echocardiography is recommended for valve replacement surgery with a stentless xenograft, homograft or autograft valve (Level of Evidence: B)
3. Intraoperative transesophageal echocardiography is recommended for valve surgery for infective endocarditis (Level of Evidence: B)

Class IIa

1. Intraoperative transesophageal echocardiography is reasonable for all patients undergoing cardiac valve surgery (Level of Evidence: C)

MANAGEMENT OF PATIENTS WITH PROSTHETIC HEART VALVES

ANTIBIOTIC PROPHYLAXIS

Infective Endocarditis

All patients with prosthetic valves need appropriate antibiotics for prophylaxis against infective endocarditis.

Recurrence of Rheumatic Carditis

Patients with rheumatic heart disease continue to need antibiotics as prophylaxis against recurrence of rheumatic carditis.

ANTITHROMBOTIC THERAPY

Class I

1. After AVR with bileaflet mechanical or Medtronic Hall prostheses, in patients with no risk factors,* warfarin is indicated to achieve an INR of 2.0–3.0. If the patient has risk factors, warfarin is indicated to achieve an INR of 2.5–3.5 (Level of Evidence: B)
2. After AVR with Starr-Edwards valves or mechanical disk valves (other than Medtronic Hall prostheses), in patients with no risk factors,* warfarin is indicated to achieve an INR of 2.5–3.5 (Level of Evidence: B)
3. After MV replacement with any mechanical valve, warfarin is indicated to achieve an INR of 2.5–3.5 (Level of Evidence: C)
4. After AVR or MV replacement with a bioprosthesis and no risk factors,* aspirin is indicated at 75–100 mg/day (Level of Evidence: C).
5. After AVR with a bioprosthesis and risk factors,* warfarin is indicated to achieve an INR of 2.0–3.0 (Level of Evidence: C)
6. After MV replacement with a bioprosthesis and risk factors, * warfarin is indicated to achieve an INR of 2.0–3.0 (Level of Evidence: C)
7. For those patients who are unable to take warfarin after MV replacement or AVR, aspirin is indicated in a dose of 75–325 mg/day (Level of Evidence: B)
8. The addition of aspirin 75–100 mg once daily to therapeutic warfarin is recommended for all patients with mechanical heart valves and those patients with biological valves who have risk factors* (Level of Evidence: B)

Class IIa

1. During the first 3 months after AVR with a mechanical prosthesis, it is reasonable to give warfarin to achieve an INR of 2.5–3.5 (Level of Evidence: C)
2. During the first 3 months after AVR or MV replacement with a bioprosthesis, in patients with no risk factors,* it is reasonable to give warfarin to achieve an INR of 2.0–3.0 (Level of Evidence: C)

Class IIb

1. In high-risk patients with prosthetic heart valves in whom aspirin cannot be used, it may be reasonable to give clopidogrel (75 mg/day) or warfarin to achieve an INR of 3.5–4.5 (Level of Evidence: C)

*Risk factors include atrial fibrillation, previous thromboembolism, LV dysfunction and hypercoagulable condition.

BRIDGING THERAPY IN PATIENTS WITH MECHANICAL VALVES WHO REQUIRE INTERRUPTION OF WARFARIN THERAPY FOR NONCARDIAC SURGERY, INVASIVE PROCEDURES OR DENTAL CARE

Class I

1. In patients at low risk of thrombosis, defined as those with a bileaflet mechanical AVR with no risk factors,* it is recommended that warfarin be stopped 48–72 hours before the procedure (so the INR falls to < 1.5) and restarted within 24 hours after the procedure. Heparin is usually unnecessary (Level of Evidence: B)
2. In patients at high risk of thrombosis, defined as those with any mechanical MV replacement or a mechanical AVR with any risk factor, therapeutic doses of intravenous UFH should be started when the INR falls below 2.0 (typically 48 hours before surgery), stopped 4–6 hours before the procedure, restarted as early after surgery as bleeding stability allows and continued until the INR is again therapeutic with warfarin therapy (Level of Evidence: B)

*Risk factors: atrial fibrillation, previous thromboembolism, LV dysfunction, hypercoagulable conditions, older-generation thrombogenic valves, mechanical tricuspid valves or more than 1 mechanical valve.

Class IIa

1. It is reasonable to give fresh frozen plasma to patients with mechanical valves who require interruption of warfarin therapy for emergency noncardiac surgery, invasive procedures or dental care. Fresh frozen plasma is preferable to high-dose vitamin K_1 (Level of Evidence: B)

Class IIb

1. In patients at high risk of thrombosis, therapeutic doses of subcutaneous UFH (15 000 U every 12 hours) or LMWH (100 U/kg every 12 hours) may be considered during the period of a subtherapeutic INR (Level of Evidence: B)

Class III

1. In patients with mechanical valves who require interruption of warfarin therapy for noncardiac surgery, invasive procedures, or dental care, high-dose vitamin K_1 should not be given routinely, because this may create a hypercoagulable condition (Level of Evidence: B)

THROMBOSIS OF PROSTHETIC HEART VALVES

Class I

1. Transthoracic and Doppler echocardiography is indicated in patients with suspected prosthetic valve thrombosis to assess hemodynamic severity (Level of Evidence: B)
2. Transesophageal echocardiography and/or fluoroscopy is indicated in patients with suspected valve thrombosis to assess valve motion and clot burden (Level of Evidence: B)

Class IIa

1. Emergency operation is reasonable for patients with a thrombosed left-sided prosthetic valve and NYHA functional Class III-IV symptoms (Level of Evidence: C)
2. Emergency operation is reasonable for patients with a thrombosed left-sided prosthetic valve and a large clot burden (Level of Evidence: C)
3. Fibrinolytic therapy is reasonable for thrombosed right-sided prosthetic heart valves with NYHA functional Class III-IV symptoms or a large clot burden (Level of Evidence: C)

Class IIb

1. Fibrinolytic therapy may be considered as a first-line therapy for patients with a thrombosed left-sided prosthetic valve, NYHA functional Class I-II symptoms, and a small clot burden (Level of Evidence: B)
2. Fibrinolytic therapy may be considered as a first-line therapy for patients with a thrombosed left-sided prosthetic valve, NYHA functional Class III-IV symptoms, and a small clot burden if surgery is high risk or not available (Level of Evidence: B)
3. Fibrinolytic therapy may be considered for patients with an obstructed, thrombosed left-sided prosthetic valve who have NYHA functional Class II-IV symptoms and a large clot burden if emergency surgery is high risk or not available (Level of Evidence: C)
4. Intravenous UFH as an alternative to fibrinolytic therapy may be considered for patients with a thrombosed valve who are in NYHA functional Class I-II and have a small clot burden (Level of Evidence: C)

FOLLOW-UP VISITS

Class I

1. For patients with prosthetic heart valves a history, physical examination, and appropriate tests should be performed at the first postoperative outpatient evaluation, 2–4 weeks after hospital discharge. This should include a transthoracic Doppler echocardiogram if a baseline echocardiogram was not obtained before hospital discharge (Level of Evidence: C)
2. For patients with prosthetic heart valves, routine follow-up visits should be conducted annually, with earlier re-evaluations (with echocardiography) if there is a change in clinical status (Level of Evidence: C)

Class IIb

1. Patients with bioprosthetic valves may be considered for annual echocardiograms after the first 5 years in the absence of a change in clinical status (Level of Evidence: C)

Class III

1. Routine annual echocardiograms are not indicated in the absence of a change in clinical status in patients with mechanical heart valves or during the first 5 years after valve replacement with a bioprosthetic valve (Level of Evidence: C)

DIAGNOSIS OF CORONARY ARTERY DISEASE

Class I

1. Coronary angiography is indicated before valve surgery (including infective endocarditis) or mitral balloon commissurotomy in patients with chest pain, other objective evidence of ischemia, decreased LV systolic function, history of CAD or coronary risk factors (including age). Patients undergoing mitral balloon valvotomy need not undergo coronary angiography solely on the basis of coronary risk factors (Level of Evidence: C)
2. Coronary angiography is indicated in patients with apparently mild-to-moderate valvular heart disease, but with progressive angina (Canadian Heart Association functional Class II or greater), objective evidence of ischemia, decreased LV systolic function, or overt congestive heart failure (Level of Evidence: C)
3. Coronary angiography should be performed before valve surgery in men aged 35 years or older, premenopausal women aged 35 years or older who have coronary risk factors, and postmenopausal women (Level of Evidence: C)

Class IIa

1. Surgery without coronary angiography is reasonable for patients having emergency valve surgery for acute valve regurgitation, aortic root disease or infective endocarditis (Level of Evidence: C)

Class IIb

1. Coronary angiography may be considered for patients undergoing catheterization to confirm the severity of valve lesions before valve surgery without pre-existing evidence of CAD, multiple coronary risk factors or advanced age (Level of Evidence: C)

Class III

1. Coronary angiography is not indicated in young patients undergoing nonemergency valve surgery when no further hemodynamic assessment by catheterization is deemed necessary and there are no coronary risk factors, no history of CAD and no evidence of ischemia (Level of Evidence: C)
2. Patients should not undergo coronary angiography before valve surgery if they are severely hemodynamically unstable (Level of Evidence: C)

TREATMENT OF CORONARY ARTERY DISEASE AT THE TIME OF AORTIC VALVE REPLACEMENT

Class I

1. Patients undergoing AVR with significant stenoses (≥ 70% reduction in luminal diameter) in major coronary arteries should be treated with bypass grafting (Level of Evidence: C)

Class IIa

1. In patients undergoing AVR and coronary bypass grafting, use of the left internal thoracic artery is reasonable for bypass of stenoses of the left anterior descending coronary artery greater than or equal to 50–70% (Level of Evidence: C)
2. For patients undergoing AVR with moderate stenosis (50–70% reduction in luminal diameter), it is reasonable to perform coronary bypass grafting in major coronary arteries (Lever of Evidence: C)

AORTIC VALVE REPLACEMENT IN PATIENTS UNDERGOING CORONARY ARTERY BYPASS SURGERY

Class I

1. AVR is indicated in patients undergoing CABG who have severe AS who meet the criteria for valve replacement (Level of Evidence: C)

Class IIa

1. AVR is reasonable in patients undergoing CABG who have moderate AS (mean gradient 30–50 mm Hg or Doppler velocity 3–4 m/sec) (Level of Evidence: B)

Class IIb

1. AVR may be considered in patients undergoing CABG who have mild AS (mean gradient < 30 mm Hg or Doppler velocity < 3 m/sec) when there is evidence, such as moderate-severe valve calcification, that progression may be rapid (Level of Evidence: C)

Index

Entries from figures/flow charts and tables are represented by locators with *italics* suffix "*f*" and "*t*", respectively.

A

α_1-Adrenergic receptors
  and hypertrophy, 26–27
β-Adrenergic receptor antagonists, 78
  in hypertension, 1135*t*
β-Adrenergic signaling
  and calcium regulation, 24
  receptor mediated, 23
β-Arrestin. *See* G-protein receptor kinase-2 (GRK-2)
5 As
  cigarette cessation, 833, 1879–1880
AAA/AHA guidelines, for ambulatory electrocardiographic monitoring, 784–786
$ABCD_2$ score, in TIA and stroke prediction, 1909*t*
Abciximab, 133, 882
  in dialysis patients, 1701
  in high-risk angioplasty, 548
Abdominal aortic aneurysm (AAA)
  and 9p21, 1942
  modular Z-stent-based stent grafts, 1177
  polymer filled stent grafts, 1177–1178
  ringed stent grafts, 1177
  and tobacco smoking, 1873
  unibody stent grafts, 1177
  uni-iliac stent grafts, 1177
Abdominojugular reflux. *See* Hepatojugular reflux
ACC/AHA guidelines, 908
  preoperative diagnostic testing, 1790*t*
  preoperative management, 1793*t*
  risk mitigation
    other management, 1792*t*
    pharmacological management, 1791*t*
ACC/AHA/ACP-ASIM guidelines, for management of stable angina, 935
Accelerated digoxin administration, 99
Accelerated idioventricular rhythm, in electrocardiograph, 199*f*
Accidental Death and Disability: the Neglected Disease of Modern Society, 790
Accreditation Council for Graduate Medical Education (ACGME), in safe workforce creation, 1973
Acetazolamide, 54, 57, 58*t*
  and loop diuretics, 1242
Acetylsalicylic acid (ASA). *See* Aspirin
"Acoustic shadowing", in IVUS imaging, 353*f*
Acquired immunodeficiency syndrome (AIDS), 845, 852, 1622, 1629, 1636. *See also* Human immunodeficiency virus (HIV) infection
Acquired long QT syndrome, 693, 1812, 1825*t*
Acromegaly, 1718
  cardiac hypertrophy in, 1719
  valvular heart disease in, 1719
Acute ischemic stroke
  definition, 1909
  treatment of, 1920–1922
Action in diabetes and vascular disease (ADVANCE) trial, 1716
Action potential
  for automaticity and contraction, 572–573
  in ion channel and cellular properties, 570–572
  ion channel opening and inactivation, 569–570
  by surface electrocardiogram, 573–574
Action to control cardiovascular risk in diabetes (ACCORD) trail, 111, 114, 1608, 1716
  fenofibrate and statin therapy, 1801
Activated clotting time (ACT), 119
Activated factor X (Xa), 1761
Activated partial thromboplastin time (aPTT), 116, 1761
ACTIVE (A Clinical Trial in IPF to Improve Ventilation and Exercise) trial, 1523
ACTIVE A trials (Atrial Fibrillation Clopidogrel with Irbesartan for Prevention of Vascular Events), 1944
Active ischemia, 694
Active smoking, and cardiovascular disease, 1874–1875
ACUITY trial, heparin versus bilvarudin, 1837
Acupressure-based massage, 2032
Acute and Chronic Therapeutic Impact of a Vasopressin Antagonist in Congestive Heart Failure (ACTIV in CHF), 1277
Acute aortic dissection (AAD), 316, 865, 1166, 1172
  and chest pain, 145
  type A dissection outcome, 1172
  type B dissection outcome, 1172–1173
Acute aortic regurgitation, 162*t*, 476, 1047, 1056, 1741
Acute cardiopulmonary response, to exercise, 215
Acute chest pain syndromes, imaging in, 392
Acute coronary artery thrombosis, due to cocaine usage, 1616
Acute coronary syndrome (ACS), 119, 123, 508–509, 871–887, 927, 1692, 1956
  clinical features, 873–875
    creatinine kinase (CK), 874–875
    electrocardiogram (ECG), 874
    physical examination, 874
    troponins, 875
  definite ACS, 875
  early invasive strategy, 884–885
  early medical therapy, 877–884
    antiplatelet agents, 879–883
    antithrombotic agents, 883–884
    beta blockers, 878–879
    calcium channel blockers, 879
    general measures, 878
    morphine, 878
    nitrates, 878
  initial conservative strategy, 884–885
  noncardiac chest pain, 875
  pathophysiology, 871–873
    etiology, 871–872
    platelets and coagulation system, 872–873
    systemic factors (vulnerable patient), 872
    vulnerable plaque, 872
  and physical examination, 151
  possible ACS, 875
  revascularization, 885–887
  risk stratification, 875–877
    biomarkers, 876–877
    electrocardiogram (ECG), 876
    history, 876
  stable angina, 875
  STEMI. *See* ST segment elevation myocardial infarction (STEMI)
Acute coronary syndromes, cardiogenic shock in *See* Cardiogenic shock, in acute coronary syndromes
Acute decompensated heart failure (ADHF), 1281
Acute Decompensated Heart Failure National Registry (ADHERE)
  risk classification system, 1283i
Acute decompensation, therapy for
  for cor pulmonale, 1764
Acute DVT treatment , 123
Acute heart failure syndromes (AHFS), 1298
  classification, 1299–1300
  clinical trial, 1306–1307
    T1 translation phase, 1307
  definition, 1298
  epidemiology, 1298
  pathophysiology, 1300
    cardiac metabolism, 1301
    congestion, 1300
    myocardial injury, 133
    renal impairment 1301
    untoward drug effects, 1301
    vascular failure, 1301
    viability, 1301
  patient's characteristics, 1298–1299
    preserved versus reduced systolic function, 1299*t*

Acute heart failure syndromes management, 1301–1302
phases of, 1302*t*
reconstruction phase, 1306
vulnerable phase, 1306
stabilization phase, 1302
diagnosis, 1302
disposition, 1303
goals of, 1303
precipitants, 1302
treatment, as per clinical profile, 1302
transition to evidence-based phase, 1303–1305
goals of, 1305–1306
quality measures, 1306
Acute hemorrhagic stroke
treatment of, 1922–1923
Acute limb ischemia (ALI), 1149
treatment of, 1155
Acute myocardial infarction (AMI)
hemodynamic subsets in, 508*t*
left ventricular thrombus in, 310
and renal function monitoring, 1281
and tobacco smoking, 1873
Acute myocardial ischemia
characteristic of, 873
myocardial response to, 1811*t*
and sodium channels, 1617, 1618
Acute pericarditis
presentation and etiology, 1489–1490
diagnosis, 1490
and management of, 1492*f*
examination, 1490
treatment, 1490–1491
Acute pulmonary embolism (acute PE), 145, 1750
Acute rejection
in transplant patients, 1341
types of, 1343*t*
Acute renal failure (ARF), 62, 1283
and ARBs, 77
renin-angiotensin-aldosterone inhibitors, 1158
Acute stroke, 1919–1920
emergency management, 1920*t*
Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF) trial, 1294, 1306
Acute type B dissection, 1182–1183
Acyanotic heart disease, 1551
atrial septal defects, 1559–1562
coarctation of aorta, 1554–1557
congenital valvar aortic stenosis, 1551–1554
patent ductus arteriosus, 1566–1568
right ventricular outflow tract obstruction, 1557
subvalvar aortic stenosis, 1554
subvalvar pulmonic stenosis, 1559
supravalvar aortic stenosis, 1554
supravalvar pulmonic stenosis, 1559
valvar pulmonic stenosis, 1557–1559
ventricular septal defects, 1562–1566
Acyanotic lesions
Ebstein's anomaly, 1568–1570
Adeno-associated virus (AAV), 2004–2005
Adenosine dinucleotide phosphate (ADP), 880
Adenosine, 594, 678, 679, 668, 859–860
Adenoviruses, 2004
cardiotropic virus, 488
in myocarditis, 1426
ADHERE registry
systolic and diastolic heart failures, demographic differences between, 1211*t*
Adhesion molecules, in molecular imaging, 456
Adipose tissue derived stem cells (ASCs), 1989, 1993
Adjunctive coronary interventional devices
directional coronary atherectomy, 552
rotational coronary atherectomy, 552
thrombectomy, 551–552
Adrenal disorders
adrenal insufficiency, 1722
Cushing's syndrome, 1721–1722
paraganglioma, 1720
pheochromocytoma, 1720
primary aldosteronism, 1720–1721
Adrenergic inhibitors, 1140–1141
in hypertension, 1135*t*
Adrenergic-blocker therapy, neurogenic cardiac injury, 1692
Adria cells, doxorubicin cardiotoxicity, 1481
Adult AIDS Clinical Trials Group (AACTG), HAART-related hyperlipidemia management, 1640
Adult congenital heart disease (ACHD), 266*t*, 426, 1557*f*. *See also* Congenital heart disease (CHD)
Adult respiratory distress syndrome (ARDS)
balloon flotation catheter, 509
and septic shock, 506
Adult stem cells, 1987
ADVANCE trial, 1608
Advanced cardiac therapies, identifying candidates for
heart transplantation
donor selection and perioperative period, 1339–1343
indications and contraindications, 1338–1339
survival with, 1343
mechanical circulatory support, 1343–1345
future directions, 1350
indications and contraindications, 1345–1347
myocardial recovery with device explanation, 1349–1350
postoperative patient and device management, 1348–1349
recipient care, 1348
survival with mechanical circulatory support, 1349
VAD, design and postimplant physiology, 1347–1348
VAD, patient selection, 1345
recognition of poor prognosis, 1335
evaluation of patient referred for, 1336–1338
functional assessment, 1336
optimal medical management, 1336
preoperative assessment of, 1338
prognostic determinants and risk scores, 1335–1336
prognostic scores, 1336
Advanced life support (ALS), 791, 795–799
advanced airway management, 795
defibrillation, 797–799
pharmaceutical interventions, 795–796
success rate, 795
Aerobic exercise, 1890
in pressure lowering, 1134
Aerosolized Randomized Iloprost Study (AIR trial), 1539
African-American Heart Failure Trial (A-HeFT), 73, 1241
Afterload reduction
in HF, immediate postoperative management, 1340
with nitroprusside, 1940–1941
Afterload, LV ejection impedance, 71
Age
as heart failure risk factor, 1900
cellular aging, 1830–1832
Aggrastat. *See* Tirofiban
AgomiRs, 28
Airway management, 793
Ajmaline, 693
AL cardiomyopathy (AL-CMP), 1458
symptoms of, 1459
Alagille syndrome, treatment of, 1036
Alanine transaminase (ALT), 110
Alcohol and arrhythmia
alcohol consumption
atrial flutter, 1596–1597
chronic atrial fibrillation, 1596–1597
sudden cardiac death, 1597–1598
binge drinking, 1596
ethanol exposure effects, 1595
ethanol ingestion, 1595–1596
guidelines, 1598
Alcohol, 1631
and CHD, 838
Aldosterone
role of, 79*f*
and systolic heart failure, 78–80
Aldosterone antagonists, 46
for heart failure, 1607
Aldosterone receptor antagonists, 78
Aldosterone Receptor Blockade in Diastolic Heart Failure (ALDO-DHF), 1260
Allgrove syndrome, 1195
Allosensitization prevention, transplant list patients, 1338
Alpha agonists, 796
Alpha-2 adrenergic receptor agonists, in perioperative period, 1782
Alteplase, 902
Alveolar hypoventilation, diseases of, 1763
Alzheimer's disease, 1831
Ambrisentan (Letairis®), for PAH, 1539
Ambulatory ECG monitoring, variant angina diagnosis, 941

Ambulatory electrocardiographic (AECG) monitoring
AAA/AHA guidelines for, 784–786
characteristics of, 778*t*
event recorder, 780–782
Holter monitoring, 777–780
implantable loop recorders (ILRs), 783
mobile cardiac outpatient telemetry, 782
modality selection, considerations for, 779*t*, 783–784
Ambulatory heart failure, renal impairment in, 1282*t*
American College of Cardiology (ACC)
exercise suggestion, 1891
exercise testing, physicians guidelines, 209
heart failure, concept of, 1899
American College of Cardiology Foundation (ACCF), 3994
American College of Physicians (ACP)
exercise testing, physicians guidelines, 209
American College of Sports Medicine (ACSM)
exercise suggestion, 1891
American Diabetes Association (ADA), 129
American Heart Association (AHA), 788
air pollution, statement on, 1884
exercise testing, physicians guidelines, 209
heart failure, concept of, 1899
American Heart Association and American College of Cardiology (AHA/ACC)
sports eligibility criteria, 1824–1825
American Society of Echocardiography (ASE), 310, 324
LV mass, 266
on LVEF, 229
American Society of Nuclear Cardiology (ASNC), 394
workup algorithm, for women, 1804*f*
American trypanosomiasis. *See* Chagas disease
American-Australian-African Trial with Dronedarone in AF or Flutter Patients for the Maintenance of Sinus Rhythm (ADONIS), 591
Amiloride, 54, 55, 58*t*, 62, 64, 66
in CHF and renal dysfunction, 1289
in hypertension, 1138
Amino-terminal pro-B-type natriuretic peptide (NT-proBNP), 1903
in heart failure, 1221–1222
Amiodarone, 588–590, 655, 667, 680, 681, 688, 690, 691
for cardiac arrest, 821–822
for CPR, 796
Amiodarone-induced thyroid disease, due to cardiac complications, 1717–1718
Amlodipine, 74, 1242
arteriolar dilating drug, 72
for stable angina and CAD, 931
AMP-activated protein kinase (AMPK)
in Cushing syndrome, 1721
Amyloid, history of, 1454–1455
Amyloid A (AA) amyloidosis, 1457
Amyloid cardiomyopathy, treatment of
device therapies, 1465
heart failure medical management, 1464–1465
heart transplantation, 1466–1467
underlying amyloid disease, 1465–1466
Amyloid fibril proteins, classification of, 1457*t*
Amyloid heart disease
amyloid cardiomyopathy, treatment of
device therapies, 1465
heart failure medical management, 1464–1465
heart transplantation, 1466–1467
underlying amyloid disease, 1465–1466
amyloid, history of, 1454–1455
amyloidogenesis, 1455–1456
amyloidosis, classification of, 1456
cardiac amyloidosis, 1456–1457
clinical features of, 1459–1464
overview of, 1456
familial (hereditary) systemic amyloidosis, 1458–1459
isolated atrial natriuretic factor, 1459
light chain (AL) amyloidosis, 1457–1458
secondary amyloidosis, 1459
senile systemic amyloidosis. 1458
Amyloid light (AL). *See* Light chain (AL) amyloidosis
Amyloid transthyretin (ATTR),
Amyloidosis, 492, 493–494, 1455–1456
restrictive cardiomyopathy, 1452
Anabolic steroids, 1627–1628
Anaconda stent graft, 1177
Anaerobic threshold (AT). *See* Ventilatory threshold (VT)
Analgesics, for cocaine abuse treatment, 1619
Ancure, stent graft design, 1176
Andersen disease, 495
Androgenic anabolic steroid
on myocardial function, in athletes 1824*t*
Anemia
due to CKD, 1699–1700
coronary blood flow during, 42
Anemia, in HF patients
erythropoietin stimulating proteins (ESPs) in, 1266
safety concerns on, 1266–1268
HF treatment, 1265–1266
using ESPs, 1266–1267
iron deficiency and iron replacement in, 1268–1270
mechanism of, 1264–1265
overview, 1264
prevalence, 1264
prognostic significance of, 1265
AneuRx, stent graft design, 1176
Aneurysm, 464
clinical aneurysm inflammation imaging, 465
preclinical aneurysm imaging investigations, 466
Angina
aortic stenosis, symptoms, 987–988
coronary circulation during, 42–43
Angina pectoris, 143, 144, 219, 544. *See also* Ischemia
Anginal chest pain, 873
Anginal equivalents, 145
Anginal pain, in HF, 1358
Angiogenesis, 2007, 2008*f*
inflammation, in atherosclerosis, 1850
Angiogenesis, basic concepts of
angiogenic growth factors and response to hypoxia, 2010–2011
blood vessel growth, 2007–2009
cellular involvement in, 2009–2010
Angiogenic gene therapy
in animal models, 2011–2012
for chronic heart failure, 2014
clinical trials in heart, 2010–2014
Angiogenic growth factors
and hypoxia, response to, 2010–2011
Angiogenic protein therapy, 2011
Angiographic versus IVUS Optimization (AVIO) study, 361
Angiography versus IVUS-directed stent placement (AVID) trial, 360
Angioplasty, and cardiac rehabilitation, 1895
Angioplasty Compared to Medical Therapy Evaluation (ACME) trial, 553, 977
Angiopoietin, 1525, 2011
Angiotensin converting enzyme (ACE) inhibitors, 72, 74–77, 78, 1140
arteriolar dilator drug, 72
chemotherapy-induced cardiomyopathy, 1485
congenital valvar aortic stenosis, 1553
in diastolic heart failure, 1257, 1258
in heart failure prevention, 1901
for heart failure, 1289, 1607
in hyponatremia, 1272
in LVEF, 267
in LVH regression, 1698
in PPCM, 1475
stroke prevention, 1917
for stable angina and CAD, 930
Angiotensin converting enzyme (ACE), 61
Angiotensin II
in atherosclerotic lesions, 1850
neurohormone, 74
Angiotensin II receptor-1 (AT-1), 38
Angiotensin inhibitors, in HF treatment, 1238*t*
Angiotensin receptor blocker (ARB), 61, 72, 77, 78, 1140
for diastolic heart failure, 1257, 1258
for heart failure, 1607, 1901
in LVH regression, 1698
in PPCM, 1475
stroke prevention, 1917
trials and inference, 77
Angiotensinogen, 75
Angle of Louis, 154
Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), 1904
Ankle-brachial index (ABI), 840, 1145
as PAD diagnosis, 1150
and PAD prevalence, 1146*t*
Ankylosing spondylitis, 152, 1651
Annulus, in tricuspid valve anatomy, 1019
Anomalous coronary artery from the opposite sinus (ACAOS), 530
"Anomalous left coronary artery from the pulmonary artery" (ALCAPA), in hibernating myocardium, 1325

Anomalous origin of the LCA from the pulmonary artery (ALCAPA), 529
Anorexia, 1628
as HF symptom, 1214, 1359
AntagomiRs, 28
Anthracycline-induced cardiomyopathy
pathophysiology
cardiac changes, 1480
histopathologic changes, 1481
prevention of, 1484*t*
Antiadrenergic therapy, 1606
Antianginal drug therapy
invasive vs. optimal, 933
pharmacologic actions of, 928*t*
precautions, 928*t*
vs. revascularization, 931–932, 933–934, 934*f*
side effects and contraindications of, 928*t*
for stable angina, 928–930
Antiarrhythmic drugs (AADs), 578–579, 655–656
antiarrhythmic efficacy, 1963
arrhythmia mechanisms and, 579
in atrial fibrillation, 595
calcium channel blockers, 1962–1963
classification scheme, 579
clinical implications, 1963
on defibrillation and pacing thresholds, 597*t*
digoxin, 1962–1963
drug-device interactions, 597
emerging drugs, 595
and implantable cardioverter defibrillators, 596–597
indications for, 579
major drug interactions of, 583*t*
out-patient versus in-hospital initiation for, 595–596
perioperative arrhythmia prevention, 1782
in pregnancy and lactation, 596
procainamide, 1963
propafenone, 1963
toxicity, 1963
Antiarrhythmic Trial with Dronedarone in Moderate to Severe Congestive Heart Failure Evaluating Morbidity Decrease (ANDROMEDA), 592
Anticoagulation, 908–909
risk of bleeding, 1099*t*
Antidiuretic hormone, and dieresis, 1286
Antihypertensive and Lipid-Lowering to prevent Heart Attack Trial (ALLHAT), 63
Antihypertensive therapy
antihypertensive agents, 1135*t*
lifestyle management, 1133
alcohol restriction, 1134
cigarette smoking, 1134–1135
exercise, 1134
non-antihypertensive drugs, 1135
obesity, 1134
salt, 1134
pharmacological therapy, 1135
Antilipid agents, 104
add-on to statin therapy, 110–111
appropriate uses, 104
bile acid sequestrants, 111
efficacy, 111
safety, 111
drug development, 114
ezetimibe, 111
efficacy, 111
safety, 111–112
fibrates, 105, 113
efficacy, 113
safety, 113–114
lipid lowering options, 110*t*
lipid treatment goals and strategies, 105
lipid-modifying drug mechanisms, 106*f*
niacin, 112
efficacy, 112
flushing, 112
safety, 112–113
omega-3 fatty acids, 114
efficacy, 114
safety, 114
residual risk, 111
statins, 104, 105
drug interactions, 106–108, 109*t*
efficacy, 105
lipid level change , 107*t*
liver safety, 110
muscle safety, 105–106
pharmacokinetics, 109*t*
renal excretion, 108
symptom management, 108*f*, 110
triglyceride-lowering therapy, 113
Antioxidant defense, in dyslipidemia, 1863
Antiphospholipid antibody syndrome (APLAS), 121, 1656
Antiphospholipid syndrome (APS). *See* Antiphospholipid antibody syndrome
Antiplatelet agents, cardiovascular pharmacogenomics, 1943–1945
Antiplatelet agents, 127, 128*f*, 879–883, 908
adenosine dinucleotide phosphate (ADP), 880
aspirin, 879–880
glycoprotein IIb/IIIa inhibitors, 882–883
clopidogrel, 880–881
resistance to, 881
platelet activation inhibitors
ADP/P2Y12 signaling inhibitors, 129–130
phosphodiesterase inhibitors, 131–132
prasugrel, 130–131
thrombin receptor antagonists, 132–133
TXA2 pathway inhibitors, 128–129
platelet adhesion inhibitors, 127–128
platelet aggregation inhibitors, 133
prasugrel, 881–882
therapeutics, 116
ticagrelor, 882
in VAD implantation, 1349
Antischkow myocyte, 1928
Anti-streptolysin O (ASO), 1931
Antithrombotic agents, 883–884
direct thrombin inhibitors, 884
fondaparinux, 120, 884
heparin, 883
and indirect Xa inhibitors, 119
idrabiotaparinux, 120–121
low-molecular weight heparins (LMWH), 119, 883–884
warfarin, 884
therapeutics, 116
Anxiety
and physical examination, 151
Aorfix stent graft, 1177
Aorta, inflammation of, 453
in molecular imaging, 453
Aortic atherosclerotic plaques, and hypertension, 310
Aortic balloon valvotomy, in adolescents or young adults, 1119
Aortic dissection
anatomical classification, 1168
clinical manifestations
physical findings, 1169–1170
symptoms, 1169
Debakey classification, 1168
diagnosis
chest X-ray, 1170
D-dimer, 1170
electrocardiography, 1170
imaging, 1170–1171
new classification, 1168–1169
predisposing factors
atherosclerosis, 1166–1167
inherited disease, 1167–1168
Stanford classification, 1168
treatment
acute aortic dissection outcome, 1172–1173
endovascular repair, 1172
initial treatment, 1171–1172
Aortic impedance components, 72*t*
Aortic insufficiency, plain film imaging, 185
Aortic regurgitation (AR), 1119, 1741
aortic valve replacement, 1110
cardiac catheterization, 1110
coronary blood flow during, 41
diagnosis and valuation, 1109
cardiac catheterization, 995
chest X-ray, 994
echocardiography, 994–995
electrocardiograph, 994
exercise testing, 995
imaging modalities, 995
etiology of, 992
aortopathy, 992–993
leaflet abnormalities, 993
medical therapy, 1109
natural history of, 993–994
pathophysiology of, 993
in perioperative setting, 1777
physical examination, 994
symptoms, role of, 993–994
treatment of
acute severe AR, 995–996
AVR, surgery and timing of, 995
medical therapy, 995
Aortic regurgitation severity, classification of, 279*t*
Aortic root motion, amplitude of, 232
Aortic stenosis (AS)
aortic balloon valvotomy, 1108–1109
aortic valve replacement, 1108

in asymptomatic adolescents or young adults, 1118–1119
cardiac catheterization, 1107
catheter-based therapies for, 1045
percutaneous aortic balloon valvuloplasty, 1045–1047
percutaneous aortic valve implantation, 1047–1048
coronary blood flow in, 41
diagnosis of
calcium scoring, 989
cardiac catheterization, 989
chest X-ray, 989
echocardiography, 989
electrocardiograph, 989
natriuretic peptides, 989
echocardiography for, 1107
in elderly patients, 991
etiology of
calcific aortic stenosis, 985–986
rheumatic disease, 986
left ventricular hypertrophy
growth, 987
physiologic and pathologic, comparison of, 987
low ejection fraction, 990–991
low gradient, 990–991
natural history of, 987
normal ejection fraction, 991
pathophysiology of, induced left ventricular pressure overload, 986–987
in perioperative setting, 1776–1777
physical examination, 988
plain film imaging, 183–185
symptoms, 987
angina, of, 987–988
heart failure, of, 988
syncope, of, 988
treatment of
asymptomatic, AVR in, 990
medical therapy, 990
symptomatic, AVR for, 990
Aortic stenosis progression observation: measuring effects of rosuvastatin (ASTRONOMER) study, 1605
Aortic stenosis severity, classification of, 277*t*
Aortic valve disease
description of, 985
regurgitation of *See* Aortic regurgitation
stenosis. *See* Aortic stenosis (AS)
Aortic valve replacement (AVR)
in asymptomatic AS, 990
during coronary artery bypass surgery, 1126
during coronary artery disease treatment, 1126
surgery and timing of, 995
for symptomatic AS, 990
Aortic valve, 3, 15–16
major criteria for, selection, 1122
valvular disorders, assessment of, 334
Aortography, of aortic dissection, 1171
Aortopathy, etiology of, 992–993
AP films, 174
vs PA films, 175*f*
pulmonary vascular congestion, 180*f*
Apical hypertrophic cardiomyopathy (ApHCM), 1408
Apixaban, 123–124
Apolipoprotein C (apo C), 106
Apolipoprotein E (*ApoE*) locus, 1953–1954
Apoliporotein B (Apo B), and CHD, 839
APOLLO trial, for ASCs benefits, 1993
Apoptosis, in molecular imaging, 460
Apoptosis inducing factor (AIF), 28
Apoptosome, 28
"Apple-green" birefringence, of amyloid, under polarized light, 1455, 1456, 1460
Aquaporin-2 (AQP-2), water transport, 1275
Argatroban, 125–126, 1762
Arginine vasopressin (AVP), 76
and dieresis, 1286
hyponatremia in HF, pathophysiology of, 1274, 1275
neurohormone, 74
Argyria, 152
Arm sign, 144*f*
Aroylhydrazone, in cardiotoxicity, 1485
Arrhythmia initiation
action potentials
for automaticity and contraction, 572–573
in ion channel and cellular properties, 570–572
ion channel opening and inactivation, 569–570
by surface electrocardiogram, 573–574
molecular and cellular mechanisms, 565–569
proarrhythmic substrates, 575
Arrhythmias, 1702–1703, 1777
atrial fibrillation
4q25 SNPs, 1942–1943
4q25 variant carriers, 1943
and conduction abnormalities, 1785–1786
QT interval and sudden cardiac death, 1943
variant angina, treatment of, 943–944
Arrhythmogenic right ventricular cardiomyopathy (ARVC), 444–445, 806
EMB in, 492
Arrhythmogenic right ventricular dysplasia and cardiomyopathy (AVRD/C)
clinical diagnosis, 709
arrhythmias, 712
depolarization abnormalities, 711–712
ECG criteria, 711
endomyocardial biopsy, 711
family history, 712–713
global and/or regional dysfunction and structural alterations, 709–711
repolarization abnormalities, 712
clinical presentation, 708–709
differential diagnosis, 713–714
epidemiology, 708
molecular and genetic background
autosomal dominant disease, 707–708
autosomal recessive disease, 707
desmosomal dysfunction and pathophysiology, 706–707
desmosome structure and function, 706
non-desmosomal genes, 708
molecular genetic analysis, 714
non-classical subtypes
Carvajal syndrome, 713
left dominant type, 713
Naxos disease, 713
prognosis and therapy, 714–715
Arrhythmogenic substrate, due to percutaneous alcohol septal ablation, 1408–1411
Arterial dissection, 1909*t*
Arterial pulse, monitoring of, 157–159
Arterial stiffness, and tobacco smoking, 1878
Arteriogenesis, 2008, 2009*f*
Arteriovenous oxygen difference
exercise testing, peripheral factor for, 216–217
arterial oxygen content, 217
venous arterial content, 217
Arthropathy, in hemochromatosis, 1450
Artichoke leaf extract, for dyslipidemia, 2034–2035
ARTS I trial, 978
ARTS II registry, 979
Aschoff's bodies, and ARF, 1928
Ashman's phenomenon, 677
Aspirin, 128, 908, 909
and bleeding, 1837
for cardiovascular disease, 1958
for carditis, 1932
for chest pain syndrome, 1808
and clopidogrel, 881, 1808, 1919, 1943
for cocaine abuse treatment, 1619–1620
in LV dysfunction, 1695
for MI, 879–880
in noncardiac perioperative setting, 1783
for PCI, 545
in pericardial injury, 1734
for stroke, 1918
TxA2 pathway inhibitor, 128*f*
versus warfarin, 884, 1982
ASSERT trial (Aortic Stentless vs Stented valve assessed by Echocardiography Randomized Trial), 1078
Asymmetric septal hypertrophy (ASH), 238, 1380
Asymptomatic left ventricular systolic dysfunction, 1902–1903
Atenolol, 722
for stable angina and CAD, 929
ATHENA trial, 591
Atherosclerosis
due to diabetes mellitus, 1714*f*
endothelial activation in, 1848–1850
inflammation
angiogenesis, 1850
plaque rupture and thrombosis, 1850–1852
inflammation role in, 1848*t*
innate immunity, toll-like receptors, 1850
macrophage heterogeneity in, 1850
predilection sites for, 1847–1848
and tobacco smoking, 1876–1877
triggers of inflammation in, 1850
Atherosclerosis Risk in Communities (ARIC) cohort study, anemic rate in, 1264
Atherosclerosis, molecular imaging of, 453
apoptosis, 460
calcification, 460–461

inflammation
additional promising preclinical molecular imaging strategies. 456
adhesion molecules, 456
cell tracking, 456–458
coronary arteries, 456
large arteries, 453–456
macrophages, 456
molecular CT imaging, 456
NIRF imaging, 456
proteases, 456
neovascularization, 459–460
oxidative stress, 458–459
Atherosclerosis, surrogate measures of
brachial artery flow-mediated dilation, 1641
carotid artery intima-media thickness, 1641
coronary artery calcium scoring, 1641
Atherosclerotic lesions, 872
Atherosclerotic plaques, 1851*f*
in IVUS imaging, 354*f*
Atherosclerotic renal artery stenosis (ARAS), 1157
epidemiology and natural history of, 1158
Atherosclerotic risk factors, management of, 1151
Atherothrombosis. *See* Atherosclerosis
Athlete's heart
and exercise physiology, 1818–1819
exercise-induced cardiac remodeling
aorta, 1820
left atrium, 1820–1821
left ventricle, 1819–1820
right ventricle, 1820
historical perspective, 1818
issues relevant to cardiovascular care,
arrhythmia, 1821–1823
clinical approach to, 1821
left ventricular hypertrophy, etiology of, 1821
steroids and sport performance supplements, 1824
sudden death and preparticipation disease screening, 1824–1825
syncope, 1923–1824
Athletes
with cardiovascular disease
medical-legal framework for, 1406*t*
with hypertrophic cardiomyopathy, 1405
ATI-5923, 122
Atorvastatin, for stable angina and CAD, 930, 931
Atorvastatin therapy: effects on reduction of macrophage activity (ATHEROMA) trial, 453–454
ATP-binding cassette, sub-family B (MDR/TAP), member 1 (ABCB1) gene, 1953
Atrial activity, identification of,
electrocardiogram, 194–201
Atrial Arrhythmia Conversion Trials (ACT), 594
Atrial effective refractory period (AERP), 1812
Atrial fibrillation (AF), 313, 647, 768, 799
arousal from sleep, 2022
in athletes, 1823
and cardiac rehabilitation, 1895
in constrictive pericarditis, 1499
cost-effectiveness, 1982
definition and classification, 647
diagnosis
diagnostic testing, 653
electrocardiogram, 652–653
physical examination, 652
presentation, 652
epidemiology
incidence and prevalence, 647–648
natural history, 648–649
etiology and pathogenesis, 649–650
electrophysiological abnormalities, 650
lone atrial fibrillation, 651
non-cardiac causes, 651
structural heart disease, 650
guidelines, 659–660
in HCM, 1412–1413
left atrial thrombus in, 310
management
new-onset atrial fibrillation, 653
rate control strategies, 657–658
recurrent AF, rate control versus rhythm control in, 653–654
sinus rhythm maintenance, 655–657
sinus rhythm restoration, 654–655
thromboembolism prevention, 658
and OSA, 2025
Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study, 1812
Atrial flutter, 667–668
ablation of CTI dependent, 734–735
ablation of non-CTI dependent, 735
catheter ablation clinical implications and indication, 734
in electrocardiograph, 195*f*
end-point of CTI ablation, 735
history of nonpharmacologic treatment in patients, 734
left atrial flutter circuits, 735–736
right atrial flutter circuits, 735
Atrial pressure, measurement of, 153–154
Atrial septal aneurysms, 312
Atrial septal defects (ASDs), 335, 1738–1739
associated anomalies, 1560
classification of, 1559–1560
clinical findings, 1560–1561
diagnostic studies, 1562
endocarditis prophylaxis, 1562
general considerations, 1559–1560
genetic inheritance, 1560
guidelines, 1562
pathophysiology, 1560
pregnancy, 1562
treatment and prognosis, 1562
tricuspid regurgitation in, 169
Atrial switch operations (ASOs)
for d-TGA, 1579–1580
Atrial tachycardia, 668
and pulmonary venous activity, 650
Atrial-based AV nodal independent SVT, 666
atrial flutter, 667–668
atrial tachycardia, 668
focal atrial tachycardia, 668
intra-atrial reentrant tachycardia, 668–669
multifocal atrial tachycardia, 669–670
sinoatrial re-entry tachycardia, 669
sinus tachycardia, 666–667
Atrioventricular (AV) nodal dependent SVT, 680
atrioventricular nodal reentrant tachycardia, 670–672
atrioventricular re-entry tachycardia, 672–673
junctional ectopic tachycardia, 674
permanent junctional reciprocating tachycardia, 674
pre-excitation syndromes, 673–674
and regular SVT, 678–680
Atrioventricular (AV) node, 189
Atrioventricular nodal re-entrant tachycardia, 729
catheter ablation, 730
electrophysiology, 729–730
Atrioventricular node tumors, 1675
Atrio-ventricular reentratachycardia
in electrocardiograph, 197*f*
Atrioventricular valve
and arterial valve, relationship of, 8*f*
Atropine, 678, 701
Atropine, for CPR, 796
ATS valve, 1075
Attenuated plaques
in IVUS imaging, 355*f*
Augmented right atrial contraction
compensatory role of, 962
"Augmented unipolar leads", 191
Auscultation, 160–163
of heart murmurs, 166
ejection systolic murmurs, 166–167
innocent murmurs, 167
pulmonary outflow obstruction, 167–168
S_3 and S_4 heart sounds, 163–167
Austin Flint" murmur, 170, 172
Autologous iPS cells, 1996. *See also* Induced pluripotent stem cells (iPSCs)
Automatic external defibrillators, 794
Automatic implantable cardioverter defibrillator (AICD), 794
Autonomic dysfunction, in HCM, 1387
Autonomic nervous system (ANS), 1187
and cigarette smoking, 1879
components of, 1187–1188
in heart metabolic demands, 1689
Autonomic testing, 1190
baroreflex sensitivity, 1191
cardiac sympathetic imaging, 1193
catecholamine blood measurement, 1192–1193
heart rate recovery, 1192
heart rate variability, 1191–1192
orthostatics, 1190
resting heart rate, 1191
valsalva maneuver, 1190–1191
Autoregulatory vascular resistance, 35–36
Autosomal dominant disease, 707–708
Autosomal recessive disease, 707
AVE5206, 121
Average peak velocity (APV), 38
aVF lead, 191

aVL lead, 191
aVR lead, 191
AVRO (A Phase III Superiority Study of Vernakalant versus Amiodarone in Subjects With Recent Onset Atrial Fibrillation) trial, 594
Axial scanning, 409
Azimilide Cardioversion Maintenance Trial (ACOMET II) study, 593
Azimilide dihydrochloride, 593
AzimiLide post-Infarct surVival Evaluation (ALIVE) trial, 593
Azimilide Supraventricular Tachyarrhythmia Reduction (A-STAR) trial, 593

B

B cell alloantigens, and ARF, 1928
Bachmann's bundle, 16
Bacterial endocarditis, 152, 153, 1414
  tricuspid regurgitation in, 169
Balloon valvotomy
  valvar pulmonic stenosis, treatment of, 1033–1034
Baltimore Longitudinal Study on Aging (BLSA), 1833
Bare metal stents (BMS), 553
  versus DES, 553–555
BARI-2D study, revascularization benefits, 1809
Barlow's disease, degenerative mitral valve disease, pathology of, 1011
Barth syndrome, 1379
Basic fibroblast growth factor (bFGF), 40
Basic life support (BLS), 791, 792–795
  automatic external defibrillators, 794
  cardiopulmonary resuscitation
    complications of, 794–795
    compression only type, 793
    dispatcher assisted, 793
    mechanical devices for, 793–794
  chest compressions or airway management, 793
  emergency medical services (EMS) activation, 792–793
  pacemaker or automatic implantable cardioverter defibrillator, 794
  bystanders, role of, 792
"Batista" procedure, left ventricular volume reduction surgery, 1245
BEAUTIFUL (morBidity mortality EvAlUaTion of the If inhibitor ivabradine in patients with coronary disease and left ventricULar dysfunction) trial, 595, 1244
Becker and Duchenne muscular dystrophy, dystrophin in, 495
Beijing registry, 979
Bendroflumethiazide, 54, 56, 58*t*, 60, 62, 63, 64, 65
BENEFIT trial, in Chagas disease, 1517
Benzathine penicillin, for RF, 1933*t*
Benzodiazepine
  for cocaine abuse treatment, 1619
  for dyspnea, in HF, 1358
  in TEE, 310
Beta blockers, 219, 878–879, 909, 1938. *See also* Beta-adrenergic receptor blockers
  mechanism of action, 1138
Beta-adrenergic blockade, preoperative pharmacologic intervention, 1780–1781
Beta-adrenergic blocking agents
  chemotherapy-induced cardiomyopathy, 1485
Beta-adrenergic pathways and signaling
  in VAD, 1348
Beta-adrenergic receptor blockers. *See also* Beta-blockers (BBs)
  in hypertension, 1138
Beta-blocker evaluation survival trial (BEST), 1239
Beta-blockers (BBs), 1960–1961
  adverse events, 1962
  clinical benefit, in cardiovascular disease
    ADBR1, 1962
    ADBR2, 1962
    GRK1, 1962
  clinical implications, 1962
  congenital valvar aortic stenosis, 1553
  for HCM, 1405
  for heart failure, 1607
    cardiovascular pharmacogenomics, 1945–1946
  heart rate and blood pressure reduction
    ADBR1, 1961
    ADBR2, 1961
    CYP2D6, 1961
    GRK1, 1962
  in hyponatremia, 1272
  in LVEF, 267
  for stable angina and CAD, 928–929
  ventricular function improvement, in systolic heart failure, 1962
Beta-glucan
  for dyslipidemia, 2034
Bevacizumab (Avastin)
  in left ventricular dysfunction, 1480*t*
Bezafibrate Infarction Prevention (BIP) study on β-blockers, 1698
Bezold-Jarisch reflex, 1197
Bicarbonate, for cocaine abuse treatment, 1620
Bicuspid aortic valve related aortic disease, 1168
Bicuspid aortic valve with dilated ascending aorta, 1110–1111
Bicuspid aortic valves (BAVs), 1551, 1552
  NOTCH1 gene mutation, 1552, 1555
  systolic murmur, 1556
Bicycle ergometer, 212
BiDil®, 72
Bidirectional tachycardia, 691
Bile acid sequestrants, 111
Bile-acid sequestering agents (BAS), 106
Bioprosthetic valves, 1101
Biphasic defibrillators, 797–798
Biplane imaging, 321
Birmingham Treatment of Atrial Fibrillation in the Aged Study (BAFTA), 1838
Bivaliridin, 124–125, 884, 909, 1762
Bjork-Shiley valve, 1073
Blood alcohol concentration (BAC), and normal cardiac conduction system, 1595–1596
Blood pool imaging, 398
Blood pressure (BP)
  chemoreflex influence on, 1189
  classification of, 1130*t*
  during exercise, 218
  measurement, 1129–1130
    in cardiac rehabilitation, 920
  regulation of, 1188–1189
Blood urea nitrogen (BUN), 77
  in hyponatremia, 1272
  survival predictor, 1282
"Blooming", in IVUS imaging, 351*t*
Blunt cardiac injury (BCI), 1734–1735. *See also* Myocardial contusion
Blunt injury, 1730–1731. *See also* Myocardial contusion; Non-penetrating injury
Body mass index (BMI), 231, 920, 1798, 1894
  anthracycline cardiotoxicity, 1480
  as HF risk factor, 1901
  obesity classification by, 836
  in LV function assessments, 231
Body surface area (BSA), 1019, 1820
  in LV function assessments, 231
  nomogram for, 231*f*
Bone marrow cells, 1994
Bone marrow derived stem cells, 1987–1989
Bone marrow mononuclear cells (BMMNCs), 1991–1993
Bone morphogenetic protein receptor type 2 (BMPR2), mutations in
  in PAH, 1524
BOOST Trial, using BMC post-MI, 1991, 1992*t*
Bortezomib (Velcade), in left ventricular dysfunction, 1480*t*
Bosentan (Tracleer®), for PAH, 1538–1539
Bosentan Use in Interstitial Lung Disease (BUILD-1) trial, 1524
Botanical medicines
  with adverse cardiovascular effects, 2047–2048
  for dyslipidemia, 2033–2037
  for hypertension, 2038–2040
  and heart failure, 2045–2047
  for hypertension, 2038–2040
Both ventricles endomyocardial fibrosis (BVEMF), 1442
Brachial artery flow-mediated dilation, 1641
"Brady heart". *See* Hypertrophic cardiomyopathy (HCM)
Bradyarrhythmias, 2021
  in athletes, 1821, 1823
Bradycardia and heart block, 698
  AV node disease
    first-degree AV block, 701
    paroxysmal AV block, 701
    pathology, 700–701
    second-degree AV block, 701
    third-degree AV block, 701
  bradycardia syndromes and diseases, cardiac transplantation, 699–700
    familial, 699
    iatrogenic and noncardiac causes, 698–699
    vagal tone, 699
  bundle branch block
    LBB block, 702

RBB block, 702
clinical presentation, 700
conduction system anatomy and development, 698
hemiblock, 701–702
measurement/diagnosis, 700
sinus node disease
sick sinus syndrome, 700
treatment, 702–703
Brain attack. *See* Acute ischemic stroke
Brain natriuretic peptide (BNP), 1780
cardiac marker, for myocardial wall stress, 1780
in heart failure, 1221–1222
as mortality predictor, 1355
"Braking" phenomenon, 56
Branched stent grafts, 1180
Brazilian Ministry of Health Trial
clinical trial, in post-MI patients, 1993
Breast cancer, radiation-induced cardiotoxicity, 1505
Brugada syndrome, 693–694, 724, 805, 2022
in athletes, 1823
clinical manifestations, 724
in cocaine use, 1618
diagnosis, 724–725
genetics, 724
pathogenesis, 724
prognosis, risk stratification and therapy, 725
B-type natriuretic peptide (BNP), 147, 877
in diastolic heart failure, 1254
in euvolemic CKD patients, 1703
myocyte stress, 1286
in PPCM, 1475
in SAH, 1691
Budget-impact analysis, 1983
Bulemia, 1628
Bumetanide, 54, 58*t*, 59, 65*t*
for CRS, 1288
to relieve congestive symptoms, 1242
Bundle branch block
LBB block, 702
RBB block, 702
Bundle of His, 189, 190
Bundles of Kent, 17
Bupropion, 918
anti-depressant drug, 834
in nicotine replacement therapy, 918
sustained release (SR)
tobacco dependency, first-line treatment for, 1151*t*, 1880, 1881, 1882*t*
"Burned-out phase"
end-stage LVH, 1380
Bypass Angioplasty Revascularization Investigation (BARI), 978

C

C statistic, 832–833
Ca^{2+}-induced Ca^{2+} release (CICR), 573
Cachexia
in HF, 1359
CAD, and 9p21, 1942
CAD diagnosis, prognostic variables in
combined clinical variables, 300
exercise variables, 300
imaging variables, 300
Cadiovascular trauma, 1729–1730
classification and physics of, 1730
non-penetrating injury, 1730–1731
penetrating injury, 1730
intracardiac injuries, 1737–1738
aortic and arterial trauma, 1742–1744
coronary artery laceration, 1742
iatrogenic cardiovascular injuries, 1745–1746
intracardiac fistulas, 1741–1742
retained foreign bodies, 1744–1745
septal defects, 1738–1739
thrombosis, 1742
valvular injuries, 1739–1741
pathology of, 1731
thoracoabdominal injury, management of, 1731–1732
cardiac laceration, 1734
cardiac tamponade, 1732–1733
cardiovascular injuries, 1732
myocardial contusion, 1734–1737
penetrating cardiac injury, 1733*t*
pericardial injury, 1733–1734
CADUCEUS, for cardiosphere-derived stem cells, 1993–1994
Caffeine, in athletes, 1823
Calcific aortic stenosis, 985–986
Calcific coronary sclerosis, 530
Calcification, inflammatory lesions, 460–461
Calcified valvular disease, 1100
Calcium, in pressure lowering, 1134
Calcium antagonists, 1139–1140
in hypertension, 1135*t*
variant angina, treatment of, 944–946
Calcium channel blockers (CCBs), 879, 1962–1963
for HCM, 1405
in HTN due to CKD, 1698–1699
in LV dysfunction, 1695
in perioperative risk reduction, 1781–1782
for stable angina and CAD, 929
stroke prevention, 1917
Calcium chloride, for CPR, 796
Calcium regulation, 24
and β-adrenergic signaling, 24
receptor mediated, 23
Calcium scoring, diagnosis of, 989
Calcium sensitizers, 97
levosimendan, 97–98
Calcium/calmodulin kinase II (CamKII), 24
"Calcium-binding HCM", 1378
Calmodulin-dependent protein kinase II (CaMKII), 573
Camellia sinensis, 2036. *See also* Green tea extract, for dyslipidemia
Can routine ultrasound improve stent expansion (CRUISE) trial, 360
Canadian Amiodarone Myocardial Infarction Arrhythmia Trial (CAMIAT), 589
Canadian Cardiovascular Society (CCS), 145
functional classification, 146*t*
specific activity scale, 146*t*
Canadian Registry of Atrial Fibrillation (CARAF) database, 1812
Canadian Trial of AF (CTAF), 589
Candesartan in heart failure assessment of reduction in mortality and morbidity (CHARM) trial, 1238
Candesartan in Heart Failure-Assessment of Reduction in Mortality and Morbidity-Preserved (CHARM-Preserved) trial, 1252
Cangrelor, 131
CarboMedics valve, 1074–1075
Carbonic anhydrase inhibitors, 57
Carcinoid heart disease
primary tricuspid valve regurgitation, surgical treatment of, 1026
tricuspid regurgitation in, 169
Carcinoid syndrome, 1723
Cardiac innervations, 3, 21–22
Cardiac "abnormalities", in athletes, 1818
Cardiac "syndrome X", 43
coronary blood flow during, 42, 43*t*
Cardiac action potentials, 570. *See also* Myocardial action potentials
Cardiac aging, 30–31
Cardiac amyloidosis, clinical features
cardiac catheterization hemodynamics, 1463–1464
cardiac magnetic resonance imaging, 1463
diagnostic tests, 1460
electrocardiography, 1460–1461
findings, 1461–1462
history and physical examination, 1459–1460
laboratory findings, 1462–1463
prognosis, 1464
radiologic findings, 1460
serum amyloid P component scintigraphy, 1465
tissue diagnosis, 1460
Cardiac apical impulse, in HCM, 1388
Cardiac arrest, 789–790
advanced life support (ALS), 791, 795–799
advanced airway management, 795
defibrillation, 797–799
pharmaceutical interventions, 795–796
success rate, 795
basic life support (BLS), 791, 792–795
automatic external defibrillators, 794
bystanders, role of, 792
cardiopulmonary resuscitation, complications of, 794–795
cardiopulmonary resuscitation, compression only, 793
cardiopulmonary resuscitation, dispatcher assisted, 793
cardiopulmonary resuscitation, mechanical devices for, 793–794
chest compressions or airway management, 793
emergency medical services (EMS) activation, 792–793
pacemaker or automatic implantable cardioverter defibrillator, 794
cardiac resuscitation, drug therapy in, 821–822

cardiac resuscitation centers, 822–823
myocardial ischemia causing cardiac arrest, 823
therapeutic mild hypothermia, 822–823
etiology and pathophysiology of, 812–821
bystander resuscitation efforts, 818
cardiocerebral resuscitation, prehospital component, 819–821
coronary perfusion pressures, during resuscitation efforts, 813–814
primary cardiac arrest, ability to identify 818
primary cardiac arrest, assisted ventilation in, 814–815
primary cardiac arrest, in children and adolescents, 812
primary cardiac arrest, not following guidelines for, 815–816
primary cardiac arrest, pathophysiology of, 812–813
public mindset, 817–818
ventricular fibrillation (VF), phases of, 818–819
post-resuscitative care, 800
cardiac interventions, 800
cardiopulmonary support, 800
therapeutic hypothermia, 800
termination of resuscitation, 799–800, 823
Cardiac arrhythmias
by afterdepolarizations, 575
autonomic perturbations associated with, 1200
due to cocaine usage, 1617
and sex, 1812–1813
Cardiac arrhythmias surgical and catheter ablation, 728
atrial flutter, 734–736
atrioventricular nodal re-entrant tachycardia, 729–730
atrioventricular re-entrant tachycardia, 730–731
focal atrial tachycardia, 731–734
idiopathic ventricular tachycardia, 744–751
supraventricular tachycardia, 728–729
ventricular tachycardia ablation, in patients with structural cardiac disease, 736–744
Wolff-Parkinson-White syndrome, 730–731
Cardiac assist devices, in PPCM, 1475
Cardiac biopsy
analysis of EMB tissue, 487–488
cardiotropic virus detection, 488
light microscopy and stains, 488
cardiac transplantation, 497–498
disease states
EMB in cardiomyopathy, 491–492
EMB in special cardiac disease states, 492–497
guidelines, 499
history and devices, 485
indications, 488–491
safety and complications, 487
techniques, 485–487
Cardiac cachexia, end stage heart failure, 1215
Cardiac catheterization
aortic regurgitation, diagnosis of, 995
aortic stenosis, diagnosis of, 989
basic, 470–471
complications and risks for, 537*t*
contraindications to, 519*t*
and coronary angiography, risks of, 471*t*
isolated infundibular stenosis, 1034
mitral regurgitation, 1014
right heart catheterization, 472
supravalvar stenosis, 1036
valvar pulmonic stenosis, 1032
Cardiac chambers, normal dimensions, 232*t*
Cardiac chest pain, 143*t*
Cardiac complications, substance abuse, 1613–1614
alcohol and tobacco, 1631
body image drugs
anabolic steroids, 1627–1628
anorexia and bulemia, 1628
diet drugs, 1628
club drugs, 1625
gammahydroxybutyrate, 1626
ketamine, 1626–1627
methylenedioxymethamphetamine, 1625–1626
Rohypnol, 1627
cocaine, 1615–1622
hallucinogenic drugs, 1627
lysergic acid diethylamide, 1627
hashish, 1624–1625
inhalants, 1628
magnitude of the problem, 1614
adolescents, 1614
college and medical students, 1614
iatrogenic issues, 1614–1615
trauma associations, 1614
unemployed adults, 1614
marijuana, 1624–1625
methamphetamine, 1622–1624
narcotics
heroin, 1629–1630
methadone, 1630
over the counter drugs, 1630–1631
phencyclidine, 1624
phenylpropanolamine, 1624
tetrahydrocannabinol, 1624–1625
Cardiac computed tomography (Cardiac CT)
incidental findings, 423
technical aspects
basic principles, 408–411
contrasting, 413–414
image analysis, 411–413
image quality and artifacts, 413
radiation, 411
future, 423
guidelines, 424–426
Cardiac contractility, 89
Cardiac cycle pressure waveforms
atrial pressures, 473
ventricular pressures, 473–474
Cardiac dyspnea, and physical examination, 151
Cardiac electrophysiology studies, 601–604
ablative therapy guidance
three-dimensional mapping systems, 624–625
cardiac access and catheterization, 604–605
complications, 625
for drug therapy evaluation, 623–624
fundamentals, 605
conventions, 605
normal propagation patterns, 605–607
sinus rhythm and normal atrioventricular conduction parameters, 607–609
programmed electrical stimulation and associated, 609–610
atrial stimulation, 613, 615
atrioventricular conduction disease evaluation, 615–616
baseline observations, 613
continuous pacing, 610
intermittent and interrupted pacing with extrastimuli, 610
short-long-short pacing cycles, 610–611
sudden cardiac arrest survivors, 621–623
unexplained syncope evaluation, role in, 621
ventricular stimulation assessment, 616–621
ventriculoatrial conduction assessment, 616–621
signals and filtering, 605
Cardiac energy metabolism, 1603*f*. *See also* Myocardial energy metabolism
Cardiac evaluation and care algorithm, 1774*f*
Cardiac fibroma, 1673
histopathology, 1674
imaging, 1673–1674
Cardiac function
calcium regulation, 24
cardiac muscle hypertrophy, 26
cardioprotection, 28–30
energy production, 23
ischemia/reperfusion injury, 28
mitochondria and, 24–26
β-adrenoceptors, 23
Cardiac glycosides, 1228
Cardiac hemodynamics, and coronary physiology
cardiac catheterization, 470–472
cardiac cycle pressure waveforms, 473–474
cardiomyopathy, 479–481
catheterization computations, 472–473
coronary hemodynamics, 482–484
in pericardial disease, 481–482
in valvular heart disease, 474–479
Cardiac hypertrophy, due to acromegaly, 1719
Cardiac infections, EMB in, 496
Cardiac Insufficiency Bisoprolol Study (CIBIS), 84
Cardiac Insufficiency Bisoprolol Survival (CIBIS II) trial, 1239
Cardiac laceration, 1734
Cardiac lymphatics, 3, 21
Cardiac magnetic resonance imaging (CMRI), 326, 331
ischemic versus nonischemic LV dilatation, 1425
Cardiac masses, 445
Cardiac muscle hypertrophy, 26
α_1-adrenergic receptors and, 26–27
Cardiac myxoma, 1667–1668
microscopic diagnosis, 1669–1670

imaging techniques, 1668–1669
pathology, 1669
treatment, 1669
Cardiac neoplastic disease, 1663
benign cardiac neoplasms, 1667
atrioventricular node tumors, 1675
cardiac fibroma, 1673–1674
cardiac myxoma, 1667–1670
cardiac paraganglioma, 1675
hemangioma, 1674
lipomas, 1674
lipomatous hypertrophy, 1674
papillary fibroelastoma, 1670–1672
rhabdomyoma, 1672–1673
clinical symptoms, 1663–1665
common neoplasms, locations of, 1664*t*
imaging techniques, 1665–1667
malignant tumors, 1675
angiosarcoma, 1679
leiomyosarcoma, 1681
malignant fibrous histiocytoma, 1679
osteosarcoma, 1679–1681
primary cardiac sarcomas, 1675–1679
rhabdomyosarcoma, 1681
synovial sarcoma, 1681
undifferentiated sarcomas, 1681
metastatic tumors, 1684–1686
pericardial mesothelioma, 1683–1684
primary cardiac lymphoma, 1681–1683
Cardiac nervous system dysfunction, 650
Cardiac output, catheterization computation, 472
Cardiac pain, 143
Cardiac papillary fibroelastoma (CPF), 1670–1671
histology, 1672
imaging techniques, 1671
pathology, 1671–1672
Cardiac paragangliomas, 1675
Cardiac rehabilitation, 919–921, 1890
advantages of, 921
clinical population considerations, 1895
core components, 1893
exercise training, 1894
medical assessment, 1893
medication assessment and management, 1894
nutrition, 1894
psychosocial assessment and management, 1893–1894
risk factor management, 1894
definitions and goals, 1892
phases of
early outpatient (phase II), 1893
inpatient (phase I), 1892–1893
long-term outpatient (phase III), 1893
referral, 1895
reimbursement issues, 1895–1896
in United States, 921
Cardiac resuscitation, drug therapy in, 821–822
Cardiac resynchronization therapy (CRT), 85, 289, 327, 758
for acute decompensated heart failure, 770
benefit summary, 761–762
complications, 767–768
phrenic nerve simulation, 767
dyssynchrony imaging role, 764, 777
magnetic resonance imaging, 765–766
multidetector computed tomography, 766–767
nuclear imaging, 766
PROSPECT trial, 765
real-time three dimensional echocardiography, 766
septal to posterior wall motion delay, 764
speckled tracking, 765
strain rate imaging, 765
tissue Doppler imaging, 764
tissue synchronization imaging, 764–765
emerging indications
atrial fibrillation, 768
minimally symptomatic heart failure, 769–770
narrow QRS, 768
pacemaker dependant patients, 768–769
guidelines, 770–773
in HF, 1360
in women, 1810
loss, 767
LV lead placement, 767
in practice, 759
CARE-HF trial, 759, 761
COMPANION study, 759
MIRACLE study, 759
prediction of response to therapy, 762
BIV capture, 762–763
device optimization, 763–764
rational for use, 758–759
and ventricular arrhythmias, 767–768
Cardiac resynchronization-heart failure (CARE-HF), 1426
Cardiac retransplantation, 1343
Cardiac rhabdomyomas, 1672
imaging, 1672–1673
pathology, 1673
Cardiac rupture, cardiogenic shock in acute coronary syndromes, cardiac causes of, 953, 954*f*
Cardiac sarcomere, 1378*f*
Cardiac stem cells (CSCs), 1989
Cardiac surface anatomy, 3, 6–8
Cardiac tamponade, 506, 1172, 1732–1733
in cardiac catheterization, 1495
diagnostic testing in, 1494*t*
TTE in, 273
Cardiac temponade
Cardiac thrombi, 445
Cardiac transplantation. *See also* Heart transplantation
cardiopulmonary stress testing, 1338*t*
contraindications in, 1338*t*
EMB in, 497–498
in PPCM, 1475
post-transplant infections, 1342*t*
survival with, 1343
Cardiac troponin I (cTnI)
in AL amyloidosis, 1463
cardiac marker, for myocardial injury, 1780
Cardiac troponin T (cTnT)
in asymptomatic ESRD patients, 1703
in asymptomatic multiple vessel coronary artery stenoses, 1703
in AL amyloidosis, 1463
cardiac marker, for myocardial injury, 1780
Cardiac tumors, 1663. *See also* Cardiac neoplastic disease
primary tumors, 1667*t*
surgical series, 1664*t*
types and symptoms, 1665*t*
Cardiac veins, 419–420
Cardiac venous system, 34
Cardioactive agents, 622–623
Cardiocerebral resuscitation, prehospital component, 819–821
Cardioembolic stroke, neurologic abnormalities, 151
Cardiogenic shock, 506
mental status evaluation, 151
Cardiogenic shock, in acute coronary syndromes
cardiac causes, 951–954
cardiac rupture, 953
mitral regurgitation, 953–954
right ventricular infarction, 951–952
ventricular septal rupture, 952
description of, 949
diagnosis of, 954
incidence of, 949
mechanical support, 954–957
Impella, 956–957
intra-aortic balloon pump, 955
left ventricular assist devices, 955–956
TandemHeart, 956
medical management for, 954
mortality, 949–950
pathology of, 951
pathophysiology of, 950–951
predictors of, 950
revascularization, 957–958
Cardiologists, in tobacco control, 1884
Cardiomegaly, 1718
Cardiomyopathy
due to cocaine usage, 1621
definition, 1424–1425
classification, 1424*f*
Cardiomyopathy, and insulin resistance, 1600*f*
diastolic heart failure, 1601–1602
dyslipidemia, 1604
epidemiology, 1600–1601
lipotoxicity, 1604
metabolic effects of, 1603–1604
@3detection of, 1604–1605
myocardial energy metabolism, 1602–1603
pathophysiology, 1602
structural effects of, 1605
antiadrenergic therapy, 1606
diastolic dysfunction, 1605–1606
insulin sensitization, 1608–1609
insulin therapy, 1607–1608
metabolic modulators, 1609
systolic dysfunction, 1606
Cardiomyopathy, hemodynamics in, 479
hypertrophic obstructive cardiomyopathy, 479
restrictive cardiomyopathy, 479–481
Cardioplegia additives, 969–970
Cardioprotection, mechanism of,–30

Cardiopulmonary bypass (CPB), 119
Cardiopulmonary exercise (CPX) testing, 1314
  conducting test, 1316
  dyspnea, 1317–1318
  exercise measurement, 1315
    oxygen pulse, 1315–1316
    oxygen uptake, 1315
    respiratory exchange ratio, 1316
    ventilation, 1316
    ventilatory efficiency, 1316
    ventilatory threshold, 1315
  heart failure, indications for, 1316–1317
    deconditioning and deriving exercise prescription, 1318
    peak VO_2 and prognosis, 1317
Cardiopulmonary resuscitation (CPR), 790
  complications of, 794–795
  compression only, 793
  dispatcher assisted, 793
  emergency medical services (EMS), 790–792
  evolution of, 788–789
  forward blood flow during, 788
  mechanical devices for, 793–794
  pump model, 789, 789*f*
  termination of resuscitation, 799–800
Cardiorenal syndrome (CRS), in congestive heart failure, 1281, 1284*t*
  definition of, 1283–1284, 1301
  development of, 1286*f*
  evidence-based therapies
    ACE-I AND ARB, 1289–1290
    diuretics, 1288–1289
    inotropes, 1290–1292
  pathophysiology of, 1286
  ultrafiltration on diuretic resistance, 1292
  treatment of, 1292–1296
    dialysis, 1295
    vasodilators, 1294
Cardiorenal syndrome. *See* Chronic kidney disease (CKD)
Cardiosphere-derived stem cells, 1993–1994
Cardiothoracic ratio (CTR), 174
Cardiotoxin, exposure to
  as heart failure risk factor, 1902
  chemotherapeutic agents for, 1902*t*
Cardiovascular aging, 1829–1830
  age-related changes, 1830, 1832*f*
    attenuating age-related changes, 1833–1834
    cellular aging, 1830–1832
    electrophysiologic changes, 1833
    exercise-related changes, 1833
    myocardial changes, 1833
    vascular changes, 1832–1833
  clinical syndromes, 1834
    conduction disease, 1837–1838
    heart failure, 1834–1835
    ischemic heart disease, 1836–1837
    isolated systolic hypertension, 1835–1836
    valvular disease, 1838–1839
  special issues,
    end-of-life care, 1839–1840
    prevention, 1839
Cardiovascular care
  arrhythmia, 1821–1822
  for athletes, clinical approach, 1821
  cost of, 1976
    CV contribution to, 1977
  left ventricular hypertrophy, etiology, 1821
Cardiovascular complications, cocaine usage, 1616
Cardiovascular conditions, autonomic perturbations associated with
  baroreflex failure, neurogenic hypertension, 1198
  cardiac arrhythmias, 1200
  heart failure and ischemic heart disease, 1198–1199
  obstructive sleep apnea, 1199
  pheochromocytoma, 1199–1200
Cardiovascular disease (CVD), 129, 829, 844
  global response for, 850–852
  in high income countries, 844–845
  prevention levels in, 830*t*
  in low income countries, 845–849
  in middle income countries, 845–849
  risk factors for, 829*t*, 849–850
  risk prediction scores for, 830–832, 831*t*
Cardiovascular disease, and gender
  heart failure in women, 1809–1812
  IHD in women
    acute ischemic syndromes, 1806–1808
    diagnostic approaches, 1803–1806
    prevalence in, 1798–1799
    risk factors, identification and management of, 1799–1802
  myocardial ischemia
    symptom assessment, 1802–1803
  sex and cardiac arrhythmias, 1813–1814
  sex-specific research, 1814
  stable CAD, 1808
    coronary angiography and revascularization, 1809
    medical therapy and risk factor management, 1808–1809
    treatment strategies, 1808
Cardiovascular disease, genomics of
  arrhythmias
    atrial fibrillation, 1942–1943
    QT interval and sudden cardiac death, 1943
  cardiovascular pharmacogenomics, 1943
    antiplatelet agents, 1943–1945
    beta-blockers, in heart failure, 1946
    statins, 1945–1946
    warfarin, 1945
  coronary artery disease
    9p21, 1942
    lipoprotein (a), 1941–1942
  future directions, 1947
  genomic primer, 1937–1940
  intermediate phenotypes
    hypertension, 1940–1941
    lipid traits, 1940
  SNP profiling studies, 1946–1947
Cardiovascular injuries, 1732
Cardiovascular magnetic resonance (CMR)
  in hemochromatosis, 1450
  information, 431–432
  normal values for, 431*t*
Cardiovascular magnetic resonance coronary angiography, 433
Cardiovascular magnetic resonance imaging
  mitral regurgitation, 1014
Cardiovascular magnetic resonance-guided therapy, 440
Cardiovascular medicine, economics of
  basic concepts, 1978–1979
  cost of, 1976
  cost-effectiveness
    of atrial fibrillation, 1982
    benchmarks for, 1979
    of coronary artery disease, 1981–1982
    of heart failure, 1981
    of quality improvement interventions, 1982–1983
  efficiency, 1980
  evaluating uncertainty, 1979–1980
  future estimates, 1983
  government's use of cost-effectiveness
    Britain's NICE, 1980–1981
    in United States, 1980
  health expenditures
    US vs non-US, 1976–1977,
  perspective, 1980
  resource
    scarcity and value, 1977–1978
    usage, variations in, 1977
  rising cost, CV contribution to, 1977
Cardiovascular medicine, preventing errors, 1969
  communication and culture, 1971–1972
  diagnostic error prevention, 1973
  learning from mistakes, 1972
  patient safety
    computerization, 1970–1971
    modern approach to, 1969–1970
    standardization and forcing functions, 1970
  patients role, 1973
  policy context, 1973–1974
  safe workforce creation, 1973
Cardiovascular nuclear medicine
  blood pool imaging, 398
  equilibrium gated imaging, ERNA, 399–401
  first pass curve analysis
    left-to-right shunt analysis, 399
    ventricular function, 398–399
  functional imaging, value of, 401
  general and specific patient populations, risk assessment of
    CAD in women, of 393
    diabetics, 393
    elderly, myocardial perfusion imaging in, 393
    general principles, 393
    heart failure, 394
    noncardiac surgery, preoperative evaluation for, 393
    perfusion imaging, 394
    postrevascularization, 393–394
  imaging myocardial sympathetic innervations, 401–402
  imaging myocardial viability
    nonscintigraphic imaging options, 396
    principles, 395–396

scintigraphic imaging options, metabolism based, 396
scintigraphic imaging options, perfusion related, 396
imaging perfusion
nitrogen (^{13}N) ammonia, 397
rubidium (^{82}Rb) chloride, 397
myocardial perfusion imaging
ACS evaluation strategy, 393
CAD-related risk, nonperfusion indicators of, 391–392
dense cavitary photopenia, 392
diagnostic accuracy and cost effectiveness, 390–391
gated-myocardial perfusion imaging, 385–389
image acquisition protocols, 385
image display, 385
interpretation, 389–390
multivessel coronary artery disease and related risk, indicators of, 391
myocardial perfusion imaging, clinical applications of, 392
transient ischemic dilation, 392
unstable angina/non-ST elevation myocardial infarction, 392
pathophysiologic considerations
ischemic cascade, 383
lesion severity, 382
stress testing, 383–385
stress testing deficiencies, 383
phase analysis, 401
positron emission tomography perfusion and metabolism
PET and SPECT technology, 394–395
radiation concerns, 402–405
regional coronary flow and flow reserve, quantitation of, 397–398
Cardiovascular pharmacogenetics
antiarrhythmic drugs
antiarrhythmic efficacy, 1963
calcium channel blockers, 1962–1963
clinical implications, 1963
digoxin, 1962–1963
procainamide, 1963
propafenone, 1963
toxicity, 1963
antiplatelet agents, 1943–1945
aspirin, 1958
beta-blockers, 1960–1961
adverse events, 1962
blood pressure reduction, 1961–1962
clinical benefit, in cardiovascular disease, 1962
clinical implications, 1962
heart rate reduction, 1961–1962
ventricular function improvement, in systolic heart failure, 1962
beta-blockers, in heart failure, 1946
diuretics
blood pressure lowering response, 1960
clinical outcomes, 1960
future directions, 1963
HMG-CoA reductase inhibitors
cardiovascular events, reduction in, 1954–1955
clinical implications, 1955–1956
compliance with statin therapy, 1955
low-density cholesterol lowering, 1953–1954
statin induced musculoskeletal side effects, 1955
principles of, 1951–1953
variation sources, 1952*t*
recent breakthroughs, 1944*t*
statins, 1945–1946
thienopyridines, 1956
clinical implications, 1958
clinical response to, 1957–1958
laboratory response to, 1956–1957
warfarin, 1945
clinical response, 1960
dose requirements, 1958–1960
tailored therapy, 1960
Cardiovascular phenotypes, gene variants, 1938*t*
Cardiovascular prognosis, influencing factors, 1811*t*
Cardiovascular radionuclide studies, radiation dosage of, 405*t*
Cardiovascular system, autonomic regulation of, 1187–1188
blood pressure, regulation of, 1188–1189
chemoreflex influence on heart rate and blood pressure, 1189
heart rate control, 1189
orthostatic hypotension, 1189–1190
Cardiovasular disease
and SHS exposures, 1875–1876
and tobacco smoke, pathophysiology, 1876
arterial stiffness, 1878
atherosclerosis, 1876–1877
autonomic effects and heart rate variability, 1879
dyslipidemia, 1878
endothelial dysfunction, 1877
impaired oxygen transport, 1879
inflammation, 1878–1879
oxidative stress, 1879
platelet activation and thrombosis, 1878
Cardioversion usage, DC, 681
Carditis, echo, role of, 1930
CARE-HF trial, 759, 761
Carey-Coombs murmur, 172
Carnitine deficiency, 495
Carotid artery disease
diagnosis, 1156
management, 1156–1157
natural history and risk stratification, 1155
pathophysiology, 1155
screening, 1155–1156
Carotid artery intima-media thickness, 1641
Carotid artery, inflammation of, 453
in molecular imaging, 453
Carotid endarterectomy (CEA)
in ipsilateral infarction, 1919
Carotid IMT
in HIV patients, major studies in, 1642*t*
See also Carotid artery intima-media thickness
Carotid pulse
in HCM, 1388
Carotid Revascularization Endarterectomy versus Stenting Trial (CREST), 1157
Carotid sinus massage, 679
Carvajal syndrome, 713
Carvedilol
arteriolar dilator drug, 72
and dobutamine, 94
in LV dysfunction, 1695
relative risk reduction, 1904, 1905*f*
Carvedilol or Metoprolol European trial (COMET), 1239
Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS), 84, 1239
Catecholamine polymorphic VT, 805
Catecholaminergic PVT, 695
Catecholamines
and action potential, 572
sources of, 1193*f*
Catheter ablation, 656, 681–682
Catheter designs
historical perspective and evolution of, 503
Catheter-based biopsy system, 485
Catheter-based imaging devices, characteristics of, 376*t*
Catheterization computations, 472
cardiac output, 472
Fick method, 472
indicator dilution method, 472–473
intracardiac shunt ratio, 473
vascular resistance, 473
CAuSMIC trial
catheter based study, after myoblast transplantation, 1994
Caves-Schultz-Stanford bioptome, 485, 486*f*
C-E Perimount valve, 1076
Cell therapy, randomized clinical trials
for acute myocardial infarction, 1992*t*
for CAD, 1995*t*
Cell tracking
in molecular imaging, 456–457
Center for Medicare and Medicaid Services (CMS), 1979, 2032
Centers for Disease Control (CDC)
exercise suggestion, 1891
Central nervous system (CNS)
in myocardial activity, 1689
Central sleep apnea, 2028
heart failure, 2028
treatment of central sleep apnea, 202
Central venous catheterization (CVC) guided therapy, 510
Central venous pressure (CVP)
assessment, in thoracoabdominal injury, 1732
Centrally-acting postsympathetic alpha-adrenergic agonists, 1141
Cerebral autosomal dominant arteriopathy with subcortical leukoencephalopathy (CADASIL), 1911

Cerebral edema, as neurologic symptom, of hyponatremia, 1276
Cerebral hemorrhage, 1571
in chronic cyanosis, 1571
Cerebrovascular disease
in HIV infection, 1643
CHADS2 score, stroke risk in AF, , 1911*t*
Chagas disease
cardiac magnetic resonance imaging, 1516
clinical manifestations, 1513–1515
echocardiography, 1516
epidemiology, 1513
left ventricular apical aneurysm, 1515*t*
life cycle, 1513
natural history of, 1516
prevention, 1517
Romaña's sign, 1515*f*
transmission, 1513
treatment, 1516–1517
mortality predictors, 1517
in United States, 1517
Channelopathies
due to cocaine usage, 1617
potassium channels, 1618
sodium channel, 1617–1618
Charcot-Bouchard aneurysm, 1910
CHARM-Preserved trial
candesartan, 1835
Chemotherapy-induced cardiac dysfunction
alkylating agents, 1482
anthracyclines, 1482
antimetabolites, 1482
antimicrotubule agents
monoclonal antibody-based tyrosine kinase inhibitors, 1482–1483
proteasome inhibitors, 1483
small molecule tyrosine kinase inhibitors, 1483–1484
Chemotherapy-induced cardiotoxicity
classification of, 1479
diagnosis, 1483–1484
management
dose limitation, 1485
preventive strategies, 1484–1486
monitoring, 1484
risk factors, 1480
treatment
adrenergic inhibition therapy, 1485–1486
angiotensin inhibition therapy, 1485
Chest compressions management, 793
Chest discomfort. *See also* Chest pain
cardiac causes of, 144*f*
hypertension, with cardiac involvement, 1129
Chest film technique, 174
inspiratory vs expiratory, 175*f*
Chest pain, 143, 854–868. *See also* Canadian Cardiovascular Society (CCS); Dyspnea; Syncope
acute aortic dissection, 145, 146*t*
in acute coronary syndromes, 145*t*
acute pericarditis, 146*t*
acute pulmonary embolism, 145, 146*t*
angina, 855–856
anginal equivalents, 145
cardiac pain, 143*t*
due to cocaine usage, 1619
diagnostic testing, 859–863
invasive coronary angiography, 863
MPI and stress ECHO, comparison of, 862
noninvasive computed tomographic angiography, 863
positron emission tomographic (PET) perfusion imaging, 861
stress myocardial perfusion imaging, 860–861
stress testing with echocardiogram imaging, 861–862
stress testing with myocardial imaging, 860
treadmill exercise stress testing (ETT), 860
differential diagnosis, 854–855
by system, 855*t*
edema, 149
Framingham risk score, 857*f*
functional classification, 146*t*
as HF symptom, 1213
history, 854
investigations
chest X-ray, 858
electrocardiogram (ECG), 858
laboratory investigations, 858
noncardiac pain, 144*t*
past medical history, 856
patient's description, 855
alleviating and aggravating factors, 855
associated symptoms, 855
pain, 855
patient's gestures during, 144*f*
physical examination, 856–858
risk estimation, 859
scope, 854
specific activity scale, 146*t*
stable angina, 145*f*, 145*t*
vasospastic angina, 145
Chest radiographs
aortic regurgitation, diagnosis of, 994
aortic stenosis, diagnosis of, 989
cardiac anatomy on, 176–177
isolated infundibular stenosis, 1034
supravalvar stenosis, 1035
tricuspid valve disease, 1021
valvar pulmonic stenosis, 1031
Chest roentgenogram. *See* Chest radiographs
Chest X-ray. *See* Chest radiographs
Cheyne-Stokes respiration, 147
and physical examination, 151
Chiari network, 10
Chlorothiazide, 54, 56, 58*t*, 60
Cholesterol 7α hydroxylase deficiency, 1860
Cholesteryl ester transfer protein (CETP), 1857
Chordate tendineae, 10
tricuspid valve anatomy, 1019
Chorea, 1930
management of, 1933
signs of, 1930
Chronic aortic regurgitation, 476
Chronic atrial fibrillation
in HCM, 1413
Chronic coronary artery disease
coronary artery bypass grafting *See* Coronary artery bypass grafting (CABG)
major clinical trials in, 976–979
surgery, outcomes of
anginal symptoms, relief of, 976
graft patency, 975
left ventricular function, 976
quality of life, 976
survival, 976
technique of surgical therapy for, 969
Chronic heart failure
definition of, 1228
drugs used, 78*t*
hemodynamic subsets in, 510
"Chronic ischemia", 396. *See also* Hibernation
Chronic kidney disease (CKD)
and cardiovascular disease, treatment of, 1704
cardiovascular risk factors in
abnormal divalent ion metabolism and vascular calcifications, 1700
anemia, 1699–1700
arteriosclerosis, 1700
arteriovenous fistulae, 1700
diabetes mellitus, 1699
hyperhomocysteinemia, 1700
hyperlipidemia, 1699
hypertension, 1698–1699
hypoalbuminemia, 1700
increased extracellular volume, 1700
left ventricular hypertrophy, 1699
oxidative stress and inflammation, 1700
prothrombotic factors, 1700
smoking, 1699
diagnostic tests
cardiac markers, 1703
computerized tomography scans, 1704
coronary angiography, 1704
echocardiography, 1703
electrocardiography, 1703
stress tests, 1703–1704
epidemiology, 1697
kidney transplant recipients, 1704–1705
in patients with heart failure
epidemiology of, 1281–1282
pathophysiology, 1698
spectrum of cardiovascular disease in, arrhythmias, 1702–1703
congestive heart failure, 1702
infective endocarditis, 1702
ischemic heart disease, 1700–1702
pericardial disease, 1702
valvular heart disease, 1702
Chronic mesenteric ischemia (CMI), 1160
Chronic obstructive pulmonary disease (COPD), 1763
in constrictive pericarditis, 1499
Chronic orthostatic intolerance
orthostatic hypotension, treatment of, 1196–1197
postural orthostatic tachycardia syndrome. 1195–1196
Chronic relapsing pericarditis
diagnosis, 1493

presentation and etiology, 1491–1493
Chronic resynchronization treatment with or without ICD
for refractory systolic heart failure, 1244
Chronic stable angina, 145*f*
Chronic thromboembolic pulmonary hypertension, WHO Group 4 PH, 1524
Chronic type B dissection, 1183–1184
Chronic venous insufficiency, 149
Churg-Strauss vasculitis, 1657–1658
Chylomicrons, 1856–1857
Chymase inhibitors, in myocardial fibrosis, 1261
Cilostazol (Pletal), 132, 1151
in stroke prevention, 1918
Circulating angiogenic cells (CACs), 1988, 1993
Cirrhosis, 66
and cardiovascular dysfunction, 1429
in hemochromatosis, 1450
secondary hyperaldosteronism in, 66
CKD-CVD interaction, 1697
CV risk factors, 1698
and diabetes mellitus, 1699
Class effect theory, 64
Classic angina. *See* Heberden's angina
Classification and regression tree (CART) analysis, 1282
Claudication, and cardiac rehabilitation, 1895
Cleft tricuspid valve, 1026
Clinical arrhythmias, and sex, 1812*t*
Clinical congestion
versus hemodynamic congestion, 1300*t*
Clofarabine (Clolar)
in left ventricular dysfunction, 1480*t*
Clonidine
tobacco dependency, second-line treatment for, 1883
Clopidogrel resistance, 881
Clopidogrel, 128, 545, 880–881, 908. *See also* Thienopyridines
clinical response to
CYP2C19, 1957–1958
laboratory response to
ABCB1, 1957
CYP2C19, 1956–1957
in LV dysfunction, 1695
in stroke prevention, 1918–1919
Clotting, 116–119, 117*f*
fibrin production, 117*f*
platelet activation, 118*f*
Club drugs, 1625–1626
in college students, 1614
gammahydroxybutyrate, 1626
ketamine, 1626–1627
methylenedioxymethamphetamine, 1625–1626
rohypnol, 1627
Clubbing, 153
Coarctation of aorta
associated anomalies, 1555
and BAVs, 1552
clinical findings, 1555–1556
diagnostic studies, 1556
general considerations, 1554–1555
genetic inheritance, 1555
guidelines, 1557
pathophysiology, 1555
pregnancy, 1557
prognosis and treatment, 1556–1557
Coat-hanger headache", 1190
"Cocaine washout", 1622
Cocaine, 1615
acute coronary artery thrombosis, 1616
cardiac arrhythmias, 1617
cardiovascular complications, 1616
channelopathies, 1617
potassium channels, 1618
sodium channel, 1617–1618
channelopathies, 1617–1618
chest pain, 1619
coronary artery atherosclerosis, 1617
coronary artery vasoconstriction, 1616
direct myocardial damage, 1616–1617
ECG changes, 1618
epidemiology, 1615
myocardial ischemia and infarction, 1618
pharmacology, 1615–1616
subacute and chronic problems, 1620–1622
treatment, 1619–1620
Cockcroft-Gault formula, 587*t*, 588, 1283*f*
Cockroft-Gault equation, 1282, 1831*t*
Cocoa (*Theobroma cacao*), for dyslipidemia, 2035–2036
Coenzyme Q10 (CoQ10)
in cellular ATP production, 1382
for dyslipidemia, 2036–2037
for hypertension, 2038–2039
Colchicine, 914
for acute pericarditis, 1490–1491
Combination therapy
for stable angina and CAD, 930
Communication, with end-stage patients
steps in, 1361*t*
COMPANION study, 759
Complementary and alternative medicine (CAM)
categories of, 2031–2032
Complete blood count (CBC), in hypertension measurement, 1132
Complex polygenic traits, 1937
Compression only cardiopulmonary resuscitation, 793
Compressive vascular resistance, 35
Computed tomographic angiography (CTA), 863
Computed tomography, mitral regurgitation, 1014
Computer assisted tomography (CAT), 409
Concomitant valvular lesions, 1348
in MCS, 1348
Conduction system disease, 650, 1509
Conduction system, 3, 16–18
Congenital absence of pericardium
plain film imaging, 188
Congenital autonomic failure
Congenital central hypoventilation syndrome, 1195
Congenital heart disease (CHD), 641, 806–807, 1777
Congenital long QT interval syndrome, 692–693
Congenital pulmonic stenosis
description of, 1028
isolated infundibular stenosis. *See* Isolated infundibular stenosis
supravalvar stenosis. *See* Supravalvar stenosis
valvar pulmonic stenosis. *See* Valvar pulmonic stenosis
Congenital valvar aortic stenosis
associated anomalies, 1552
clinical findings, 1552–1553
diagnostic studies, 1553
general considerations, 1551–1552
genetic inheritance, 1552
pregnancy, 1554
prognosis, 1554
treatment, 1553–1554
Congenitally corrected transposition of the great arteries (CCTGA)
general considerations, 1582
recommendations for
CCTGA, 1582–1583
surgical intervention, 1583
Congestion
assessment of, 1300*t*
Congestive heart failure (CHF), 23, 27–28, 1702
beta blocker therapy studies, 84*f*
catecholamine level, 23
diuretics in, 66
due to diabetes mellitus, 1601*f*, 1715
Framingham study criteria for, 1213*t*
gender differences, 1210*t*
glucose disposal rate, 1601*f*
racial differences, 1210*t*
radiographic manifestations of, 179–182
cephalad redistribution, 180*f*
interstitial edema, 181*f*
Kerley lines, 181
pulmonary edema, 181*f*
pulmonary vascular congestion, 180*f*
vascular pedicle, 182*f*
and renal dysfunction, 1282
Congestive Heart Failure Survival Trial of Antiarrhythmic Therapy (CHFSTAT), 589
Conivaptan, for euvolemic and hypervolemic hyponatremia, 1279
Connective tissue disease (CTD), inflammatory changes in
in PAH, 1524
Constrictive pericarditis
diagnosis, 1497–1502
Doppler echocardiographic features, 1500*f*
and management of, 1503*f*
examination, 1497
presentation and etiology, 1496–1497
physical findings, 157*t*
from restrictive cardiomyopathy, differentiation, 277*t*
TTE in, 273, 274
treatment, 1502–1503
Continuous chest compression (CCC) [CCO CPR], 814, 815, 816–817
Continuous positive airway pressure (CPAP), 2025
in HCM, 1413
Contrast-enhanced echocardiography, 236–237
Contrast-induced nephropathy (CIN), 536

Control of Ventricular Rate during AF (ERATO) study, 591
Convulsive disorders, 149
Cool-down period
in exercise training, 1894
Cooperative north candinavian enalapril survival study (CONSENSUS), 1237
Cor pulmonale
echocardiography, 1764
pulmonary function testing, 1763
signs and symptoms, 1763
studies, 1763
therapy, 1764
CoreValve ReValving System, 1839
Cori disease, 495
Coronary allograft vasculopathy (CAV)
in transplant patients, 1341
Coronary and/or graft cannulation, general principles for, 531
coronary bypass graft cannulation, 532
gastroepiploic artery (GEA), 534
internal mammary artery grafts, 533–534
left main coronary artery cannulation, 531–532
right coronary artery cannulation, 532
saphenous vein grafts (SVGs), 532–533
standardized projection acquisition, 534–535
Coronary aneurysms, 416
Coronary angiogram, potential errors in interpretation, 543
catheter-induced spasm, 543
coronary anomalies, 543–544
eccentric stenoses, 544
inadequate vessel opacification, 543
incomplete study, 543
microchannel recanalization, 544
superimposition of vessels, 544
total occlusion of coronary artery, 544
Coronary angiography, 517, 863, 911–912, 1806
in AAD diagnosis, 1171
access site hemostasis, 536–537
angiographic projections, 524
arterial nomenclature and extent of disease, 523–254
cardiac catheterization, complications of, 537–538
access site complications, 538
other complications, 538–539
catheters for bypass grafts, 522
transradial specific catheters, 522–523
catheters for coronary angiography, 520–522
Amplatz-type catheters, 522
Judkins-type coronary catheters, 521–522
multipurpose catheter, 522
clinical outcomes, 553
DES versus BMS, 553–555
contraindications for, 518
contrast media
characteristics of, 535–536
reactions, 535
contrast-induced renal failure, 536
coronary and/or graft cannulation, general principles for, 531–535
coronary angiogram, potential errors in interpretation of, 543–544
coronary circulation, congenital anomalies of, 528–531
degenerated saphenous vein grafts, 540
fluoroscopic imaging system, 535
indications for, 517–518
lesion calcification, 540
coronary perfusion, 541
thrombus, 540
total occlusion, 540
lesion quantification
angulated lesions, 540
bifurcation lesions, 540
lesion complexity, 539–540
lesion length, 540
ostial lesions, 540
quantitative angiography, 539
non-atherosclerotic coronary artery disease and transplant vasculopathy
coronary artery spasm, 542
spontaneous coronary artery dissection, 542
transplant vasculopathy, 542–543
vasculitis, 542
normal coronary anatomy, 524–528
patient preparation, 518–519
percutaneous coronary intervention, 544–545
antiplatelet therapy
pharmacotherapy for, 545–548
physiologic assessment of angiographically indeterminate coronary lesions
fractional flow reserve (FFR), 541
relative contraindications to, 471*t*
translesional physiologic measurements, clinical use of, 541–542
vascular access, sites and techniques of, 519–520
Coronary Angioplasty versus Bypass Revascularization Investigation (CABRI), 978
Coronary arteries, 3, 18–19, 1656
in molecular imaging, 456
Coronary arteriography
variant angina, diagnosis of, 942
Coronary artery atherosclerosis
due to cocaine usage, 1617
Coronary artery bypass grafting (CABG), 880, 885, 887, 902, 911, 912
aortic valve replacement in, 1126
contraindications, 972
in-hospital mortality, 972
modifiable risk factors, 973–974
nonmodifiable risk factors, 974–975
indications, 971–972
and medical management, comparison of, 976–977
and multivessel PTCA (trials comparing), 978
and OPCAB, 1329
vs PCI, 957, 1976, 1977*f*
and percutaneous coronary transluminal angioplasty using bare metal stent, 978–979
population undergoing, 971
and PTCA, comparison, 971
for stable angina and CAD, 932–933
surgical coronary revascularization advantages over medical treatment, 970–971
Coronary artery calcium (CAC) score, 839–840, 1641
Coronary artery disease (CAD), 291, 381, 414, 807–808
9*p*21, 1942
anomalous coronary arteries, 416
botanical medicines and supplements
arginine, 2042
B vitamins, 2043
beta-carotene, 2043
calcium, 2043
carnitine, 2043
fish oil, 2042
folate, 2043
garlic, 2042
ribose, 2043
vitamin E, 2043
chelation, 2043–2044
contrast CT and coronary angiography, 414–415
appropriate indication, 415
coronary bypass grafts, 415–416
coronary stent, 415
due to diabetes mellitus
endothelial changes in, 1713–1714
gout, 1715
homeostatic mechanisms, 1714
lipid abnormalities, 1714
platelets changes, 1714–1715
diagnosis of, 1125
diet, 2040
enhanced external counterpulsation, 2042
exercise, 2040–2041
lipoprotein (a), 1941–1942
mental health, 2041
mind-body medicine therapies, 2041–2042
noncontrast CT and coronary calcifications, 414
pretest probability, 210*t*
risk factors, 146
sleep, 2041. *See also under* Hypertension
and stable angina. *See* Stable angina
and sudden cardiac death, 2025
survival curves, 45*f*
as systolic heart failure risk factor, 1229
treatment
during aortic valve replacement, 1126
cost-effectiveness of, 1981–1982
weight loss, 2041
Coronary artery disease (CAD), in women. *See* Ischemic heart disease (IHD), in women
Coronary artery disease, and SE
and exercise stress echo
ESE in ischemia, 300–302
ESE in special population, 302
prognostic variables in, 299–300
prognosis assessment, 299

Coronary artery risk development in young adults (CARDIA) study, 1425
Coronary artery spasm
pathophysiology, questions of, 939
Coronary artery stenosis (CAS), 432
Coronary artery surgery study (CASS) registry, 1328
angina, definition, 292
Coronary Artery Surgery Study (CASS), 523, 970, 976–977
Coronary artery vasoconstriction, due to cocaine usage, 1616
Coronary blood flow (CBF), 40
adenosine effect on, 36
alpha-adrenergic blocking agent on, 47*f*
angiotensin converting enzyme inhibitor on, 39*f*, 47*f*
antianginal drugs on, 43*t*
B-type natriuretic peptide, 40
coronary collateral circulation, 39
determinants of, 35
during hypertension, 40–41
flow mediated regulation, 36
hormonal modulation, 38-39
in hypertrophic cardiomyopathy, 42
in ischemic heart disease, 42–44
metabolic factors, 36
myocardial oxygen demand effect on, 43*f*
nesiritide on, 47*f*, 48*f*
neurohormonal abnormalities on, 45*t*
neurohormonal regulation, 40
reserve, 45
in systolic heart failure, 44–48
in valvular heart disease, 41–42
Coronary circulation
coronary blood flow, modulation of, 36
flow mediated regulation, 36
hormonal modulation, 38–39
metabolic factors, 36
neurogenic modulation, 37–38
coronary blood flow regulation, 34
myocardial oxygen demand, 34–35
myocardial oxygen supply, 35
coronary circulation in
hypertension, 40–41
hypertrophic cardiomyopathy, 42
ischemic heart disease, 42–44
metabolic disorders, 42
systolic heart failure, 44–48
valvular heart disease, 41–42
coronary collateral circulation, 39–40
coronary vascular anatomy, 34
coronary vascular resistance, 35
autoregulatory resistance, 35–36
compressive resistance, 35
myogenic resistance, 36
viscous resistance, 35
Coronary circulation, congenital anomalies of, 528–529
anomalous coronary artery, from opposite sinus, 529–530
congenital coronary stenosis or atresia, 530–531
coronary arteries, anomalous pulmonary origin, 529
coronary artery fistulae, 530
myocardial bridging, 531
Coronary collateral vessels, 39
Coronary computed tomographic angiography (CCTA), 1806
Coronary fistulas, 417
Coronary heart disease (CHD)
risk categories, 832*t*
risk factors for, 829–840
alcohol, 838
apolipoprotein B (Apo B), 839
clustering and multiplicative effects, 830
diabetes, 838
emerging risk factors, 838–839
European Risk Scores, 832
fibrinogen and other hemostatic factors, 839
Framingham Risk Score (FRS), 830–832
Framingham Risk Score for General Cardiovascular Disease, 831*t*
high-sensitivity C-reactive protein (hs-CRP), 838–839
hyperhomocysteinemia, 839
hyperlipidemia, 837–838
hypertension, 837
lifestyle risk factors, 833–837
lipoprotein (A) [LP(A)], 839
lipoprotein-associated phospholipase A2 (LP-PLA2), 839
modifiable risk factors, 833–838
non-modifiable risk factors, 833
QRISK, 831*t*, 832
Reynolds Risk Score, 831*t*, 832
risk estimation, 830–832, 831*t*
risk prediction models, measures to evaluate, 832–833
SCORE, 831*t*, 832
sub-clinical atherosclerosis, 839–840
Third Report of NCEP Adult Treatment Panel, 831*t*
traditional risk factors, 833
translating risk factor screening into event reduction, 840
screening and prevention, 830, 830*t*
and tobacco smoking, 1873
Coronary heart disease (CHD), in women. *See* Ischemic heart disease (IHD), in women
Coronary hemodynamics
coronary flow reserve, 483–484
fractional flow reserve, 482–483
microcirculatory resistance, index of, 484
Coronary intervention
procedural success and complications related to, 555
Coronary interventions, equipment for, 549
balloons
general use balloons, 550
guide catheters, 549
guidewire, 549–550
specialized intracoronary balloons
cutting balloons, 550
perfusion balloon catheter, 550
Coronary lesions, characteristics of, 539*t*
Coronary perfusion pressures (CPP), during resuscitation efforts, 813–814
Coronary plaque
lysophosphatidylcholine in, 373*f*
Coronary revascularization
MI prevention, during surgery, 1783
Coronary sinus defects, 1559
"Coronary steal" mechanism, 383
Coronary stents, 550–551
Coronary vascular system, 34. *See* Coronary blood flow (CBF)
acetylcholine effects, 37
angiotensin receptor blocking agent's effect, 38*f*
coronary arterial system, 37
coronary blood flow determinants of, 35
coronary vascular tone, 38
myocardial oxygen demand, 34–35
myocardial oxygen supply, 35
nitric oxide, 38
NO-synthase inhibitors, 39*f*
vascular resistance, 35–36
Coronary vascular tone, 38
Coronary vasodilators, 915
Coronary veins, 3, 19–21
Coronary heart disease (CHD), as heart failure risk factor, 1901
Correction of Hemoglobin and Outcomes in Renal Insufficiency Trial (CHOIR), 1266
Cost-benefit analysis, 1983
Cost-effectiveness analysis, 1983
Cost-minimization analysis, 1984
Costs-direct, 1984
Costs-indirect, 1984
Cost-utility analysis, 1984
Cough, paroxysms of, 149
Coumadin. *See* Warfarin
COURAGE study, revascularization benefits, 1809
Coxsackievirus, in myocarditis, 1426
CPR guidelines, 788
"Crack". *See* Cocaine
C-reactive protein (CRP), 876–877
inflammatory marker, 1780
valve disease and heart failure, discrimination, 1223
in variant angina syndrome, 540
Creatine kinase (CK), 858, 874–875
in cardiac injury, 1736
Crescendo systolic ejection murmur, in HCM, 1388
CREST syndrome (calcinosis, Raynaud phenomenon, esophageal motility disorder, sclerodactyly and telangiectasia)
and PAH, 1527
and scleroderma, 152
Cribier-Edwards valve model, 1839. *See also* Edwards SAPIEN valve model, 1839
Crista supraventricularis, 11
Critical limb ischemia, 1148–1149
Cross-sectional area (CSA), 38
CT angiogram (CTA), in AAD diagnosis, 1170
CT protocol terms, 409*t*
"dose modulation" protocol, 410

"prospective" "axial-sequential" protocol, 411
"retrospective" protocol, 410
Culture-negative endocarditis
medical therapy of, 1063–1066
microbiology of, 1059
CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events), 1944
Current thoracic aortic stent graft designs, 1181
Cushing's syndrome, 1721–1722
Cutaneous systemic sclerosis (SSc), and PAH, 1527
Cyanosis, reduced hemoglobin, 151–152
Cyanotic congenital heart disease, 1570–1571
classifications of, 1571*f*
double-inlet left ventricle, 1587–1588
double-outlet right ventricle, 1584–1586
Eisenmenger's syndrome, 1589–1590
endocarditis, 1572
great arteries
congenitally corrected transposition of, 1582–1583
d-transposition of, 1578–1582
hypoplastic left heart, 1588–1589
palliative shunts, 1571–1572
pregnancy and contraception, 1572
tetralogy of Fallot, 1572–1577
total anomalous pulmonary venous return, 1583–1584
tricuspid atresia/univentricular heart, 1586–1587
truncus arteriosus, 1577–1578
Cyclic adenosine monophosphate (cAMP), 23, 26, 81, 131
and positive inotropy, 89
Cyclic guanosine monophosphate phosphodiesterase (cGMP-PDE), 132
Cyclooxygenase (COX), 128
Cyclophosphamide (Cytoxan)
in inducing cardiotoxicity, 1482
in left ventricular dysfunction, 1480*t*
Cystatin C
for renal dysfunction, 1223
Cystic medial degeneration, 1166
Cytochrome P450 enzyme (CYP), 106
drug metabolizing enzyme, 1955
Cytomegalovirus (CMV)
cardiotropic virus, 488
in myocarditis, 1427
Cytoskeletal proteins, 567

D

2,3-Diphosphoglycerate (2,3-DPG)
in systolic heart failure, 45–46
3,4-Dihydroxy-L-phenylalanine (dopa), 1192
Dabigatran, 126–127
thrombin inhibitor, in stroke prevention, 1918
DAD study, for HIV infection, 1636
Dalteparin (Fragmin®), 1761
Danish Investigators of Arrhythmia and Mortality on Dofetilide trial (DIAMOND), 587
Darbepoetin alfa, safety concerns, 1266
Dasatinib (Sprycel)
in inducing heart failure, 1483
in left ventricular dysfunction, 1480*t*
DASH diet (from the Dietary Approaches to Stop Hypertension trial), 2037
Daunorubicin, cardiotoxic effects in, 495
Davie's disease. *See* Tropical endomyocardial fibrosis
Debakey classification, of aortic dissection, 1168
Decreased cardiac output, in CRS, role of, 1286–1287
Decrescendo systolic ejection murmur, in HCM, 1388
Deep venous thrombosis (DVT), 914, 1750. *See also* Venous thromboembolism (VTE)
Deferiprone, in cardiotoxicity, 1485
Defibrillation, 797–799
"critical mass" theory, 797
"extension of refractoriness" theory, 797
risk
to environment, 798
to patient, 798
to rescuer, 798–799
types, 797–798
"upper limit of vulnerability" theory, 797
Degenerative mitral valve disease
clinical diagnosis
physical signs, 1011
symptoms, 1011
complications, 1011
natural history of, 1011
pathology of, 1010–1011
pathophysiology of, 1011
Degenerative valvular disease, 1100
Delayed afterdepolarizations (DADs), 574
in life-threatening arrhythmias, 574
Delayed hyperenhancement magnetic resonance imaging (DHE-MRI)
in HCM finding, 1396
"Delayed orthostatic hypotension", 1190
Demeclocycline, for congestion in HF, 1276
Dense cavitary photopenia, 392
Depression, in HF, 1359
Desferrioxamine, in cardiotoxicity, 1485
Desmosomal dysfunction, and ARVD/C pathophysiology, 706–707
Desmosome, structure and function, 706
"Destination therapy", 1335
Detection of Ischemia in Asymptomatic Diabetics (DIAD) study, 223
Dexfenfluramine, 836
diet drug, 1628
Dexrazoxane, in cardiotoxicity, 1485
Diabetes Control and Complications Trial (DCCT), 1716
Diabetes management, in cardiac rehabilitation, 920
Diabetes mellitus
and cardiac rehabilitation, 1895
and CHD, 838
and CKD and CVD interaction, 1699
coronary blood flow in, 42
as heart failure risk factor, 1901
in hemochromatosis, 1450
with hypertension, 1132
necrobiosis diabeticorum, 152
as systolic heart failure risk factor, 1229
Diamorphine, on exercise tolerance, in HF, 1358
Diastolic dysfunction, in HCM, Doppler inflections, 1395
Diastolic dysfunction, 1605–1606
detection of, 1606
Diastolic function, 242, 259, 270–272
Doppler indices in, age-related changes, 272*t*
formulae, 249–250
left ventricular filling pressures, evaluation of, 248–249
measurement of, 259
cardiac computed tomography, 256–257
cardiac magnetic resonance imaging, 259–260
echocardiography, 259
nuclear scintigraphy, 259
RV, ischemia on, 961
technical aspects of, 242–248
early diastolic flow, propagation velocity of, 243–245
left atrial volume and function, 247–248
mitral annular motion in diastole, Doppler tissue imaging of, 246–247
pulmonary venous flow, 245–246
transmitral flow, 242–243
types of, 248
left ventricle, impaired relaxation of, 248
pseudonormal filling, 248
restrictive filling, 248
Diastolic heart failure, 1207, 1251, 1253*t*. *See also* Heart failure with preserved ejection fraction (HFPEF)
clinical presentation, 1255–1256
CMRI in, 1256
definition, 1251
diagnosis, 1256
epidemiology, 1251–1252
future directions, 1261
management strategies, 1261*t*
MMPs/TIMPs ratio, 1253
myocardial structure and function in, 1253*t*
pathophysiology
functional derangements, 1254–1255
hemodynamic consequences, 1255
neurohormonal changes, 1253–1254
ventricular remodeling, 1252–1253
prognosis, 1256–1258
treatment strategies, 1258–1261
versus systolic heart failure, 1252*t*, 1252–1253
morbidity and mortality in, 1258*t*
symptoms and signs of, 1256*t*
Diastolic murmur
"Austin flint" murmur, 172
Carey-Coombs murmur, 172
continuous murmur, 172
early diastolic murmur, 169
aortic regurgitation, 169–171
pulmonic regurgitation, 171
mid-diastolic murmurs, 171
mitral stenosis, 171
tricuspid stenosis, 171–172
Diastolic pressure time index (DPTI), and the systolic pressure time index (SPTI), 41
Diet drugs, 1628

Dietary lipids, and CHD, 834
Diffuse intravascular coagulation (DIC), 124
Diffusing lung capacity for carbon monoxide (DLCO), 1753
Diflunisal, for SCA, 1835
DiGeorge syndrome, with TOF, 1573
Digital imaging and communications in medicine (DICOM) Standard 3.0, for IVUS imaging, 349
Digitalis Investigation Group (DIG) trial, 98–99
Digitalis purpura, 1228
Digitalis. *See* Digoxin
Digitalization". *See* Accelerated digoxin administration
Digoxin, 98, 668, 680, 723, 1962–1963
  agents affecting serum concentrations, 100
  indications and application, 99
Digoxin-toxic dysrhythmias, 100
Dihydroxyphenylacetic acid (DOPAC), 1192
Dihydroxyphenylglycol (DHPG), 1192
Dilatation, 207
Dilated aortic roots
  at risk, during pregnancy, 1572
Dilated cardiomyopathy (DCM), 238, 434, 1379, 1425
  EMB in, 491
  epidemiology, 1425
  etiology, 434
    cirrhosis, 1429
    coronary artery stenoses, 434
    familial dilated cardiomyopathy, 1427–1428
    HCM, dilated hypokinetic evolution of, 1429
    hemodialysis and end-stage renal failure, 1429
    ischemic versus nonischemic etiology, 1425–1426
    myocarditis, 434–435, 1426–1427
    nutritional deficiency, 1429–1430
    stress-induced cardiomyopathy, 1429
    tachycardia-induced cardiomyopathy, 1428–1429
  mortality, predictors of, 1430–1431
  PA chest radiograph, 187*f*
  pathology, 1425
  prognosis, 1430
    ischemic dilated cardiomyopathy, 435–436
Diltiazam, 293, 679, 680, 879. *See also* Calcium channel blockers (CCBs)
  in variant angina, 944
  for HCM, 1405
DIONYSOS trial, 591
Dipyridamole perfusion scintigraphy (DPS), 1778
Dipyridamole stress echocardiography (DiSE), 296
  and CAD, prognosis in, 304
Dipyridamole stress protocol, 296–297
Dipyridamole, 859–860
  and adenosine, in SE, 292
  in myocardial ischemia, 1385
  in stroke prevention, 1918
Direct factor XA inhibitors, 122
  apixaban, 123–124
  rivaroxaban, 122–123
Direct myocardial damage
  due to cocaine usage, 1616–1617
Direct pulmonary vasodilator therapy
  for cor pulmonale, 1764
Direct thrombin inhibitors, 118, 124, 884, 1761–1762
  argatroban, 125–126
  bivalirudin, 124–125
  dabigatran, 126–127
  hiurdin, 124
  ximelagatran, 126
Direct-acting vasodilators
  in hypertension, 1135*t*
Discount rate, 1984
Disease burden, 844–853
Disopyramide, 586, 723
Dispatcher assisted cardiopulmonary resuscitation, 793
Diuretic optimization strategies evaluation (DOSE), 1289
Diuretic resistance, 67
Diuretic-induced hyponatremia, 1277
Diuretics, 53, 54
  action sites, 54, 55*t*
  adaptations to administration, 56–57
  adverse effects, 67–68
  blood pressure lowering response, 1960
  class effect theory, 64
  classes
    carbonic anhydrase inhibitors, 57
    loop diuretics,58–59
    osmotic diuretic, 62
    potassium-sparing diuretics,61–62
    thiazide diuretics, 60–61
  classification, 54–55*t*
  clinical outcomes, 1960
  clinical pharmacology,
  clinical use, 62
    in edematous disorders, 64–67
    in hypertension, 63–64
  complications, 68
  distal convoluted tubule diuretics, 1288–1289
  dose and response, 56*f*
  glomerular filtration rate, 62
  history, 53–54
  in hypertension, 1135*t*, 1136
  in hyponatremia, 1272
  in morbidity and mortality, 1289–1290
  loop diuretics, 1288
  pharmacokinetic parameters, 58*t*
  pharmacology of, 55–56
  potassium sparing diuretics, 1289
  renal solute handling, 53
  uses, 55*t*, 62
Diuretics, individual classes
  carbonic anhydrase inhibitors, 57
    acetazolamide, 57
  loop diuretics,58–59
  osmotic diuretic, 62
  potassium-sparing diuretics,61–62
  thiazide diuretics, 60–61
Dizziness
  as HF symptom, 1213
Dobutamine, 91, 859–860, 1243. *See also* Inotropes
  administration and dosing, 93–94
  clinical indications and applications, 92*t*, 93
  in CO and renal function, 1290–1291
  dose and hemodynamic effects, 94*f*
  in heart failure, 93*f*
  ischemic stress agent, 384
  undesirable effects, 95
Dobutamine echocardiography
  for hibernation myocardial diagnosis, 1425
Dobutamine stress echocardiographic (DSE) study, 296, 1778
  and CAD, prognosis in, 302–303
    prognostic variables in, 303
  and ischemia, prognosis in, 303
  and special settings, prognosis in, 303–304
Dobutamine stress protocol, 296
Docetaxel (Taxotere)
  in left ventricular dysfunction, 1480*t*
Dock's murmur, 171
Docohexanoic acid (DHA), 114
Docosahexaenoic acid (DHA), 834, 2033. *See also* Fish oil
Documented orthodeoxia-platypnea, 1562
Dofetilide, 587, 656
Door to balloon (D2B), 894, 902, 906
Dopamine, 95, 1243. *See also* Inotropes
  for cardiac arrest, 822
  in CO and renal function, 1290–1292
  hazard ratio, 96*f*
  for renal perfusion, 1171
Doppler peak tricuspid regurgitant velocity (TRV), 1532
Dore" procedure
  left ventricular volume reduction surgery, 1245
Double inversion-recovery ("black blood") techniques, 440
Double product (HR times BP), 856
"Double-chambered right ventricle", 1563
Double-inlet left ventricle, 1587
  clinical findings, 1587
  diagnostic studies, 1587–1588
  Fontan operation, 1587
  Fontan repair, guidelines for, 1588
  recommendations for
    Fontan repair, 1588
    prior Fontan repair, 1588
  treatment and prognosis, 1588
Double-outlet right ventricle (DORV)
  associated anomalies, 1584
  general considerations, 1584
  treatment and prognosis, 1584–1586
Down syndrome, 152
Doxorubicin (Adriamycin)
  cardiotoxic effects in, 495
  in left ventricular dysfunction, 1480*t*
Doxorubicin cardiomyopathy, 1479*t*. *See also* Doxorubicin cardiotoxicity
  prevention of, 1484*t*
Doxorubicin cardiotoxicity, 1481*t*
  electron microscopic findings, 1482*t*
  hemodynamic grading, 1484*t*
  histopathologic ounsel in, 1481

Dressler's syndrome, 914
Dronedarone, 590–593, 656, 688
Drug eluting stents (DES), 129, 361, 548, 1784–1785
  versus BMS, 553–555
Drug-induced and toxin-induced PAH, 1526
d-Transposition of the great arteries (d-TGA)
  associated anomalies, 1579
  clinical findings, 1579
  diagnostic studies
    atrial switch, 1579–1580
    Rastelli procedure, 1580
  general considerations, 1578–1579
  guidelines, 1580–1582
  pregnancy, 1580
  prognosis, 1579–1580
  treatment, 1579
Dual-chamber pacemaker, for HCM, 1411–1412
Duchenne muscular dystrophy (DMD), gene repair strategy, 2004
Duke activity status index (DASI), 292, 294*t*
Duke treadmill score, 221*t*
Dutch Echocardiographic Risk Evaluation Applying Stress Echocardiography (DECREASE-III) study, 1781
Dutch randomized endovascular aneurysm management (DREAM) study, 1176
"Dye dilution" analysis, 399
Dynamic exercise testing, 383
Dynamic exercise, 212
Dysbetalipoproteinemia, 1862
Dyslipidemia
  botanical medicines and supplements
    artichoke leaf extract, 2034–2035
    beta-glucan, 2034
    cocoa, 2035–2036
    coenzyme Q10, 2036–2037
    fish oil, 2033
    garlic, 2035
    green tea extract, 2036
    guggul (*Commiphora mukul*), 2036
    niacin, 2036
    plant stanols and sterols, 2034
    policosanol, 2036
    psyllium, 2034
    red rice yeast, 2033–2034
  diagnosis of
    laboratory analysis, 1859
  diet, 2032–2033. *See also under* Coronary artery disease (CAD)
  exercise, 2033
  as heart failure risk factor, 1901
  hyperlipoproteinemia, 1859
    pattern 1: elevated cholesterol, normal triglycerides, 1859–1860
    pattern 2: increased triglycerides and moderate cholesterol, 1860–1862
    pattern 3: increased cholesterol and triglycerides increased, 1862
  hypoalphalipoproteinemia, 1863
  in insulin-resistance, 1604
  lipid transport, 1856–1858
  lipoprotein
    metabolism, 1856–1858
    treatment goals, 1859
  management considerations, 1863
  NCEP evidence statements, 1865–1872
  and tobacco smoking, 1878
  weight loss, 2033
Dyspnea, 146–148
  cardiac causes of, 146*t*, 148*t*
  etiology of, 147–148
  exertional dyspnea, 147
  in HCM, 1387
  as HF symptom, 1213, 1357–1358
  idiopathic restrictive cardiomyopathy, 1451
  orthopnea, 147
  paroxysmal nocturnal dyspnea, 147
  pulmonary causes of, 146*t*
  pulmonary edema, 147*f*
  pulmonary embolism, 147
  sleep-disordered breathing, 147
  tachyarrhythmias, 147
  wheezing, 147
Dysrhythmias, and STEMI, 913–914
Dyssynchrony imaging role and CRT, 764, 777
  magnetic resonance imaging, 765–766
  multidetector computed tomography, 766–767
  nuclear imaging, 766
  PROSPECT trial, 765
  real-time three dimensional echocardiography, 766
  septal to posterior wall motion delay, 764
  speckled tracking, 765
  strain rate imaging, 765
  tissue Doppler imaging, 764
  tissue synchronization imaging, 764–765

E

Early afterdepolarizations (EADs), 574
  in life-threatening arrhythmias, 574
Early invasive strategy, 884–885
Early repolarization, on ECG, 805
EARLY study, on PAH, 1539
Ebstein's anomaly
  associated anomalies, 1568–1569
  clinical findings, 1569
  diagnostic studies, 1569
  general considerations, 1568
  genetic inheritance, 1569
  guidelines, 1570
  pathophysiology, 1569
  pregnancy, 1570
  primary tricuspid valve regurgitation, surgical treatment of, 1025
  treatment and prognosis, 1569–1570
  tricuspid regurgitation in, 169
Ecarin clotting time (ECT), 124
ECG exercise testing, 209
  after the test
    ECG interpretation, 220
    exercise induced arrhythmias, 220–221
    prognostic utilization of, 221
    silent ischemia, 220
  before the test
    with acute coronary syndromes, 210
    after myocardial infarction, 211
    contraindications to, 211
    for diagnosis, 209–210
    with heart failure, 210–211
    indications for, 209
    for prognosis, 210
  during the test
    autonomic control, 217
    autonomic modulation, 217
    clinical correlations, 218–220
    physiology review, 213–217
  guidelines, 224–225
  methodology of, 211
    modalities, 212
    pretest preparations, 212
    safety precautions and equipment, 211–212
  rules of, 223–224
  screening, 221–222
  termination of, indications, 212*t*
ECG studies
  variant angina, diagnosis of, 940
Echo right heart catheterization, 273*f*
Echocardiography, 631
  aortic regurgitation, diagnosis of, 994–995
  aortic stenosis, diagnosis of, 989
  infective endocarditis, 1061–1062
  isolated infundibular stenosis, 1034
  mitral regurgitation, 1013–1014
  mitral stenosis, 1003–1004
  supravalvar stenosis, 1035–1036
  tricuspid valve disease, 1021–1023
    detection of, 1022
    morphology, 1021–1022
    quantitation of, 1023
  valvar pulmonic stenosis, 1031
Ecstasy, 1614, 1625. *See also* Methylenedioxymethamphetamine (MDMA)
Ectopic adrenocorticotropic hormone syndrome, 1721
Edema, 149
  in HF, 1358–1359
Edwards SAPIEN valve model, 1839
EFFECT model, in hyponatremia, 1274
Effective blood flow (EBF)
  catherization computation, 473
Effective orifice area (EOA), 1074, 1075
  and PPM, 1081
  normal reference values
    for aortic prostheses, 1082*t*
    for mitral prostheses, 1082*t*
Efficacy of Vasopressin Antagonism in hEart failuRE Outcome Study with Tolvaptan (EVEREST) trial, 1278, 1280
Efficiency, 1984
Effient. *See* Prasugrel
Ehler-Danlos syndrome, 152, 1168
Eicosapentaenoic acid (EPA), 114, 834, 2033. *See also* Fish oil
Einthoven's triangle, 192, 193
Eisenmenger's physiology, due to PDA. *See* Patent ductus arteriosus (PDA)
Eisenmenger's syndrome
  at risk, during pregnancy, 1572
  pulmonary arterial hypertension, 1589

recommendations for
medical therapy of Eisenmenger's physiology, 1589–1590
pulmonary arterial hypertension, 1589
for reproduction, 1590
Ejection fraction, 990, 992*f*, 1283*t*. *See also* Left ventricular ejection fraction (LVEF)
in AHFS therapy, as prognostic indicator, 1305*t*
AR stages, 993*f*
cardiac resynchronization therapy, study design, 760*t*
cardiovascular prognosis, influencing factor, 1811*t*
after coronary angiography, 538
in structural heat disease, 639*f*
systolic vs diastolic heart failure, 1252*t*, 1258*t*, 1282*t*
in workup algorithm, in women, 1804*f*
Ejection systolic murmurs, 166–167
"Eject-obstruct-leak" mechanism, and MR, 1385
Elderly patients
aortic stenosis in, 991
and cardiac rehabilitation, 1895
Elective coronary angiography, 906
Electrical and mechanical data
pump management, in MCS, 1349
Electricity for cardioversion and defibrillation, 789
Electrocardiogram (ECG), 189, 631
for ACS, 874
aortic regurgitation, diagnosis of, 994
aortic stenosis, diagnosis of, 989
atrial activity, identification of, 194–201
basics of, 189–190
component parts of, 191
electrode misplacements, 192–193
left arm, 193
right leg electrode, 193–194
exercise testing
and SE, 291
interpretation of, 194
isolated infundibular stenosis, 1034
lead systems in, 191–192
mitral regurgitation, 1012
mitral stenosis, 1003
monitoring, continuous
external devices, 632
implantable loop recorders, 632, 634
P wave characteristics, 677
QRS complex, characterization of, 201–206
QT interval, 207
abnormalities, 207
signal averaged, 634
for STEMI, 895–901
ST-T wave abnormalities, 206
supravalvar stenosis, 1035
tricuspid valve disease, 1021
"U" wave, 206–207
valvar pulmonic stenosis, 1031
wide QRS tachycardia, 677–678
Electrocardiogram (EKG).
See Electrocardiogram (ECG)
Electromagnetic interference (EMI), during surgery, 1787–1788
Electron beam computed tomography (EBCT), 408, 863. *See also* Ultrafast CT
for coronary artery calcium, 1220–1221
Electron transport chain (ETC), 24
Electrophysiologic Study Versus Electrocardiographic Monitoring (ESVEM) trial, 587
Electrophysiology studies, 678
Elevated central venous pressure, in renal perfusion, 1287
Embolic protection devices (EPDs), 1156
Embolism, sources of, 310
Embryonic stem cells, 1986–1987
Emergency medical services (EMS), 790–792
activation, 792–793
components of, 790–791, 791*t*
emergency medical technician-basic (EMT-B), 791, 792
emergency medical technician-intermediate (EMT-I), 791, 792
first responder, 791, 792
paramedics, 791, 792
systems, 791
Emory Angioplasty versus Surgery Trial (EAST), 978
Empty heart syndrome", 1197
EMS Systems Act, 790
Enalapril
effects on congestive heart failure, 75*f*
in long-term survival, 1905*f*
End diastolic volume (EDV), 228
End diastolic volume index, normal values for, 236*t*
End of life care in heart failure, palliative medicine. *See also* Heart failure
communication and patient's understanding, 1355–1356, 1357*t*
prognostication, issues of, 1355
suffering in, 1357
End systolic volume (ESV), left ventricular, 228, 232–233
and clinical outcome, 234–235
EF component, 232–233
physiologic basis of, 233–234
End systolic volume index, normal values for, 234*t*
Endarterectomy versus Angioplasty in Patients with Severe Symptomatic Carotid Stenosis (EVA-3S), 1157
Endocarditis prophylaxis, 1093–1095
Endocarditis, 313, 1572. *See also* Infective endocarditis
Endocrine disorders
in hemochromatosis, 1450
Endocrine heart disease
adrenal disorders
adrenal insufficiency, 1722
Cushing's syndrome, 1721–1722
paraganglioma, 1720
pheochromocytoma, 1720
primary aldosteronism, 1720–1721
carcinoid syndrome, 1723
diabetes mellitus, 1713
congestive heart failure, 1715
coronary artery disease, 1713–1715
metabolic syndrome, 1715
sudden death, 1715–1716
parathyroid disorders
hypoparathyroidism, 1722–1723
primary hyperparathyroidism, 1722
pituitary disorders
growth hormone excess, 1718–1719
hypopituitarism, 1719–1720
thyroid disease, 1716
amiodarone-induced thyroid disease, 1717–1718
hyperthyroidism, 1716–1717
hypothyroidism, 1717
End-of-life considerations, 1373–1374
Endoleak, 1179
Endomyocardial biopsy (EMB). *See also* Cardiac biopsy
clinical scenarios, role of, 489*t*
for myocardial fibrosis, 1224, 1225*f*
in cardiomyopathy
arrhythmogenic right ventricular cardiomyopathy, 492
dilated cardiomyopathy, 491
hypertrophic cardiomyopathy, 491
restrictive cardiomyopathy, 491–492
in special cardiac disease states
amyloidosis, 493–494
cardiac infections, 496–497
drug toxicity, 495–496
hemochromatosis, 494–495
sarcoidosis, 492–493
storage diseases and myopathy, 495
tissue, analysis of, 487–488
Endomyocardial biopsy, 711
Endomyocardial fibrosis (EMF), 1440, 1442–1443
endocardial calcification, 1443
Endomyocardial fibrosis, 492
Endothelial dysfunction, and tobacco smoking, 1877
Endothelial progenitor cells (EPCs), 2009–2010
Endothelial substances, in vascular wall health, 1982
Endothelins, 38
neurohormone, 74
Endothelium-derived hyperpolarizing factors (EDHF), 36
Endovascular aortic repair (EVAR), 1175, 1176
adjunctive devices and techniques, 1178
angulated neck, 1178
iliac aneurysm, 1179
narrow iliac arteries, 1178
short neck, 1178
anatomic substrate for, 1175, 1177
devices of, 1176
follow-up imaging, 1180
history of, 1176
late-occurring complications of. 1179
endotension, 1179
migration, 1179
neck dilatation, 1179–1180
thoracic aortic aneurysms, 1181
End-stage heart disease
and physical examination, 151

End-stage hypertrophic cardiomyopathy (ESHCM), 1413–1414
End-systolic volume
exercise testing, central factor for, 216
Endurance exercise, 1819. *See also* Isotonic exercise
Endurant stent graft, 1177
Energy metabolism
insulin resistance, metabolic effects of, 1603–1604
Enhanced CCD array cameras, 375
Enhanced external counterpulsation (EECP), for CAD, 2042
Enoxaparin (Lovenox®), 1761
Enoxaparin, 883
Enterococcal endocarditis, 1063
Enteroviruses, cardiotropic virus, 488
Eosinophilic heart disease, 1440
Ephedrine, 1197
Epicardial anatomy
acute margin, 7*f*
inferior surface, of heart, 8*f*
transverse sinus, 4, 5*f*
Epicardial coronary arteries, 34
Epicardial coronary artery stenosis, diagnosis of, 432
Epicedial coronary arterial heart disease
hypertension, with cardiac involvement, 1129
Epidemiological transition theory, 845, 845*t*
Epinephrine, 96
for cardiac arrest, 821
for CPR, 796
Epirubicin (Ellence), in left ventricular dysfunction, 1480*t*
Episodic autonomic failure, syndromes associated with
carotid sinus hypersensitivity, 1197–1198
hemorrhage, 1197
inferior wall myocardial ischemia/infarction, 1197
neurocardiogenic syncope, 1197
Eplerenone in patients with systolic heart failure and mild symptoms (EMPHASIS–HF) trial, 1240
Eplerenone, 61–62. *See also* Potassium-sparing agents
in CHF and renal dysfunction, 1289
in hyperkalemia, 1137–1138
in left ventricular remodeling, 1240
Epoetin alfa, safety concerns, 1266
E-point to septal separation (EPSS), 232
Epoprostenol (Flolan® and Veletri®), for PAH, 1538
Epoxyeicosatrienoic acids (EETs), 36
Epstein-Barr virus
cardiotropic virus, 488
in myocarditis, 1427
Eptifibatide, 133, 882
Equilibrium radionuclide angiography (ERNA), 398
ERACI trial, 978, 979
Ermenonville classification, 372
Erythropoietin stimulating proteins (ESPs), 1264
in treating anemia, 1266
safety concern on, 1266
ESCAPE trial, 1294
ESC-derived cardiomyocytes (ESCCM), 1986
Esmolol, 680, 1171
Estimated glomerular filtration rate (eGFR), 1697
Estudio Piloto Argentino de Muerte Sfibita y Amiodarone (EPAMSA), 589
Ethacrynic acid, 58*t*, 59
for CRS, 1288
to relieve congestive symptoms, 1242
Ethanol exposure, on heart cells and tissues, 1595
Ethanol ingestion, and normal cardiac conduction system, 1595–1596
Etomoxir, FFA, beta-oxidation, 1609
European Coronary Surgery Study, 970, 977
European Myocardial Infarction Amiodarone Trial (EMIAT), 589
European Risk Scores, 832
European Society of Cardiology (ESC)
classification of AHFS, 1299*f*
exercise suggestion, 1891
sports eligibility criteria, 1824–1825
European Trial in AF or Flutter Patients Receiving Dronedarone for the Maintenance of Sinus Rhythm (EURIDIS), 591
EuroQual 5D, quality of life assessment, 1269
EuroSCORE model, 1072
Eustachian valve, 10. *See also* Chiari network
Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial, 1287
Event recorder, in ambulatory electrocardiographic monitoring, 780–782
loop recorders, 780–781
non-loop (postevent) recorders, 781–782
EVEREST clinical status trials, on tolvaptan, 1306
Ex vivo gene therapy with retrovirus, 2006
Excitation-contraction coupling, of myocardial cells, 569*f*
Excitation-excitation coupling, 572
Excluder, stent graft design, 1176
Exercise
for CAD, 2040–2041
for dyslipidemia, 2033
and heart failure, 2044
for hypertension, 2037
measurements by CPX, 1315–1316
normal response to, 1312–1313
response in heart failure, 1313–1314
technical aspects, 1315
Exercise capacity, 218, 1890–1891
Exercise prescription recommendation, 1320
Exercise protocol, selection of, 293–295
Exercise stress echo (ESE), and CAD diagnosis
assessment prior to, 292
conducting of, 295
interpretation of, 295–296
protocol selection of, 293–295
Exercise stress echo (ESE), in ischemic disease
after PCI, prognosis, 302
atypical chest pain, 301–302
early studies and prognosis, 301
with suspected CAD, 302
Exercise test modalities, 212
adds-on to, 213
bicycle ergometer versus treadmill, 212
exercise protocols, 212–213
Exercise testing, 362
aortic regurgitation, diagnosis of, 995
in cardiac rehabilitation, 920
in heart failure, 1246*t*
Exercise testing, clinical correlations, 218
diagnostic scores, 219–220
exercise capacity, 218–219
heart rate, 218
hemodynamics, 218
recovery after exercise, 219
women, 219
Exercise testing, physiology review, 213
acute cardiopulmonary response to, 215–216
central factors, 216
metabolic equivalents term, 215
oxygen consumption 213–215
peripheral factors, 216–217
Exercise tests, in heart failure, 1223–1224
Exercise training, in heart failure
bed rest, deleterious effects of, 1318
benefits of, 1319
guideline recommendation, 1319–1320
history of, 1318–1319
mortality and morbidity, 1319
safety, 1319
Exercise, 1890
benefits of, 1891
clinical population considerations, 1895
definitions, 1890–1891
and inflammation and endothelial function, 1891–1892
performing capacity, 1891
recommendations, 1891
recovery from, 219
referral, 1895
reimbursement issues, 1895–1896
response to, 1891
safety considerations, 1892
Exercise-induced arrhythmias, 220–221
Exercise-induced cardiac remodeling (EICR), 1818–1819
aorta, 1820
left atrium, 1820–1821
left ventricle, 1819–1820
right ventricle, 1820
Exercise-induced ischemia, 215
Exertional dyspnea, 147
Exertional fatigue, as HF symptom, 1213
Exertional hypotension, and exercise, 219
Expansion of extracellular fluid volume (ECFV), in GFR, 1286
Extended-release dipyridamole (ERDP), 132
Extracorporeal Membrane Oxygenation (ECMO), for MCS, in HF, 1341
"Eye-balling" method, 324
Ezetimibe (EZE), 106, 111–112

F

^{18}FDG-PET imaging
for aneurysm, 451*t*, 465, 466*f*
for atherosclerosis detection, 451*t*, 453

for cardiac regeneration, 451*t*
for hibernation myocardial diagnosis, 1425
in metabolic syndrome, 455*f*
^{18}F-Fluorodeoxyglucose
in molecular imaging
coronary arteries, 456
for large arteries, 454–456
Fabry's disease, 495
Facilitated percutaneous coronary intervention (PCI), 902–906
elective angiography and PCI after successful thrombolysis, 905–906
full dose thrombolytic agent, 903
Familial (hereditary) systemic amyloidosis (ATTR and others), 1458–1459
Familial combined hyperlipidemia (FCH), 1860
Familial dilated cardiomyopathy (FDC), 1427–1428
Familial dysautonomia, 1195
Familial hypercholesterolemia (FH), 1860
Familial hypoalphalipoproteinemia, 1863
Familial ligand-defective apo B-100, 1860
Family history, as heart failure risk factor, 1900
Fasting, before TEE, 310
Fatigue, in HF, 1359
Fenestrated stent grafts, 1180
Fenfluramine, 836
diet drug, 1628
Fenofibrate intervention and event lowering in diabetes trial (FIELD trial), 114
Ferinject Assessment in Patients with IRon Deficiency and Chronic Heart Failure Trial (FAIR-HF), 1269
safety endpoints, 1269*t*
Fetal and umbilical cord blood cells, 1989–1991
Fibrates, 113–114
Fibrin production,117*f*
Fibrinogen and other hemostatic factors and CHD, 839
Fibrinolysis in STEMI, contraindications and cautions for, 904*t*
Fibrin-rich thrombi, clinical imaging of, 462–464
Fibroblast growth factor (FGF), 2010–2011
Fibroelastic deficiency (dysplasia), degenerative mitral valve disease, pathology of, 1011
Fibrous pericardium, 1489
Fick equation, 1818
Fick equation, for oxygen consumption rate, 1833
Fick method, catherization computation, 472
First pass curve analysis
left-to-right shunt analysis, 399
ventricular function, 398–399
First pass radionuclide angiography (FPRNA), 398
First-degree AV block, in athletes, 1821
Fish oil
for CAD, 2042
for dyslipidemia, 2033
and heart failure, 2046
for hypertension, 2038
Flail mitral valve, assessment using TEE, 313
Flamm formula, 473
Flavin adenine dinucleotide (FAD), 25
Flavin mononucleotide (FMN), 25
Flecainide, 585, 667, 681
Flow characteristics, pump management, in MCS, 1349
"Flow drag" phenomenon, in LVOT obstruction, 1382
Flow-mediated vasodilatation (FMD), 36
Fludrocortisones, for POTS, 1196
Flufenamic acid, for SCA, 1835
Flunitrazepam. *See* Rohypnol
Fluorescence spectroscopy, 374
Focal atrial tachycardia, 668, 731–732
catheter ablation
efficacy, 733–734
indications, 732
techniques, 732–733
differentiation of the mechanisms, 732
mechanisms and classification, 732
Focal ectopic atrial tachycardia, in electrocardiograph, 196*f*
Focused Assessment by Sonography in Trauma (FAST) examination, 1732, 1733
Fondaparinux, 120, 884, 1761
Forkhead box (Fox), 26
Fourth (S4) heart sounds, 163–164
artificial valve sounds, 166–167
early diastolic high-frequency sounds, 165–166
ejection sounds, 164–165
midsystolic click, 165
Fractional flow reserve (FFR), coronary hemodynamics, 482–483
Fractional shortening, 232
Framework Convention on Tobacco Control (FCTC), 1883
Framingham Heart Study
on heart failure, 1899
BMI on, 1901
Framingham Risk Score for General Cardiovascular Disease, 831*t*
Framingham risk score, 857*f*
Frank-Starling mechanism, 1189, 1440
Free (unesterified) fatty acids (FFA), 1856
Free cholesterol (FC), 106
Free fatty acids (FFA), 106
Free radicals in disease, 1863
Freestyle aortic root bioprosthesis, 1078
French maritime pine tree (*Pinus pinaster*), 2039. *See also* Pycnogenol
Friedreich's ataxia, 530
Furosemide, 54, 56, 57, 58*t*, 59, 65*t*, 67
for CRS, 1288
in hyperuricemia, 1137
to relieve congestive symptoms, 1242

G

Gabapentin, for pain, in HF, 1358
Gäisbock syndrome, with hypertension, 1132
Gallavardin sign, 166
Gammahydroxybutyrate (GHB), 1626
Ganglion blockers, 1141
Gantry, of CT scanner, 409
Ganz, William, 504
Garlic
for CAD, 2042
for dyslipidemia, 2035
for hypertension, 2038
Gastrointestinal bleeding (GIB), 129
Gastrointestine (GI), 127
GEMINI study, for insulin-resistance, 1607
Gene therapy
ex vivo gene therapy with retrovirus, 2006
gene replacement, gene correction and gene overexpression, 2003–2004
gene transfer to myocardium, 2006–2007
plasmid DNA delivery versus viral transduction
adeno-associated virus (AAV), 2004–2005
adenovirus, 2004
lentivirus, 2005–2006
Gene transfer to myocardium, 2006
Genetic arrhythmia syndromes
due to ion channel protein mutation, 574*t*
Genetic linkage and recombination on disease risk, 1939*f*
Genome-Wide Association Studies (GWAS), 1937
Gerbode defect, 1019
German Angioplasty Bypass Surgery Investigation (GABI), 978
Gallop sounds
and HF, 1214
Giant cell arteritis, 1658. *See also* Giant cell arteritis
Giant cell myocarditis (GCM), 489*f*
in DCM, 1427
EMB for, 488
Giant T wave inversions, 1218*t*
GISSI-HF trial, 1240–1241
Glomerular filtration rate (GFR), 57, 62–63
renal disease, indicator, 1281
Glossopharyngeal syncope, 149
Glucose management, 917–918
Glucose transporters (GLUT), in energy metabolism, 1603
Glycoprotein IIb/IIIa inhibitor (GPI), 125, 908
platelet aggregation inhibition, 133
Glycoprotein IIb/IIIa inhibitors (GPI), 882–883
Glycosylated hemoglobin (HbA1c)
in DM, with hypertension, 1132
Good bag-valve-mask (BVM), 795
Gorlin equation, 475
G-protein coupled receptors
in angiotensin II binding, 1275
rhodopsin-like receptors, in AVP binding, 1275
G-protein receptor kinase-2 (GRK-2), 23
GRACE risk score, 877
Graft related sequelae, 1341–1343
management of, 1341–1342
Granulomatosis with polyangiitis (GPA), 1658
See also Wegener's granulomatosis
Green tea extract, for dyslipidemia, 2036
Griffonia simplicifolia
biotinylated isolectin
for endothelial cell detection, 2012
Group A beta hemolytic streptococci (GABHS) infection, in RF, 1927

Grupo de Estudio de la Sobrevida en la Insuficiencia Cardiaca en Argentina (GESICA), 589
Guggul (*Commiphora mukul*), for dyslipidemia, 2036
Guillain-Barre syndrome, 1194
GUSTO-1 study, 950

H

3-Hydroxy-3-methylglutarul coenzyme A reductase (HMG CoA reductase), 1953
  inhibition
    by guggulsterones, 2036
    by luteolin, 2034
    by statins, 105, 837, 917, 1402, 1699
Hakki formula, 475
Hallucinogenic drugs, 1627
Haloperidol, for chorea, 1933
Hashish, 1624–1625
HCM proband, diagnostic pathway, 1401*f*
HCM with restrictive features, 492
HCM, clinical presentation
    symptoms, , 1387–1388
    physical examination, 1388–1390
  diagnosis
    electrocardiogram, 1390
    Holter monitoring, 1390
    chest X-ray, 1390
    echocardiography, 1391–1394
    Doppler inflections, 1394–1395
    cardiac magnetic resonance imaging,
    cardiac catheterization, 1396–1399
    stress test, 1400
HCM, dilated hypokinetic evolution of, 1429
Health economics
  measuring cost, 1978–1979
  measuring outcome, 1979
  quality of life, incorporation, 1979
  trials versus modeling, 1978
  in US vs non-US, 1976–1977
Healthcare-associated endocarditis, 1053–1054
Heart
  autonomic nerve supply, 21*f*
  fibrous skeleton, 3, 8
  internal structure, 3, 8
  and pericardium, 3–6
Heart failure (HF), 650, 912–913
  aortic stenosis, symptoms, 988
  botanical medicines and supplements
    arginine, 2046
    carnitine, 2046
    CoQ10, 2045–2046. *See also under* Hypertension
    creatine, 2046–2047
    fish oil, 2046
    hawthorn (*Crataegus monogyna*), 2045
    magnesium, 2047
    ribose, 2046
    taurine, 2046
    thiamine, 2047
  comprehensive HF program, 1362–1362*t*
  cost-effectiveness of individual treatments and strategies, 1981
  diet, 2044
  drugs used, 78*t*
  economic impact of, 1352–1353
  enhanced external counterpulsation, 2045
  epidemiology of, 1207, 1352
    in USA, 1207*t*
  exercise, 2044
  in hemochromatosis, 1450
  incidence, 1209
    gender differences, 1210
    geographic differences, 1210
    racial differences, 1209–1210
  and ischemic heart disease, 1198–1199
  mental health, 2044
  mind-body therapies, 2044-2045
  optimization of, 1339
  palliative care, feasibility of, 1354–1355
  perioperative complications, 1776
  prevalence, 1207–1209
  risk factors for, 1209*t*
    risk factors, comparison of, 1337*t*
  secular trends, 1211
  sleep, 2044
  spironolactone and eplerenone, 80–81
  and STEMI, 912–913
  symptom management in, 1357
    anorexia/cachexia, 1359
    depression, 1359
    dyspnea, 1357–1358
    edema, 1358–1359
    fatigue, 1359
    pain, 1358
  thermal vasodilation, 2045
  and tobacco smoking, 1873
Heart failure guidelines, 1366
  practice guidelines, implementation, 1374
  recommendations for
    initial clinical assessment, 1366–1367
    @3serial clinical assessment, 1367
Heart failure management
  in VAD implantation, 1349
Heart failure survival score (HFSS), 1336
  in hyponatremia, 1274
  as mortality predictor, 1355
Heart failure with concomitant disorders
  recommendations, 1373
Heart failure with normal ejection fraction (HFNEF), 1439
Heart failure with preserved ejection fraction (HFPEF), 1207, 1323, 1833, 1834
  etiology
    SCA, 1835
  See also Diastolic heart failure
Heart failure with preserved ejection fraction (HfpEF)
  renin-angiotensin-aldosterone system, 1810
Heart failure with reduced ejection fraction (HFREF), 1323. *See also* Systolic heart failure
  definition of, 1207
Heart failure, diagnosis
  biomarkers, 1221–1223
  cardiac magnetic resonance, 1220
  cardiac tomography, 1220–1221
  chest radiograph
    cardiomegaly, 1218*f*
    pulmonary edema, 1218*f*
  coronary arteriography, 1224
  echocardiography, 1218–1219
  electrocardiogram, 1215–1218
    anterolateral myocardial infarction, 1216*f*
    apical hypertrophic cardiomyopathy, 1217*f*
    concentric left ventricular hypertrophy, 1216*f*
    eccentric left ventricular hypertrophy, 1217*f*
  endomyocardial biopsy, 1224, 1225*f*
  exercise tests, 1223–1224
  genetics studies, 1225
  myocardial ischemia, 1224
  physical examination, 1214–1215
  radionuclide ventriculography, 1219–1220
  routine laboratory tests, 1221
  six-minute walk test, 1224
  symptoms, 1213–1214
    new classification, 1215*t*
Heart failure, exercise response
  central factors, 1313–1314
  peripheral changes, 1314
  skeletal muscle changes in, 1314*t*
Heart failure, in women, 1809–1812
Heart failure, prevention of
  future perspective, 1905
  risk factors of, 1900*t*
  Stage A heart failure, 1900–1902
  Stage B heart failure, 1902–1905
  stages, classification of, 1899*t*
Heart rate
  chemoreflex influence on, 1189
  control of, 1189
  exercise testing
    central factor for, 216
    clinical correlation, 218
  myocardial oxygen requirement, 34
  non-dihydropyridine, 43
  recovery, 1192
  resting rate, 1191
  variability, 1191–1192
Heart rate variability (HRV), and tobacco smoking, 1879
Heart Rhythm Society (HRS), 1361
Heart transplantation
  of advanced heart failure, 1334
  donor selection and perioperative period, 1339
    donor heart transplantation, 1340
    donor management, 1339–1340
    hemodynamic stabilization, 1340–1341
    immediate postoperative management, 1340
    immunosuppressive and antimicrobial management, 1341
    long-term management, 1341
    organ explanation and prevention, 1340
  during amyloid cardiomyopathy, 1466–1467
  indications and contraindications for, 1338–1339

long-term problems associated with, 1344*t*
survival with, 1343
waiting list patient, management, 1339
HeartMate XVE trial, 1344–1345
Heberden's angina, 144–145
coronary blood flow during, 42, 43*t*
Heberden's nodes, 153
Helical (or spiral) scanning, 409
Hemangiomas, 1674
Hematopoietic stem cells (HSCs), 1988
Hemiblock, 701–702
Hemochromatosis, 492, 494–495, 1450
Hemodialysis 1429
and end-stage renal failure, 1429
Hemodynamic congestion, versus clinical congestion, 1300*t*
Hemodynamic derangement
in aortic stenosis, with aortic valve thickness, 183
heart failure, 1198
in left ventricular hypertrophy, 1553
myocardial ischemia, 1198
pulmonary regurgitation, after repair, 1576
in RV pacing, 768
Hemodynamic monitoring
in noncardiac surgery, 1787
Hemodynamic optimization
in noncardiac surgery, 1786
Hemodynamic stabilization
in aortic dissection treatment, 1171
in BiVAD patients, 1348
in immediate postoperative management, 1340, 1348
in LVAD, 1348
Hemodynamic subsets
in acute myocardial infarction, 508*t*
in prognosis assessment, 511
Hemodynamics, 1446. *See also* Cardiac hemodynamics, and coronary physiology
apex cardiogram, 160
cardiac catheterization, 1463–1464
exercise testing, clinical correlation, 218
in cardiomyopathy, 479–481
in mitral stenosis, 1001–1002
in pericardial disease, 481–482
and pulmonary embolism, 1752
of valvular disease, 304–305, 474–479
Hemolysis, 957, 1057, 1095
methyldopa-induced, 1132
in nitric oxide deficient state, 1528
Hemoptysis, 149, 1170, 1757*t*,
in Eisenmenger's syndrome, 1564
in PA perforation, 512
in PE patients, 1754
in pulmonary venous congestion, 1002
Hemorrhagic stroke, 1909*t*
differential diagnosis of, 1914*t*
See also Ischemic stroke
Heparins, 119, 883, 909, 1760–1761
for cocaine abuse treatment, 1619–1620
Heparin-induced thrombocytopenia (HIT), 119, 121
Hepatitis C virus (HCV)
cardiotropic virus, 488
in myocarditis, 1426
Hepatocyte growth factor (HGF), 2011
Hepatojugular reflux, 157
Heritable PAH (HPAH), 1525–1526
Heroin, 1629–1630
Herpes simplex virus, cardiotropic virus, 488
HF-ACTION, 1319
Hiatal hernia, 423
Hibiscus (*Hibiscus sabdariffa*), for hypertension, 2039
High density lipoprotein (HDL)
in atherosclerotic disease, 1856
and cigarette smoking, 833
as CV risk factors, 1698
and endogenous estrogen, 1800
and exercise, 920
after menopause, 1799
in metabolic syndrome, 237, 1604, 1628
High volume systemic to pulmonary shunts in PAH, 1524
High-ceiling diuretics. *See* Loop diuretics
High-dose digoxin administration. *See* Accelerated digoxin administration
High-dose melphalan (HDM)/SCT, in AL amyloidosis, 1464, 1465
Highly active antiretroviral therapy (HAART) for HIV infection, 1636, 1639–1640
High-sensitivity C-reactive protein (hs-CRP)
in HIV patients, 1638
and CHD, 838–839
Hirschsprung disease, 1195
His-Purkinje system, 689
Histone deacetylases (HDACs), 26
History and physical examination, 143
general approach, 143
symptoms analysis
chest pain, 143–146
cough, 149
dyspnea, 146–148
edema, 149
hemoptysis, 149
palpitation, 148
syncope, 148–149
Hirudin, 124
HIV infection, CHD in
clinical characteristics, 1638–1639
cardiovascular risk factors, 1639
epidemiology, 1636–1638
hyperlipidemia, 1640
risk factors, modification of, 1640–1641
observational studies in, 1637*t*
pathogenesis, 1639
treatment, 1639
highly-active antiretroviral therapy, 1639–1640
HIV Medicine Association (HIVMA), in HAART initiation, 1640
HIV-associated pulmonary arterial hypertension, 1641–1643
HIV-related left ventricular dysfunction, 1643
HLA association, and acute RF, 1927–1928
HMG-CoA (3-hydroxy-3-methylglutaryl-coenzyme A) reductase inhibitors
low-density cholesterol lowering, 1953
ABCB1, 1953
APOE, 1953–1954
HMGCR, 1953
PCSK9, 1954
Hodgkin's lymphoma, radiation for
radiation-induced cardiotoxicity, 1505
extensive myocardial fibrosis, 1507
Holiday heart, 1596, 1598
Holo-uptake receptor (HUR), 106
Holter ambulatory monitoring, 777–780
Holt-Oram syndrome, 152
Homocysteine, and CHD, 839
Homocystinuria, 530
Hong Kong Diastolic Heart Failure Study, 1258
Hormonal studies, hypertension, 1131*t*
Hospitalized patients, recommendations, 1371–1372
Human herpes 6 (HHV-6)
cardiotropic virus, 488
in myocarditis, 1426
Human immunodeficiency virus (HIV) infection, 1636
cardiotropic virus, 488
in myocarditis, 1426
Human leukocyte antigen-DR (HLA-DR), in atherosclerotic lesions, 1849
"Hump-like" convex ST segment elevation, acute pericarditis, 1490
Hurler syndrome, 530
Hydralazine, 72–73, 100
arteriolar dilating drug, 72
positive inotropic properties, 100
Hydrochlorothiazide, 58*t*
"Hyparterial" bronchus, 13
Hypereosinophilic syndromes (HESs), 492, 1449–1450
Hyperhomocysteinemia, and CHD, 839
Hyperlipidemia
and CHD, 837–838
in CKD, 1699
HAART related, 1640
in HIV infection, treatment, 1640*f*
Hyperlipoproteinemia, 1859
pattern 1: elevated cholesterol, normal triglycerides
genetic disorders, 1860
secondary causes, 1859–1860
pattern 2:increased triglycerides and moderate cholesterol, 1860–1861
genetic disorders, 1861–1862
secondary causes, 1861
pattern 3: increased cholesterol and triglycerides increased
genetic disorders, 1862
secondary causes, 1862
Hypertension (HTN)
botanical medicines and supplements
coenzyme Q10, 2038–2039
fish oil, 2038
garlic, 2038
hibiscus, 2039
L-arginine, 2040
pomegranate, 2039

potassium, 2039
Pycnogenol, 2039
stevia, 2040
and cardiac rehabilitation, 1895
coronary blood flow during, 40–41
diet, 2037
due to cocaine usage, 1616
eplerenone, 61–62
exercise, 2037
and CHD, 837
in CKD, 1698–1699
as heart failure risk factor, 1900–1901
mental health, 2037
mind-body medicine, 2037
biofeedback, 2037–2038
meditation, 2038
perioperative complications, 1776
and SDB, 2024–2025
sleep, 2037
sodium reabsorption, 53
as systolic heart failure risk factor, 1229
spironolactone, 61
weight loss, 2037
whole medical systems, 2040
in women, 1798, 1800
Hypertension, evaluation of
antihypertensive therapy, 1133–1135
chest roentgenogram, 1133
clinical manifestations, 1129
clinical pharmacologic concepts, 1136
diuretics, 1136
mechanisms of action, 1136–1137
metabolic effects, 1137–1142
thiazides and congeners, 1136
electrocardiography, 1133
hemodynamic concepts, 1135–1136
laboratory studies, 1130–1132
blood chemistries, 1132
complete blood count, 1132
urinary studies, 1133
physical findings
BP measurement, 1129–1130
cardiac examination, 1130
optic fundi, 1130
peripheral pulses, 1130
treatment algorithms
hypertensive emergencies, 1142–1143
individualized stepped-care approach, 1142
stepped care approach, 1142
Hypertensive heart disease
classification of, 1130*t*
Hypertensive hemorrhages, 1910
Hyperthyroidism
due to cardiac complications, 1716–1717
Hypertriglyceridemia (HTG), 1940
Hypertrophic cardiomyopathy (HCM), 42, 437, 640, 650, 806
2D echocardiographic views of, 1383*f*
atrial fibrillation, 1412–1413
CMR images, 1380*f*
coronary blood flow in, 42
correlative findings, 438–439
definition, 1377
diagnosis, 437
cardiac catheterization, 1396–1399
cardiac magnetic resonance imaging, 1395–1396
chest X-ray, 1390
Doppler inflections, 1394–1395
echocardiography, 1391–1394
electrocardiogram, 1390
Holter monitoring, 1390
stress test, 1400
EMB in, 491
end-stage hypertrophic cardiomyopathy, 1413
epidemiology and genetic considerations, 1377–1379
infective endocarditis, 1414
management, 1402
of sudden death, 1403–1405
hypertrophic cardiomyopathy, in athletes, 1405
dual-chamber pacemaker, 1411–1412
genetical and family screening, 1402–1403
medical therapy, 1405–1407
percutaneous alcohol septal ablation, 1408–1411
septal myectomy, 1407–1408
natural history, 1400–1402
and obstructive sleep apnea, 1413
and OSA, 2025–2026
pathology, 1379–1381
pathophysiology, 1381–1382
arrythmogenic substrate and sudden death, 1386
autonomic dysfunction, 1387
diastolic dysfunction, 1384–1385
left ventricular outflow tract obstruction, 1382–1384
mitral regurgitation and mitral valve abnormalities, 1385–1386
myocardial fibrosis, 1386–1387
myocardial ischemia, 1385
systolic dysfunction, 1385
phenocopies, 1379*t*
physical examination, 1388–1390
and pregnancy, 1413–1414
primary HCM, 238
echocardiographic features, 238–239
prognosis, 437–438
secondary HCM, 239
echocardiographic features, 239
susceptibility genes, 1378*t*
symptoms, 1387–1388
Hypertrophic obstructive cardiomyopathy (HOCM), 479
Hypertrophic osteodystrophy, in chronic cyanosis, 1571
Hypertrophy, 207
Hyperuricemia, in hypertension, 1137
Hyperuricemia, in chronic cyanosis, 1571
Hypoalbuminemia, due to dialysis, 1700
Hypoalphalipoproteinemia, 1863
Hypodiastolic failure", 1251
Hypokalemia
as thiazide side effect, 1137
factors responsible for, 1131*t*
Hyponatremia, and congestive heart failure, 1272–1274
causal mechanism
arginine vasopressin, 1275–1276
renin-angiotensin-aldosterone system, 1275
sympathetic nervous system, 1274
conivaptan, 1279
diuretic therapy in, 68, 1276–1277
EFFECT model, 1274
lixivaptan, 1278–1279
as mortality predictor, 1273, 1274
tolvaptan, 1277–1278
treatment of, 1276
vasopressin receptor antagonists in, 1277
Hypoparathyroidism, 1722
Hypopituitarism, due to vascular disease, 1719–1720
Hypoplastic left heart syndrome (HLHS), 1588–1589
Hypothyroidism
due to cardiac complications, 1717
and heart failure, 100
Hypovolemic shock, 506
HYVET trial, 1939
indapamide, with perindopril, 1836

I

^{123}I-Metaiodobenzylguanidine (^{123}I-MIBG), 1193
for cardiac sympathetic imaging, 1194, 1433
for coronary spasm, 942
for extra adrenal tumors, 1199
^{123}I-β-Methyl-*p*-iodophenyl pentadecanoic acid (BMIPP), 1326*t*
for abnormal fatty acid metabolism, 1483–1484
for coronary spasm, 942
with SPECT imaging, 1327–1328
Iatrogenic VT, 691–692
Ibutilide, 579, 588, 654
Ibutilide repeat dose study, 588
ICOPER study, 1760
Idarubicin (Idamycin PFS), in left ventricular dysfunction, 1480*t*
Idiopathic dilated cardiomyopathy (IDC), 435–436, 1425
prognosis in, 436–437
Idiopathic left ventricle VT, 691
Idiopathic pulmonary arterial hypertension (IPAH), 1522*t*, 1525
Idiopathic restrictive cardiomyopathy, 491, 1440, 1451–1452
Idiopathic ventricular tachycardia, 744
catheter ablation, 748, 750, 751
cusp VT, 746
ECG recognition, 748, 750
epicardial VT, 746–747
ILVT and fascicular VT, 748
LVOT VT, 746
management, 747–748
mitral annular VT, 750
outflow tract-ventricular tachycardia, 744
RVOT VT, 744–745
tricuspid annular VT, 751

VT arising from the pulmonary artery, 746
Idiopathic ventricular fibrillation, 695
Idrabiotaparinux, 120–121. *See also* Fondaparinux
Ifosfamide (Ifex)
in inducing cardiotoxicity, 1482
in left ventricular dysfunction, 1480*t*
Iliofemoral artery, inflammation of, 453
in molecular imaging, 453
Illicit drug use, endocarditis in, 1053
Iloprost (Ventavis®), for PAH, 1538
Images, technetium-99 m labeled agents, for hibernation myocardial diagnosis, 1425
Imaging, common modes, 323*t*
Imatinib mesylate (Gleevec)
in inducing cardiotoxicity, 1483
in left ventricular dysfunction, 1480*t*
Immunosuppressants
and side effects, in heart transplantation, 1341*t*
Immunosuppression related organ dysfunction, 1342
Impaired oxygen transport, and tobacco smoking, 1879
Impella, cardiogenic shock, mechanical support in, 956–957
Implantable cardiac defibrillator (ICD), 637
cost of, and QALYs, 1979
for heart failure, in women, 1810
management of, 1360–1361
in PPCM, 1475
for SD prevention, 1386
Implantable loop recorders (ILRs), 783
IN-CHF, hyponatremia in HF, 1274
Incomplete right bundle branch block (RBBB)
in atrial septal defects, 1560
Incraft stent graft, 1177
Increased myocardial demand, due to cocaine usage, 1616
Indapamide, 54, 58*t*, 60, 64
Indicator dilution method, catherization computation, 472–473
Indinavir, and AZT, in HIV infection, 1643
Induced pluripotent stem cells (iPSCs), 1991
Inducible nitric oxide synthase (iNOS), 951
in hibernating myocardium, 1325
Infection prevention
in transplant list patients, 1338
in VAD implantation, 1349
Infectious Disease Society of America (IDSA), HAART-related hyperlipidemia management, 1640
Infectitious endocarditis, 1414. *See also* Bacterial endocarditis
Infective endocarditis (IE), 1093, 1702
description of, 1052
epidemiology of, 1052
adults, 1052–1054
children, 1054
management, 1062, 1116
anticoagulation, 1067
definitive medical therapy, 1063–1066
empiric medical therapy, 1063
endocarditis, prevention of, 1067–1068
persistent fever, 1067
surgical therapy, 1066–1067
timing of surgery, 1066–1067
manifestations of, 1055
embolization, 1056
immunologic manifestations, 1057
metastatic foci of infection, 1056–1057
periannular extension, 1056
valvular destruction, 1055–1056
microbiology of, 1057
culture-negative endocarditis, 1059
native valve, 1057–1058
prosthetic valve, 1058–1059
pathogenesis of, 1054
abnormal pressure-flow dynamics, 1054
host response, 1055
manifestations of infection, 1055
microbial factors, 1055
non-bacterial thrombotic endocarditis, 1055
patient presentation and diagnosis, 1059
blood culture, 1060–1061
clinical presentation, 1060
echocardiography, use of, 1061–1062
mimickers of infectious endocarditis, 1062
other diagnostic studies, 1062
primary tricuspid valve regurgitation, surgical treatment of, 1026
transesophageal echocardiography, 1116–1117
transthoracic echocardiography, 285, 1116
Inferior myocardial infarction (IMI), concomitant RVI, 960
Inflammation, 1878–1879
in atherosclerosis, 1832
to diagnose myocarditis, 490
and tobacco smoking, 1878–1879
Inflow cannula, position of, in MCS, 1348
Influenza virus, cardiotropic virus, 488
In-hospital ECG recording, variant angina, diagnosis of, 941–942
Initial conservative strategy, 884–885
Innocent murmurs, 167
Inodilators. *See* Phosphodiesterase inhibitors
Inotropes, 1290–1291, 1339
Inotropic support, 966, 1294, 1347
in CO and renal function, 1290–1291
by dobutamine, 91
in HF, immediate postoperative management, 1340
Insufficient physical activity, 1890
Insulin sensitization, 1608–1609
Insulin therapy, 1607–1608
Integrated Backscatter (IB) IVUS, 355
Integrative cardiology, 2032
Integrative medicine, 2031–2032
for cardiovascular conditions, 2032
Integrilin. *See* Eptifibatide
Intention-to-treat (ITT) analysis, 932
Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS), 1335
advanced heart failure patients, classification of, 1346*t*
heart transplantation need for, 1338
Intercellular adhesion molecule-1 (ICAM-1), 1848
in HIV patients, 1638
Interleukin-1 (IL-1), in LDL binding, 1849
Interleukin-6 (IL-6)
in rheumatoid arthritis, 1650
in variant angina syndrome, 540
Intermediate density lipoprotein (IDL), 1856
Intermediate density lipoprotein cholesterol (IDL-C), 106
International AIDS Society USA Panel guidelines in early HAART initiation, 1639
International Cooperative Pulmonary Embolism Registry (ICOPER) study, 1750
International Registry of Aortic Dissection (IRAD), 1166
International Society of Heart and Lung Transplantation (ISHLT) guidelines, 1338
Interstitial fibrosis, in HCM, 1386–1387
Interstitial lung disease, 1763
Interventricular septum (IVS), 1380. *See also* Asymmetric septal hypertrophy (ASH)
Intestinal angina, 1160. *See also* Chronic mesenteric ischemia (CMI)
Intestinal bile acid transporter (IBAT), 106
Intra-aortic balloon pump (IABP) support, 912–913
cardiogenic shock, mechanical support in, 955
for MCS, in HF, 1341
Intra-atrial reentrant tachycardia, 668–669
Intra-atrial septum, lipomatous hypertrophy of, 423
Intracardiac echocardiography (ICE), 335
Intracardiac fistulas, 1741–1742
Intracardiac injuries, 1737–1738
aortic and arterial trauma, 1742–1744
coronary artery laceration, 1742
iatrogenic cardiovascular injuries, 1745–1746
intracardiac fistulas, 1741–1742
retained foreign bodies, 1744–1745
septal defects, 1738–1739
thrombosis, 1742
valvular injuries, 1739
aortic regurgitation, 1741
mitral regurgitation, 1740–1741
pulmonic valvular regurgitation, 1741
tricuspid regurgitation, 1739
Intracardiac masses, TTE in, 285–286
Intracardiac shunt ratio, catherization computation, 473
Intracardiac shunt, 443
Intracellular Ca^{2+}, in arrhythmia initiation, 565
Intracerebral hemorrhage (ICH), 1908, 1910
clinical features of, 1913*t*
Intracoronary angioscopy, 370
clinical experience, 372
future directions, 374
image interpretation, 371–372
imaging systems and procedures. 371
safety and limitations, 373–374
vulnerable plaque, detection of, 372–373
Intracranial aneurysm, and 9p21, 1942
Intracranial hemorrhage (ICH), 121
Intramural hematoma, 1186
Intramural vessels, 3, 19

Intraoperative TEE, 316–317. *See also* Procedural adjunct TEE
Intravascular coronary ultrasound. *See* Intravascular ultrasound (IVUS)
Intravascular ultrasound (IVUS)
balloon angioplasty, 358–359
procedural guidance, 359
bare metal stent implantation, 359
long-term outcomes, 360–361
procedural guidance, 359–360
basics of and procedures, 349
drug-eluting stent implantation, 361
long-term outcomes, 361–362
procedural guidance, 361
future directions, 363–364
interventional applications, 356–357
measurements, 352
normal vessel morphology, 349–352
plaque formation and distribution, 356
preinterventional imaging, 357–358
safety, 362–363
tissue characterization, 352–356
Intravenous catecholamines, in refractory heart failure, 1243
Intravenous urography, hypertension, 1131*t*
Intraventricular hemorrhage (IVH), 1908, 1910
Invasive coronary angiography, 863
Invasive evaluation, mitral stenosis, 1004
Iodinated contrast agents, in cardiac angiography, 536*t*
"Iodine mapping", 411
Ion channel protein mutation, and genetic arrhythmia syndromes, 574*t*
Ion channels, 569
I-PRESERVE trial, irbesartan, 1835
IRB irbesartan versus placebo, 1835
Irbesartan in patients with heart failure and preserved ejection fraction (I-PRESERVE) trial, 1252
Iron chelators, in cardiotoxicity, 1485
Iron deficiency and iron replacement, in heart failure, 1269–1270
ISAR-SHOCK study, 957
Ischemia
in coronary anomalies, 529*t*
during postoperative setting, 1788
Ischemia/reperfusion injury, 28
reperfusion injury salvage kinase, 29
"Ischemic burden", 382
Ischemic cardiomyopathy, 1425
and exercise, 219
Ischemic cascade, 383
Ischemic heart disease (IHD), 650, 927
coronary blood flow in, 42–44
noncardiac surgery for, 1776
CHD in CKD, 1700–1701
interventional therapy, 1701–1702
medical therapy, 1701
and tobacco smoking, 1873
Ischemic heart disease (IHD), in women
diagnostic approaches, 1803–1804
cardiovascular MR assessment, 1805–1806
coronary angiography, 1806
coronary computed tomographic angiography, 1806
exercise ECG, 1804
stress-induced perfusion abnormality assessment, 1804–1805
stress-induced wall motion abnormality assessment, 1805
management of
acute ischemic syndromes, 1806–1808
prevalence of, 1798–1799
risk factors, and management of
aspirin, 1801
dietary modifications, 1800
lipid lowering therapy, 1801
risk factors, identification
diabetes, 1800
HTN, 1800
postmenopause, 1800
premenopause, 1799
tobacco use, 1800
with RA, 1799
Ischemic RV dysfunction
natural history of, 962–963
reperfusion effects on, 963–964
Ischemic stroke, 1908, 1909*t*. *See also* Stroke
clinical features, 1913*t*
differential diagnosis of, 1914*t*
prevention of, 1915*t*
Isolated atrial natriuretic factor, 1459
Isolated infundibular stenosis
clinical findings, 1034
differential diagnosis, 1035
laboratory investigations
cardiac catheterization, 1034
chest roentgenogram, 1034
echocardiography, 1034
electrocardiogram, 1034
natural history, 1034
pathological anatomy, 1034
pathophysiology, 1034
treatment of, 1035
Isometric exercise, 212, 1819
Isometric exercise. *See* Aerobic exercise
Isoproterenol, 95–96, 622–623, 678, 691, 693
Isosorbide dinitrate/hydralazine effect, 73*f*
Isotonic exercises, 1819
and hypertension, 1134
Isotope renography, hypertension, 1131*t*
IV immune globulin (IVIG), in PPCM, 1475
Ivabradine, 595, 1244
for stable angina and CAD, 930

J

Jaccoud's arthritis, 1929
Janus kinases (JAKs), 26
Japan, incidence of heart failure in, 1210
Jugular venous pressure (JVP), 154–157
in HCM, 1388
and HF, 1214
Jugular venous pulsations, 155–158
prominent "a" wave, 156
prominent "v" wave, 156
Junctional bradycardia, in athletes, 1821
Junctional ectopic tachycardia, 674
JUPITER (Justification for the Use of Statin in Prevention: an Intervention Trial Evaluating Rosuvastatin) trial
genetic data, on CRP, 1939
statin use, 1801
J-wave syndromes, 695

K

Kansas City Cardiomyopathy Questionnaire (KCCQ), quality of life measure, 1266, 1268
Kaplan-Meier survival curves, 910*f*
Kawasaki disease (KD), 542, 1657
CMR coronary angiography, 433
Ketamine, 1626–1627
Kidney/disease outcomes quality initiative (K/DOQI) guidelines, 1698
Koch's triangle, 17, 190*f*
Konno-Sakakibara bioptome, 485
Krebs cycle, 25
Kruppel-like factor 2 (KLF2), 1847
Kussmaul's sign, 157

L

12-Lead surface electrocardiogram, 762
for acute coronary syndrome, 874
during angina, 940*f*
for AVRD/C, diagnosis of, 711
of Brugada syndrome, 694*f*
hypertrophic cardiomyopathy, 1381*f*, 1390*f*
12-Lead resting electrocardiography, 866, 1778, 1790*t*, 1893
LA pressure, in constrictive pericarditis, 1499
Labetalol
for cocaine abuse treatment, 1620
for heart rate maintenance, 1171
Lactate dehydrogenase (LDH), in cardiac injury, 1736
Lapatinib (Tykerb)
in left ventricular dysfunction, 1480*t*
in symptomatic left ventricular dysfunction, 1483
Lardaceous disease, 1454–1455
L-Arginine, for hypertension, 2040
Late gadolinium enhancement (LGE), 434, 436, 439
Leads orientation
in electrocardiogram, 194*f*
and vector forces, in electrocardiogram, 192*f*
Leaflets
in aortic regurgitation, etiology of, 993
tricuspid valve anatomy, 1019
Left atria, assessment of, 330–331
Left anterior hemiblock (LAH), 702
Left atrial appendage (LAA), 331
Left atrial enlargement, 178–179, 207
Left atrial thrombus, 310
Left atrium, 3, 13
Left bundle branch block (LBBB), 702, 759
Left dominant ARVD/C (LDAC), 713
Left fibrous trigone, 8
Left heart, normal dimensions, 232*t*
Left ventricle (LV), 3, 14–15, 228

cardiac dysfunction, etiology of, 237–238
contrast-enhanced echocardiography, 236–237
diastolic function, 242
formulae, 249–250
left ventricular filling pressures, evaluation of, 248–249
technical aspects of, 242–248
types of, 248
dilated cardiomyopathy, 238
echocardiographic findings, 238
ischemic cardiomyopathy, 238
distinct anatomical features, 15
fiber orientation, 15
intramural vessels, 19
hypertrophic cardiomyopathy
primary hypertrophic cardiomyopathy, 238–239
secondary hypertrophic cardiomyopathy, 239
left ventricular noncompaction, 240
restrictive cardiomyopathy, 239
amyloid infiltrative cardiomyopathy, 239–240
diabetes mellitus, 239
endomyocardial fibrosis, 240
strain-derived indices, 237
systolic dysfunction, visual qualitative indicators of, 240
left ventricular mass, 240–242
systolic function, 228
components of ejection fraction, 232–236
echo-derived indices of, 237
left ventricular ejection fraction, 229–232
Left ventricle trabeculations and noncompaction, 445
Left ventricular apical ballooning (LVAB) cardiomyopathy, 940
Left ventricular assist devices (LVADs), 27. *See also* Ventricular assist devices (VADs)
of advanced heart failure, 1334
anticoagulation, 1348
cardiogenic shock, mechanical support in, 955–956
hemodynamic stabilization, 1348
pump management, 1348–1349
Left ventricular biopsy, 487
Left ventricular dysfunction, chemotherapy associated, 1480*t*
Left ventricular ejection fraction (LVEF), 1820
assessment of, 909–910
CHARM-Preserved trial, 1835
during aging, 1933, 1834
mortality, 267
pulsus alternans, 158
tachycardia-induced cardiomyopathy, 1429
Left ventricular ejection fraction (LVEF), components of, 228
end diastolic volume, 236
end systolic volume, 232–233
physiologic basis of, 233–234
and clinical outcome, 234–236
Left ventricular end-diastolic pressure (LVEDP), in PAH, 1522
Left ventricular endomyocardial fibrosis (LVEMF), 1442, 1446–1447
angiographic diagnosis of, 1447–1448
etiology, 1449
pathology, 1448–1449
treatment, 1449
cardiac catheterization, hemodynamics, 1447
Left ventricular enlargement, 177–178
Left ventricular function, at inotropic stress and rest, assessment of, 432–433
Left ventricular hypertrophy (LVH), 1379
due to CKD, 1699
growth, 987
hypertension, with cardiac involvement, 1129
physiologic and pathologic, comparison of, 987
and thick ventricle, in HCM, 1391–1393
Left ventricular mass, determination of, 330
Left ventricular noncompaction (LVNC), 1379
Left ventricular outflow tract (LVOT) disease, 71, 231, 1554
Left ventricular performance, determinants of, 252
afterload, 253
contractile element, velocity of, 254–255
contractile state, 253
maximum rate of pressure development, 253–254
preload, 252–253
ventricular-arterial coupling, 253
Left ventricular posterior wall flattening, in constrictive pericarditis, 1499*f*
Left ventricular pump function
ejection fraction, 256
assessment of
cardiac computed tomography, 256–257
cardiac magnetic resonance imaging, 257
contrast ventriculography, 257
echocardiography, 256
nuclear scintigraphy, 257
pressure-volume relations, 257–258
ventricular function curve, 255–256
Lentivirus, 2005–2006
LEOPARD syndrome, 152
Lepirudin, 1762
Levine sign, 144*f*
Levitronix Centrimag device, for MCS, in HF, 1341
Levosimendan Infusion Versus Dobutamine (LIDO) Study, 1291
Levosimendan, 97–98. *See also* Inotropes
in CO and renal function, 1290–1291
Lewy body disorders, 1193
Libman-Sachs endocarditis, 152
Lidocaine, 586–587
for CPR, 796
Lifestyle Heart Trial, 2032
Light chain (AL) amyloidosis, 1457–1458
Lightheadedness, 630, 639
as HF symptom, 1213
in nicotine withdrawal, 1880
with POTS, 1195
RV outflow VT, 691
in syncope, 1823
with stroke, 1913
third-degree AV block, 701
Limbus of the fossa ovalis, 9
Linked angina, 43
coronary blood flow during, 42, 43*t*
Lipid abnormalities, in HIV patients, 1639
Lipid lowering options, 110*t*
Lipid lowering therapy, for stable angina and CAD, 930–931
Lipid management, 917
in cardiac rehabilitation, 920
Lipid treatment goals and strategies, 105*t*
Lipid-modifying drug mechanisms, 106*f*
Lipodystrophy, HIV associated, 1639
Lipomas, 1674
Lipomatous hypertrophy, 1674
Lipoprotein
composition, 1856*t*
metabolism, 1856–1858
treatment goals, 1859
Lipoprotein (A) [LP(A)], 1856
and CHD, 839
Lipoprotein lipase (LPL), 106
in VLDL metabolism, 1857
Lipoprotein lipase deficiency, 1861–1862
Lipoprotein-associated phospholipase A2 (LP-PLA2), and CHD, 839
Lipotoxicity, in diabetes, 1604*f*
Liver X receptor/retinoid X receptor heterodimer (LXR), 106
Livedo reticularis, 152
Lixivaptan, 1278–1279
Loeffler's endocarditis, 1449–1450
Loeys-Dietz syndrome, 1167
Loffler's endocarditis, 491–492
Long QT syndromes (LQTS), 571, 718, 805
clinical manifestations, 718
diagnosis, 721
genetic testing, 721–722
genotype-phenotype correlation studies and risk, 720–721
genotype-specific therapy, 722
ICD therapy, 722
left cardiac sympathetic denervation, 722
molecular genetics, 719–720
pathogenesis, 718–719
therapy, 722
Loop diuretics, 58
in hyperuricemia, 1137
in sodium retention, 1277
therapeutic regimens, 65
Losartan heart failure survival study (ELITE II), 1238
Low cardiac output, signs of, 1215
Low density lipoprotein (LDL), 1231, 1507, 1971
in atherosclerotic disease, 1856, 1876
in cardiovascular complications, 1628
in premenopausal women, 1800
Low density lipoprotein cholesterol (LDL-C), 104, 1132, 1834
aerobic exercise, 2033
dietary lipids, 834
and diuretics, 68
and exercise, 917
Low molecular weight heparins (LMWH), 116, 119–120, 883–884

Low-tar cigarettes, 1876
Lp(a) hyperlipoproteinemia, 1860
Lung/heart ratio (LHR), 391
  CAD related risk, 391–392
Lunulae, 12
LV dysfunction and afterload stress, 71*f*
LV function assessments, linear dimensions, 231–232
LV internal dimensions at end-diastole (LVIDd), for TTE, 265
LV internal dimensions at end-systole (LVIDs), for TTE, 265
LV noncompaction, 694
LV systolic dyssynchrony index (LVSDI), 327
LVOT obstruction, at risk, during pregnancy, 1572
Lyme disease, 1194
  annular skin rash, 152
Lymphocytic myocarditis, 489*f*
  EMB for, 488
Lyposomal anthracyclines, in cardiotoxicity, 1485–1486
Lysergic acid diethylamide, 1627. *See also* Hallucinogenic drugs
Lysophosphatidylcholine, 373*f*, 374

M

6 minute walking test (6MWT), 760*t*, 1048
  AHFS management
    phases of, 1302*t*
    prognosis of, 1305*t*
  quality of life measure, 759, 769, 1269, 2044
Macroglossia, in systemic amyloidosis, 1460
Macrophage colony stimulating factor (M-CSF), in LDL binding, 1849
Macrophages, in molecular imaging, 456
MADIT II, ICD primary prevention trial, 1839
MAGIC (Myoblast Autologous Grafting in Ischemic Cardiomyopathy), clinical trial, 1994
Magnesium, in pressure lowering, 1134
Magnesium sulfate, for CPR, 796
Magnetic resonance imaging (MRI), 765–766, 865, 1756
  in AAD diagnosis, 1171
  of cardiac tumors, 422
  with endocarditis, 1056
  with TOF, 1573
Mahaim fiber, 674, 675*f*
MAIN-COMPARE registry, 361
Major histocompatability complexes (MHC), 126
Malaysia, incidence of heart failure in, 1210
Malignant tumors, 1675
  angiosarcoma, 1679
  leiomyosarcoma, 1681
  malignant fibrous histiocytoma, 1679
  osteosarcoma, 1679–1681
  primary cardiac sarcomas, 1675–1679
  rhabdomyosarcoma, 1681
  synovial sarcoma, 1681
  undifferentiated sarcomas, 1681
Manganese superoxide dismutase (MnSOD), 26
Mannitol, 54, 55, 58*t*, 62
Marfan syndrome, 152, 806, 1167, 1553
  Ghent nosology for, 1197*t*
Marijuana, 1624–1625
Masses, 422
  malignant cardiac neoplasm, 422
  noncancerous masses, 422–423
Masters series valves, 1074
Matrix metalloproteinases (MMPs), 27, 1253
Maximal oxygen uptake, 1891
Maximum heart rate (MHR), during exercise, 1833
Maximum intensity projection (MIP), 412
Mean circulatory filling pressure, 812
Mean pulmonary artery pressure (MPAP), 504
Mechanical circulatory support (MCS), 1334, 1343–1345
  VAD patient selection, 1345
  indications and contraindications for, 1345–1347
  patient care
    intraoperative management, 1348
    preoperative management, 1348
  survival with, 1349
Mechanical circulatory support, 1339*t*
  in HF, immediate postoperative management, 1341
Mechanical prosthetic valves, anticoagulation regimen in pregnancy, 1118
Mechanical valves, 1100–1101
  binding therapy, 1124
Mechanically rotating single-transducer system, and solid-state dynamic aperture system, 350*t*
Mediastinal radiation
  anthracycline cardiotoxicity, risk factor, 1480*t*
  cardiovascular complications of, 1505*t*
"Medication reconciliation", 1971
Mediterranean diet, for CAD, 2040
Medtronic-Hall valve, 1073–1074
Membranous septum, atrioventricular portion of, 15
Membranous VSDs, 1563
Men, heart failure risk factor in, 1900
"Mendelian randomization" principles, 1939
Mercurial diuretics, 58
Mesenchymal stem cells (MSCs), 1988, 1993, 1994
Mesenteric ischemia, 1160
Metabolic equivalents term (MET), 215, 1891
Metabolic modulators, and glucose utilization, 1609
Metabolic syndrome, 1861
  due to diabetes mellitus, 1715
  as heart failure risk factor, 1901
  HIV associated, 1639
  and physical examination, 151
Metaiodobenzylguanidine (MIBG), 401. *See also* ^{123}I-metaiodobenzylguanidine (^{123}I-MIBG)
  cardiac adrenergic denervation, 1483
  imaging of congestive heart failure, 404*f*
  in X syndrome, 43
Metastatic secondary tumors, EMB in, 496
Metastatic tumors, 1684–1686
Methadone, 1630
Methamphetamine, 1622
  cardiovascular complications, 1623–1624
  epidemiology, 1623
  in energy metabolism, 1603
  noncardiac complications, 1624
  pharmacology, 1623
Methylenedioxymethamphetamine (MDMA), 1625–1626
Methylphenidate, use in athletes, 1824
Metolazone, 54, 58*t*, 60, 64, 66
  diuretic agent in HF, 1288
Metoprolol, 46*t*, 680, 1239
Metoprolol CR/XL randomized intervention trial in congestive heart failure (MERIT-HF), 84, 1239, 1982
Metoprolol in Dilated Cardiomyopathy (MDC), trial, 84, 1238
Mexiletine, 584, 693, 723
Micro-RNAs (miRs), 28
Microvascular angina, 43
Microvascular structure and function, in VAD, 1348
Micturition syncope, 149
Mid-diastolic murmurs, 171
Midodrine, for POTS, 1197
Migraine headache, in variant angina syndrome, 540
Milrinone, 96–97. *See also* Inotropes
  in CO and renal function, 1290–1291
Mind-body medicine, 2032
Mineralocorticoid (aldosterone) receptor blockers
  aldosterone and systolic heart failure, 78–80
  eplerenone, in chronic heart failure, 80–81
  spironolactone, in chronic heart failure, 80–81
Minimum intensity projection (MinIP), 412
Minnesota Living with Heart Failure Questionnaire, quality of life measure, 1266–1267
MIRACLE study, 759
Mitochondria, in cardiac myocytes, 24–26
Mitochondrial encephalopathy with lactic acidosis and stroke like episodes (MELAS), 1911
Mitochondrial myopathies, 495
Mitral annular calcifications, 183
Mitral balloon valvuloplasty, 316
Mitral cusp VT, aortic sinus of, 691
Mitral regurgitation (MR), 1120, 1740–1741
  acute mitral regurgitation, 1011–1012
  cardiac catheterization, 1114–1115
  cardiogenic shock in acute coronary syndromes, cardiac causes of, 953–954
  clinical diagnosis
    physical signs, 1009–1010
    symptoms, 1009
  complications, 1010
  degenerative mitral valve disease. *See* Degenerative mitral valve disease
  etiology of, 1008–1009
  in HCM, Doppler inflections, 1395
  hemodynamics of, 1007–1008
  and mitral valve abnormalities, 1385
  infective endocarditis, caused by, 1011
  investigations
    cardiac catheterization, 1014

cardiovascular magnetic resonance imaging, 1014
computed tomography, 1014
echocardiography, 1013–1014
electrocardiogram, 1012
radiological evaluation, 1012–1013
management
medical treatment, 1014
secondary mitral regurgitation, treatment of, 1016–1017
surgical treatment, 1015–1016
natural history of, 1010
pathophysiology of, 1007–1008
percutaneous therapies for, 1043
perioperative events, 1777
plain film imaging, 186
rheumatic heart disease, 1009
secondary mitral regurgitation, 1012
severity, classification of, 282*t*
in systolic heart failure, 1214
transesophageal echocardiography, 1114
transthoracic echocardiography for, 1114
Mitral stenosis (MS), 1120
asymptomatic patients, 1113
clinical diagnosis
physical signs, 1002–1003
symptoms, 1002
echocardiography for, 1111
etiology of, 1001
hemodynamic of, 1001–1002
invasive hemodynamic evaluation, 1112
investigations
echocardiography, 1003–1004
electrocardiogram, 1003
invasive evaluation, 1004
radiological evaluation, 1003
stress testing, 1004
management
mechanical relief of obstruction, 1005–1007
medical treatment, 1004–1005
medical therapy, for systemic embolization, 1111
natural history of, 1004
pathology of, 1001
pathophysiology of, 1001–1002
percutaneous mitral balloon valvotomy, 1112–1113
in perioperative setting, 1777
plain film imaging, 185–186
severity, classification of, 281*t*
special populations, 1004
surgery for, 1112
symptomatic patients, 1113–1114
Mitral valve disease
assessment of, 331–334
catheter-based treatment of
mitral regurgitation, percutaneous therapies for, 1043
percutaneous balloon mitral valvuloplasty, 1040–1043
percutaneous mitral annuloplasty, 1043
percutaneous mitral leaflet repair, 1043–1044
pregnancy, mitral valvuloplasty in, 1043
management, 1115
mitral valve operation, 1115–1116
normal mitral valve morphology and function, 1000
regurgitation of *See* Mitral regurgitation
rheumatic heart disease, global burden of, 1000–1001
stenosis of *See* Mitral stenosis
Mitral valve prolapsed, 1100
assessment using TEE, 313
Mitral valve prosthesis, selection of, 1122–1123
Mitral valve, 3, 13–14
chordate, groups of, 14
Mixed angina, 43
coronary blood flow during, 42, 43*t*
Mixed connective tissue disease (MCTD), 1654
and PAH, 1527
M-mode echocardiograms, LVOT obstruction, 1389*f*
Mobile cardiac outpatient telemetry (MCOT), 782
Mobitz type I AV block, in athletes, 1821
Moderator band courses, 12
Modular Z-stent-based stent grafts, 1177
Molecular imaging, of vascular diseases, 450
animal imaging modalities, comparison of, 452*t*
of coronary arteries, 456
fundamentals, 450–452
imaging agents, 451*t*
modalities, 452–453
of plaque inflammation, 458*f*
of vascular disease processes, 453
aneurysm, 464–466
atherosclerosis, 453–461
outlook, 467
thrombosis, 461–464
vascular injury, 466
Monacolins, 2033
Monascus purpureus, red rice yeast, 2033, 2034
Monitored anesthesia care (MAC), 1787
Monocyte-derived macrophages, in atherosclerosis, 1849
Monocytes, in variant angina syndrome, 540
Monomorphic ventricular tachycardia
in association with structurally normal heart, 691–692
myocardial VT in association with structural heart disease, 687–690
Monophasic defibrillators, 797–798
Mood, and CHD, 2041
Mood-altering substances, 1613
MOOD-HF trial, on escitalopram, 1359
"Morganroth hypothesis", 1820
Morphine, 878, 907–908
on breathlessness, in HF, 1358
for CPR, 796
Morrow procedure. *See* Septal myectomy
Motion-based mode (m-mode), 265
Moxonidine in heart failure (MOXCON) trial, 1239
Moyamoya syndrome, 1911
MPI and stress ECHO, comparison of, 862
Mucocutaneous lymph node syndrome". *See* Kawasaki disease
MUerte Subita en Insuficiencia Cardiaca (MUSIC) score, 1336
Multicenter Automatic Defibrillator Implantation Trial I (MADIT I), for HCM, 1404
Multicenter InSync randomized clinical evaluation (MIRACLE), 1426
Multicenter Study of Perioperative Ischemia (McSPI) Epidemiology II Study, 973
Multicenter Ultrasound-guided Stent Implantation in Coronaries (MUSIC) trial, 360
Multi-cycle reconstruction, 409
Multidetector computed tomography (MDCT), 766–767, 863
coronary artery disease, 1221
Multifocal atrial tachycardia, 669–670
Multifunctional Ca^{2+}, 573
Multiple system atrophy, 1194
Multi-segment reconstruction, 409
Mural thrombosis, in atherosclerotic lesions, 1849
Muscle of Lancisi, 11*f*
Muscular VSDs, 1563
Musculoskeletal abnormalities, 152
of cardiovascular disorders, 153*f*
Musculoskeletal side effects
statin induced, 1955
clinical implications, 1955–1956
CYP450 drug metabolizing enzymes, 1955
SLCO1B1, 1955
statin therapy, compliance with, 1955
Myeloperoxidase, in heart failure, 1223
Myocardial action potentials, 570
Myocardial bridging, 416
Myocardial contrast imaging
and quantification of perfusion, 330
Myocardial contusion, 1734
clinical picture of, 1735
diagnosis of, 1735
imaging techniques, 1735
incidence of, 1734
laboratory data
cardiac enzymes, 1736–1737
echocardiography, 1736
electrocardiogram, 1736
magnetic resonance imaging, 1736
multidetector computed tomography, 1736
late complications, prognosis and development of, 1737
management of, 1737
Myocardial energy metabolism, 1602–1603
Myocardial fibrosis. *See also* Interstitial fibrosis
in HCM, 1386–1387
in idiopathic DCM, 436–437
Myocardial hibernation
and stunning, 1325
definition, 1323–1324
detection of, 1325
rationale, 1325
techniques, 1325–1328
historical perspective, 1323
pathophysiology, 1324–1325
revascularization of
changes in prognosis, 1328–1331
changes in ventricular function, 1328
Myocardial hypertrophy, 694

Myocardial infarction(MI), 116, 432, 912–913
and rheumatoid arthritis, 1650
as systolic heart failure risk factor, 1229
Myocardial infarction heart failure efficacy and survival study (EPHESUS), 79, 80*f*, 81
Myocardial interstitial fibrosis, 1718–1719
doxorubicin cardiotoxicity, 1481
Myocardial ischemia
coronary artery occlusion, 39
in coronary artery disease, 1224
in women, symptom assessment, 1802–1803
Myocardial ischemia and infarction, due to cocaine usage, 1618
Myocardial ischemia causing cardiac arrest, 823
Myocardial oxygen consumption, 213*t*, 213–214
Myocardial oxygen demand, 34–35
Myocardial oxygen supply, 35
Myocardial perfusion imaging, 433
Myocardial revascularization
vs. antianginal drug therapy, 931–932, 933–934, 934*f*
for stable angina and CAD, 931–932
in rheumatoid arthritis, 1650
Myocardial structure, in VAD, 1348
Myocardial stunning, 1323
Myocardial ventricular tachycardia, in association with structural heart disease
fibrosis and scar, 687–689
monomorphic VT
with arrhythmogenic right ventricular dysplasia, 690
due to bundle branch reentry, 689–690
post surgery for congenital heart disease, 690
Myocardial viability, and stress echo, 304
Myocarditis
clinical scenarios, diagnosis of, 490*t*
causes of, 1426*t*
in HIV infection, 1643
in MCTD, 1654
Myocardium
and chambers, 417–418
contractility, 34
Myocyte hypercontraction
in EMB tissue, 487
Myocyte necrosis
to diagnose myocarditis, 490
Myofilament HCM, 1379*t*
Myogenic resistance, 36
Myxomatous mitral valve, 1122

N

^{13}N-Ammonia positron emission tomography (^{13}N PET)
myocardial blood flow quantification, 42, 942
Nadolol, 692, 722, 1139, 1405, 1938*t*
National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) guidelines, 104, 1640
National Hospice and Palliative Care Organization (NHPCO), 1353, 1354
National Institute for Health and Clinical Excellence (NICE)
for cost-effectiveness, in Britain, 1981
National Institutes of Health (NIH), 2031
National Research Council's Committee on the Biological Effects of Ionizing Radiation (BIER), 403
Native valve endocarditis
epidemiology of, 1052–1053
microbiology of, 1057
drug users, 1058
non-drug users, 1057–1058
surgery for, 1117
Native valve endocarditis
Native valvular heart disease, 1100
anticoagulation INR range for, 1099*t*
Natriuretic peptides
aortic stenosis, diagnosis of, 989
in heart failure, 1221
Naxos disease, 713
palmer and planter keratoses, 152
Near-infrared (NIR) spectroscopy, 374
Necrotizing eosinophilic myocarditis
EMB for, 488
Nellix stent graft, 1176, 1178
Neovascularization, in molecular imaging, 459–460
Nephrogenic systemic fibrosis, 1150
Nephron, 53, 54*f*
"braking" phenomenon, 56
Nephrotic syndrome, 67
Nernst equation, 565
for K^+, 566
Nesiritide,83
BNP, 1243
in CRS, 1294
safe vasodilator, 95
Neural control mechanisms
for cardiovascular response, 217
Neuraxial anesthesia care (MAC), 1787
Neurocardiogenic syncope, 148, 1197
Neurogenic cardiomyopathy, 1689
clinical features, 1689
arrhythmias, 1689–1690
cardiac biomarkers, 1690–1691
ECG abnormalities, 1689
left ventricular dysfunction, 1691
diagnosis, 1692
pathophysiology, 1691–1692
prognosis, 1693
treatment, 1692–1693
Neurogenic hypertension, 1198
Neurohormonal milieu, in VAD, 1348
Neurohormones, in heart failure, 76*f*
Neutrophil gelatinase-associated lipocalin (NGAL), in heart failure, 1223
New Approaches to Coronary Intervention (NACI) Registry
percutaneous revascularization, women versus men, 1807
New classification, of aortic dissection, 1168–1169
New York Heart Association (NYHA) classification, functional class assessment, 1215
New York Model, 1072
New York State registry, 979
Niacin, 112–113, 917, 2036
Nicotine delivery formulations (NRT), tobacco dependency, first-line treatment for, 1880
Nicotine replacement therapy, 918, 1881
Nicotine withdrawal, 1880
Niemann-Pick C1-Like 1 transporter (NPC1L1 transporter), 106
Nifedipine, 879
congenital valvar aortic stenosis, 1553
for stable angina and CAD, 929
in variant angina, 944
vasospasm, prevention of, 1692
Nimodipine, 1139, 1692, 1693, 1923
NIRF imaging
of atherosclerosis inflammation, 458*f*
of coronary arteries, 456
Nitrates, 878, 906–907, 1228
arteriolar dilator drug, 72
in LV dysfunction, 1695
safe vasodilator, 95
for stable angina and CAD, 928
Nitric oxide (NO), 81
Nitrogen (^{13}N) ammonia
imaging perfusion, 397
Nitroglycerin (NTG), 73, 907
for cocaine abuse treatment, 1619
intravenous, 82
limitations of, 82–83
pulmonary capillary wedge pressure, effect on, 83*f*
and isosorbide dinitrate, 73
for stable angina and CAD, 928
in vasodilatation, 1782
venodilator, 1243
Nitroprusside (NP), 82, 97*f*
in CRS, 1294
metabolism and toxicity of, 82
and severe heart failure, 82
Nitroprusside sodium, for heart rate maintenance, 1171
Nocturnal cough, as HF symptom, 1213–1214
Nocturnal stress, in HCM, 1413
Nodes of Ranvier, 572
Nomogram
for body surface area, 231*f*
in exercise stress testing, 300
Non-acute coronary syndromes, 509–510
Nonalcoholic fatty liver disease, 1861
Non-anginal pain, in HF, 1358
Non-atrial septal defect, 1741–1742
Non-bacterial thrombotic endocarditis (NBTE), 1055
Noncardiac chest pain, 144*t*, 875
Noncardiac surgery, in cardiac patients, 1773
implanted electronic devices, management of, 1787–1788
intraoperative management, 1786
anesthesia, choice of, 1786–1787
hemodynamic monitoring, 1787
postoperative management, 1788
ischemia, surveillance for, 1788
pain management, 1789
postoperative arrhythmias, 1788–1789
pulmonary artery catheters, 1788

preoperative diagnostic testing, 1778
12-lead resting electrocardiography, 1778
ambulatory electrocardiography, 1778
cardiac biomarkers, 1780
coronary angiography, 1779–1780
heart rate variability, 1778
left ventricular function, assessment, 1778
myocardial ischemia, noninvasive studies for, 1778–1779
preoperative risk assessment, 1773–1774
arrhythmias, 1777
congenital heart disease, 1777
general risk stratification, 1774–1776
heart failure, 1776
hypertension, 1776
ischemic heart disease, 1776
valvular heart disease, 1776–1777
preoperative risk mitigation strategies
nonpharmacologic and other interventions, 1783–1786
pharmacologic interventions, 1780–1783
Noncompaction, of LV, 806
Non-conventional therapies, and cardiology, 2031
Non-desmosomal genes, 708
Nonesterified fatty acid (NEFA), in energy metabolism, 1603
"Non-HDL cholesterol", 1859
Non-highdensity lipoprotein cholesterol (non-HDL-C), 104
Non-Hispanic blacks, heart failure risk factor in, 1900
Noninvasive computed tomographic angiography, 863
Non-ischemic cardiomyopathy (NICM), 640–641, 807
Non-penetrating injury, 1730
Non-pitting lymphedema, 149
Non-rapid eye movement (NREM) sleep, on cardiac physiology, 2021
Non-restrictive VSDs, 1563
Non-ST elevation myocardial infarction (NSTEMI), 517
stress testing in, 210
Nonsteroidal anti-inflammatory agents (NSAIDs), 112
drug interaction, 1290
Non-syndromic familial thoracic aortic aneurysms and dissections, 1167–1168
Nonuniform rotational distortion (NURD), 351*f*
Non-ventricular septal defect, 1741–1742
Norepinephrine, 96, 1192
neurohormone, 74
in hypotensive patients, 1244
hazard ratio, 96*f*
Normal coronary anatomy
co-dominant or balanced coronary circulation, 527
coronary collateral circulation, 527–528
left anterior descending artery (LAD), 525–526
left circumflex artery (LCX), 526
left dominant coronary circulation, 527
left main coronary artery (LMCA), 524–525
right coronary artery (RCA), 526–527
right dominant coronary circulation, 527
North Glasgow MONICA Risk Factor Survey
BNP role in, 1904
Nortriptyline, 1359
tobacco dependency, second-line treatment for, 1883
N-terminal pro-brain natriuretic peptide (NT pro-BNP), 147, 1780
in AL amyloidosis, 1463
cardiac marker, for myocardial wall stress, 1780
LV systolic dysfunction, 1703
NTG tolerance, 73*f*, 74*f*
Nuclear cardiology. *See* Cardiovascular nuclear medicine
Nuclear factor of activated T cells (NFAT), 26
Nuclear imaging, 766
Nucleus tractus solitarii (NTS), 1188, 1189
Nutrition, and CHD, 834
Nutritional counseling, in cardiac rehabilitation, 920
Nutritional deficiency, in HF,1429–1430
calcium, 1429–1430
L-carnitine, 1430
selenium, 1429
vitamin B, 1430
vitamin D, 1429

O

O'Brien valve, 1078
Obesity
and CHD, 834–836
classification, by body mass index, 836*t*
effects on organs, 836*t*
ethnic specific values for abnormal waist circumference, 836*t*
as heart failure risk factor, 1901
and hypertension, 1134
as systolic heart failure risk factor, 1229
Obliterative cardiomyopathy. *See* Endomyocardial fibrosis (EMF)
Obstructive sleep apnea (OSA)
autonomic perturbations associated with, 1199
cardiac physiology, effects on
atrial fibrillation, 2025
coronary artery disease and sudden cardiac death, 2025
hypertension, 2024–2025
hypertrophic cardiomyopathy, 2025–2026
stroke, 2026
in HCM, 1413
treatment of
continuous positive airway pressure, 2027–2028
obesity and treatment position, 2027
oral appliances and surgery, 2028
OCT for DES SAfety (ODESSA), 368
Off-pump coronary artery bypass surgery (OPCAB)
and CABG, 1329
Older-adults. *See also* Aging; Cardiovasular aging
beta-blockers, use in, 1835
calorific restriction, 1834
cellular aging, cardiovascular mechanisms in, 1831*t*
common comorbidities in, 1831*t*
conduction disease, 1837
epidemiology, 1837
management, 1837–1838
pathogenesis, 1837
CVD in, 1829
demographics, 1830*f*
end-of-life care, 1839–1840
exercise, 1833
heart failure
epidemiology, 1834
pathogenesis, 1834–1835
therapy, 1835
ischemic heart disease
epidemiology, 1836
management, 1837
pathogenesis, 1836
valvular disease, 1838
epidemiology, 1838
management, 1838–1839
pathogenesis, 1838
Omega 3 fatty acids, 114, 917
in left ventricular ejection fraction, 1240
"Ondine's curse". *See* Congenital central hypoventilation syndrome
On-X LTI valves, 1075
Open heart surgery, 4
for constrictive pericarditis, 1502
versus endovascular repair (OVER) study, 1176
Opioids, for dyspnea, in HF, 1358
Optical coherence tomography (OCT)
clinical experience, 366–368
detection of vulnerable plaque, 368–370
future directions, 370
image interpretation, 365–366
imaging systems and procedures, 364–365
safety and limitations, 370
Optimal medical therapy (OMT). *See also* Antianginal drug therapy
for stable angina and CAD, 933
Optimal Pharmacologic Therapy in Cardioverter Defibrillator Patients (OPTIC) trial casts, 597
Oral hydralazine therapy, for chronic heart failure, 1228
Oral nitrates, 74
for variant angina, 943
Oral penicillin, for RF, 1933*t*
Oral β-adrenergic blocking drugs, 83–85
Orally administered positive inotropic agents, 98
digoxin, 98–100
Organisation for Economic Cooperation and Development (OECD) countries
CV contribution status, 1977
health expenditure, trends in, 1976
Orlistat, 836
Ornish diet, for CAD, 2040
Orthopnea, 147
Orthostatic hypotension, 149, 151, 629, 1189–1190, 1836

treatment of, 1196
non-pharmacologic therapy, 1196
pharmacologic therapy, 1196–1197
Orthotopic heart transplantation (OHT), 1336
Orthotopic heart transplantation (OHT)/SCT
in AL amyloidosis, 1464
Ortner's syndrome, 149
Osler maneuver, 154
Osler-Weber-Rendu syndrome, 152
Osmotic diuretic, 62
Ostium primum, 9, 1559
Ostium secundum, 1559
Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbation of Chronic Heart Failure (OPTIME-CHF) study, 1272, 1426
Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbation of Heart Failure (OPTIME-HF) study, 1272
Out-of hospital cardiac arrest (OHCA), 811–812
Ovation stent graft, 1176, 1178
Over the counter drugs, 1630–1631
Over weight. *See also* Obesity
and hypertension, 1134
Oxidative stress
in molecular imaging, 458
and tobacco smoking, 1879
Oxygen
for cocaine abuse treatment, 1619–1620
for CPR, 796, 800
Oxygen consumption (MVO2), 34
Oxygen therapy
for cor pulmonale, 1764
Oxyhemoglobin, for CPR, 800

P

β-PRESERVE, metoprolol versus placebo, in HFPEF, 1835
P wave characteristics, 677
P waves, 191
P2Y1 receptor, 873
P2Y12 activation
inhibition, 128*f*
P2Y12 receptor, 873, 880
PA films, 174
absence of pericardium, 188*f*
aortic stenosis, 186*f*
vs AP films, 175*f*
dilated cardiomyopathy, 187*f*
interstitial edema, 181*f*
left atrial enlargement, 179*f*
left ventricular aneurysm, 184*f*
left ventricular enlargement, 178*fi*
mitral annular calcification, 184*f*
mitral valve insufficiency, 187*f*
normal arterial-bronchial relationship, 176*f*
normal films, 176*f*, 177*f*
pericardial cyst, 188*f*
pericardial effusion, 187*f*
pulmonary valve stenosis, 187*f*
right atrial enlargement, 179*f*
right ventricular enlargement, 178*f*
PA occlusion pressure. *See also* Pulmonary capillary wedge pressure (PCWP)
pulmonary venous and left atrial pressure, indirect assessment of, 504
Pacemaker dependant patients, 768–769
Pacemaker, 794
PAD Awareness, Risk and Treatment: New Resources for Survival (PARTNERS) trial, 1147
PAH, disease specific therapies
endothelin receptor antagonists, 1539–1540
phosphodiesterase type 5 inhibitors, 1540–1541
prostacyclin analogs, 1538–1539
PAH, surgical options
atrial septostomy, 1541
lung transplantation, 1541
PAH, survival
associated with
connective tissue disease, 1536
portal hypertension, 1536
schistosomiasis, 1536
in congenital heart disease, 1536
in HIV, 1536
and prognostic factors of, 1535–1536
PAH, therapeutic options, 1536–1537
anticoagulation, 1537
calcium channel blockers, 1537–1538
digitalis, 1537
oxygen,1537
PAH, treatment algorithm, 1541–1542
Pain control
in perioperative setting, 1789
Pakistan
incidence of heart failure in, 1210
Palliative care
history of, 1353–1354
multidisciplinary approach to, 1354*f*
Palliative shunts, 1571–1572
Palm sign, 144*f*
Palpitations, 148
as HF symptom, 1213
symptom of mild hypertension, 1129
Papillary muscles
tricuspid valve anatomy, 1019
Parachute mitral valve
and BAVs, 1552
Paradoxic embolization, 311–312
Paradoxical embolism, 1562
Paraganglioma, 1720
Paraneoplastic process, 1194–1195
Parasympathetic nervous system (PNS)
in cardiac functioning, 1691
Paravalvular regurgitation, 1095
Parenteral anticoagulant therapy, 548
bivalirudin, 549
enoxaparin, 549
heparin, 548–549
Parkinson's disease, 1193
Paroxysmal atrial fibrillation (PAF)
in HCM, 1413
Paroxysmal atrioventricular block, 701
Paroxysmal nocturnal dyspnea, 147
Paroxysmal orthostatic tachycardia syndrome (POTS) syncope, 148
Paroxysmal supraventricular tachycardia, 196
Particulate air pollution
mechanism of, 1883–1884
Parvovirus B19
cardiotropic virus, 488
in myocarditis, 1426
"PAT with block". *See* Digoxin-toxic dysrhythmias
Patent ductus arteriosus (PDA)
and BAVs, 1552
associated anomalies, 1567
clinical findings, 1567
diagnostic studies, 1567–1568
general considerations, 1566
guidelines, 1568
pathophysiology, 1566–1567
pregnancy, 1568
treatment and prognosis, 1568
PCI
for cocaine abuse treatment, 1619–1620
indications for, 546*t*
PCI, complications specific to, 555
acute thrombotic closure, 556
no-reflow, 556
perforation, 556
threatened or acute closure, 555–556
PCI, pharmacotherapy for, 545
antiplatelet therapy
aspirin, 545
IIb/IIIa platelet receptor inhibitors, 548
thienopyridine, 545–548
"Peak and dome" configuration
Peak VO2 consumption, as mortality predictor, 1355
Penetrating aortic ulcer, 1186
Penetrating injuries, 1730
Penetrating thoracic trauma, 1733*t*
Pentoxifylline (Trental), 1151–1152
PEP-CHF study, perindopril, 1835
Percutaneous alcohol septal ablation
for HCM, 1408–1411
arrhythmogenic substrate, 1409
limitations of, 1410–1411
major complications, 1408
morphologic heterogeneity, 1409–1410
patient selection in, 1408
and septal myectomy, 1412*t*
Percutaneous coronary intervention (PCI), 125, 349, 800, 880, 882–883, 884, 885, 886, 894, 902, 906, 911
vs CABG, 957, 1976, 1977*f*
creatinine signals, 1285
and medical management, comparison of, 977–978
Percutaneous lead, position of
in MCS, 1348
Percutaneous transluminal coronary angioplasty (PTCA), 125, 358, 550, 1762
and CABG, comparison, 971
for stable angina and CAD, 933
for variant angina, 946
Perhexiline, FFA, beta-oxidation, 1609
Pericardial calcifications, 183
Pericardial cysts, plain film imaging, 188
Pericardial disease, 445, 1702
acute pericarditis, 1489–1491
chronic relapsing pericarditis, 1491–1493

constrictive pericarditis, 1496–1503
hemodynamics in, 481
cardiac tamponade, 482
constrictive pericarditis, 481–482
pericardial effusion and pericardial tamponade, 1493–1496
TTE in, 273–274
Pericardial effusion
and pericardial tamponade
diagnosis, 1494–1496
examination, 1493–1494
presentation and etiology, 1493
treatment, 1496
plain film imaging, 187–188
TTE in, 273
Pericardial injury, 1733–1734
Pericardial mesothelioma, 1683–1684
Pericardial reflections, 5*f*
clinical importance of, 4
Pericarditis, 421, 914
and heart in mediastinum, 3–6
Perimount Magna aortic valve, 1076
Perindopril. *See also* Angiotensin-converting enzyme inhibitors
in diastolic heart failure, 1259
for stable angina and CAD, 930
Periorbital purpura, in systemic amyloidosis, 1460
Peripartum cadiomyopathy (PPCM)
clinical presentation
biomarkers, 1473–1474
laboratory evaluation, 1474
definition, 1473
etiology, 1473
incidence, 1473, 1474*t*
labor and delivery, 1475–1477
prognosis, 1474–1475, 1476*t*
treatment, 1475
in women, 1473
Peripheral arterial disease (PAD), 130
and cardiac rehabilitation, 1895
causes of, 1145
clinical presentation and natural history, 1146–1147
asymptomatic and symptomatic, 1147–1148
critical limb ischemia, 1148–1149
@3acute limb ischemia, 1149
diagnosis
ankle-brachial index, 1150
noninvasive vascular modalities, 1150
epidemiology, 1145–1146
management, 1151–155
risk factors for, 1146
screening for, 1150
and tobacco smoking, 1873
vascular history and physical examination, 1146
Peripheral nervous system, 1187
Peripheral vascular disease (PVD)
Perivascular landmarks
in IVUS imaging, 352*f*
Permanent junctional reciprocating tachycardia, 674
Persantine, 132, 679*t*
Personality factors, and CAD, 2041
Pharmacologic stress echo
assessment prior to, 296
complications of
dipyridamole, 297
dobutamine, 297
conducting of, 297
interpretation of, 297–298
protocols of, 296–297
dipyridamole stress protocol, 296–297
dobutamine stress protocol, 296
Pharmacologic stress testing, 383–385
Pharmacotherapy, in molecular imaging, 453–454
Phencyclidine, 1624
Phenobarbital, for chorea, 1933
Phenoxybenzamine, for coronary spasm, 943
Phenteramine, diet drug, 1628
Phentolamine, 96
for coronary spasm, 943
in hypotensive patients, 1244
neurogenic cardiac injury, 1692
Phenylpropanolamine, 1197, 1624
Pheochromocytoma, 1720
autonomic perturbations associated with, 1199–1200
PHIRST (PAH and Response to Tadalafil) trial, 1540
Phosphodiesterase 5 (PDE 5), 81
Phosphodiesterase III (PDE III), 96
antagonism of, 1291
Phosphodiesterase inhibitors, 96
milrinone, 96–97*f*
Phospholamban, 24
in hibernating myocardium, 1324
Phrenic nerve simulation, 767
Physical activity, 1890
and CHD, 834
Physical examination, 151
for ACS, 874
general appearance, 151
jugular venous pulse, 154
of musculoskeletal system, 152–153
of skin, 151–152
Physical inactivity, 1890
Pituitary apoplexy, 1909*t*
Pituitary disorders
growth hormone excess, 1718–1719
hypopituitarism, 1719–1720
Placement of balloon flotation catheters, placement of, 503–504
Plain film imaging, of adult cardiovascular disease
acquired valvular heart disease
aortic insufficiency, 185
aortic stenosis, 183–185
mitral regurgitation, 186
mitral stenosis, 185–186
pulmonary valve insufficiency, 186
pulmonary valve stenosis, 186
tricuspid insufficiency, 187
cardiac anatomy on, 176–177
cardiac calcifications, 182–183
cardiac chamber enlargement
left atrial enlargement, 178–179
left ventricular enlargement, 177–178
right atrial enlargement, 179
right ventricular enlargement, 178
cardiomediastinal anatomy, overview of, 175–176
chest film technique, 174
congestive heart failure, 179–182
pericardial disorders
congenital absence of pericardium, 188
pericardial cysts, 188
pericardial effusion, 187–188
Plant fox gloves, 1228
Plant stanols and sterols, for dyslipidemia, 2034
Plaque neovascularization, cardiovascular molecular imaging, 459*f*
Plasma B-type natriuretic peptide (BNP), 1903
Plasma homocysteine, in atherosclerosis, 1850
Plasma renin activity, hypertension, specialized studies, 1131*t*
Plasma volume, hypertension, 1131*t*
Plasmid DNA delivery
versus viral transduction, 2004
adeno-associated virus (AAV), 2004–2005
adenovirus, 2004
lentivirus, 2005–2006
Platelet activation and thrombosis, and tobacco smoking, 1877
Platelet activation inhibitors, 128
ADP/P2Y12 signaling inhibitors, 129–130
PDE inhibitors, 131–132
prasugrel, 130–131
thrombin receptor antagonists, 132–133
TXA2 pathway inhibitors, 128–129
Platelet activation, mechanism of, 118*f*
Platelet adhesion, in atherosclerotic lesions, 1849
Platelet adhesion inhibitors, 127–128
Platelet aggregation inhibitors, 133
Platelet factor 4 (PF4), 119
Platelet Inhibition and Patient Outcomes (PLATO) trial, 1944
Platelet-derived growth factor (PDGF), 2011
Platelets, 872–873, 873*f*
Pleiotrophin, 2011
Plexiform lesion, in PAH, 1525
Pluripotent stem cells
human tissue differentiation, 1987*f*
Pointing sign, 144*f*
Policosanol, for dyslipidemia, 2036
Poly (ADP-ribose) (PAR), 28
Poly (ADP-ribose) polymerase 1 (PARP-1), 28
Polyarteritis nodosa, 1656–1657
"Polycythemia", of hypertension, 1132
Polymer filled stent grafts, 1177–1178
Polymorphic ventricular tachycardia
with long QT interval, 692–693
with normal QT prolongation, 693–695
with short QT syndrome, 695–696
Polymyositis-dermatomyositis, 1653
clinical features, 1653
treatment, 1653–1654
Polymyositis-dermatomyositis, 1653–1654
Polysubstance abuse, 1622
Polytetrafluoroethylene (PTFE) fabric, in stent grafts, 1178, 1181
Pomegranate (*Punica granatum*), for hypertension, 2039

Pompe disease, 495
Positive inotropes. *See* Positive inotropic drugs
Positive inotropic drugs, 89
adrenergic receptor agonists, 89–90
calcium sensitizers, 97–98
digoxin, 98–100
dobutamine, 91–93
adverse effects, 95
applications, 93
dosing, 93–94
dopamine, 95
epinephrine, 96
hemodynamic profiles, 90*t*
isoproterenol, 95–96
levosimendan, 97–98
milrinone, 96–97
norepinephrine, 96
phenylethylamine molecule, 91*f*
phenylephrine, 96
spectrum of net vascular properties of, 91*t*
thyroxine, 98
Positive inotropic interventions, intravenously administered, 97
thyroxine, 98
Positive inotropic therapy
DIG trial, 98–99
hydralazine, 100
intravenously administered interventions, 97
intravenously administered, short term, 89
adrenergic receptor agonists, 89–90
calcium sensitizers, 97
dobutamine, 91–95
dopamine, 95
epinephrine, 96
isoproterenol, 95–96
levosimendan, 97–98
norepinephrine, 96
phenylephrine, 96
mechanism, 90*f*
orally administered drugs
digoxin, 98–100
istaroxime, 98
phosphodiesterase inhibitors, 96
milrinone, 96–97
thyroid hormone replacement, 100
Positron emission tomographic (PET) perfusion imaging, 861
Positron emission tomography (PET), 381
Post infectious auto immune neurological diseases (PANDA), 1930
Post MI exercise testing, benefits of, 211*t*
Post myocardial infarction care, 909–912
Post strep reactive arthritis (PSRA), 1929
Postganglionic neuronal depletors, 1141
Post-myocardial infarction (post-MI), therapeutic strategy, limitation, 1986
Postoperative arrhythmias, 1788–1789
Post-resuscitative care, 800
Postsurgical cardiac rehabilitation, 1895
Postsynaptic (peripheral) alpha-receptor antagonists, 1141–1142
Postural orthostatic tachycardia syndrome (POTS), 666, 1195–1196
Potassium, in pressure lowering, 1134
Potassium-sparing agents, in hyperkalemia, 1137–1138
Potassium-sparing diuretics, 61
Powerlink stent graft, 1177
Prasugrel, 545, 881–882, 908
in stroke prevention, 1918
versus clopidogrel, 1837
Prealbumin, 1831, 1835 *See also* Transthyretin-related (TTR) amyloid molecules
transthyretin, 1458
PRECISE, dose escalation trial, refactory angina, 1995
Precordial honk, 164
Precordial pulsation, examination of, 159–160
Predictors and outcomes of stent thrombosis (POST) registry, 360
Pregnancy
and contraception
and CHD, 1572
and HCM, 1413–1414
and lactation
drug safety during, 1477*t*
and valvular heart disease, 1102
Preinfarction angina", 1328
Preload reduction
in HF, immediate postoperative management, 1340
with nitroprusside, 1940–1941
Preoperative diagnostic testing, 1778
12-lead resting electrocardiography, 1778
ambulatory electrocardiography, 1778
cardiac biomarkers, 1780
coronary angiography, 1779–1780
heart rate variability, 1778
left ventricular function, assessment, 1778
myocardial ischemia, noninvasive studies for, 1778–1779
Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial, 1810
Pre-shock or shock syndromes
hemodynamic features of, 506*t*
Prima porcine prosthesis, 1078
Primary aldosteronism, 1720–1721
Primary amyloidosis. *See* Light chain (AL) amyloidosis
Primary cardiac arrest
assisted ventilation in, 814–815
bystander resuscitation efforts, 818
cardiocerebral resuscitation, prehospital component, 819–821
in children and adolescents, 812
coronary perfusion pressures, during resuscitation efforts, 813–814
not following guidelines for, 815–816
pathophysiology of, 812–813
prompt identification, 818
public mindset, 817–818
ventricular fibrillation (VF), phases of, 818–819
Primary cardiac lymphoma, 1681–1683
Primary chronic autonomic failure, 1193
multiple system atrophy, 1194
pure autonomic failure, 1193–1194
Primary hyperparathyroidism, 1722
Primary tricuspid valve regurgitation
surgical treatment of
carcinoid heart disease, 1026
cleft tricuspid valve, 1026
Ebstein's anomaly, 1025–1026
infective endocarditis, 1026
rheumatic valve disease, 1025
traumatic tricuspid regurgitation, 1026
Proarrhythmia, 579
Proarrhythmic substrates, 575
and triggers, in failing hearts, 575–576
Probucol, in dyslipidemia, 1863
Procainamide, 583, 623, 680, 693, 796, 1963
Procedural adjunct TEE, 316–317
Progeria, 530
Programmed cell death. *See* Apoptosis
Progressive CKD. *See* Type 2 CRS (chronic CRS)
Propafenone, 1963, 585–586, 655, 667, 681
Propranolol, 692. *See also* Beta-blockers
for cocaine abuse treatment, 1620
for HCM, 1405
neurogenic cardiac injury, 1692
Proprotein convertase subtilisin/kexin type 9 serine protease (*PCSK9*) gene, 1954
PROSPECT trial, 765
Prospective cardiovascular Münster (PROCAM), 831*t*
Prospective investigation of pulmonary embolism diagnosis (PIOPED) II, 1754
Prospective randomized amlodipine survival evaluation (PRAISE) study, 74, 1242
Prospective Randomized Study of Ventricular Failure and the Efficacy of Digoxin (PROVED), 98
PROSPER study
pravastatin, 1839
Prosthesis-patient mismatch (PPM), 1081–1084
Prosthetic aortic valve regurgitation
Doppler parameters of, 1089*t*
severity of, 1086*t*
Prosthetic heart valves
follow-up visits, 1125
long-term complications
hemolysis, 1095
paravalvular regurgitation, 1095
structural valve deterioration, 1092–1095
thromboembolic and bleeding complications, 1090–1092
long-term management
antithrombotic therapy, 1084–1085
echocardiography follow-up, 1085–1090
management of
antibiotic prophylaxis, 1123
antithrombotic therapy, 1123–1124
optimal prosthesis selection, 1079–1081
prosthesis-patient mismatch, 1081–1084
prosthetic valves, types of, 1073
bioprosthetic valves, 1075–1078
homograft, 1078–1079
mechanical valves, 1073–1075
pulmonic valve autotransplantation, 1079
thrombosis of, 1124–1125
valve replacement risks, 1072–1073

Prosthetic mitral valve regurgitation
Doppler parameters of, 1089*t*
severity of, 1089*t*
Prosthetic valve endocarditis
epidemiology of, 1053
microbiology of, 1058
early prosthetic valve endocarditis, 1059
late prosthetic valve endocarditis, 1059
surgery for, 1117–1118
Prosthetic valve thrombosis, 1090–1091
Prosthetic valves, 1073
anticoagulation INR range for, 1101*t*
in perioperative setting, 1777
mechanical valves, 1100–1101
thrombogenicity of, 1099*t*
valvular disorders, assessment of, 334–335
Protease, in molecular imaging, 456
Protease inhibitors (PI), 123
PROTECT-CAD trial, refactory angina, 1995
Protein kinase A (PKA), 24
Protein kinase G, in myocardial distensibility, 1261
Proteinuria, in chronic cyanosis, 1571
Prothrombin time (PT), 116
Proton pump inhibitors (PPIs), 127
Provocative testings, variant angina, diagnosis of, 942
Pseudoaneurysms, 182
Pseudoephedrine, 1197
Psychosocial factors, and CHD, 836–837
Psychosocial intervention, in cardiac rehabilitation, 920–921
Psyllium (*Plantago ovate*), 2034
for dyslipidemia, 2034
Pulmonary arterial hypertension (PAH), 272–273, 443, 1521, 1562
associated with
chronic hemolytic anemias, 1528
congenital heart disease, 1527
connective tissue diseases, 1526–1527
HIV infection, 1527
schistosomiasis, 1527–1528
clinical classification, 1522
WHO Group 1 PH, 1522–1523
WHO Group 2 PH, 1523
WHO Group 3 PH, 1523–1524
WHO Group 4 PH, 1524
WHO Group 5 PH, 1524
clinical presentation, 1529–1531
diagnostic evaluation, 1528–1529
chronic thromboembolic pulmonary hypertension, 1534
clinical presentation and physical examination, 1529–1531
echocardiography, 1531–1532
laboratory studies, 1533
nocturnal polysomnography, 1534
pulmonary function testing, 1533
right heart catheterization, 1534
vasoreactivity testing, 1534–1535
echocardiography, 1531
hemodynamic classification, 1521–1522
pathophysiology and epidemiology of, 1524–1525
drug-induced and toxin-induced PAH, 1526
heritable PAH, 1525–1526
idiopathic PAH, 1525
portopulmonary hypertension, 1527
pulmonary capillary hemangiomatosis, 1528
pulmonary veno-occlusive disease, 1528
therapy of decompensated right heart failure in, 1542–1544
Pulmonary arterial hypertension,
Pulmonary arterial systolic pressures (PASP), in HIV patients, 1641
Pulmonary arterial wedge pressure (PAWP), in PAH, 1522
Pulmonary arteries, 3, 13
Pulmonary artery catheterization (PAC), 503, 510
in postoperative management, 1788
Pulmonary artery catheters, 1788
Pulmonary artery disease. *See* Pulmonary arterial hypertension (PAH)
Pulmonary artery systolic pressure (PASP), 1532
Pulmonary capillary hemangiomatosis (PCH), 1528
as PAH, 1522
Pulmonary capillary wedge pressure (PCWP), 73
in constrictive pericarditis, 1499
pulmonary venous and left atrial pressure, indirect assessment of, 504
Pulmonary crackles, in pulmonary venous congestion, 1214
Pulmonary edema, 147*f*
Pulmonary embolism, 147, 914
Pulmonary endarterectomy (PEA), 1524
"Pulmonary heart disease", 1763. *See also* Cor pulmonale
Pulmonary hypertension
during stem cell clinical trial, 1996
in MCTD, 1654
Pulmonary infarction, 1753
Pulmonary outflow obstruction, 167–168
regurgitant murmurs, 168
mitral regurgitation, 168–169
tricuspid regurgitation, 169
Pulmonary stenosis, definition, 1558
Pulmonary system, and cardiovascular system, 1314
Pulmonary valve disease
catheter-based treatment of
percutaneous pulmonic balloon valvuloplasty, 1044
percutaneous pulmonary valve implantation, 1044–1045
Pulmonary valve insufficiency
plain film imaging, 186
Pulmonary valve stenosis
PA film, 187*f*
plain film imaging, 186
Pulmonary vascular resistance (PVR), 505, 1521, 1562, 1762
Pulmonary veins, 418–419
Pulmonary veno-occlusive disease (PVOD), 1528
as PAH, 1522
Pulmonary venous hypertension, WHO Group 2 PH, 1523
Pulmonic cusp VT, aortic sinus of, 691
Pulmonic stenosis
in adolescents and young adults, 1121
balloon valvotomy in, 1121–1122
Pulmonic valve autotransplantation, 1079
Pulmonic valve, 3, 12–13
Pulmonic valvular regurgitation, 1741
Pump optimization
pump management, in MCS, 1349
Pure autonomic failure, 1193–1194
Purkinje fibers, 16
PURSUIT risk score, 877
PURSUT study, eptifibatide, 1837
Pycnogenol, for hypertension, 2039

Q

Q wave, 191
in myocardial loss, 1325
Qigong, 2032. *See also* Mind-body medicine
QRISK, 831*t*, 832
QRS complex, characterization of, 201–206
left bundle branch block,201, 202*f*
left ventricular hypertrophy, 205*f*
myocardial infarction, 203*f*
right bundle branch block, 202*f*
right ventricular hypertrophy, 204*f*
Quality adjusted life-years (QALYs), 1978, 1979, 1984
and ICD therapy cost, 1979
Quality improvement (QI) interventions
cost-effectiveness, 1982–1983
Quinidine, 581–583, 693, 723

R

5 Rs
cigarette cessation, 1880
^{82}Rb positron emission tomography (^{82}Rb PET), 386*f*, 405*t*
for blood flow quantification, 1805
for CAD, 397
R waves, 191
in myocardial loss, 1325
RA pressure waveforms, 504
RAAS system modulators, 656
Race, as heart failure risk factor, 1900
Radiation-induced heart disease (RIHD)
carotid and other vascular disease, 1509
conduction system disease. 1509
prevention, 1509
risk factors, 1510*t*
strategies, 1510*t*
radiation-induced
coronary artery disease, 1507–1508
myocardial disease, 1506–1507
pericardial disease, 1505–1506
valvular heart disease, 1508–1509
Radionucleotide scintigraphy
variant angina, diagnosis of, 942
Radionuclide ventriculography, 910

RADT (Rapid antigen tests), 1931
Raman scattering, 374
Raman spectroscopy, 374, 375
Ramipril, for stable angina and CAD, 930
Randomized Aldactone Evaluation Study (RALES) trial, 79, 80*f*, 811, 239
Randomized Assessment of the effect of Digoxin in Inhibitors of the Angiotensin-Converting Enzyme (RADIANCE), 98
Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial, 1353
Randomized Intervention Treatment of Angina (RITA) trial, 978
Randomized Intervention Treatment of Angina-2 (RITA-2) trial, 977
Ranolazine, 595
  for stable angina and CAD, 929–930
Rapid eye movement (REM) sleep
  on cardiac physiology, 2021–2022
Rasmussen Score, 831*t*
Rastelli operation, for d-TGA, 1580
Rate Control versus Electrical Cardioversion (RACE) study, 1812
Rauwolfia slkaloids, 1141
Raynaud's phenomenon
  in MCTD, 1654
  in scleroderma, 1651–1652
  in variant angina syndrome, 540
Reactive arthritis, 1651
Reactive oxygen species (ROS), 25
  in arrhythmia initiation, 565
Real time 2DTEE, 335
Real-time three-dimensional echocardiography (RT3DE), 256, 319–320, 766
  clinical applications
    left and right atria, assessment of, 330–331
    left ventricular mass, determination of, 330
    left ventricular volumes and function, determination of, 323–327
    miscellaneous conditions, 335
    myocardial contrast imaging and quantification of perfusion, 330
    percutaneous procedures, guidance of, 335–339
    regional wall motion and dyssynchrony, determination of, 327–328
    right ventricular volumes and function, assessment of, 330
    stress imaging, applications to, 328–329
    valvular disorders, assessment of, 331–335
  future directions, 339–342
  limitations, 342–345
  technique, 320–324
    commonly used pathways, 321*f*
    diagnostic value, factors, 321–323
Receiver operating characteristic (ROC), 832–833
Recurrent chest discomfort, and STEMI, 914
Red rice yeast
  for dyslipidemia, 2033–2034
Red wine (Pinot noir), 1596
RED-HF, 1267
Refractory angina, 1996
REGEN-AMI
  clinical trial, in post-MI patients, 1993
Regurgitant orifice area (ROA), 324
Rehabilitation
  post stroke survivors, 1924
Reiter's syndrome. *See* Reactive arthritis
RELAX trial
  sildenafil, 1835
Relief for acutely fluid-overload patients with decompensated congestive heart failure (RAPID-CHF) trial, 1243
REMATCH trial, 1344, 1360
Renal arterography
  hypertension, specialized studies, 1131*t*
Renal artery stenosis (RAS)
  fibromuscular dysplasia, 1158
  and hypertension, 1158
  medical management, 1158
  revascularization, 1158–1159
  screening and diagnostic tests, 1158
Renal function
  as mortality predictor, 1355
Renal impairment
  in ambulatory heart failure, 1282*t*
  in community setting, 1282*t*
  in heart failure hospitalizations, 1283*t*
Renal insufficiency, 65–66
Renal scans
  hypertension, specialized studies, 1131*t*
Renal solute handling, 53
Renin, neurohormone, 74
Renin angiotensin aldosterone system (RAAS) and GFR level, 1288
Renin inhibitors, 1140
Renin-angiotensin system inhibitors, in hypertension, 1135*t*
Renin-angiotensin-aldosterone, for left ventricular hypertrophy regression, 1905
Renin-angiotensin-aldosterone axis inhibition, 916–917
Renin-angiotensin-aldosterone system (RAAS), 75
  hyponatremia in HF, pathophysiology of, 1274, 1275
Renin-angiotensin-aldosterone system blockers (RAAS blockers), ACE inhibitors, 74
REPAIR-MI, clinical trial, using BMC post-MI, 1991, 1992*t*
Reperfusion injury salvage kinase (RISK) pathway, 29
Reperfusion, for STEMI, 902–906
  facilitated percutaneous coronary intervention (PCI), 902–906
  primary coronary intervention, 906
  thrombolysis, 902
Reperfusion, for STEMI, 902–906
Repetitive stunning hypothesis, 1324
Rescue breaths, 815
Resistance training, 1890
Respiratory syncytial virus
  cardiotropic virus, 488
Restrictive cardiac disorders, 1440*t*
Restrictive cardiomyopathy (RCM), 239, 439–440, 479–480, 1440–1442
  amyloid infiltrative cardiomyopathy, 239–240
  diabetes mellitus, 239
  diagnosis, 440
  Doppler features of, 1440
  EMB in, 491–492
  endomyocardial fibrosis, 240
  etiology, 440
  physical findings, 157*t*
"Restrictive filling pattern", in advanced HF, 1219
Restrictive VSDs, 1563
Reteplase, 902
Retrovirus
  replication, 2005*f*
  ex vivo gene therapy with, 2006
Revascularization, 885–887, 911–912. *See also* Myocardial revascularization
  for PAD, 1152
    infrainguinal revascularization, 1152–1155
    infrapopliteal occlusive disease, 1155
    suprainguinal (aortoiliac) revascularization, 1152
  mortality and morbidity in patients, 1330*t*
REVEAL Registry, 1528
Revised Cardiac Risk Index (RCRI), 1774
Reynolds Risk Score, 831*t*, 832
Rheumatoid arthritis (RA)
  and conducting system, 1650
  coronary artery disease, 1650
  endocardial and valvular involvement, 1649–1650
  myocardial involvement, 1649
  pericardial involvement, 1648–1649
Rheumatic fever (RF), 1927
  chorea, management of, 1933
  clinical features
    age and gender, 1929
    arthritis, 1929
    carditis, 1929–1930
    chorea, 1930
    erythema marginatum, 1930
    preceding Group A strep infection, 1930–1931
    subcutaneous nodules, 1930
    tests for, 1931
  diagnosis of, 1928–1929
    recurrence of, 1929
  epidemiology, 1928
  pathogenesis
    Aschoff's body, 1928
    GABHS infection, 1927
    host factors, susceptibility to, 1927–1928
    immune response, 1928
  primary prevention of, 1106*t*
  residual heart disease, 1933
  secondary prevention, 1107*t*
  treatment
    anti-inflammatory drugs, 1932
    drugs and recurrence rates, 1933

prevention, 1933
recommended bed rest, 1932
secondary prevention, 1932
secondary prophylaxis, duration of, 1932
streptococci eradication, 1931–1932
treatment algorithm, 1933
Rheumatic heart disease
aortic stenosis, cause of, 986
global burden of, 1000–1001
mitral regurgitation, 1009
Rheumatic mitral stenosis, left atrial thrombus in, 310
Rheumatic valve disease, surgical treatment of, 1025
Rheumatic valvular heart disease, 1100
Rheumatoid arthritis, 152
Rhythm disorders and reflexes associated with
bradyarrhythmias, 964
hypotension, 964
ventricular arrhythmias, 964
Rhythm management, immediate postoperative management, 1341
Right atria, assessment of, 330–331
Right atrial enlargement, 179, 207
Right atrial ischemia, deleterious impact of, 962
Right atrium (RA), 3, 8–10
pectinate muscle, 10
Right bundle branch block (RBBB), 702
due to percutaneous alcohol septal ablation
Right fibrous trigone, 8
Right heart catheterization, 472
Right heart failure
in constrictive pericarditis, 1497–1498
hypotension with, 965*t*
Right ventricle, 3, 11–12
distinct anatomical features, 12
Right ventricular endomyocardial fibrosis (RCEMF), 1444–1446
hemodynamics, 1446
Right ventricular endomyocardial fibrosis (RVEMF), 1442
Right ventricular enlargement, 178. *See also* Right ventricular hypertrophy (RVH)
Right ventricular hypertrophy (RVH)
Right ventricular hypertrophy (RVH)
in valvar pulmonic stenosis, 1558
Right ventricular infarction (RVI)
augmented right atrial contraction, compensatory role of, 962
cardiogenic shock in acute coronary syndromes, cardiac causes of, 951–952
clinical presentations, 964–965
coronary compromise, patterns of, 960–961
description of, 960
diastolic function, effects of ischemia on, 961
differential diagnosis, 965
evaluation, 964–965
hemodynamic evaluation, 965
ischemic RV dysfunction
natural history of, 962–963
reperfusion effects on, 963–964
mechanical complications associated with, 964
mechanics of, 961
noninvasive evaluation, 965
oxygen supply-demand, 961
rhythm disorders and reflexes associated with
bradyarrhythmias, 964
hypotension, 964
ventricular arrhythmias, 964
right atrial ischemia, deleterious impact of, 962
RV performance in severe RVI, determinants of
augmented right atrial contraction, compensatory role of, 962
right atrial ischemia, deleterious impact of, 962
systolic ventricular interactions, importance of, 961–962
systolic function, effects of ischemia on, 961
systolic ventricular interactions, importance of, 961–962
therapy, 965
anti-ischemic therapies, 966
inotropic stimulation, 966
mechanical assist devices, 966–967
physiologic rhythm, 966
preload, optimization of, 966
reperfusion therapy, 966
Right ventricular infarction, and STEMI, 912
Right ventricular myocardial infarction
tricuspid regurgitation in, 169
Right ventricular outflow tract, VT from, 691
Right ventricular outflow tract (RVOT) obstruction, 1557
Right ventricular predominance, diseases with, 442–443
arrhythmogenic right ventricular cardiomyopathy, 444–445
intracardiac shunt, 443
pulmonary artery hypertension, 443
Right ventricular systolic pressure (RVSP), in pulmonary stenosis, 1558
Rimonabant, 836
Ringed stent grafts, 1177
Risk, Injury, and Failure; Loss; and End-stage kidney disease (RIFLE) consensus, 1285
Ritonavir, drug interaction, in HIV patients, 1643
Rivaroxaban, 122–123
Rohypnol, 1627
Ross procedure. *See* Pulmonic valve autotransplantation
Rubella syndrome, 530
Rubidium (^{82}Rb) chloride
imaging perfusion, 397
Rumbles". *See* Mid-diastolic murmurs
RV infarct, diagnosis, 952
RV myocardial performance index, for PAH, 1531
Rytand's murmur. *See* Carey-Coombs murmur

S

2D speckle tracking echocardiography (2DSTE) in multidirectional myocardial strain, 328
S waves, 191
SADHART-HF trial, on sertraline, 1359
SAFE-T trial, 590
Salt. *See* Sodium
Saquinavir, drug interaction, in HIV patients, 1643
Sarcoidosis, 492–493
restrictive cardiomyopathy, 1452
"Sarcomeric HCM", 1378
Sarcoplasmic reticulum (SR), 24
Sarcoplasmic-calcium ATPase (SERCA2a) in hibernating myocardium, 1324
Saturated fatty acids, and CHD, 834
Saver" procedure, left ventricular volume reduction surgery, 1245
SCD-HeFT, ICD primary prevention trial, 1839
Scleroderma, 1651–1652
abnormal coronary perfusion, 1652–1653
conduction disturbance, 1653
myocardial disease, 1652
pericarditis, 1652
pulmonary hypertension, 1653
restrictive cardiomyopathy, 1452
SCORE, 831*t*, 832
Seattle heart failure model (SHFM), 1336
Seattle Heart Failure Score (SHFS), as mortality predictor, 1355
Second heart sound
clinical conditions of, 163*t*
Secondary amyloidosis, 1459. *See also* Amyloid A (AA) amyloidosis
Secondary autonomic failure, 1194–1195
Second-hand smoke (SHS) exposures, cardiovascular disease, 1874, 1875–1876
Selective angiography, tricuspid valve disease, 1023
SELECT-MI randomized trial, for epicardial coronary circulation, 1993
Self-initiated transtelephonic ECG monitoring, variant angina, diagnosis of, 941
Senile systemic amyloidosis (SSA), 1458
"Senile" cardiac amyloidosis (SCA), 1831
SENIORS trial, 1239
nebivolol, 1835
Sensitivity analysis, 1984
Septal bounce, in constrictive pericarditis, 1499*f*
Septal myectomy
for HCM, 1407–1408, 1409*f*
and percutaneous alcohol septal ablation, 1412*t*
Septic shock, 504
Serotonin receptor inhibitors (SSRIs)
for depression, in HF patients, 1359
Serous pericardium, 1489
Serum brain-type natriuretic peptide (BNP)
in AL amyloidosis, 1463
Serum glutamic oxaloacetic transaminase (SGOT), in cardiac injury, 1736
Serum uric acid, in hypertension, 1132
Severe pulmonary hypertension, during pregnancy, 1572
SHock Inhibition Evaluation with azimiLiDe (SHIELD) trial, 593
SHOCK trial, 950, 951, 957, 958
mechanical reperfusion therapies, 1807
Shone's syndrome, 1552
Short QT syndrome, 805
Shy-Drager syndrome, and physical examination, 151

Sicilian Gambit" scheme, 579, 581*f*
Sildenafil (Revatio), 81
in diastolic heart failure, 1260*t*
drug interaction, in HIV patients, 1643
for PAH, 1540
Sildenafil citrate (Revatio®), 81
Sildenafil Trial of Exercise Performance in Idiopathic Pulmonary Fibrosis (STEP-IPF) trial, 1523
Silent ischemia, after exercise testing, 220
Simple 'monogenic' disorders, 1937
Simvastatin, for stable angina and CAD, 931
Simvastatin therapy, atherosclerotic plaque inflammation, 457*f*
Singapore, incidence of heart failure in, 1210
Single nucleotide polymorphisms (SNPs), 1939*f*
Single photon emission computed tomography (SPECT), 256, 326, 381, 860–861
for coronary spasm, 942
Sinoatrial (SA) node, 16
histology of, 16*f*
Sinoatrial conduction time (SACT), 615
Sinoatrial node (SAN) action potentials, 572
Sinoatrial re-entry tachycardia, 669
Sinus bradycardia
in athletes, 1821
with junctional escape rhythm
in electrocardiograph, 198*f*
Sinus node recovery time (SNRT), 615, 636
Sinus rhythm
maintenance
invasive approaches, 656–657
pharmacological approaches, 655–656
restoration, 654–655
Sinus tachycardia, 666–667
due to cocaine usage, 1617
Sinus venarum cavarum, 10
Sinus venosus defect, 1559
Sirolimus-eluting stents, 361
Six-minute walk test, 1224
Skeletal myoblast cells, 1994–1996
Skin abnormalities. *See also* Skin discoloration
of cardiovascular disorders, 153*f*
Skin discoloration
argyria, 152
carcinoid heart disease, 152
cyanosis, 151–152
hemochromatosis, 152
jaundice, 152
Skin pigmentation, in hemochromatosis, 1450
Sleep and heart
arousal, 2021
arrhythmias and sleep
atrial fibrillation, 2022
bradyarrhythmias, 2021
Brugada syndrome, 2022
heart rate variability, 2021
nocturnal QT interval changes, 2021–2022
sudden infant death syndrome, 2022
unexplained nocturnal death syndrome, 2022
ventricular arrhythmias, 2022
cardiovascular physiology, effects of
non-rapid eye movement sleep, 2020
obstructive sleep apnea
rapid eye movement sleep, 2021
central sleep apnea, 2028
heart failure, 2028
treatment of central sleep apnea, 2028
diagnosis of sleep apnea, 2026
overnight oximetry, 2026
polysomnography, 2026–2027
screening questionnaires, 2026
physiologic sleep, 2020
sleep disordered breathing, 2022
obstructive sleep apnea, 2022–2026
treatment of obstructive sleep apnea
continuous positive airway pressure, 2027–2028
obesity and sleeping position, 2027
oral appliances and surgery, 2028
Sleep disordered breathing (SDB), 147, 1763, 2022
in HCM, 1413
obstructive sleep apnea, 2022–2024
effects on cardiovascular physiology, 2024–2026
"Smart heart hypothesis", 1324
Smoking
and CHD, 833
and CKD, 1699
Smoking and air pollution
active smoking and cardiovascular disease, 1874–1875
cardiologists role, 1884
epidemiology of, 1874
low-tar cigarettes, 1876
particulate air pollution, 1883–1884
pathophysiology of, 1876
arterial stiffness, 1878
atherosclerosis, 1876–1877
autonomic effects and heart rate variability, 1879
dyslipidemia, 1878
endothelial dysfunction, 1877
impaired oxygen transport, 1879
inflammation, 1878–1879
oxidative stress, 1879
platelet activation and thrombosis, 1878
second-hand smoke and cardiovascular disease, 1875–1876
smoke-free environments, 1883
smoking cessation, 918–919, 1879–1880
benefits of, 1873–1874
nicotine withdrawal, 1880
pharmacotherapy, 1880–1883
Smooth muscle vasodilators, 1142
Snti-digoxin Fab-fragment immunotherapy, 100
Social factors, and CAD, 2041
Society for the Recovery of Drowned Persons, 788
Society of Thoracic Surgeons (STS) Database, 1072
Sodium
and CHD, 834
and hypertension, 1134
reabsorption, 53
retention, in CRS, 1286
Sodium-calcium exchanger
in hibernating myocardium, 1324
Solid-state dynamic aperture system, and mechanically rotating single-transducer system, 350*t*
Solute carrier organic anion transporter family, member *1B1* gene (*SLCO1B1*), 1955
Sondergaard's groove, 8
in mitral valve assessment, 7
Sorin group stentless valves, 1078
Sotalol, 586–587, 655, 656, 681, 688, 690, 691
Southeast Asians, incidence of heart failure in, 1210
Special population treatment, recommendations, 1372–1373
Speckled tracking, 765
SPECTroscopic Assessment of Coronary Lipid (SPECTACL) study, 376
Spectroscopy, for coronary applications, 374–375
clinical experience, 376
experimental data, 375
future directions, 376
imaging systems and procedures, 375
safety and limitations, 376
Sphingosine 1-phosphate (S1P), 29
Spike and dome arterial pulse
Spironolactone, 54, 55, 58*t*, 61, 62, 64, 66, 67. *See also* Potassium-sparing agents
in CHF and renal dysfunction, 1289
in hyperkalemia, 1137–1138
in left ventricular remodeling, 1240
survival curves for, 80*f*
Spondyloarthropathies, 1651
ankylosing spondylitis, 1651
reactive arthritis, 1651
scleroderma, 1651–1653
Sprituality, and CHD, 2041
SQT syndrome, 722–723
clinical manifestations, 723
diagnosis, 723
molecular genetics, 723
pathogenesis, 723
therapy, 723–724
SR calcium ATPase (SERCA-2), 24
ST segment elevation, during angina, 940*f*
ST segment elevation myocardial infarction (STEMI), 85, 145, 517
St. Vitus dance. *See* Chorea
Stable angina, 145*t*, 875
and CAD, patients with, 927–935
antianginal drug therapy, 928–930, 931–932
combination therapy, 930
current therapeutic approaches for, 927–928
myocardial revascularization for, 931–932
percutaneous revascularization vs medical therapy, 933–934, 934*f*
clinical features of, 145*f*
Stable coronary artery disease, 1808
coronary angiography and revascularization, 1809
medical therapy and risk factor management, 1808–1809

beta-blockers, 1809
calcium antagonists, 1809
lipid-lowering drugs, 1808
nitrates, 1809
treatment strategies, 1808
Stage A heart failure, 1900
age, 1900
cardiotoxin, exposure to, 1902
coronary artery disease, 1901
diabetes mellitus, 1901
dyslipidemia, 1901
family history, 1900
gender, 1900
hypertension, 1900–1901
metabolic syndrome, 1901
obesity, 1901
race, 1900
treatment for, 1902
Stage A high risk patients
recommendations, 1367–1368
Stage B cardiac structural abnormality patients
no HF symptoms, 1368
Stage B heart failure, 1902
asymptomatic left ventricular systolic dysfunction, 1902–1903
cardiac imaging for screening, 1904
cost-effect screening for, 1904
electrocardiogram and biomarker evaluation, 1903–1904
treatment for, 1904–1905
Stage C patients
with HF symptoms, 1368–1371
STAMINA-HeFT, 1267
Stanford classification
of aortic dissection, 1168
Staphylococcal endocarditis, 1063
Statin therapy, 840. *See also* Lipid lowering therapy
in heart failure prevention, 1905*f*
in perioperative cardiac events, 1781
Statins, 104, 105. *See also* HMG-CoA (3-hydroxy-3-methylglutaryl-coenzyme A) reductase inhibitors
add-on to statin therapy, 110–111
cardiovascular pharmacogenomics, 1945–1946
drug interactions, 106–108, 109*t*
efficacy, 105
lipid level change, 107*t*
liver safety, 110
muscle safety, 105–106
muscle symptom management, 108*f*, 110
musculoskeletal side effects, 1955
clinical implications, 1955–1956
CYP450 drug metabolizing enzymes, 1955
SLCO1B1, 1955
pharmacokinetics, 109*t*
renal excretion, 108
therapy, compliance with, 1955
ST-elevation myocardial Infarction (STEMI), 892
Stellate ganglion, 21
Stem cell clinical trials, 1991
Stem cell therapy and cardiology
adipose tissue derived stem cells, 1989
cardiac stem cells, 1989
fetal and umbilical cord blood cells, 1989–1991
induced pluripotent stem cells, 1991
skeletal myoblast, 1989
stem cell clinical trials
acute myocardial infarction, 1991–1994
chronic coronary artery disease and chronic heart failure, 1994–1996
pulmonary hypertension, 1996
refractory angina, 1996
routes and methods of cell delivery, 1996–1997
stem cells, 1986
adult stem cells, 1987
bone marrow derived stem cells, 1987–1989
embryonic stem cells, 1986–1987
Stem cell transplantation (SCT)
in AL amyloidosis, 1464
STEMI. *See also* Acute coronary syndrome (ACS)
clinical presentation, 894–902
emergency room evaluation, 894–902
prehospital assessment, 894
with cocaine use, 915
complication
dysrhythmias, 913–914
heart failure, 912–913
recurrent chest discomfort, 914
right ventricular infarction, 912
continued medical therapy for patients with a myocardial infarction, 916–919
glucose management, 917–918
lipid management, 917
renin-angiotensin-aldosterone axis inhibition, 916–917
smoking cessation, 918–919
in diabetic population, 914–915
discharge, 919–922
MI, rehabilitation and prevention, 919–921
nitrates, 919
predischarge education, 921–922
early medical therapy, 906–909
anticoagulation, 908–909
antiplatelet agents, 908
beta blockers, 909
general measures, 906
morphine, 907–908
nitrates, 906–907
in elderly, 916
pathophysiology of, 893–894
cocaine-associated, 893–894
methamphetamine-associated, 893–894
stent thrombosis, 893
post myocardial infarction care, 909–912
coronary angiography, 911–912
left ventricular ejection fraction assessment, 909–910
revascularization, 911–912
stress testing prior to discharge, 910–911
post myocardial infarction depression, 915–916
reperfusion, 902–906
facilitated percutaneous coronary intervention (PCI), 902–906
primary coronary intervention, 906
thrombolysis, 902
survivors of out of hospital cardiac arrest, 916
in women, 916
Stent deployment techniques on clinical outcomes of patients treated with the cypher stent (STLLR) trial, 361
Stent deployment, 551
Stent graft design, 1176–1177
for abdominal aortic aneurysm, 1177
Stent or Surgery (SoS) trial, 979
Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial, 1156
Stent-Protected Angioplasty versus Carotid Endarterectomy (SPACE), 1157
Stents, types of, 551
Steroids
and sport performance supplement, 1824
Stevia (*Stevia rebaudiana*), for hypertension, 2040
STICH trial, 1329
Still's disease, 1648. *See also* Systemic juvenile inflammatory arthritis
Stokes-Adams-Morgagni syndrome, 148
"Stop-action" heart imaging, 408
Storage diseases, and myopathy, 495
Strain rate imaging, 765
Strategies for management of antiretroviral therapy (SMART) study, 1636
Strength training, 1819. *See also* Isometric exercise
Streptococcal endocarditis, 1063
Streptokinase, 902
Streptozyme test, 1931
Stress, and CAD, 2041
Stress cardiomyopathy, 1693–1694
clinical features, 1694
arrhythmias, 1694
cardiac biomarkers, 1694
ECG abnormalities, 1694
left ventricular dysfunction, 1694
diagnosis, 1695
due to dobutamine, 95
pathophysiology, 1694–1695
prognosis, 1695
treatment, 1695
Stress echocardiography (SE electrocardiogram, 291
and coronary artery disease
diagnosis of, 292–299
estimating risk or prognosis in, 299–304
endpoints for, 295*t*
future of, 305
and hemodynamics of valvular disease, assessment of, 304–305
and myocardial viability, 304
pathophysiology involved in, 291–292
Stress imaging, applications to, 328–329
Stress myocardial perfusion imaging, 860–861
Stress testing
CAD, detection of, 293*t*

contraindications to, 293*t*
with echocardiogram imaging, 861–862
in HCM, 1400
mechanism of, 383*t*
mitral stenosis, 1004
with myocardial imaging, 860
prior to discharge, 910–911
Stress-induced cardiomyopathy, 1429
Stroke
and SDB, 2026
and tobacco smoking, 1873
Stroke, prevention and treatment
definitions, 1908–1909
general acute treatment, 1919–1920
general in-hospital care, 1924–1925
prevention, 1916–1919
rehabilitation, 1925
as symptom 1909–1911
clinical presentations, 1912–1913
diagnostic evaluation, 1914–1916
differential diagnosis, 1913–1914
epidemiology and highest risk groups, 1911–1912
subtypes and causes, 1909*t*
treatment
acute ischemic stroke, 1920–1922
of acute hemorrhagic stroke, 1922–1923
Stroke Prevention using an Oral Thrombin Inhibitor (SPORTIF) trial, 1812
Stroke volume
exercise testing, central factor for, 216
Stromal cell-derived factor-1 (SDF-1), 2011
Structural valve assessment, 313–316
Structural valve deterioration, 1092–1095
ST-segment analysis, after exercise testing, 220
ST-segment elevation, during exercise, 218
ST-segment elevation myocardial infarction (STEMI), and cardiogenic shock, 949
ST-T wave abnormalities, 206
Studies of Left Ventricular Dysfunction (SOLVD), 1209, 1289
on neuroendocrine activation, 1275
Subaortic stenosis, and BAVs, 1552
Subarachnoid hemorrhage (SAH), 1908, 1909–1910
differential diagnosis of, 1913*t*
meningeal irritation, 1913
Subclavian artery stenosis (SAS), 1159–1160
Sub-clinical atherosclerosis, and CHD, 839–840
Subendocardial plexus, 34
Subvalvar aortic stenosis, 1554
Subvalvar pulmonic stenosis, 1559
Sudden cardiac death (SCD), 432, 804–808
arrhythmogenic right ventricular cardiomyopathy (ARVC), 806
Brugada syndrome, 805
catecholamine polymorphic VT, 805
congenital heart disease (CHD), 806–807
coronary artery disease (CAD), 807–808
definition, 804
early repolarization, 805
hypertrophic cardiomyopathy (HCM), 806
in healthy athletes, 804–805
long QT interval syndrome, 805
Marfan syndrome, 806
noncompaction, 806
non-ischemic cardiomyopathy (NICM), 807
short QT syndrome, 805
and tobacco smoking, 1873
Wolff-Parkinson-White (WPW) syndrome, 805–806
Sudden Cardiac Death Heart Failure Trial (SCD-HeFT), 597
Sudden death (SD)
arrythmogenic substrate and, 1386
due to diabetes mellitus, 1715–1716
during exercise, 219
due to HCM, prevention, 1403–1404
ICD therapy, 1404
preparticipation screening, 1824
cardiovascular conditions, 1825*t*
Sudden infant death syndrome (SIDS), 2022
Sulfadiazine, for RF, 1933*t*
Sunitinib (Sutent)
in inducing cardiotoxicity, 1483
in left ventricular dysfunction, 1480*t*
SUPER-1 trial (Sildenafil Use in Pulmonary Arterial Hypertension), 1540
Supplemental oxygen, 906
Supravalvar aortic stenosis, 1554
Supravalvar pulmonic stenosis, 1559
Supravalvar stenosis
clinical course, 1035
clinical findings
history, 1035
physical examination, 1035
laboratory investigations
cardiac catheterization, 1036
chest roentgenogram, 1035
echocardiography, 1035–1036
electrocardiogram, 1035
natural history, 1035
pathological anatomy, 1035
pathophysiology, 1035
treatment of
Alagille syndrome, 1036
Williams-Beuren syndrome, 1036
Supravalvular aortic stenosis, 530
Supraventricular tachycardia (SVT), 650, 665, 799
cardiac-surgical ablation, 729
catheter ablation, 729
classification, 665–666
atrial-based AV nodal independent SVT, 666–670
AV nodal dependent SVT, 670–674
clinical electrophysiologic studies history, 729
diagnosis, 674, 677
electrocardiograpahic recordings, 677–678
electrophysiology studies, 678
treatments
acute care, 678–681
long-term management, 681–682
Surgical Care Improvement Project (SCIP), 973
Surgical treatment for ischemic heart failure (STICH) study, 434
Survival With Oral d-Sotalol (SWORD) trial, 587
Survivor activating factor enhancement (SAFE) pathway, 29
Suspected heart failure syndromes1303*f*
Swan, H.J.C., 504
Swan-Ganz catheters
abnormal pressures and waveforms, 506–507
clinical applications
acute coronary syndromes, 508–509
cardiac catheterization laboratory, 507–508
chronic heart failure, 510
non-acute coronary syndromes, 509–510
pulmonary hypertension, 510–512
complications, 512
guidelines, 513–514
indications for use of, 512*t*
normal pressures and waveforms, 504–506
pulmonary artery catheterization, indications for, 512
Swedish Doppler-echocardiographic study (SWEDIC), 1259
Swiss cheese model, for systems thinking, 1970
Sydenham's chorea. *See* Chorea
Sympathetic nervous system (SNS), 76
hyponatremia in HF, pathophysiology of, 1274
Symptomatic systolic heart failure
non-pharmacologic treatments, 1244–1245
pharmacologic treatments, 1237–1244
Syncope, 148–149, 627
aortic stenosis, symptoms, 988
in athletes, 1823–1824
diagnostic tests, 629
blood tests, 630
cardiac catheterization, 638
continuous ECG monitoring, 632, 634
echocardiography, 631
electrocardiogram, 631
electrophysiology study, 636–638
exercise testing, 632
history and physical examination, 629–630
neurologic tests, 638
signal averaged ECG, 634
upright tilt table testing, 634–636
and driving, 642
epidemiology
causes and classification, 628–629
economic burden, 628
incidence and prevalence, 628
evaluation approach, 638–639
guidelines, 642–644
specific patient groups, 639
congenital heart disease, 641
elderly patients, 641
hypertropic cardiomyopathy, 640
nonischemic cardiomyopathy, 640–641
vasovagal (neurocardiogenic) syncope, 639–640
SYNTAX trial, 979
Systemic amyloidosis (SSA), 1455
Systemic and pulmonary venous congestion in diastolic heart failure, 1258
Systemic autoimmune diseases
antiphospholipid antibody syndrome, 1656
Churg-Strauss vasculitis, 1657–1658

coronary arteritis, 1656
giant cell arteritis, 1658
Kawasaki disease, 1657
mixed connective tissue disease, 1654
polyarteritis nodosa, 1656–1657
polymyositis-dermatomyositis, 1653
clinical features, 1653
treatment, 1653–1654
rheumatoid arthritis, 1648
coronary artery disease, 1650
disease of the conducting system, 1650
endocardial and valvular involvement, 1649–1650
myocardial involvement, 1649
pericardial involvement, 1648–1649
spondyloarthropathies, 1651
ankylosing spondylitis, 1651
reactive arthritis, 1651
scleroderma, 1651–1653
systemic lupus erythematosus, 1654
coronary artery disease, 1655–1656
electrophysiological disturbance, 1655
endocarditis, 1655
myocarditis, 1655
pericarditis, 1654–1655
Takayasu's arteritis, 1658
Wegener's granulomatosis, 1658
Systemic inflammatory response syndrome (SIRS)
in acute coronary syndromes, 949
Systemic juvenile inflammatory arthritis, 1648
Systemic lupus erythematosus (SLE), 1654
coronary artery disease, 1655–1656
electrophysiological disturbance, 1655
endocarditis, 1655
myocarditis, 1655
pericarditis, 1654–1655
with PAH (SLE-PAH), 1527
Systemic sclerosis, 1651–1653. *See also* Scleroderma
Raynaud's phenomenon, 1651–1652
Systemic vascular resistance (SVR)
calculation, 71
Systolic "whoop", 164
Systolic anterior motion (SAM)
in LVOT obstruction, 1382
of mitral valve
in HCM, 1393–1394
Systolic blood pressure
in hyponatremia, 1272
Systolic dysfunction
detection of, 1606
visual qualitative indicators of, 240
left ventricular mass, 240–242
Systolic function
ejection fraction, components of
end systolic volume, 232–233
LVESV physiologic basis of, 233–234
left ventricular ejection fraction, 229–231
linear measurements in the assessment, 231–232
RV, ischemia on, 961
Systolic heart failure (SHF), 44, 1207, 1228. *See also* Heart failure with reduced ejection fraction (HFREF)
converting enzyme inhibitor, 46
coronary circulation in, 44
follow-up evaluation, 1245–1246
functional derangements and hemodynamic consequences, 1235
historical perspective, 1228
definitions, 1229
risk factors, 1229
initial treatment of, 1235–1237
myocardial metabolic function, 45
myocardial oxygen consumption, 46*f*
myocardial oxygen demand, 45
myocardial structure and function in, 1253*t*
symptomatic failure, 1237–1245
therapies, 46*t*
ventricular remodeling, 1229–1235
versus diastolic heart failure, 1252*t*, 1252–1253
morbidity and mortality in, 1258*t*
prognosis in, 1257*t*
symptoms and signs of, 1256*t*
Systolic Hypertension in the Elderly Program (SHEP), 1836
Systolic time ratio (STR), 174
Systolic ventricular interactions, importance of, 961–962

T

T cell activation, in HIV patients, 1638
T wave, 191
T2-star" (T2*) technique, in hemochromatosis, 1450
Tachyarrhythmias, 147
in athletes, 1823
Tachycardia-induced cardiomyopathy, 1428–1429
Tachycardias, 799
classification of, 799*t*
due to cocaine usage, 1616
and mild hypertension, 1129
Tadalafil (Adcirca®), 81
for PAH, 1540
Tai-chi, 2037*f*
Takayasu's arteritis, 1658
Takotsubo cardiomyopathy. *See* Stress cardiomyopathy
TandemHeart
cardiogenic shock, mechanical support in, 956
for MCS, in HF, 1341
Tansient ischemic attack (TIA), 1908–1909
clinical features of, 1913*t*
differential diagnosis of, 1914*t*
Tedisamil, 594
Tei index. *See* RV myocardial performance index, for PAH
Telemedicine interventional monitoring in heart failure (TIM-HF) trial, 1245
Temporal arteritis, 1658
Temporal resolution, 409
Tenecteplase (TNK-tPA), 902
Tetrahydriocannabinol, 1624–1625
Tetralogy of Fallot (TOF)
associated anomalies, 1572–1573
clinical findings, 1573
diagnostic studies, 1573–1575
general considerations, 1572
guidelines, 1576–1577
pathophysiology, 1572
pregnancy, 1576
prognosis, 1575–1576
treatment, 1575
Thallium-201 myocardial perfusion imaging, for hibernation myocardial diagnosis, 1425
Thebesian veins, 19
Therapeutic mild hypothermia, 822–823
Thiazide diuretics, 54, 55*t*, 57, 58*t*, 60
diuretic agent in HF, 1288
hemodynamic responses to, 61*f*
in hyponatremia, 1276–1277
Thiazide-like diuretics, 54, 55*t*,
Thiazides, in hyperuricemia, 1137
Thienopyridines, 908, 909, 1956
clinical implications, 1958
laboratory response to
ABCB1, 1957
CYP2C19, 1956–1957
clinical response to
CYP2C19, 1957
P2RY12, 1957
ABCB1, 1958
Thin-cap fibroatheroma (TCFA), 356
Third (S3) heart sounds, 163–164
artificial valve sounds, 166–167
early diastolic high-frequency sounds, 165–166
ejection sounds, 164–165
midsystolic click, 165
pericardial knock, 164
Third Report of NCEP Adult Treatment Panel, 831*t*
Thoracic aortic aneurysms and dissections (TAAD), 1167
Thoracic aortic dissection, 1181–1182
Thoracic endovascular aortic repair (TEVAR)
complications of, 1184
endoleak, 1184
failed insertion, 1184–1185
neurological complications, 1184
Thoracic valves, types of, 1073
bioprosthetic valves, 1075
stented porcine valves, 1075–1076
stented bovine pericardial, 1076
stentless, 1076–1078
homograft, 1078–1079
mechanical valves, 1073
bileaflet tilting-disk design, 1074–1075
single tilting-disk design, 1073–1074
Starr-Edwards caged-ball valve, 1073
pulmonic valve autotransplantation, 1079
Thoracic veins, 6*f*
Thoracoabdominal injury, 1731–1732
Thoratec HeartMate II trial, 1344
ventricular assist device, 1810
Three-dimensional echocardiography (3DE), 319
common artifacts, 323*f*
protocol of, 324*t*
Three-dimensional wall motion tracking (3DWMT), 326*f*

Thrombin, 873
Thrombin receptor antagonists (TRA), 132
Thrombin time (TT), 127
Thrombolysis in Myocardial Infarction (TIMI) risk score, 877
Thrombolysis in Myocardial Infarction (TIMI) study group, 541
Thrombolysis in Myocardial Ischemia (TIMI)-IIIB clinical trial, 977–978
Thrombolysis, 902, 904–905
  alteplase, 902, 903*t*
  reteplase, 902, 903*t*
  streptokinase, 902, 903*t*
  tenecteplase (TNK-tPA), 902, 903*t*
Thrombolytics
  for cocaine abuse treatment, 1619–1620
Thrombopoietin, 2011
Thrombosis management
  in VAD implantation, 1349
Thrombosis, 461–462
  fibrin-rich thrombi, clinical imaging of, 462–464
  preclinical thrombus imaging strategies, 464
Thrombotic valve complications
  diagnosis of, 1101–1102
Thromboxane A2 (TXA2), 119, 1753
Thrombus formation, propensity for, 312–313
Thyroid disease, 1716
  amiodarone-induced thyroid disease, 1717–1718
  hyperthyroidism, 1716–1717
  hypothyroidism, 1717
Thyroid hormone replacement
  in myocardial contractility, 100
Ticagrelor, 545, 882
  in stroke prevention, 1918
Ticlopidine, 545, 1957
  $P2Y_{12}$ inhibitor, 130
  in stroke prevention, 1918
Time in therapeutic range (TTR), 121, 127
Tinzaparin (Innohep®), 1761
Tirofiban, 133, 882
  in dialysis patients, 1701
Tissue Doppler imaging (TDI), 328, 764
Tissue factor (TF), 116
Tissue inhibitors of metalloproteinases (TIMPs), 27, 1253
Tissue synchronization imaging, 764–765
Titin, in diastolic heart failure, 1253
Tobacco cessation, in cardiac rehabilitation, 920
Tobacco dependence, 5As for intervention, 833*t*
Tobacco smoking. *See* smoking
Tobacco, 1631
Tocopherols, in dyslipidemia, 1863
Toll-like receptors (TLRs), and atherosclerosis, 1850
Tolvaptan, to treat euvolemic hyponatremia, 1277
TOPCAT trial, spironolactone, 1835
Toronto Stentless Porcine valve, 1077
Torsades de pointes, in electrocardiograph, 199*f*
Torsemide, 54, 58*t*, 59, 65, 67
  for CRS, 1288
  to relieve congestive symptoms, 1242
Total anomalous pulmonary venous return (TAPVR), 1583–1584
Total artificial hearts, in HF, 1360
Trabeculae carneae, 11
Transcendental meditation (TM), 2038
Transcutaneous energy transfer system (TETS), 1350
Transduction, 2004. *See also* Viral transduction
Transesophageal echocardiography (TEE)
  in AAD diagnosis, 1170
  acute aortic dissection, 316
  atrial fibrillation, 313
  in coarctation, localization, 1556
  endocarditis, 313
  guidelines, 309
  history, 309
  major clinical applications
    embolism, sources of, 310
    masses, 310–311
    paradoxic embolization, passageways for, 311–312
    thrombus formation, propensity for, 312–313
  performance, 309–310
  procedural adjunct or intraoperative TEE, 316–317
  safety, 310
  in septal myectomy, 1408
  structural valve assessment, 313–316
  tricuspid valve disease, 1023
  views, 310
Transesophageal three-dimensional echocardiography (3D TEE), 319
Trans-fatty acids, 834
Transforming growth factor-beta (TGF-beta)
  in myocardial fibrosis, 1261
Transient ischemic dilation (TID), 391, 392
Transplant vasculopathy, pathogenesis of, 1342*f*
Transthoracic echocardiography (TTE), 265, 309
  in AAD diagnosis, 1170
  appropriate indications for, 266*t*
  cardiac resynchronization therapy, 289
  chamber quantitation, 265–269
  contrast echocardiography, 286–288
  diastolic function, 270–272
  Doppler echo, 269–270
  infective endocarditis, 285
  intracardiac masses, 285–286
  pericardial disease, 273–274
  pulmonary hypertension, 272–273
  valvular heart disease
    aortic regurgitation, 279
    aortic stenosis, 274–279
    mitral regurgitation, 281–282
    mitral stenosis, 279–281
    pulmonic regurgitation, 285
    pulmonic stenosis, 284–285
    tricuspid regurgitation, 284
    tricuspid stenosis, 283
Transthyretin (TTR), 1458
Transthyretin-related (TTR) amyloid molecules SCA, 1831–1832
  in HFPEF, 1835
Trastuzumab (Herceptin), in left ventricular dysfunction, 1480*t*
Traumatic ruptured chordate, tricuspid regurgitation in, 169
Traumatic tricuspid regurgitation, 1026
Treadmill exercise, 212
Treadmill exercise stress testing (ETT), 860
Treadmill exercise testing, in variant angina diagnosis, 942
Treat Angina with aggrastat and determine Cost of Therapy with an Invasive or Conservative Strategy—Thrombolysis In Myocardial Infarction (TACTICS-TIMI), 210
Treatment of Hyponatremia Based on Lixivaptan in NYHA Class III/IV Cardiac Patient Evaluation (BALANCE) trial, 1279
  in phase 3 clinical trials, 1278–1279
Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT), 1260
Treprostinil (Remodulin®), for PAH, 1539
Treprostinil (Tyvaso™), for PAH, 1538
Triamterene, 54, 55, 58*t*, 62, 64
  in CHF and renal dysfunction, 1289
  in hypertension, 1138
Tricuspid annular plane systolic excursion (TAPSE), 1531
  for PAH, 1531
Tricuspid atresia/univentricular heart, 1586
  bilateral Glenn, 1586–1587
  classification, 1586
Tricuspid insufficiency, plain film imaging, 187
Tricuspid regurgitation (TR), 1739
  in heart failure, 1214–1215
  interventions in, 1121
  intraoperative assessment, 1123
  in pulmonary stenosis, 1558
  severity, classification, 284*t*
  tricuspid valve surgery, 1123
Tricuspid valve, 3, 10–11
Tricuspid valve disease
  in adolescents or young adults, 1120
  anatomy of, 1019
    annulus, 1019
    chordae tendineae, 1019
    leaflets, 1019
    papillary muscles, 1019
  assessment of, 334
  clinical presentation
    physical signs, 1021
    symptoms, 1021
  description, 1018
  dysfunction, 1019
  embryology, 1018
  etiology of
    primary tricuspid valve disease, 1019–1020
    secondary or functional tricuspid valve disease, 1020
  laboratory diagnosis
    cardiac catheterization, 1023
    chest radiograph, 1021
    echocardiography, 1021–1023
    electrocardiogram, 1021
    selective angiography, 1023
    transesophageal echocardiography, 1023
  normal tricuspid valve function, 1019

percutaneous tricuspid balloon valvuloplasty, 1045
regurgitation of, 1024–1025
replacement, 1025
stenosis of, 1024
treatment of, 1023
appropriate timing, 1023–1024
management strategies, 1024–1025
medical treatment, 1024
for primary tricuspid valve regurgitation, 1025–1026
surgical treatment, 1024–1025
Tricuspid valve regurgitation, 1024–1025
primary tricuspid valve regurgitation, surgical treatment of
carcinoid heart disease, 1026
cleft tricuspid valve, 1026
Ebstein's anomaly, 1025–1026
infective endocarditis, 1026
rheumatic valve disease, 1025
traumatic tricuspid regurgitation, 1026
Tricuspid valve stenosis, 1024
Tricyclic antidepressants (TCAs)
for pain, in HF, 1358
Triggered arrhythmias
and afterdepolarizations, 574–575
Triglyceride-lowering therapy, 113
Trimetazidine, 1244
FFA, beta-oxidation, 1609
"Tripartite" signature, of RVI, 961
Triple-H therapy" (HHH—hypertension, hypervolemia and hemodilution), 1692
TRITON TIMI-38, 1944
TRIUMPH-1 trial (*TReprostinil* sodium inhalation Used in the Management of Pulmonary Hypertension-1), 1539
Tropical endomyocardial fibrosis, 1442
clinical features, 1444
definition, 1442–1443
epidemiology, 1443
natural history, 1443–1444
Troponin I (TnI), 858. *See also* Cardiac troponin I
in chronic heart failure, 1222, 1223
Troponin T (TnT), 858. *See also* Cardiac troponin I
in chronic heart failure, 1222, 1223
Troponin, 875, 876–877
myocardial ischemia, 1286
Truncus arteriosus (TA)
classification, 1577–1578
clinical findings, 1578
diagnostic studies, 1578
general considerations, 1577
genetic inheritance, 1578
pregnancy, 1578
treatment and prognosis, 1578
Trypanosoma cruzi
Chagas disease, 1513
life cycle of, 1514*f*
Tui Na, 2032. *See also* Acupressure-based massage
Tumor necrosis factor alpha (TNF-α)
in hibernating myocardium, 1324
in LDL binding, 1849
in rheumatoid arthritis, 1650
Turner's syndrome, 152
Two-dimensional echocardiography (2DE), 319
TxA2 pathway, aspirin as inhibitor, 128*f*
Type 1 CRS (acute CRS), 1285
Type 2 CRS (chronic CRS), 1285
Type 2 diabetes, 1831
Type 3 CRS (acute renocardiac syndrome), 1285–1286
Type 4 CRS (chronic renocardiac syndrome), 1286
Type 5 CRS (secondary CRS), 1286
Type A acute aortic dissection, 1172
Type B acute aortic dissection, 1172

U

U wave, 191, 206–207
acute pericarditis, 207*f*
Ubiquinone, 2039
Uhl's syndrome, tricuspid regurgitation in, 169
UK-HEART, hyponatremia in HF, 1274
Ultrafast CT, 408
Ultrasmall superparamagnetic iron oxide (USPIO) nanoparticle enhanced MRI for atherosclerosis detection, 453
Ultrasmall superparamagnetic iron oxide (USPIO), 453
Ultrasound contrast agents, reuse, warning, 295
Unfractionated heparin (UFH), 119, 883, 1760–1761. *See also* Antithrombotic agents; Heparins
Unibody stent grafts, 1177
Unifit stent graft, 1177
Uni-iliac stent grafts, 1177
United Kingdom, incidence of heart failure in, 1210
United Network of Organ Sharing (UNOS), 1335
United States of America
Chagas disease in, 1517
heart failure
epidemiology of, 1207*t*
prevalence of, 1207*t*
Medical Coverage Advisory Commission (MCAC), 1980
University of Iowa, CABG, 970
UNLOAD study, 1243
Unrecognized myocardial infarction, 433–434
Unstable angina (UA) and non-ST-elevation myocardial infarction (NSTEMI), 871, 872, 874, 876, 877, 879, 880, 884, 892–893
Upright tilt table testing, 634–636
Urine toxicology screen, for STEMI, 901
Utility, 1984

V

VA treadmill score, 221*t*
Vagally mediated atrial fibrillation". *See* Atrial fibrillation
Valproate, for chorea, 1933
Valsalva aneurysm, 3
Valsalva cusp VT, aortic sinus of, 691
Valsartan heart failure trial (Val-Heft), 1238
Value, 1984
Valvar pulmonic stenosis
anatomy of, 1028–1029
associated anomalies, 1558
clinical course, 1029–1030
clinical findings, 1558
history, 1030
physical examination, 1030–1031
diagnostic studies, 1558–1559
differential diagnosis, 1032
endocarditis prophylaxis, 1559
exercise, effects of, 1029
general considerations, 1557
genetic inheritance, 1558
guidelines, 1559
laboratory investigations
cardiac catheterization, 1032
chest roentgenogram, 1031
echocardiography, 1031
electrocardiogram, 1031
natural history of, 1029–1030
pathology of, 1028–1029
pathophysiology of, 1029, 1557–1558
pregnancy, 1559
treatment and prognosis, 1032, 1559
balloon valvotomy, 1033–1034
surgery, 1033
Valve replacement
risks of, 1072–1073
operative mortality, 1073
perioperative stroke, 1072
Valve thrombosis, 1102
Valvular disease, 420–421
hemodynamics, and stress echo, 304–305
Valvular disorders, assessment of
aortic valve, 334
mitral valve, 331–334
prosthetic valves, 334–335
tricuspid valve, 334
Valvular heart disease, 152, 440–441, 650, 1098, 1702
due to acromegaly, 1719
aortic regurgitation, 279
aortic stenosis, 274–279
butterfly rash, 152
general considerations, 1098–1099
risk of thromboembolism, 1099*t*
hemodynamics in
aortic regurgitation, 475–476
aortic stenosis, 474–475
mitral regurgitation, 477–478
mitral stenosis, 476–477
pulmonic regurgitation, 478
pulmonic stenosis, 478
tricuspid regurgitation, 478–479
tricuspid stenosis, 478
management issues
elective surgery, 1102
endocarditis, 1102–1103
pregnancy, 1102
thrombotic valve complications, 1101–1102
valve thrombosis, 1102

mitral regurgitation, 281–282
mitral stenosis, 279–281
in perioperative setting, 1776–1777
prophylactic antithrombic therapy, 1099
pulmonic regurgitation, 285
pulmonic stenosis, 284–285
tricuspid regurgitation, 284
tricuspid stenosis, 283
valve stenosis, 441
valvular regurgitation, 441–442
valvuloplasty and valve repair, 1101
Valvular heart diseases guidelines
cardiac murmurs, 1104
classification, 1104
echocardiography, 1105
interventions, 1104
endocarditis prophylaxis, 1105–1106
for dental procedures, 1106
Valvular lesions
during surgery, 1785
Vanguard, stent graft design, 1176
Varenicline, 918
tobacco dependency, first-line treatment for, 1880, 1881, 1882*t*
Variant angina
arrhythmias, treatment of, 943–944
calcium antagonists, 944–946
clinical presentation of, 939–940
description of, 938
diagnosis of
ambulatory ECG monitoring, 941
coronary arteriography, 942
ECG studies, 940
history, 940
in-hospital ECG recording, 941–942
laboratory findings, 940
noninvasive studies, 940–942
physical examination, 940
provocative testings, 942
radionucleotide scintigraphy, 942
self-initiated transtelephonic ECG monitoring, 941
treadmill exercise testing, 942
differential diagnosis, 942–943
incidence of, 938
management
arrhythmias, treatment of, 943–944
calcium antagonists, 944–946
medical therapy, 943–946
surgical and percutaneous intervention, 946
natural history, 946–947
pathophysiology of, 939
predisposing risk factors, 938
prognosis, 946–947
Vascular access, sites and techniques of, 519
brachial artery approach, 520
femoral artery approach, 519–520
transradial approach, 520
Vascular cell adhesion molecule 1 (VCAM-1), 1848
in HIV patients, 1638
Vascular closure devices, advantages and disadvantages of, 537*t*
Vascular endothelial growth factor (VEGF), 40, 2009
members of, 2010
Vascular injury, 467
Vascular permeability factor (VPF), 2010
Vascular resistance
autoregulatory, 35–36
catheterization computation, 473
compressive, 35
myogenic resistance, 36
neurogenic modulation, 37
and normal pressures, 475*t*
viscous, 35
Vasculogenesis, 40, 2007
Vasoconstrictors, 38
Vasodilation in the management of acute congestive heart failure (CHF) (VMAC) study, 1243
nesiritide, 83
Vasodilators
aldosterone receptor blockers
aldosterone and systolic heart failure, 78–80
spironolactone and eplerenone in chronic heart failure, 80–81
and low blood pressure, 72
aortic impedance components, 72*t*
arterial versus venous effects of,
in systolic heart failure, 72
arteriolar vasodilators
amlodipine, 74
hydralazine, 72–73
oral nitrates, 74
enalapril effects, 75*f*
intravenous vasodilators
intravenous nitroglycerin limitations in heart failure, 82–83
intravenous nitroglycerin, 82
nesiritide, 83
nitroprusside, 82
isosorbide dinitrate/hydralazine effect, 73*f*
LV dysfunction and afterload stress, 71*f*
NTG tolerance, 73*f*, 74*f*
oral β-adrenergic blocking drugs, 83–85
phosphodiesterase type 5 inhibitors
sildenafil and tadalafil, 81–82
RAAS blockers
ACE inhibitors, 74–77
angiotensin receptor blockers, 77
Vaso-occlusive disease, 1847
Vasopressin receptors
on AVP, 1276*t*
Vasopressin, 38, 45
for cardiac arrest, 821
for CPR, 796
Vasopressor support, immediate postoperative management, 1340
Vasopressors, in refractory heart failure, 1243
Vasospastic angina, 145
coronary blood flow during, 42, 43*t*
Vasovagal syncope, 639–640. *See also* Neurocardiogenic syncope
Vaughan-Williams classification, 580*t*
beta-adrenoceptor blockers, Class II, 586
calcium channel antagonists, Class IV, 593–594
drugs that prolong repolarization, Class III, 586–593
sodium channel blockers, Class I, 579–581
Class IA, 581–583
Class IB, 583–584
Class IC, 584–586
Vegetative lesions, of infective endocarditis, 310
VEGF-C. *See also* VEGF-2
in lymphangiogenesis. 2013
Vein of Marshal, 21
Velocity time integral (VTI), 324
Venoluminal channels, 19
Venous bypass graft PCI, embolic protection devices for, 552
distal embolic filters, 552
distal occlusion devices, 552–553
proximal occlusion devices, 553
Venous thromboembolism (VTE), 121
acute management, 1759
anticoagulation therapy, 1760
inferior vena cava filters, 1762–1763
new anticoagulants, 1763
parenteral anticoagulants, 1760–1762
clinical manifestations, 1754
diagnostic approach, 1757
high probability clinical assessment, 1758
low probability clinical assessment, 1757–1758
moderate probability clinical assessment, 1758
diagnostic testing, 1755–1757
epidemiology, 1750–1751
etiology, 1751–1752
high-risk death patients, management of, 1759–1760
intermediate risk populations, 1760
low risk populations, 1760
mortality risk assessment, 1759
optional pathways, 1758–1759
outcomes, 1753–1754
pathophysiology, 1752–1753
risk factors for, 1751*t*
signs, 1754–1755
surgical and catheter-based thrombectomy, 1760
symptoms, 1754
thrombolysis, 1760
Venous thrombosis, 1909*t*
Ventilatory oxygen consumption, 213*t*
Ventilatory threshold (VT)
in exercise measurement, 1315
Ventral septal defect, 1738–1739
Ventricular arrhythmias, 2022
and CRT, 767–768
Ventricular assist devices (VADs)
Center for Medicare services approved indications for, 1346*t*
contraindications to, 1346*t*
design of, 1347
in HF, 1360
long-term complications in, 1350*t*
monitoring of, 1348

patient selection, 1345
physiology of, 1347
structural and molecular effects of mechanical unloading, 1347–1348
Ventricular fibrillation (VF), 789, 798–799
phases of, 818–819
Ventricular function, assessment and clinical application, 252
determinants of left ventricular performance, 252–255
diastolic function, 259
heart rate, 258–259
left ventricular functional assessment during stress, 259–260
left ventricular pump function, 255–258
right ventricular function, 260–262
Ventricular septal defects (VSDs), 335
associated anomalies, 1563–1564
and BAVs, 1552
classification of, 1563*f*
clinical findings, 1564
diagnostic studies, 1564–1565
general considerations, 1562–1563
guidelines, 1566
pathophysiology, 1563
pregnancy, 1566
treatment and prognosis, 1565–1566
Ventricular septal myectomy, 1408. *See also* Septal myectomy
Ventricular septal rupture, cardiac causes of, 952
Ventricular tachycardia (VT), 686–687, 789, 798–799, 1777
monomorphic
myocardial VT in association with structural heart disease, 687–690
with structurally normal heart, 691–692
nonsustained, 1777
polymorphic
with long QT interval, 692–693
with normal QT prolongation, 693–695
with short QT syndrome, 695–696
sustained, 1777
Ventricular tachycardia ablation, in structural cardiac disease, 736–737
12-lead localization, 738
ablation, approach to, 738
activation mapping (focal tachycardias), 738
anatomic substrate, 737
electroanatomic three-dimensional mapping, 740
entrainment mapping, 739–740
epicardial VT, 743–744
pace mapping, 741–742
patient selection, 737–738
prior to ablation, 738
re-entrant tachycardia, 738–739
safety, 742–743
substrate-based ablation, 742
voltage mapping, 740–741
Ventricular thrombus, 423
Venturi effect, in LVOT obstruction, 1382
Verapamil ordiltiazem, 1171
Verapamil, 293, 679, 680, 691, 879. *See also* Calcium channel blockers (CCBs)
for HCM, 1405
in variant angina, 945
Vernakalant, 594–595
Vertebrobasilar artery stenosis (VAS), 1160
Very low density lipoprotein (VLDL), 1856–1858
fish oils, 2033
metabolism, 1857*f*
Very low density lipoprotein cholesterol (VLDL-C), 106, 111
Very small embryonic-like stem cells (VSELs), 1988
Veteran Administration Diabetes Trial (VADT) trail, 1716
Veterans Affairs Coronary Artery Bypass Surgery Cooperative Study Group (VA-CABSCSG), 970, 977
Veterans Affairs HDL Intervention Trial (VAHIT) study, 1716
VF lead, 191
Viral transduction, 2004
and plasmid DNA delivery, 2004
adeno-associated virus (AAV), 2004–2005
adenovirus, 2004
lentivirus, 2005–2006
Virtual Histology™ (VH) IVUS, 355
Viscous vascular resistance, 35
Vitamin C, in dyslipidemia, 1863
Vitamin D, in dyslipidemia, 1863
Vitamin K antagonists (VKAs), 121–122, 1762
warfarin, 121–122
Vitamin K epoxide reductase (VKOR), 121
subunit 1 (*VKORC1*) gene, 1959
VL lead, 191
Volatile agents versus opiates, as anesthetic choice, 1786–1787
Voltage-gated ion channels, 567
Volume adjustment, for cocaine abuse treatment, 1619
von Willebrand Factor (vWF), 118, 127
Vorapaxar, 132
VR lead, 191

W

Waldenström's macroglobulinemia, in AL amyloidosis, 1457
Wall motion abnormality, 291
Wall stress, 252
Warfarin, 121–122, 884, 1958–1959
cardiovascular pharmacogenomics, 1945
clinical response to, 1960
dose requirements
CYP2C9, 1959
CYP4F2, 1959
VKORC1, 1959
side effects, 1969
tailored therapy, 1960
Warm-up period, in exercise training, 1894
Weber classification, functional impairment, 1315*t*
Wegener's granulomatosis, 1658
Weight management, in cardiac rehabilitation, 920
Wellen's syndrome, 874
Wheezing, 147
White blood cells (WBC)
in variant angina syndrome, 540
White coat hypertension, 153
Wide QRS tachycardia, 677–678
Williams-Beuren syndrome, supravalvar stenosis, treatment of, 1036
Wilson's central terminal, 192
Wolff-Parkinson-White (WPW) syndrome, 673, 680, 805–806
in AF patients, 588
cardiac-surgical contribution, 730
catheter ablation complications, 731
catheter ablation development, 731
catheter ablation efficacy and challenges for accessory pathways, 731
classification and localization of accessory pathways, 731
historical evolution of ventricular pre-excitation, 730
WPW syndrome clinical implications and AVRT, 731
Women
evaluation of CAD in, 393
exercise testing in, 219
Women's Health Initiative (WHI) study, 1945
Worsening renal function (WRF), 1281
during heart failure hospitalization, 1284*t*
prognosis of, 1282

X

Ximelagatran, 126, 1762
X-SOLVD study
in enalapril benefits, 1904

Z

"Z-disc HCM", 1378
Zenith Low Profile stent graft, 1177
Zenith stent graft, 1177
Zidovudine
in HIV infection, 1643
Zoom mode, 321